Report on the Second International Workshop on Human Chromosome 9

Prepared by David J. Kwiatkowski[1], John Armour[2], Allen E. Bale[3], Jane W. Fountain[4], David Goudie[5], Jonathan L. Haines[6], Margaret A. Knowles[7], Alison Pilz[8], Susan Slaugenhaupt[6], and Sue Povey[8]

[1]Division of Experimental Medicine, Brigham and Women's Hospital, Boston, MA; [2]Department of Genetics, University of Leicester, England; [3]Department of Genetics, Yale University, New Haven, CT; [4]Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA; [5]Department of Pathology, University of Cambridge, England; [6]Molecular Neurogenetics Laboratory, Massachusetts General Hospital, Boston, MA; [7]Marie Curie Research Institute, The Chart, Surrey, England; [8]MRC Human Biochemical Genetics Unit, The Galton Laboratory, University College London, England.

The Second International Workshop on Human Chromosome 9 was held in Chatham, Massachusetts on April 18-20, 1993. The meeting was attended by 66 participants from 9 countries, including 26 Europeans, and 2 participants from other countries. Fifty-three abstracts were received and the data presented on posters. The purpose of the meeting was to bring together all interested investigators working on the map of chromosome 9, many of whom had disease-specific interests. However, several individuals with genome-wide interests were present and contributed a more global perspective (see below). After a brief presentation of interests and highlighted results, the meeting broke up into the following subgroups for production of consensus maps: 9p; 9cen-q32; 9q32 ter. A global mapping group also met. Reports of each of these working groups is presented in the summary. Alison Pilz represented the mouse mapping community and presented regions of synteny between mouse chromosomes and human 9. A presentation of the new version (5.0) of GDB was made by Jamie Cuticchia. A workshop on tuberous sclerosis occurred on the day following the meeting, and because of the relevance to chromosome 9 is included in this report. The CEPH consortium mapping group met to consider finishing touches on the consortium map of the chromosome which is about to be submitted for publication.

This workshop was made possible by the support of the NIH NCHGR (HG00886), the US DOE (DE-FG02-93ER61576), the UK MRC Human Genome Mapping Project, and the EC through HUGO. The organizers wish to thank John Attwood for implementing the electronic database and mail service for the chromosome 9 community, and Darlene M. Jackson for administration and organization of the meeting.

Address reprint requests to: David J. Kwiatkowski, Division of Experimental Medicine, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115.

Within the text of this report a name without a date refers to an abstract at this meeting (see end of report). A name with a date refers to a publication listed in the references and these are generally limited to very recent or in press references. A verbal communication at the meeting is identified as a personal communication. For authoritative referencing of published information the reader should consult GDB. It was decided that a third workshop on chromosome 9 should be held in about a year's time, and Sue Povey has again offered to host this meeting in Cambridge, England.

9p

Several groups met to construct a consensus map of chromosome 9p, and were coordinated by Jane Fountain and Manuel Diaz (Fig. 1). The map is comprehensive in current localizations for all known markers on 9p, incorporating information available from consortium (Attwood et al.) and index mapping efforts (Kwiatkowski et al.), results of the Genethon mapping group (Weissenbach et al., 1992) and unpublished data of Pertti Sistonen (Sulisalo et al.). It includes 15 new STR markers and provides considerably improved map resolution compared with last year.

Detailed map information is available in the region of the familial melanoma locus (MLM), which maps near the IFN gene cluster (Cannon-Albright et al.). Several years ago, this region was first found to be heterozygously and homozygously deleted in some human cancers and this phenomenon has by now been observed in glioma, melanoma, lung cancer, acute lymphoblastic leukemia, and bladder cancer (see also below). The region between IFNB1 and D9S126 has been the focus of physical mapping efforts for purposes of identifying this gene(s) (Fountain et al.; Fountain et al., 1992; Olopade et al., 1992). At this time extensive YAC and cosmid contigs are being constructed by the Chicago and MIT groups, and as yet are incomplete. The IFNA - D9S126 interval is estimated to measure 5 - 6 Mb, of which over half is now covered in YACs.

