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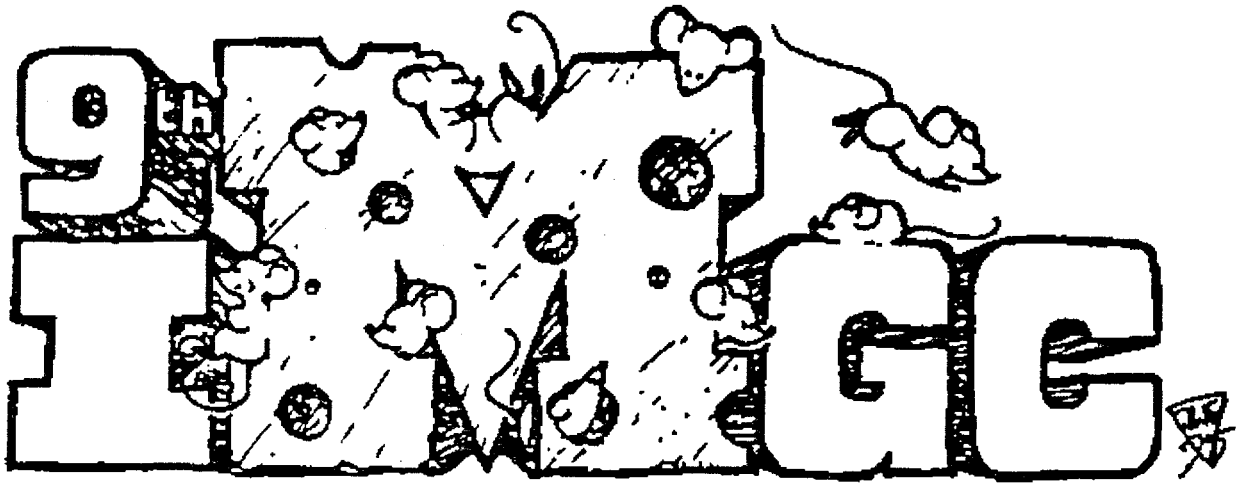

9th International Mouse Genome Conference

November 12 - 16, 1995

Ann Arbor, Michigan

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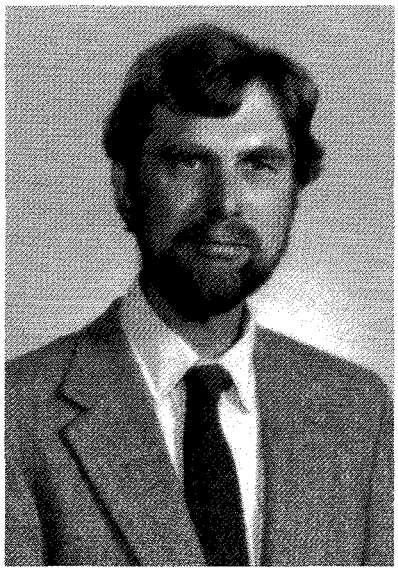

Verne M. Chapman, Ph.D.

October 4, 1938-August 30, 1995

With the sudden death of Verne Chapman on August 30, the International Mammalian Genome Society lost an outstanding leader. He was a warm and generous colleague whose influence was widely felt throughout the field.

After receiving the Ph.D. in Genetics from Oregon State University in 1965, Verne carried out postdoctoral work with Wes Whiten at the Jackson Laboratory (1966-68), Frank Ruddle at Yale (1968-1970), and Ann McLaren in Edinburgh, Scotland (1971). In 1972, he joined the Department of Molecular Biology at Roswell Park, where he remained for the rest of his career, succeeding Ken Paigen as Department Chair in 1982. Verne made Roswell Park an international center for mouse genetics, hosting scientists from around the world for short visits and lengthy collarborations. He trained an outstanding group of young scientists who carry forward the research traditions of his laboratory.

Verne made original and fundamental contributions to our understanding of X chromosome inactivation, early embryonic development, and the evolution of the pseudoautosomal region. He contributed to the collection of genetic diversity from wild mice, and he shipped mice from his extensive colony all over the world. Many investigators received valuable assistance from Verne, frequently initiated by his understated suggestion, *I think I may have some mice that could be helpful to you.* Verne used ENU mutagenesis to generate mutations in the dystrophin gene that are widely used for evaluating gene therapy for muscular dystrophy. Most recently, he pioneered the application to mouse genetics of Restriction Landmark Genome Scanning (RLGS), including construction of linkage maps, identification of imprinted genes, and detection of genome rearrangements in cancer.

Verne was instrumental in the organization of the International Mouse Chromosome Committees in 1990. He coordinated the mapping conferences in Annapolis (1990) and Buffalo (1992), and was Principal Investigator on the NIH and DOE grants that support this series of meetings. Verne personally recruited many Chromosome Committee Chairs and Co-chairs, and his spirit animated the work that brings us to this meeting. His friendly presence, contagious enthusiasm and dedication to the mouse genetics community will be greatly missed.

More than 400 friends and colleagues attended a memorial service in Buffalo, New York, on September 19, 1995. A Memorial Fund to support educational activities and an endowed Fellowship has been established at Roswell Park. Contributions made out to the Verne M. Chapman Memorial Fund can be mailed to Health Research, Inc., P.O. Box 1216, Buffalo, NY 14240.

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40. **INTEGRATED PHYSICAL AND GENETIC IRS-PCR MAPPING.** *L.C. Schalkwyk, L. McCarthy, H. Himmelbauer+, H. Lehrach+. Imperial Cancer Research Fund, Box 123 Lincoln's Inn Fields, London UK; +Max-Planck-Institut fuer Molekulare Genetik, Ihnestrasse 73 Berlin D-14195 Germany.*

41. **RAPID GENOME-WIDE LOH ANALYSIS IN MOUSE.** *R. Elango, W. Held*, K. Hunter, K.A.Kearns*, Ya-Qin Zang*, D.E. Housman. Center for Cancer Research, M.I.T., E17-536, 40 Ames Street, Cambridge, MA02139, USA; *Molecular and Cell Biology, Roswell Park Cancer Institute, Buffalo, NY, USA.*

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We would like to acknowledge the assistance of numerous faculty, staff and graduate students of the Universityof Michigan who helped with many of the details of the conference. In particular, we thank David Burke, Margit Burmeister, James Galt, Jeffrey Innis, Linda Samuelson and Susan Smelroth.

Special thanks to John Watkins-Chow for the design of the meeting logo.

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Preface

This book contains abstracts of the plenary sessions and poster presentations of the Ninth International Mouse Genome Conference, November 12-16, 1995, Ann Arbor, Michigan.

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Program

Sunday Nov. 12

1:30 p.m.	Nomenclature Committee
2:30	HUGO Committee
3:30	IMGS Secretariat
4:30	Chromosome Committee Chairs and Co-Chairs
6:30	Reception and Buffet Dinner

Monday Nov. 13

Morning Session: ***Mutation Identification*** *Chairs, Miriam Meisler, Sally Camper*

9:00 a.m.	Miriam Meisler	*Welcome*
9:05	Ken Paigen	*Verne M. Chapman: A Scientific Appreciation.*
9:30	Kiran Chada	*The Pygmy Gene is an Architectural Factor Involved in Tumorigenesis. (1)*
9:45	Dave Kohrman	*Mutations of a Novel Sodium Channel Gene, SCN8A, at the Motor Endplate Disease Locus* (med). *(2)*
10:00	Nila Patil	*Molecular Cloning of the Weaver Locus Identifies a Point Mutation in a Potassium Channel. (3)*
10:15	Karen Artzt	*Is There a Brother of Brachyury? Cloning and Analysis of Brachyury the Second Next to the Brachyury the First. (4)*
10:30	Jeff Innis	*Genetics of Vertebrate Digital Arch Formation. (75)*
10:35	Kevin Brady	*Absence of a Novel Putative Transporter Causes Osteopetrosis in the* oc/oc *Mouse.* (83)
10:45	*Coffee*	
11:15	Linda Siracusa	*The Molecular Basis of the Mouse Tight Skin* (Tsk) *Mutation Reveals its Relationship to the Microfibrillar Protein, Fibrillin 1* (Fbn1). *(5)*
11:30	Armin Shumacher	*Positional Cloning of* eed, *a Gene Required for Anterior Mesoderm Organization in Mice. (6)*
11:45	Nancy Jenkins	*Cloning of the Mouse Snell's Waltzer Deafness Gene. (7)*
12:00 noon	David King	*Genetic and Physical Mapping of the Clock Locus.* (8)
12:15 p.m.	Brett Spear	*Transgenic Mice Expressing Ectopic H-2Dd Proteins in Early Development Exhibit Neural Tube Defects. (44)*
12:20	Margit Burmeister	*The Neurological Mouse Mutations Jittery and Hesitant are Allelic and Map to the Region of Mouse Chromosome 10 Homologous to Human 19.* (69)
12:30	*Lunch*	

Afternoon Session

2:00	*Future of Mouse ESTs: Discussion Chair, Steve Brown*
3:00	*Chromosome Committee Meetings; Computer Demonstrations*
4:00	*Poster Session*
6:00	*Dinner*

Evening Session: ***Comparative Mapping*** *Chair, Neal Copeland*

8:00	Sydney Brenner	*The Analysis of a Compact Vertebrate Genome. (9)*
8:45	Roger Reeves	*Cross Referencing Yeast Genetics and Mammalian Genomes. (10)*
9:00	Joe Nadeau	*Synteny Conservation, Chromosome rearrangements, and Rates of Mammalian Evolution. (11)*
9:15	Mike Seldin	*Analysis of Mouse/Human Homologies Throughout the Genome.* (12)
9:30	Priscilla Tucker	*Duplication of the Mammalian Sex Determining Locus,* SRY. *(184)*
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9:40	Alan Ashworth	*A Contravention of Ohno's Law in Mice. (186)*

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Morning Session: ***Informatics and Complex Traits*** *Chairs, Ken Manly, Ian Jackson*

9:00 a.m.	Janan Eppig	*Mouse Genome Informatics: an Update. (13)*
9:15	Joel Richardson	*SQL Access to MGD: How and Why. (14)*
9:30	Bill Dove	*Second-Site Genetic Analysis of Multiple Intestinal Neoplasia. (15)*
9:45	Art Buchberg	*The Secretory Phospholipase a2* (Pla2s) *Gene is a Candidate for the* mom1 *Locus. (16)*
10:00	Bill Pavan	*Genetic Interactions Coordinating Piebald Spotting. (17)*
10:15	Karen Mohlke	*Localization of a Novel Gene Regulating von Willebrand Factor Levels in the RIIIS/J Mouse. (19)*
10:30	*Coffee*	
11:00	Lee Silver	*QTLs that Predispose B6 Mice to Extreme Alcohol Intake. (20)*
11:15	Ben Taylor	*Analysis of Multigenic Obesity in Strain Crosses. (21)*
11:30	Argabin Matin	*A Candidate Linkage for a Gene Involved in Modifying Disease Severity of the* $CFTR^{m1hsc}$ *Mouse. (22)*
11:45	Al Malkinson	*Assignment of* PAS *(Pulmonary Adenoma Susceptibility) and* Paht *(Pulmonary Adenoma Histogenesis Type) Genes to Chromosomal Loci by Quantitative Trait Locus Interval Mapping of the AXB and BXA Recombinant Inbred Strains. (110)*
12 noon	Mike Seldin	*Identification of Putative QTLS in MRL-*lpr *x B6-*lpr *crosses. (113)*
12:10 p.m.	Ron DeBry	*Analysis of Diet-Induced Diabetes in RI Strains. (119)*
12:30	*Lunch*	

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2:15	Kathleen Anderson	*High Frequency in the Identification of Insertional Mutants from Lines of Transgenic Mice. (24)*
2:30	J. Jongstra	*Susceptibility to N-Methyl-N-Nitrosourea Induced T-Lymphoma. (25)*
2:45	Toshihiko Shiroishi	*Polydactylous Mouse Mutants with a Duplicated Zone of Polarizing Activity* (ZPA). *(26)*
3:00	Murray Brilliant	*The Pink-Eyed Dilution Unstable* (p^{un}) *Mutation in Mouse (and Man?). (27)*
3:15	Sally Camper	*Targeted Disruption of the Pituitary Glycoprotein Hormone Alpha-Subunit Produces Hypogonadal and Hypothyroid Mice. (28)*
3:30	William Dove	*Future Directions*
3:40	*Chromosome Committee Meetings; Computer Demonstrations*	
4:30	*Poster Session*	
6:30	*Dinner*	

Evening Session: ***Gene Identification and New Technology*** *Chair, Karen Steel*

8:00	Mike Lovett	*Direct cDNA Selection as a Tool for Positional Cloning and Genome Annotation. (29)*
8:45	David Cunningham	*Cloning and Characterization of a Gene Located 50 kb 3' to* XIST. *(30)*
9:00	David Beier	*Generation of a Expressed Sequence Map of the Mouse Using Single-Strand Conformation Polymorphism (SSCP) Mapping of cDNAS. (31)*
9:15	Gail Herman	*Candidate Genes for Mouse Models of X-Linked Dominant Disorders. (32)*
9:30	Jean-Louis Guenet	*Consomic and Interspecific Recombinant Congenic Strains. (33)*
9:45	Phil Avner	*Establishment of a Mouse Chromosome - Specific YAC Probe Collection for* In Situ *Hybridization. (148)*
9:50	Doug Mortlock	*Identification of Genes Within Large Genomic Clones Using Promoter Capture. (151)*
9:55	Henry Heng	*High Order Structure Studies of Meiotic Chromosomes Using Transgenic Mice. (146)*

(Abstract Number)

Wednesday Nov. 15

Morning Session: ***Genetic and Physical Mapping*** *Chairs, Yoshihide Hayashizaki, Christine Kozak*

9:00 a.m.	Kathleen Gardiner	*Transcriptional Mapping on Human Chromosome 21: Lessons Learned and Future Directions. (34)*
9:45	Tomoya Ohsumi	*Genome-wide Scanning of DNA Alteration in Mouse Hepatoma Using 575 Premapped RLGS Loci. (35)*
10:00	Christoph Plass	*Genetic Analysis of an Imprinted Region on Mouse Chromosome 9. (36)*
10:15	Steve Brown	*An Anchored YAC Framework Map of the Mouse X Chromosome. (37)*
10:30	*Coffee*	
11:00	Lucy Rowe	*The Jackson Laboratory Interspecific Backcross Update: Current Status and New Directions. (38)*
11:15	Kent Hunter	*Genetic and Physical Mapping of the Mouse Genome by IRS-PCR Genomics: Progress Towards a Complete Map. (39)*
11:30	L.C. Schalkwyk	*Integrated Physical and Genetic IRS-PCR Mapping. (40)*
11:45	Ramu Elango	*Rapid Genome-Wide LOH Analysis in Mouse. (41)*
12 noon	Paul Lyons	*Genetic and Physical Mapping of the Diabetes Polygene, IDD3, on Chromosome 3. (42)*
12:15 p.m.	Cristophe Chevillard	*Cloning the Mouse IGH Locus in YACS. (141)*
12:20	Ann Navin	*Isolation of Y-Specific Probes Using Representational Difference Analysis (RDA). (150)*
12:25	Eric Lander	*Status of the Physical Map of the Mouse Genome*
12:30	*Lunch; IMGS Society Meeting*	
2:30	*Mouse Genome Database User's Meeting*	
3:00 - 6:00	*Buses to Ann Arbor Available (15 minute ride)*	
5:30	*Reception, Pendleton Room, Michigan Union (Second Floor)*	
7:00	*Banquet, Michigan Union Ballroom*	
9:00	*Music; Cash Bar*	

(Abstract Number)

1. THE PYGMY GENE IS AN ARCHITECTURAL FACTOR INVOLVED IN TUMORIGENESIS.

X. Zhou, H. Ashar, K. Benson, A. Tkachenko, K. Chada. Department of Biochemistry, UMDNJ-RWJMS 675 Hoes Lane, Piscataway, NJ 08854.

Pygmy is unique amongst the dwarf mutants because its phenotype cannot be explained by aberrations in the growth hormone endocrine pathway. We show that the pygmy phenotype arises from inactivation of *Hmgi-c* which functions as an architectural factor critical in the assembly of stereospecific transcriptional complexes. In addition, *Hmgi-c* and the other *Hmgi* family member, *Hmgi (y)*, were expressed predominantly during embryogenesis. These results demonstrate the important role of HMGI proteins in mammalian growth and development.

In conjunction with the above studies, the human HMGI-C gene was cloned and mapped to 12q14-15. We demonstrated that the human HMGI-C gene was disrupted at the 12q14-15 chromosomal breakpoint in lipomas, the most common neoplasm in humans. Chimeric transcripts were isolated from two lipomas in which HMGI-C DNA-binding domains (A-T hook motifs) are fused to either a LIM or an acidic transactivation domain. These results identify the first gene rearranged in a benign neoplastic process and suggest a role for HMGI-C in adipogenesis and mesenchyme differentiation.

Overall, these studies demonstrate the important role of *Hmgi-c* in growth, so that the null mutation in mice gives rise to pygmy mice whereas its deregulation leads to cellular hyperproliferation.

2. IDENTIFICATION OF SCN8A MUTATIONS IN THREE SPONTANEOUS ALLELES OF THE MOUSE NEUROLOGICAL MUTANT *MOTOR ENDPLATE DISEASE.*

D.C. Kohrman, J.M. Jones, M.H. Meisler. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109-0618.

Three spontaneous alleles at the motor endplate disease locus have been described. The severe alleles *med* and *med^{J}* produce early onset paralysis, extensive muscle atrophy, and death by one month of age. The mild *jolting* allele *med^{jo}*, produces ataxia and degeneration of Purkinje cells, but affected mice do not become paralyzed and survive beyond 18 months. We have cloned a novel voltage-gated sodium channel alpha subunit gene, Scn8a, from the insertion site of a transgene induced allele, *med^{tg}* *(Kohrman et al., Genomics 26: 171; Burgess et al., Nature Genetics 10: 461).* In normal mice, Scn8a is expressed at high levels in spinal cord and in brain, but not in muscle. The transgene insertion was accompanied by an intragenic deletion that resulted in loss of expression of Scn8a. Muscle atrophy in med mice is thus secondary to failure of transmission at the neuromuscular junction, due to loss of Scn8a expression.

In order to identify the mutations in the spontaneous alleles of med, RNA was isolated from brains of affected mice and amplified by RT-PCR. The sequences of abnormally sized products from *med* and *med^{J}* are consistent with splice site mutations that produce reading frame null mutations like *med^{tg}*. In contrast, the *med^{jo}* cDNA contains a single bp substitution, resulting in an amino acid change within a highly conserved portion of the protein. The effects of this mutation are evidently more profound in the cerebellum than in motor neurons.

3. MOLECULAR CLONING OF THE WEAVER LOCUS IDENTIFIES A POINT MUTATION IN A POTASSIUM CHANNEL

N. Patil[1], D. R. Cox[1], D. Bhat[2], M. Faham[1], R.M. Myers[1], A.S. Peterson[2].
[1]Department of Genetics, Stanford University Medical School, Stanford, CA, 94305; [2]Departments of Genetics and Neurobiology, Duke University Medical Center, Durham, NC, 27710.

The mouse neurological mutation weaver is responsible for impaired cerebellum development. The mutation arose spontaneously in the C57Bl/6J strain. Mice homozygous for the mutation are small in size, uncoordinated, and develop ataxia as well as tremors. The weaver locus (wv) is on mouse chromosome 16 between cbr and erg in a region of synteny with human chromosome 21 . Given that the physical map of human chromosome 21 is better defined than the map of the homologous segment of mouse 16 containing the wv locus, we used a combined physical and transcript map of this segment of chromosome 21 to isolate candidates for the weaver gene. DNA sequence analysis of one of these transcripts identified strong homology to mouse GIRK2, a potassium channel gene expressed in the brain. We mapped GIRK2 to a portion of distal chromosome 16 where the weaver mutation has been mapped. We compared the coding region sequence of GIRK2 between weaver and C57Bl/6J. This analysis revealed a point mutation that alters a highly conserved glycine to a serine in the pore-forming domain of the protein.

4. IS THERE A BROTHER OF *BRACHYURY*? CLONING AND ANALYSIS OF *BRACHYURY THE SECOND* NEXT TO *BRACHYURY THE FIRST*.

E. Lader[1#], G.M. Rennebeck[1#], Q. Chen[1], R.A. Bohm[1], L.A. Flaherty[2], Z.S. Cai[3], C. Faust[4], T. Magnuson[4], L.R. Pease[3], K. Artzt[1]. [1]Department of Zoology, University of Texas, Austin, TX; [2]Wadsworth Center, NY State Depart-ment of Health, Albany, NY; [3]Department of Immunology, Mayo Clinic, Rochester, MN; [4]Department. of Genetics, Case Western Reserve University, Cleveland, OH. #G.M.R. & E.L. contributed equally.

A new mouse mutation mapping to the *t*-complex, *Brachyury the second*$^{Brother\ of\ Brachyury}$ ($T2^{Bob}$), is characterized by a shortened tail in heterozygotes and homozygous failure to form an organized notochord. The phenotype of $T2^{Bob}$ superficially resembles that of *Brachyury (T)*, however, there are several important differences. *T* homozygotes fail to make posterior somites, notochord, floor plate in the neural tube, and a placental connection, resulting in death by 10.5 days of development. In contrast, $T2^{Bob}$ homozygotes make posterior somites, scattered notochord cells, and floor plate, and achieve a placental connection but still cease development at 11.5 days. We have cloned a novel gene residing at the insertion site 25 kb centromeric to *T*. It encodes a low abundance message, consists of 8 exons spanning 30 kb and points in the same direction as *T*. Two exons have been deleted by the insertion. The *Bob* cDNA has no sequences in common with *T*. *Bob is* a dominant allele of the *tct* gene from *t* haplotypes because two different *t* haplotypes sequenced have the same base change in the stop codon. The two *T* genes together with the unlinked *t int* are examples of non-allelic noncomplementation. The existence of a second gene mapping near *T* and affecting the same developmental processes was alluded to over 50 years ago by L.C. Dunn and has been debated ever since. *(This work is dedicated to the memory of L.C. Dunn, 1893-1974, belatedly on the centennial of his birth by his above academic descendants.)*

5. THE MOLECULAR BASIS OF THE MOUSE TIGHT SKIN *(Tsk)* MUTATION REVEALS ITS RELATIONSHIP TO THE MICROFIBRILLAR PROTEIN, FIBRILLIN 1 *(Fbn1)*.

Linda D. Siracusa[1], Rodney McGrath[2], Qing Ma[1], Jayanthi Manne[1], John J. Moskow[1], Paul J. Christner[2], Arthur M. Buchberg[1], Sergio A. Jimenez[2]. [1]Department of Microbiology and Im-munology, Jefferson Cancer Institute; [2]Department of Medicine, Jefferson Medical College, 233 South 10th Street, Philadelphia, PA, 19107.

Mice heterozygous for the spontaneous *Tsk* mutation display thickened skin and enlarged skeletons. Most organs exhibit an overabundance of extracellular matrix proteins. Embryos homozygous for *Tsk* die at ~8 days *in utero*. *Tsk*/+ mice have served as models for the study of connective tissue diseases such as scleroderma, myocardial hypertrophy and hereditary emphysema. As a first step towards identifying the gene responsible for the *Tsk* mutation, we mapped *Tsk* with respect to molecular markers on chromosome 2. The cosegregation of the *Fbn1* gene with *Tsk* led us to investigate the candidacy of *Fbn1*. We isolated and sequenced mouse *Fbn1* cDNA clones and identified differences in *Fbn1* expression between *Tsk*/+ and +/+ mice. In addition, we searched for genomic alterations specific for *Tsk* and have now defined the molecular basis and genetic lesion responsible for the *Tsk* mutation. The conclusions lead to a unifying hypothesis for the diverse phenotypes observed in *Tsk* mice. *(Research supported by NIH grants AR32564 and DK45717. LDS is the recipient of an ACS JFRA.)*

6. POSITIONAL CLONING OF *eed*, A GENE REQUIRED FOR ANTERIOR MESODERM ORGANIZATION IN MICE.

Armin Schumacher, Cynthia Faust, Terry Magnuson. Department of Genetics, Case Western Reserve University, Cleveland, OH, USA.

One of the few classical mouse mutations affecting gastrulation is *eed* (*e*mbryonic *e*ctoderm *d*evelopment), a recessive mutation falling into the radiation-induced albino deletion complex on distal chromosome 7. The *eed* phenotype is most obvious at E8.5; although extraembryonic mesoderm is produced extensively, little embryonic mesoderm is detected, and there is no organization of axial mesoderm into notochord or somites and no neural induction. mRNA in situ hybridization of spatially and temporally expressed marker genes confirmed that *eed is* playing an early role in anterior primitive streak function.

Extensive genetic and physical analysis located *eed* in a 150-kb region in the distal part of the deletion complex. Genetic evidence for a single gene causing the phenotype was derived from an ENU-induced putative point mutation allele (*17Rn5*^{3354SB}). A probe from a CpG island in the *eed* region allowed the isolation of a full length 1.95 kb cDNA from an E7.5 mouse cDNA library. The ORF encodes a novel protein of 441 amino acids with five WD-40 repeats which represent potential domains for protein-protein interaction. Sequence analysis of RT-PCR products from *17Rn5*^{3354SB} E8.5 embryos identified a T^{1040}->C transition which cosegregates with the mutant phenotype. The mutation changes a leucine to a proline residue in the second WD-40 repeat indicating that the repeat is functionally essential. *eed is* ubiquitously expressed both in adult tissues and in E6.5 - E8.5 embryos. Although expression is low at E6.5 and E7.5, a dramatic increase occurred at E8.5, which is coincident with full manifestation of the mutant phenotype.

7. CLONING OF THE MOUSE *SNELL'S WALTZER* DEAFNESS GENE.

K.B. Avraham[1], T. Hasson[2], K.P. Steel[3], D.M. Kingsley[4], L.B. Russell[5], M.S. Mooseker[6], N.G. Copeland[1], N.A. Jenkins[1]. ABL-Basic Research Program, Frederick, MD[1]; Yale University, New Haven, CT[2]; MRC Institute of Hearing Research, Nottingham, UK[3]; Stanford University School of Medicine, Stanford, CA[4]; Oak Ridge National Laboratory, Oak Ridge, TN[5].

The mouse represents an excellent model system for the study of genetic deafness in humans. Many mouse deafness mutations have been identified and the anatomy of the mouse and human ear is similar. Using a positional cloning approach, we have identified the gene encoded by one such deafness mutation, the mouse *Snell's waltzer (sv)* deafness mutation on chromosome 9. We show that *sv* encodes an unconventional myosin, myosin VI, which is expressed within, and appears required for maintaining the structural integrity of the sensory hair cells of the inner ear. These results, combined with previous reports indicating that another mouse deafness mutation, *shaker-1*, encodes myosin VIIa, implicates the myosins as important family of molecules in hearing. These studies further identify myosin VI as a likely candidate for a human deafness gene.

8. GENETIC AND PHYSICAL MAPPING OF THE *CLOCK* LOCUS.

David P. King, Martha H. Vitaterna, Marina Antoch, William F. Dove, Lawrence H. Pinto, Fred W. Turek, Joseph S. Takahashi. NSF Center for Biological Timing, Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208; *McArdle Laboratory for Cancer Research and Laboratory of Genetics, University of Wisconsin, Madison, WI 53706.*

We have recently reported the isolation of a novel mutation in the mouse that has several effects on the circadian rhythm of locomotor activity *(Vitaterna et al., Science 264, 719, 1994)*. This semidominant mutation identifies a single, autosomal locus, designated *Clock*, mapping to the midportion of chromosome 5. Studies of the deletion allele W^{19H} indicate that the *Clock* allele behaves as an antimorph. As part of a continuing effort to clone the *Clock* gene by position, we have generated a high-resolution genetic map of the *Clock* region, and have used these data to construct a contig containing *Clock*. Three interstrain crosses in which *Clock* segregates were used to map the mutation. The *Clock* mutation is carried on the C57BL/6J (B6) background. Both BALB/cJ (C) and C3H/HeJ (C3H) were used as counterstrains. DNA was obtained from >700 [(C X B6)F1 X B6]N_2 backcross mice, >200 (C X B6)F_2 mice, and >200 [(C3H X B6)F1 X B6]N_2 backcross mice. Simple sequence length polymorphisms (SSLPs) and restriction fragment length polymorphisms were used as DNA markers. We have localized *Clock* to a region 1-2 centimorgans (cM) distal to the *c-kit* locus on chromosome 5. Using genetic markers tightly linked (<1 cM) to *Clock*, we have now begun isolating yeast artificial chromosome (YAC) clones in the *Clock* region. The Whitehead Institute YAC library *(Kusumi et al., Mamm. Genome 4, 391, 1993)* was screened by PCR, using SSLPs as sequence tagged sites (STS). Additional STS were derived from the sequence of genes (and YAC end clones) in the *c-kit* region. We have now isolated 42 YAC clones surrounding the *Clock* locus, and have constructed a 2cM contig of 26 overlapping YACs that contains *Clock*. It will be interesting to see whether contemporary genetic and physical mapping resources will join with other molecular techniques to permit the positional cloning of mutations induced by a point mutagen, chosen for its efficiency. *(Supported by grants from the NSF Center for Biological Timing and the MacArthur Foundation to J.S.T., F.W.T., and L.H.P. and the NIH to W.F.D.)*

9. THE ANALYSIS OF A COMPACT VERTEBRATE GENOME. *Sydney Brenner. School of Medicine, University of Cambridge.*

10. CROSS REFERENCING YEAST GENETICS AND MAMMALIAN GENOMES.

DE Bassett[1,3], MS Boguski[1], MGoebl[2], P Hieter[1], R Kim[1], RH Reeves[1], F Spencer[1], S Tugendreich[1]. [1]Johns Hopkins Schl of Med, Baltimore, MD; [2]Indiana Univ. Med. Schl., Indianapolis, IN; [3]Natl. Center for Biotechnology Information, Bethesda, MD.

Information about yeast genes of known function is being transferred systematically onto genetic maps of mice and human beings. Rapidly expanding EST data provides the source of mammalian gene sequences that are repeatedly searched using S. *cerevisiae* protein sequence queries with the BLAST algorithm. cDNAs from which the ESTs are derived are mapped onto the Jackson Laboratory BSS backcross. Human chromosomal assignments are made using somatic cell hybrid panel DNAs and regional localization is inferred using known conserved synteny between the mouse and human genomes. The goal of the project is to facilitate initial identification of genes responsible for mammalian phenotypes by adding the functional information accruing to the yeast sequence to highly conserved homologs in human beings and mice. Establishment of these homologies also suggests functional studies that can be carried out in yeast to further characterize the mammalian proteins. To date, 58 clones have been used to map 98 loci on the JAX BSS panel and more than 65 loci have been assigned to human chromosomes.

The project is run as a service to the community and has recently expanded to accommodate a number of model organisms in addition to 5. *cerevisiae*. While all matches are reported to each client monthly, not all are mapped. Priority for mapping is based primarily on the significance of the match. The service is supported by the NCHGR and NLM with no charge to the user. Access XREFdb and obtain project information via the World Wide Web at the following URL: http://www.ncbi.nlm.nih.gov/XREFdb. An e-mail help message can also be obtained by sending a message

11. SYNTENY CONSERVATION, CHROMOSOME REARRANGEMENTS, AND RATES OF MAMMALIAN EVOLUTION.

J.H. Nadeau, J. Ehrlich, D. Sankoff. McGill University, Princeton University, and Universite de Montreal.

A major challenge in using comparative mapping data for studying mammalian genome evolution is correctly estimating the number of conserved chromosome segments, especially for species that have synteny maps but not genetic maps. The number of these segments can be estimated by comparing synteny relations between mammalian species. However, there are three sources of underestimation: non-independence of many comparisons, conserved segments that have yet to be identified, and redundant rearrangements. We corrected the nonindependence problem in published measures of synteny conservation. More importantly, we developed a new measure of synteny conservation based on an estimate of the total number of conserved segments. This estimate includes segments that have already been identified and those that remain to be discovered. For humans and mice, we estimate the total number of conserved syntenic segments to be 107-112 and that more than 90% of all conserved syntenic segments have already been found. For species such as humans and mice, the relative number of interchromosomal vs intrachromosomal rearrangements was estimated to be ~3:1. With measures of synteny conservation for many mammalian species, it was possible to estimate lineage-specific rates of synteny disruption. These rates were found to vary widely. Rates for some lineages such as cats were nearly 20-fold less than the rates for lineages leading to humans and mice. Finally, we found a poor correlation between rates of synteny disruption and nucleotide substitution; the relative number of substitutions: rearrangements was 2- to 3-fold higher in the mouse lineage than in the cow or human lineages. These results provide insight into the relative importance of molecular, cellular, organismic, and population factors in determining the rates of evolution.

12. ANALYSIS OF MOUSE/HUMAN HOMOLOGIES THROUGHOUT THE GENOME.

R.W. DeBry, M.F. Seldin. Duke University, Durham, NC.

Linkage, cytogenetic and/or physical mapping studies provide chromosomal locations for over 1000 genes mapped in both the mouse and human species. The data are most accurate when genes are mapped by linkage in the same data set or for when precise physical maps have been constructed. Not surprisingly, compilation of these data still suggest the conservation of genomic organization for large chromosomal segments. However, in contrast to previous reviews, the increasing resolution of gene locations now suggest that over 170 different homology groups can be defined and indicate that many previous groupings include multiple segments that are conserved between disparate regions of the same mouse and human chromosome. Precise definition of these homology groups will be of major importance in attempts to define complex genetic disease in which inbred and natural populations have different distinct advantages.

13. MOUSE GENOME INFORMATICS: AN UPDATE.

J.T. Eppig, J.A. Battles, R.E. Blackburn, D.W. Bradt, G. Colby, L.E. Corbani, G. Davis, M.T. Davisson, D.P. Doolittle, T.E. Drake, K.S. Frazer, J. Gilbert, P.L. Grant, M. Lennon-Pierce, L.J. Maltais, M.E. May, M.G. McIntire, J.E. Ormsby, D.J. Reed, J.E. Richardson, M.D. Ringwald, S.F. Rockwood, S.B. Sharpe, S.C. Shroder, A.G. Smith, M.L. Stanley-Walls, D.O. Walton. The Jackson Laboratory, Bar Harbor, ME 04609, USA.

The goal of the Mouse Genome Informatics Project is to develop a comprehensive database of mouse genetic and biological information along with software for managing, analyzing, displaying and distributing these data. Major releases of the Mouse Genome Database (MGD), which are made quarterly, reflect significant enhancements in data accessibility and organization and interface improvements. Our World Wide Web homepage allows access to MGD data, the *Encyclopedia of the Mouse Genome*, other resources such as Mouse Nomenclature Rules and Guidelines, and News and Announcements. Connecting pointers enable the user to reach our Mirror Site in the U.K. and Bioinformatics Web sites elsewhere.

Changes associated with version 2.0 include an interface for displaying composite RI strains data, the addition of abstracts to literature citations, the addition of MFW Festing's Inbred Strains Listing, the ability to generate *Encyclopedia* maps directly from MGD data, and the addition of a tool to generate Postscript files for printing 'paper' maps. The structure of MGD query forms has also been revised.

Current projects include developing protocols for regular downloads of haplotype data from major mouse mapping panels and stabilizing the MGD schema for SQL access. Data enhancements underway include expansion of Inbred Strains information and reorganization of alleles and polymorphisms to improve access and analysis. Future plans include reorganization of phenotypic data and the addition of physical mapping data. *(Supported by NIH grant HG00330.)*

14. SQL ACCESS TO MGD: HOW AND WHY.

J.E. Richardson, J.A. Battles, R.E. Blackburn, D.W. Bradt, G. Colby, L.E. Corbani, J.T. Eppig, G. Davis, M.T. Davisson, D.P. Doolittle, T.E. Drake, K.S. Frazer, J. Gilbert, P.L. Grant, M. Lennon-Pierce, L.J. Maltais, M.E. May, M.G. McIntire, J.E. Ormsby, D.J. Reed, M.D. Ringwald, S.F. Rockwood, S.B. Sharpe, S.C. Shroder, A.G. Smith, M.L. Stanley-Walls, D.O. Walton. The Jackson Laboratory, Bar Harbor, ME 04609, USA.

The Mouse Genome Database (MGD) is now available on the Internet for direct SQL access. SQL (Structured Query Language) is a standard language for querying relational databases. Although the World Wide Web has been used successfully to implement public querying and browsing interfaces for MGD, an SQL interface is needed to provide the maximum flexibility in searching and data analysis, and to allow other programs to access MGD. This talk will briefly describe the MGD database schema and will examine several example SQL queries. (This discussion is aimed at a general audience. No prior knowledge of SQL will be assumed.) This talk also outlines the reasons for providing SQL access, reasons why a user might want such an account, and instructions for obtaining one.

The Mouse Genome Informatics Project is supported by NIH grant HG00330.

15. SECOND-SITE GENETIC ANALYSIS OF MULTIPLE INTESTINAL NEOPLASIA.

W. Dove, K. Gould, D. Katzung, C. Luongo, A. Moser, A. Shoemaker (McArdle Laboratory, University of Wisconsin); L. Donehower (Baylor College of Medicine); K. Hong, W. Dietrich, E. Lander (Whitehead Institute, MIT).

A common strategy to identify genetic networks is to screen for alleles at secondary loci that modify the phenotype caused by a mutation at a primary effector *locus*. *Mom-1* modifies the multiplicity of intestinal adenomas in mice heterozygous for the *Min* allele of the *Apc* locus. Analysis of *Mom-1* homozygotes and heterozygotes indicate that *Mom-1* acts in semi-dominant fashion. MacPhee and her collaborators *(CELL 81: 957, 1995)* have proposed that resistance alleles of *Mom-1* encode the secretory type 11 phospholipase *(Pla2s)* and that sensitivity alleles fail to express this enzyme. Candidates in the region of *Mom-1* including *Pla2s* are being tested.

Is Mom-1 the only polymorphic modifier locus for *Min*? The strain AKR carries more than one modifier locus; when *Min is* congenic on the AKR background, the tumor multiplicity is less than 1.0 for the entire intestinal tract.

To expand the set of *Mom* loci, one must look beyond polymorphisms to mutant alleles including those that are homozygous lethal. Heterozygotes for *dnmt, a* recessive lethal deficiency in DNA cytosine maintenance methylase, develop a reduced number of Min-induced adenomas *(Laird et al., CELL 81: 197, 1995)*. Modification of the phenotype of Min/+ animals by a null allele of *p53* will be discussed.

16. THE SECRETORY PHOSPHOLIPASE A2 (*Pla2s*) GENE IS A CANDIDATE FOR THE *Mom1* LOCUS.

Melina MacPhee[1], Kathleen E. Bickel[1], Rebecca A. Liddell[1], Kenneth P. Chepenik[2], Rita Mulherkar[3], Linda D. Siracusa[1], Arthur M. Buchberg[1]. [1]Jefferson Cancer Center; [2]Department of Pathology, Jefferson Medical College, 233 South 10th Street, Philadelphia, PA 19107-5541; [3]Cancer Research Institute, Tata Memorial Center, Bombay, India.

Mutations in the *APC* gene are responsible for sporadic and familial colorectal cancers. *Min* mice carry a dominant mutation in the *Apc* gene and develop multiple adenomas throughout their small and large intestines. QTL studies identified a locus, *Mom 1* on the distal region of chromosome 4, that dramatically modifies *Min*-induced tumor number. *Pla2s* is a candidate gene for the *Mom1* locus. *Pla2s* maps to the same region that contains *Mom1*, and displays 100% concordance between allele type and tumor susceptibility. Expression and sequence analysis revealed that *Mom1* susceptible strains are most likely null for Pla2s activity. Immunohistochemistry reveals that $Mom1^r$ mice express high levels of Pla2s within the intestinal crypts while $Mom1^s$ mice have a much lower level of immunostaining. Our results indicate that *P1a2s* acts as a novel gene which modifies polyp number by altering the cellular microenvironment within the intestinal crypt. *(Research supported by NIH grants CA58586 and DK45717. MM and RAL are NRSA recipients. LDS is an ACS JFRA recipient.)*

17. GENETIC INTERACTIONS COORDINATING *PIEBALD* SPOTTING.

[1]*H. Rhim*, [2]*M. Cheng*, [2,3]*S. Tilghman*, [1]**W. Pavan.** [1]*Lab of Genetic Disease Research, Natl Center for Human Genome Research, Natl Inst of Health, Bethesda, MD;* [2]*Dept of Molecular Biology;* [3]*Howard Hughes Medical Inst, Princeton University, Princeton, NJ.*

The black and white spotting pattern observed in *piebald (s)* mice results from abnormal neural crest development due to a mutation in endothelin receptor B (EDNRB). The severity and distribution of the pigment patterns are vastly different in two inbred strains carrying the s mutation (Mayers/s and C3H *s/s)*. We hypothesized that additional genes may be responsible for coordinating the differences in patterning observed. Quantitative genetic analysis of backcross progeny from these two strains identified four genetic modifiers located on Chromosomes 2, 5, 8 and 10.

The modifier on Chromosome 10 increases the dorsal spotting 2-fold more than ventral spotting (19.7% vs 9.1%, $p < 0.0001$), suggesting this modifier has spatial or temporal affects on pigment patterning. Analysis of mapping data implicates *Steel* (mast cell growth factor) as a candidate gene for this locus. Sequence comparison of cDNA isolates did not indicate any differences in the coding region, however differences in the level of steady state mRNA in adult tissues was observed by Northern blot analyses. Comparison of the genomic structure of the *Steel* gene demonstrated 12/12 restriction enzymes showing differences in the size of DNA fragments, however no differences were observed in two un-linked genes, EDNRB and endothelin 3. These results suggest the increased dorsal spotting observed in the Mayer strain of *s* mice is due to a mutation that alters the *Steel* expression pattern.

19. LOCALIZATION OF A NOVEL GENE REGULATING VON WILLEBRAND FACTOR LEVELS IN THE RIIIS/J MOUSE.

K.L. Mohlke, W.C. Nichols, K.A. Cooney, E.K. Novak, R.T. Swank, D. Ginsburg.
University of Michigan, Ann Arbor, MI; Roswell Park Cancer Institute, Buffalo, NY.

Moderately low levels of human plasma von Willebrand factor (VWF) result in type 1 von Willebrand disease (VWD), a common bleeding disorder affecting up to 1% of the population. Inheritance of type 1 VWD is autosomal dominant with reduced penetrance and variable expression. An animal model for type 1 VWD, the inbred mouse strain RIIIS/J has decreased plasma VWF antigen levels inherited by progeny of three crosses in an autosomal dominant fashion. The phenotypic distributions of progeny suggest the presence of a major gene with additional modifiers. Analysis of intragenic polymorphisms excludes the murine *Vwf* locus as a significant determinant of VWF level in the RIIIS/J mouse. To map the major locus modifying VWF levels, pooled DNA samples from F2 progeny with plasma VWF levels in the top and bottom 5% of a phenotypic distribution were typed for 41 SSR markers. By this scan as well as additional genotyping with an expanded cross, the major VWD gene in the mouse was mapped to an ~1 cM interval on chromosome 11. VWF levels of progeny F2 mice homozygous for the wild-type allele near the chromosome 11 locus are significantly lower than levels of the wild-type parental strain, indicating that at least one minor gene also contributes to mouse plasma VWF level. Characterization of the major novel murine chromosome 11 VWD gene by positional cloning may identify a homologous VWF modifying locus in humans and lead to greater understanding of the interactions which affect VWD penetrance and severity.

