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Robert M. Gemmill, Ph.D.

Grant Title: International Workshop on Chromosome 12 Held at St. Catherine's College, Oxford, England, September 18-20, 1992

Abstract

The First International Mapping Workshop on Human Chromosome 12 was held on Sept. 18-20, 1992, at St Catherine's College, Oxford, UK. The meeting was hosted by Ian Craig and organized by Drs. Craig, Gemmill and Kutcherlapati. It was attended by 50 participants primarily from Europe and the USA. The workshop was highly successful and achieved the major goal of fostering direct and personal interactions between investigators with strong research interests in this chromosome. Participants reviewed the status of several critical aspects of chromosome mapping and prepared consensus views of the current state of knowledge. In addition, lists of resources available for this chromosome including somatic cell hybrids, individual DNA clones and libraries and genetic markers were prepared.

Final Report

The first International Workshop on chromosome 12 mapping was held on Sept. 18-20, 1992, at St Catherine's College, Oxford, and was attended by 50 participants from Europe and the USA. The workshop was highly successful and achieved the major goal of bringing together investigators from around the world with research interests in this chromosome. Participants reviewed the status of several critical aspects of chromosome mapping and prepared consensus views of the current state.

The session on physical mapping reviewed both pulsed field gel based linkage and YAC contig development. The genetic linkage session reviewed the polymorphic markers and the developing genetic maps for this chromosome. Resources identified to assist the mapping process included a number of somatic cell hybrids and recombinant DNA libraries specific for 12. A session on diseases and translocations reviewed efforts to isolate specific disease genes that map to chromosome 12. Particular examples include the mapping of heritable skin blistering diseases due to cytokeratin mutations and isolation of the gene found rearranged in myxoid liposarcoma (CHOP). Finally, the relationship between chromosome 12 and syntenic regions on mouse chromosomes 5, 6, 10 and 15 were discussed and further refined.

This first workshop was highly successful and has led to plans for the second workshop to be held this year. A report describing the workshop and the consensus maps generated was published in Cytogenetics and Cell Genetics Volume 61, p 243-251, 1992. A copy of the publication is appended to this final grant report.

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Report of the first international workshop on human chromosome 12 mapping

Prepared by Ian Craig, Robert Gemmill and Raju Kucherlapati with the assistance of Sally Craig

The meeting, held at St Catherine's College, Oxford, was attended by 50 participants from Europe and the USA. It was supported by the European Commission (through HUGO), the Medical Research Council, UK, the National Institutes of Health and the Department of Energy, USA. The operation of the workshop was divided between five working parties whose reports were presented and approved in plenary session and whose main conclusions form the subsequent sections of this report.

Since HGM11, very considerable progress in extending the range of markers available and incorporating these into physical and genetical maps has been achieved. The number of genes (many of them cloned) has increased from 132 to 147, the number of DNA segments reported since the submission of the HGM11 report has more than doubled from 63 to 175, and the number of YACs increased from 1 to >45. Furthermore, very significant improvements to the genetic maps have been achieved and substantial new data in addition to that from the CEPH studies has been accumulated. The list of reference loci has been extended from 8 to 14.

Physical mapping
(R. Gemmill and R. Kucherlapati)

Substantial progress was reported on physical mapping efforts on both arms of the chromosome. A number of investigators have isolated YACs corresponding to markers along the chromosome, as detailed in Table 1. Altogether, details on about 50 YACs were reported corresponding to over 14 loci. Of particular interest is the YAC, HTY3049, reported by Dr. Donis-Keller that appears to map to pter and includes presumed telomeric sequences. In addition, two YAC contigs have been developed. One, located at 12p13, includes the genes F8VWF-PZP-TNFR1 and D12S119, while the second contains GLI and SAS genes located at 12q13.3. Anyone wishing to obtain these YACs should contact the appropriate investigators listed in the Table.

A pulsed field map has been developed for the 12q13.3 region. By combining data from two laboratories, it was possible to link A2MR, GLI, CHOP (= GADD153) and SAS. Inclusion of additional information from the malignant fibrous histiocytoma amplification domain suggested that MDM2 is also linked to this group. The CHOP gene was described and shown to be the target of rearrangement in myxoid liposarcoma with a t(12;16)(q13.3;p11.2); thus the physically linked group of markers embraces the 12q13.3 breakpoint and can be accurately positioned cytogenetically.