Petty et al. described in further detail a patient with a de novo constitutional cytogenetic rearrangement involving

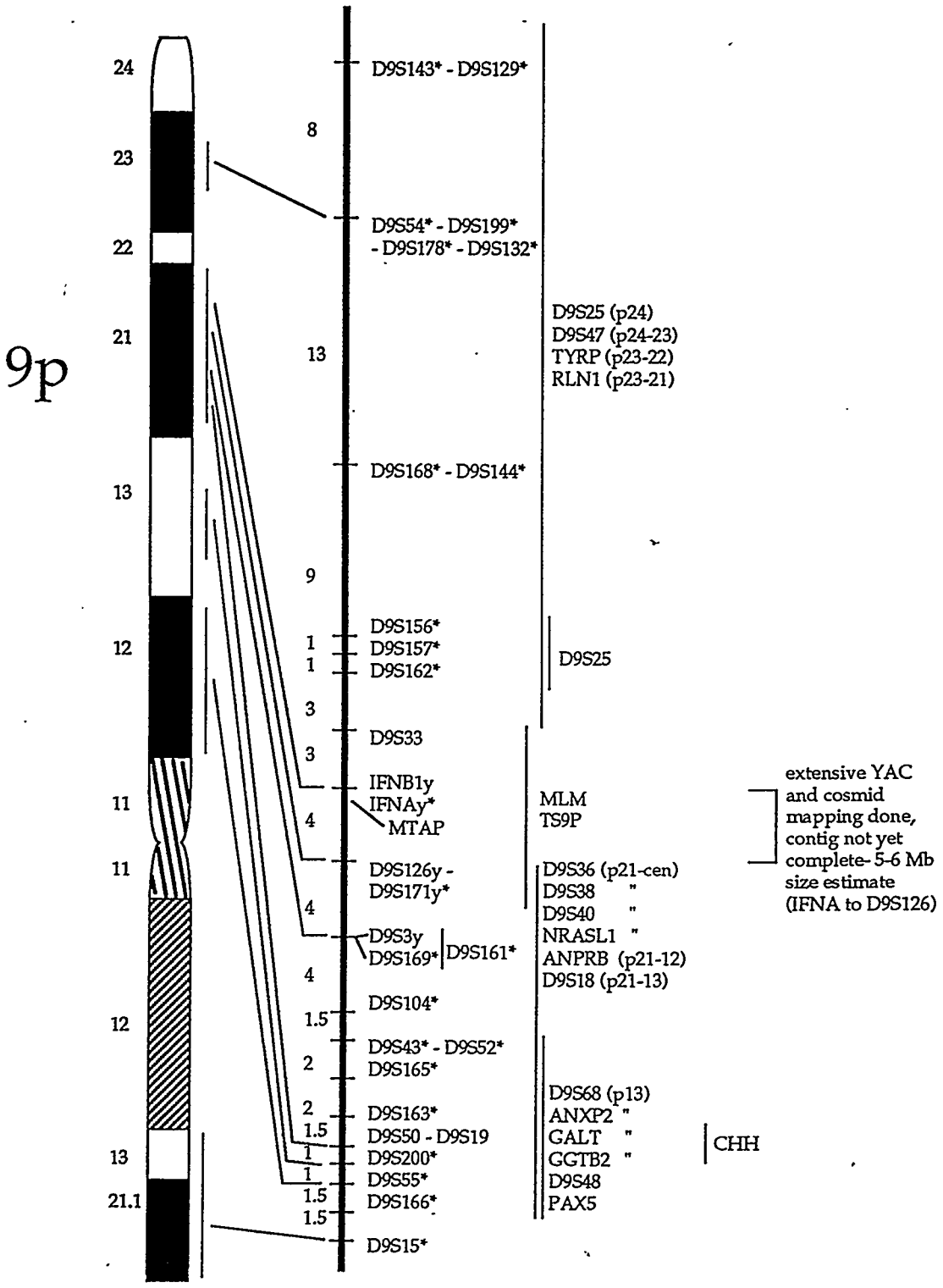

Figure 1. The map of human chromosome 9p. * denotes marker assayed by PCR. y denotes YAC clone identified for marker. Numbers shown are consensus intermarker distances in cM, sex-average.