20. QTLs THAT PREDISPOSE B6 MICE TO EXTREME ALCOHOL INTAKE.

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A large-scale outcross-backcross was performed between the alcohol-preferring strain B6 and the alcohol avoiding strain DBA. Each N2 animal was subjected to a two-bottle choice of water or 10% ethanol. 15% of the backcross animals reproducibly preferred the ethanol solution at a level equal to or greater than the one standard deviation range observed for B6 mice. These animals were subjected to a whole genome scan. The results indicate the presence of a previously unidentified QTL with $P < 0.0002$. Haplotype analysis maps this Alcohol preferring 1 (*Alcp1*) locus between markers that bracket a 5 cM region containing a candidate locus involved in neurotransmission. A second potential QTL associated with a related candidate gene is currently under investigation. The strategy taken – with an outcross-backcross breeding protocol, selective genotyping, and haplotype analysis – has increased statistical power for demonstrating linkage and increased resolving power for mapping loci compared to pedigree-based QTL analysis with the two generation outcross-intercross.

21. ANALYSIS OF MULTIGENIC OBESITY IN STRAIN CROSSES.

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We have begun the analysis of several genetic crosses with respect to the segregation of quantitative trait loci (QTLs) affecting obesity. Our goal is to identify and analyze loci that predispose specific mouse strains to obesity. In Wayne Frankel's laboratory, it was noticed that a portion of the (129/Sv x EL)F1 x EL backcross progeny showed pronounced obesity. (The EL strain is susceptible to spontaneous seizures and is being studied as a genetic model of epilepsy.) EL strain mice are large with a predisposition toward obesity. Mice of the 129/Sv strain are nonobese and of average size. We have analyzed a large (N=310) (129/Sv x EL)F2 cross. Mice were weighed, bled and killed at 16 weeks of age. The inguinal, gonadal, and retroperitoneal fat pads were dissected and weighed. DNA was extracted from spleens for genetic analysis. The sum of the three fat pad weights divided by body weight was used as an adiposity index. Male and female values were normalized to standard deviates. DNA pools were made from the 47 leanest and 47 fattest mice, respectively. These pools were then analyzed with MIT microsatellite markers to look for differential allelic representation. Allelic enrichment was observed for Chr 7 loci. Typing of extreme individuals for several markers revealed that inheritance of EL Chr 7 alleles was clearly associated with a higher adiposity index (LOD=7.5). The results indicate that a Chr 7 gene (or genes) affects obesity in both sexes, in all three fat pads, and accounts for about 10% of the total variation in the adiposity index. The data are most consistent with partial dominance of EL allele(s) conferring obesity. The results are discussed in relation to previously described obesity QTLs and potential candidate genes. DNA pooling provides an efficient way to screen large genomes for QTLs.

22. A CANDIDATE LINKAGE FOR A GENE INVOLVED IN MODIFYING DISEASE SEVERITY OF THE CFTR^{M1HSC} MOUSE.

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129/Sv mice homozygous for disruption of the cystic fibrosis transmembrane conductance regulator (*Cftr*) gene (*Cftr*^{M1HSC}/*Cftr*^{M1HSC}) die within several weeks after birth mainly due to mucus-associated obstruction of the intestinal tract. However, a significant number of the *Cftr*$^{-/-}$ F2 progeny resulting from intercross between *Cftr*^{M1HSC}/+ -129/Sv and CD-1, C57BL/6J or BALB/cJ show prolonged survival (more than 7 weeks) due to amelioration of the symptoms involved in mortality of the mice. We used pooled DNA from 30 of such surviving F2 (*CFTR*^{M1HSC}/+ -129/Sv x CD-1)^2 mice to perform a genome scan by PCR-typing for simple sequence length polymorphisms (SSLPs) and have established excess homozygosity for a CD-1 locus that segregates in the F2 mice of the surviving group. Our results show that the *Cftr*$^{-/-}$ F2 progeny are either homozygous or heterozygous for the CD-1 derived locus. This candidate modifier CD-1 locus will be important for understanding the basis of the varying disease severity in cystic fibrosis in humans and in developing novel gene therapies.

23. FURTHER UPDATE ON CHLORAMBUCIL MUTAGENESIS.

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We have set up a large scale mutagenesis experiment to determine the frequency of deletions/chromosomal rearrangements induced by chlorambucil (CHL). In previous studies, we have found that this drug induces a high incidence of recessive visible mutations. The frequency of these mutations is dependent on the dose and mouse strain used. In past studies, C3H/HeJ males, injected with 7.5 mg/kg of CHL and mated to B6/J females, was a particularly successful combination. Therefore, approximately 200 male C3H/HeJ mice were treated with CHL. Progeny from matings with B6/J that occurred between 2 and 3 weeks post-injection were kept and assayed for mutations. One hundred of the resulting (B6 X C3H)F1 males were tested for a variety of blood parameters including cholesterol, glucose, creatine kinase, lactate, and immunoglobulin levels. They were then individually mated to 4 B6 females. The resulting (B6 X C3H)F1 X B6 progeny are now being tested for these same blood parameters. In addition, four of the (B6 X C3H)F1 X B6 female progeny from each of the 100 males were mated to their fathers. Progeny of these crosses are now being observed for recessive visible mutations. Our expectation is that approximately 1 out of every ten males should test positive for a new visible mutation. From this group, we have already obtained at least 2 new recessive mutations.

24. HIGH FREQUENCY IN THE IDENTIFICATION OF INSERTIONAL MUTANTS FROM LINES OF TRANSGENIC MICE.

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Thirty lines of transgenic mice were screened for the presence of insertional mutants. Siblings heterozygous for the transgene were mated to homozygosity. Southern blot analysis was performed on DNA obtained from tail samples and quantitated by phosphoimager analysis for the presence of one versus two copies of the transgene array. Animals identified as homozygotes for the transgene insertion were bred with nontransgenic mice. The litters from these matings were scored for the presence of the transgene by PCR analysis of ear clip samples. Animals producing litters in which all the pups were transgenic were confirmed as homozygotes. Breeding was continued until both male and female homozygotes had been obtained. These homozygote animals were then screened for the presence of physical defects or the development of tumors or disease. Of the thirty lines analyzed, 11 mutations due to the transgene insertion were identified. The phenotypes included ventricular hypertrophy, a kinky tail defect, cataracts and early death, kidney agenesis, retinal degeneration, ovarian cysts and uterine endometriosis, lack of female homozygotes, and 4 embryonic lethals.

25. SUSCEPTIBILITY TO N-METHYL-N-NITROSOUREA INDUCED T-LYMPHOMA.

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Apart from a handful of genes shown to be mutated in a few well established hereditary cancer syndromes, not much is known about genetic susceptibility to cancer in humans, especially to major diseases such as lymphoma/leukemia and lung cancer. To set up a mouse model system we first screened a number of mouse strains for their susceptibility to N-methyl-N-nitrosourea induced T-lymphoma. Mice received a single i.p injection of 75 mg MNU per kg bodyweight. All AKR/J, RF/J, 129/SvJ and C57L/J mice developed T-lymphoma between 60 and 150 days after injection. Only 25% of BALB/cJ mice had developed T-lymphoma 180 days after injection. We analyzed a large cohort of F2 mice derived from AKR/J and BALB/cJ parents, using a genome wide screen with 60 polymorphic microsatellite markers distributed over all chromosomes. So far we have identified three loci on chromosomes 1, 3 and 11 which are linked to the appearance of MNU induced T-lymphoma. In addition two loci, on chromosomes 2 and 7 show loss of heterozygosity in tumours from MNU induced AKR/JxBALB/cJ F1 mice. Thus in a single mouse cross we have identified 5 genetic loci involved in tumour development induced by a common alkylating agent. Additional crosses are being developed to answer the question whether the susceptibility of other mouse strains involves the same set or additional sets of genes.

26. POLYDACTYLOUS MOUSE MUTANTS WITH A DUPLICATED ZONE OF POLARIZING ACTIVITY (ZPA).

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The positional signaling along the anteroposterior axis of the developing vertebrate limb is provided by zone of polarizing activity (ZPA) that is located at the posterior margin. Recently, it was established that *Sonic hedgehog (Shh)* mediates ZPA activity. Here, we report that a new mouse mutant, *Recombination induced mutant 4 (Rim4)*, and two old mutants, *Hemimelic extra toes (Hx)* and *Extra toes (Xt)*, exhibit mirror-image duplication of the skeletal pattern of the digits. In situ hybridization of the embryos of these mutants revealed ectopic expression of *Shh and fibroblast growth-4 (FGF-4)* genes at the anterior margin of limb buds. The new mutation, *Rim4*, was mapped to chromosome 6 with linkage to *HoxA* but no linkage to other known polydactylous mutations was detected. In this mutant, ectopic expression of *Hoxd11* gene that may play the downstream function of *Shh* gene was also observed at the anterior margin of the limb buds. All the result indicated the presence of the additional ZPA at anterior limb buds of these mutant mice.

27. THE PINK-EYED DILUTION UNSTABLE (p^{un}) MUTATION IN MOUSE (AND MAN?).

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The p^{un} mutant allele of the mouse pink-eyed dilution locus, *p*, is associated with a high frequency of somatic reversion (~3.8%). Previously, we have demonstrated that the p^{un} allele is associated with a tandem, same sense, duplication of ~70 kb of genomic DNA within the *p* gene. Reversion of *pun is* coupled with the loss of one of the duplicated copies. We report here the sequence of the transcript encoded by the p^{un} mutant allele and the results of various genetic crosses that give insight into the mechanism of reversion. Mutations of the human homolog, P, lead to tyrosinase positive oculocutaneous albinism (OCA2). We recently found an OCA2 patient with evidence of somatic reversion. Interestingly, while one of the P alleles of this patient encodes a critical amino acid substitution, the other P allele of this patient appears to be associated with a duplication of the P gene.

28. TARGETED DISRUPTION OF THE PITUITARY GLYCOPROTEIN HORMONE ALPHA-SUBUNIT PRODUCES HYPOGONADAL AND HYPOTHYROID MICE.

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The first evidence of commitment to the anterior pituitary gland is the expression of the α-subunit gene in the hypophyseal placode. Alpha-subunit is an essential component of the heterodimeric hormones TSH, LH and FSH, and it is secreted as a glycosylated monomer with unknown function. The provocative spatial and temporal pattern of a-subunit expression, together with its structural similarity to a family of cystine knot growth factors, suggested that it might influence pituitary gland development. Because there are no known variants in the human or mouse α-subunit genes, we generated a targeted disruption by homologous recombination in ES cells. Homozygous mutants had severe growth insufficiency and infertility attributable to the lack of TSH, LH and FSH. Development of the thyroid was arrested in late gestation, and gonadal development was blocked in the perinatal period. The hypothyroid and hypogonadal phenotypes were similar to those observed in *hyt* and *hpg* mutants. Although the five major hormone-producing cells of the anterior pituitary were present, the relative proportions of each cell type were dramatically altered. Hypertrophy and hyperplasia of thyrotropes occurred at the expense of somatotropes and lactotropes, consistent with the lineage relationship for these cells predicted by the Ames and Snell dwarf mice. The effectiveness of thyroid hormone and gonadal steroid replacement therapy in rescuing the growth and gonadal defects is being assessed. This study has clarified the roles of fetal pituitary hormones in development and provides a valuable animal model for assessing the contribution of pituitary hormones to hyperplasia and tumorigenesis.

29. DIRECT cDNA SELECTION AS A TOOL FOR POSITIONAL CLONING AND GENOME ANNOTATION. *Mike Lovett, The McDermott Center, University of Texas, Dallas, TX.*

30. CLONING AND CHARACTERIZATION OF A GENE LOCATED 50 KB 3′ TO *XIST*.

David Cunningham, Philippe Clerc, Marie-Christine Simmler, Dominique Segretain[1], Jean Michel Claverie[2], Jean Weissenbach[3], Philip Avner. Unite de Genetique Moleculaire Murine, Institut Pasteur, 75024 Paris, France. [1]Faculte de Medicine, 45 rue des St. Peres, 75006 Paris, France; [2]Information Genetique et Moleculaire, C.N.R.S. 31 Chemin Joseph-Aiguier, 13402 Marseille, France; [3]Genethon, 91002 Evry, France.

The X inactivation center *(Xic)* is a genetically and cytologically defined interval on the mouse X chromosome that is required in *cis* for X inactivation in the female during embryogenesis. The *Xist* gene lies within *Xic* and may play a direct role in the process of X inactivation. *Xist* is the only gene known to be transcribed specifically from the inactive X chromosome. As part of our ongoing molecular characterization of Xic, we determined the sequence of 100 kb of genomic DNA lying 3′ to the *Xist* gene. One objective of this project is to identify any additional transcription units within this region in order to determine whether or not *Xist is* unique in its pattern of expression. A computer-assisted search of the 100 kb of sequence provided predictions of potential exons based on open reading frames, consensus splice sites, codon usage and similarity to known coding sequence. The predicted exons were tested by probing Northern blots with PCR products that included the putative exon sequences. Of 23 predictions tested, 2 detected the same message. These probes were then used to isolate a cDNA clone from a mouse cDNA library. The sequence of the cDNA clone reveals that it originates from a gene lying within 50 kb of the 3′ end of *Xist*. The predicted amino acid sequence of the cDNA shows no striking similarity to sequences in the databases. We are currently characterizing the expression pattern of this gene, specifically in relation to *Xist* expression.

31. GENERATION OF A EXPRESSED SEQUENCE MAP OF THE MOUSE USING SINGLE-STRAND CONFORMATION POLYMORPHISM (SSCP) MAPPING OF cDNAS.

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We have previously described the utility of single-strand conformational polymorphism (SSCP) analysis as a means to identity polymorphisms in 3′ untranslated regions that are useful for cDNA mapping *(Mamm. Genome 4: 627-631, 1993)*. We are presently using this strategy as means to do large scale mapping of murine expressed sequences. Over 1000 cDNAs from a brain cDNA library have been isolated and analyzed by single-pass sequencing of their 5′ and 3′ ends. Putative functions could be assigned to approximately 50% of the cDNAs based upon their sequence similarity to previously cloned mammalian genes or conservation of functional amino acid motifs. 20% of the mouse cDNAs were homologous to human ESTs, and the remaining 30% of the expressed sequences showed no similarity to any sequences in the public domain databases.

In order to map these ESTs, primers are designed that amplify 150-250 bp fragments from their 3′ region. These are tested for SSCPs using a panel of inbred mouse strains and species. Of the greater than 600 primer pairs tested to date, 89% were polymorphic. 22% of the primers exhibited polymorphisms between inbred strains, and over 60 have been mapped on the BxD, AKxL, or BxH recombinant inbred panel. The remaining 65% were polymorphic between B6 and *M. spretus;* over *200* have been mapped using the (C57BL/6J x *M. spretus)* x *M. spretus (BSS)* interspecific backcross developed by investigators at the Jackson Laboratory *(Bar Harbor, ME)*. We anticipate this collection of mapped cDNAs will prove generally useful, including as a means to integrate the genetic and physical maps of the mouse genome.

32. CANDIDATE GENES FOR MOUSE MODELS OF X-LINKED DOMINANT DISORDERS.

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Our laboratory is interested in the identification of genes involved in several X-linked dominant disorders and the delineation of their roles in mammalian development. To this end, we have mapped the bare patches *(Bpa)* and striated *(Str)* mutations to an overlapping critical interval of ~600 kb between *DXHXS1104* and *DXHXS52*. This interval is covered by YACs which have been subcloned into cosmids. The syntenic human region is also spanned by YACs and independent cosmids isolated from a flow-sorted library. We have utilized exon trapping, cDNA selection, cross-species hybridization with primary porcine mRNA from selected tissues, and mapping of CpG islands to identify transcribed sequences within the critical region. Independent mapping or sequence analysis of trapped exons has led to the identification of 3 known genes – caltractin, *xlr3*, and an additional GABA receptor. Trapped exons and/or partial cDNAs have been isolated and sequenced for potentially seven additional novel genes. Two appear to be present in multiple copies within the critical region. By RT-PCR, several are expressed in murine embryos (day 9.5-birth) and neonatal skin. Expression data and comparative mapping of the candidate cDNAs as well as RT-PCR analysis in affected embryos and skin fibroblasts will be presented.

33. CONSOMIC AND INTERSPECIFIC RECOMBINANT CONGENIC STRAINS. x.

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We have developed two alternative approaches to permanently introduce approximately 5% of *Mus spretus* genome in a C57BL/6 inbred background. More than 50 Interspecific Recombinant Congenic Strains (IRCS) are now being inbred. Preliminary genotyping has been performed and shows an heterogeneous distribution of the loci that have been successfully "imported" from *Mus spretus*. In parallel, we are creating a set of Interspecific Consomic Strains (ICS) in which each strain has one chromosome of *Mus spretus* origin, also in a C57BL/6J background. Breeding data will be presented. Some of these strains have already been instrumental for the study of imprinted genes or for positional cloning projects. Once they will be fully inbred, they should be useful to all those who wish to make focused interspecific crosses without having to breed wild mice.

34. TRANSCRIPTIONAL MAPPING OF HUMAN CHROMOSOME 21: LESSONS LEARNED AND FUTURE DIRECTIONS.

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The detailed physical and clone maps of human chromosome 21 have made it ideal for transcriptional mapping efforts. cDNA selection applied to 16 Mb of YAC clones and to a set of random cosmids, as well as use of motif screening, mapping of ESTs, and reciprocal cDNA/cosmid library screening, have yielded a large number of new cDNAs, representing probably 100 novel genes, all with very precise map positions. Gene densities vary considerably - from > 1/10 kb to < < 1/1000 kb, and suggest that as many as 40% of the genes may reside in as little as 12% of the chromosome. This observation has implications for the current mouse model of Down Syndrome (partial trisomy 16). In addition, with so many novel cDNAs on hand, the pressing question now becomes functional analysis. Approaches include genomic sequencing, tissue in situ hybridization, sequence comparisons with mouse, and mutational analysis. The role of model organisms assumes increasing importance as transcriptional mapping proceeds, not only on chromosome 21, but in the human genome as a whole.

35. GENOME-WIDE SCANNING OF DNA ALTERATION IN MOUSE HEPATOMA USING 575 PRE-MAPPED RLGS LOCI.

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We have developed a Restriction Landmark Genomic Scanning (RLGS) system which can be used to detect DNA alterations in mouse tumor tissues. In a previous genetic study using BSS backcross progeny, 575 C57BL/6 and M. spretus specific spots from a NotI-PvuII-PstI RLGS pattern have been mapped. These mapped spots provide the basis for a unique and very powerful method for rapid genome wide scanning of tumor DNA: 1) alterations at the 575 mapped spot loci can be detected in a single gel; 2) since the spots are quantitatively end labeled, DNA amplifications as well as losses (Loss of Heterozygosity (LOH)) can be identified; 3) since the spots represent either C57BL/6 or M. spretus haploid loci, allele-specific alterations due to genomic imprinting or strain-specific effects can be detected; 4) also, since the spot represents a DNA fragment containing an end-labeled NotI site and NotI digestion is methylation sensitive, RLGS can detect tumor-specific changes in DNA methylation.

In this study, we applied RLGS to do a genome-wide search for LOH in liver tumors from interspecific F1 hybrid mice between M. spretus and C57BL/6 containing a Mouse Major Urinary Protein (MUP) SV 40 T antigen transgene. By comparing the RLGS profiles of each tumor with that of normal tissue, a LOH map of each tumor was prepared. Analysis of 30 tumors indicates a high frequency of LOH at loci on chromosomes 1, 5, 7 and 13. In addition, several regions of hypermethylation commonly seen in these tumors will be reported.

36. GENETIC ANALYSIS OF AN IMPRINTED REGION ON MOUSE CHROMOSOME 9. c.

Plass, H. Shibata[1], I. Kalcheva, L. Mullins[2], H. Sasaki[3], R. Kato[3], S. Hirotsune[1], Y. Okazaki[1], K. Yoshino[1], Y. Hayashizaki[1], V. Chapman, Dept. of Molec. and Cell. Biology, Roswell Park Cancer Inst., Buffalo NY 14263; USA; [1]Genome Science Lab., RIKEN, Tsukuba, Japan; [2]AFRC Center for Genome Res., Univ. of Edinburgh, UK; [3]Inst. of Genetic Information, Kyushu Univ., Japan.

The restriction landmark genomic scanning technique using the methylation sensitive restriction enzyme *Not*I (RLGS-M) was used to identify a number of landmarks (spots) which show parent of origin specific methylation. The C57BL/6J (B6) specific spot, Irlgs-3, was identified in reciprocal crosses of B6 and DBA/2J (D2) as a labeled spot which appeared only in the (B6xD2)F_1, but not in the (D2xB6)F_1 profiles. The appearance of Irlgs-3 correlates with a maternal transmission suggesting a paternally methylated allele. A 1.8 kb *Not*I-*Mbo*I fragment was recovered as a NotI boundary clone using the RLGS spot cloning procedure. The clone identifies restriction variation that maps with Irlgs-3 on mouse chromosome 9 in the *BSS-Jackson* backcross panel, 2.13 cM distal to *Mod-1*. Southern blot experiments determined the minimal size of 3 kb for the paternal allele specific methylation. The monoallelic methylated region contains a 41 bp tandemly repeated motif (repeated 40 times) which is found 200 bp downstream of the *NotI* restriction site. This repeated sequence is present in different Mus species *(M.musculus* and *M.spretus).* The physical characteristics of Irlgs-3 have been studied in cosmid and P1 clones that identify a genomic region of 85 kb. The exon amplification protocol was used to identify potential coding sequences within the genomic region. Eight different exon clones have been isolated and three of these exons map 3′ to the Irlgs-3 locus and identify transcripts that show paternal allele-specific expression.

37. AN ANCHORED YAC FRAMEWORK MAP OF THE MOUSE X CHROMOSOME.

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A program directed towards the coverage of the mouse X chromosome with YAC contigs is in progress. The St. Mary's and ICRF mouse YAC libraries have been arrayed three dimensionally and DNA pools recovered for rapid PCR screening. Screening the 3-D library with available genetically mapped STSs has allowed us to complete an anchored YAC framework map of the mouse X covering an estimated 55% of the chromosome: Over 360 STS-YAC hits have been identified from 135 genetically mapped STSs and the bulk of identified YACs have been archived. 18 contigs incorporating two or more STSs have been identified. Average YAC insert size determined from 80 clones chosen at random was 490kb. The development of the anchored YAC map is greatly assisted by the development in parallel of a high resolution microsatellite map of the mouse X chromosome using the European Collaborative Backcross (EUCIB) facility. A high resolution genetic map for the proximal half of the X chromosome is complete and high resolution genetic mapping of the distal half of the mouse X chromosome is underway. The production of a high resolution genetic map of STSs helps confirm contig integrity as well as aiding contig orientation, generation and extension. Physical mapping data is compiled within the EUCIB *MBx* database (*Tailor* et al.) to allow comparison and integration with the available high resolution genetic map data. Physical maps are assembled using SAM (System for Assembling Markers - version 2.5) and displayed through the WWW that also incorporates a multimap display to illustrate the genetic/physical map relationships of STSs on the anchored YAC physical map (http://www.mrc.ac.uk/MBx/MBxHomepage.html).

38. THE JACKSON LAB INTERSPECIFIC BACKCROSS UPDATE: CURRENT STATUS AND NEW DIRECTIONS.

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The Jackson Laboratory interspecific backcross panels are now typed for more than 700 loci in the BSB and 1900 loci in the BSS cross. Four groups have initiated large scale cDNA mapping projects using these DNA panels, facilitating the placement of identified coding loci on the maps. Over 130 different labs have contributed linkage data. New public data sets are placed on the World Wide Web at approximately 6 week intervals. In collaboration with Dr. Rosemary Elliott and Dr. Verne Chapman at Roswell Park, we have mapped the centromeres in our backcross panels by close linkage to MIT markers mapped with respect to *Hc* in the Roswell interspecific backcrosses. Some telomeres have also been mapped, allowing new estimates of overall genome size.

Toward the possibility of making available for distribution high density marker filters which can be used to completely genotype any cross, we have been developing a reverse-phase hybridization mapping strategy. Using our interspecific backcross panel DNAs as templates for PCR with the mouse B1 repeat consensus sequence as primer, we have generated hybridization probes which give plus-minus hybridization signals to selected inter-B1 repeat clones and mouse cDNA clones. In this way we are mapping large numbers of new markers associated with the B1 repeat distribution differences between strains of mice. These markers will be screened for polymorphism among commonly used inbred strains to establish a set of markers gridded on high density filters that can be hybridized to probes made with individual segregants in any mapping cross to scan the complete genome.

39. GENETIC AND PHYSICAL MAPPING OF THE MOUSE GENOME BY IRS-PCR GENOMICS: PROGRESS TOWARDS A COMPLETE MAP.

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Last year we described an integrate physical and genetic mapping strategy based on the hybridization of individual IRS-PCR products to gridded IRS-PCR products of Jackson Laboratory BSS interspecific backcross panel and YAC 3 dimensional coordinate pools of three YAC libraries, MIT/Whitehead, ICRF, and St. Mary's Hospital. At present, a minimum of 15% of the YAC clonable regions of the mouse genome have been assembled into contig islands, and 20% of the contig islands are anchored to the genetic map. A variety of methodologies have been explored to improve the sensitivity of the technique and increase the efficiency. The current strategies for completion of the integrated map will be discussed.

40. INTEGRATED PHYSICAL AND GENETIC IRS-PCR MAPPING.

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IRS-PCR (for example inter B1 PCR) is an easy way of obtaining a dispersed, mouse-specific subset of the DNA in a variety of materials, such as genomic DNAs, somatic cell hybrid DNAs and clones. The fragments produced generally contain some unique sequence and are useful as hybridisation probes and targets. This provides a streamlined way of producing genetic markers and finding YACs which contain them, thus making anchored YAC contigs by simple hybridisation based techniques. This process is being scaled up to produce an integrated physical and genetic map.

41. RAPID GENOME-WIDE LOH ANALYSIS IN MOUSE.

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The loss of heterozygosity of a locus in tumors help us in identifying the tumorogenesis related genes, including the tumor suppressor genes. In most of the cases, genome-wide LOH analysis is difficult to carry out due to very little tumor DNA available for such a study. To circumvent this major problem, we have decided to use the IRS-PCR amplification polymorphisms between C57 and *M. spretus* strains of mice *(see K Hunter, et.al. abstract 1995)* to scan the whole genome of tumors from F1 animals. This requires only 50-100 ng of DNA for the whole genomic scan. In the present study, different tumor DNA samples, from F1 animals of transgenic mice (C57 background) expressing T antigen with *M. spretus* or *M. castaneus*, were collected. Strain-specific markers (both C57 and *M. spretus* markers) were hybridized to IRS-PCR products of tumors. It is easy to screen more than 300 samples with 96 markers in a week by this method. So far we have scanned 180 tumor samples with more than 100 markers. Results have shown frequent loss of two chromosomes in many tumors. New loci showing LOH in some tumor types are being confirmed with other methods.

42. GENETIC AND PHYSICAL MAPPING OF THE DIABETES POLYGENE, *Idd3*, ON CHROMOSOME 3.

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Several linkage studies using crosses of the nonobese diabetic (NOD) mouse strain to a variety of nondiabetic strains have shown that diabetes is polygenic with up to 14 genes contributing to disease development. The dominant mode of inheritance of these loci has made it impossible to map the genes involved using conventional backcross analyses. Instead we have adopted the approach of using congenic strains to define smaller and smaller chromosome segments that contain *Idd* loci. Using such congenic strains, which carry resistance alleles from the C57BL6 (B6) strain on an NOD background, we have confirmed the presence of 2 *Idd* loci, *Idd3* and *Idd10*, on chromosome 3. Idd3 has been localised to a < 2cM interval between, but not including, the microsatellite markers *D3Nds40* and *D3Mit240*. To facilitate the cloning of *Idd3* we are currently constructing a YAC contig across the interval. In addition, we are developing new microsatellite markers from these YACs to more precisely define the ends of the introgressed segments carried by our congenic strains. Of the genes currently mapped within the *Idd3* interval Interleukin 2 remains the best candidate. Sequence analysis has shown that polymorphisms exist between the NOD and B6 forms of IL2, however, as of yet no functional differences between the two proteins have been described. The threonine at position 3' of the mature human IL2 protein has previously been shown to be glycosylated. This residue is contained within the motif PTSS which is present once in the B6 form of IL2 and 3 times in the NOD form. We have preliminary data showing that the NOD form of IL2 migrates more slowly on SDS-PAGE gels than the B6 form. It is conceivable that this difference is due to differences in glycosylation which might affect the function of the protein.

43. **A NEW ALOPECIA MOUSE MUTANT AROSE IN C3H.** *A. Yoshiki[1] C. Poirier[2], S. Sato[1], N. Matsumoto[1], J-L. Guenet[2], M. Kusakabe[1]. [1]Division of Experimental Animal Res., RIKEN, 3 Koyadai, Tsukuba, Ibaraki 305, Japan; [2]Unite de Genetique des Mammiferes, Institute Pasteur, 25 Rue du Dr Roux 75724, Paris, CEDEX 15, France.*

44. **SINGLE AFP ENHANCERS EXHIBIT UNIQUE REGULATORY ACTIVITIES IN TRANSGENIC MICE.** *T. Ramesh, K. Li, M. A, Green, B.T. Spear. Dept. of Micro. & Immunol., Univ. of Kentucky College of Medicine, Lexington, KY 40536.*

45. **A RAT HOMOLOGUE OF THE MOUSE DEAFNESS MUTANT JERKER *(je).*** *G. E. Truett[1], J. A. Walker[1], J.W. Brock[2]. [1]Pennington Biomedical Research Center, Baton Rouge, LA; [2]Brain and Development Research Center, University of North Carolina, Chapel Hill, NC USA.*

46. **FLAILER, A NEW NEUROLOGICAL MUTANT ON MOUSE CHROMOSOME 9.** *Julie M. Jones, Scott J. Popma, Karl Herrup*, Miriam H. Meisler. Dept of Human Genetics, University of Michigan, Ann Arbor, MI 48109-0618; *Alzheimer Research Laboratory, Case Western Reserve University, Cleveland, OH 44106.*

47. **DNA SEQUENCE CHARACTERIZATION OF THREE INDUCED MUTATIONS AT THE MOUSE PHENYLKETONURIA LOCUS.** *J. David McDonald, Cynthia Charleton. Wichita State University, Department of Biological Sciences, Wichita, KS USA.*

48. **A SCREEN FOR DOMINANT MUTATIONS THAT AFFECT BEHAVIOR.** *P.M. Nolan[1], D. Tobin[1], A. Gupta[1], D. Xiong[1], M. Bucan[1,2]. Depts of Psychiatry[1] and Genetics[2], University of Pennsylvania, Philadelphia, PA 19104, USA.*

49. **LINKAGE OF *HFI* MOUSE CATARACT MUTATION TO CHROMOSOME 10.** *D.J. Sidjanin, J. Favor*, D. Stambolian. Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA, USA; *GSF-Institut fur Saugetiergenetik, D-8042 Neuherberg, Germany.*

50. **EFFECTS OF γ IRRADIATION ON EMBRYONIC STEM (ES) CELLS.** *Yun You, Becky Bergstrom, John Schimenti. The Jackson Laboratory, Bar Harbor, ME, USA.*

51. **ALLELIC LOSSES IN MOUSE PRIMARY LYMPHOMAS INDUCED BY GAMMA IRRADIATION.** *Santos. J., Perez de Castro, I., Herranz, M., Fernandez-Piqueras, J. Departamento de Biologia. Unidad de Genetica. Facultad de Ciencias. Universidad Autonoma de Madrid. 28049-Madrid. Spain.*

52. ***Xist* EXPRESSION FROM AN *Xist* YAC TRANSGENE CARRIED ON THE MOUSE Y CHROMOSOME.** *S. Matsuura, V. Episkopou, S.D.M. Brown. Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London W2 1PG, UK.*

43. A NEW ALOPECIA MOUSE MUTANT AROSE IN C3H. *A. Yoshiki[1] C. Poirier[2], S. Sato[1], N. Matsumoto[1], J-L. Guenet[2], M. Kusakabe[1]. [1]Division of Experimental Animal Res., RIKEN, 3 Koyadai, Tsukuba, Ibaraki 305, Japan; [2]Unite de Genetique des Mammiferes, Institute Pasteur, 25 Rue du Dr Roux 75724, Paris, CEDEX 15, France.*

We have found a mouse with curly whiskers and wavy coats in the course of breeding C3H/HeN. The genetic analysis indicated that this hair abnormality was an autosomal dominant trait with incomplete penetrance. Heterozygotes have curly whiskers and wavy hair. Homozygotes have extremely curled hair, begin to lose body hair from 2 weeks of age, completely lose the first hair by 3 weeks, and become alopecia. In adults, short curly hair grows sparsely. Histopathological analyses revealed that formation of hair follicles, especially differentiation of cells in the Huxley's layer of inner root sheath was deficient in the mutant. We are now trying to map this mutant locus by using interspecific crosses between the mutant and *Mus musculus castaneus*.

44. SINGLE AFP ENHANCERS EXHIBIT UNIQUE REGULATORY ACTIVITIES IN TRANSGENIC MICE. *T. Ramesh, K. Li, M. A, Green, B.T. Spear. Dept. of Micro. & Immunol., Univ. of Kentucky College of Medicine, Lexington, KY 40536.*

The mouse α-fetoprotein (AFP) gene is expressed at high levels in the yolk sac and fetal liver and low levels in the fetal gut. Transcription is dramatically repressed at birth, leading to very low levels of mRNA in the adult liver and gut. This repression is reversible as AFP can be reactivated during liver regeneration and in hepatocellular carcinomas. The five distinct *cis*-acting regions that control AFP expression are the promoter, a repressor required for postnatal repression, and three upstream enhancers, EI, EII, and EIII.

Transgenic mice containing hybrid genes consisting of individual AFP enhancer elements linked to a heterologous promoter were generated. All three enhancers were active in the tissues where AFP is normally expressed. EIII was also active in the brain. Interestingly, homozygous mice from different EIII founders also exhibited severe craniofacial defects, suggesting that the transgene in these mice alters normal development. *In situ* immunohistochemistry revealed that each enhancer was zonally active the adult liver. EI and EII were active primarily in pericentral hepatocytes with a gradual reduction in expression towards the portal triad. EIII was active exclusively in hepatocytes that surround the central vein. Each enhancer exhibits different changes in activity during liver regeneration. Experiments to determine the basis for zonal activity will be discussed.

45. A RAT HOMOLOGUE OF THE MOUSE DEAFNESS MUTANT JERKER *(je)*. *G. E. Truett[1], J.A. Walker[1], J.W. Brock[2]. [1]Pennington Biomedical Research Center, Baton Rouge, LA; [2]Brain and Development Research Center, University of North Carolina, Chapel Hill, NC, USA.*

An autosomal recessive deafness mutant was discovered among progeny of Crl:ZUC rats bred in our facility. Our characterization of this mutant suggests that the disrupted locus likely represents the rat homologue of the mouse jerker *(je)* locus. Like jerker and other shaker-waltzer deafness mutants, behavior of affected rats is characterized by stargazing, jerky head movements, hyperactivity, circling, walking backwards, drawing backwards, inability to swim, elevated food intake and ventral curling when lifted by the tail. Affected rats also fail to generate auditory action potentials under 90 decibel stimulus, and develop progressive degeneration of cells in the acoustic ganglion. These characteristics classify this mutant among the neuroepithelial degeneration class of deafness mutants, a class that includes the jerker mouse. Finally, linkage analysis in 40 affected progeny of a (Pbrc:ZUC x BN/Crl) F1 intercross segregating the mutation placed the mutation 21.5 cM distal of *Oprd1* on rat Chr 5. This region of rat Chr 5 shares conserved synteny homology with the mouse Chr 4 region harboring *je*. These observations suggest that the rat mutant should also be named jerker *(je)*, although formal proof of homology between these two loci will await the cloning of the disrupted gene. The availability of two mutations should be useful in evaluating candidate genes for this locus.

46. FLAILER, A NEW NEUROLOGICAL MUTANT ON MOUSE CHROMOSOME 9. *Julie M. Jones, Scott J. Popma, Karl Herrup*, Miriam H. Meisler. Dept. of Human Genetics, University of Michigan, Ann Arbor, MI 48109-0618; *Alzheimer Research Laboratory, Case Western Reserve University, Cleveland, OH 44106.*

We recently identified and mapped a new neurological mutation, flailer, to mouse Chromosome 9. flailer was originally considered to be the tb^{2J} allele of tumbler on Chromosome 1, based on noncomplementation with *tbJ*. We intercrossed (*flail*/+ X CAST/Ei)F_1 mice in order to map the mutation at higher resolution. The mutant gene was unlinked to *D1Mit4*, *D1Mit5* or *D1Mit140* on chromosome 1, indicating that it was not allelic with tumbler. We have designated the new mutant flailer (gene symbol *flail*), for the characteristic rapid leg movements of mice attempting to right themselves. Preliminary evidence suggests excessive loss of cerebellar granule cells at 3 weeks of age. A genome scan to locate the flailer locus was undertaken using the phenotypic pooling method of Taylor et al. *(Genomics 21: 626-632)*. Flailer was mapped to Chromosome 9 with the gene order *D9Mit4* – (10.9±4.6) – *flail* – (8.7±4.1) – *D9Mit50* – (8.7±4.1) – *D9Mit148*. The map position suggested possible allelism with staggerer, but a test cross demonstrated complementation between the two mutants. flailer is thus a novel neurological mutant on mouse Chromosome 9.

47. DNA SEQUENCE CHARACTERIZATION OF THREE INDUCED MUTATIONS AT THE MOUSE PHENYLKETONURIA LOCUS.

J. David McDonald, Cynthia Charleton. Wichita State University, Department of Biological Sciences, Wichita, KS USA.

Three mutations at the mouse phenylketonuria locus, located within the protein coding sequence of the phenylalanine hydroxylase gene, have been induced by high-efficiency mutagenesis of the mouse germline with the chemical mutagen ethylnitrosourea. The mutations were first localized within the phenylalanine hydroxylase coding sequence with the single-strand conformation polymorphism technique by amplifying sequential regions of phenylalanine hydroxylase cDNA with PCR. Direct sequencing of the indicated regions was then undertaken to reveal the precise mutational lesions induced. In a complete correspondence to the relation between genotype and phenotype seen among human phenylketonuria patients, two of the mouse mutations which cause a severe phenotype in mice were localized to parts of the protein coding sequence often associated with a severe phenotype in humans. Likewise, one mutation causing a milder mouse phenylketonuria phenotype was located in a region of the coding sequence typically associated with milder phenotypes in humans. These sequencing findings not only document the molecular similarity of mouse phenylketonuria to the human disease but, by revealing these genotype/phenotype correlations, imply that these mouse models manifest an overall disease process that is similar to human phenylketonuria on many other levels as well.

48. A SCREEN FOR DOMINANT MUTATIONS THAT AFFECT BEHAVIOR.

P.M. Nolan[1], D. Tobin[1], A. Gupta[1], D. Xiong[1], M. Bucan[1,2]. Depts of Psychiatry[1] and Genetics[2], University of Pennsylvania, Philadelphia, PA 19104, USA.

We present the initial results of a screen for novel behavioral mutations in the mouse. Subjects used in this study are progeny of C57BL/6J females crossed to males mutagenized with the potent mutagen N-ethyl-N-nitrosourea (ENU, one dose of 175 mg/kg or three weekly doses of 100 mg/kg). First generation offspring are being screened for dominant behavioral mutations using a battery of simple tests. Pilot studies have shown that the C57BL/6J strain is most suitable for behavioral analysis and that these tests are age-dependent.

We currently screen offspring of mutagenized males using the following sequence of behavioral tests: mice are kept for five weeks in group housed cages; the mice are transferred to constant dark conditions in cages equipped with running wheels in order to measure endogenous circadian period; after a period of acclimation to normal light/dark conditions, mouse behavior is assessed using the Porsolt forced swim test, open field/novel object test and the startle response test. To date several hundred mice have been screened according to the above protocol. Using statistical analysis, we have identified several anomalous individuals and are currently breeding these mice to determine whether the behavioral abnormalities are due to single gene defects.

49. LINKAGE OF *HFI* MOUSE CATARACT MUTATION TO CHROMOSOME 10. *D.J. Sidjanin, J. Favor*, D. Stambolian. Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA, USA; *GSF-Institut fur Saugetiergenetik, D-8042 Neuherberg, Germany.*

A mouse mutant called *Hfi* has an autosomal dominant cataract mutation recovered in the F_1 generation after parental treatment with X-rays. In order to identify the gene responsible for the *Hfi* mutation we screened 25 progeny with microsatellite markers Three markers were selected for chromosomes 1-13 and two markers for chromosomes 14-19. In order to genotype backcross progeny for simple sequence repeats (SSR) polymorphisms PCR reactions were performed and products were visualized on polyacrylamide gels. Data was analyzed by Map Manager The results show linkage to chromosome 10. The closest marker to the *Hfi* locus identified so far is D10Mit179 (two crossovers per twenty three progeny), which is about 8.69 cM distance from the cataract locus. In order to determine a more precise location of the *Hfi* mutation we are presently screening an additional 100 progeny.

50. EFFECTS OF γ IRRADIATION ON EMBRYONIC STEM (ES) CELLS. *Yun You, Becky Bergstrom, John Schimenti. The Jackson Laboratory, Bar Harbor, ME, USA.*

To access the effects of γ irradiation on ES cells as a part of a long term project to create chromosome deletions, ES cells were exposed to 0, 100, 200, 300 and 400 rads and the effects on ability to colonize the germline were investigated.

Experiments were also performed to create deletions at the *D17Aus 9 locus* in the mouse *t* complex of chromosome 17. Neo and TK genes were integrated by homologous recombination followed by exposing to 400 rads. After FIAU selection, 70 $FIAU^r$ cell lines were selected and analyzed by Southern blot hybridization. While most of them lost the Neo-TK genes, only 5-10% of them appeared to be deletions.

The long term goal of above experiments is to develop a method of making a series of targeted deletions in any region of mouse chromosome to functionally map the mouse genome.

51. ALLELIC LOSSES IN MOUSE PRIMARY LYMPHOMAS INDUCED BY GAMMA IRRADIATION. *Santos. J., Perez de Castro, I., Herranz, M., Fernandez-Piqueras, J. Departamento de Biologia. Unidad de Genetica. Facultad de Ciencias. Universidad Autonoma de Madrid. 28049- Madrid. Spain.*

An allelotype analysis of chromosome 4 using microsatellite DNA polymorphic markers was performed in 47 gamma-radiation-induced primary thymic lymphomas of C57BL/6J x RF/J F1 (B6RFF1) hybrid mice to assess the involvement of tumor suppressor genes in the development of these tumors. Microsatellites were selected with focus on chromosome 4 around the region containing the interferon alpha gene cluster *(D4Mit17, D4Wsm1, D4Mit9* and *D4Mit205)* and on a more distal region *(D4Mit12, D4Mit54* and *D4Mit13).* Allelic losses were detected in 21/47 (44.7%) gamma-radiation-induced thymic lymphomas. Analysis of markers located on six other chromosomes as well as on the proximal region of chromosome 4 *(D4Mit50)* illustrates the specificity of the occurrences of LOH appearing on certain regions of chromosome 4 in murine thymic lymphomas. This analysis led us to define two candidate tumor suppressor gene regions on chromosome 4 (TLSRs, *Thymic Lymphoma Suppressor Regions):* a critical region of about 2cM between the markers *D4Wsm1* and *D4Mit9* (TLSR1), and another more distal region centered at the marker *D4Mit54* (TLSR2). *(This work was supported by the Spanish Ministry of Education grant PB93-0249.)*

52. *Xist* EXPRESSION FROM AN *Xist* YAC TRANSGENE CARRIED ON THE MOUSE Y CHROMOSOME. *S. Matsuura, V. Episkopou, S.D.M. Brown. Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London W2 1PG, UK.*

The *Xist* gene located in the region of the X-inactivation centre in both mouse and human has been postulated to be involved in the initiation of X-inactivation. We have constructed mouse transgenic lines carrying a 350kb YAC clone encompassing the *Xist* gene in order to investigate the factors influencing *Xist* expression and the initiation of X-inactivation. Two transgenic lines were derived – one carrying 34 copies integrated at an autosomal site and a second line carrying 3-4 copies integrated at a long arm site on the Y chromosome. *Xist* expression was not observed in mice carrying the autosomal insertion. However, *Xist* expression from the Y-inserted transgene was observed and at levels commensurate with that found in normal female mice, indicating that only one of the *Xist* genes within the Y-linked transgenic array appears to be expressed. No sex reversal was seen in the transgenic line carrying the expressed *Xist* gene on the Y chromosome. Methylation sites in the autosomal transgene both 5′ and 3′ of the *Xist* gene are hypermethylated and appear to reflect methylation patterns observed on the active X chromosome. For the Y-linked transgene, methylation sites 5′ and 3′ of the *Xist* gene are hypomethylated reflecting patterns found on the inactive X chromosome. However, the 5′ and 3′ methylation levels have been decoupled at the active transgenic locus. The data suggests that sequences in the vicinity of *Xist* are sufficient to initiate many of the features that are associated with the initiation of X-inactivation including the mechanism of chromosome counting.