The new reference marker map for chromosome 12 is shown in Figure 1. Well defined markers with high degrees of polymorphism as well as other markers which could define specific regions of the chromosome are illustrated. This map includes 14 reference markers (listed on the left hand side of the diagram) whose order can be unambiguously defined and are recommended for inclusion in further mapping studies of all types to facilitate integration of maps. This represents an approximate doubling of reference markers since HGM11. With regard to other markers listed, HTY3049 and D12S158 may define the terminal boundary of 12p.

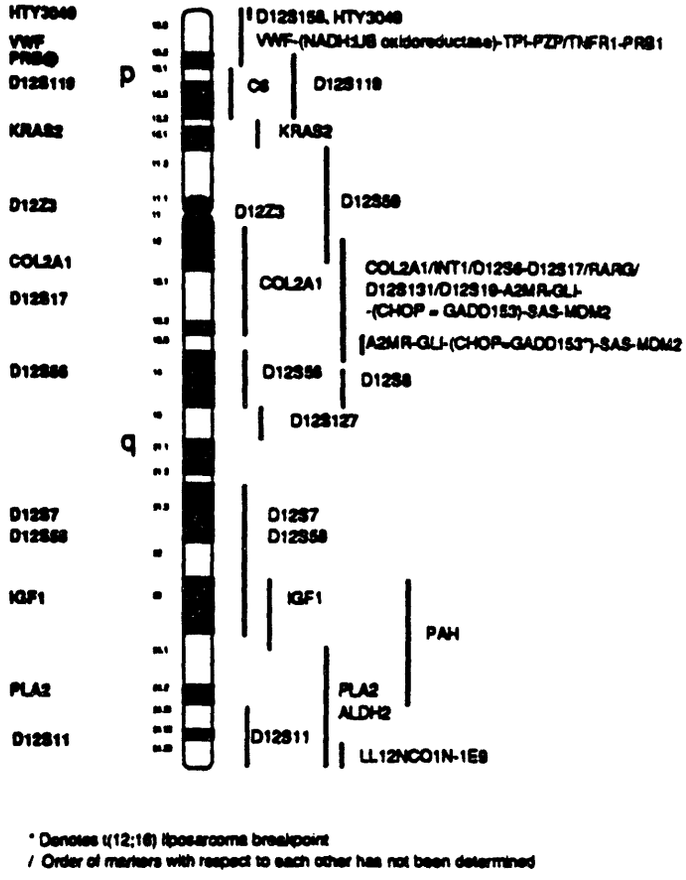


Figure 1. Representation of reference markers (left hand side) and ordered physical markers (right hand side).

HTY3049 is a 950 kb YAC derived from a telomere library and maps to the telomeric region. D12S158 is a cosmid which also maps to the telomeric region and contains sub-telomeric repeat sequences as well as a CA repeat. The F8VWF YAC contig includes a new gene, described at this workshop, which encodes a subunit of NADH:ubiquinone oxidoreductase (Marynen et al., this meeting). The marker C6 is a cosmid mapped by FISH. The physical order of markers in proximal 12q was established by combining data from several laboratories and is shown in Figure 1. D12S11 is included as a reference marker because it constitutes the most distal genetic marker as defined by