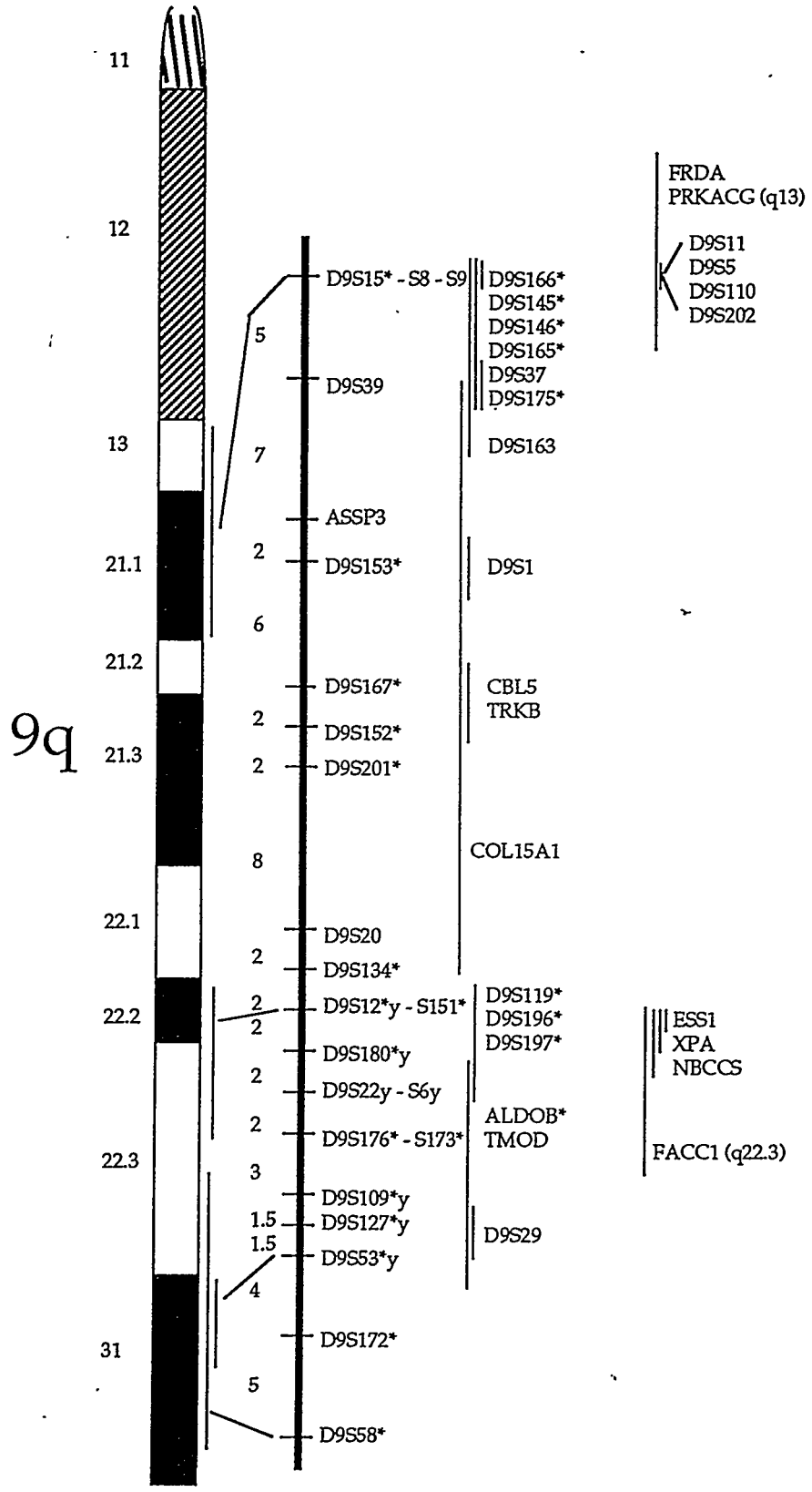

Figure 2. The map of human chromosome 9qcen-q31. * denotes marker assayed by PCR. y denotes YAC clone identified for marker. CBL5 is an unpublished STR marker. Numbers shown are consensus intermarker distances in cM, sex-average.