53. INTRODUCTION OF YEAST ARTIFICIAL CHROMOSOMES INTO EMBRYONIC STEM CELLS VIA HOMOLOGOUS RECOMBINATION. *R.M. Tucker, D.T. Burke, University of Michigan, Ann Arbor. MI, USA.*

54. TARGETED ABLATION OF CELLS IN THE PITUITARY PRIMORDIA OF TRANSGENIC MICE. *Heather L. Burrows[1], Theresa S. Birkmeier[1], Audrey F. Seasholtz[2], Sally A. Camper[1]. Departments of Human Genetics[1] and Biochemistry[2], University of Michigan Medical School, Ann Arbor, MI 48109-0618, USA.*

55. GENETIC ANALYSIS OF THE MURINE *DISHEVELLED* ORTHOLOGS *Dvl-1, Dvl-2* and *Dvl-3*. *Lijam. N[1], Godley, L[2], Larson, D[1], Yasheng, Y[3], Tsang, M[3], Steitz, S[3], Varmus, H[2], Sussman, D[3], Wynshaw-Boris, A[1]. NCHGR, NIH, Bethesda, MD 20892[1]; NCI, NIH, Bethesda, MD 20892-4470[2]; Division of Human Genetics, University of Maryland, Baltimore, MD 21201-1559[3].*

56. MAPPING PHENOTYPIC MODIFIERS OF AN EGFR-NULL ALLELE. *David W. Threadgill, Terry Magnuson. Dept of Genetics, Case Western Reserve University, Cleveland, OH, USA.*

57. THE INFLUENCE OF IGF2 ON TUMOR PROGRESSION IN SV40 T-ANTIGEN (Tag) INDUCED LIVER TUMORS. *R. Haddad, K. Kerns, Y.Q. Zhang, A. Efstratiadis*, W. Held, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, New York 14263, USA; * Department of Genetics and Development, Columbia University, New York, NY, 10032, USA.*

53. INTRODUCTION OF YEAST ARTIFICIAL CHROMOSOMES INTO EMBRYONIC STEM CELLS VIA HOMOLOGOUS RECOMBINATION.

R.M. Tucker, D.T. Burke. University of Michigan, Ann Arbor. MI, USA.

The classical "knock-out" experiment involves construction of a vector containing the gene of interest with a neo^r cassette inserted into the coding region of the gene. This cassette acts as both a selectable marker and the introduced mutation. The disadvantage of using the "knock-out" technique is that it only allows for complete disruption of the gene leading to a null allele. Attempts at generating subtle mutations in mammalian cells have been successful, but these are either too inefficient or technically difficult to be of routine use.

Yeast Artificial Chromosome (YACs) have been used as vehicles for introducing entire genes and their regulatory regions into mammalian cells. YACs have been introduced into both mouse embryonic stem (ES) cells and single cell embryos. Both have led to germ line transmission of YAC derived sequences following random integration of DNA. Many of these introduced genes show correct expression patterns implying that all or many of the regulatory sequences necessary are contained upon the transferred constructs

As yet, experiments involving homologous recombination of YACs into ES cells have not been described. YACs have the advantage over small knockout constructs in that the markers necessary for selection of recombinants can be placed at a distance from the targeted region. As a consequence. they should have little to no effect upon the normal regulatory elements of a given gene. The proposed experimental strategy will allow for introduction of the mutations within a region and may lead to fine structure/function studies of a particular gene.

54. TARGETED ABLATION OF CELLS IN THE PITUITARY PRIMORDIA OF TRANSGENIC MICE.

Heather L. Burrows[1], Theresa S. Birkmeier[1], Audrey F. Seasholtz[2], Sally A. Camper[1]. Departments of Human Genetics[1] and Biochemistry[2], University of Michigan Medical School, Ann Arbor, MI 48109-0618, USA.

The anterior pituitary develops from Rathke's pouch, which is first identified as a thickening and invagination of the oral ectoderm, known as the pituitary placode. The various hormones of the mature pituitary are expressed in a specific temporal and spatial pattern during organogenesis, which is interpreted as a reflection of a temporal pattern of pituitary cytodifferentiation. The first pituitary transcripts detected are from *αGSU*, which encodes the α-subunit common to the gonadotropins (FSH and LH) and thyrotropin (TSH). TSHβ-subunit transcripts appear several days later, but precede transcription of the growth hormone and FSHβ and LHβ-subunit genes. To determine the lineage relationship between the α-subunit expressing cells and the other hormone producing cells of the anterior pituitary, we have employed the technique of transgene ablation. This technique has previously been used to demonstrate a dependence of the cells that produce prolactin on those that produce growth hormone. Transgenic mice that express diphtheria toxin in pituitary gonadotrope and thyrotrope cells were generated. The absence of detectable transcripts for α-subunit or TSHβ-subunits by *in situ* hybridization confirmed that ablation was complete. In spite of the absence of gonadotropes and thyrotropes, the pituitaries were capable of developing growth hormone and adrenocorticotropin producing cells. These results imply that although thyrotropes appear early in pituitary development, they are not obligate intermediates in the developmental pathway. Instead, commitment to individual differentiated pituitary cell fates must occur autonomously or prior to the expression of currently known differentiation markers.

55. GENETIC ANALYSIS OF THE MURINE *DISHEVELLED* ORTHOLOGS *Dvl-1, Dvl-2* and *Dvl-3*. *Lijam, N[1], Godley, L[2], Larson, D[1], Yasheng, Y[3], Tsang, M[3], Steitz, S[3], Varmus, H[2], Sussman, D[3], Wynshaw-Boris, A[1]. NCHGR, NIH, Bethesda, MD 20892[1]; NCI, NIH, Bethesda, MD 20892-4470[2]; Division of Human Genetics, University of Maryland, Baltimore, MD 21201-1559[3].*

We are studying the mouse orthologs of *dishevelled*, a segment polarity gene required for *wingless* signal transduction in *Drosophila*. This pathway appears to be conserved in the mouse, where mutations in murine orthologs of this pathway result in a variety of specific abnormalities. Three orthologs of *dishevelled*, *Dvl*-1, *Dvl*-2 and *Dvl*-3 have been isolated. All three *Dvl* genes are expressed in a similar pattern in embryos and adults, indicating that there may be redundancy of function between these family members. To address the function of these genes during mammalian development, we are generating mice homozygous for targeted disruptions of each of the *Dvl* genes. Mice homozygous for a null allele of *Dvl*-1 are viable and fertile, with no detectable structural abnormalities. Generation of *Dvl*-2 and *Dvl*-3 mutant mice are in progress. *Dvl*-2 chimeras have been produced, which have transmitted the mutant allele to offspring. *Dvl*-3 targeting constructs have been transfected into embryonic stem cells and are currently being analyzed for correct targeting events. When produced, we will analyze the phenotypes of single, double and triple mutants of the *Dvl* gene family. To genetically analyze this important, conserved developmental pathway, we have crossed these mice with transgenic mice that develop mammary adenocarcinomas under the influence of a *Wnt-1* transgene and we are investigating the role of *Dvl*-1 in mammary gland hyperplasia and neoplasia. In addition, we have crossed the *Dvl*-1 null mutants with a *Wnt-3a* hypomorph*(vestigial tail)* which has a shortened tail and lumbosacral vertebral anomalies, to look for epistatic interation between *Dvl*-1 and *Wnt-3a*.

56. MAPPING PHENOTYPIC MODIFIERS OF AN EGFR-NULL ALLELE. *David W. Threadgill, Terry Magnuson. Dept of Genetics, Case Western Reserve University, Cleveland, OH, USA.*

The expression pattern and functional analysis of epidermal growth factor receptor (EGF-R) and several of its five known ligands suggests that EGF-R is important for numerous physiological functions. Changes in various cellular activities have been attributed to EGF-R signal transduction. The nature of these changes depend on cell type and show some degree of ligand specificity.

In order to assign distinct functions to EGF-R in vivo, a null-allele (*Egfr*^{tm1Cwr}) at the *Egfr* locus was created by homologous recombination. After introduction into the germ line, strain-specific differences in the phenotype of *Egfr*^{tm1Cwr} homozygotes were observed. Homozygosity for *Egfr*^{tm1Cwr} resulted in peri-implantation lethality on a CF-1 genetic background, mid-gestation lethality on a 129/Sv background, and viability to term on a CD-1 background. Crosses between the strains suggested that there is a genetic hierarchy with the CD-1 phenotype being dominant to the 129/Sv phenotype which is dominant to the CF-1 phenotype. Reciprocal embryo transfers between the strains showed that the resulting phenotypes are specific to the genetic background of the embryo and are not influenced by the genetic background of the host uterus. Preliminary backcross analysis revealed that one or two CD-1 loci are sufficient to rescue the 129/Sv phenotype. Additionally, at least one of the loci is paternally imprinted. These results have major implications regarding previous work on EGFR. Virtually all experimental observations have been made within the context of undefined genetic backgrounds. Progress towards identification of the loci responsible for producing the strain-dependent phenotypes of *Egfr*^{tm1Cwr} homozygotes will be presented.

57. THE INFLUENCE OF IGF2 ON TUMOR PROGRESSION IN SV40 T-ANTIGEN (Tag) INDUCED LIVER TUMORS.

R. Haddad, K. Kerns, Y.Q. Zhang, A. Efstratiadis, W. Held. Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA; * Department of Genetics and Development, Columbia University, New York, NY 10032, USA.*

Previous experiments have suggested that an imprinted gene on chromosome 7 is involved in liver tumorigenesis in MUP-Tag transgenic mice *(Cancer Res. 54: 6489-6495)*. As well, two oppositely imprinted genes on chromosome 7, Igf2 and H 19, are reexpressed in tumors. Igf2 re-expression also correlates with the rapidity of tumorigenesis in different MUP-Tag lines. To investigate the requirement for Igf2 expression during liver tumorigenesis, we created Igf2(+/-) heterozygous null MUP-Tag mice. Liver tumors were analyzed for IGF2 and Hl9 expression. Alterations in tumor size and histology will be discussed.

58. MOUSE MUTANT MOTOR ENDPLATE DISEASE *(MED)* RESULTS FROM MUTATION OF A NOVEL SODIUM CHANNEL GENE, SCN8A. *D.L. Burgess[1], D. C. Kohrman[1], J. Galt[1], N. W. Plummer[1], J. M. Jones[1], B. Spear[2], M.H. Meisler[1]. [1]Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109-0618; [2]Department of Microbiology, Immunology & Pathology, University of Kentucky, Lexington, KY 40536.*

59. POSITIONAL CLONING OF THE *MND2* GENE. *J.S. Weber, W. Jang, J. Yu, M. Meisler, The University of Michigan, Ann Arbor, MI, USA.*

60. MOLECULAR GENETIC ANALYSIS OF DISTAL MOUSE CHROMOSOME 6 DEFINES GENE ORDER AND POSITIONS OF THE DEAFWADDLER AND OPISTHOTONOS MUTATIONS. *V.A. Street, L.C. Robinson, S.K. Erford, B.L Tempel. Geriatric Research Education and Clinic Center (182-B), Veterans Administration Medical Center, Seattle, WA 98108; the Departments of Otolaryngology – HNS and Pharmacology, University of Washington School of Medicine, Seattle, WA 98185, USA.*

61. POSITIONAL CLONING OF *LEGS AT ODD ANGLES (Loa)*. *Bermingham[1], N., Peters[2], J., Martin[3], J.E., Fisher[1], E.M.C. [1]Dept. Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, Imperial College, Norfolk Place, London W2 1PG, U.K.; [2]MRC Radiobiology Unit, Chilton, Didcot, U.K.; [3]Dept. Histopathology, The Royal London Hospital, Whitechapel, London, U.K.*

62. POSITIONAL CLONING OF *STARGAZER:* A MOUSE MODEL FOR EPILEPSY. *Verity A. Letts, Alicia Valenzuela, Hope O. Sweet, Muriel T. Davisson, Wayne N. Frankel. The Jackson Laboratory, Bar Harbor, ME 04609.*

63. A PHYSICAL MAPPING APPROACH TO CLONING THE EPILEPSY GENE, TOTTERING. *Cathleen M. Lutz, Wayne N. Frankel. The Jackson Laboratory, Bar Harbor, ME, USA.*

64. TOWARD THE POSITIONAL CLONING OF NOT ONE, NOT TWO, BUT THREE MUTANT GENES: *FIDGET*, SLOW-WAVE EPILEPSY AND NEUROMUSCULAR DEGENERATION. *G.A. Cox, J.L.M. Gervais, C.M. Lutz, W.N. Frankel. The Jackson Laboratory, Bar Harbor, ME, USA.*

65. PROGRESS TOWARDS THE POSITIONAL CLONING OF *LOOP-TAIL:* A MOUSE GENE RESPONSIBLE FOR A SEVERE FORM OF NEURAL TUBE DEFECT. *Jenny Henson[1], Jane Eddleston[2], Andrew Copp[1], Philip Stanier[2]. [1]Institute of Child Health, London, UK; [2]Institute of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, London, UK.*

66. HIGH RESOLUTION MAPPING OF MUSCLE DEFICIENT (*mdf*: Chr 19). *C. Poirier[1], S. Blot[2], G.F. Carle[3] and J.-L. Guenet[1]. [1]Unite de Genetique des Mammiferes, Institut Pasteur, Paris France; [2]Ecole Nationale Veterinaire de Maisons-Alfort, Maisons-Alfort France; [3]Laboratoire d'Etude du Genome Murin, Universite de Nice Sophia-Antipolis, Nice France.*

67. COMPARATIVE MAPPING OF THE PROXIMAL REGION OF MOUSE Chr 13. *C.M. Perou[1], A.L. Perchellet[2], J. Kaplan[1], M.J. Justice[2]. [1]Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84132; [2]Division of Biology, Kansas State University, Manhattan, KS 66506; [3]Biology Division, Oak Ridge Laboratory, Oak Ridge, TN 37831.*

68. GENETIC AND CHROMOSOME STRUCTURAL ANALYSIS OF THE *ckr* MOUSE. *D.J.Smiraglia, A.K.Ratty, C.Wu, K.W. Gross. Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY, USA.*

69. THE NEUROLOGICAL MOUSE MUTATIONS JITTERY AND HESITANT ARE ALLELIC AND MAP TO THE REGION OF MOUSE CHROMOSOME 10 HOMOLOGOUS TO 19p13.3. *D. Kapfhamer[1], H.O. Sweet[4], D. Sufalko[1], S. Karlson[2], K. R. Johnson[4], M. Burmeister[1,2,3]. [1]Mental Health Research Institute, Depts. of [2]Human Genetics and [3]Psychiatry, University of Michigan, Ann Arbor MI; [4]The Jackson Laboratory, Bar Harbor ME, USA.*

70. *QUAKING:* COMPLEXITIES IN GENE STRUCTURE AND EXPRESSION. *C. Vernet[1], T. Ebersole[2], K. Artzt[1]. [1]Department of Zoology, The University of Texas at Austin, Austin, TX 78712 USA; [2]Department of Genetics, Cambridge University, Cambridge, CB2 3EH, England.*

71. IDENTIFICATION OF MOUSE REELER GENE ENCODING A PROTEIN WITH AN EGF-LIKE MOTIF BY RLGS-BASED HIGH-SPEED POSITIONAL CLONING SYSTEM. *S. Hirotsune[1], T. Takahara[1], Y. Okazaki[1], K. Hirose[1], N. Sasaki[1], H. Okuizumi[1], T. Ohsumi[1], A. Yoshiki[1], T. Ohashi[1], M. Kusakabe[1], M. Muramatsu[1], K. Nakao[2], M. Katsuki[2], V. M. Chapman[3], Y. Hayashizaki[1]. (1) Genome Science Laboratory and Cell Biology Laboratory, The Inst. of Phys. and Chem. Res. (RIKEN), 3-1-1, Koyadai Tsukuba, Ibaraki, 305 Japan; (2) Med. Inst. of Bioregulation, Kyushu Univ; (3) Mol. and Cell. Biol. Dept., Roswell Park Cancer Institute, Buffalo, NY.*

72. GENOMIC ORGANIZATION OF THE REELER GENE REGION. *I. Royaux, I. Bar, C. Lambert de Rouvroit, B. Bernier, A.M. Goffinet. Dept. Physiology, FUNDP Med. Sch., B-5000 Namur, Belgium.*

73. MOLECULAR ANALYSIS OF MOTTLED MUTANTS. *Vivienne Reed, Yvonne Boyd. MRC Radiobiology Unit, Chilton, OXON, OX11 ORD, UK.*

74. A MOUSE MODEL FOR POLYCYSTIC KIDNEY DISEASE. *Elizabeth C. Bryda, Lorraine Flaherty. Wadsworth Center, Albany, NY.*

75. GENETICS OF VERTEBRATE DIGITAL ARCH FORMATION. *L.C. Post[1], D.P. Mortlock[1], S. Darling[3], J.W. Innis[1,2]. Department of Human Genetics[1], Department of Pediatrics[2], University of Michigan, Ann Arbor, MI, USA, University College, London, UK[3].*

76. FUNCTIONAL CHARACTERIZATION AND ANALYSIS OF THE MOUSE LIMB MUTANT HYPODACTYLY. *K.E. Robertson, C. Tickle, S.M. Darling. Dept. of Anatomy and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK.*

77. GENETIC AND PHENOTYPIC ANALYSIS OF DANFORTH'S SHORT-TAIL MOUSE. *J. B. Alfred[1], K. A. Rance[2], S. J. Phillips[3], B. A. Taylor[3], C. M. Abbott[1], I.J. Jackson[1]. [1]MRC Human Genetics Unit, Edinburgh, UK; [2]Institute of Cell and Animal Population Biology, University of Edinburgh, UK; [3]The Jackson Laboratory, Bar Harbor, ME, USA.*

78. **LINKAGE ANALYSIS OF THE MOUSE MYELENCEPHALIC BLEBS MUTATION.** *E.Bentley (1), A.Gossler (2), S.M. Darling (1). 1. Dept. of Anatomy and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK; 2. The Jackson Laboratory, Bar Harbor, ME, USA.*

79. **MAPPING OF BRACHYRRHINE TO DISTAL MOUSE CHROMOSOME 17.** *Yvonne Boyd, Colin Beechey, Hester Hughes, Vivienne Reed,Tony Searle. MRC Radiobiology Unit, Chilton, Oxon OX11 ORD, UK.*

80. **ANTERIOR PITUITARY CELLS DEFECTIVE IN THE CELL-AUTONOMOUS FACTOR, *df*, UNDERGO CELL LINEAGE SPECIFICATION BUT NOT EXPANSION.** *Philip J. Gage, Michelle L. Roller, Thomas L. Saunders, Lori M. Scarlett, Sally A. Camper, Kathy Mahon*. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI; *National Institutes of Health, Bethesda, MD, USA.*

81. **ANALYSIS OF THE MOUSE ANOREXIA MUTATION.** *J. Johansen[1], I. Efanova[2], C. Broberger[3], Shi Tie Jun[3], T. Hokfelt[3], P-O. Berggren[2], M. Schalling[1]. [1]Neurogenetics Unit, [2]The Rolf Luft Center for Diabetes Research, Department of Molecular Medicine, Karolinska Hospital, S-171 76 Stockholm; [3]Department of Neuroscience, Karolinska Institute, S-171 77 Stockholm, Sweden.*

82. **LINKAGE MAPPING AND EMBRYOLOGICAL ANALYSIS OF *DOMINANT MEGACOLON*, A MOUSE MODEL FOR HIRSCHSPRUNG'S DISEASE.** *E. M. Southard-Smith, K.J. Smith,W.J. Pavan. Lab of Genetic Disease Research, Natl Cntr for Human Genome Research, Natl. Inst. of Health, Bethesda, MD, USA 20892.*

83. **ABSENCE OF A NOVEL PUTATIVE TRANSPORTER CAUSES OSTEOPETROSIS IN THE *oc/oc* MOUSE.** *K.P. Brady, D.R. Beier. Genetics Division, Brigham and Women's Hospital, Harvard Medical SchooL Boston, MA 02115.*

84. **FINE MAPPING OF THE OSTEOSCLEROSIS LOCUS (*oc*) IN THE PERICENTROMERIC REGION OF MMU19.** *A. Franchi, G.F. Carle. LEGM - URA 1462 C.N.R.S. Universite de Nice, France.*

85. **TOWARD CHARACTERIZATION OF THE MOUSE OSTEOPETROTIC GREY-LETHAL MUTATION.** *Jean Vacher, Hugues Bernard Clinical Research Institute of Montreal, Montreal, Quebec, Canada.*

86. **TOWARDS POSITIONAL CLONING OF THE AMES DWARF LOCUS.** *D.E. Watkins-Chow, M.S. Buckwalter, M.L. Roller, F.J. Probst, D.D. Baker, M.N. Newhouse, A.C. Lossie, K. Liggett, S.A. Camper. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI, 48109-0618 USA.*

87. **GENETIC AND PHYSICAL MAPPING OF THE *js* GENE ON MOUSE CHROMOSOME 11.** *Y. Kikkawa[1], U. Gangadharan[2], S. Wakana[3], Y. Kohara[1], M. Okamoto[1], Y. Matsuda[4], R. Kominami[5], K. Moriwaki[6], T. Shiroishi[6], H. Yonekawa[1]. [1]Tokyo Met. Inst. Med. Sci., Tokyo 113, Japan; [2]St. Mary Hospital Med. School, London W21 PG, UK; [3]Cent. Inst. Exp. Animals, Kawasaki 216, Japan; [4]Natl. Inst. Radol. Sci., Chiba 263, Japan; [5]Niigata Univ. School of Med., Niigata 951 Japan; [6]Natl. Inst. Genet., Mishima 411, Japan.*

88. **PHYSICAL MAPPING IN THE VICINITY OF THE wi LOCUS ON MOUSE CHROMOSOME 4.** *A. Paige[1], J. Fleming[2], A. Varela[1], M. Rogers[2], D.C. Hughes[2], S.D.M. Brown[1], K.P. Steel[2]. 1. Dept. of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London W2 1PG, UK; 2. MRC Institute of Hearing Research, Nottingham, NG7 2RD, UK.*

89. **THE MYOSIN VII GENE UNDERLYING THE MOUSE SHAKER-1 RECESSIVE DEAFNESS MUTATION.** *P. Mburu[1], F. Gibson[1], J. Walsh[1], A. Varela[1], X. Liu[1], K.P. Steel[2], S.D.M. Brown[1]. [1]Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London W2 1PG, UK; [2]MRC Institute of Hearing Research, University Park, Nottingham NG7 2RD, UK.*

90. **GENETIC AND FUNCTIONAL ANALYSIS OF PIROUETTE, A MOUSE NEUROEPITHELIAL DEAFNESS MUTANT.** *D.C. Kohrman, M.H. Meisler. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109 USA.*

91. **HIGH RESOLUTION MAPPING OF MURINE GENES WHICH AFFECT PIGMENTATION AND PLATELET FORMATION/ FUNCTION.** *Richard T. Swank[1], Edward K. Novak[1], Edward P. O'Brien[1], Michael E. Rusiniak[1], Michael B. Gorin[2], Albert B. Seymour[2]. [1]Dept. of Mol. & Cell. Bio., Roswell Park Cancer Inst., Buffalo, NY, USA; [2]Depts. of Ophthalmology & Human Genetics, Univ. of Pittsburgh, Pittsburgh, PA, USA.*

92. **HIGH RESOLUTION MAPPING OF THE X-LINKED MOUSE MUTANT LINED.** *Ifeanyi Uwechue, Yvonne Boyd. MRC Radiobiology Unit, Genetics Division, Chilton, OXON, OX11 ORD, UK.*

93. **TOWARDS CLONING THE REPEATED EPILATION (*Er*) MUTATION.** *Rebecca A. Liddell, Jill K Fisher, Arthur M Buchberg, Linda D. Siracusa. Department of Microbiology and Immunology, Jefferson Cancer Institute, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107.*

94. **THE LINKAGE ANALYSIS OF THE MOUSE RADIATION INDUCED CATARACT GENE, *Tcm*.** *[1]E. Zhou, [1]D.J. Sidjanin, [2]J. Favor, [1]D. Stambolian. University of Pennsylvania, Dept. of [1]Ophthalmology, Philadelphia, PA, USA; [2]GSF-Institute Fur Saugetiergenetik, Neuherberg, Germany.*

95. **HIGH-RESOLUTION LINKAGE MAP IN THE CHROMOSOMAL REGION SURROUNDING THE *Lps* LOCUS.** *[1]S. Qureshi, [1]L. Lariviere, [2]G. Sebastiani, [1]S. Clermont, [4]G. Duyk, [4]K. Moore, [1]E. Skamene, [2]P. Gros, [1,3]D. Malo. Departments of [1]Medicine, [2]Biochemistry, [3]Human Genetics, McGill University, Montreal; [4]Millennium Pharmaceuticals, Inc.*

96. **TO THE POSITIONAL CLONING OF THE *HYBRID STERILITY I* GENE: EVALUATION OF CANDIDATE GENES.** *Z. Trachtulec*[*#], *S. Gregorova*[#], *M. Mnukova*[#], *R.M.J. Hamvas*[**], *H. Lehrach*[**], *J. Klein*[*+], *V. Vincek*[*], *J. Forejt*[#]. [*]*University of Miami, Dept. Microbiology and Immunology, Miami, FL;* [#]*Institute of Molecular Genetics, Acad.Sci. Czech Rep., Prague;* [**]*ICRF, London;* [+]*MPI fuer Biologie, Tuebingen.*

97. **TOWARDS CLONING OF THE *LETHAL-2* and *HST-1* GENES.** *Renata M.T. Hamvas, Zdenek Trachtulec*[1], *Alexandra Shedlovsky*[2], *Monika Mnukova*[3], *James Ripley, Roger D. Cox*[4], *Elaine Levy*[4], *Susan Lewis*[5], *Vladimir Benes, Fiona Frances, Camille S. Connelly*[2], *Sona Gregorova*[3], *Paraj Mandrekar*[2], *Jane Barclay*[6], *Jiri Forejt*[3], *William F. Dove*[2], *Jan Klein*[1], *Peter Little*[6], *Hans Lehrach. Genome Analysis Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London;* [1]*University of Miami School of Medicine, Miami, FL;* [2]*McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, USA;* [3]*Institute of Molecular Genetics, Czech Academy of Sciences, Prague, Czech Republic;* [4]*Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN;* [5]*Research Triangle Park, NC, USA;* [6]*Department of Biochemistry, Imperial College, London SW7 2AZ.*

58. MOUSE MUTANT MOTOR ENDPLATE DISEASE *(MED)* RESULTS FROM MUTATION OF A NOVEL SODIUM CHANNEL GENE, SCN8A.

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The mouse neurological mutation 'motor endplate disease' *(med)* causes early onset progressive paralysis, skeletal muscle atrophy, ataxia and juvenile lethality. Three spontaneous alleles have been described, in which affected mice differ in age of onset and severity of phenotype. A new allele, *med ^{tg}*, was identified by our group and shown to result from a transgene insertion into this locus *(Kohrman et. al. 1994, Genomics 26:171)*. P1 phage clones spanning the insertion site were isolated. Using a combination of exon amplification and direct cDNA selection, several exons and partial cDNAs were isolated which showed a high degree of sequence homology to voltage-gated sodium channel alpha subunit genes. The full coding sequence was obtained by RT-PCR of cerebellar RNA and vector-insert PCR of a mouse fetal brain cDNA library. This new sodium channel gene was designated Scn8a *(Burgess et. al. 1995, Nature Genetics 10:461)*. The scn8a gene in *med ^{tg}* mice was shown to have an intragenic deletion of coding sequences as a result of the transgene insertion. The human SCN8A gene was localized to chromosome 12q13 by fluorescence in-situ hybridization and is a likely candidate for inherited human neuromuscular disease and cerebellar ataxia. Polymorphic markers from the human gene are being developed for analysis of such pedigrees.

59. POSITIONAL CLONING OF THE *MND2* GENE.

J.S. Weber, W. Jang, J. Yu, M. Meisler. The University of Michigan, Ann Arbor, MI, USA.

The *mnd2* mutation causes an autosomal recessive disorder characterized by muscle atrophy and severe wasting. Between two and three weeks of age, affected mice develop an unsteady gait and fail to grow. These mice die within 40 days after birth. *mnd2* has been localized to a region on mouse Chromosome 6 between *Tgfα* and *Sftp3*. We generated a high resolution genetic map of this region using F2 animals from an interspecific cross between *mnd2*/CAST/Ei F1 animals. A nonrecombinant interval of 0.21 ± 0.09cM was defined by 5/2340 recombinants between the closest flanking markers. Six mouse genomic YAC and P1 libraries were screened to generate a contig of ~300kb spanning the nonrecombinant region. We are using exon amplification and cDNA selection with P1 clones to identify genes from the nonrecombinant region. Three genes have already been mapped to the nonrecombinant region, and are being test to detect differences between *mnd2* and the strain of origin, C57BL/6J.

60. MOLECULAR GENETIC ANALYSIS OF DISTAL MOUSE CHROMOSOME *6* DEFINES GENE ORDER AND POSITIONS OF THE DEAFWADDLER AND OPISTHOTONOS MUTATIONS. *V.A. Street, L.C. Robinson, S.K. Erford, B.L Tempel. Geriatric Research Education and Clinic Center (182-B), Veterans Administration Medical Center, Seattle, WA 98108; the Departments of Otolaryngology – HNS and Pharmacology, University of Washington School of Medicine, Seattle, WA 98185, USA.*

Two neurological mutants deafwaddler (*dfw*) and opisthotonos *(opt)*, and a cluster of three Shaker-like potassium (K) channel genes *Kcna*1, *Kcna*5, and *Kcna*6 were all independently mapped to distal mouse chromosome six (Chr *6)*. In this study, genetic and molecular techniques were employed to assess directly the linkage of the two mutants and to investigate the likelihood that a mutation in one of the three K channel genes may underlie *dfw* and/or *opt*. Genetic crosses testing for allelism showed that the *dfw* and *opt* mutations complement each other. Additional crosses demonstrated that the mutants are separated by a recombination distance of 3.1 $\pm$ 1.8 cM. Microsatellite marker analysis of the crossover chromosomes recovered from the *opt, dfw* recombination study indicated that *opt* maps centromeric to *dfw*. The location of the K channel genes relative to the *dfw* mutation was determined by mapping these genes and fifteen microsatellite markers in an intersubspecific backcross (IB) segregating for *dfw* [(CAST/Ei- +/+ x C3HeB/FeJ-*dfw*/*dfw*) X C3HeB/FeJ-*dfw*/*dfw*]. Analysis of the backcross progeny positioned the *dfw* locus in the interval between the microsatellite markers *D6Mit11* and *D6Mit55, D6Mit63*. The K channel cluster maps telomeric to *dfw*. This study establishes the gene order cen - *opt* - *dfw* - *Rho (D6Mit44)* - *Kcna*1, *Kcna*5, *Kcna6* on distal mouse Chr 6 and suggests that the neurological mutants *opt* and *dfw* affect two different genes, neither of which is caused by a mutation in any one of the three clustered K channels.

61. POSITIONAL CLONING OF *LEGS AT ODD ANGLES (Loa)*. *Bermingham[1], N., Peters[2], J., Martin[3], J.E., Fisher[1], E.M.C.*
[1]Dept. Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, Imperial College, Norfolk Place, London W2 1PG, U.K.; [2]MRC Radiobiology Unit, Chilton, Didcot, U.K.; [3]Dept. Histopathology, The Royal London Hospital, Whitechapel, London, U.K.

Legs at odd angles (Loa) is an autosomal dominant, homozygous lethal mutation. It arose in the progeny of a male C3H/HeH mouse which had been treated with 200-250mg of ENU per kg and crossed to a PTP female.

Mice are detected at weaning by the abnormal posture of the hind limbs which tend to be held in flexion. Life span and fertility of the heterozygote appear normal with a penetrance that appears to be 100%. *Loa* mice show a mid to late onset lower motor neurone degeneration. The spinal cord shows loss of anterior horn cells and ghost cell changes in degenerating lower motor neurones in the lumbar spinal cord. Remaining lumbar motor neurones show pronounced vacuolation of anterior horn cells.

We have established an intra specific backcross in order to generate over 1000 *Loa* mice to enable us to map and isolate the mutant gene. To date we have excluded most of the genome. We aim to carry out a number of behavioural tests to ascertain whether the mice show any behavioural deficits.

Initial results suggests that *Loa is* a good model for a late onset neurodegenerative disorder and it is hoped that the cloning of this gene will give us an insight into the causes of motor neurone degeneration.

62. POSITIONAL CLONING OF *STARGAZER:* A MOUSE MODEL FOR EPILEPSY. *Verity A. Letts, Alicia Valenzuela, Hope O. Sweet, Muriel T. Davisson, Wayne N. Frankel. The Jackson Laboratory, Bar Harbor, ME 04609.*

Our interest in studying inherited epilepies has focused on both single and multigene models of epilepsy in mouse. The fine-mapping and positional cloning of *stargazer (stg)*, a single recessive gene mutation on mouse Chr. 15, will be presented. This mutation was first described by Noebels *et al.* in 1990 *(Epilepsy Res. 7, 129)*. The *stargazer* mouse exhibits frequent cortical discharges characteristic of generalized absence seizures in humans. It has a striking phenotype, including head tossing and an ataxic gait and can be identified as soon as the pups are mobile.

We have established a fine-map of *stg* by analyzing intercross (F2) and backcross (BC) mice originating from a cross between *stargazer* and *Mus musculus castaneus* (CAST/Ei). From 1,000 F2 and BC progeny, a panel of recombinant DNAs has been assembled between the mouse markers, *D15Mit3* and *D15Mit2*, around the *stg* locus. YACs, BACs and P1s have been isolated and a contig of the *stg* region has been completed. Interestingly, this region has a high representation of small YACs and rearranged P1s. Expressed sequences within the 150 kb *stg* region have been isolated and we will present our progress towards identifying the *stg* gene.

63. A PHYSICAL MAPPING APPROACH TO CLONING THE EPILEPSY GENE, TOTTERING. *Cathleen M. Lutz, Wayne N. Frankel. The Jackson Laboratory, Bar Harbor, ME, USA.*

The tottering *(tg)* mouse has been characterized as a neurological mutant exhibiting seizure phenotypes that closely resemble spontaneous generalized epilepsy in humans. Electrophysiologically, *tg/tg* mice have been shown to exhibit cortical spike-wave discharges that accompany behavioral petit-mal seizures *(Noebels and Sidman, 1979 Science 204:1334-6)*. The cause of neuronal excitation patterns with concurrent seizures has been attributed to increased levels of norepinephrine and the hyperinnervation of norepinephrine containing neurons of the locus ceruleus *(Noebels, 1984. Nature 310: 40911)*. Other alleles of tottering include leaner (tg^{la}) and rolling Nagoya (tg^{rol}) which display neurological phenotypes that differ from tottering as well as from each other.

We are currently attempting to identify the tottering gene using positional cloning techniques. To accomplish this, we have fine mapped the tottering locus in an intersubspecific F2 cross using a strain congenic for the tg^{la} mutation and *Mus musculus castaneus*. (CAST/Ei). To date, we have genotyped over 1000 F2 progeny to generate a genetic map between the flanking markers *D8Mit104* and *D8Mit150*. Given this high resolution map, we are now attempting to physically map this region using yeast artificial chromosomes (YACs). Upon completion of the physical map, methods involving cDNA selection will be utilized in the attempt to identify the gene within the YAC contiguous region. Once the tottering gene has been identified, tissue specific and development specific expression studies of the various tottering and wildtype alleles will be examined. Knowledge of the gene defect in the tottering mutant mouse will hopefully increase our understanding of the molecular basis of epilepsy.

64. TOWARD THE POSITIONAL CLONING OF NOT ONE, NOT TWO, BUT THREE MUTANT GENES: *FIDGET, SLOW-WAVE EPILEPSY* AND *NEUROMUSCULAR DEGENERATION*.

G.A. Cox, J.L.M. Gervais, C.M. Lutz, W.N. Frankel. The Jackson Laboratory, Bar Harbor, ME, USA.

A positional cloning approach has been undertaken to identify the genes involved in three autosomal recessive mutations. The developmental mouse mutant fidget (*fi*) is a single gene mutation on Chromosome 2 that displays specific abnormalities in the membranous labyrinth, the eyes and the skeleton. We have fine-mapped *fi* in an intersubspecific intercross. From over 1000 F2 progeny, a panel of recombinant DNAs has been assembled between the mouse markers *D2Mit61* and *D2Mit56*, around the *fi* locus. Using flanking markers, YACs have been isolated and aligned relative to the recombinant panel and to each other to begin preparation of a contig of this region.

Slow-wave epilepsy *(swe) is* a new spontaneous mutant on the SJL background discovered at The Jackson Laboratory and characterized by locomotor ataxia and a novel epilepsy phenotype. Mutant mice exhibit frequent spike-wave seizures in the 3/sec range that are associated with behavioral arrest similar to inherited human generalized absence epilepsies. The *swe* gene has been localized to Chromosome 4 between the markers *D4Nds2* and *D4Mit54* in an F2 intercross.

Neuromuscular degeneration, *nmd, is* a new spontaneous mutation characterized by severe hindlimb muscle atrophy due to progressive degeneration of motor neurons in the brain and spinal cord. Two independent mutant alleles (*nmd* and *nmd*^{2J}) were discovered at The Jackson Laboratory and in both the paralysis progresses rapidly, with the mutant mice rarely surviving beyond three and one-half weeks of age. The *nmd* gene has been mapped to the proximal region of mouse Chromosome 19 by an intersubspecific intercross. Potential candidate genes known to map to the region such as ciliary neurotrophic factor *(CNTF)* and muscle glycogen phosphorylase *(PYGM)*, have been ruled out based on genetic mapping.

65. PROGRESS TOWARDS THE POSITIONAL CLONING OF *LOOP-TAIL: A* MOUSE GENE RESPONSIBLE FOR A SEVERE FORM OF NEURAL TUBE DEFECT.

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The mouse mutant *loop-tail (Lp)* is a model of the most severe form of human neural tube defect, cranio-rachischisis. Homozygous embryos exhibit a neural tube that is open from the midbrain/hindbrain boundary throughout the spinal cord, due to a failure to initiate neural tube closure in the future cervival region at about 8.5 days gestation. These embryos die at around the time of birth. Heterozygous mutants are both viable and fertile although most have looped tails and exhibit head-wobbling behaviour.

Linkage analysis has been carried out using an intraspecific backcross between LPT/Le (an inbred strain carrying the *Lp* mutation) and CBA/Ca. This has mapped the gene to between *D1Mit113* and *Fcer1α* on distal chromosome 1 *(Stanier et al (1995) Genomics 26: 473478)*. A syntenic region exists on human chromosome 1q21-q23, suggesting a human homologue of the *Lp* gene resides within this interval.

Generation of a YAC contig across the 1.46 cM interval is well underway. To isolate genes from this region that are expressed at the time of neural tube closure we are screening an 8.5 day mouse embryo cDNA library using cDNA Selection. Evaluation of candidates should enable the *Lp* gene to be identified.

66. HIGH RESOLUTION MAPPING OF MUSCLE DEFICIENT (*mdf*: Chr 19). *C. Poirier[1], S. Blot[2], G.F. Carle[3], J.-L. Guenet[1]. [1]Unite de Genetique des Mammiferes, Institut Pasteur, Paris France; [2]Ecole Nationale Veterinaire de Maisons-Alfort, Maisons-Alfort France; [3]Laboratoire d'Etude du Genome Murin, Universite de Nice Sophia-Antipolis, Nice France.*

The autosomal recessive mutation *mdf is* characterized by a distinct waddle and an inability to fully extend the rear legs. The fertility of the females is very low and epididymal sperm counts in males are markedly reduced.

Homozygous mice develop the clinical features between 4 and 8 weeks. The mutation was mapped to the centromeric region of chromosome 19 in 1983.

We have shown that this mutation is characterized by a progressive motor neuronopathy and, in order to isolate the gene by positional cloning, we have introduced *mdf* in a molecular genetic map. In a 389-progeny intraspecific intercross we have observed no recombinant between *mdf* and *Fau* (the cellular homolog of the *fox* sequence of the Finkel-Biskis-Reilly murine sarcoma virus). These 2 genes are therefore within a genetic interval of less than 0.8 cM.

We have isolated 2 YACs (250 and 550kb respectively) containing the *Fau* gene. We are currently undertaking chromosomal walking to isolate the *mdf* locus.

67. COMPARATIVE MAPPING OF THE PROXIMAL REGION OF MOUSE Chr 13. *C.M. Perou[1], A.L. Perchellet[2], J. Kaplan[1], M.J. Justice[2]. [1]Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84132; [2]Division of Biology, Kansas State University, Manhattan, KS 66506; [3]Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831.*

The proximal end of mouse Chromosome 13 contains regions conserved on human chromosomes 1q41-q43, 6p23-p21, and 7p22-p13. These regions contain numerous models for human disease, such as Chediak Higashi syndrome (mouse *beige*), Greig cephalopolysyndactly syndrome (mouse *extra-toes*), and cancer. As a first step in examining the function of genes in the proximal region of mouse chromosome 13, we are creating a fine structure genetic linkage map of genomic region encompassing *beige (bg)* and *satin (sa)*. An interspecific backcross involving SB/Le and *Mus spretus* mice was used to generate a molecular genetic linkage map of mouse chromosome 13. This map provides the gene order of the two phenotypic markers *bg* and *sa* relative to restriction fragment length variants and simple sequence length variants, Our initial study involves 132 backcross animals, and spans the entire chromosome. The results from these data will direct "interval mapping" of the *bg-sa* region on an additional 400 animals.