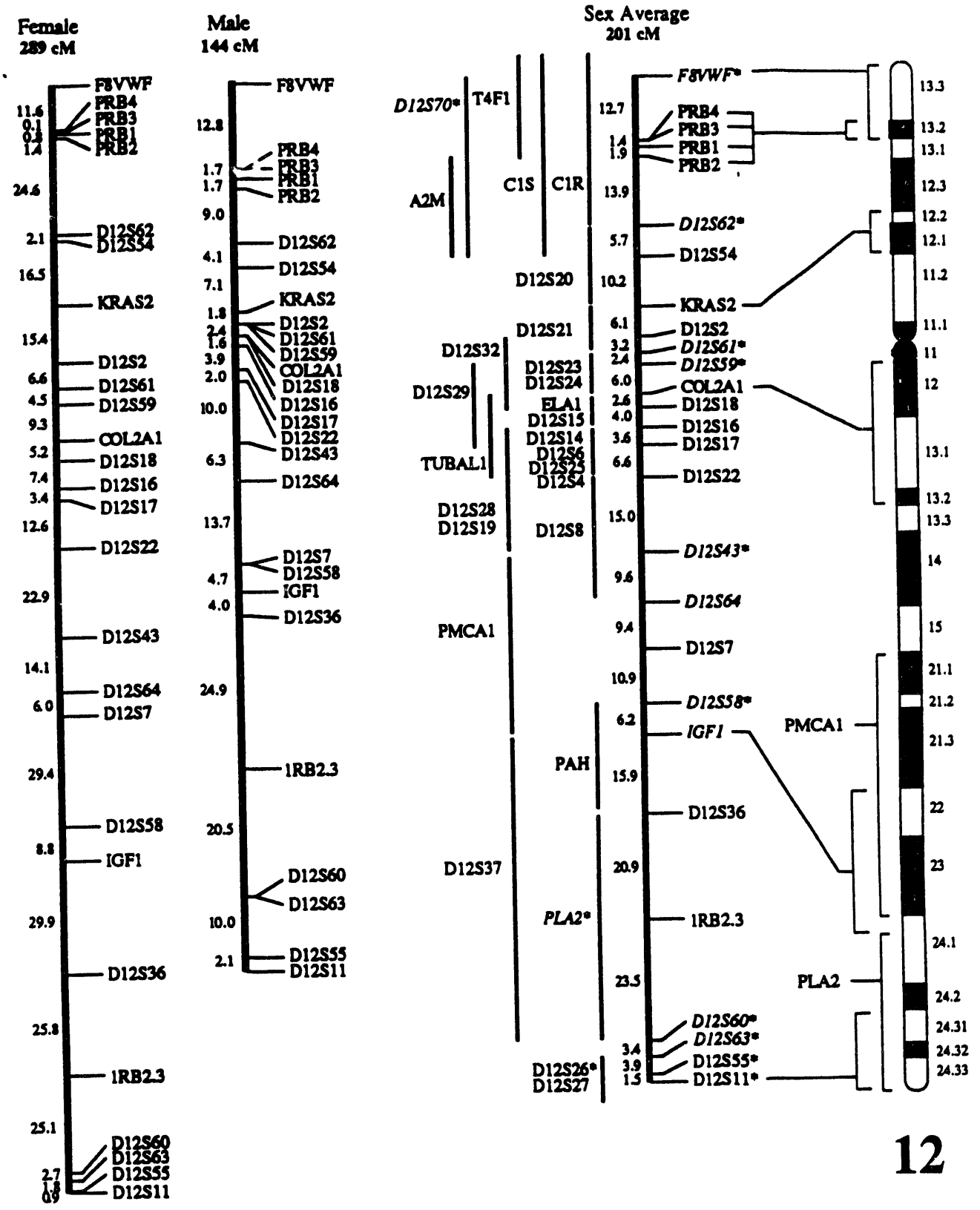


Figure 2. Genetic map for chromosome 12 based on CEPH families

the linkage map. LL12NCO1N-1E9 is a cosmid that maps to the telomeric region by FISH and contains a CA repeat.

Montgomery et al., (this meeting) reported on mapping 107 cosmids by FISH. Several of these cosmids are included in GDB. Enquiries concerning them should be directed to Dr. Kucherlapati.

Other new loci assigned between HGM11 and this workshop and are recorded in GDB include; cyclin D2 (CCND2) to 12p13, antigen CD69 (p60, early T-cell activation antigen) to 12, myosin, light polypeptide 2 (MYL2) to 12q22-q24.1, protein tyrosine phosphatase (PTPN6) 12p13 and ubiquitin (UBC) to 12q24.3. New loci associated with diseases are reported in the appropriate section (below). Also reported at this workshop was the localisation of protein serine/threonine phosphatase gamma (PPP1C) to 12q24.1-q24.2 (Craig et al., this meeting), the assignment of a novel putative transcription factor (bZIP class) to 12 (Kolsto et al., this meeting) and the refinement of PMCH to 12q23-q24. Brain nitric oxide synthetase has been assigned to chromosome 12 by hybrid panel analysis (Kishimoto et al.., 1992).

Linkage

(T. Gedde-Dahl and H. Donis-Keller)

A chromosome 12 map based on CEPH families tested on 54 loci and spanning 289 cM in females and 144 cM in males was presented by Holt et al. ,(Science in press and this meeting Donis-Keller, pers.onal communication). The genotypes of the CEPH families will be entered subsequently into GDB. Figure 2 shows this map updated for regional assignments. An additional marker, apparently on the tip of the 12p arm and distal to F8VWF, was reported by the same group (Korte-Safarty et al., this meeting). The map is still lacking an extreme distal 12q marker. CEPH families are currently being tested independently in the EUROGEM program (Banchs et al, this meeting).