chromosomes 5p and 9p, in which deletion of IFNA, D9S126, D9S3, D9S104 were shown by in-situ hybridization and/or gene dosage studies (Petty et al., 1993). The patient has had 8 primary malignant melanomas and a plexiform neurofibroma. Analysis of deletional events in tumor DNA samples suggests that the critical region is close to the IFN gene cluster in the case of acute lymphoblastic leukemia and gliomas (Olopade, et al., 1992), and is centromeric to the MTAP gene in melanomas (Fountain, et al., 1992; Coleman et al.). These observations suggest that either there is more than one gene in this region with a tumor suppressor role in carcinogenesis, or that the gene involved is very large.

MacGeoch et al. presented a linkage study in their families with melanoma/dysplastic nevus syndrome. Evidence for heterogeneity was seen with a lack of linkage to 9p markers in some families.

A new disease gene, CHH (cartilage-hair hypoplasia, McKusick type metaphyseal chondrodysplasia), has been mapped to this region with limiting markers D9S43 and D9S50 (Sulisalo et al.). In addition, strong linkage dysequilibrium was seen with the marker D9S50. The PAX5 gene was also mapped to 9p (Pilz et al., 1993; Stapleton et al., 1993), and is inferred to be in bands p12-21 based upon mouse-human synteny (Pilz et al., see below).

9cen-q31

The map of 9cen-q31 was coordinated by Allen Bale, David Goudie, and Sue Slaugenhaupt (Fig. 2). Genetic family data were combined from Lucente et al., Blumenfeld et al., Farndon et al., Dean et al., Goudie et al. and (Goudie et al., 1993), the CEPH consortium (Attwood et al.), the index mapping groups (Kwiatkowski et al.), and from (Weissenbach, et al., 1992). Mapping of D9S109 and D9S127 was also done by sperm typing (Furlong et al.). New markers since the last meeting include 16 GT repeats from Genethon (Weissenbach) and new markers presented at this meeting by Liebert et al. (CBL5, TRKB), Attwood et al. (ET15.5-6), Kwiatkowski et al. (D9S201), and D9S202.

The XPA gene and the markers D9S180, D9S22 and D9S6 all fall on the same 600 kb YAC. The markers D9S180, D9S22, D9S6, D9S176, and D9S173 were not separable genetically but were ordered by physical means, using PCR of flow sorted chromosomes from translocation breakpoints giving the order (XPA, D9S180) - (D9S22, D9S6) - (D9S176, D9S173) (Goudie, et al., 1993; Goudie et al.). The deletion breakpoint in the somatic cell hybrid GAT11 separates D9S29 and D9S53 on 9q31 from the adjacent proximal markers D9S109 and D9S12 (Bale et al.), but linkage analysis in DYS families places D9S29 proximal to D9S109. This discrepancy will be resolved by further physical mapping and YAC contig construction in the region. Pulsed field mapping places ORMA (probe alpha I AGP2), ALAD, and D9S16 (also designated D9S28) on the same 1.3 Mb NotI fragment. ORM and D9S16 fall within 20 kb of each other on a cosmid (Harris et al., 1993). Note also that D9S56 is D9S12.

Two new disease genes have been mapped to this region since the last meeting. These are FACC (Fanconi's anemia, group C) on 9q22.3 (Strathdee et al., 1992), and Familial dysautonomia (Riley-Day Syndrome, DYS) on 9q31. Additional genes recently added to the physical map include TRKACG (the catalytic subunit C gamma of the cAMP-dependent protein kinase) on 9q13 (Foss et al., 1992), COL15A1 (collagen type 15 alpha chain) on 9q21-q22 (Huebner et al., 1992), TAL2 (T-cell acute lymphoblastic leukemia) on 9q32 (Xia et al., 1991), TRKB (tyrosine receptor kinase B) (Liebert et al.) and the enzyme beta-1,6-N-acetylglucosaminyltransferase (Bierhuizen et al., 1993). The location of ALDOB (aldolase B) has been narrowed from 9q13-32 to 9q22.3-31 by analysis of flow sorted chromosomes from the translocation cell lines, 9T20 and 9T06 (Goudie, et al., 1993). Anonymous markers that have been physically mapped but not yet placed on a linkage map include JDS19 (q31-q32), JDS4 (q31-q32), JDS15 (q32) (Bale et al.), and D9S202 (q13-q21).