In parallel to the genetic linkage mapping, we are creating a physical map of the region using *Nidogen (Nid)* as a molecular starting point for cloning a YAC contig. Molecular clones from the YAC contig are being used to identify alterations associated with the alleles of *bg*. The results show that this region of mouse Chr 13 is highly conserved on human Chr 1q41-q43. The genetic and physical mapping results will provide valuable resources for the molecular identification of the gene altered in the bg mutations, as well as for further functional studies of the conserved genes in the region using induced mutations. *(M.J.J. is supported by the U.S. Department of Energy, work proposal No. ERKP507, by the National Institutes of Health, 7R29CA63229-02, and by an award from the American Cancer Society, JFRA-553. J.K. is supported by the National Institutes of Health, HL26922, and C.M.P. is a recipient of an NIH Genetics Training Grant T32GM07464.)*

68. GENETIC AND CHROMOSOME STRUCTURAL ANALYSIS OF THE *ckr* MOUSE.

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The *chakragati* mouse *(ckr)* is a transgenic insertional mutant that exhibits excessive circling behavior. The phenotype is transmitted as an autosomal recessive mutation, presumably reflecting a loss of function. Structural analysis of cloned DNA indicates that 2.5 copies of the transgene have integrated at the *D16Ros1* locus along with a duplicated segment of unknown size of the *D16Ros2* locus *(D16Ros2tg)*. Interspecific backcross analysis has shown that in normal mice *D16Ros1 is* 10 cM proximal to *D16Ros2*, but in the *ckr* mouse they are only separated by 1 cM. Intercross analysis confirms the apparent suppression of recombination in the *ckr* mouse. Further genetic analysis indicate that segregation of the phenotype is tightly linked to *D16Ros2tg* and *D16Ros1*, but not to *D16Ros2*. Southern analysis with probes proximate to *D16Ros1* have shown that there has not been a deletion >5kb near the transgene integration site. Taken together, these data strongly suggest that the disrupted gene responsible for the circling phenotype is located in the immediate proximity of *D16Ros1*. Therefore, we are currently attempting to identify all transcribed sequences near *D16Ros1* via exon trapping of a 17 kb wild type genomic lambda clone containing *D16Ros1*. We are also attempting to obtain a P1-clone from this region to extend structural gene analysis, and to use as preliminary to gene correction. Identification of the disrupted gene responsible for the phenotype should afford insight into the complex circuitry involved in controlling motor behavior.

69. THE NEUROLOGICAL MOUSE MUTATIONS JITTERY AND HESITANT ARE ALLELIC AND MAP TO THE REGION OF MOUSE CHROMOSOME 10 HOMOLOGOUS TO 19p13.3.

D. Kapfhamer[1], H.O. Sweet[4], D. Sufalko[1], S. Karlson[2], K. R. Johnson[4], M. Burmeister[1,2,3]. [1]Mental Health Research Institute, Depts. of [2]Human Genetics and [3]Psychiatry, University of Michigan, Ann Arbor MI; [4]The Jackson Laboratory, Bar Harbor ME, USA.

Jittery *(ji)* is a recessive mouse mutation on Chromosome 10 characterized by progressive ataxic gait, dystonic movements, spontaneous seizures, and death by before fertility. Recently, a viable neurological recessive mutation, hesitant, was discovered, characterized by hesitant movements, an exaggerated stepping and male infertility. We present data from a complementation test and genetic mapping that show that hesitant and jittery are allelic. In several large intersubspecific backcrosses and intercrosses we have genetically mapped *ji* near the marker Amh and microsatellite markers *D10Mit7*, *D10Mit21* and *D10Mit23*. This high resolution genetic map shows that *ji* is closely linked to the loci for the mouse mutations grizzled and mocha in a region of mouse chromosome 10 that is homologous to human 19p13.3. The closely linked markers will facilitate positional cloning of the *ji* gene. Most genes that map to 19p13.3 and mouse Chromosome 10 are nonrecombinant in our cross. By excluding genes that map to human 21q22.3 and 12q23, we can conclude that jittery is not a genetic mouse model for human Unverricht-Lundborg Progressive Myoclonus Epilepsy (EPMI) on 21q22.3 or Spinocerebellar Ataxia type II (SCA2) on 12q22-24, but might be a model for recently described ataxias on 19p13.

70. *QUAKING:* COMPLEXITIES IN GENE STRUCTURE AND EXPRESSION. *C. Vernet[1], T. Ebersole[2], K. Artzt[1]. [1]Department of Zoology, The University of Texas at Austin, Austin, TX 78712 USA; [2]Department of Genetics, Cambridge University, Cambridge, CB2 3EH, England.*

Quaking is an autosomal recessive disorder characterized by a tremor when the animal is in motion. The major neuropathological finding is that the entire central nervous system is very deficient in myelin in all ages studied. The cause is a dysmyelin without showing degeneration nor inflammation. The mutation is associated with a large deletion on chromosome 17 and the gene which overlaps the proximal breakpoint has been cloned. It has a complex pattern of expression, especially m the developing nervous system. Furthermore, a point mutation in one of the ENU-induced *quaking* mutants has been characterized *(Ebersole, Chen, Justice and Artzt, submitted).* All these results together argue that the gene cloned is *quaking (qk).* Our data show that the gene is complex in terms of genomic structure. We have defined two classes of transcripts. Three messages (7, 6 and 5 kb) are expressed in brain and heart, and together define the so-called quaking class I transcripts implicated in embryogenesis. We are focusing our attention on the class II isoforms: 5 kb, highly expressed in muscle, heart and peripheral nervous system, and 2 and 1.4 kb in polyA+ RNA brain. The class II transcripts are either truncated, absent or down regulated in the *quaking* mouse compared to the wild type. A developmental study of qkII expression and the genomic structure will be discussed.

71. IDENTIFICATION OF MOUSE REELER GENE ENCODING A PROTEIN WITH AN EGF-LIKE MOTIF BY RLGS-BASED HIGH-SPEED POSITIONAL CLONING SYSTEM. *S. Hirotsune[1], T. Takahara[1], Y. Okazaki[1], K. Hirose[1], N. Sasaki[1], H. Okuizumi[1], T. Ohsumi[1], A. Yoshiki[1], T. Ohashi[1], M. Kusakabe[1], M. Muramatsu[1], K. Nakao[2], M. Katsuki[2], V. M. Chapman[3], Y. Hayashizaki[1]. (1) Genome Science Laboratory and Cell Biology Laboratory, The Inst. of Phys. and Chem. Res. (RIKEN), 3-1-1, Koyadai Tsukuba, Ibaraki, 305 Japan; (2) Med. Inst. of Bioregulation, Kyushu Univ; (3) Mol. & Cell. Biol. Dept., Roswell Park Cancer Inst, Buffalo, NY.*

We have identified a strong candidate cDNA for the mouse reeler (rl) gene using RLGS-based high-speed positional cloning system which consists of RLGS spot bombing (the method for identifying RLGS spots tightly linked to a specific phenotype) and RLGS YAC contig mapper. To identify the RLGS markers linked to rl locus, we used the pooled DNA of backcrosses carrying the rl mutation. Backcross mice homozygous (rl/rl) should have a 50% probability of being heterozygous for unlinked genes but they should be predominantly homozygous for closely linked genes and the corresponding non-mutant parent alleles should be absent. We identified 31 spots that were located on chromosome 5 linked to rl in the analysis of a total of 29954 spots. Three spots out of 31 showed no recombination with rl locus and DNA fragments from three spots were cloned by spot-cloning method. Using these RLGS spot clones, we isolated 7 YACs (3 RIKEN YACs and 4 Princeton YACs). RLGS YAC contig mapper was the method used for connecting the YAC clones which is based upon the principle that the RLGS patterns of the YACs covering the common genomic DNA region share the same RLGS spots/landmarks. Using this system, the contig map which covered the rl region was constructed using these YACs. Because D5mit61 was the closest marker showing no recombination in a total of 583 progeny with the rl phenotype, the transcripts around this marker were surveyed and finally one strong candidate transcript was isolated. This 12 kbp transcript encodes a protein carrying EGF-like motifs. Two independent mutant alleles were assayed. "Jackson reeler" had a deletion of the entire region of this gene and "Orleans reeler" a 220 bp deletion in open reading frame (ORF) which included the last EGF-like motif, resulting in a frame shift in the original ORF. In situ hybridization data showed that the transcripts could be detected only in the pioneer neurons which guide neuronal cell migration along the radial array. These data offer an explanation for how the reeler mutant phenotype causes disturbance of the three-dimensional complex architecture of the neuronal network.

72. GENOMIC ORGANIZATION OF THE REELER GENE REGION. *I. Royaux, I. Bar, C. Lambert de Rouvroit, B. Bernier, A.M. Goffinet. Dept. Physiology, FUNDP Med. Sch., B-5000 Namur, Belgium.*

The gene affected by the mouse neurological mutation *reeler*, dubbed *reelin*, has recently been cloned using a transgenic insertion mutation *(D'Arcangelo et al Nature 374: 719-23, 1995)*. We have cloned the corresponding genomic region as a YAC contig from which several gene fragments are being characterized, including exons of the *reelin* gene. The *reelin* cDNA is encoded by a genomic interval extending over 400-450 kbp. The 5' end of the gene is distal to the microsatellite *D5Mit72* and associated with a CpG island mapped by the clustering of *BssHII* and *SalI* sites. The 3' end maps distally and close to *D5Mit61*, within the 150 kbp segment which is deleted in *rl/rl* mutant mice. Alterations in the *reelin* gene have been demonstrated in five alleles of the *reeler* mutation, suggesting strongly that defects of reelin are indeed responsible for the *reeler* phenotype. Two exons from genes distinct from *reelin* have been isolated from the genomic region that is deleted in *rl/rl* DNA. These exons are not homologous to any expressed sequence tag described in databases. Using a combination of cDNA affinity capture and exon trapping, several other candidate gene fragments have been isolated from the YAC contig. One of them corresponds to the mouse gene for subunit 7 of the 26S proteasome. The other fragments have no significant homologs in databases. The characterization of those genes is in progress in order to build a transcriptional map of the region.

73. MOLECULAR ANALYSIS OF MOTTLED MUTANTS. *Vivienne Reed, Yvonne Boyd. MRC Radiobiology Unit, Chilton, OXON, OX11 ORD, UK.*

X-linked mottled mutants have defects in copper homeostasis which result in pleiotropic effects including hypopigmentation and neurological, skeletal and connective tissue abnormalities. Similarities in phenotype together with comparable map positions indicated that mottled is a homologue of Menkes' disease (MNK=ATP7A) in man. We have confirmed the mapping data and shown that *Atp7a* cosegregates with the mottled blotchy phenotype in approximately 200 interspecific backcross offspring. However, no causal alterations in the *Atp7a* locus were found after genomic analysis of 14 independent alleles including some which were radiation-induced. Initial RT-PCR studies on 8 male-viable mutants revealed the presence of normal sized *Atp7a* transcripts. Three mutants (blotchy, brindled, 13H) also had additional truncated products from the 5' coding region. No sequence changes have been found in these small products, the normal-sized products or the intervening introns of this region of the *Atp7a* gene. We are currently sequencing the full coding region of the gene in brindled, viable-brindled and 13H in an attempt to find the molecular lesions underlying the resultant phenotypes.

74. A MOUSE MODEL FOR POLYCYSTIC KIDNEY DISEASE. *Elizabeth C. Bryda, Lorraine Flaherty. Wadsworth Center, Albany, NY.*

An autosomal recessive mouse model for polycystic kidney disease (PKD) was generated by chlorambucil mutagenesis. The gene has been designated *jcpk* (juvenile congenital polycystic kidney disease). In homozygous *jcpk*/*jcpk* mice, this mutation causes an early onset PKD, more severe than any previously described mouse PKD mutant. Homozygotes are detectable as early as 5 days after birth by a protruding abdomen and generally die by 10 days. Kidneys are grossly enlarged. Histologically, homozygote *jcpk*/*jcpk* kidneys are highly abnormal, with cysts appearing in the entire nephron. Extrarenal effects include enlargement of the gallbladder and extreme dilations of both the bile and pancreatic ducts. A late onset polycystic disease is also present in a number of aged heterozygotes. In these animals, glomerulocystic disease with some extrarenal involvement was noted. The *jcpk* gene had previously been mapped to mouse Chromosome 10 by linkage analysis. Using Simple Sequence Length Polymorphism (SSLP) analysis of affected and normal animals, *jcpk* has been precisely mapped between D10Mit224 and D10Mit174, closely linked to *Ank3* (ankyrin). Currently, Bacterial artificial chromosome (BAC) and Yeast artificial chromosome (YAC) libraries are being screened using probes to markers flanking *jcpk* to isolate clones containing the *jcpk* gene. Additionally, time course studies in heterozygote aged mice are being conducted to study disease progression. Results indicate that glomerular cysts are first noticeable in 9 month old animals. Disease progresses with increasing age such that at 12 months, only 18% of the +/*jcpk* mice have signs of disease whereas at 20 months, 50% of the heterozygote animals were positive for the disease.

75. GENETICS OF VERTEBRATE DIGITAL ARCH FORMATION. *L.C. Post[1], D.P. Mortlock[1], S. Darling[3], J.W. Innis[1,2]. Department of Human Genetics[1], Department of Pediatrics[2], University of Michigan, Ann Arbor, MI, USA; University College, London, UK[3].*

Organization of prechondrogenic condensations in the developing limb occurs via three main mechanisms: *de novo* condensation, bifurcation of single elements, and segmentation of existing mesenchyme. Perturbation of any of these events during development will lead to limb abnormalities. Therefore, investigation of natural and induced mouse mutations affecting the limb will lead to the identification of some of the genetic determinants mediating these processes.

Hypodactyly *(Hd) is* a semidominant mutation in mice that maps to mouse chromosome six near the *Hoxa* locus. Homozygous affected mice fail to form the digital arch. Our goal is to examine the mechanisms responsible for digital arch formation in vertebrates by identification and analysis of the normal and affected gene product(s) at the *Hd* locus.

Towards this goal, we have built a high-resolution genetic map of the *Hd* locus using genetic crosses with CASA/Rk and *Mus spretus* involving over 1,500 mice. We have identified markers nonrecombinant with the locus, oriented the *Hoxa* complex on the chromosome, and positioned *Hd* distal to *Hoxa2*. We have constructed a contig of genomic clones which spans the proximal breakpoint and extends distal to *Hoxa* and the *Evxl* gene. We are currently testing the possibility of allelism between *Hd* and the 5′ *Hoxa* genes and *Evxl* .

76. FUNCTIONAL CHARACTERiZATION AND ANALYSIS OF THE MOUSE LIMB MUTANT HYPODACTYLY. *K.E. Robertson, C. Tickle, S.M. Darling. Dept. of Anatomy and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK.*

Limb development is an intricate process requiring the coordinate expression of many genes as shown by the large number of genetically distinct limb mutations found in mammals. We are interested in the specific roles of certain genes and molecules in mouse limb development. Hypodactyly is a semidominant lethal mutation; *Hd/+* animals show a reduction in the length of digit I in the hindlimbs, whilst *Hd/Hd* animals have only one digit on each of the four limbs. Our initial observations show that the limb abnormality arises during the later stages of limb development when patterning of the more distal elements is occurring. Histological analysis suggests that there may be a breakdown in the signal between two of the major components of the developing limb; the apical ectodermal ridge and the underlying mesenchyme. We are currently performing grafting experiments and gene expression studies to test this hypothesis.

77. GENETIC AND PHENOTYPIC ANALYSIS OF DANFORTH'S SHORT-TAIL MOUSE. *J. B. Alfred[1], K. A. Rance[2], S. J. Phillips[3], B. A. Taylor[3], C. M. Abbott[1], I.J. Jackson[1]. [1]MRC Human Genetics Unit, Edinburgh, UK; [2]Institute of Cell and Animal Population Biology, University of Edinburgh, UK; [3]The Jackson Laboratory, Bar Harbor, ME, USA.*

The semi-dominant mutation Danforth's short-tail *(Sd)*, causes abnormalities in the development of the notochord and urogenital organs. Heterozygotes have a highly variable phenotype with a reduction in size of one, or both, kidneys. Homozygotes are tailless and die soon after birth due to a complete absence of kidneys and urogenital openings.

We have generated a 336 progeny, interspecific backcross *[(Sd x* cast) x CBA] to finely map the region of mouse chromosome 2 around *Sd*. Backcross offspring have been typed with a panel of microsatellite repeats, and closely flanking markers have been used to isolate YACs in order to generate a YAC contig in the region of *Sd*. Since tail length in the backcross varies considerably, we have also scanned the genome of backcross progeny with microsatellite markers to identify genes affecting the expressivity of *Sd*. We see association of regions of the genome with more or less severely affected tails, and are applying QTL analysis to these data to confirm the presence of *Sd* modifiers at these loci.

Using an *in vitro* organ culture assay, we have also looked at the development of embryonic kidneys from *Sd* mice and have found that, although mutant ureteric buds are able to induce the metanephric mesenchyme to condense and epithelialise, they are themselves unable to branch properly.

78. LINKAGE ANALYSIS OF THE MOUSE MYELENCEPHALIC BLEBS MUTATION. *E. Bentley (1), A.Gossler (2), S.M. Darling (1). 1. Dept. of Anatomy and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK; 2. The Jackson Laboratory, Bar Harbor, ME, USA.*

Myelencephalic blebs (*my*) is a recessively inherited mutation which is located on mouse chromosome 3. In *my* mutants, embryonic subepidermal blebs cause abnormalities of the eyes, skin, hair and clubbing of the feet; other abnormalities include preaxial polydactyly, syndactyly of the middle digits, acrania, renal agenesis and pseudencephaly. Two intersubspecific backcrosses, [(my^{UCL}/my^{UCL} x M. mus PWK) F1 x my^{UCL}/my^{UCL}] and [(my^{UCL}/my^{UCL} x M. cast) F1 x my^{UCL}/my^{UCL}], have been analysed to refine the map position of my on chromosome 3. A more detailed genetic map around the my locus is being generated using a 1000-progeny intersubspecific backcross, [(my^{UCL}/my^{UCL} x M. cast) F1 x my^{UCL}/my^{UCL}]. The closest flanking markers will be used to isolate YAC's spanning the *my* region and a physical map of this region will then be constructed.

79. MAPPING OF BRACHYRRHINE TO DISTAL MOUSE CHROMOSOME 17. *Yvonne Boyd, Colin Beechey, Hester Hughes, Vivienne Reed, Tony Searle. MRC Radiobiology Unit, Chilton, Oxon OX11 ORD, UK.*

The brachyrrhine *(Br)* mutation arose in a neutron irradiation experiment and is an autosomal semidominant with postimplantation lethality in the homozygote. Heterozygotes are small and are characterised by a much shortened snout and a deeper than usual median cleft in the upper *lip*. *Br/+* mice also have hypoplastic kidneys with a decreased number of glomeruli and increased interlobular connective tissue. Approximately two-thirds of the genome was excluded as containing a site for *Br* by testing for linkage to visible marker genes and translocation breakpoints. An interspecific backcross was therefore established between *Br/+* and *Mus spretus*. 54 backcross progeny were tested for linkage between *Br* and microsatellite loci that mapped outside the excluded regions and *Br* was found to be linked to *D17Mit39*. Analysis with additional microsatellite markers from chromosome 17 revealed that *Br* lay at the distal end of chromosome 17 and established genetic distances (in cM) between loci as *D17Mit9* - (18.4±6.3) -*D17Mit39* - (10.2±4.3) - *D17Mit41*- (5.8±3.2) - *Br* - *telomere*.

80. ANTERIOR PITUITARY CELLS DEFECTIVE IN THE CELL-AUTONOMOUS FACTOR, *df*, UNDERGO CELL LINEAGE SPECIFICATION BUT NOT EXPANSION. *Philip J. Gage, Michelle L. Roller, Thomas L. Saunders, Lori M. Scarlett, Sally A. Camper, Kathy Mahon*. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI; *National Institutes of Health, Bethesda, MD, USA.*

The Ames dwarf mutation *(df)* (MMU 11) identifies a crucial gene for pituitary ontogeny. Homozygotes exhibit profound anterior pituitary hypoplasia due to a deficiency of thyrotrope, somatotrope and lactotrope cells. By immunohistochemical analysis, we establish that *df/df* mice are capable of limited commitment to these three cell types through expression of the pituitary specific homeobox gene, *Pit-1*, in rare clusters of cells. However, analysis of *df/df* pituitaries revealed that *df* acts upstream of Pit-1. By e14.5, prior to the onset of Pit-1 transcription, the hypocellularity of *df/df* pituitaries is evident, and abnormalities in expression of pituitary specific molecular markers were detected by in *situ* hybridization. Although the developing hypothalamus is known to exert inductive influences on anterior pituitary cytodifferentiation, analysis of aggregation chimeric mice demonstrates that *df* functions by a cell-autonomous mechanism. Thus, *df* is intrinsic to the pituitary precursor cells common to the three Pit-1 dependent cell lineages, and it is required for proliferation of these precursor cells early in ontogeny. Knowledge of the time and place of *df* expression is important for identification of this important gene by positional cloning.

81. ANALYSIS OF THE MOUSE ANOREXIA MUTATION. *J. Johansen[1], I. Efanova[2], C. Broberger[3], Shi Tie Jun[3], T Hokfelt[3], P-O. Berggren[2], M. Schalling[1]. [1]Neurogenetics Unit, [2]The Rolf Luft Center for Diabetes Research, Department of Molecular Medicine, Karolinska Hospital, S-171 76 Stockholm; [3]Department of Neuroscience, Karolinska Institute, S-171 77 Stockholm, Sweden.*

We are studying the anorexia mutation (anx), a recessive mutation that causes starvation in mice *(Maltais et al., J. Hered., 75, 468-472 (1984)*. Mutant mice are characterized by growth failure, an emaciated appearance and neurological symptoms including body tremors, headweaving, hyperactivity and uncoordinated gait. The animals die by 22 days. The mutation is located approximately 20 cM proximal to the agouti locus on chromosome 2.

Using polymorphic CA-repeats we have identified a 3-4 cM region with several markers closely linked to the phenotype. We are now performing neurophysiological and immunohistochemical analysis of mutant mice.

In the region linked to anx we have identified a trinucleotide repeat sequence that is unstable and markedly expanded in some strains.

82. LINKAGE MAPPING AND EMBRYOLOGICAL ANALYSIS OF *DOMINANT MEGACOLON*, A MOUSE MODEL FOR HIRSCHSPRUNG'S DISEASE.

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Animals heterozygous for *Dominant megacolon (Dom/+)* exhibit multiple defects in neural crest development including reduced numbers of melanocytes in the skin and an absence of myenteric ganglion in the colon. A human congenital disorder, Hirschsprung disease also exhibits rectocolic aganglionosis and can be associated with hypopigmentation. Thus *Dom/+* mice serve as one mouse model for this disease. *Dom* arose and has been maintained on a C57BL/6JLe X C3HeB/FeJLe-a/a ($B6C3F_1$) hybrid background, however the severity of the phenotype is dramatically influenced by genetic background: both spotting and survival are increased in *Dom*/C3 lines in comparison to *Doml*/B6 lines. Genotype analysis of *Dom*/B6 N7 and *Dom*/C3 N11 backcross pedigrees with simple sequence repeat markers defined the region containing *Dom* to 5.6 cM, bounded by D15Mit68 and D15Mit189. Additional analysis in inter- and intra-subspecific crosses has narrowed the interval containing *Dom* to $\leq$ 1 cM (8 recombinants/807 meioses).

To evaluate the phenotype of *Dom/Dom* homozygous mice, the most closely linked markers were applied to genotype intercross progeny. Previous reports indicated that *Dom/Dom* homozygotes die *in utero*, prior to embryonic day 13.5. Consistent with this finding, no *Dom/Dom* pups have been identified at weaning (0/40 mice); however *Dom/Dom* embryos were identified at e16.5, suggesting that the time of embryonic lethality, like spotting and post-natal survival, is variable. Data to be presented will include genetic & physical mapping of the *Dom* locus, candidate gene analysis, and description of neural crest development in *Dom/Dom* mutant embryos.

83. ABSENCE OF A NOVEL PUTATIVE TRANSPORTER CAUSES OSTEOPETROSIS IN THE *oc/oc* MOUSE.

K.P. Brady, D.R. Beier. Genetics Division, Brigham and Women's Hospital, Harvard Medical School. Boston, MA 02115.

We have used a method of differential display that has been modified to utilize the entire cDNA sequence as a template (rather than just the 3' end) to clone a novel gene that has localized homology to a family of 12-transmembrane domain proteins with transport functions. We have determined by SSCPanalysis that this gene maps to the partial portion of mouse chromosome 19, in a region to which the osteosclerosis (*oc*) mutation has been previously assigned. The phenotype of *oc/oc* mutant mice includes osteopetrosis, and a variety of studies suggest that osteoclasts in these mice are present but non-functional. The important role of transport functions in bone metabolism suggested the possibility that this transport protein is a candidate for the *oc* gene.

The transporter is expressed only in distal tubules of the kidney and in bone marrow. There is no detectable transporter present in kidneys from *oc/oc* mice when analyzed by Northern blots. Heterozygous *oc/+* mice express reduced amounts of the transporter compared to wild-type sibs. Southern analysis of the transporter locus reveals that it is intact and unrearranged in *oc/oc* mutants. It thus appears likely that the absence of the transporter results in an osteopetrosis phenotype in mice. We are presently confirming this hypothesis by identifying the putative mutation in *oc* mice by sequence analysis. Given the evidence of abnormal osteoclast function in *oc* mice, we anticipate that the transporter will be expressed in osteoclasts; this is being tested using *in situ* hybridization. In humans, osteopetrosis is a well-described clinical disorder that usually presents during the first year of life, and is almost always fatal. It is also considered to potentially be an osteoclast defect, since they are present but apparently non-functional. We are exploring whether this disorder is due to a defect in the human homolog of the transporter that is deficient in the *oc/oc* mouse.

84. FINE MAPPING OF THE OSTEOSCLEROSIS LOCUS *(oc)* IN THE PERICENTROMERIC REGION OF MMU19. *A. Franchi, G.F. Carle. LEGM - URA 1462 C.N.R.S. Universite de Nice, France.*

Osteosclerosis *(oc) is* an osteopetrotic mutation in the mouse inherited as an autosomal lethal recessive. The *oc/oc* homozygote mice usually die around three weeks of age, and the mutation has been maintained in *oc/+* heterozygotes, which display no abnormal phenotype. Affected animals *(oc/oc)* exhibit the characteristic radiologic and histologic features of osteopetrosis including a generalized increase in skeletal density and absence of marrow cavities. Ten years ago, S.C. Marks *et al.*[1] mapped *oc* in the vicinity of MMU19 centromere with a fairly low resolution. We have been able to refined the genetic localization of the *oc* gene in the pericentromeric region of mouse chromosome 19 using an interspecific backcross of the type (B6C3-*a/a* F1 *oc/+ x Mus spretus)*F1*oc/+* x B6C3-*a/a* F1*oc/+* as well as (B6C3-*a/a* F1*oc/+* x *Mus spretus)*F1*oc/+* x (B6C3-*a/a* F1*oc/+* x *Mus spretus)*F1*oc/+*. Using a dozen of microsatellite markers, we were able to define in our inbred strain an area of C57BL/6 DNA (where the mutation arose) imbedded in a C3H background. The analysis of the recombinant affected animals is in process and will be presented along with the approach for the positional cloning of the gene.

[1]*S.C. Marks, M.F. Seifert and P.W. Lane (1985), J. Hered. 76, 171-176.*

85. TOWARD CHARACTERIZATION OF THE MOUSE OSTEOPETROTIC GREY-LETHAL MUTATION. *Jean Vacher, Hugues Bernard. Clinical Research Institute of Montreal, Montreal, Quebec, Canada.*

The mouse grey-lethal *(gl)* mutation is responsible for an osteopetrotic phenotype, involving a block in the differentiation pathway of the osteoclast cell population. Osteoclast are the only cells capable of resorbing bone tissue during development and throughout adult life. The homozygous *gl* animals die at approximately three weeks of age displaying growth retardation, poor development of the bone marrow space, no teeth eruption and coat color defect. A positional cloning strategy has been developed to clone and characterize this mutation, localized between the *c-fyn* and *c-ros* loci on mouse chromosome 10. First, a backcross panel has been generated between *Mus spretus* and the grey-lethal mouse which is on a *Mus domesticus* background. We have studied 400 progeny from this backcross and established a genetic map around the *gl* locus on chromosome 10 by using molecular markers (cloned genes and microsatellites). Secondly, a chromosome walk has been initiated from the gene *c-fyn*, which is approximately 1cM from *gl*, and a yeast artificial chromosome (YACs) contig covering 2Mb has been generated. During this study, several polymorphisms have been identified as specific for the *gl* phenotype, thereby allowing to study the *gl* chromosome transmission. Overlapping YACs including these polymorphisms have been isolated and search for transcribed sequences has been initiated.

86. TOWARDS POSITIONAL CLONING OF THE AMES DWARF LOCUS. *D.E. Watkins-Chow, M.S. Buckwalter, M.L. Roller, F.J. Probst, D.D. Baker, M.N. Newhouse, A.C. Lossie, K. Liggett, S.A. Camper. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI, 48109-0618 USA.*

Ames dwarf is a recessive mouse mutation that causes panhypopituitarism and severe dwarfism. Affected mice are one third normal size and their hypocellular anterior pituitary glands essentially lack the cells which produce thyroid stimulating hormone, growth hormone, and prolactin. The gene mutated in Ames dwarf mice *(df)* is involved in anterior pituitary cell proliferation. To clone *df*, we have characterized over 3000 meioses from *M. castaneus* and *M. molossinus* backcross and intercross progeny. No significant difference in recombination rate was observed between the *df* stock and the two wild species of *Mus*. A comparison of the mouse gene order determined with this high resolution cross with the gene order in the corresponding region of HSA 5q revealed that linkage conservation exists only over short intervals. In addition, genetic mapping eliminated all currently available candidate genes. To clone *df*, a chromosome walk was initiated by screening YAC libraries for markers flanking *df*. YAC ends were obtained either by inverse PCR or by homologous recombination/plasmid end rescue and genetically mapped to confirm linkage and establish orientation relative to *df*. A contig consisting of 25 YACs and 12 P1 clones has been assembled and spans approximately 3.5 Mb. A small gap remaining between the two flanking contigs is currently being filled with P1 clones. The size of the nonrecombinant interval is less than 630 kb, based on preliminary physical mapping. Transcripts from the region are being identified by pituitary cDNA selection and exon trapping. The cloning of *df* will reveal an important player in the process of pituitary cytodifferentiation. *(NIH RO 1 HD30428, T32 HD07048)*

87. GENETIC AND PHYSICAL MAPPING OF THE *js* GENE ON MOUSE CHROMOSOME 11. *Y. Kikkawa[1], U. Gangadharan[2], S. Wakana[3], Y. Kohara[1], M. Okamoto[1], Y. Matsuda[4], R. Kominami[5], K. Moriwaki[6], T. Shiroishi[6], H. Yonekawa[1]. [1]Tokyo Met. Inst. Med. Sci., Tokyo 113, Japan; [2]St. Mary Hospital Med. School, London W21 PG, UK; [3]Cent. Inst. Exp. Animals, Kawasaki 216, Japan; [4]Natl. Inst. Radol. Sci., Chiba 263, Japan; [5]Niigata Univ. School of Med., Niigata 951 Japan; [6]Natl. Inst. Genet., Mishima 411, Japan.*

Jackson shaker (*js*) is a recessive mutation affecting hearing, the locus of which is mapped on the distal part of the chromosome 11. The hearing loss is caused by disarray of stereocilia of the outer hair cells in the inner ear. To survey DNA markers closely linked to this locus, we have employed detailed linkage analysis using two allelic forms, *js* and *seal by intersubspecific* backcrosses between the mutant stocks and a wild derived inbred strain, MSM. Using 500 segregants of the *js* -MSM backcross and 300 segregants of the *seal-MSM* backcross, we have found six microsatellite markers which are located within 0.6 cM at the *js* locus. In particular, no recombinant was found between *js/seal* and three microsatellite markers. These markers were used to screen YAC libraries. In addition, using the end clones prepared from each YAC checked by FISH, we are constructing YAC contigs.

88. PHYSICAL MAPPING IN THE VICINITY OF THE wi LOCUS ON MOUSE CHROMOSOME 4.

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High resolution genetic maps in the vicinity of the *wi* locus have been constructed using large interspecific and intraspecific backcrosses segregating the *wi* mutation. In 598 animals genotyped from a *M. castaneus* interspecific backcross, the closest flanking markers are *AMBP/D4Mit87* and *Hxb* mapping 0.17cM proximal and 0.5 cM distal respectively of the wi locus. In 335 mice genotyped from the intraspecific cross, the closest flanking markers have been identified as *Mup1* and *Hxb* mapping 0.3cM proximal and 0.6cM distal respectively of *wi*. In addition, in the EUCIB backcross analysis of 273/325 recombinant mice in the *Mos - b* interval has identified a marker order of *D4Mit44 - D4Mit87 - D4Mit17 - D4Mit82 - D4Mit25 - D4Mit178 - D4Mit7* across the *wi* region. We have begun the construction of a YAC clone contig across the *wi* region and YACs have been identified to *Mup1, D4Mit87, D4Mit17* and *Hxb*. We are using a combination of rapid methods to extend the embryonic YAC contigs and complete a YAC contig covering the non-recombinant region surrounding the *wi* locus. We are employing both vectorette PCR for recovering YAC end clones for the extension of YAC contigs along with the generation of B1 IRS-PCR products for the rapid generation of new internal STSs from recovered YACs. These new internal B1 STSs provide a powerful tool for establishing the genetic versus physical map relationship using SSCP.

89. THE MYOSIN VII GENE UNDERLYING THE MOUSE SHAKER-1 RECESSIVE DEAFNESS MUTATION.

P. Mburu[1], F. Gibson[1], J. Walsh[1], A. Varela[1], X. Liu[1], K.P. Steel[2], S.D.M. Brown[1]. [1]Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London W2 1PG, UK; [2]MRC Institute of Hearing Research, University Park, Nottingham NG7 2RD, UK.

We have recently reported the use of a positional cloning approach to identify the mouse shaker-1 recessive deafness gene *(Gibson et al., 1995 Nature 374: 62-64)*. Use of a large interspecific backcross segregating the mouse shaker-1 mutation allowed us to delineate a small physical map region of mouse chromosome 7 in which we identified an unconventional myosin gene – a myosin VII . Analysis of shaker-1 mutant alleles in the available 2.5kb head region sequence from this myosin demonstrated three mutations – two missense mutations and a 3' splice site mutation leading to an in-frame deletion. Mutations have also been detected in the human homologue of the myosin VII gene in Usher syndrome type 1b *(Weil et al., 1995 Nature 374: 60-61)*. The myosin VII gene produces a 9.5kb transcript. Transcripts are detected in the cochlea, as well as retina, lung, kidney and testes. Using cDNA walking we are progressing with the determination of the complete structure of myosin VII that will allow us to relate the genotype of all seven available shaker-1 mutant alleles to the critical functional domains of this protein as well as relate genotype to mutant phenotype. In addition, we have begun to screen British Usher type 1 families for further mutations in the myosin VII gene in order to build a more comprehensive picture of the range of Usher 1b mutations in the human population. Relating human Usher type 1 mutations to the critical functional domains of myosin VII should provide additional insights into the structure and function of myosin VII.

90. GENETIC AND FUNCTIONAL ANALYSIS OF PIROUETTE, A MOUSE NEUROEPITHELIAL DEAFNESS MUTANT. *D.C. Kohrman, M.H. Meisler. Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109 USA.*

Recent isolation of the shaker1 gene underscored the utility of mouse deafness mutants for identification of critical components of cochlear function. We have initiated analysis of the deafness mutant pirouette *(pi)* which, like shaker1, exhibits cell degeneration in the organ of Corti. Pirouette arose as a spontaneous mutation in the inbred strain C3H at the Jackson Laboratory in 1943, and was recognized by its circling behavior *(J. Hered. 36:281-284, 1945)*. The circling phenotype is inherited as an autosomal recessive trait with complete penetrance. The pirouette locus was previously localized to central chromosome 5 in a conserved linkage group containing genes from human chromosome 4p16-q31. A congenic line carrying the *pi* mutation was generated at the Jackson Laboratory by 15 generations of backcrossing to strain C57BL/6J. In order to initiate this study, N15 mice were retrieved from the frozen embryo repository. We have analyzed *pi/pi* genomic DNA (N15) with microsatellite markers and found that the C3H-derived region in the congenic line is 5.4 $\pm$ 2.4 cM. ABR analysis indicates that 1 month old *pi/pi* mice exhibit a selective, high frequency hearing loss, consistent with published studies indicating greater cell loss in the basal cochlea. Genetic crosses for positional cloning and additional electrophysiological analysis of cochlear function are in progress.

91. HIGH RESOLUTION MAPPING OF MURINE GENES WHICH AFFECT PIGMENTATION AND PLATELET FORMATION/ FUNCTION. *Richard T. Swank[1], Edward K. Novak[1], Edward P. O'Brien[1], Michael E. Rusiniak[1], Michael B. Gorin[2], Albert B. Seymour[2]. [1]Dept. of Mol. & Cell. Bio., Roswell Park Cancer Inst., Buffalo, NY, USA; [2]Depts. of Ophthalmology & Human Genetics, Univ. of Pittsburgh, Pittsburgh, PA, USA.*

A significant number (14) of naturally-occurring recessive mouse mutations cause pigment dilution and platelet storage pool deficiency. Several appear to be appropriate animal models for human Hermansky-Pudlak Syndrome (HPS). In order to initiate the molecular characterization of these genes, a series of interspecific backcrosses have been constructed to identify molecular markers near six pigment genes. Also, immortalized melanocyte cultures of several mutant lines have been partially characterized. The genes include muted *(mu)*, pearl *(pe)* and sandy *(sdy)* on chromosome 13, pale ear *(ep)* and ruby-eye *(ru)* on chromosome 19 and gunmetal *(gm)* on chromosome 14. In the chromosome 13 cross, approximately 1,100 progeny have been typed for 39 microsatellite markers and 6 cDNAs. The chromosome 19 cross involves 1,200 progeny typed for 39 microsatellites and 10 cDNAs. In the chromosome 14 cross, 700 progeny have been typed for 22 microsatellites and 14 cDNAs. Several molecular markers have been found to be tightly linked to the pigment loci. Also, several expressed genes have been excluded as candidate genes for the pigment loci. These markers will be useful as entry points in the molecular identification of these genes by positional/candidate approaches. Their identification should 1) reveal whether the various pigment genes are related at the molecular level, 2) provide insights into the mechanism of action of genes which simultaneously regulate the biosynthesis/processing of related intracellular organelles and, 3) determine which mouse mutant is the appropriate animal model for specific forms of HPS.

92. HIGH RESOLUTION MAPPING OF THE X-LINKED MOUSE MUTANT LINED. *Ifeanyi Uwechue, Yvonne Boyd. MRC Radiobiology Unit, Genetics Division, Chilton, OXON, OX11 ORD, UK.*

Comparative mapping allows homologous genes in man and mouse to be identified and can lead to the development of murine models for human genetic disease. High resolution mapping of the X-linked mouse mutant lined *(Li)* has been undertaken to assess its suitability as a homologue of Incontinentia Pigmenti type 1 (IP1). Earlier genetic mapping positioned *Li* at the distal end of the mouse X chromosome which contains a region of homology with the pericentromeric region of the human X chromosome defined by ALAS2 in both species. IP1 is phenotypically similar to *Li* and is associated with several translocation breakpoints, some of which may lie in this conserved block. Results from interspecific mapping studies have refined the map position for *Li* and indicate that it lies between DXMit35 and DXMit28. In addition, phenotypic analysis of *Li* will determine the extent of its similarities with IP1 and ascertain its usefulness as a potential murine model for this disease.

93. TOWARDS CLONING THE REPEATED EPILATION (*Er*) MUTATION. *Rebecca A. Liddell, Jill K. Fisher, Arthur M. Buchberg, Linda D. Siracusa. Department of Microbiology and Immunology, Jefferson Cancer Institute, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107.*

Development of skin requires the differentiation of five distinct histological layers and a number of diverse appendages including the hair follicles. The Repeated epilation *(Er)* mouse provides an animal model in which these developmental paradigms have been disrupted. *Er* is γ radiation-induced dominant mutation. Mice homozygous for the mutation die immediately after birth and display disturbances in epidermal organization along with major morphological disruptions in growth and development of the limbs, tail and facies. *Er/+* mice display a unique phenotype of repeated hair loss and regrowth throughout life. Additionally, mice heterozygous for the mutation have an increased risk of cutaneous papillomas. As the first step in identifying the gene(s) responsible for this disrupted cellular differentiation, we established an intersubspecific backcross to map the *Er* mutation with respect to microsatellite markers and genes. The results indicate that *Er* must lie within the region *D4Mit203 - Er - D4Mit13* on mouse chromosome 4. Our studies rule out several genes as candidates for the *Er* mutation *(Research supported in part by ACS grant PF-4230 to RAL and NCI grant CA21124 to LDS and AMB.)*

94. THE LINKAGE ANALYSIS OF THE MOUSE RADIATION INDUCED CATARACT GENE, *Tcm*. *[1]E. Zhou, [1]D.J. Sidjanin, [2]J. Favor, [1]D. Stambolian. University of Pennsylvania, Dept. of [1]Ophthalmology, Philadelphia, PA, USA; [2]GSF-Institute Fur Saugetiergenetik, Neuherherg, Germany.*

The mouse *Tcm* mutation was induced by X irradiation and phenotypically has a total cataract and microphthalmia. The *Tcm* mutation is an autosomal dominant cataract caused by a single dominant gene. In order to find the location of the *Tcm* mutation, the simple sequence repeats polymorphism (SSRP) method was used to analyze 100 mouse progeny generated by backcross mating. Initially, each chromosome was screened with 2-3 microsatellite markers for 16 progeny, which allowed us to exclude chromosomes 1 and 5-17 because of 50% recombination. Additional markers and progeny eliminated chromosomes 2, 3, 18, 19 and identified chromosome 4 as the location for the *Tcm* mutation. The *Tcm* mutation is located between marker *D4Mit193* and *D4Mit101*. Three crossovers out of 32 progeny were observed with *D4Mit193* and 2 crossovers out of 32 progeny for *D4Mit101*, placing *Tcm* 2 cM from *D4Mit101* and 10 cM from *D4Mit193*. More microsatellite markers in this region will be chosen to screen our backcross panel to more precisely locate the *Tcm* loci.

95. HIGH-RESOLUTION LINKAGE MAP IN THE CHROMOSOMAL REGION SURROUNDING THE *Lps* LOCUS. *[1]S. Qureshi, [1]L. Lariviere, [2]G. Sebastiani, [1]S. Clermont, [4]G. Duyk, [4]K. Moore, [1]E. Skamene, [2]P. Gros, [1,3]D. Malo. Departments of [1]Medicine, [2]Biochemistry, [3]Human Genetics, McGill University, Montreal; [4]Millennium Pharmaceuticals, Inc.*

Sepsis syndrome is a leading cause of death among the elderly, immunocompromised, and critically ill. Lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria is the prime initiator of sepsis and septic shock. Through spontaneous mutation, the C3H/HeJ inbred mouse strain exhibits natural tolerance to the lethal effects of purified LPS. C3H/HeJ macrophages are hyporesponsive to *in vitro* challenge with LPS, and do not develop a full activation phenotype. This defect is under the control of a single genetic locus on mouse chromosome 4, designated *Lps*, which exists in two allelic forms, defective (Lps^d) and normal (Lps^n).

We will present a high-resolution linkage map in the region of *Lps*. This has been developed using 1604 informative meioses derived from interspecific and intraspecific backcross mice. The segregation of *Lps* was determined with respect to 50 loci known to map to mid-chromosome 4, including tenascin *(Hxb)*, aminolevulinate dehydratase *(Lv)*, alpha-1-microglobulin/bikunin precursor *(Ambp)*, CD30 antigen ligand *(Cd301)*, interferon-alpha *(Ifa)*, and brown *(b)*, as well as anonymous microdissected probes and microsatellite markers mapping to the same chromosomal region.

96. TO THE POSITIONAL CLONING OF THE *HYBRID STERILITY I* GENE: EVALUATION OF CANDIDATE GENES. *Z. Trachtulec*[*#], *S. Gregorova*[#], *M. Mnukova*[#], *R.M.J. Hamvas*[**], *H. Lehrach*[**], *J. Klein*[*+], *V. Vincek*[*], *J. Forejt*[#]. [*]*University of Miami, Dept. Microbiology and Immunology, Miami, FL;* [#]*Institute of Molecular Genetics, Acad.Sci. Czech Rep., Prague;* [**]*ICRF, London;* [+]*MPI fuer Biologie, Tuebingen.*

Hybrid sterility 1 or *Hst1 is* the major gene responsible for a breakdown in spermatogenesis of hybrids between *Mus musculus* and certain mouse strains. The study of the *Hst1 is* therefore important for understanding both post-mating isolation of closely related species and male fertility. We have mapped the *Hst1* gene on mouse chromosome 17 and cloned the relevant region in a set of overlapping YAC clones. Biotinylated YAC clones have been used for direct selections of cDNAs from testes cDNA libraries. We will present the physical and genetic maps of the cDNA clones from genes of the region and discuss their relevance as candidates for *Hst1*.