Independent families (termed IOPS) collected by the Institute of Psychiatry, London, were analysed for 22 microsatellite loci by multipoint and two-point analysis using CRI-MAP (Dawson et al.,, this meeting). Based on 5 loci common to the CEPH and IOPS-maps and ordered unambiguously in both with interspersed markers, the F8VWF to D12S64 distance measures 158 cM and 79 cM in females and 68 cM and 52cM in males, respectively. As the IOPS sex ratio of 1.5 is the same as found for the majority of early detected linkage groups in man, it will be of interest to investigate whether the higher recombination in CEPH females reflects human diversity in the frequency of recombination.

The gene symbol SCA2 for spino-cerebellar ataxia was reserved at HGM11 for the locus in families not linked to chromosome 6 (SCA1). At this meeting, two groups (Auburger et al., Twells et al.) reported on 12 tested and informative Cuban families among many of probable common descent. Their combined data are in press and show unambiguously that SCA2 maps between D12S58 and PLA2. Twells et al. (this meeting) also tested CEPH families for the flanking markers, D12S58 and IGF1 and obtained the identical two-point theta max (0.07) as found by the CEPH-consortium (lods 5.57 and 8.76).

Keratin genes, particularly the cooperating K5/K14 polypeptide pair coded by KRT5 on chromosome 12 and KRT14 on 17, have long been candidate genes for the basal cell "tonofibrillar clumping" disease epidermolysis bullosa simplex Dowling-Meara (EBS-DM). Likewise KRT1 (on 12) and KRT10 (on 17) have been the candidate genes for suprabasal cell "tonofibrillar clumping" epidermolytic hyperkeratosis (EHK). Lately, these predictions have been partly proven. One "cytolytic, localized" form (EBS-Weber-Cockayne, EBS-WC,) family and one generalized (EBS-Kobner, EBS-K) family had been assigned by linkage to chromosomes 12 and 17 respectively (Bonifas et al., 1991). Subsequent to HGM11, one EBS-K family was assigned to 12 by absolute linkage to D12S17 (lod +5.55) (Ryynanen et al., 1991), one EBS-DM family was shown to have a mutation in KRT5 (Lane et al.,1992), and lastly, one EHK family showed absolute linkage to KRT1 and D12S17 (Compton et al., 1992). Further EBS-WC families linked to 12 are known (Epstein; pers comm). At this meeting, Gedde-Dahl et al. have expanded two families reported at HGM11 (Hoyheim et al, 1991), one being linked to COL2A1 at theta max = 2/33 = 0.06 (lod +6.66) and the other being unlinked to COL2A1. The 19-allele typing system for COL2A1 (Berg and Olaisen, this meeting) was used in this investigation. Bearing in mind that EBS-DM mutations in KRT14 are well documented (chromosome 17), there are only two exceptions yet to be reported to the rule that all types of dominant EBS and EHK could appear on either of chromosomes 12 and 17, that is EBS-WC and EHK have yet to be confirmed on chromosome 17. If all of the chromosome 12- linked, assumed keratin diseases (i.e. EBS2 & EHK) and the KRT1-PCR (as typed in EHK) are pooled in one KRTII type cluster, no recombination has been reported versus D12S17 (31 meioses) and the distance to COL2A1 is 9 cM, which may be compared with 10.2 cM for the CEPH COL2A1-D12S17 distance. In the current absence of highly polymorphic KRT-markers, D12S17 is recommended as a reference marker.

Birdwood et al. (this meeting) excluded D12S43-linkage to cataract in a dominant family, testing a hypothesis based on the presence of cataract loci on the homologous mouse chromosome, 10, and the existence of a possible human candidate gene MIP. The regional mapping (12cen-q14) of the latter still allows it to be a candidate gene.

Resources

(M. Liao, A. Geurts van Kessel and P. J. de Jong)