The localization of the ESS1 (multiple self-healing squamous epitheliomas) gene has been refined by linkage studies that show D9S12 to be a proximal flanking marker (one recombinant) and linkage disequilibrium analysis that places the gene proximal to D9S180 (Goudie, et al., 1993; Goudie et al.)

Several groups (Dean et al., Farndon et al., Reis et al., Wicking et al.) contributed to fine mapping of the NBCCS (nevoid basal cell carcinoma syndrome) locus. All groups presented data supporting D9S127 as a distal marker and three groups had evidence that D9S12 is a proximal flanking marker. Reis et al. identified one recombinant that would place the gene proximal to D9S176. Bare et al. showed that 24% of sporadic medulloblastomas and 11% of meningiomas, tumors that are often seen in NBCCS, arise with allelic loss of chromosome 9q22-31. Gailani et al. described a NBCCS patient with a constitutional deletion of chromosome 9q22-31, indicating that the disease can be caused by deletion of the gene.

Familial dysautonomia (DYS) has been mapped to 9q31-33 (Blumenfeld et al.; Blumenfeld et al., 1993) with closest flanking markers D9S172 (proximal) and D9S105 (distal). This disease shows very strong allele association with the highly polymorphic marker D9S58 with which it is very closely linked (lod score 21.1 at $q = 0$).

The similar physical mapping localization for the XPA, NBCCS, ESS1, and FACC1 genes is intriguing. Two or more of these disorders may be due to distinct mutations in a single gene.

9q31-qter

The map of 9q31-qter was coordinated by Jonathan Haines. The genetic map of markers from 9q33-qter was derived from data presented at this meeting in a number of abstracts and posters. These included a high resolution map of 9q34.1 including several new and highly polymorphic markers in the Venezuelan pedigrees (Henske et al.), an index