97. TOWARDS CLONING OF THE *LETHAL-2* and *HST-1* GENES. *Renata M.T. Hamvas, Zdenek Trachtulec*[1], *Alexandra Shedlovsky*[2], *Monika Mnukova*[3], *James Ripley, Roger D. Cox*[4], *Elaine Levy*[4], *Susan Lewis*[5], *Vladimir Benes, Fiona Frances, Camille S. Connelly*[2], *Sona Gregorova*[3], *Paraj Mandrekar*[2], *Jane Barclay*[6], *Jiri Forejt*[3], *William F. Dove*[2], *Jan Klein*[1], *Peter Little*[6], *Hans Lehrach. Genome Analysis Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London;* [1]*University of Miami School of Medicine, Miami, FL;* [2]*McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, USA;* [3]*Institute of Molecular Genetics, Czech Academy of Sciences, Prague, Czech Republic;* [4]*Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN;* [5]*Research Triangle Park, North Carolina, USA;* [6]*Department of Biochemistry, Imperial College, London SW7 2AZ.*

Lethal-2, *(L(17)2-pas)* has previously been shown to map 0.1cM distal to the *D1766D* cluster of loci on mouse chromosome 17. Homozygous embryos carrying this mutation are grossly disorganised at 7.5 days of gestation and are aborted. The Hybrid sterility locus *(Hst-1)* maps 0.3cM distal to the *D1766D* loci. YAC and P1 clone contigs encompassing the *Sod-2* to *B2A10* interval, that includes both genes, are being assembled. These physical maps have been aligned with genetic maps that are being constructed in parallel. Areas of recombination suppression have been identified in both mouse crosses. The localised repetitive sequence families, D1766D and B2A10 cause high levels of YAC clone instability.

98. MOUSE MODEL FOR DOWN SYNDROME. *M. Davisson[1], C. Schmidt[1], R. Bronson[1], N. Irving[2], T. Moran[2], Cheryl Kitt[2], R. Reeves[2]. [1]The Jackson Laboratory, Bar Harbor, Maine; [2]Johns Hopkins School of Medicine.*

99. THE GENETICS OF OCULAR RETARDATION:MODIFIERS ADD COMPLEXITY TO A SIMPLE RECESSIVE TRAIT. *Sharmila Basu[1,2], Jakub Novak[5], Lynda Ploder[5], Mei-Ying Liang[6], Norman L. Hawes[7], Benjamin Taylor[7], Thomas H. Roderick[7], Daniel Goldman[2,4], Mark H. Hankin[6], Roderick R. McInnes[5], Margit Burmeister[1,2,3]. [1]Mental Health Research Institute and Depts. of [2]Human Genetics, [3]Psychiatry, [4]Biological Chemistry, The University of Michigan, Ann Arbor, MI, USA; [5]Dept. of Genetics, The Hospital for Sick Children, Toronto, Ontario, Canada; [6]Dept. of Anatomy and Neurobiology, Medical College of Ohio, Toledo, OH, USA; [7]The Jackson Laboratory, Bar Harbor, ME, USA.*

100. GENETIC ANALYSIS OF LOCI THAT CAUSE AND MODIFY AUTOSOMAL RECESSIVE POLYCYTICK KIDNEY DISEASE IN THE *jck* MOUSE. *O.A. Iakoubova[1], H. Dushkin[1], J. Serge[2], E. Lander[2], D.R. Beier[1]. [1]Genetics Division, Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [1]Whitehead Institute, MIT, Cambridge, MA.*

101. GENETICALLY COMPLEX LETHAL DEVELOPMENTAL THRESHOLD TRAITS ANALYSIS OF THE SELH/BC EXENCEPHALY BIRTH DEFECT. *T.M. Gunn, D.M. Juriloff, M.J. Harris. Department of Medical Genetics, University of British Columbia, Vancouver, B.C. V6T 1Z3, Canada.*

102. THE FIRST ARCH MUTATION: REFINEMENT OF MAP POSITION AND PROGRESS IN MAPPING OF MAJOR MODIFIER LOCI. *R.T. Dreger, D.M. Juriloff, M.J. Harris. Department of Medical Genetics, University of British Columbia, Vancouver, B.C., V6T 1Z3, Canada.*

103. A MODEL TO UNDERSTAND GENETIC MECHANISMS OF INCOMPLETE PENETRANCE: RENAL AGENESIS/DYSGENESIS OF FOUR DISTINCT LIMB DEFORMITY (*ld*) MUTANTS. *G. Ryan, A. Wynshaw-Boris. Laboratory of Genetic Disease Research, NCHGR, NIH, Bldg 49, room 4A 67, Bethesda, MD 20892-4470.*

104. WHOLE GENOME SEARCHING FOR QUANTITATIVE TRAIT LOCI (QTL) CONTROLLING MURINE GROWTH, BODY COMPOSITION AND REPRODUCTION. *Daniel Pomp[1], Gene Eisen[2]. Department of Animal Science, University of Nebraska[1], Lincoln, NE, USA; North Carolina State University[1], Raleigh, NC, USA.*

105. MAPPING OF TUMOR PROGRESSION SUSCEPTIBILITY GENES IN SENCAR B/PT. *M.C. Stern, C.J. Conti. University of Texas, M.D. Anderson Cancer Center, Science Park - Research Division, Smithville, TX, USA.*

106. THE GENETICS OF SENSITIVITY TO SKIN CARCINOGENESIS IN MICE. *B. Mock, C. Padlan, D. T. Lowry, S. Yuspa, M. Potter, H. Hennings. NCI, NIH, Bethesda, MD 20892-4255, USA.*

107. HISTORY OF THE SL FAMILY MICE. *H. Hiai, P. Abujiang, Y. Yamada, T. Kamoto, K. Kanehira, L.M.Lu. Dept. Pathology and Biology of Diseases, Kyoto University Graduate School of Medicine, Kyoto 606, Japan.*

108. HEPATOCARCINOGEN-SENSITIVITY GENES ACT CELL-AUTONOMOUSLY IN C57BR/cdJ⇔C57BU6J CHIMERIC MICE. *Teresa A. Chiaverotti, Norman R. Drinkwater. McArdle Laboratory for Cancer Research, University of Wisconsin Medical School, Madison, WI 53706.*

109. STRAIN-DEPENDENT VARIATION IN THE FREQUENCY OF *HRAS1* MUTATIONS IN MURINE HEPATOCARCINOGENESIS. *R.A. Carabeo, G.H. Lee*, N.R. Drinkwater, McArdle Lab for Cancer Research, University of Wisconsin Medical School, Madison, WI 53706; *Dept. of Pathology, Asahikawa Medical College, 4-5-3-11, Nishikagura, Asahikawa, Hokkaido 078, Japan*

110. ASSIGNMENT OF Pas (PULMONARY ADENOMA SUSCEPTIBILITY) AND Paht (PULMONARY ADENOMA HISTOGENESIS TYPE) GENES TO CHROMOSOMAL LOCI BY QUANTITATIVE TRAIT LOCUS INTERVAL MAPPING OF THE AXB AND BXA RECOMBINANT INBRED STRAINS. *Al M. Malkinson[1], Steven C. Christensen[2], Lin Lin3, Ming You[3]. School of Pharmacy[1] and Institute For Behavioral Genetics[2], University of Colorado, Denver[1] and Boulder[2], CO; Medical College of Ohio[3], Toledo, OH, USA.*

111. HIGH DENSITY LINKAGE MAPS OF THE SUPPORT INTERVALS ENCODING *Aod1* and *Aod2*: IMMUNOREGULATORY LOCI CONTROLLING SUSCEPTIBILITY TO NEONATAL THYMECTOMY-INDUCED AUTOIMMUNE DISEASE. *J.K. Lunceford, C. Teuscher, Department of Microbiology, Brigham Young University, Provo, UT, USA.*

112. HIGH DENSITY LINKAGE MAPS OF THE SUPPORT INTERVALS ENCODING *Orch3*, *Orch4*, and *Orch5*: THREE NOVEL IMMUNOSUPPRESSION GENES. *R. Paynter, K.D. Livingstone, N.D. Meeker, C. Teuscher.Department of Microbiology, Brigham Young University, Provo, UT, USA.*

113. IDENTIFICATION OF PUTATIVE QTLS IN MRL-*lpr* X B6-*lpr* CROSSES. *A. Osborn, G.S. Gilkeson, R.W. Debry, J.M. Rochelle, P. Ruiz, M.A.Thompson, M.F. Seldin. Duke University, Durham, NC, USA; University of Miami, Miami FL.*

114. GENETIC REGULATION OF AIRWAY HYPERRESPONSIVENESS: EVIDENCE FOR LINKAGE TO MURINE CHROMOSOME 6. *SL Ewart, RC Levitt. Michigan State University, East Lansing, MI 48824; The Johns Hopkins Medical Institutions, Baltimore, MD 21205 USA.*

115. MURINE EAE: IDENTIFICATION OF NEW CLINICAL SUBTYPES AND MAPPING OF DISEASE MODIFYING LOCI. *J.D. Sudweeks[1], E.P. Blankenhorn[2], R. Komgold[3], J.C. Marini[3], J.W. Rose[4], C. Teuscher[1]. [1]Brigham Young Univ., Provo, UT; [2]Hahnemann Univ., Philadelphia, PA; [3]Jefferson Medical College, Philadelphia, PA; [4]Veterans Administration Medical Center, Salt Lake City, UT.*

116. DEVELOPMENTAL VARIATION IN THE DEGREE OF DOMINANCE OF DIABETES *(db)*. *G.E. Truett[1], R.J. Tempelman[2], J.A. Walker[1], P. Xu[1]. [1]Pennington Biomedical Research Center, Baton Rouge, LA 70808; [2]Department of Animal Science, Michigan State University, East Lansing, MI 48824.*

117. INTERACTION OF NON-MHC SUSCEPTIBILITY GENES TO IDDM IN MICE. *Shigeharu Wakana[1)], Yuko Katakai[1)], Toshihiko Shiroishi[2)], Kazuo Moriwaki[3)], Chika Maruyama[4)], Tatsuji Nomura[1)]. 1) Central Institute for Experimental Animals, Kawasaki 216 Japan; 2) National Institute of Genetics, Mishima 411 Japan; 3) Graduate Univ.for Advanced Studies, Hayama 240-01 Japan; 4) DNARD, Kawasaki 216 Japan.*

118. INTRA-MHC RECOMBINANT NOD MICE AT CLASS I K REGION FAILED IN DEVELOPMENT OF TYPE I DIABETES. *T. Toyonaga, M. Hattori, A. McMurray, T. Lund, M. Yoshino, K. Moriwaki, T. Shiroishi. Joslin Diabetes Center, Boston; Whitehead Institute, Cambridge; UCL, London; Natl Institute of Genetics, Mishima.*

119 ANALYSIS OF DIET-INDUCED DIABETES IN RI STRAINS. *R.W. DeBry, A. Petro, Z. Xue, B. Paigen[*], M.F. Seldin, R. Surwit. Duke University, Durham, NC, USA; [*]The Jackson Laboratory, Bar Harbor, ME, USA.*

120. STUDIES OF THE VARIABLE PHENOTYPES OF THE HYPERVARIABLE YELLOW (A^{hvy}) MUTATION AT THE MURINE AGOUTI LOCUS. *A.C. Argeson, K.K. Nelson, L.D. Siracusa. Department of Microbiology and Immunology, Jefferson Cancer Institute, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107-5541.*

121. MOLECULAR CHARACTERIZATION OF MOUSE X CHROMOSOME CONTROLLING ELEMENT *(XCE)* EFFECTS IN (C57BL/6J X *MUS SPRETUS/EI)* FEMALE F1 HYBRIDS. *A.D. Greenwood, M. Southard-Smith, D.T. Burke. Department of Human Genetics, University of Michigan, M4708 Medical Science II, Ann Arbor, MI 48109-0618.*

122. MOUSE MODEL SYSTEMS FOR THE STUDY OF GENES AND AGING. *David T. Burke[+*#], Anne U. Jackson[+], Alison P. Fornes[+], Sasha M. Engle[@], Lisa A. Mullins[@], Richard A. Miller[@*#], Department of Human Genetics[+], Department of Pathology[#], Geriatrics Center[*], Institute of Gerontology[@], University of Michigan, Ann Arbor, MI.*

123. GENETIC CONTROL OF RECOMBINATION IN MICE. *Kerry Schimenti, J. Ramana Murti, Deborah Cooper, John Schimenti. The Jackson Laboratory, Bar Harbor, ME, USA.*

124. IDENTIFICATION OF A QUANTITATIVE TRAIT LOCUS FOR GENERAL ANESTHETIC SENSITIVITY NEAR THE MOUSE ALBINO LOCUS. *B.A. Rikke, B. Bennett, P.D. Markel, V.J. Simpson, D.K. Johnson[*], L. Montoliou[**], T.E. Johnson. Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA, [*]Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA; [**]Department de Bioquimica i de Biologia Molecular, Universitat Autonoma de Barcelona, Barcelona, Spain.*

125. MAPPING QTLs INFLUENCING ETHANOL-INDUCED ANESTHESIA IN LS AND SS MICE: F_2 CONFIRMATION. *B. Bennett, P.D. Markel, M. A. Beeson, L. Gordon, T.E Johnson. Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA.*

126. GENETIC ANALYSIS OF BEHAVIORAL TRAITS USING THE AXB/BXA RI SET. *J.M. Tiller, R.S. Surwit, R.W. DeBry, M.F Seldin. Duke University Medical Center, NC, USA.*

127. GENETIC MAPPING OF QUANTITATIVE TRAIT LOCI ASSOCIATED WITH STRESS REACTIVITY IN THE WISTAR-KYOTO HYPERACTIVE RAT. *Moisan M.P., Courvoisier H., Mormede P. Genetique du Stress et Neurobiologie de l'Adaptation INSERM CJF 94-05-INRA-Universite de Bordeaux II France.*

128. TOWARDS A GENETIC ANALYSIS OF MOUSE TESTICULAR STEROIDOGENESIS. *A.V. Osadchuk, K.V. Svechnikov, Institute of Cytology & Genetics, Novosibirsk, 630090, Russia.*

129. EFFECTS OF MOTOR NEURON DEGENERATION ARE MORE SEVERE IN T~E NZB-ELICITED WOBBLER *(NEW)* MOUSE HYBRID THAN IN THE ORIGINAL C57BL/6J WOBBLER MOUSE. *T. Ishiyama, E.P. Pioro, B. Klinkosz, H. Mitsumoto, Depts of Neurology & Neuroscience, The Cleveland Clinic Foundation, Cleveland, OH 44195.*

98. MOUSE MODEL FOR DOWN SYNDROME. M. *Davisson*[1], *C. Schmidt*[1], *R. Bronson*[1], *N. Irving*[2], *T. Moran*[2], *Cheryl Kitt*[2], *R. Reeves*[2]. [1]*The Jackson Laboratory, Bar Harbor, ME;* [2]*Johns Hopkins School of Medicine.*

At least 18 genes from human Chr 21 (HSA21), which is trisomic in Down Syndrome (DS), are conserved in distal mouse Chr 16 (MMU16). Mice with trisomy for all of MMU16 (Ts16) have been used since the mid 1970s as a model for DS. The model is restricted, however, because mice trisomic for the whole chromosome (1) die before or shortly after birth and (2) are trisomic for genes from other human chromosomes. We have developed an improved mouse model for Down Syndrome, with trisomy for only the distal segment of MMU16 that contains HSA21-homologous genes. Using irradiation, we produced a reciprocal translocation, T(16;17)65Dn, in which the distal end of MMU16 is carried in a small marker chromosome. T/+ females produced progeny trisomic for this small translocation product and a stock was established in which mice are trisomic for the genes carried in the small translocation chromosome, symbolized Ts(17^{16})65Dn. These segmentally trisomic mice are characterized by developmental delay early in life, learning deficits, hyperactivity, hydrocephalus, and tremors. Individual mice may show tissue specific inflammation, such as rhinitis and otitis, kidney cysts, and pelvic dilation. Genetic mapping in somatic cell hybrids shows that the T65Dn translocation breaks MMU16 at the *D16Mit68* locus and contains the HSA21-homologous genes from *App* to qter. Northern and Western blotting and enzyme activity assays demonstrate that genes on the translocation product are expressed at elevated levels in segmentally trisomic animals.

99. THE GENETICS OF *OCULAR RETARDATION*:MODIFIERS ADD COMPLEXITY TO A SIMPLE RECESSIVE TRAIT. *Sharmila Basu*[1,2], *Jakub Novak*[5], *Lynda Ploder*[5], *Mei-Ying Liang*[6], *Norman L. Hawes*[7], *Benjamin Taylor*[7], *Thomas H. Roderick*[7], *Daniel Goldman*[2,4], *Mark H. Hankin*[6], *Roderick R. McInnes*[5], *Margit Burmeister*[1,2,3]. [1]*Mental Health Research Institute and Depts. of* [2]*Human Genetics,* [3]*Psychiatry,* [4]*Biological Chemistry, The University of Michigan, Ann Arbor, MI, USA;* [5]*Dept. of Genetics, The Hospital for Sick Children, Toronto, Ontario, Canada;* [6]*Dept. of Anatomy and Neurobiology, Medical College of Ohio, Toledo, OH, USA;* [7]*The Jackson Laboratory, Bar Harbor, ME, USA.*

Ocular retardation *(or) is* a recessive mutation in the mouse characterized by reduced proliferation and arrested differentiation of retinal precursor cells, resulting in an incompletely developed retina, lack of optic nerve, severe microopthalmia, and corresponding blindness. We genetically mapped the *or* locus and found that it co-segregated with the homeobox-containing gene *Chx10* on Mouse Chromosome 12. DNA sequence analysis of the *Chx10* gene from *or* mice identified a premature stop codon within its homeobox encoding region, indicating that *or* is caused by lack of the *Chx10* protein. Our results imply that *Chx10* plays an important role in retinal differentiation.

Within our backcross, we noticed a modifying effect of the CASA genome on the *or* phenotype where variation in eye size without increase in visual ability was observed in about 40% of the *or* homozygotes. To isolate the modifier loci, we have set up backcross and intercross lines to create congenic and recombinant inbred strains, respectively, of the modified *or* mice; preliminary data indicate the involvement of 2-3 genes. Using a genome scan approach, we are attempting to identify areas of the genome linked to the modifier loci. Since many of the components in retinal development are known, we hope to identify candidate genes in the modifier regions that would likely interact with *Chx10* to partially alleviate the *or* phenotype.

100. GENETIC ANALYSIS OF LOCI THAT CAUSE AND MODIFY AUTOSOMAL RECESSIVE POLYCYTIC KIDNEY DISEASE IN THE *jck* MOUSE.

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We have previously described a new mouse mutation called juvenile cystic kidney (*jck*) which predisposes to the development of autosomal recessive polycystic kidney disease (PKD). We have mapped *jck* to a 0.5 cM region on mouse chromosome 11, near the nude (*nu*) locus, using an intraspecific intercross between C57BL/6J and DBA/2J mice. We have found one microsatellite marker to the very tightly linked to *jck* (no crossovers/1500 meotic events), and are now using cDNA selection of a 1Mb YAC carrying this marker to identify candidate genes for *jck*.

In addition, we have identified two modifiers that mediate the severity of PKD in the *jck* mouse. One of them – DBA/2J-related – has been mapped on chromosome 10, and the second one – C57BL/6J-related – on chromosome 1. We have proposed that the severity of PKD in the *jck* mouse is a result of an interaction between C57BL/6J and DBA/2J modifying genes (*Genomics (1995) 26:107-114*). We have confirmed the localization of these modifying genes using a new intraspecific intercross between C57BL/6J and FVB/N mice in which severity of PKD in F2 *jck* progeny is again markedly more variable than in the original C57BL/6J background.

To localize more precisely the C57BL/6J-related modifier, congenic mice carrying C57BL/6J-derived regions of chromosome 1 on a DBA/2J background were generated. Parental mice with 10 different haplotypes were selected and tested for their association with PKD severity. The result of this analysis suggests the possibility that there may be more than one locus on chromosome 1 that contribute to disease severity. This hypothesis is supported by our previous QTL analysis that showed an association of a large portion of chromosome 1 with increased severity of PKD (with a LOD score greater than 8 for a 70 cM interval). To confirm this hypothesis we are testing a consomic strain carrying a C57BL/6J-derived chromosome 1 on a DBA/2J background.

101. GENETICALLY COMPLEX LETHAL DEVELOPMENTAL THRESHOLD TRAITS ANALYSIS OF THE SELH/BC EXENCEPHALY BIRTH DEFECT.

T.M. Gunn, D.M. Juriloff, M.J. Harris. Department of Medical Genetics, University of British Columbia, Vancouver, B.C. V6T 1Z3, Canada.

Developmental studies have shown that neural tube closure is abnormal in all SELH embryos, and therefore that the exencephalics and ataxics reflect extremes of a distribution of a quantitative variable beyond a critical threshold value. Cranial neural tube closure fails completely in 10-20% resulting in lethal exencephaly, and fails partially in 5-10% resulting in a cleft cerebellum and ataxia. Frequency data from crosses to each of three normal strains indicate that exencephaly in SELH mice is due to the combined action of 2-3 loci, probably with additive effects on risk. Our strategy to map the major loci involved has been to test for non-random distribution of microsatellite alleles in the extreme upper and lower 10% of 100 F2 sires, each testcrossed by 100 progeny, and to compare this result with marker distributions in 31 F2 exencephalic embryos. Preliminary results indicate that relevant loci are located on Chr 13, 10 and 2, and that additive inheritance may cause the typing of testcrossed F2's to be a more powerful approach than direct typing of exencephalics.

102. THE FIRST ARCH MUTATION: REFINEMENT OF MAP POSITION AND PROGRESS IN MAPPING OF MAJOR MODIFIER LOCI. *R.T. Dreger, D.M. Juriloff, M.J. Harris. Department of Medical Genetics, University of British Columbia, Vancouver, B.C., V6T 1Z3, Canada.*

Homozygotes for the First arch mutation (Far) have severe lethal craniofacial defects, confined to the maxillary region of the developing head. Heterozygotes are functionally normal in the BALB/c genetic background, but have a high frequency of severe hemifacial deficiency in the ICR/Bc genetic background. We have used microsatellite polymorphisms to refine the map position of Far, to an approximately 1 cM region linked to the Hoxd cluster on Chromosome 2. We have a large study in progress to determine the number and map position of the major loci that modify Far dominance. Individual first backcross males are being typed for frequency of hemifacial deficiency among 100 progeny each and for parental alleles at microsatellite markers, beginning with the three paralogous Hox-containing regions, on Chr 6, 11, and 15. Preliminary frequency data suggest the presence of two major modifier loci. Preliminary mapping data show a non-Mendelian segregation pattern for the Chr 6 and Chr 15 regions among affected heterozygotes. Current data will be presented.

103. A MODEL TO UNDERSTAND GENETIC MECHANISMS OF INCOMPLETE PENETRANCE: RENAL AGENESIS/DYSGENESIS OF FOUR DISTINCT LIMB DEFORMITY *(ld)* MUTANTS. *G. Ryan, A. Wynshaw-Boris. Laboratory of Genetic Disease Research, NCHGR, NIH, Bldg 49, room 4A 67, Bethesda, MD 20892-4470.*

The limb deformity locus, *ld*, was originally identified in mice as an autosomal recessive syndrome consisting of completely penetrant reduction and fusion anomalies of the long bones and digits of all four limbs, and incompletely penetrant renal agenesis/dysgenesis. Several alleles of *ld* mutations have arisen on different genetic backgrounds, three of which are ld^{Bri}, ld^{In2}, and *ldJ*. The ld^{Bri} and ld^{In2} mutants have a 20-30% penetrance of renal abnormalities, whereas the *ldJ* mutants have a 98% penetrance. The *ld* gene encodes four alternatively-spliced isoforms (I-IV). Isoform IV null mice (ld^{G}) have been generated by gene targeting. The limb and kidney phenotypes were separated in the null mice. ld^{G}/ld^{G} mice have a 6% incidence of renal agenesis, yet have perfectly normal limbs. We aim to determine whether the variability of the penetrance of the renal phenotype of the various *ld* mutants is allele-specific, background-specific or both. We have generated various combinations of compound *ld* heterozygotes that have been mated. The F2 offspring have been scored for limb and renal abnormalities. Our preliminary results indicate that the renal agenesis/dysgenesis phenotype correlates with the *ld* allele and not the genetic background.

104. WHOLE GENOME SEARCHING FOR QUANTITATIVE TRAIT LOCI (QTL) CONTROLLING MURINE GROWTH, BODY COMPOSITION AND REPRODUCTION.

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We have created large populations of mice segregating for identifiable marker genotypes and for alleles controlling growth, body composition and reproduction, in order to identify autosomal regions harboring QTL for these traits. Cross 1 (backcross; n=420) was between the inbred lines M16i (long-term selection for rapid weight gain; large body size, obese, high fecundity) and Cast/Ei (wild origin; small, lean). Growth rates and body composition were evaluated. Cross 2 (intercross; n=1,000) was between M16i and L6 (long-term selection for low 6 wk body weight; very small, low fecundity). Growth rates, body composition (males) and reproduction (females) were evaluated. Genotypes were determined at 3-4 evenly spaced microsatellite markers per autosome using PCR and agarose gels. Mixed-model analysis of variance procedures were used to identify markers linked to QTL and their relative effects. Many highly significant markers indicating the presence of QTL were identified in each cross for all traits studied. In general, individual QTL had greatest effect on body fat percentage (4-7% variance explained) followed by body weight (3-5%), while effects on ovulation rate and litter size were smaller (1-3%). One marker on distal chromosome 2 indicated the presence of a QTL with much greater effect on fat and weight (15-20% variance explained). Genotyping of 18 additional chromosome 2 markers, including PCR-RFLPs developed within the candidate loci agouti and GHRH, localized two closely linked QTL with major effect on growth and body composition.

105. MAPPING OF TUMOR PROGRESSION SUSCEPTIBILITY GENES IN SENCAR B/PT.

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The outbred stock of SENCAR mice has been a useful tool in the study of the mechanisms involved in multi stage carcinogenesis, given its high sensitivity to the two-stage protocol. However, the outbred condition represents a disadvantage at the time of making genetic studies. In this sense, several different inbred strains have been derived from the outbred SENCAR gene. One of them, the SSIN, resulted to be more sensitive to the two-stage carcinogenesis protocol, developing a higher number of papillomas per mouse than the SENCAR, under the same doses of DMBA and TPA. Further studies focused on the progression stage, showed that even though the SSIN mice develop a higher number of papillomas per mice, the lesions rarely progress to Squamous Cell Carcinomas (SCC). These results suggested that during the selection and inbreeding of the SSIN mice, the gene or genes involved in the susceptibility to tumor promotion, were dissociated from the ones involved in tumor progression. Another line derived from the SENCAR stock, SENCAR B/Pt, showed a promotion susceptibility number similar to the SSIN mice but these mice have a SCC incidence similar or higher to the SENCAR outbred. Previous studies that we carried out using the outbred SENCAR have suggested the presence of at least one susceptibility gene involved in tumor progression.

In order to define a genetic model of the progression susceptibility, and to map the putative susceptibility genes we are currently studying the susceptibility of F1, F2 and backcrossed mice between SSIN and SENCAR B/Pt. We have already identified several polymorphic microsatellite markers among both strains and we are analyzing the segregation of these markers in susceptible and resistant F2 and backcrossed mice.

106. THE GENETICS OF SENSITIVITY TO SKIN CARCINOGENESIS IN MICE. *B. Mock, C. Padlan, D. T. Lowry, S. Yuspa, M. Potter, H. Hennings. NCI, NIH, Bethesda, MD 20892-4255, USA.*

Inbred SENCAR A/Pt mice are sensitive to the induction of both papillomas and carcinomas. Initiation of SENCAR A/Pt mice with 2 ug 7,12-dimethylbenz[a]anthracene (DMBA) and promotion by 2 ug 12-O-tetradecanoylphorbol-13-acetate (TPA) for 20 weeks induced 16.5 papillomas/mouse and squamous cell carcinomas in 15 of 20 mice. In contrast, resistant BALB/cAnPt mice treated by the same protocol did not develop tumors. The F1 hybrid between SENCAR A/Pt males and BALB/cAnPt mice treated by the same protocol developed only 0.41 papillomas/mouse and no carcinomas; thus, resistance is dominant in the F1 hybrid. Fewer than half of the backcross progeny from the cross (BALB/cAnPt x SENCAR A/Pt)F1 x SENCAR A/Pt were sensitive to tumor initiation and promotion suggesting that sensitivity to skin carcinogenesis is a complex genetic trait. Preliminary linkage analyses suggest that genes on Chrs 5, 8 and 9 may contribute to the Sencar strain's sensitivity to tumor promotion.

107. HISTORY OF THE SL FAMILY MICE. *H. Hiai, P. Abujiang, Y. Yamada, T. Kamoto, K. Kanehira, L.M.Lu. Dept. Pathology and Biology of Diseases, Kyoto University Graduate School of Medicine, Kyoto 606, Japan.*

The SL is a family of inbred mouse strains derived from an original SL stock with high spontaneous leukemia incidence. The SL family members, SL/Am, SL/Ni, SL/Kh and SL/Qdj, show distinct biological and genetical properties. SL/Kh develop acute pre-B lymphomas at a high incidence by 6 months of age, while SL/Am develop either follicular center cell type lymphomas or myeloid leukemia much later in life. SL/Ni and SL/Qdj rarely develop lymphomas. We analyzed genetic markers of 4 SL members and related strains. Data on microsatellites, endogenous MuLV, MTV and Mx gene indicate that (1) SL/Am and SL/Ni were very close if not identical, (2) SL/Kh probably derived from a cross between SL/Am and AKR. Host genes determining susceptibility to lymphomas, *Esl-1*, *foc-1*, *Tlsm-1* and *MHC* will be discussed. *(Supported by Grants-in-Aid from MECS, Japan.)*

108. HEPATOCARCINOGEN-SENSITIVITY GENES ACT CELL-AUTONOMOUSLY IN C57BR/cdJ⇔C57BU6J CHIMERIC MICE.

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Female C57BR/cdJ (BR) mice are more sensitive to chemically-induced hepatocarcinogenesis than females of any other inbred strain, while male BR mice are intermediate among strains in their sensitivity; C57B/6J (B6) males and females are both relatively resistant. Two loci have been identified in a BRB6F_1 x B6 backcross and BRB6F_2 intercross that account for the sensitivity of BR mice to hepatocarcinogenesis. To determine whether these loci act at the level of the target hepatocyte, we analyzed liver tumors from BR↔B6 chimeric mice. Chimeras were treated at 12 days of age with a single dose of N,N-diethylnitrosamine (DEN) and individual tumors were dissected at 32 weeks and 50 weeks for males and females, respectively. PCR analysis using simple sequence repeat markers was used to determine the origin of each tumor. The majority of liver tumors analyzed to date originated from BR hepatocytes, indicating that BR hepatocarcinogen-sensitivity genes act cell-autonomously.

109. PRECISION MAPPING OF *Scc1*, ONE OF THE MULTIPLE GENES CONTROLLING COLON CANCER SUSCEPTIBILITY.

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Susceptibility to DMH induced colon tumours in the mouse is controlled by multiple genes. We use the CcS/Dem Recombinant Congenic Strain genes to dissect this multigenic trait. Analysis of the susceptibility of strains CcS-17 and CcS-19, and {BALB/cHeA x (BALB/cHeA x CcS-19)} backcross-1 mice, revealed that a susceptibility locus, *Scc1*, is located in a ± 30 cM region on chromosome 2. Subsequently, 39 recombinant haplotypes within this 30 cM region were selected and tested. LOD score analysis showed that *Scc1* is located in the ±7.7 cM region between D2Mit9 and D2Nkl1 (99% confidence interval). To further narrow down the *Scc1* map position, we produced 42 recombinants in the 7.7 cM region. Tests of 15 of these recombinant haplotypes locate *Scc1* in a region ± 0.15 cM. We are selecting and testing further recombinants in order to confirm and improve this very precise mapping. The accurate mapping of Scc1 demonstrates that it is a distinct genetic entity unambiguously linked to the phenotype. A YAC-contig covering the ± 5 cM region between D2Mit75 and D2Mit13 has been constructed from a C57BL/6 YAC-library of the MIT. This contig is being used to make a detailed physical map of the 0.15 cM region encompassing *Scc1*, and to obtain new simple sequence repeats in the *Scc1* region.

110. ASSIGNMENT OF *Pas* (PULMONARY ADENOMA SUSCEPTIBILITY) AND *Paht* (PULMONARY ADENOMA HISTOGENESIS TYPE) GENES TO CHROMOSOMAL LOCI BY QUANTITATIVE TRAIT LOCUS INTERVAL MAPPING OF THE AXB AND BXA RECOMBINANT INBRED STRAINS. *Al M. Malkinson[1], Steven C. Christensen[2], Lin Lin3, Ming You[3]. School of Pharmacy[1] and Institute For Behavioral Genetics[2], University of Colorado, Denver[1] and Boulder[2], CO; Medical College of Ohio[3], Toledo, OH, USA.*

The *Pas* genes that regulate susceptibility to lung tumor formation and the *Paht* genes that determine lung tumor structure were assigned chromosomal locations by allelotyping 135 markers spanning the entire genome. The *Pas* (tumor multiplicity in response to a single urethane injection) and *Paht* (percentage of these lung tumors with a solid, as opposed to a papillary, structure) phenotypes of the AXB and BXA strains derived from A/J and C57Bl/6J progenitors had been determined previously. Five provisional *Pas* loci with degrees of assigned significance ranging from $p < 0.0005$ to $p < 0.02$ and seven provisional *Paht* loci ($p < 0.005$ to $p < 0.05$) were detected. Three of these same *Pas* sites were previously elucidated by other mapping strategies; the *Paht* genes have never heretofore been mapped. Candidate genes at these sites are suggested for future concordance studies. *(Supported by ES02370.)*

111. HIGH DENSITY LINKAGE MAPS OF THE SUPPORT INTERVALS ENCODING *Aod1* and *Aod2*: IMMUNOREGULATORY LOCI CONTROLLING SUSCEPTIBILITY TO NEONATAL THYMECTOMY-NDUCED AUTOIMMUNE DISEASE. *J.K. Lunceford, C. Teuscher. Department of Microbiology, Brigham Young University, Provo, UT, USA.*

Neonatal mice thymectomized at three days of age develop, during adulthood, a variety of organ-specific autoimmune diseases including autoimmune ovarian dysgenesis (AOD). AOD is characterized by the development of anti-ovarian autoantibodies, oophoritis, and atrophy. Temporally, atrophy is observed during and following the regression of inflammatory infiltrates from the ovary. Histologically, atrophy appears as areas devoid of ovarian follicles in all stages of development that have been replaced by luteinized interstitial cells. The development of anti-oocyte autoantibodies as well as oophoritis is controlled by *Aod1* which maps to chromosome 16 *(PNAS 92:4758, 1995).* In contrast, *Aod2*, the locus controlling the development of atrophy maps to chromosome 3 within a region encoding *Il2* and *Fgfb*. Most significant, however, is the observation that *Aod2* maps within the same maximum support interval as *Idd3*, a susceptibility gene which plays a role in autoimmune insulin-dependent type 1 diabetes mellitus (IDDM) in the NOD mouse. Our results support the concept that two classes of autoimmune disease susceptibility loci may exist: Those that play a role in multiple autoimmune diseases and those that are disease specific. *(Supported by NIH HD27275).*

112. HIGH DENSITY LINKAGE MAPS OF THE SUPPORT INTERVALS ENCODING *Orch3*, *Orch4*, and *Orch5*: THREE NOVEL IMMUNOSUPPRESSION GENES. *R. Paynter, K.D. Livingstone, N.D. Meeker, C. Teuscher. Department of Microbiology, Brigham Young University, Provo, UT, USA.*

Experimental allergic orchitis is an organ-specific autoimmune disease which can be induced in mice by active immunization with autologous or homologous mouse testicular homogenate in conjunction with complete Freund's adjuvant and pertussis toxin. Previously, we identified three novel immunoregulatory genes which control dominant resistance to autoimmune orchitis *(PNAS* 92:5684, 1995). *Orch3* maps to chromosome 11, whereas *Orch4* and *Orch5* map to the telomeric and centromeric regions of chromosome 1, respectively. Of particular immunologic significance is the observation that *Orch3* and *Orch5* map near *Idd4* and *Idd5*, respectively. These results suggest that certain autoimmune disease modifying genes may play a role in multiple diseases. In order to more precisely map *Orch3*, 4, and 5, we generated high density linkage maps of the support intervals encoding the three loci. Our results indicate that the most likely physical positions of *Orch3* and *Orch5* are within the maximum support intervals encoding *Idd4* and *Idd5*, and that they may, in fact, be the same genes. *(Supported by NIH HD2 1926.)*

113. IDENTIFICATION OF PUTATIVE QTLS IN MRL-*lpr* X B6-*lpr* CROSSES. *A. Osborn, G.S. Gilkeson, R.W. DeBry, J.M. Rochelle, P. Ruiz, M.A.Thompson, M.F. Seldin. Duke University, Durham, NC, USA and University of Miami, Miami FL.*

MRL-*lpr* mice develop autoimmune disease with features of both SLE and RA. Crosses with other strains indicate that immune complex nephritis, inflammatory synovitis, and lymphadenopathy are dependent both on the Fas apoptosis mutation *(lpr)* and background genes. These background gene contribution was evaluated by a QTL analysis of 138 (MRL-*lpr* x B6-*lpr*)F2 intercross mice. Mice were typed for 100 chromosomal markers that divided approximately 90% of the genome in to 20 cM intervals. Quantitative indices and estimated genetic variances ($V_G=V_T-V_E/V_T$) were determined for: nephritis, 0.60; synovitis, 0.46; lymphoid mass, 0.60; αssDNA,0.77; αdsDNA,0.56; IgMRF, 0.41. Putative QTLs were identified for several of the phenotypes using the MAPMAKER/QTL program:

Phenotype	*Marker/Chromosome*	*LOD*	*VG*	*Relative Gene Effect*		
				MM	*MB*	*BB*
Nephritis (female)	*D10Mit42* middle Chr 10	2.8	28	.57	.58	.30
Synovitis	*D3Mit38* distal Chr 3	3.0	28	.40	.19	.25
	D11Mit41 middle Chr 11	3 .2	34	.14	.34	.16
Lymphoid Mass	*D13Mit8* middle Chr 13	4.2	28	.67	.49	.44
anti-ssDNA	*D4Mit12* distal Chr 4	3.5	18	.74	1.11	1.14
IgM RF	*D4Mit12* distal Chr 4	4.4	39	.38	.58	.93
	D7Nds5 proximal Chr 7	3.1	36	.82	.57	.43

Of note, QTLs were not associated with the MHC, TCRB or loci suggested by previous studies using other MRL-*lpr* crosses. The current data provide new insight in to the complex genetic interactions underlying generalized autoimmune disease manifestions.

114. GENETIC REGULATION OF AIRWAY HYPERRESPONSIVENESS: EVIDENCE FOR LINKAGE TO MURINE CHROMOSOME 6. *SL Ewart, RC Levitt. Michigan State University, East Lansing, MI 48824; The Johns Hopkins Medical Institutions, Baltimore, MD 21205 USA.*

Airway hyperresponsiveness (AHR) is an essential feature of asthma and other obstructive pulmonary disorders. A genetic predisposition for AHR to a variety of stimuli can be demonstrated in humans and in many animal models. To investigate the mechanisms of AHR we have designed a study to localize and identify the genes which de.ermine this phenotype in a murine model. We have previously described a model in which acetylcholine (ACh)-induced AHR segregates with up to four loci in the C3H/HeJ and A/J mouse strains. These strains are characterized as hyporesponsive (C3H/HeJ) and hyperresponsive (A/J) based on a six fold difference in AHR following ACh challenge. Studies were performed in C3H/HeJ, A/J and [(C3H/HeJ x A/J) x A/J] backcross mice. The time-integrated change in peak inspiratory pressure, termed the airway pressure time index (APTI), following a single iv bolus of ACh (50 μg/kg) was characterized in 196 [(C3H/HeJ x A/J) x A/J] mice and genomic DNA was isolated for genotypic analysis from 21 hyporesponsive and 21 hyperresponsive animals. A genome screen was conducted at approximately 20 cM intervals with 94 simple sequence repeat (SSR) DNA markers which varied in C3H/HeJ and A/J mice using the polymerase chain reaction (PCR). Quantitative trait locus (QTL) linkage analysis comparing airway responsiveness phenotypes and marker genotypes was performed using MAPMAKER/QTL. One QTL was detected on chromosome 6 with a maximum lod score of 3.11 achieved in the interval spanning the markers *D6Mit62* and *D6Mit13*. These results refine our understanding of the genetic regulation of cholinergic-mediated airway responsiveness in mice and can be used to facilitate similar linkage studies of human asthma. *(NIH RR00097.)*

115. MURINE EAE: IDENTIFICATION OF NEW CLINICAL SUBTYPES AND MAPPING OF DISEASE MODIFYING LOCI. *J.D. Sudweeks[1], E.P. Blankenhorn[2], R. Komgold[3], J.C. Marini[3], J.W. Rose[4], C. Teuscher[1]. [1]Brigham Young Univ., Provo, UT; [2]Hahnemann Univ., Philadelphia, PA; [3]Jefferson Medical College, Philadelphia, PA; [4]Veterans Administration Medical Center, Salt Lake City, UT.*

Experimental allergic encephalomyelitis (EAE) is the principal animal model of multiple sclerosis (MS). The clinical course of murine EAE is usually described as either an acute or relapsing disease. In contrast, the clinical spectrum of MS is characterized by several different phenotypes not usually seen in murine EAE, raising concerns about the clinical validity of EAE as a model for MS. During the generation of a large, segregating F2 population derived from EAE-susceptible SJL/J and EAE-resistant B10.S/DvTe inbred lines we identified four clinical courses of murine EAE which parallel those observed in MS. These clinical subtypes include acute progressive (AP) EAE which appears to be analogous to acute disseminated sclerosis; chronic nonremitting (CNR) EAE corresponding to primary progressive MS; remitting/relapsing (R/R) EAE equivalent to remitting/relapsing MS; remitting/non-relapsing (RNR) EAE which is analogous to benign MS. Histopathologic analyses of spinal cord, brain stem, cerebellum, and cerebrum sections revealed pathology differences between AP and the other disease types in the spinal cord and a difference in cerebral pathology between AP and the remitting forms of EAE. Preliminary mapping data indicates linkage of overall EAE susceptibility to chromosomes 3, 5, 7, 15 and 18 ($p \leq 0.005$). In addition, the different clinical subtypes exhibited linkage to other regions of the genome. *(Supported by NMS RG2659A1/2.)*

116. DEVELOPMENTAL VARIATION IN THE DEGREE OF DOMINANCE OF DIABETES *(db)*. *G.E. Truett[1], R.J. Tempelman[2], J.A. Walker[1], P. Xu[1]. [1]Pennington Biomedical Research Center, Baton Rouge, LA 70808; [2]Department of Animal Science, Michigan State University, East Lansing, MI 48824.*

The rat mutant fatty (*fa*) and the mouse mutant diabetes (*db*), which are likely to be homologs, are classified as recessive alleles under qualitative descriptions of genetic dominance. However, studies on the early development of obesity in rat populations segregating *fa* have revealed remarkable variation in the degree of *fa* dominance; the degree of *fa* dominance on body weight, for example, is high for the first three weeks of life and rapidly decreases at sex-specific ages, day 20 for females and day 22 for males. The purpose of this project is to determine whether *db* dominance also varies over early development.