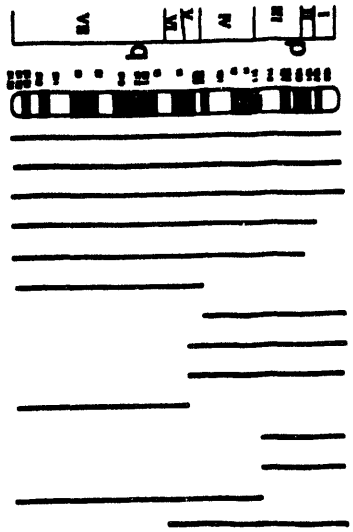
Somatic cell hybrids

Two somatic cell hybrids (E4E;GM10868) are currently available that contain a normal chromosome 12 as their only human constituent. Another line (A3TE-7B) contains 12 and an additional small chromosome 17-derived fragment. Altogether a panel of fourteen cell hybrids has been assembled that divides the chromosome into seven distinct regions (I-VII). These hybrids include such well defined landmarks as the myxoid liposarcoma (MLS)-associated t(12;16)(q13;p11)breakpoint at the CHOP (GADD153) locus, balanced constitutional rearrangements, and also some radiation-induced or spontaneous chromosomal breaks (see Figure 3). Radiation-reduced hybrid panels have been generated for the entire chromosome (Kucherlapati; Auburger; Liao) or for 12p (Sinke). It was agreed that these panels should be made available and that, in order to obtain material, the respective researchers should be contacted directly. In addition,

two human cell lines derived from an osteosarcoma (OSA-CL) and a rhabdomyosarcoma (RMS13), which respectively contain an amplicons encompassing either the 12q13 loci GLI, SAS, MDM2 or A2MR and GLI as reported at this meeting. These cell lines are available through Dr Forus (Oslo) for mapping purposes.

Recombinant DNA resources:

Three lambda libraries from flow-sorted chromosome 12 were made at Lawrence Livermore National Laboratory (LLNL) and Los Alamos National Laboratory (LANL). Two of the libraries were constructed in the Charon21A vector using total digest fragments generated by *Hind*III (LL12NS01) or *Eco*RI (LA12NS01). The third library (LL12NL01) was constructed in the Charon 40 replacement vector using *Mbo*I-partial digest fragments (10-20 kb inserts). All three libraries are available through the American Type Culture Collection (ATCC). One of the lambda libraries (LL12NS01) has been subcloned into the Bluescribe plasmid vector. This plasmid library is available from Dr Gray (UCSF, San Francisco).



Hybrid	Rodent parent	Contact	Other human chromosomes	Ref.
B4R	CHO-K1	Lisa	none	1
A3TE-7B	CH-A3	Geurts van Kessel	17q	2
GM10868	GM4589A	NIGMS	none	3
A3JA5B	CH-A3	Geurts van Kessel	yes	unpubl.
37A9	CHO-K1	Lisa	none	1
D3	mouse A9	Schoenmakers	yes	4
MLS-12	CHO-K1	Lisa	yes	5
16-16	CHO-K1	Lisa	yes	1
A1WBP2	CH-A3	Geurts van Kessel	yes	6
A1WCB	CH-A3	Geurts van Kessel	yes	6
F11-13	CHO-K1	Jones	11	7
M28	LMTK -	Maryann	none	8
F11-1	CHO-K1	Jones	11	7
1219G2	CH-A3	Geurts van Kessel	yes	9

Figure 3. Diagrammatic representation of segments of chromsome 12 present in somatic cell hybrids and related data

References; (1) Law ML, Tung L, Morse HG, Berger R, Jones C, Cheah KSE., Solomon E.: The human type II collagen (COL2A1) assigned to 12q14.3. Ann.Hum.Genet 50: 131-137 (1986). (2) Looijenga LHJ, Smits VTHBM, Wessels JW, Mollevanger P, Oosterhuis JW, Cornelisse CJ, Devilee P: Localization and polymorphism of a chromosome 12-specific alpha satellite DNA sequence. Cytogenet.Cell. Genet. 53:216-218 (1990). (3) GM10868, Warburton D, Gerson S, Yu MT, Handelin B, Houseman D: Monosomal rodent human hybrid from microcell fusion of human lymphoblastoid cells containing an inserted dominant selectable marker. Genomics 6: 358-366 (1990) (4) Schoenmakers E, Kools P, Mols R, Geurts J, Bullerdiek J, and van de Ven W: 12q13-q15 breakpoints of myxoid liposarcoma, lipoma and pleiomorphic adenoma of the salivary gland fall within the 7cM region between linkage probes CRi-C86 and p7G11 - this meeting. (5) Liao M, Xu Y, Li E, Gemmill R, Kao F T, Craig R: Gene encoding a positive host cell factor, HIVE1, involved in HIV1 expression, is mapped on human chromosome 12q11-q13.3 - this meeting. (6) Van 't Veer LJ, Geurts van Kessel A, van Heerikhuizen H, van Ooyen A, Nusse R: Molecular cloning and chromosomal assignment of the human homolog of Int-1, a mouse gene implicated in mammary tumorigenesis. Molec Cell Biol 4:2532-2534 (1984). (7) Jones C, and Moore EE: Localisation of a gene which complements branched-chain amino acid transaminase deficiency to the short arm of human chromosome 12. Hum Genet 66: 206-211 (1984) (8) Zhang J, Marynen P, Devriendt K, Fryns JP, van den Berghe H, Cassiman JJ: Molecular analysis of the isochromosome 12p in the Pa'lister-Killian syndrome: construction of a mouse-human hybrid cell line containing an i(12p) as the sole human chromosome. Hum Genet 83:359-363 (1989). (9) Schonk D, Coerwinkel-Driessen M, Dalen I, Oerlemans F, Smeets B, Schepens J, Hulsebus T, Cockburn D, Boyd Y, Davis N, Rettig W, Shaw D, Roses A, Ropers H, Weiringa B. Definition of subchromosomal intervels around the myotonic dystrophy gene region at 19q. Genomics 4:384-396 (1989).