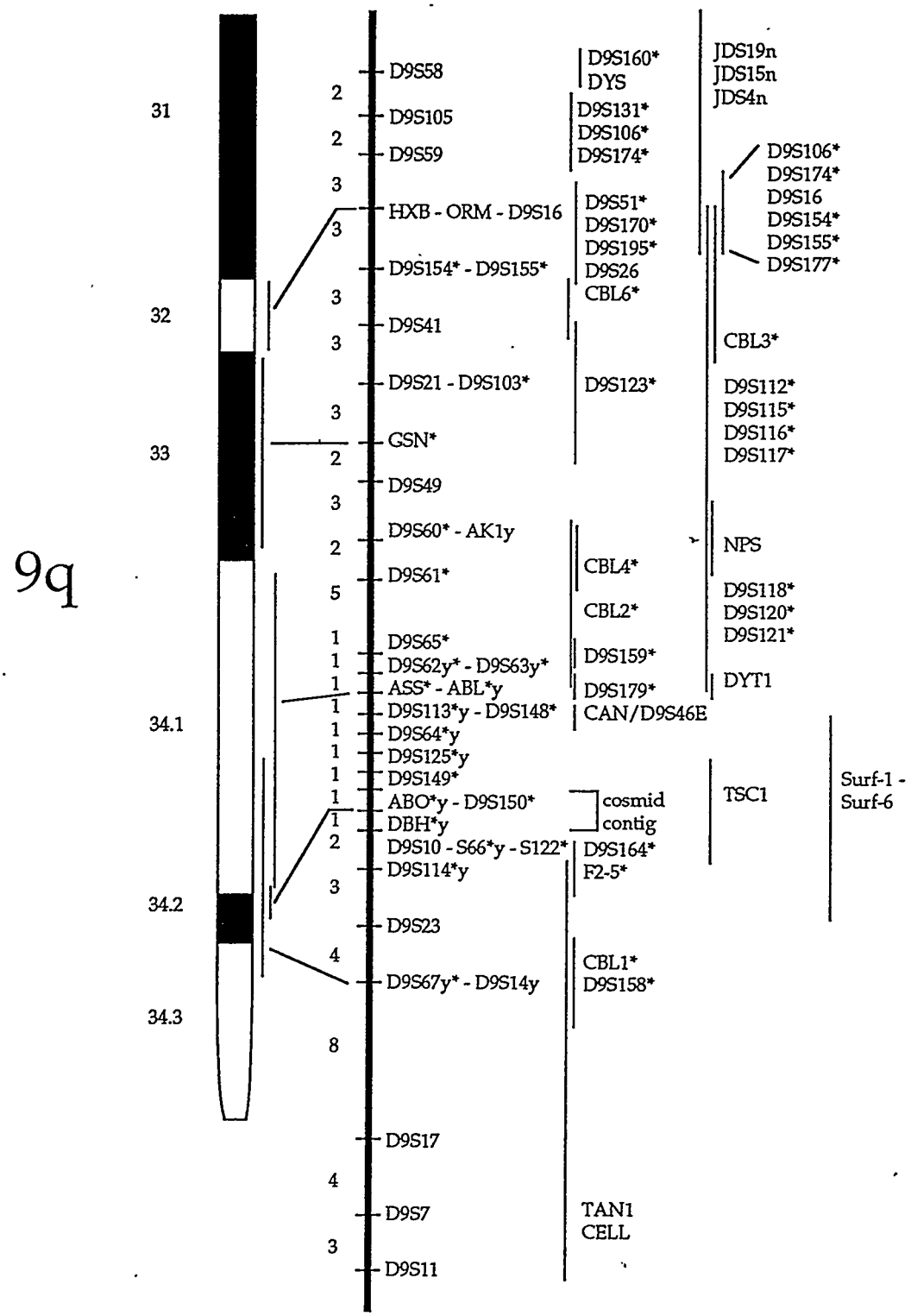

Figure 3. The map of human chromosome 9q31-ter. * denotes marker assayed by PCR. y denotes YAC clone identified for marker. CBL and JDS are local names for unpublished STR markers (see Table II). Numbers shown are consensus intermarker distances in cM, sex-average.

marker map using PCR markers in the CEPH pedigrees (Kwiatkowski et al.) and other maps incorporating variable amounts of new information into the CEPH data (Attwood et al., Liebert et al., Haines et al.; Weissenbach, et al., 1992). Also available were conclusions from the CEPH consortium mapping group (most of those listed above, also Collins et al., Falk et al., and others not present at the meeting, see abstract presented by John Attwood). The order given on the left in Fig. 3 is supported at odds of 1000 to 1 by genetic analysis or by firm physical data for some very close markers (e.g. ABL and ASS, D9S10 and D9S66.). There are four Genethon markers in this region; additional typing of CEPH families by Margaret Pericak-Vance (Haines et al.) has allowed more certain placement of D9S164 and S158, although not at odds of 1000 to 1. The Genethon marker D9S158 is probably currently the most distal PCR-able marker in 9q34 and further distal markers are still required.

There was no conflict between different data sets as regards order of markers but estimates of the distance from HXB to GSN were considerably larger in the CEPH consortium data than in the new PCR-able index marker map presented by Kwiatkowski et al., presumably because of errors in older RFLP data. The genetic distances given on the consensus map must be regarded as very approximate and it is for this reason that only sex-averaged distances are shown.

Refinement of the map of the ASS-ABL-DBH-ABO region of 9q34.1-34.2 has occurred (Fig. 4). Physical data presented at the last meeting (Harris, et al., 1993) suggested that the region between ASS and DBH may be as little as 2 Mb. Confirmation of this distance has not yet been obtained but independent pulsed field gels have indicated that ABO and DBH are approximately 250 kb apart (Janssen et al.) and on a 450 kb NruI fragment (Henske et al.). Fitzgibbon et al. however found DBH to lie on the distal part of a 450 kb SalI fragment which was not recognised by ABO. D9S125 and D9S149 are on a 610 kb NruI fragment (Henske et al.). Several groups have found D9S10 and D9S66 to lie within 10 kb of each other on cosmids (Nellist et al., Fitzgibbon et al.) and Nellist et al. presented a 250 kb cosmid contig including DBH-D9S10-D9S66. Several YACs and small YAC contigs were reported from the region (see Fig. 4) and a 250 kb cosmid contig was derived by subcloning of a YAC for ABO (Zhou et al.). Laurie Ozelius (personal communication) provided further information on the D9S62-ASS region. Murrell et al. described a YAC which contains both D9S14 and D9S67.