Pbrc:C57BL/6J *m db* mice were produced in our colony. They were marked and weighed daily from day 4 of life to day 70. Genotypes were scored as +/+ if mice had the misty coat color, as *db*/+ if they were black and lean, and *db*/*db* if they were black and obese. The effect of *db* genotype on body weight was estimated under a mixed linear model incorporating litter as a random factor and sex and *db* genotype as fixed factors. *db* genotype effects were statistically detectable on every day of observation. The degree of *db* dominance was consistently very high during the first three weeks of life, and rapidly decreased after day 20. The mutant effect increased steadily over early development, while the heterozygote effect increased until the end of the third week of life, then decreased thereafter. This analysis confirms that there is considerable variation in the degree of *db* dominance over early development. The marked change in dominance that begins at the end of the third week of life is likely to be mediated by specific physiologic mechanisms. *(Supported by National Institutes of Health Grant DK 48233.)*

117. INTERACTION OF NON-MHC SUSCEPTIBILITY GENES TO IDDM IN MICE. *Shigeharu Wakana[1)], Yuko Katakai[1)], Toshihiko Shiroishi[2)], Kazuo Moriwaki[3)], Chika Maruyama[4)], Tatsuji Nomura[1)]. 1) Central Institute for Experimental Animals, Kawasaki 216 Japan; 2) National Institute of Genetics, Mishima 411 Japan; 3) Graduate Univ.for Advanced Studies, Hayama 240-01 Japan 4) DNARD, Kawasaki 216 Japan.*

The NOD mouse is a widely used animal model for insulin-dependent diabetes mellitus (IDDM). At least fifteen susceptibility genes to IDDM, named *Idd* genes, have been reported *(J.A.Todd et al 1991, S. Ghosh et al 1993)*. In order to investigate the function of the *Idd-3* and *Idd-4* genes, located on chromosomes 3 and 11, without the influence of other susceptibility genes to diabetes, we have established two congenic strains for the *Idd*-3 and *Idd-4* genes by introducing the chromosomal segments from a Japanese wild mouse-derived MSM strain into the genetic background of NOD mice. At present, the backcrosses have reached the 12th generation. The NOD.*Idd*-3^{MSM} congenic mice showed a reduced level of IDDM. On the other hand, the incidence of diabetes and insulitis in the NOD.*Idd4*^{MSM} congenic mice was not lower than that in NOD mice. We produced a "Double Congenic Strain" with MSM alleles at both *Idd*-3 and *Idd-4* loci. All double congenic mice NOD/Shi *Idd*-$3^{NOD/MSM}$, *Idd*-$4^{NOD/MSM}$ surprisingly developed more severe insulitis by the age of 6 months. The *Idd*-4^{MSM} gene seemed to result in more rapidly progressive insulitis than the *Idd*-4^{NOD} gene under the presence of *Idd*-3^{MSM} allele. This result confirmed the presence of the susceptibility genes to IDDM, which are located on chromosomes 3 and 11, and suggested that the function of these genes is cooperative in the development of diabetes.

118. INTRA-MHC RECOMBINANT NOD MICE AT CLASS I K REGION FAILED IN DEVELOPMENT OF TYPE I DIABETES.

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To localize the responsible MHC region for diabetes in the NOD mouse (MHC: H-2g^7), intra-MHC recombinant NOD mice were established by introducing a recombinational hot spot from B10.A(R209) mice (H-2r^{209}: wm7, k, k and d at K, I-A, I-E and D, respectively) into NOD mice. The B10.A (R209) mouse has a hot spot that causes intra-MHC recombinations between MHC class I-K and class II I-A region. The backcross (BC) 3 heterozygous mice (H-2r^{209}/g^7 at K or at I-A, I-E and D regions) were intercrossed and typed for MHC haplotypes. The incidence of diabetes and insulitis in the N4 intercross mice at 10 months of age is listed below.

MHC		*Diabetes*			*Insulitis*
K	*A - D*	*Female*	*Male*	*Total*	*(%)*
g7/g7	g7/g7	7/10	4/10	11/20	78/109(72)
g7/r209	g7/g7	1/5	0/5	1/10*	20/172(12)
r209/r209	g7/g7	0/5	0/4	0/9*	17/186 (9)
g7/g7	g7/r209	0/5	0/5	0/10*	59/248(24)
g7/g7	r209/r2D9	0/5	0/5	0/10*	15/173 (9)

*vs. MHC: g7/g7 at K and A-D, P<O.OS (X^2 test, corrected), P=0.0002 (Log-Rank test)

The parental BC1 and N4 intra-MHC recombinant animals showed a recombinational site at Lmp-2 that is proximal side to Tap-1 gene. The results suggest that a gene between K and Lmp-2 is important for diabetes in addition to the MHC class II.

119. ANALYSIS OF DIET-INDUCED DIABETES IN RI STRAINS.

R.W. DeBry, A. Petro, Z. Xue, B. Paigen, M.F. Seldin, R. Surwit. Duke University, Durham, NC, USA; *The Jackson Laboratory, Bar Harbor, ME, USA.*

When fed a high fat, simple carbohydrate diet, B/6J mice develop a phenotype similar to human type 2 (non-insulin dependent) diabetes mellitus. Crosses between B/6J and diabetes-resistant A/J mice showed that diabetes susceptibility is controlled by a small number of recessive genes. Based on strain distribution patterns in several AXB and BXA recombinant-inbred (RI) strains, muscle glycogen synthase (*Gys*, Chr 7) was suggested as a candidate locus for hyperglycemia, while a more distal Chr 7 locus was suggested for hyperinsulinemia. We have cloned the mouse *Gys* gene, and found it to be identical in sequence between A/J and B/6J mice. Further, *Gys* expression is similar in the two strains, thus excluding *Gys*. To further analyze this model, we have extended our analysis of AXB and BXA RI strains to include more strains (30), and to use a QTL approach. Both phenotypes (insulin and glucose) give high x^2 values (27.8 and 14.4) at Chr 7 positions similar to the previously suggested position for hyperinsulinemia. To assess the statistical significance of the these x^2 values, we randomly permuted the phenotype data 500 times each and looked for QTL associations in each of the permuted datasets. For insulin, none of the permuted data sets included a x^2 value as high as 27.8, indicating that the linkage in the original data is indeed significant. For glucose, the observed x^2 of 14.4 was exceeded in about 16% of the permutations. Recombinant congenic strains and progeny testing of backcross mice are being analyzed to confirm and extend these findings.

120. STUDIES OF THE VARIABLE PHENOTYPES OF THE HYPERVARIABLE YELLOW (A^{hvy}) MUTATION AT THE MURINE AGOUTI LOCUS.

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The protein product of the murine agouti locus regulates a switch in pigment synthesis from eumelanin (black or brown pigment) to phaeomelanin (yellow or red pigment) by hair bulb melanocytes. The many alleles at the agouti locus produce mice ranging in color from yellow to black. The A^{hvy} mutation is responsible for the largest range of phenotypes yet identified at the agouti locus, producing mice that are obese with yellow coats to mice that are of normal weight with black coats. Northern blot analysis has shown that agouti gene expression is altered both temporally and spatially in A^{hvy} mutants; however the transcript size appears unchanged. Expression levels are positively correlated with the degree of yellow pigmentation and the degree of obesity in A^{hvy} mice, consistent with results from other dominant yellow mutations. Sequencing of 5′ RACE clones revealed that A^{hvy} resulted from the integration of an intracisternal A-particle (IAP) in an antisense orientation within a 5′ untranslated hair cycle-specific exon. We postulate that an enhancer and/or cryptic promoter within the LTR of the IAP is usurping control of the agouti gene in A^{hvy} mice. We are attempting to identify loci that influence the variability of A^{hvy} phenotypes through the use of genetic crosses and to determine if the material environment is a factor. *(Research supported by NIH grant DK45717 to LDS and NRSA 5T32CA09678 to ACA.)*

121. MOLECULAR CHARACTERIZATION OF MOUSE X CHROMOSOME CONTROLLING ELEMENT *(XCE)* EFFECTS IN (C57BL/6J X *MUS SPRETUS/EI)* FEMALE F1 HYBRIDS.

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Different alleles of the X chromosome controlling element *(Xce)* can influence random X inactivation in female mice such that it deviates significantly from a predicted 1:1 ratio. Coat color markers, vibrissa counts, and Pgk-1 protein polymorphisms have been used to infer different alleles at the *Xce* locus. This study uses RNase protection and quantitative single nucleotide primer extension (SNuPE) to analyze the effects of different *Xce* alleles in (C57BL/6J x *Mus spretus/Ei)* F1 hybrid females mice at the level of transcription. The X linked genes Otc, Mo^{blo}, and Hprt are examined for differential response to Xce alleles, variance between animals, and the influence of age on this phenomenon.

122. MOUSE MODEL SYSTEMS FOR THE STUDY OF GENES AND AGING. *David T. Burke[+*#], Anne U. Jackson[+], Alison P. Fornes[+], Sasha M. Engle[@], Lisa A. Mullins[@], Richard A. Miller[@*#]. Department of Human Genetics[+], Department of Pathology[#], Geriatrics Center[*], Institute of Gerontology[@], University of Michigan, Ann Arbor, MI.*

We are developing a genetically heterogeneous (HET) mouse resource for experimental gerontology. The HET mice are the product of a four-way cross of common inbred mouse lines, ie [BALB/cJ X C57BL/6J] F1 hybrid females mated to [C3H/He/J X DBA/2J] F1 hybrid males. These mice serve as an artificial population whose members are genetically unique but are derived from well-defined genetic sources. Consequently, the strain of origin for both chromosomal copies can be determined unambiguously by DNA typing at any polymorphic locus. Experimental power is gained by the reproducibility of the HET mouse population since new members can be generated at any time from pure inbred grandparental lines.

An initial cohort of 200 HET animals has been generated and maintained in a specific pathogen-free facility. Phenotypic data is being gathered as the mice age, including memory and helper T cell counts, bodyweight, cancer incidence, and life span. Each HET animal is being genotyped at simple sequence polymorphism loci distributed at approximately 20 cM intervals throughout the genome. Analysis of variance and interval mapping are being performed to identify regions of the genome which contain potential quantitative trait loci contributing to the observed phenotype. The HET genotype and phenotype data will be used to derive mouse lines having delayed reproductive effort and possible extended life spans.

123. GENETIC CONTROL OF RECOMBINATION IN MICE. *Kerry Schimenti, J. Ramana Murti, Deborah Cooper, John Schimenti. The Jackson Laboratory, Bar Harbor, ME, USA.*

In previous work, we devised a transgenic mouse strategy to visualize gene conversion events by histochemical staining of spermatids. Particular gene conversions of the transgene template produced *lacZ*- positive gametes. Up to 1% of spermatids were found to have undergone intrachromosomal gene conversion. Ectopic conversion between unlinked trangenes was also observed at rates between 0.1-0.7% of spermatids. PCR amplification of the *lacZ* - positive spermatids confirmed the planned sequence transfers.

The original studies were performed in a random bred background of mice. Upon breeding of the transgenes into the C57BL/6J background, intrachromosomal rates decreased dramatically to under 0.01%. Transgenic mice that were congenic on this background were then crossed to several other inbred strains. Preliminary data indicates that while the conversion rate in F1 animals remained low, about 1/4 N2 progeny in the 129/J background displayed a 10 fold increase. Breeding analyses are continuing to investigate the number of genes involved in this apparent regulation of illegitimate recombination. Potential epigenetic mechanisms for the phenomenon, such as methylation, are also being evaluated.

124. IDENTIFICATION OF A QUANTITATIVE TRAIT LOCUS FOR GENERAL ANESTHETIC SENSITIVITY NEAR THE MOUSE ALBINO LOCUS. *B.A. Rikke, B. Bennett, P.D. Markel, V.J. Simpson, D.K. Johnson*, L. Montoliou**, T.E. Johnson. Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA, *Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA; **Department de Bioquimica i de Biologia Molecular, Universitat Autonoma de Barcelona, Barcelona, Spain.*

A quantitative trait locus (QTL) that appears to influence sleep-times induced by the general anesthetics ethanol, enflurane, isoflurane, and propofol was identified near the mouse albino locus (tyrosinase gene) by association and interval mapping of recombinant inbreds. Heterogeneous stock allele association and interval mapping of F2s are being used to confirm the QTL. To support positional cloning, a high resolution genetic map of the mouse albino region is being developed using the European Backcross Panel and a panel of 22 albino-locus deletion mutants. The combined deficiencies cover a 6-11 cM region encompassing the QTL. The extent of each deficiency was mapped using 19 MIT simple-sequence length polymorphism (SSLP) markers. Two deletion mutants with overlapping deficiencies are being crossed with short-sleep and long-sleep recombinant inbreds to localize the QTL to either the left, right, or central portion of the deficiency region. Two or three additional mutants will then be used to further define the QTL target region. Approximately fifty different yeast artificial chromosomes from the MIT/Whitehead C57BL/6 library have also been identified using the SSLP markers to provide a framework for physical mapping. Transgenic and coisogenic strains are being used to test whether the tyrosinase gene is the QTL.

125. MAPPING QTLs INFLUENCING ETHANOL-INDUCED ANESTHESIA IN LS AND SS MICE: F_2 CONFIRMATION. *B. Bennett, P.D. Markel, M. A. Beeson, L. Gordon, T.E Johnson, Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA.*

We have used a multi-stage strategy (Johnson et *al., Behavior Genetics* 22: 635-653) to map quantitative trait loci (QTLs) for ethanol-induced anesthesia (sleep time) in the LS and SS selected lines of mice. The first stage identified molecular markers polymorphic between the LS and SS lines. In the second stage, 129 of these polymorphic markers were characterized in the 27 LSXSS recombinant inbred strains. Eleven provisional QTLs emerged with uncorrected p values of 0.1 or lower. In the third and final stage of mapping, we used 186 F_2 animals from an ILSxISS cross to confirm the provisional QTLs. These animals were selected as the extremes of the sleep time phenotype. Two of the highly significant markers ($p<0.001$) from the RI map (on chromosomes 1 and 2) were confirmed. On chromosome 1, at approximately 47 cM, the QTL had a LOD of 4.14, explaining 7.7% of the F_2 variance. The QTL on chromosome 2 occurs at approximately 85 cM with a LOD score of 6.8, explaining 15.6% of the F_2 variance. Two additional QTLs, on chromosomes 11 and 15, were found in the F_2 mice but not in the RIs, highlighting the lack of power in the use of RIs for QTL mapping. The QTL on chromosome 11 is located at approximately 49 cM with a LOD of 5.91 explaining 11.1% of the variance. On chromosome 15, the QTL, at approximately 48 cM, with a LOD of 4.53, explained 12.7% of the F_2 variance. These four QTLs alone explain 47% of the genetic variance and 13.5% of the phenotypic variance. *(Supported by M08940.)*

126. GENETIC ANALYSIS OF BEHAVIORAL TRAITS USING THE AXB/BXA RI SET. *J.M. Tiller, R.S. Surwit, R.W. DeBry, M.F Seldin. Duke University Medical Center, NC, USA.*

Behavioral traits were examined in male A/J and C57BL/6J mice and, for a subset of behaviors, in 27 AXB, BXA RI strains. Activity level, alcohol preference, performance in the hole board and plus maze, "emotionality" & novelty suppressed feeding were determined individually for each mouse while social behaviors were rated per cage. Significant differences were observed between the progenitors, with >3SD between means for most traits. Activity, rearing and social nosing showed a larger variance in the RI strains than in either of the parental strains. Estimates of narrow-sense genetic heritability of: activity, 0.49; rearing, 0.52; and nosing 0.52 were obtained. Threshold traits were analyzed using the MAPMANAGER program, the highest lod score obtained was 2.5 for mounting. Normally distributed phenotypes were analyzed using QTL MANAGER. While a number of significant loci were obtained the highest Chi-squared was 17 ($p= 0.0004$) for activity index. Due to the difficulty in determining appropriate p values we performed permutations (using the actual data sets) for these phenotypes. The most robust finding was for activity level where 500 permutations were performed. X values greater than obtained in the real data set were observed in 12.6% (ie $p=0.126$) of the permuted data sets. Recombinant congenic strains are being analyzed to confirm and extend these findings.

127. GENETIC MAPPING OF QUANTITATIVE TRAIT LOCI ASSOCIATED WITH STRESS REACTIVITY IN THE WISTAR-KYOTO HYPERACTIVE RAT. *Moisan M.P., Courvoisier H., Mormede P. Genetique du Stress et Neurobiologie de l'Adaptation INSERM CJF 94-05-INRA-Universite de Bordeaux II France.*

In order to better understand the molecular mechanisms of interindividual variability of the stress response and its pathological outcomes we have undertaken a genetic linkage analysis on a F2 intercross between 2 rat strains (Wistar-Kyoto Hyperactive and Wistar-Kyoto) that differ markedly in their stress reactivity. The phenotyping consisted of 3 behavioral tests and several neuroendocrine measures. A multifactorial analysis was performed in order to synthesise these data and to classify each F2 rat according to its degree of reactivity. Each of these 196 F2 rats were also genotyped using rat microsatellite genetic markers that were polymorphic for the parental strains. Potential genetic linkage was judged from an ANOVA test. Preliminary results showed that one marker on chromosome 8 is linked to the hyperactivity trait ($p<0.0007$). We are actually pursuing the analysis with more markers and more animals to confirm these data.

128. TOWARDS A GENETIC ANALYSIS OF MOUSE TESTICULAR STEROIDOGENESIS. *A.V. Osadchuk, K.V. Svechnikov. Institute of Cytology & Genetics, Novosibirsk, 630090, Russia.*

In previous experiments with inbred mice, we found the genetic variations in plasma testosterone to be of great adaptive value, i.e., positively correlated with reproductive success and social dominance. This strain-related diversity can serve as a good model for studying the genetic control of testicular steroidogenesis and clarifying its key determinant factors. For this purpose, interstrain differences in cAMP-dependent signaling pathway of testosterone production, substrate-dependent testosterone production and microsomal steroidogenic enzyme activities in Percoll-purified Leydig cells between six inbred mouse strains (A/He, CBA/Lac, C57BL/6J, DD, YT and PT) were studied. Significant interstrain differences were found in the testosterone production in response to increasing concentrations of hCG, cholera toxin, forskolin, d,b-cAMP, pregnenolone and Δ^4-precursors of testosterone biosynthesis. Similar marked interstrain differences in Δ^5-3β-hydroxysteroid dehydrogenase-isomerase, 17α-hydroxylase, $C_{17\text{-}20}$-lyase and 17-ketosteroid reductase activities were demonstrated. Based on the principal components analysis, correlative interstrain variations in the studied characters were established. The results suggest that the revealed correlative variability may be due to major gene effect on steroidogenic activity of Leydig cells.

129. EFFECTS OF MOTOR NEURON DEGENERATION ARE MORE SEVERE IN T-E NZB-ELICITED WOBBLER *(NEW)* MOUSE HYBRID THAN IN THE ORIGINAL C57BL/6J WOBBLER MOUSE. *T. Ishiyama, E.P. Pioro, B. Klinkosz, H. Mitsumoto, Depts of Neurology & Neuroscience, The Cleveland Clinic Foundation, Cleveland, OH 44195.*

The wobbler (*wr*) mouse (in C57BL/6J) is an extensively studied animal model of an autosomal recessive motor neuron (MN) disease that manifests clinically by 3-4 weeks of age. Although the *wr* gene 011 mouse chromosome 11 remains uncharacterized, a variable microsatellite region in the closely associated pseudogene glutamine synthetase *(glns)* of New Zealand Black (NZB) x C57BL/6J *wr* mouse cross, allows preclinical identification of the hybrid animal's genotype by polymerase chain reaction (PCR). Prior to using the NZB-elicited wobbler (New) mouse in studies of MN degeneration, its features should be compared with the original C57BL/6J *wr* that has been previously used. Compared to the original *wr*, *New* mice had earlier onset of disease, and by 4 weeks of age, showed more severe paw deformity, walking abnormalities, and markedly less ($p<0.001$) grip strength. However, *New* mice survived at least as long as regular *wr* mice. In contrast to the clinical differences, histological features (vacuolar degeneration of cervical cord MNs and numbers of exons in C5 and C6 ventral roots) were similar in 8 week-old *New* and *wr* mice. Preclinical PCR identification of affected *New* mice will permit studies at the onset of MN degeneration.

130. **PHYSICAL MAPPING AND CHARACTERIZATION OF THE MOUSE X CENTROMERIC REGION.** *C.A. Goble, R.M. Tucker, R.L.Tavakkol, R.S. Thun, A.U. Jackson, A.D. Greenwood, P. Sachdev, D.T. Burke. University of Michigan, Ann Arbor, MI.*

131. **COMPARATIVE PHYSICAL MAPPING OF THE MOUSE X CHROMOSOME BETWEEN *Ids* AND *Dmd* AND HUMAN Xq28.** *A. Chatterjee, B. de Gouyon, M. Levin, N. Quaderi[1], S.D.B. Brown[1], Gail E. Herman. Department of Molecular and Human Genetics, Baylor College of Medicine; [1]Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London.*

132. **A PHYSICAL MAP OF THE REGION WHICH CONTAINS THE X-LINKED MUTANTS TATTERED AND SCURFY.** *Helen Blair[1], Emmanuelle Gormally[1], Ifeanyi Uwechue[1], Gail Herman[2], Jonathan Derry, Uta Francke, Nandita Quaderi[3], Steve Brown[3], Tony Monaco[4], David Burke[5], Yvonne Boyd[1]. [1]MRC Radiobiology Unit, Chilton, Oxon OX11 ORD, UK; [2]Baylor College of Medicine, Houston, TX, USA; [3]St. Mary's Hospital Medical School, London, UK; [4]The Wellcome Trust Centre for Human Genetics, Oxford, UK; [5]University of Michigan, USA.*

133. **LARGE-SCALE STRUCTURAL INSTABILITY IN THE MOUSE PSEUDOAUTOSOMAL REGION.** *David Kipling, Eduardo C. Salido*, Howard J Cooke. MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK; *Department of Pediatrics, University of California, San Francisco, CA.*

134. **DEFINING THE DISTAL IMPRINTING REGION ON CHROMOSOME 2.** *S.T. Ball, H.J. Miller, E.R. Dutton, C.M. Williamson, J. Peters. MRC Radiobiology Unit, Chilton, Didcot, Oxon, OX11 ORD, UK.*

135. **MOLECULAR GENETICS OF THE *KIT- PDGFRA* INTERGENIC REGION ON MOUSE CHROMOSOME 5: DEVELOPMENTAL DEFECTS ARISING FROM CHROMOSOMAL REARRANGEMENTS.** *R. B. Hough[1], D.L. Nagle[1], B.W. Nieuwenhuijsen[1], M. Bucan[1,2]. [1]Depts. of Psychiatry; [2]Genetics, University of Pennsylvania, Philadelphia, PA 19104, USA.*

136. **PHYSICAL MAPPING IN DISTAL MOUSE CHROMOSOME 6; A REGION IMPLICATED IN TYPE I DIABETES SUSCEPTIBILITY.** *Amanda N. Stafford, Isabelle Poras*, Louis M. Jones**, Evie Melanitou, Florence Joly, Philip Avner. Unite de Genetique Moleculaire Murine, Institut Pasteur, Paris, 75724; *Genethon, Evry, 91002, France; **Service d'Informatique Scientifique, Institut Pasteur, Paris, 75724.*

137. **PHYSICAL AND GENETIC MAPPING OF THE PERICENTROMERIC REGION OF MOUSE CHROMOSOME 19.** *F. Rotomondo[1], M. Fernandes[1,2], F. Lespinasse[1], A. Franchi[1], C. Poirier[3], P. Gaudray[2], J.L. Guenet[3], G.F. Carle[1]. [1]LEGM; [2]LGMCH, CNRS URA 1462 Universite de Nice, France; [3]Unit. Genet. Mamm., Institut Pasteur, Paris, France.*

138. **ALLELIC INACTIVATION OF THE *A4* INTEGRIN GENE IN FIBROSARCOMA LINES AND ITS RELEVANCE TO METASTASIS.** *Shuichi Sato, Katsumasa Tunashima, Yoshio Mafune, Hiroshi Ohtsuka, Ryo Kominami. First Department of Biochemistry, Niigata University School of Medicine, Asahimachi-doori 1-757, Niigata 951, Japan.*

139. **INACTIVE ALLELE-SPECIFIC METHYLATION AND CHROMATIN STRUCTURE OF THE IMPRINTED GENE U2AFBP-RS ON MOUSE CHROMOSOME 11.** *H. Shibata[1], K. Yoshino[1], T. Ueda[2], S. Sunahara[3], Y. Gondo[3], M. Katsuki[3], M. Kamiya[1], M. Muramatsu[1], I. Kalcheva[4], C. Plass[4], V. M. Chapman[4], Y. Hayashizaki[1]. (1) Genome Science Laboratory and Cell Biology Laboratory, The Inst. of Phys. and Chem. Res. (RIKEN), 3-1-1, Koyadai Tsukuba, Ibaraki, 305 Japan; (2) Research Laboratory for Mol. Genet Niigata Univ.; (3) Med. Inst. of Bioregulation, Kyushu Univ.; (4) Mol. and Cell. Biol. Dept., Roswell Park Cancer Institute, Buffalo, NY.*

140. **MEIOTIC RECOMBINATIONAL HOTSPOTS IN THE MOUSE MHC: A PARADIGM FOR THE REGULATION OF RECOMBINATION IN MAMMALS?** *H.C. Passmore, D. Heine, S. Khambata. Department of Biological Sciences, Rutgers University, Piscataway, NJ 08855-1059, USA.*

141. **CLONING THE MOUSE IGH LOCUS IN YACS.** *C. Chevillard, J.H. Ozaki, C. Herring, R. Riblet. Medical Biology Institute, La Jolla, CA, USA.*

142. **THE *Ea* RECOMBINATIONAL HOTSPOT OF THE MOUSE MHC MAPS TO THE FOURTH INTRON OF THE *Ea* GENE.** *Shirin Khambata, Jeannie Mody, Howard C. Passmore. Department of Biological Sciences, Rutgers University, Piscataway, NJ 08855-1059, U.S.A.*

143. **CHARACTERIZATION OF A NOVEL, EXPRESSED SUBFAMILY OF *H2* CLASS IB GENES.** *EP Jones, I Carlo, Q-R Jiang, R Arapalli, D Singer*, S Rudikoff*, K Fischer Lindahl. Department of Microbiology and Howard Hughes Medical Institute, University of Texas Southwestern Medical Center at Dallas, TX; *Laboratory of Genetics, National Cancer Institute, National Institute of Health, Bethesda, MD.*

144. **CHARACTERIZATION OF THE MURINE CD1 PROMOTER.** *Yi-Hua Chen, S. Muthyala-Bhooshi, C.-R. Wang. The University of Chicago, Chicago, IL, USA.*

145. **A HUMAN DNA FRAGMENT HOMOLOGOUS TO THE POSITION-SPECIFIC CONTROL ELEMENT OF MURINE HOXA-7 DETERMINES THE ANTERIOR BOUNDARY OF EXPRESSION IN TRANSGENIC MICE.** *Myoung Hee Kim*, Wongi Min, Seungik Jang, Sun-Hwa Park[1], Chulsang Lee, Moo-Hyung Jun[2]. Genetic Resources Center, Korea Research Institute of Bioscience and Biotechnology, KIST, Taejon, Korea. 305-606; [1]Dept. of Anatomy, College of Medicine, Korea Univ.; [2]College of Veterinary Medicine, Chungnam National Univ. Korea.*

130. PHYSICAL MAPPING AND CHARACTERIZATION OF THE MOUSE X CENTROMERIC REGION. *C.A. Goble, R.M. Tucker, R.L.Tavakkol, R.S. Thun, A.U. Jackson, A.D. Greenwood, P. Sachdev, D.T. Burke. University of Michigan, Ann Arbor, MI.*

A four megabase physical map of a region on the mouse X chromosome extending from the centromere to the OTC gene has been assembled. The map contains 3 YAC contigs each containing at least one major gene. YACs were obtained from the Princeton, MIT, and Baylor mouse libraries. The GATA 1 contig is comprised of 4 YACs with a minimum length of 460kb. The CYBB contig contains 11 YACs spanning 700-800kb and the OTC region is a well defined contig of 6 YACs covering 620kb. Over half of the ends have been isolated and contig lengths were determined by PFG sizing and mapping ends to at least one other YAC in the same contig. Chimerism was determined by FISH for 3 YACs and backcross data for 2 other YACs. All relevant MIT markers from the current data set were tested against our YACs with the resulting overlaps: [DXMIT26-DXMIT136-DXMIT124- CYBB] [DXMIT89-OTC]. We then ordered the MIT markers from the centromere to OTC using backcross DNA obtained from G. Herman. Given our present data the map is as follows: Cen, DXWas70, DXMIT101, DXMIT123, DXMIT55, [DXMIT161,TFE3,GATA1], DXMIT26, DXMIT136, DXMIT124, CYBB, DXMIT89, OTC.

131. COMPARATIVE PHYSICAL MAPPING OF THE MOUSE X CHROMOSOME BETWEEN *Ids* AND *Dmd* AND HUMAN Xq28. *A. Chatterjee, B. de Gouyon, M. Levin, N. Quaderi[1], S.D.B. Brown[1], Gail E. Herman. Department of Molecular and Human Genetics, Baylor College of Medicine; [1]Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London.*

Our laboratory has developed detailed genetic and physical maps for the region of the mouse X chromosome homologous to human Xq28. This interest is in part focused on the isolation of genes for the mouse homolog of the human myotubular myopathy gene (MTMI) and two X-linked dominant mouse mutations – bare patches *(Bpa)* and striated *(Str)* – which may be homologous to human X-linked dominant chondrodysplasia punctata (CDPX2) and incontinentia pigmenti (IP), respectively. Our current YAC contig spans approximately 5 Mb from *Ids* to *Dmd*, and consists of 74 YACs. There are 2 small gaps between *G6pd* and *Cf8* and between *Cf8* and *Dmd*. Several known human genes have been mapped onto the contig, including caltractin *(Calt)*, the renin binding protein *(Renbp)*, host cell factor-1 encoding gene *(Hcfc1)*, and filamin-1 *(Fln1)*. In collaboration with D. Toniolo, a comparative transcription map has been prepared between *Rsvp* and *G6pd* and demonstrates conservation of gene order and transcriptional domains over the 250 kb region.

132. **A PHYSICAL MAP OF THE REGION WHICH CONTAINS THE X-LINKED MUTANTS TATTERED AND SCURFY.** *Helen Blair[1], Emmanuelle Gormally[1], Ifeanyi Uwechue[1], Gail Herman[2], Jonathan Derry, Uta Francke, Nandita Quaderi[3], Steve Brown[3], Tony Monaco[4], David Burke[5], Yvonne Boyd[1]. [1]MRC Radiobiology Unit, Chilton, Oxon OX11 ORD, UK; [2]Baylor College of Medicine, Houston, TX, USA; [3]St. Mary's Hospital Medical School, London, UK; [4]The Wellcome Trust Centre for Human Genetics, Oxford, UK; [5]University of Michigan, USA.*

A high resolution genetic map of the proximal region of the mouse X chromosome has established the order *(DXWas70, DXHXF34)-ClcnS-(DXMit55, DXMit26, Syp)-Tfe3-Gatal-Xk-Cybb-Otc*. During the past year, other groups have positioned two mouse mutants, tattered *(Td)* and scurfy *(sf)*, into the *DXWas70 - Otc* interval, with both mutants cosegregating with *DXMit26, Tfe3* and *Gatal* (other markers were not tested). Further analysis of critical recombinants in the *Td* cross has revealed that *Td* must lie between *DXMit55* and *Xk*. This refined map position eliminates the possibility that *Td is* caused by mutations in a locus homologous to the one disrupted in human patients suffering from incontinentia pigmenti type 1. We have now isolated YAC clones for *DXMit26, Gatal* and *Cybb* and established a contig (with a single gap between *Galal/Wasp)* and that includes these three loci, *Syp, Tfe3, Wasp, Xk* and four other partially-characterised conserved sequences. We are currently attempting to bridge this gap with further YAC and P1 clones.

133. **LARGE-SCALE STRUCTURAL INSTABILITY IN THE MOUSE PSEUDOAUTOSOMAL REGION.** ***David Kipling, Eduardo C. Salido*, Howard J. Cooke.** *MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK; *Department of Pediatrics, University of California, San Francisco, CA.*

The pseudoautosomal region (PAR) is a segment of shared homology which enables the sex chromosomes to pair and recombine in male meiosis It has a crucial role in meiotic chromosome segregation but in the mouse is poorly understood at the molecular level. We have derived a preliminary long-range restriction map of the mouse PAR using four available PAR probes PAR-4, *DXYMov15*, and $(TTAGGG)_n$ are physically linked by PFGE analysis These fragments are tightly sex-linked in male meiosis. In contrast *Sts is* not sex-linked and is located on a different restriction fragment. This implies that *Sts is* telomeric to the PAR-4/DXYMov15/$(TTAGGG)_n$ region and that there is an internal $(TTAGGG)_n$ array in the mouse pseudoautosomal region.

Certain large (> 1 Mb) fragments containing PAR-4, *DXYMov 15*, and $(TTAGGG)_n$ show striking structural instability, with new size alleles readily occurring in family studies. We speculate that the instability of the PAR region may have caused the *M. musculus* and *M. spretus* PARs to rapidly diverge during evolution, and that this large-scale PAR structural dissimilarity underlies interspecific sterility.

134. DEFINING THE DISTAL IMPRINTING REGION ON CHROMOSOME 2. *S.T. Ball, H.J. Miller, E.R. Dutton, C.M. Williamson, J. Peters. MRC Radiobiology Unit, Chilton, Didcot, Oxon, OX11 ORD, UK.*

The imprinting region on distal Chromosome (Chr) 2 is currently defined as lying distal to the breakpoint of the reciprocal translocation T(2;8)2Wa, (T2Wa) in band H3 and proximal to T(2;16)28H, (T28H) in band H4. The translocation breakpoints on Chr 2 have been positioned on the linkage map with T2Wa being near to *Ada*, and T28H being close to *Acra4*. High resolution mapping with EUCIB has been carried out to order markers which must lie close to the translocation breakpoints. Physical mapping of YAC and P1 clones by FISH has shown that *Ada, D2Mit49* and *Ppgb* are proximal to T2Wa and *Acra4 is* distal to T28H. Work is continuing to define the precise position of the breakpoints on the linkage map in relation to DNA and gene markers.

135. MOLECULAR GENETICS OF THE *KIT- PDGFRA* INTERGENIC REGION ON MOUSE CHROMOSOME 5: DEVELOPMENTAL DEFECTS ARISING FROM CHROMOSOMAL REARRANGEMENTS. *R. B. Hough[1], D. L. Nagle[1], B. W. Nieuwenhuijsen[1], M. Bucan[1,2]. [1]Depts. of Psychiatry; [2]Genetics, University of Pennsylvania, Philadelphia, PA 19104, USA.*

Physical mapping studies, as well as expression analysis of *Kit* in developing mutant embryos, showed recently that *Ph*, w^{bd}, W^{sh} and *Rw* represent a cluster of position effect mutations, as least with respect to their dominant effect on pigmentation. The intergenic region between *Kit* and *Pdgfra* – two homologous genes encoding receptor tyrosine kinases on mouse chromosome 5 – contains the breakpoints of chromosomal rearrangements associated with these mutations. In an attempt to identify new genes and tissue specific regulatory elements which affect *Kit* and/or *Pdgfra* expression, we initiated detailed characterization of DNA in the "breakpoint cluster region". We are currently investigating the unusual nature of the nucleotide sequence composition, as well as extensive arrays of common and rare repetitive elements, which are potentially responsible for the chromosomal breakage observed in numerous spontaneously derived and induced mutant alleles.

136. PHYSICAL MAPPING IN DISTAL MOUSE CHROMOSOME 6; A REGION IMPLICATED IN TYPE I DIABETES SUSCEPTIBILITY. *Amanda N. Stafford, Isabelle Poras*, Louis M. Jones**, Evie Melanitou, Florence Joly, Philip Avner. Unite de Genetique Moleculaire Murine, Institut Pasteur, Paris, 75724; *Genethon, Evry, 91002, France; **Service d'Informatique Scientifique, Institut Pasteur, Paris, 75724.*

The distal chromosome 6 region has been identified as containing a locus accounting for around 20% of the diabetes phenotype seen in a new experimental cross between the murine IDDM model, the NOD mouse, and a diabetes resistant *Mus mus* strain PWK. Congenic strains are being developed to provide additional evidence implicating this region and further clarify the relative contributions of NOD and PWK genome in this region to the diabetic phenotype.

Physical mapping via construction of a YAC contig is underway to allow the congenic intervals to be defined as physical distances, to allow accurate localisation of known distal chromosome 6 genes and to provide resources for more detailed mapping and gene isolation efforts. A 20cM region of distal chromosome 6, defined by its synteny to human 12p, is the focus of our efforts. Screening of the ICRF and MIT YAC libraries with the 65 MIT markers and 27 genes localised to this region has been completed yielding an average of of 6.7 YACs per marker. Work is currently underway to develop murine STSs for 19 human 12p genes and 73 recently described transcripts derived from 12p which have not hitherto been mapped in the mouse. These will be useful not only as markers but will contribute to the development of a transcription map of this region. End clone isolation will be undertaken to provide closure of the contig where necessary.

137. PHYSICAL AND GENETIC MAPPING OF THE PERICENTROMERIC REGION OF MOUSE CHROMOSOME 19. *F. Rotomondo[1], M. Fernandes[1,2], F. Lespinasse[1], A. Franchi[1], C. Poirier[3], P. Gaudray[2], J.L. Guenet[3], G.F. Carle[1]. [1]LEGM; [2]LGMCH, CNRS URA 1462 Universite de Nice, France; [3]Unit. Genet. Mamm., Institut Pasteur, Paris, France.*

A physical map of the pericentromeric region of mouse chromosome 19 involving long range mapping by PFG electrophoresis as well as YAC contig establishment is in the process of being built. This physical map is based on a genetic map backbone which is taking into account three main sets of data: the first one, is a high resolution genetic map derived from the EUCIB panel (interspecific backcross of the type (C57BL/6 x Mus spretus) F1 x C57BL/6 and the reciprocal cross); the second set is based on the SSLP genetic map of the Whitehead Institute; and the last set is from our own interspecific backcross of the type (B6C3-*a/a* F1 x *Mus spretus*) F1 x B6C3-*a/a* F1. About seventy YACs (400 kb average size) were isolated from four different libraries by PCR screening with mainly microsatellites derived primer pairs, and checked for mitotic stability as well as chimerism (FISH). Colony filters were generated and hybridized with inter-B1 PCR products derived from each YAC. These data have been combined with an STS content map and long range PFG analysis to construct a first physical map of this region of the mouse genome.

138. ALLELIC INACTIVATION OF THE *A4* INTEGRIN GENE IN FIBROSARCOMA LINES AND ITS RELEVANCE TO METASTASIS.

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Allele-specific inactivation is observed in imprinted genes. We previously showed that such allelic inactivation frequently occurs in tumors using murine fibrosarcomas (MST) derived from intersubspecific F1 mice; five genes underwent among fourteen genes examined. The present paper demonstrates that the allelic inactivation of the *a4* integrin gene is involved in the acquisition of spontaneous metastasis. We obtained a series of tumor cell lines (MSTP) with different malignancies by repeated transplantations. RT-PCR and SSCP analysis revealed that the first three MSTP cell lines, which did not metastasize subcutaneously, showed a decreased *a4* integrin expression of only the C57BL allele, whereas the other seven cell lines having ability of spontaneous metastasis formation exhibited decreased expressions of both alleles. No allelic loss was detected with LOH analysis. A similar relationship was also observed in two other lines. These results suggest that allelic inactivation of the *a4* integrin gene may play a key role in tumor progression, although the mechanism governing this inactivation is not clear at present.

139. INACTIVE ALLELE-SPECIFIC METHYLATION AND CHROMATIN STRUCTURE OF THE IMPRINTED GENE U2AFBP-RS ON MOUSE CHROMOSOME 11.

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The imprinted U2afbp-rs gene that was mapped to mouse chromosome 11 is predominantly expressed from the paternal allele. We examined the methylation of genomic sequences in and around the U2afbp-rs locus to establish the extent of sequence modifications that accompanied the silencing of the maternal allele. The analysis of HapII or HhaI sites showed that the silent maternal allele was hypermethylated in a block of CpG sequences that covered more than 10 kbp. By comparison, the expressed paternal allele was unmethylated from a CpG island upstream of the transcribed region through 2 kbp. An analysis of DNase I hypersensitivity of a putative promoter of U2afbp-rs showed an open chromatin conformation only on the unmethylated, expressed paternal allele. These result suggest that allele-specific hypermethylation covering the gene and its upstream CpG island play a role in maternal allele repression of U2afbp-rs which is reflected in altered chromatin conformation of DNase I hypersensitive sites. This allele specific pattern was completed in the early developmental stage between E4.5 day and E12.5 day, suggesting that the methylation signal of critical region may regulate the allele specific expression and extent cover U2afbp-rs gene during the early development.

140. MEIOTIC RECOMBINATIONAL HOTSPOTS IN THE MOUSE MHC: A PARADIGM FOR THE REGULATION OF RECOMBINATION IN MAMMALS? *H.C. Passmore, D. Heine, S. Khambata. Department of Biological Sciences, Rutgers University, Piscataway, NJ 08855-1059, USA.*

In the mouse Major Histocompatibility Complex (MHC), clustering of recombinational breakpoints is found in regions of limited physical distance known as recombinational hotspots. Five hotspots have been defined within the /-region of the MHC which contains the Class II genes. These hotspots of meiotic crossing over have been found within the *Tap 1*, *Eb* and *Ea* genes, and near the *Pb* and *Lmp2* genes. A striking feature of these hotspots is that the site specificity of meiotic crossing over appears to be strictly regulated by the MHC haplotype involved in the recombination event. A survey of the literature from a number of laboratories, including our own, reveals that out of a total of 168 /-region recombinants reported, 165 have occurred within these five well-defined hotspots. Thus, over 98% of the recombination events that occur within a 420 kb segment containing the K and / regions, fall within recombinational hotspots of limited length (usually 1 to 4 kb). Since 1982, considerable descriptive information has accumulated on the frequency, physical location and specificity of intra-MHC recombinational hotspots. Unfortunately, little is known of the mechanism or functional components that make these sites attractive for recombination. Further, it is unclear whether recombinational hotspots represent a feature unique to the MHC or whether they are typical of other recombination sites throughout the genome. Several possible models to account for the existence of recombinational hotspots will be presented.

141. CLONING THE MOUSE IGH LOCUS IN YACS. *C. Chevillard, J.H. Ozaki, C. Herring, R. Riblet. Medical Biology Institute, La Jolla, CA, USA.*

In the mouse the immunoglobulin heavy chain (*Igh*) complex locus is composed of approximately 200 gene segments encoding the variable, diversity, joining and constant portions of the heavy chain protein. This locus is at or near the distal end of mouse chromosome 12 and is spread over 1-2 centiMorgans of recombination distance, and approximately 2 megabases of DNA, a segment of genome suitable for YAC (Yeast Artificial Chromosome) analysis. We have screened the YAC libraries made Princeton, MIT, the ICFR, and St. Mary's Hospital Medical School, London, and have identified about 40 clones containing parts of the *Igh* locus. The largest contig is 1100 kb and contains all Ch, Jh, Dh and half of the Vh gene segments. Using "restriction site-PCR" and Taq cycle sequencing we characterized 43 YAC ends; 29 were unique sequences suitable for use as probes, and 14 were repetitive elements (8 L1 and 6 Bam). A set of large YACs covering the locus is being subjected to B1 fragmentation, and the stepwise deletion derivatives are being characterized to efficiently map all the gene segments present in the locus. Individual Vh genes are being isolated from YACs and sequenced. Our goal is to completely clone and define the *Igh* locus and identify and sequence all Vh gene segments to provide the framework for functional and evolutionary studies.