An extensive cosmid library has been constructed from flow-sorted chromosome 12, derived from a human/hamster hybrid. Approximately 70% of the clones in the Lawrist16 vector have human inserts and about 25,000 clones in this library (LL12NC01) have been arrayed in microtiter dishes. Evidence from Dr Kucherlapati's group suggest that preferential cloning of three areas of chromosome 12 has occurred: p13, q13-q14, q22-qter. Copies of the arrayed library can be obtained by contacting Dr de Jong.

A small YAC library has been prepared from the E4E hybrid by Dr Gemmill. About 20-30 chromosome 12 YAC clones (average inserts of 200-250kb) have been isolated from the library and 9 of them have been FISH-mapped (Suijkertbuijk and Geurts van Kessel, Nijmegen). Details on other YACs and their availability are provided in Table 1.

Several microdissection libraries have been constructed and

are being characterized. Two of these libraries, both for 12q13, have been generated by Dr Meltzer (Ann Arbor) and another one has been constructed by Dr Claussen (Erlangen). These libraries are not yet generally available.

Diseases and translocations
(C. Turc-Carel and P. Meltzer)

In the interval since HGM11 there has been significant progress in the localisation of disease genes and of translocations involved in neoplasia. In addition to the localisation of spinocerebellar ataxia type 2 (SCA2), a series of reports has provided evidence linking heritable skin blistering phenotypes to mutations in either cytokeratin 1 (KRT1) or cytokeratin 5 (KRT5); these topics are discussed in more detail under LINKAGE.

Among metabolic defects, the enzyme 4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27) which is decreased or absent in activity in hereditary tyrosinemia type I (MIM 276700) and absent in 4-hydroxyphenylpyruvate dioxygenase deficiency (MIM 276710) has been localized to chromosome 12q14-qter by somatic cell hybrid analysis (Stenman et al., this meeting). Additionally, the gene for mevalonate kinase, the enzyme which is deficient in mevalonic aciduria has been mapped to chromosome 12 (Schafer et al., 1992). The localisation of the HIVE1 locus, which is involved in HIV-1 expression, has been refined to 12q11-q13.3.

In myxoid liposarcoma, tumors are characterized by the presence of a translocation t(12;16)(q13;p11) (HGM11). The breakpoint on 12q has been sublocalized to 12q13.3 (Eneroth et al.., 1990). A physical map of this region including

TABLE I. Status and availability of chromosome 12 YACs

Marker	Location	No. of YACs	Note	Contact
HTY 3049	pter	1	From telomere library	Donis-Keller
F8VWF	p13	1		Kidd
D12S132	p13	7	contig contains F8VWF, TNFR1, PZP and D12S119	Kucherlapati
IIIE1/YAC 5	p11.2-12.1	1		Gemmill*
VD10/YAC17	p11.1-11.2	1		Gemmill*
D12S59	p11-q12	3		Kidd
A2MR	q13.3	1		Gemmill
GLI	q13.3	2	overlaps with two SAS YACs	Gemmill
SAS	q13.3	3		Gemmill/Meltzer
D12S120	q13	7		Kucherlapati
D12S19	q13	4		Schoenmakers
C10	q13	1		Gemmill*
GLI/A2MR	q13.3	4		Forus and Schoenmakers
D12S8	q13-q14	10		Schoenmakers
VB11/YAC16	q21.3	1		Gemmill*
IIIF2/YAC 6	q21.3-22.1	1		Gemmill*
IVG5/YAC11	q21.3-22.1	1		Gemmill*
D12S7	q21.3-23	5		Kucherlapati
D12S7	q21.3-23	2	from ICI library	HGMP UK Resource Center
D12S58	q21.3-23	2		Kidd
IIF1/YAC 4	q23	1		Gemmill*
IGF1	q23-24.11	1		Kidd
ALDH2	q24.1-qter	3		Kidd
IVG12/YAC12	q24.2-24.3	1		Gemmill*
VB10/YAC15	q24.3	1		Gemmill*