142. THE *Ea* RECOMBINATIONAL HOTSPOT OF THE MOUSE MHC MAPS TO THE FOURTH INTRON OF THE *Ea* GENE. *Shirin Khambata, Jeannie Mody, Howard C. Passmore. Department of Biological Sciences, Rutgers University, Piscataway, NJ 08855-1059, U.S.A.*

The majority of recombination events detected within the mouse major histocompatibility complex (MHC), fall into regions of limited physical distance known as hotspots of meiotic recombination. The hotspot associated with the *Ea* gene appears to be active only in the presence of the *p* haplotype of the intra-MHC recombinant strain B10.F(13R). In order to study the frequency, regulation, and haplotype specificity of recombination at the *Ea* hotspot, progeny from three different backcrosses involving B10.F(13R), were analyzed for recombination events across the MHC using microsatellite markers. The screening of a total of 750 backcross progeny permitted the identification of seven recombinants within the *Ea* gene. Using restriction site polymorphisms and sequence-based nucleotide polymorphisms unique to the parental alleles involved in the recombination event, the recombination breakpoints in all seven *Ea* recombinants were mapped to two adjacent segments of 71 bp and 348 bp in intron four of the *Ea* gene.

143. CHARACTERIZATION OF A NOVEL, EXPRESSED SUBFAMILY OF *H2* CLASS IB GENES. *EP Jones, I Carlo, Q-R Jiang, R Arapalli, D Singer*, S Rudikoff*, K Fischer Lindahl. Department of Microbiology and Howard Hughes Medical Institute, University of Texas Southwestern Medical Center at Dallas, TX; *Laboratory of Genetics, National Cancer Institute, National Institute of Health, Bethesda, MD.*

Class Ib genes are encoded in the distal half of the *H2* complex, on chromosome 17, and are grouped in three regions, *H2-Q, T* and *M*, with *H2-M* at the telomeric end. The physical map of the *M* region has been extended into the *T* region by ordering all known class I genes and DNA markers within > 1.5 Mb of DNA cloned in YACs, organized in two contigs. Probing of the YACs with the conserved fourth exon of class I genes detected 21 class I fragments. Only *M2* and *M3*, both expressed genes, were found in the distal contig of 700 kb; *T1* together with *M1, M4-M8* and 12 other class I fragments were found in the proximal contig of 800 kb.

Cloning and sequencing of the new class I genes is in progress. *M9*, a new member of the *M1* subfamily, has been mapped near the *M1-M7-M8* cluster. Efforts to map *M10*, another member of this family, uncovered a group of eight very closely related class I genes in the genome, all of which are present in the proximal contig. Three of the members sequenced so far show high DNA homology and amino acid identity, including in exon 5, which is thought of as one of the most divergent exons. Further features of this gene subfamily will be presented.

144. CHARACTERIZATION OF THE MURINE CD1 PROMOTER. *Yi-Hua Chen, S. Muthyala-Bhooshi, C.-R. Wang. The University of Chicago, Chicago, IL, USA.*

CD1 molecules are MHC-unlinked class Ib molecules. Each mammalian species examined possesses at least one to two classes of CD1 genes. Five CD1 genes in human (CD1a,b,c,d, and e) and two in the mouse (mCD1.1 and mCD1.2) have been cloned and sequenced. Based on sequence homology, CD1 genes can be grouped into two distinct classes: "classic" CD1 class (human CD1a,b,c) and the "CD1d" class (human CD1d and both mouse CD1 genes.) Recently CD1b has been shown to present lipid or glycolipid antigen from the cell wall of mycobacteria to α/β^+ T cells. In addition, CD1 was shown to be the ligand for a unique subset of T cells ($NK1.1^+$, $CD4^+$) in the mouse.

To elucidate the mechanisms regulating the expression of the murine CD1 genes, we have cloned and sequenced the 5′ flanking region of the murine CD1.1 and CD1.2 genes. CD1.1 and CD1.2 share greater than 95% sequence homology in the coding exons and intervening introns. The striking homology extends only 90 bp 5′ of the translational start site with marked upstream divergence. There is an L1 repeat in the upstream region of CD1.2, which may explain the lower expression of CD1.2 relative to CD1.1. The promoter regions of the mouse CD1 genes show no sequence similarity to those of the MHC class Ia genes or other class Ib genes: Consensus class I regulatory elements (enhancer A and B) and interferon response element (IRE) are not present. The 5′ flanking region of mCD1.1 shares some sequence homology with its human counterpart, CD1d. IL4 and GMC-SF cannot up-regulate the expression of murine CD1 in contrast to human CD1a,b,c, and none of the cytokines tested so far significantly enhance CD1 expression. Hence, the two classes of CD1 may have evolved different regulatory patterns to subserve distinct functions.

145. A HUMAN DNA FRAGMENT HOMOLOGOUS TO THE POSITION-SPECIFIC CONTROL ELEMENT OF MURINE HOXA-7 DETERMINES THE ANTERIOR BOUNDARY OF EXPRESSION IN TRANSGENIC MICE. *Myoung Hee Kim*, Wongi Min, Seungik Jang, Sun-Hwa Park[1], Chulsang Lee, Moo-Hyung Jun[2]. Genetic Resources Center, Korea Research Institute of Bioscience and Biotechnology, KIST, Taejon, Korea. 305-606; [1]Dept. of Anatomy, College of Medicine, Korea Univ.; [2]College of Veterinary Medicine, Chungnam National Univ. Korea.*

The Hox genes have been known to be involved in pattern formation during vertebrate development through differential expression along the antero-posterior body axis. In order to study the human homologue of position specific element of murine Hoxa-7, the corresponding sequences have been identified through genomic Southern hybridization and screened from human genomic library using the position-specific control element of murine Hoxa-7 as a probe. One positive clone was isolated from the library and analyzed by subcloning as well as Southern blotting. The size of the homologous region has been reduced to about 1.1 kb. Genomic DNA sequences had been determined and highly conserved sequences between human and mouse were appeared. It was mapped on the short arm of the human chromosome 7 (7p15) by FISH technique. The transgene was constructed with human sequences along with the lacZ as a reporter, and then analyzed in the transgenic mice system. The expression pattern of the reporter lacZ was in analogy to that of the murine Hoxa-7. This result implies that the human DNA fragment we isolated is presumed to be the position-specific regulatory element of human.

146. **HIGH ORDER STRUCTURE STUDIES OF MEIOTIC CHROMOSOMES USING TRANSGENIC MICE.** *Henry H.O. Heng, John Chamberlain, Xiao-Mei Shi, Barbara Spyropoulos, Lap-Chee Tsui, Peter B. Moens. Biology Department, York University, Downsview, Ontario, Canada M3J 1P3; Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8.*

147. **THE APPLICATION OF FISH TECHNOLOGY TO MOUSE GENE & PHYSICAL MAPPING.** *Henry H.O. Heng, Ph.D. SeeDNA Biotech Inc. Biology Department, 4700 Keele St, Downsview, Ontario, Canada M3J 1P3.*

148. **ESTABLISHMENT OF A MOUSE CHROMOSOME-SPECIFIC YAC PROBE COLLECTION FOR IN SITU HYBRIDIZATION.** *F. Mongelard, I. Poras*, M. Robert-Nicoud, P. Avner**, C. Vourc'h. Dynamique de l'Organisation du Genome, Universite J. Fourier, 38041 Grenoble France. *Genethon, BP 60, 91002 Evry CEDEX, France. **Unite de Genetique Moleculaire Murine, Institut Pasteur, 75015 Paris, France.*

149. **RECOVERY OF PROBES NEAR THE JUVENILE CONGENITAL POLYCYSTIC KIDNEY DISEASE LOCUS (*jcpk*) ON MOUSE CHROMOSOME 10 USING REPRESENTATIONAL DIFFERENCE ANALYSIS.** *R.A. Baldocchi, K.E. Tartaglia, L.A. Flaherty. The Wadsworth Center, Albany, NY, USA.*

150. **ISOLATION OF Y-SPECIFIC PROBES USING REPRESENTATIONAL DIFFERENCE ANALYSIS (RDA).** *A. Navin[1], R. Prekeris[1], N.A. Lisitsyn[2], M.M. Sonti[1], D.A. Grieco[1], S. Narayanswami[1], E.S. Lander[3], E.M. Simpson[1]. [1]The Jackson Laboratory, Bar Harbor, ME, USA; [2]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA; [3]Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA, USA.*

151. **IDENTIFICATION OF GENES WITHIN LARGE GENOMIC CLONES USING PROMOTER CAPTURE.** *D.P. Mortlock[1], J.W. Innis[1,2]. Departments of [1]Human Genetics and [2]Pediatrics, University of Michigan, Ann Arbor, MI, USA.*

146. HIGH ORDER STRUCTURE STUDIES OF MEIOTIC CHROMOSOMES USING TRANSGENIC MICE.

Henry H.O. Heng, John Chamberlain, Xiao-Mei Shi, Barbara Spyropoulos, Lap-Chee Tsui, Peter B. Moens. Biology Department, York University, Downsview, Ontario, Canada M3J 1P3; Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8.

Transgenic mice are an important tool for studying the mechanism of gene function and its regulation. We also use this system to study chromosome structure. Protein-DNA co-detection on different kinds of transgenic animals has been used to visualize structural changes at the chromosome level.

At meiotic prophase, chromatin loops around a proteinaceous core, loop sizes varying between species. Comparison of the morphology of sequences-related inserts at different sites in transgenic mice demonstrates that loop size also varies with the chromosomal geography. Sequences, telomeric or otherwise, located at chromosome termini, closely associate with the meiotic proteinaceous core, forming shorter loops than identical interstitial sequences. Thus, we present evidence for different chromatin packaging mechanisms for interstitial versus terminal chromosomal regions which act separately from those operating at the level of DNA sequences.

147. THE APPLICATION OF FISH TECHNOLOGY TO MOUSE GENE & PHYSICAL MAPPING.

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Gene mapping by fluorescence in situ hybridization (FISH) is more difficult for mouse chromosome than human, since the mouse chromosomes have similar morphology. We have increased the efficiency of mouse FISH mapping by developing a reliable method of FISH mapping on DAPI-banded chromosomes. With this method large numbers of genes have been mapped to their particular region of the mouse chromosome. This method has also be used successfully to identify insertion sites for transgenic mice.

We have also developed an efficient cross species FISH mapping system to locate mouse cDNA probes on human chromosomes. This mapping system should greatly facilitate comparative gene mapping and the study of genome evolution by defining the boundary of syntenic groups between mouse and human.

We can also perform high resolution FISH mapping on released chromatin/DNA fiber, which is particularly useful to order a group of probes.

148. **ESTABLISHMENT OF A MOUSE CHROMOSOME-SPECIFIC YAC PROBE COLLECTION FOR IN SITU HYBRIDIZATION.** *F. Mongelard, I. Poras°, M. Robert-Nicoud, P. Avner°°, C. Vourc'h. Dynamique de l'Organisation du Genome, Universite J. Fourier, 38041 Grenoble France. °Genethon, BP 60, 91002 Evry CEDEX, France. °°Unite de Genetique Moleculaire Murine, Institut Pasteur, 75015 Paris, France.*

In order to facilitate the identification of mouse chromosomes, a complete collection of chromosome specific markers was established.

YAC libraries were screened by PCR using primers specific for known loci at the YAC screening center, Genethon. DNAs from positive clones were tested by in situ hybridization. One probe per chromosome was selected on the basis of high specificity (i.e. non chimerism) and good signal intensity.

This tool should be helpful for genome mapping and analysis of transgenes.

149. **RECOVERY OF PROBES NEAR THE JUVENILE CONGENITAL POLYCYSTIC KIDNEY DISEASE LOCUS *(Icpk)* ON MOUSE CHROMOSOME 10 USING REPRESENTATIONAL DIFFERENCE ANALYSIS.** ***R.A. Baldocchi**, K.E. Tartaglia, L.A. Flaherty. The Wadsworth Center, Albany, NY, USA.*

We have used representational difference analysis *(RDA, Lisitsyn, et al, Science 259:946, 1993)* to isolate probes that map to a narrow region tightly linked to the juvenile congenital polycystic kidney disease locus, *jcpk*, on mouse Chromosome 10. RDA is a PCR-based subtractive-hybridization technique that isolates the differences between two genomes. *The jcpk* mutation arose as the result of chlorambucil mutagenesis, which typically induces deletions or translocations. Briefly, the *jcpk* mutation arose in a (C3H/HeJ X 101)F1 mouse that was then backcrossed to the C57BL/6J (B6) strain for 7 generations. It is estimated that the congenic strain differs from its inbred partner by a region of 28 cM surrounding the *jcpk* locus, as well as at some unlinked loci. Thus, by subtracting B6 from B6-*jcpk*/*jcpk* DNA, RDA difference products would be expected to map within these regions.

Improvements in the RDA protocol were developed allowing recovery of more difference products in a given region. We recovered a total of 39 difference products, 26 of which were unique and represented the smaller allele of a *Bgl 11* RFLP. Seven of these were mapped to an interval from 1.7 to 3.9 cM distal to the *jcpk* locus using a (BALB/c X CAST/Ei)F1 X BALB/c backcross. Of these 7, only 1 B6-specific allele was isolated by the original RDA procedure, whereas 5 (4 more) were isolated using the same experimental setup and the improved RDA protocol. Two of these 7 were B6-*jcpk*/*jcpk*-specific alleles. The remainder of the difference products were either less tightly linked, unlinked or artifacts.

150. ISOLATION OF Y-SPECIFIC PROBES USING REPRESENTATIONAL DIFFERENCE ANALYSIS (RDA). *A. Navin[1], R. Prekeris[1], N.A. Lisitsyn[2], M.M. Sonti[1], D.A. Grieco[1], S. Narayanswami[1], E.S. Lander[3], E.M. Simpson[1]. [1]The Jackson Laboratory, Bar Harbor, ME, USA; [2]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA; [3]Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA, USA.*

One obstacle in characterizing the mouse Y chromosome is a lack of Y-specific probes. Representational Difference Analysis (RDA) is a subtraction technique capable of amplifying the differences between genomes. This technique was used to amplify the differences between male (XY) and female (XX) C57BL/6J mouse genomes; predominately the Y chromosome. Characterization of 35 of the resulting clones revealed 12 classes of sequence similarity. One member of each class was chosen for detailed analysis by Fluorescence *In Situ* Hybridization (FISH), Southern Blot analysis and the Polymerase Chain Reaction (PCR). The results demonstrate that all of the clones were derived from the Y chromosome. Ten clones can be defined as diffuse repeats along the long arm of the Y, one as a pericentric tandem repeat, and one as a low-level Y chromosome repeat as yet to be localized. Sequence analysis shows six of these clones to be novel repeats, five that share some similarity with previously published Y chromosome repeats, and one that shows similarity to a LINE sequence. Interestingly, this is believed to be the first instance of the cloning of a Y-specific LINE fragment. We conclude that the RDA technique successfully enriched for Y chromosomal sequences and is suitable for the rapid generation of new Y chromosome specific clones.

151. IDENTIFICATION OF GENES WITHIN LARGE GENOMIC CLONES USING PROMOTER CAPTURE. *D.P. Mortlock[1], J.W. Innis[1,2]. Departments of [1]Human Genetics and [2]Pediatrics, University of Michigan, Ann Arbor, MI, USA.*

Promoters and flanking sequences are outstanding tools in gene identification strategies. Probes corresponding to extreme 5′ ends of genes are more likely to allow isolation of full-length cDNAs, which are typically difficult to obtain in conventional gene isolation experiments. In addition, comparison of promoter sequences between species permits identification of evolutionarily conserved elements, and subcloning promoter sequences is a prerequisite for studies of promoter function and regulation. Therefore, our laboratory is developing new strategies to isolate gene promoters and flanking exons from vertebrate genomic DNA clones based on transcription factor binding-site density or the ability to drive transcription.

We have developed a novel method, Promoter Capture, that exploits the over-representation of clustered binding sites for transcription factors, such as Sp1, in 5′ regulatory regions. Using a GST-Sp1 fusion protein, restriction fragments with strong Sp1-binding sites are extracted from phage P1 or YAC genomic clones. The fragments are eluted, subcloned, and subjected to additional rounds of selection in plasmid form. Typical experiments with phage P1 clones enrich these fragments 100 to 200-fold. From a 300 kb contig spanning the mouse *Hoxa* gene cluster, we have used Promoter Capture to isolate 4 new CpG islands, of which three are associated with the S′ ends of known genes *(Hoxa-1, Hoxa-9, Hoxa-13)*. In addition, the *Hoxa-4* gene promoter was similarly enriched. One clone was enriched 1600-fold from total yeast DNA. Promoter Capture is capable of rapidly and efficiently generating putative promoters from isolated clones without using hybridization, radioactivity or tissue culture. This strategy will facilitate efforts to find genes and regulatory elements in selected regions of vertebrate genomes.

152. **THE MOUSE BACKCROSS DATABASE (MBx).** *D. Tailor, M. Kelly, R. Williams. MRC Human Genome Mapping Project Resource Centre, Hinxton Hall, Hinxton, Cambridgeshire, CB10 1RQ, UK.*

153. **THE MOUSE GENOME DATABASE 2.0.** *J. Battles, R. Blackburn, D. Bradt, G. Colby, L. Corbani, G. Davis, M. Davisson, D. Doolittle, T. Drake, J.T. Eppig, K. Frazer, J. Gilbert, P. Grant, M. Lennon-Pierce, L. Maltais, M. May, M. McIntire, J. Ormsby, D. Reed, J. Richardson, M.D. Ringwald, S. Rockwood, S. Sharpe, S. Shroder, A. Smith, M. Stanley-Walls, D.Walton. The Jackson Laboratory, Bar Harbor, Maine, USA.*

154. **NEW FEATURES AND ENHANCEMENTS FOR THE MOUSE GENOME DATABASE.** *T. Drake, S. Shroder, J. Battles, R. Blackburn, D. Bradt, G. Colby, L. Corbani, G. Davis, M. Davisson, D. Doolittle, J.T. Eppig, K. Frazer, J. Gilbert, P. Grant, M. Lennon-Pierce, L. Maltais, M. May, M. McIntire, J. Ormsby, D. Reed, J. Richardson, M.D. Ringwald, S. Rockwood, S. Sharpe, A. Smith, M. Stanley-Walls, D. Walton. The Jackson Laboratory, Bar Harbor, ME, USA.*

155. **ENHANCEMENTS IN MAP MANAGER 3.0.** *K.F. Manly. Roswell Park Cancer Institute, Buffalo, NY 14263-0001.*

152. THE MOUSE BACKCROSS DATABASE *(MBx). D. Tailor, M. Kelly, R. Williams. MRC Human Genome Mapping Project Resource Centre, Hinxton Hall, Hinxton, Cambridgeshire, CB10 1RQ, UK.*

The *MRx* database contains experimental data derived from the European Collaborative Interspecific Backcross project (EUCIB). It provides facilities to interrogate, map and order new DNA markers via linkage and haplotype analysis. Genetic Maps are derived from data within *MBx* by means of an overnight process and displayed using a collection of tools and display utilities including Jackson's Laboratory, Encyclopaedia of the Mouse Genome software, ACeDB and the World Wide Web. In particular, multimap displays are used to graphically visualise and compare data from MIT and *MBx* to aid in additional error checking.

MBr has now been extended to hold physical mapping data *(see Quaderi et al).* It provides a seemless facility for extracting, manipulating and construction of consensus physical maps. SAM (System for Assembling Markers) is used to interactively assemble YAC contigs and further algorithms within *MBx* are used for building consensus maps. The consensus physical maps are displayed via the World Wide Web.

The URL address for *MBx is:* http://~w.hgmp.nuc.ac.uk/MBx/MBxHomepage.html

153. THE MOUSE GENOME DATABASE 2.0. *J. Battles, R. Blackburn, D. Bradt, G. Colby, L. Corbani, G. Davis, M. Davisson, D. Doolittle, T. Drake, J.T. Eppig, K. Frazer, J. Gilbert, P. Grant, M. Lennon-Pierce, L. Maltais, M. May, M. McIntire, J. Ormsby, D. Reed, J. Richardson, M.D. Ringwald, S. Rockwood, S. Sharpe, S. Shroder, A. Smith, M. Stanley-Walls, D.Walton, The Jackson Laboratory, Bar Harbor, ME, USA.*

Release 2.0 of The Mouse Genome Database (MGD) has recently been made available via the World Wide Web (URL: http://www.informatics jax.org). MGD is a comprehensive genetic database of the mouse that is updated daily from published scientific literature and personal communications. MGD currently contains information on mouse genetic markers, PCR primers and probes information, mapping data, Festing's list of inbred strains, a comprehensive bibliography, and homologies between mouse and over 50 other mammalian species. Query forms provide an easy-to-use interface enabling users to search and retrieve data, sort query results, print reports, and generate postscript files for printing mouse genetic linkage maps. In addition MGD is integrated with the *Encyclopedia of the Mouse Genome* which provides options to run MGD and the *Encyclopedia* interactively. The Mouse Locus Catalog, a compendium of mouse gene descriptions that dates back as early as 1940, is also assessable through MGD

MGD has been designed to meet the rapidly evolving needs of the genetics community. A constant effort is being made to enhance the value of MGD as an international resource. For additional information about MGD, please contact Mouse Genome Informatics User Support, Voice: (207) 288-6445, Fax: (207) 288-2516, Email: mgi-help@informaticsjax.org. *(Supported by NIH grant HG00330.)*

154. NEW FEATURES AND ENHANCEMENTS FOR THE MOUSE GENOME DATABASE. *T. Drake, S. Shroder, J. Battles, R. Blackburn, D. Bradt, G. Colby, L. Corbani, G. Davis, M. Davisson, D. Doolittle, J.T. Eppig, K. Frazer, J. Gilbert, P. Grant, M. Lennon-Pierce, L. Maltais, M. May, M. McIntire, J. Ormsby, D. Reed, J. Richardson, M.D. Ringwald, S. Rockwood, S. Sharpe, A. Smith, M. Stanley-Walls, D. Walton. The Jackson Laboratory, Bar Harbor, ME, USA.*

Since the Mouse Genome Database (MGD) first came on-line via the World Wide Web (http://www.informatics.jax.org) in June 1994, it has continued to evolve by incorporating user suggestions and new technologies. Several new data sets have been added, including haplotype data from **large backcross mapping panels and strain distribution patterns (SDPs) from recombinant inbred** and **recombinant congenic strains.** These composite sets display marker symbols, SDPs, and associated references in hypertext format for exploration of MGD. The haplotype data and SDPs can be downloaded in tab-delimited text or MapManager format for further analysis. In addition, MGD has provided full-text searching of Dr. **Michael FW Festing's listing of inbred strains** (Mouse Genome 1994; 92(3):373-495). Two new features allow MGD users to generate, view, and print the most current mapping information in MGD. The first allows **interaction between the Encyclopedia of the Mouse Genome and MGD;** the second utilizes a new **PostScript Map tool.** The *Encyclopedia* has been improved to enable the user to create and modify genetic linkage maps.

Query forms in MGD have been expanded to allow greater variety and complexity of questions. The enhanced homology query form provides users with an easier format for **searching conserved segments.** Those interested in physical mapping will be able to query probes by vector type and chromosome. MGD provides opportunities for WAIS-based **searches of abstracts** in the master bibliography and of the text in **Mouse Locus Catalog (MLC)** records.

The Mouse Genome Informatics Project values and encourages input from the user community. User Support staff can be reached by Email (mgi-help@informatics.jax.org), by phone (207-288-6445) or by FAX (207-288-2516). *(MGD is supported by NIH grant HG00330.)*

155. ENHANCEMENTS IN MAP MANAGER 3.0. *K.F. Manly Roswell Park Cancer Institute, Buffalo, NY 14263-0001.*

Map Manager is a Macintosh program to assist genetic mapping with backcrosses, intercrosses, and recombinant inbred lines. A new version, version 3.0, is ready for user testing. This version uses a new file format which will be compatible with a Windows version of Map Manager which is under development. File sizes in the new format are about 20% smaller than in the previous format. Opening the new file type is about as fast as opening the old file type, but saving the new file type is noticeably faster. Map Manager 3.0 will open files of either old or new format.

This new file format has allowed two enhancements which have been requested by users. First, the names or numbers which identify progeny or strains can now have up to six characters. Second, notes or comments can be attached to individual progeny or to individual phenotypes. This allows, for example, an edited phenotype to be annotated with the date and reason for the change.

156. **GENOTYPING AND GENOME SCANNING BY IRS-PCR AMPLIFICATION POLYMORPHISM: GENERATION AND CHARACTERIZATION OF PROBE SETS FOR ANALYSIS OF MOST INTERSPECIFIC BACKCROSSES.** *Kent Hunter, Elango Ramu, Laura Riba, Jenny Su, David Housman. Center for Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA. 02139.*

157. **NEW DEVELOPMENTALLY REGULATED MOUSE BRAIN GENES.** *A. Corradi, C.L. Stayton, C. Pardini, D.R. Beier*, E. Boncinelli, M. Gulisano, G.G. Consalez, DIBIT-HSR, Milan, Italy; *Brigham and Women's H., Boston, MA.*

158. **SEQUENCING AND MAPPING OF cDNAs FROM MOUSE EMBRYOS.** *M.S.H. Ko, J.H. Horton, X. Wang, S. Yotsumoto, Y. Cui, T.A. Mosby, C.A. Moore. Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA.*

159. **THE EUROPEAN COLLABORATIVE INTERSPECIFIC BACKCROSS *(EUCIB)*: TOWARDS A HIGH RESOLUTION MICROSATELLITE MAP OF THE MOUSE.** *M. Rhodes[1], R. Straw[1], S. Fernando[1], R. Drake[1], A. Evans[1], T. Seaber[1], D. Tailor[1], M. Kelly[1], Franck Bourgade[2], Christophe Poirier[2], Dominique Simon[2], A. Brunalti[2], X. Montagutelli[2], J.L. Guenet[2], A. Haynes[3], S.D.M. Brown[3]. [1]MRC Human Genome Mapping Project Resource Centre, Hinxton Hall, Hinxton, Cambridgeshire, CP 10 1RQ UK; [2]Institut Pasteur, Paris, France; [3]St. Mary's Hospital Medical School, London. W2 1PG UK.*

160. **SMXA: A NEW SET OF RECOMBINANT INBRED STRAIN OF MICE CONSISTING OF 26 SUBSTRAINS AND THEIR GENETIC PROFILE.** *M. Nishimura[1], N. Hirayama[2], T. Serikawa[2], K. Kanehira[3], Y. Matsushima[4], H. Katoh[5], S. Wakana[5], A. Kojima[6], H. Hiai[3]. [1]Institute for Experimental Animals, Hamamatsu University School of Medicine, Hamamatsu 431-31; [2]Institute of Laboratory Animals; [3]Department of Pathology, Faculty of Medicine, Kyoto University, Kyoto 606; [4]Laboratory of Experimental Animal Science, Saitama Cancer Center Research Institute, Ina, Saitama 362; [5]Central Institute for Experimental Animals, Kawasaki 213; [6]Public Health Bureau, City of Nagoya, Nagoya 460, Japan.*

161. **STRAIN DISTRIBUTION PATTERN FOR 405 GENETIC MARKERS IN THE SWXJ RECOMBINANT INBRED STRAIN SET.** *Karen L. Svenson, Kathryn L. Shultz, Yin-Chai Cheah*, Wesley G. Beamer, Beverly Paigen. The Jackson Laboratory, Bar Harbor, ME; *Baylor College of Medicine, Houston, TX.*

162. **RECOMBINATIONAL AND PHYSICAL MAPS OF MOUSE CHROMOSOME 16.** *M.P. Citron, A.E. Mjaatvedt, D.E. Cabin, J. Lund, J. McKee-Johnson, L. Matesic, W. Luo, D. Patch, R.H. Reeves. Dept. of Physiology, Johns Hopkins Univ. Schl. of Med., Baltimore, MD 21205.*

163. **CHROMOSOMAL LOCALIZATION OF THE MOUSE DNA REPAIR GENE, *xpg*.** *Y.-N. Harada, Y. Matsuda, N. Shiomi, M. Koike, T. Shiomi. Genome Research Group, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263, Japan.*

164. **GENETIC AND PHYSICAL MAPPING OF A MINOR HISTOCOMPATIBILITY ANTIGEN LOCUS ON MOUSE CHROMOSOME 2.** *Aamir R. Zuberi, Julie M. Marwardt, Heidi J. Auman, Gregory J. Christianson, Derry C. Roopenian. The Jackson Laboratory, Bar Harbor, ME, USA.*

165. **GENETIC ANALYSIS OF SUSCEPTIBILITY TO PROMOTION WITH TPA IN THE TWO-STAGE SKIN TUMOR MODEL.** *J.M. Angel, L. Beltran, A. Dubowski, J. DiGiovanni. The University of Texas M.D. Anderson Cancer Center, Science Park-Research Division, Smithville, TX, USA.*

166. **MAPPING THE ERYTHROCYTIC GTP CONCENTRATION DETERMINING TRAIT (*Gtpc*) IN RELATION TO MARKERS ON MOUSE CHROMOSOME 9.** *G.J. Wiebe. E. Fung, F.F. Snyder. Departments of Medical Genetics and Medical Biochemistry, University of Calgary, Calgary, Alberta, Canada.*

167. **TNF-ALPHA HAPLOTYPES AND RESISTANCE TO TRYPANOSOMIASIS IN MHC CONGENIC MOUSE STRAINS.** *F. Iraqi, A.J. Teale. International Livestock Research Institute, P.O. Box 30709, Nairobi, Kenya.*

168. **MAPPING OF CHROMOSOMAL REGIONS CONTROLLING RESISTANCE TO TRYPANOSOMIASIS IN MICE.** *S.J. Kemp[1]*, F. Iraqi[1], A. Darvasi[2], M. Soller[2], A.J. Teale[1]. [1]International Livestock Research Institute, P.O. Box 30709, Nairobi, Kenya; [2]Department of Genetics, Hebrew University of Jerusalem, IL-91904 Jerusalem, Israel. *present address, Dept. of Genetics & Microbiology, University of Liverpool, L69 3BX, UK.*

169. **CLONING, MAPPING AND EXPRESSION OF THE MOUSE iPAF-AHα/LIS-1 GENE.** *Miklos Peterfy, Tibor Gyuris, John C. Hozier,* Bryan Hall,* Krisztina Peterfy, Laszlo Takacs. Department of Biomedical Science, Amgen, Inc., Thousand Oaks, CA, USA; *Applied Genetics Laboratories, Inc., Melbourne, FL, USA.*

170. **AN INTERSTITIAL TELOMERE-RELATED SEQUENCE ON DISTAL CHR 13.** *C.-H. Yen, R.W. Elliott, Roswell Park Cancer Inst., Buffalo, NY, USA.*

171. **WAF1/CIP1(P21): CDNA SEQUENCE, CHROMOSOMAL MAPPING AND EXPRESSION IN THE MOUSE.** *K. Huppi1, D. Siwarski[1], J. Dosik[1], P. Michieli[2], M. Chedid[2], S. Reed[3], B. Mock[1], D. Givol[2], J. F. Mushinski[1]. [1] Mol. Genetics Section, Lab. of Genetics, NCI/NIH, Bethesda, MD 20892; [2]Lab. of Cellular and Molecular Biology, NCI/NIH, Bethesda, MD 20892; [3]Scripps Research Inst., LaJolla, CA 92037-1092.*

172. **CHROMOSOMAL LOCATION OF A MOUSE hsp70 GENE HAVING A HYPERVARIABLE EXON.** *Manabu Ohashi, Mitsuru Oyanagi, Naruya Saitou*, Ryo Kominami. First Department of Biochemistry, Niigata University School of Medicine, Asahimachi-doori 1-757, Niigata 951, Japan; *Laboratory of Evolutionary Genetics, National Institute of Genetics, Mishima 411, Japan.*

173. CLONING AND GENETIC MAPPING OF THE MOUSE CCK RECEPTOR GENES. *Karen Lacourse, Jean Lay, Mike Isakoff, Lisa Swanberg, Linda Samuelson. Department of Physiology, The University of Michigan, Ann Arbor, MI, 48109-0622.*

174. CLONING AND GENETIC MAPPING OF THE MOUSE GASTRIN GENE. *Lennart Friis-Hansen[1,2], Ian Rourke[2], Jens Bundgaard2, Jens Rehfeld[2], Linda Samuelson[1]. [1]Department of Physiology, University of Michigan, Ann Arbor, MI 48109-0622; [2]Department of Clinical Biochemistry, University of Copenhagen Hospital, Copenhagen, Denmark.*

175. CLONING AND FUNCTIONAL IMPLICATIONS OF HUMAN AND MOUSE HOMOLOGUES OF YEAST SPT4, SPTS AND SPT6 GENES: A FAMILY INVOLVED IN CHROMATIN ASSEMBLY OR MODIFICATION. *P.-W. Chiang[2], W.-J. Song[1], D.M. Kurnit[1,2,4]. [1]Howard Hughes Medical Institute; Departments of [2]Pediatrics and [4]Human Genetics, U. of Michigan.*

176. HIGH RESOLUTION GENETIC MAP OF DISTAL MOUSE CHROMOSOME 19. MAPPING OF BPAG-2, α2 AND β1 ADRENERGIC RECEPTORS, FGF-8, PALE EARS, AND THE SCRAGGLY LOCUS. *Bruce Herron, Lorraine Flaherty. SUNY Albany School of Public Health, Wadsworth Center, Albany, NY, USA.*

177. FINE STRUCTURE GENETIC MAP OF THE DISTAL END OF THE MOUSE X CHROMOSOME. *O. Korobova, N. Arnheim. University of Southern California, Los Angeles, CA; P.W. Lane, M.T. Davisson, The Jackson Laboratory, Bar Harbor, ME, USA.*

156. GENOTYPING AND GENOME SCANNING BY IRS-PCR AMPLIFICATION POLYMORPHISM: GENERATION AND CHARACTERIZATION OF PROBE SETS FOR ANALYSIS OF MOST INTERSPECIFIC BACKCROSSES. *Kent Hunter, Elango Ramu, Laura Riba, Jenny Su, David Housman. Center for Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA. 02139.*

A system for rapid, first pass genome scanning of large crosses has been developed to complement the high resolution SSLP mapping techniques *(McCarthy et al., 1995)*. IRS-PCR amplification polymorphism genotyping is based on the observation that different strains of mice amplify different overlapping sets of IRSPCR products, either due to the presence or absence of individual repeats, or sequence divergents between repeats that result in differential amplification. Isolation of these individual strain or species specific IRS-PCR products permit genotype analysis of backcrosses by a plus/minus dotblot strategy. Individual DNA samples are amplified with a repetitive element primer, the products spotted on filters and hybridized with a species specific product derived from the nonrecurrent parent. Segregation of the locus can be easily scored by plus/minus hybridization. This technique permits the analysis of large numbers of animals simultaneously, and is adaptable to high through put genotyping and automation. Utilizing this strategy, we have generated over 200 species specific loci from both C57BL/6 and M. *spretus*, covering an estimated 90-95% of the genome. We are currently generating additional loci for higher density mapping, and are also developing sets of loci that are useful for analysis of intraspecific backcrosses. We believe that this strategy will be a valuable complementary technique for low to medium resolution genome scanning, prior to high resolution mapping of interesting regions by standard SSLP analysis.

157. NEW DEVELOPMENTALLY REGULATED MOUSE BRAIN GENES. *A. Corradi, C.L. Stayton, C. Pardini, D.R. Beier*, E. Boncinelli, M. Gulisano, G.G. Consalez, DIBIT-HSR, Milan, Italy; *Brigham and Women's H., Boston, MA.*

Despite recent advances, mostly based on developmental mechanisms conserved from *Drosophila* to vertebrates, our knowledge of central nervous system (CNS) development in general, and of rostral CNS specification, in particular, remains quite fragmentary. In an attempt to elucidate some of the molecular mechanisms underlying the subdivision and differentiation of primary brain structures during midgestation embryogenesis, we set out to isolate new developmentally regulated brain genes, i.e. transcripts exhibiting temporally or topographically restricted expression patterns in the embryonic mouse brain. By a modified cDNA fingerprinting1,2 protocol, we have compared different stages and regions in the developing CNS. cDNAs have been cloned, sequenced and characterized by mRNA in *situ* hybridization of mouse embryonic CNS sections. Through the analysis of the BSS backcross panel3, new differentially expressed sequence tags (DESTs) have been genetically mapped to *Mus musculus* chromosomes 1, 3, 4, 6, 10, 11, 12, 17. Our work suggests the feasibility of a systematic approach aimed at linking the isolation of developmentally regulated ESTs with map localization and gene expression studies.

1. *Liang, P & Pardee, AB (1992) Science 257: 967-971.*
2. *Welsh J et al. (1992) Nucleic Acid Res. 20: 4965-70.*
3. *Rowe LB et al. (1994) Mammalian Genome 5: 253-274*

158. SEQUENCING AND MAPPING OF cDNAs FROM MOUSE EMBRYOS. *M.S.H. Ko, J.H. Horton, X. Wang, S. Yotsumoto, Y. Cui, T.A. Mosby, C.A. Moore. Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA.*

A high resolution transcriptional map of the mouse genome will be very useful for the positional-candidate approach for the cloning of the human genetic disease genes as well as the mouse mutant genes. Because of the limited access to a certain stage of human embryos, the mouse cDNA project will be a good complement to the currently ongoing large scale human cDNA sequencing and mapping projects.

The first step of our strategy is to construct a cDNA library from various tissues of early mouse embryos. For some tissues, we have applied a cDNA equalization (normalization) technique to these cDNA library. Then, the individual cDNA clones are arrayed in the 96-well microtiter plates. Individual cDNA clones are analyzed by three methods. (1) About 350 bp of the 5'-end and 3'-end of cDNA clones are sequenced. The sequence information will be used for the blast database searches in the NCBI. (2) The localization of cDNAs on the mouse genetic map are determined by typing the Jackson laboratory's interspecific backcross mouse panels with PCR-based cDNA markers. (3) The expression patterns of the cDNA clones are examined by using in situ hybridization.

Currently we are working on the cDNA library made from the ectoplacental cone of 7.5 dpc mouse embryos. The progress of this project will be presented in this meeting.

159. THE EUROPEAN COLLABORATIVE INTERSPECIFIC BACKCROSS *(EUCIB)*: TOWARDS A HIGH RESOLUTION MICROSATELLITE MAP OF THE MOUSE. *M. Rhodes[1], R. Straw[1], S. Fernando[1], R. Drake[1], A. Evans[1], T. Seaber[1], D. Tailor[1], M. Kelly[1], Franck Bourgade[2], Christophe Poirier[2], Dominique Simon[2], A. Brunalti[2], X. Montagutelli[2], J.L. Guenet[2], A. Haynes[3], S.D.M. Brown[3]. [1]MRC Human Genome Mapping Project Resource Centre, Hinxton Hall, Hinxton, Cambridgeshire. CP 10 1RQ UK; [2]Institut Pasteur, Paris, France; [3]St. Mary's Hospital Medical School, London. W2 1PG UK.*

The European Backcross *(EUCIB)* provides a high resolution genetic mapping resource – 0.3cM (0.5Mb) with 95% confidence – a resolution comparable to the size of an average YAC clone. A major program is now underway – with the Whitehead Institute/MIT Center for Genome Research, USA – to provide a high resolution, genetically-ordered map of up to 6,000 microsatellites on the *EUCIB* backcross. To date, seven chromosomes – 11, 15, 16, 17, 18, 19 and X – have been completed. Microsatellite data is entered into the *MBx* database *(see Tailor et al.)* that handles all the necessary genetic information and genetic map production. Around 30 microsatellites a week are being added to the mouse genetic map and progress and status of the high resolution maps of individual chromosomes will be reviewed. The development of a high resolution map will underpin efforts towards the creation of a high integrity, YAC physical map of the mouse genome. In addition, *EUCIB* operates a user service for the mapping of new loci on the mouse genome and over 100 users have assigned over 400 new loci on the *EUCIB* cross to date. The current high resolution maps are available on the World Wide Web: http://www.hgmp.mrc.ac .uk/MBx/MBxHomepage.html

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We have established a new set of RI strains SMXA consisting of 26 substrains from the progenitor strains SM/J and A/J. A total of 158 loci including 134 microsatellite length polymorphisms, 14 biochemical genetic markers, 7 cell surface isoantigens, 2 coat color genes and 1 other biological marker were typed for all 26 substrains. Based on the strain distribution patterns among SMXA RI strains, 3 salivary and 1 tear protein genes were newly mapped. Because there are many noteworthy differences between SM/J and A/J in a variety of phenotypes, the SMXA set should be useful for analysis of both simple and complex genetic traits.

161. **STRAIN DISTRIBUTION PATTERN FOR 405 GENETIC MARKERS IN THE SWXJ RECOMBINANT INBRED STRAIN SET.** *Karen L. Svenson, Kathryn L. Shultz, Yin-Chai Cheah*, Wesley G. Beamer, Beverly Paigen. The Jackson Laboratory, Bar Harbor, Maine; *Baylor College of Medicine, Houston, Texas.*

We typed 366 simple sequence length polymorphisms spanning the genome in the SWXJ recombinant inbred (RI) strain set. The strain distribution pattern for these loci was combined with data from 39 previously typed loci for SWXJ, resulting in new chromosome maps for this RI set, with an average density of 3.5 cM between loci. Until now, the small number of loci typed in the SWXJ RI set has limited its usefulness. With 405 genetic loci now typed for SWXJ, it will be useful as an initial indicator of loci which might be conferring resistance and/or susceptibility to traits in which the progenitors differ, such as atherosclerosis. This data represents the first systematic attempt to develop a densely marked, error-free SDP matrix that can be used for subsequent mapping projects. All questionable results were checked, and adjacent loci that had more than the expected number of crossover events were tested on backcross animals to confirm the chromosomal linkage. With this effort, we have significantly improved the power of this genetic tool for mapping genes underlying both simple and complex genetic disorders.

162. RECOMBINATIONAL AND PHYSICAL MAPS OF MOUSE CHROMOSOME 16. *MP Citron, AE Mjaatvedt, DE Cabin, J Lund, J McKee-Johnson, L Matesic, W Luo, D Patch, RH Reeves. Dept. of Physiology, Johns Hopkins Univ. Schl. of Med., Baltimore, MD 21205.*

A recombinational map has been built to serve as a scaffold for physical mapping of mouse Chr16. The mapping template consists of 350 chromosomes 16 with defined crossover points. Recombinant chromosomes were derived from five crosses that display different regional recombination frequencies. An interval mapping strategy was used to divide the chromosome into 10 segments, and 118 markers have been placed at 69 unique positions on the map, producing average locus spacing of 0.94 cM or average marker spacing of 0.55 cM. Ten additional positional assignments were resolved on the YAC mapping panel. Nucleation of a YAC-based physical map is accomplished by screening extant YAC libraries from M.I.T. (via Research Genetics) and ICRF plus St. Mary's (via Baylor YAC Screening Service) for YACs containing genes across Chr16 and for all markers in the region of homology with HSA21. Conventional walking strategies are used to fill in these maps, resulting in coverage of approximately 5 MB on distal Chr16 and 2MB on proximal Chr16. In addition, a new vector set has been constructed to produce Chr16-specific YACs from a mouse X hamster somatic cell hybrid by homologous recombination-based cloning. Vectors are cotransformed with HMW DNA from the hybrid and yeast are selected for the vector markers. The new vectors fragment mouse but not hamster YACs, demonstrating the required specificity for cloning. Finally, minimal tiling path YACs are fragmented to produce a high resolution physical map with markers of known spacing separated by 30±32kb across 7 MB of Chr16. Fragmented ends are rescued and sequenced to produce PCR primers for screening a mouse BAC library *(in collaboration with Bruce Birren, MIT).*

163. CHROMOSOMAL LOCALIZATION OF THE MOUSE DNA REPAIR GENE, *xpg.* *Y.-N. Harada, Y. Matsuda, N. Shiomi, M. Koike, T. Shiomi. Genome Research Group, National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263, Japan.*

We have molecularly cloned the mouse counterpart of the human repair gene XPG/ERCC5. Chromosomal location of the *xpg* gene has been determined by both *in situ* hybridization and molecular linkage analysis. The *xpg* gene was localized at 2.3 cM proximal to the microsatellite locus D1 Mit18 on R-positive B band of mouse chromosome 1. *By in situ* hybridization with the mouse *xpg* probe, the rat homolog of the mouse *xpg* was localized on q22.3 band of rat chromosome 9 that has been known to have a conserved linkage homology to mouse chromosome 1. In the case of human, the XPG/ ERCC5 gene has been reported to be assigned on human chromosome 13q32.3-q33.1, where any conserved linkage homology to mouse chromosome 1 has not been found so far. Thus, these results show new regions of conserved linkage homology between mouse 1, rat chromosome 9, and human chromosome 13q.