*The location of these YACs was determined by FISH by Drs. R. Suijkerbuijk and A. Geurts van Kessel

a YAC which crosses the breakpoint has been reported (Gemmill et al.., this meeting). By testing candidate genes, a consistent rearrangement has been detected (Aman et al., 1992 and this meeting) involving the transcription factor CHOP which has been localized to 12q13 (Park et al., 1992) This gene was previously isolated by Fornace et al. (1989) and designated GADD153. Rearrangement of CHOP was detected in each of 11 tumors which exhibited the (12;16) translocation. Although breakpoints in 12q13 have been reported in various tumors, Aman and co-workers were unable to detect rearrangements of CHOP in lipoma, uterine leiomyoma, chondroma, and hemangiopericytoma. Additional tumor specific translocations meeting the HGM11 criteria have been reported. These include t(12;22)(q13;q13) in clear cell sarcoma of tendons and aponeuroses (Bridge et al., 1991, 1992; Reeves et al., 1992; Rodriguez et al.., 1992; Stenman et al., 1991 and this meeting;

Travis and Bridge, 1992)). This tumor has occasionally been described as malignant melanoma of the soft parts. Subgroups of pleiomorphic adenomas are characterized by rearrangements involving 12p13 and 12q13-q15 (HGM 11). An additional breakpoint has been reported at 12q14 in inv.(12)(q13-15q24) (Stenman et al 1992c. Finally, a breakpoint at 12p12 from t(5;12)(q13;p12) translocations characterises a subgroup of chronic myelomonocytic leukaemia (Srivistava et al. Berkowicz et al).

Comparitive mapping
(J. Peters and J.H. Edwards)

Figure 4 shows the position of those loci on chromosome 12 which have homologues that have been mapped in the mouse, sheep, cow and pig. Mouse gene symbols have been used and where these differ substantially from the human symbols, the latter are also shown. Comparative genetic studies have shown that four segments of human chromosome 12 are conserved on mouse chromosomes 5,6,10 and 15. A segment on 12p is found in distal mouse chromosome 6, and three regions in 12q are found in mouse chromosomes 15, 10 and 5 with the region showing homology to mouse chromosome 15 being most proximal on 12q and that showing homology to mouse chromosome 5 being most distal. The loci so far defined on chromosome 3 in the sheep, one arm of which is equivalent to chromosome 5 in the cow and chromosome 5 in the pig, are all on human 12.

Altogether, homologues of 43 loci on human chromosome 12 have been located in the mouse. The number for cow, sheep and pig are 6, 4 and 3 repectively. Seventeen loci on chromosome 12 are on mouse chromosome 6. Ten of these have been positioned in a single segment from 12pter-p11.2 and in a distal region of mouse chromosome 6 of about 20 cM in length extending from *Glut-3* to *Kras-2*. A further six loci have been placed in the relevant region on 12p and are known to be on mouse chromosome 6 though their position is unknown. From its location on mouse chromosome 6, M6PR is predicted to map to 12p13.

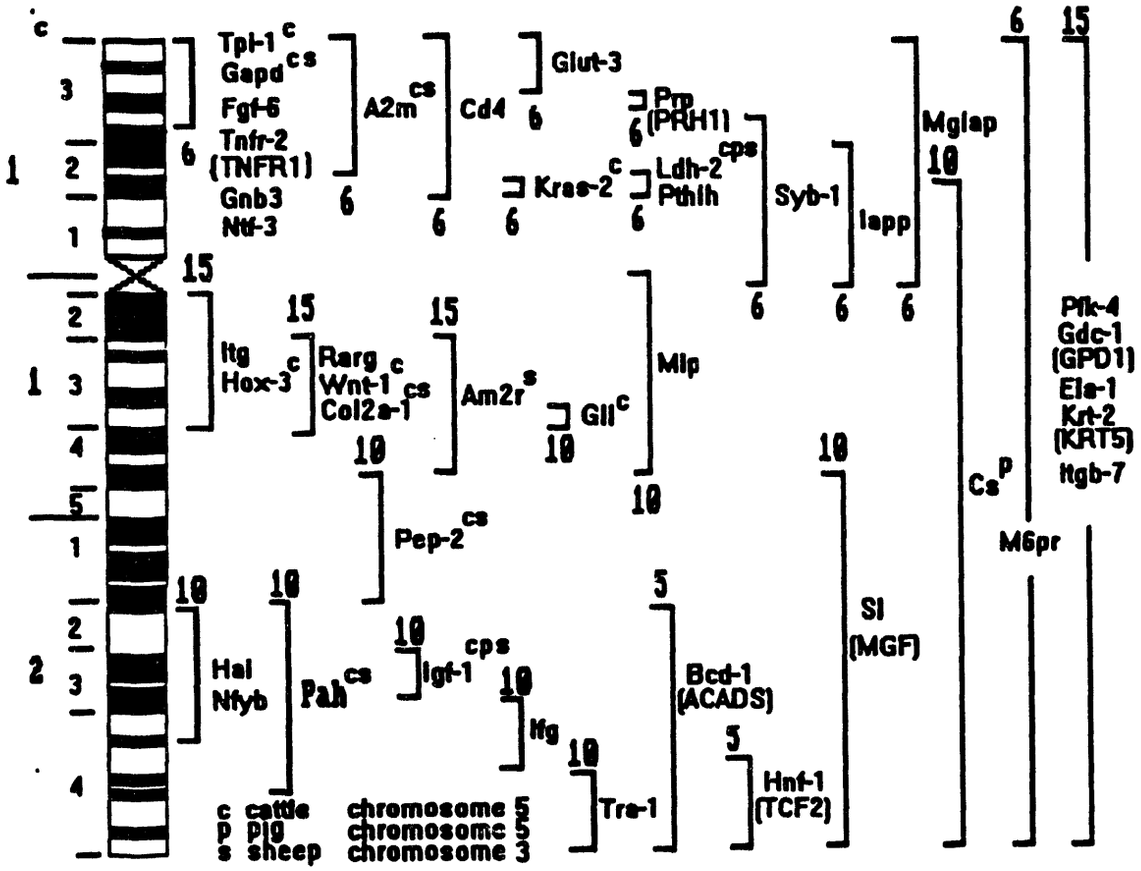


Figure 4: Annotated ideogram of loci mapped in humans and mice, with superscripts for those also mapped in cattle, p = pigs and s = sheep.

A region from the centromere to 12q14 shows homology with a segment of about 15 cM on distal mouse chromosome 15;

from *Col2a-1* to *Ela-1* and *Hox-3*. Twelve homologues have been mapped in man and mouse and six have been positioned in a single segment on human chromosome 12. The remaining six have not been localized yet in man but map to the relevant region on mouse chromosome 15. Twelve homologous loci have been mapped on mouse chromosome 10 and human chromosome 12. Ten lie between 12ql3 and 12q24 and the region in the mouse has a genetic length of about 20 cM from *Pah* to *Gli*. Both the conserved segment on mouse chromosome 10 and the one on mouse chromosome 15 show homology with 12ql3. The most proximal marker in the segment with homology to mouse chromosome 10 is GLI, recently localized to 12ql3.13 (Gemmill, this workshop) suggesting that the boundary of two separate conserved syntenic groups on mouse chromosomes 10 and 15 lies proximal to this. Finally, a segment between 12q22-qter contains two loci ACADS and TCF1 which are homologous with *Bcd-l* and *Hnf-l* in the middle of mouse chromosome 5.

When a conserved segment forms a coherent group in both species, it is difficult to know whether there has been a change in gene order since in both species this is often subject to considerable doubt. Three of the conserved segments (on mouse chromosomes 6, 10 and 15) are of the order of 15 - 20 cM in length and this is in reasonable agreement with the estimated mean genetic length of 15 cM for conserved segments in the mouse (Searle et al 1989).

Within the regions of homology, a number of mouse mutant phenotypes are known which may provide models of human genetic disorders. Some examples are *me*, motheaten, on mouse chromosome 6, which is associated with immunodeficiency and epidermal lesions, *Cat*, dominant cataract on mouse chromosome 10. On mouse chromosome 15 there is *sw*, swaying, which is allelic with *Wnt-l* (Thomas et al 1991), *med*, motor end plate disease, *Sha*, shaven, which is associated with defective keratinization of hair and *Ve*, velvet coat, in which abnormalities of the ectoderm occur.

The future

The participants recommended that a second workshop should be held in approximately one year and that one following that should be organised in Europe. Dr Kucherlapati agreed to host the 1993 workshop in New York.

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