164. GENETIC AND PHYSICAL MAPPING OF A MINOR HISTOCOMPATIBILITY ANTIGEN LOCUS ON MOUSE CHROMOSOME 2.

Aamir R. Zuberi, Julie M. Marwardt, Heidi J. Auman, Gregory J. Christianson, Derry C. Roopenian. The Jackson Laboratory, Bar Harbor, Maine, USA.

Minor histocompatibility *(H)* loci encode alloantigens that are polymorphic between different inbred strains of mice. These antigens are small peptides that are presented on the surface of cells by the major histocompatibility protein complex (MHC). We are interested in the characterization of genes that contribute to the transplantation rejection phenotype attributed to the classical *H3* minor *H* locus located on mouse Chromosome 2. Three separate genes have been identified within the *H3* complex. One gene is β2-microglobulin *(B2m)*. Polymorphism of *β2m* seems to influence the repertoire of peptides presented by the MHC. Another minor *H* gene identified is *H3a*. Alloantigens determined both by *β2m* and *H3a* are presented by class I MHC molecules and selectively stimulate $CD8^+$ cytotoxic T lymphocytes (CTLs). The third minor *H* gene is *H3b*. Alloantigens determined by *H3b* are presented by class 11 MHC molecules and selectively stimulate $CD4^+$ helper T lymphocytes.

We have completed the generation of high resolution genetic maps spanning the *H3a* and *H3b* genes. These genes are located approximately 10 -12 cM apart on the central region of Chromosome 2. We have also identified Yeast Artificial Chromosomes (YACs) that contain mouse DNA from these two regions. We describe our current progress in the completion of a physical map of these regions of the mouse genome and our attempts to identify the locations of the two minor H genes within the two YAC contigs.

165. GENETIC ANALYSIS OF SUSCEPTIBILITY TO PROMOTION WITH TPA IN THE TWO-STAGE SKIN TUMOR MODEL.

J.M. Angel, L. Beltran, A. Dubowski, J. DiGiovanni. The University of Texas M.D. Anderson Cancer Center, Science Park-Research Division, Smithville, Texas, USA.

There are significant mouse strain differences in susceptibility to two-stage, initiation-promotion skin carcinogenesis when phorbol esters such as 12-O-tetradecanoylphorbol-13-acetate (TPA) are used as promoters. Results from studies of TPA promotion in genetic crosses of the responsive inbred mouse strain DBA/2 with the non-responsive inbred mouse strain C57Bl/6 indicated that susceptibility to the tumor promoting action of TPA is a multigenic autosomal trait that displays incomplete dominance. Cluster analysis of susceptibility to TPA promotion in BXD recombinant inbred strains suggests four phenotypes: non-responsive, moderately responsive, responsive and hyper-responsive. From these studies, a three-locus genetic model has been proposed. To ascertain the chromosomal map locations of these genes we have begun to determine the genotypes at simple sequence repeat marker loci for the (C57Bl/6 x DBA/2) x C57Bl/6 mice used in these studies. Preliminary results suggest linkages of susceptibility to mouse chromosomes 9 and 10. *(Supported by USPHS grant CA37111 and ACS FRA375.)*

166. MAPPING THE ERYTHROCYTIC GTP CONCENTRATION DETERMINING TRAIT (*Gtpc*) IN RELATION TO MARKERS ON MOUSE CHROMOSOME 9.

G.J. Wiebe. E. Fung, F.F. Snyder. Departments of Medical Genetics and Medical Biochemistry, University of Calgary, Calgary, Alberta, Canada.

A survey of inbred strains for erythrocytic nucleotides segregated into two groups with respect to their GTP/ATP ratio by rankits and Student-Newman-Keuls analyses ($p = 0.01$). Strains exhibiting low GTP/ATP ratios, 0.023-0.059, are: C3H/HeHa *Pgk-1a*, CD-1, SWV, NOD/Lt, CDS/Lay, SWR/J, BALB/cByJ, SPRET-1, WC/ReJ, WB/ReJ(WB); and those having high GTP/ATP ratios, 0.248-0.315, are: CBA/FaCam, C57Bv6J(B6), DBA/2J and PERU W-1-II. ATP did not vary significantly amongst these strains, 689-1040 nmole/ml erythrocytes ($p = 0.01$). Erythrocytic GTP variation was previously shown to be governed by a single gene, *Gtpc*, and linked to *Trf* on chromosome 9 *(Genome 37:399, 1994)*. 232 backcross progeny, [(B6xWB)FIXB6]BC_1, were typed for *Gtpc* and 5 microsatellite markers. The following gene order and map distances were obtained: *D9Mit14* (0.43 ± 0.43) *D9Mit24* (1.72 ± 0.85) *Gtpc* (3.88 ± 1.27) *D9Mit200* (3.02 ± 1.12) *D9Mit20* (7.76 ± 1.76) *D9Mit1 8*. *(Supported by the Medical Research Council of Canada.)*

167. TNF-ALPHA HAPLOTYPES AND RESISTANCE TO TRYPANOSOMIASIS IN MHC CONGENIC MOUSE STRAINS.

F. Iraqi, A.J. Teale. International Livestock Research Institute, P.O. Box 30709, Nairobi, Kenya.

Early studies of MHC congenic mouse strains revealed no correlation between serologically defined H-2 haplotypes and resistance to *Trypanosoma congolense* infection (trypanotolerance). Since the mapping of trypanotolerance in mice shows a strong effect on chromosome 17, in a region which includes the MHC, TNF alpha was selected for further study in MHC congenic strains. Three regions of the TNF alpha genes of resistant and susceptible mouse strains, the promoter, first intron and the 3' untranslated regions, were examined for restriction fragment length polymorphisms in PCR-generated fragments (RFLP-PCR). A common RFLP-PCR haplotype was found in the trypanosusceptible BALB/c and AJ strains, which differs from the common haplotype occurring in the resistant C57BU6 and C57BU10 strains. MHC congenic strains produced by integration of the MHC region of the A, DBA/2 and C57BR/cd MHC haplotypes into the C57BU10 background have been shown previously to be relatively susceptible to trypanosomiasis. As expected, TNF haplotyping of the congenic strains revealed that in all cases, they possess the donor TNF alpha haplotype. The most susceptible B10.A and B10.D2 congenic strains have typically "susceptible" TNF alpha haplotypes. Of the MHC congenic strains, the B10.BR was found previously to be relatively resistant (although more susceptible than the C57BU10 recipient strain), and its TNF alpha haplotype is intermediate between that of the resistant C57BU10 and the susceptible B10.A and B10.D2 strains. These results support the hypothesis that the TNF alpha gene has a role in resistance to trypanosomiasis in inbred laboratory strains of mice.

168. MAPPING OF CHROMOSOMAL REGIONS CONTROLLING RESISTANCE TO TRYPANOSOMIASIS IN MICE.

S.J. Kemp[1], F. Iraqi[1], A. Darvasi[2], M. Soller[2], A.J. Teale[1]. [1]International Livestock Research Institute, P.O. Box 30709, Nairobi, Kenya; [2]Department of Genetics, Hebrew University of Jerusalem, IL-91904 Jerusalem, Israel. *present address, Dept. of Genetics & Microbiology, University of Liverpool, L69 3BX, UK.*

Tsetse fly-transmitted trypanosomiasis is one of the most important disease complexes of domestic livestock in Africa, with approximately 44 million cattle at risk. Some west African cattle breeds are genetically resistant to the effects of trypanosomiasis, the trait being referred to as "trypanotolerance". The ability to remain productive under trypanosomiasis challenge is the most desirable trait of these breeds which generally lack other qualities desired by livestock owners. Mapping and cloning of trypanotolerance genes will facilitate development of new breeds of livestock which combine this important disease resistance trait with desirable productivity traits. A mouse model has been used for mapping trypanotolerance genes by linkage analysis, and taking advantage of the large number of microsatellites which are now available for use in the mouse. An F2 population, derived from a cross between trypanotolerant C57BL/6 and trypanosusceptible BALB/c inbred strains, was phenotyped for resistance to the effects of *Trypanosoma congolense* infection and the phenotypic extremes were genotyped. This study has identified three chromosomal regions with large effects on responses to trypanosome infection in laboratory mice. The largest effect was found on chromosome 17 (11 LOD scores) in the region of the major histocompatibility complex (MHC). Two additional effects were found on chromosomes 1 and 5, with LOD scores of 5.5 and 4.5 respectively. The combined effects of these genetic regions account for the differences between parental strains and for more than 35% of the total variance in the F2 population studied. Currently an F6 generation is being produced to allow higher resolution mapping preparatory to positional cloning.

169. CLONING, MAPPING AND EXPRESSION OF THE MOUSE iPAF-AHα/LIS-1 GENE.

Miklos Peterfy, Tibor Gyuris, John C. Hozier, Bryan Hall,* Krisztina Peterfy, Laszlo Takacs. Department of Biomedical Science, Amgen, Inc., Thousand Oaks, California, USA; *Applied Genetics Laboratories, Inc., Melbourne, Florida, USA.*

Lissencephaly is a human brain malformation manifested by a smooth cerebral surface and severe mental retardation. The underlying cause of this neurological disorder is thought to be an impaired neuronal migration during embryonal development. In a significant number of the lissencephaly patients chromosomal deletions can be detected at 17p13.3, and recently, the disease associated gene (LIS-1) has been identified. Surprisingly, LIS-1 has been found to be a subunit of the intracellular form of platelet-activating factor acetylhydrolase (iPAF-AHα), suggesting a role in phospholipid metabolism.

In order to study the function of iPAF-AH and to gain insight into the disease mechanism of lissencephaly, we characterized the iPAF-AHα/Lis-1 gene in the mouse. We have cloned several cDNAs from a brain specific library, and identified three genes hybridizing to the Lis-1 cDNA probe. Chromosomal localization by FISH and STS content mapping to YACs indicated that one of these genes was the mouse homolog of the human LIS-1 gene. The evolutionary conservation and expression pattern of this gene have also been analyzed.

170. AN INTERSTITIAL TELOMERE-RELATED SEQUENCE ON DISTAL CHR 13. *C.-H. Yen, R.W. Elliott. Roswell Park Cancer Inst., Buffalo, NY, USA.*

We have previously presented evidence for arrays of the telomere hexamer sequence at interstitial sites on mouse Chrs 6, 8 and 11. A fourth such array was identified in lambda clones from inbred strains, C57BL/10J and BALB/cJ. Sequences from both clones have been mapped to the same genetic site in the mouse genome, using FISH, RI strain analysis and analysis of allele segregation in backcross progeny. The results suggest that *Tel-rs4 is* about 5 map units proximal to the telomere of Chr 13. YAC clones were isolated using an STS from the lambda clone from C58BL/10J and using primers for a distal SSR, D13Mit35. Maps of the YAC insert DNAs showed that the physical distance between *Tel-rs4* and *D13Mit35* is consistent with the genetic distance.

171. WAF1/CIP1(P21): CDNA SEQUENCE, CHROMOSOMAL MAPPING AND EXPRESSION IN THE MOUSE. *K. Huppi[1], D. Siwarski[1], J. Dosik[1], P. Michiel[2], M. Chedid[2], S. Reed[3], B. Mock[1], D. Givol[2], J. F. Mushinski[1]. [1] Mol. Genetics Section, Lab. of Genetics, NCI/NIH, Bethesda, MD 20892; [2]Lab. of Cellular and Molecular Biology, NCI/NIH, Bethesda, MD 20892; [3]Scripps Research Inst., LaJolla, CA 92037-1092.*

The recent discovery that expression of Waf1/Cip1 (p21), an inhibitor of cyclin-dependent kinases, is induced by the tumor suppressor p53 provides an important linkage between growth suppression and the cell cycle. We have cloned and sequenced a mouse p21 cDNA that contains the entire coding region. Hybridization of the mouse p21 probe in Southern blot analyses confirms that p21 is a single-copy gene and that the corresponding locus, *Waf1*, lies proximal to *H-2* on mouse chromosome 17. In northern analyses, the expression of p21 is found in most normal mouse tissues, but a surprising lack of correlation is found between mRNA levels of p21 and p53. In order to determine which regions of p21 are most evolutionarily conserved, we have compared the cDNA sequences for the entire p21 coding region in 13 different mouse strains or species and the human p21 sequence. We conclude that two regions (corresponding to human codons 21-60 and 130-164) are strongly conserved in p21 and that these regions may represent domains that are especially critical to a functional p21 protein.

172. CHROMOSOMAL LOCATION OF A MOUSE hsp70 GENE HAVING A HYPERVARIABLE EXON. *Manabu Ohashi, Mitsuru Oyanagi, Naruya Saitou*, Ryo Kominami. First Department of Biochemistry, Niigata University School of Medicine, Asahimachi-doori 1-757, Niigata 951, Japan; *Laboratory of Evolutionary Genetics, National Institute of Genetics, Mishima 411, Japan.*

The 70 kd heat shock proteins (hsp70) function in folding of peptides, the assembly and disassembly of protein complexes. They are encoded by a multigene family comprising both heat-inducible and constitutively expressed genes. PBP74, a member of the hsp70 family, was found a peptide-binding protein implicated in antigen processing. The gene is mapped to the centromeric region of mouse chromosome 18 by a linkage analysis using a panel of an inter-subspecific backcross mice. Its chromosomal location is different from those of the other members reported. Interestingly, an exon of this gene exhibits a unique variation among 16 laboratory mice examined;i.e., four nucleotide substitutions are found in nonsynonymous sites whereas no substitution is detected in synonymous sites. Besides, changes in one position give three different amino acids. This suggests that the gene region may be subject to over-dominant selection during evolution as in the case of the antigen recognition site of the major histocompatibility complex molecules.

173. CLONING AND GENETIC MAPPING OF THE MOUSE CCK RECEPTOR GENES. *Karen Lacourse, Jean Lay, Mike Isakoff, Lisa Swanberg, Linda Samuelson. Department of Physiology, The University of Michigan, Ann Arbor, MI, 48109-0622.*

Cholecystokinin (CCK) is an important gastrointestinal peptide hormone that regulates digestion and feeding behavior. Thus it may play a role in the genesis of eating disorders and obesity. There are two CCK receptors that differ in their sites of expression as well as in their agonist and antagonist binding characteristics. We have cloned the mouse CCK_A and CCK_B receptor genes from a genomic lambda library and gene structures have been largely determined by comparison to cDNA clones prepared by reverse transcriptase polymerase chain reaction. The chromosomal locations of the CCK receptor genes were determined using The Jackson Laboratory interspecific mouse backcross: (C57BL/6 *X Mus spretus*)F_1 *X Mus spretus*. We typed 94 backcross progeny for inheritance of the parental alleles by Southern analysis of variant restriction fragments using rat cDNA probes. This analysis localized the CCK_A and CCK_B receptors to mouse chromosomes 5 and 7, respectively. Of particular interest was the location of the CCK_B receptor on mouse chromosome 7 near *hbb*, in the region of the spontaneous obesity mutant tubby *(tub)*. To determine the physiologic functions mediated by each receptor type we are currently developing targeting vectors that can be used to disrupt the genes in mouse embryonic stem cells and create receptor-deficient mouse mutants.

174. CLONING AND GENETIC MAPPING OF THE MOUSE GASTRIN GENE. *Lennart Friis-Hansen[1,2], Ian Rourke[2], Jens Bundgaard[2], Jens Rehfeld[2], Linda Samuelson[1]. [1]Department of Physiology, University of Michigan, Ann Arbor, MI 48109-0622; [2]Department of Clinical Biochemistry, University of Copenhagen Hospital, Copenhagen, Denmark.*

The peptide hormone gastrin is an important regulator of acid secretion in the stomach. Gastrin stimulates the growth of the gastric mucosa, and greatly elevated levels have been associated with the development of ECL stomach tumors. Gastrin is also expressed during fetal development where it may function as a growth factor for pancreatic organogenesis. The mouse gastrin gene *(Gas)* was isolated from a 129/Sv genomic library and compared to cDNAs cloned from a mouse stomach cDNA library. The gene consists of three exons totaling 463 bp that code for a nascent protein of 101 amino acids. The gene structure is similar to that of the human and bovine gastrin genes, and resembles that of the gene for cholecystokinin, a related peptide hormone. We have mapped *Gas* to mouse Chromosome (Chr) 11 by typing a polymorphic dinucleotide (CA) repeat in the Jackson Laboratory BSS backcross. *Gas* was localized to the distal portion of Chr 11, near *Mpmv8*. To elucidate the role of gastrin peptides in fetal development and in gastrointestinal physiology, we are creating a gastrin-deficient mouse by gene targeting in mouse embryonic stem (ES) cells. A replacement targeting vector has been constructed to disrupt the gastrin gene in ES cells by homologous recombination. The targeting construct contains 10 kb of gastrin gene sequences and deletes the entire gene. A gene targeting experiment is currently being carried out to establish the gastrin gene deletion in ES cells so that it can be transferred to the mouse germline to create a gastrin-deficient mouse strain.

175. CLONING AND FUNCTIONAL IMPLICATIONS OF HUMAN AND MOUSE HOMOLOGUES OF YEAST SPT4, SPTS AND SPT6 GENES: A FAMILY INVOLVED IN CHROMATIN ASSEMBLY OR MODIFICATION. *P.-W. Chiang[2], W.-J. Song[1], D.M. Kurnit[1,2,4]. [1]Howard Hughes Medical Institute; Departments of [2]Pediatrics and [4]Human Genetics, U. of Michigan.*

The SPT4, SPTS and SPT6 genes of *Saccharomyces cerevisiae* function together in a transcriptional process that is essential for viability in yeast through establishment or maintenance of chromatin structure. We isolated human and mouse homologues of the yeast SPT4, SPTS and SPT6 genes. The human SPT6 homologue was localized to chromosome 17q11.2 by PCR screening of monochromosomal and regional mapping panels. Two-color FISH data mapped this gene 1-4 Mb centromeric to the NF-1 gene. The mouse Spt6 homologue was mapped by following the segregation of a polymorphism between strains to chromosome 11. Human and mouse homologues of yeast SPT4 were mapped to chromosome 2, 12, and 17 for human and chromosome 6, 10 and 11 for mouse, respectively. Northern blot results showed that the transcript size of human and mouse SPT6 are 7.5 and 7.0 kb, respectively. The transcripts were expressed in all adult tissues analyzed. There are two different transcripts for the human SPT4 homologue (0.7 and 1.4 kb) and only one for the mouse homologue (0.7 kb). Interestingly, the expression pattern of human SPT4 differs significantly among different tumor cell lines.

Cloning of the mammalian counterparts of genes that mediate chromatin formation in yeast is likely to yield genes that control development and oncogenesis in mammals. Based on the high homology to a gene family, the presence of an SH2 motif in SPT6, the function of this family in yeast and the control of the cell cycle in *C.elegans*, this family of genes is likely to be involved in mammalian tumorigenesis.

176. HIGH RESOLUTION GENETIC MAP OF DISTAL MOUSE CHROMOSOME 19. MAPPING OF BPAG-2, α2 AND β1 ADRENERGIC RECEPTORS, FGF-8, PALE EARS, AND THE SCRAGGLY LOCUS.

Bruce Herron, Lorraine Flaherty. SUNY Albany School of Public Health, Wadsworth Center, Albany, New York, USA.

Our lab is currently refining methods to generate and define heritable mutations in the mouse that are important to normal development. We have created a variety of recessive viable germline mutations using chlorambucil. In particular we have identified a mutation with skin and hair abnormalities that we have tentatively named *scraggly.* This phenotype is identified by a disheveled coat, hair loss, hyperkeratosis, and abnormally large sebaceous glands. Genetic analysis of this mutation indicates it is a single locus mapping to the distal half of chromosome 19.

In the process of positionally cloning this mutation we have generated a 700+ backcross segregating the scraggly locus and the previously described mutation pale ears. A high resolution genetic map based on GT repeat polymorphisms will be presented. To evaluate potential candidate genes mapping to this region we have also mapped several previously described loci to more precise positions in this region.

177. FINE STRUCTURE GENETIC MAP OF THE DISTAL END OF THE MOUSE X CHROMOSOME.

O. Korobova, N. Arnheim. University of Southern California, Los Angeles, California; P.W. Lane, M.T. Davisson, The Jackson Laboratory, Bar Harbor, Maine, USA.

We used an intersubspecific backcross panel [(CAST/Ei x C3H/HeJ-*Paf*/Y) *x* C3H/HeJ+/Y] of 809 animals to refine the chromosomal position of the locus patchy fur *(Paf)* in preparation for positional cloning. *Paf,* which increases the frequency of X-Y nondisjunction, was originally mapped to the distal portion of the the X chromosome and remains the most distal X-specific gene. The position of ten X chromosomal MIT markers, amelogenin (*Amg*), *Paf* and a marker for the telomere *(TelXqYq)* from clone PAR4 *(D. Kipling et al. in press)* is shown below.

Except for *Paf,* genotypes were determined using PCR. The Amg polymorphism was detected by allele-specific PCR based on two nucleotide sequence differences between the two subspecies used in the backcross. Primers derived from clone PAR4 amplify different size fragments from the two subspecies. Recombination fractions for the intervals are indicated in centimorgans and as a fraction of the animals typed.

							DXMit71					
					DXMit29		*DXMit30*					
(Cen)DXMit20	–	*DXMit122*	–	*DXMit222*	– *DXMit160*	– *DXMit223*	– *DXMit184*	– *DXMit100*	- -	*Amg*	– *Paf*	– *PAR4(Tel)*
	0.6		0.1		0.4	0.1	0.6	0.1	0.1		0.3	0.2
	5/809		1/809		3/809	1/809	5/809	1/809	1/809		2/614	2/591

178. MOUSE *BRCA1:* ISOLATION, SEQUENCING, AND IDENTIFICATION OF EVOLUTIONARILY CONSERVED DOMAINS. *K.J. Abel[1], J. Xu[1], G-Y. Yin[1], R. Lyons[1], M.H. Meisler[1], B.L. Weber[2]. [1]University of Michigan, Ann Arbor, MI, USA; [2]University of Pennsylvania, Philadelphia, PA, USA.*

179. SEVEN GENES FORMS A T-BOX FAMILY IN THE MOUSE. *Sergei I. Agulnik, Sarah N. Hancock, Nancy Garvey, Irina I. Agulnik, Ilya Ruvinsky, Virginia E. Papaioannou*, Lee M. Silver. Department of Molecular Biology, Princeton University, Princeton, NJ; *Department of Genetics and Development, Columbia University, New York, NY, USA*

180. GENETIC & PHYSICAL MAPPING OF MYODYSTROPHY, LOCATED IN THE MOUSE 8 - HUMAN 4q SYNTENIC REGION. *K.A. Mills, K.D. Mathews. Depts. of Pediatrics & Neurology, University of Iowa, Iowa City, IA, USA.*

181. PHYSICAL ANALYSIS OF THE HOMOLOGOUS SEQUENCES TO THE IMPRINTED MOUSE GENE *U2afbprs* IN THE HUMAN GENOME. *S. Pearsall[1], A. Brozowska[2], P.J. deJong[2], C. Plass[1], I. Kalcheva[1], S. Sait[2], T. Shows[2], H. Shibata[3], Y. Hayashizaki[3], V. Chapman[1]. [1]Molecular and Cellular Biology Department, [2]Human Genetics Department, Roswell Park Cancer Institute, Buffalo, NY; [3]Genome Science Laboratory, RIKEN Tsukuba Life Science Center, Tskuba Ibaraki, Japan.*

182. COMPARATIVE MAPPING OF MMU19 AND HUMAN 11q13. *M. Fernandes[1,2], F. Rotomondo1, A. Courseaux[2], P. Gaudray[2], G.F. Carle[1]. [1]LEGM, [2]LGMCH, CNRS URA 1462, Universite de Nice, France.*

183. LENGTHY ANCESTRAL HAPLOTYPES MARKED BY MOUSE $C4^k$. *P.P. Jiang, T.H. Hansen, R.D. Miller.Washington University School of Medicine, St. Louis, MO, USA.*

184. DUPLICATION OF THE MAMMALIAN SEX-DETERMINING LOCUS, *Sry*. *B.L. Lundrigan, P.K.Tucker. Museum of Zoology and Department of Biology, University of Michigan, Ann Arbor, MI, USA.*

185. EXPRESSION AND LOCATION OF GENES IN A REGION OF THE X CHROMOSOME THAT DIFFERS BETWEEN LABORATORY STRAINS AND *M. SPRETUS*. *C.M. Disteche, E. Rugarli[1], K. Tsuchiya, M.B. Dinulos, D.A. Adler, A. Ballabio[1], V.M. Chapman[2]. University of Washington, Seattle, WA, USA; [1]Tigem, Milano, Italy; [2]Roswell Park Cancer Institute, Buffalo, NY, USA.*

186. A CONTRAVENTION OF OHNO'S LAW IN MICE. *Steve Palmer, Jo Perry, Alan Ashworth. CRC Centre for Cell and Molecular Biology, Chester Beatty Laboratories, The Institute of Cancer Research, Fulham Road, London SW3 6JB, UK.*

187. COMPARATIVE ANALYSIS OF GENES OF THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) OF RAT (*RT1* SYSTEM) AND MOUSE (*H2* SYSTEM). *Doris Lambracht[1,2], Hong Xiao[1], Roger A. Schultz[3], Kurt Wonigeit[2], Kirsten Fischer Lindahl[1]. [1]Howard Hughes Medical Institute; [3]Dep. Pathology, Univ. Texas Southwestern Med. Ctr., Dallas TX, USA; [2]Medizinische Hochschule Hannover, Germany.*

188. DEVELOPMENTAL VARIATION IN THE DEGREE OF DOMINANCE OF DIABETES (*db*). *G.E. Truett[1], R.J. Tempelman[2], J.A. Walker1, P. Xu[1]. [1]Pennington Biomedical Research Center, Baton Rouge, LA 70808; [2]Department of Animal Science, Michigan State University, East Lansing, MI 48824.*

189. THE GSDB ANNOTATOR. *Carol Harger, Judy Blake*, Jillian Burton, David Crowley, Ada Espinosa-Lujan, Ken Fasman**, Gifford Keen, Mo Manning, Shelley March, Mia McLeod, John O'Neill, Alicia Power, Maria Pumilia, David Rider, Jolene Schwertfeger, Linda Smyth, Nina Thayer, Charles Troup, Ed Uberbacher#, Chris Fields. National Center for Genome Resources, Santa Fe, NM; *The Institute for Genomic Research, Rockville, MD; **Johns Hopkins University, Baltimore, MD; #Oak Ridge National Laboratory, Oak Ridge, TN.*

178. MOUSE *BRCA1:* ISOLATION, SEQUENCING, AND IDENTIFICATION OF EVOLUTIONARILY CONSERVED DOMAINS. *K.J. Abel[1], J. Xu[1], G-Y. Yin[1], R. Lyons[1], M.H. Meisler[1], B.L. Weber[2]. [1]University of Michigan, Ann Arbor, Michigan, USA; [2]University of Pennsylvania, Philadelphia, Pennsylvania, USA.*

Mutations in a gene on human chromosome 17q21 *(BRCA1),* conferring susceptibility to breast and ovarian cancer, have recently been identified. However, the broad distribution of reported *BRCAI* mutations has hindered identification of important functional domains. In an effort to identify domains conserved during mammalian evolution, we have isolated cDNAs corresponding to murine *Brca1* and have compared the nucleic acid and predicted protein sequences from both species. Human *BRCA1* probes were used to isolate cDNAs spanning at least 7 kb from an 8.5 day mouse embryo (C57BL) library. The mouse cDNA sequence predicts a protein of 1812 amino acids. Allowing for gaps to maximize alignment, the human and mouse protein sequences display 58% identity (73% similarity) overall. The more highly conserved regions lie near the amino and carboxyl termini. Of particular interest, the amino terminal regions encode a putative C3HC4 zinc-binding RING finger domain that lies within a stretch of 50 identical amino acids in both species. The strong conservation argues for the importance of this domain, perhaps mediating a role for *BRCA1* in DNA binding and/or transcription. Both human and mouse proteins also display a highly acidic domain within the COOH-terminal half, suggesting a role in transcriptional activation. Though most human *BRCA1* mutations result in protein truncation, the majority of disease-associated missense mutations (6/7) have occurred within these more highly conserved regions. Using an interspecific backcross panel, mouse *Brca1* was mapped to a region on chromosome 11 that exhibits conserved linkage with the human chromosomal region 17q21.

179. SEVEN GENES FORMS A T-BOX FAMILY IN THE MOUSE. *Sergei I. Agulnik, Sarah N. Hancock, Nancy Garvey, Irina I. Agulnik, Ilya Ruvinsky, Virginia E. Papaioannou*, Lee M. Silver. Department of Molecular Biology, Princeton University, Princeton, NJ; *Department of Genetics and Development, Columbia University, New York, NY, USA*

The Brachyury (T) gene encodes a protein with specific DNA binding activity and plays a crucial and conserved role in development of all vertebrate organisms. Six new genes have been discovered in the mouse with a 560 bp region of homology to the Brachyury gene (T-box domain). They have been named Tbx1-Tbx6. Each T-box gene is expressed in a unique spatial and temporal pattern during mouse embryogenesis and the whole family most probably serves as transcriptional regulators. Sequence analysis shows close relatedness of Tbx2 and Tbx3, and Tbx4 and 5 within the T-box region. Two pairs of genes – Tbx2 and Tbx4, and Tbx3 and Tbx5 – have been mapped close to each other on Chr 11 and Chr 5. Physical mapping with YAC clones showed that they are located within 100 kb region of each other. Tbx1 and Tbx6 have been localized separately on Chr 16 and Chr 7. Several T-box containing genes also have been discovered in Drosophila and C. elegans. Phylogenetic analysis suggests that the evolution of the T-box family occurred by means of a series of duplications and dispersion to different chromosomes. The accumulated data demonstrate an important role for the new gene family in the evolution of metazoan organisms.

180. GENETIC & PHYSICAL MAPPING OF MYODYSTROPHY, LOCATED IN THE MOUSE 8 - HUMAN 4q SYNTENIC REGION.

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The spontaneous mutation myodystrophy (*myd*) is located on midchromosome 8, flanked by genes with homologs on human 4q. *Myd is* a candidate animal model for the human disorder facioscapulohumeral dystrophy (FSHD; 4q35). We have established two panels of DNA from affected offspring (265 chromosomes) and unaffected sibs (171 chromosomes) of a B6C3Fe-*a/a-myd*/+ x CAST/Ei cross. These panels are being genotyped with anonymous STRPs and SSCPs in genes from the central portion of Chr. 8. We previously mapped *Cf11, Clc5,* and *Kal3,* proximal to *myd,* and *Ucp* distal to it. We have now localized *Ant1* between *D8Mit224* and *D8Mit53,* more than 16 cM proximal to myd, excluding *Ant1* as the causative gene. The expanding synteny between human Chr. 4q and mouse Chr. 8 (9 known genes) along with phenotypic data support the hypothesis that *myd* and FSHD are homologous. By of recombinant analysis the *myd* region has been narrowed to approximately 1 cM, and we have begun to establish a YAC contig across this region.

181. PHYSICAL ANALYSIS OF THE HOMOLOGOUS SEQUENCES TO THE IMPRINTED MOUSE GENE *U2afbprs* IN THE HUMAN GENOME.

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The imprinted mouse gene *U2afbprs* maps to mouse chromosome 11 and is expressed ubiquitously and exclusively from the paternal allele. We have undertaken a comparative analysis of this gene in the human genome to determine if the imprinted regulation is conserved. The initial mapping analyses identified a single human locus U2AFBPL on 5q23-31. We have begun the physical analysis of the homologous human sequences. Seven human genomic clones,with insert sizes ranging from 110 to 150 kbp, were isolated from a PAC library using a 600 bp mouse cDNA probe. Two separate groups of overlapping clones were recovered that contained different restriction enzymes fragment sizes with several enzymes when hybridized with the mouse *U2afprs* probe. Each set of clones had a single hybridization band that corresponded to one of the fragment sizes observed in Southern analysis of human genomic DNA. These data indicate that the homologous sequences of the mouse *U2afbprs* gene are duplicated in the human genome and that only a single copy is present in each of the PAC clones. FISH and somatic cell analysis localized one copy to human chromosome 19p and the other copy to human chromosome 5q23, the previously identified region that shows conserved homology to mouse chromosome 11. Sequence analysis of a PCR product from the 19p U2AFBPL2 clones indicate that there is a 300bp Alu element in the putative coding region of this copy, suggesting that this may be a pseudogene.

182. COMPARATIVE MAPPING OF MMU19 AND HUMAN 11q13. *M. Fernandes[1,2], F. Rotomondoi, A. Courseaux[2], P. Gaudray[2], G.F. Carle[1]. [1]LEGM, [2]LGMCH, CNRS URA 1462, Universite de Nice, France.*

The pericentromeric region of MMU19 is implicated in several murine pathologies such as susceptibility to lung tumors, muscular dystrophy *(mdf)*, neuromuscular degeneration *(nmd)*, osteosclerosis *(oc)*, osteochondrodystrophy *(ocd)*... This region is homologous with the proximal part of 11q13 which may be altered in different tumors by means of amplifications, translocations and deletions. It also bears genetic loci implicated in several diseases and syndromes: insulin-dependent diabetes, spinocerebellar ataxia, hypertrophic cardiomyopathy, Best disease, atopy, or multiple endocrine neoplasia type 1. Our lab has been involved in the establishment of a high resolution physical map of 11q13. More recently we have undertaken a similar mapping effort on the peri-centromeric region of MMU19. Our goal is to determine the degree of homology between these two regions and, more specifically, to characterize the distal and proximal syntenic disruption areas on 11q13. During our systematic comparison of the two syntenic chromosome regions, we have mapped 8 new genes -or homologs to human genes- in the pericentromeric region of MMU19. We have delineated <1Mb region where the conservation of synteny appears to end: on the centromeric side of 11q13, ClNH seems to be the first gene shown to lie outside of MMU19; the telomeric zone of syntenic disruption has been mapped between GALN and CCND1. We are using exon-trapping on YACs from 11q13 to fish out genes from the region between GALN and CCND1. The probes derived from this study will help us to define more precisely this region of syntenic disruption and check whether it corresponds to a particularly unstable area of the genome in either mouse or human which could explain its frequent implication in the rearrangements observed in cancerous cells (amplifications and translocations).

183. LENGTHY ANCESTRAL HAPLOTYPES MARKED BY MOUSE $C4^k$. *P.P. Jiang, T.H. Hansen, R.D. Miller. Washington University School of Medicine, St. Louis, Missouri, USA.*

The unique historical event of the insertion of a mouse *B2* element in intron 13 of $C4^k$ in the major histocompatibility complex, *H2*, provides evidence about the time of domestication of inbred strains of laboratory mice. Analysis of microsatellites revealed a lengthy common haplotype in all seemingly independent examples of $H2^k$. Slight mutations in microsatellites indicate that the independent examples of $H2^k$ are from a star phylogeny with a common ancestor in about 1600 A.D. These results and the high frequency of $C4^k$ in laboratory strains compared to wild mice demonstrate that laboratory mice came from nearly inbred stocks that were domesticated centuries earlier. Non-*H2* regions of the laboratory mouse genome are predicted to consist of lengthy ancestral haplotypes.

184. DUPLICATION OF THE MAMMALIAN SEX-DETERMINING LOCUS, *Sry*.

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We describe sequence variation among paralogous and orthologous copies of the male sex-determining locus, *Sry*, from six closely related species of murine rodents (subfamily Murinae). PCR amplification followed by direct sequencing revealed from two to four copies of *Sry* per species. All but two of these appear to include a complete open reading frame, with a stop codon that coincides closely with the stop codon in *Mus musculus*, a species known to have a single copy of *Sry*. Sequence divergence among paralogous copies within species ranged from <1~ to 4~. A phylogenetic analysis including all copies, and using *Mus musculus Sry* as an outgroup, suggests that for orthologous copies, sequence divergence is <1%, the HMG box is evolving more slowly than the C-terminal region, and non-synonymous substitutions occur more frequently than for most other protein coding genes.

185. EXPRESSION AND LOCATION OF GENES IN A REGION OF THE X CHROMOSOME THAT DIFFERS BETWEEN LABORATORY STRAINS AND *M. SPRETUS*.

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We recently described an exception to the conservation of linkage of the X chromosome in eutherian mammals *(Rugarli et al., 1995)*. The *Clcn4* (chloride channel 4) gene is X-linked in *M. spretus* in human but autosomal in laboratory strains. We have now mapped two other genes, *Oa1*, (ocular albumin), and *Apxl* (apical protein from *Xenopus laevis* like), which in human mapped close to *CLCN4*. In contrast to *Clcn4*, both of these genes map to the mouse X chromosome in *M. spretus* and in laboratory strains. *Oa1* and *Apxl* are located proximally to *Amel* (amelogenin) on the mouse X chromosome. In addition, mapping by FISH of YAC clones containing *Clcn4* suggest that the rearrangement between mouse species may be small. Expression analysis in F1 mice with copies of *Clcn4* on chromosome 7 and the X chromosome was done to compare expression levels between the autosomal gene and the X-linked gene which is subject to X inactivation.

186. **A CONTRAVENTION OF OHNO'S LAW IN MICE.** *Steve Palmer, Jo Perry, Alan Ashworth. CRC Centre for Cell and Molecular Biology, Chester Beatty Laboratories, The Institute of Cancer Research, Fulham Road, London SW3 6JB, UK.*

The chloride channel gene *CICN4* has been previously mapped to the X chromosome in humans. We isolated a cDNA clone for mouse *Clcn4* and used this to map the gene in an interspecific backcross. This revealed the surprising finding that the gene maps to the X chromosome in *Mus spretus* but to chromosome 7 in C57BL/6 mice. This is the first example of a gene that contravenes Ohno's law i.e. it is an X-unique gene in one eutherian species but is autosomal in another. The consequence of this chromosomal rearrangement is that the gene is lost by Mendelian segregation in a subset of the male progeny of a (C57BL/6 X *Mus spretus) X Mus spretus* backcross.

187. **COMPARATIVE ANALYSIS OF GENES OF THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) OF RAT (*RT1* SYSTEM) AND MOUSE (*H2* SYSTEM).** *Doris Lambracht[1,2], Hong Xiao[1], Roger A. Schultz[3], Kurt Wonigeit[2], Kirsten Fischer Lindahl[1]. [1]Howard Hughes Medical Institute; [3]Dep. Pathology, Univ. Texas Southwestern Med. Ctr., Dallas Texas, USA; [2]Medizinische Hochschule Hannover, Germany.*

The MHC is organized similarly in both species, and MHC class I genes are encoded by two regions, separated by genes coding for class II molecules and for factors of the humoral immune system. Of particular interest to us is the comparison of the extented region coding for numerous genes belonging to different families of class Ib genes. A number of cosmid clones of the LEW rat *(RT1^l)* could be mapped to this *RT1.C* region by analysis of restriction fragment length polymorphisms and comparison with recombinant *RT1* haplotypes. Genes with homology to mouse *H2-T* and *H2-M* region genes were isolated. The recombinant haplotype *r38* demonstrated that the *RT1.M* genes, like the mouse *M* genes, map to the end of the MHC. The relative location of other clusters of overlapping clones in the *RT1.C* region could not be determined. We are now using fluorescence in situ hybridizations to locate the clones directly on chromosome 20. Preliminary data with metaphase chromosomes demonstrate that genes of the *RT1.C* region map to the centromeric side of the MHC. This is in contrast to the mouse, in which the *H2-T* and *H2-M* region are located on the telomeric side of the MHC. Hybridizations to interphase chromosomes should further clarify the relative order of the isolated clones and will give more detailed information whether gene families present in both species have evolved independently.

188. DEVELOPMENTAL VARIATION IN THE DEGREE OF DOMINANCE OF DIABETES *(db)*. *G.E. Truett[1], R.J. Tempelman[2], J.A. Walker[1], P. Xu[1]. [1]Pennington Biomedical Research Center, Baton Rouge, Louisiana 70808; [2]Department of Animal Science, Michigan State University, East Lansing, MI 48824.*

The rat mutant fatty (*fa*) and the mouse mutant diabetes (*db*), which are likely to be homologs, are classified as recessive alleles under qualitative descriptions of genetic dominance. However, studies on the early development of obesity in rat populations segregating fa have revealed remarkable variation in the degree of *fa* dominance; the degree of fa dominance on body weight, for example, is high for the first three weeks of life and rapidly decreases at sex-specific ages, day 20 for females and day 22 for males. The purpose of this project is to determine whether *db* dominance also varies over early development.

Pbrc:C57BL/6J *m db* mice were produced in our colony. They were marked and weighed daily from day 4 of life to day 70. Genotypes were scored as +/+ if mice had the misty coat color, as *db*/+ if they were black and lean, and *db*/*db* if they were black and obese. The effect of *db* genotype on body weight was estimated under a mixed linear model incorporating litter as a random factor and sex and *db* genotype as fixed factors. *db* genotype effects were statistically detectable on every day of observation. The degree of *db* dominance was consistently very high during the first three weeks of life, and rapidly decreased after day 20. The mutant effect increased steadily over early development, while the heterozygote effect increased until the end of the third week of life, then decreased thereafter. This analysis confirms that there is considerable variation in the degree of *db* dominance over early development. The marked change in dominance that begins at the end of the third week of life is likely to be mediated by specific physiologic mechanisms.

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189. THE GSDB ANNOTATOR. *Carol Harger, Judy Blake*, Jillian Burton, David Crowley, Ada Espinosa-Lujan, Ken Fasman**, Gifford Keen, Mo Manning, Shelley March, Mia McLeod, John O'Neill, Alicia Power, Maria Pumilia, David Rider, Jolene Schwertfeger, Linda Smyth, Nina Thayer, Charles Troup, Ed Uberbacher#, Chris Fields. National Center for Genome Resources, Santa Fe, NM; *The Institute for Genomic Research, Rockville, MD; **Johns Hopkins University, Baltimore, MD; #Oak Ridge National Laboratory, Oak Ridge, TN.*

The Genome Sequence DataBase (GSDB) has developed a software tool, the GSDB Annotator, to assist users in the process of annotating sequences and browsing data in GSDB .

A primary design goal is to support an annotation process that is carried out over an extended period of time by many researchers. This "community" annotation is necessitated by the advent of laboratories using high throughput and low-pass sequencing strategies downloading megabases of relatively uncharacterized sequences into the public databases, where they will be annotated over an extended period of time by the community.

Other important design goals include: interactions with other database tools, integration of analysis tools into the GSDB Annotator via inter-process communication, and an intuitive, biologically based, graphical browsing and editing framework that will support viewing of sequence data, multiple alignments and annotation data at multiple levels of resolution.

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