The gene TAN1, homologous to the Drosophila notch gene, was shown to lie distal to ABL and CAN in somatic cell hybrids. Fluorescent in situ hybridization on both metaphase and interphase nuclei place TAN1 distal to D9S66 (Janssen et al.). Another new assignment is that of RXRA, a subunit of the retinoic acid receptor, which also lies distal to D9S66 (Jones et al., 1993). This position is rather surprising in view of its position in mouse chromosome 2 between DBH and ABL (Pilz et al.). Other new genes mapped to this region include a brain form of prostaglandin D2 synthase to 9q34.2-34.3 (White et al., 1992), and one of the subunits of the methyl aspartate receptor to 9q34.3 (Karp et al., 1993). The selectable marker folylpolyglutamate synthase, previously mapped to 9q, appears to map to 9q33-34 (Bale et al., Povey and Smith personal communication). A clone originally mapped to chromosome 18 (pMCT108.2) has recently been shown to be chimeric and as D9S203 provides a new STS in 9q33 (Lia et al., 1993). Refinement of the physical location of the surfeit cluster of genes has also been obtained (Yon et al., 1993); they map telomeric to the CAN/D9S46E gene in 9q34.1.

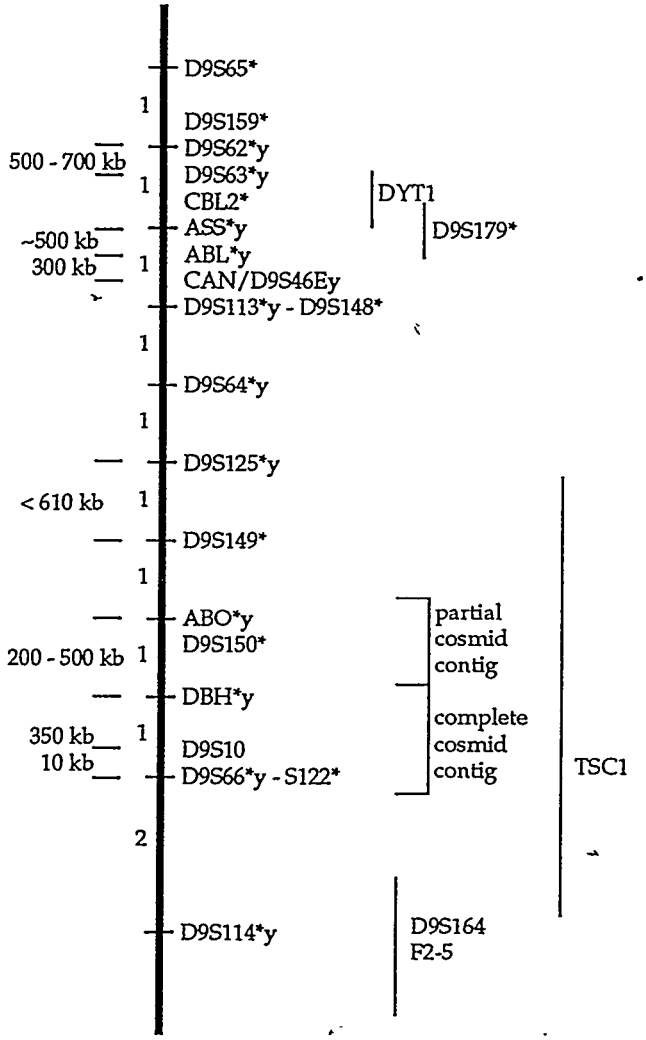

Figure 4. The map of the ASS - ABO region of human chromosome 9q34. * denotes marker assayed by PCR. y denotes YAC clone identified for marker. CBL2 is an unpublished STR marker. Small numbers shown are consensus intermarker distances in cM, sex-average. Large numbers are physical distances between adjacent markers on the map, where known. Cross-hatches indicate genetically mapped markers; intermediate markers without cross-hatches are physically mapped.

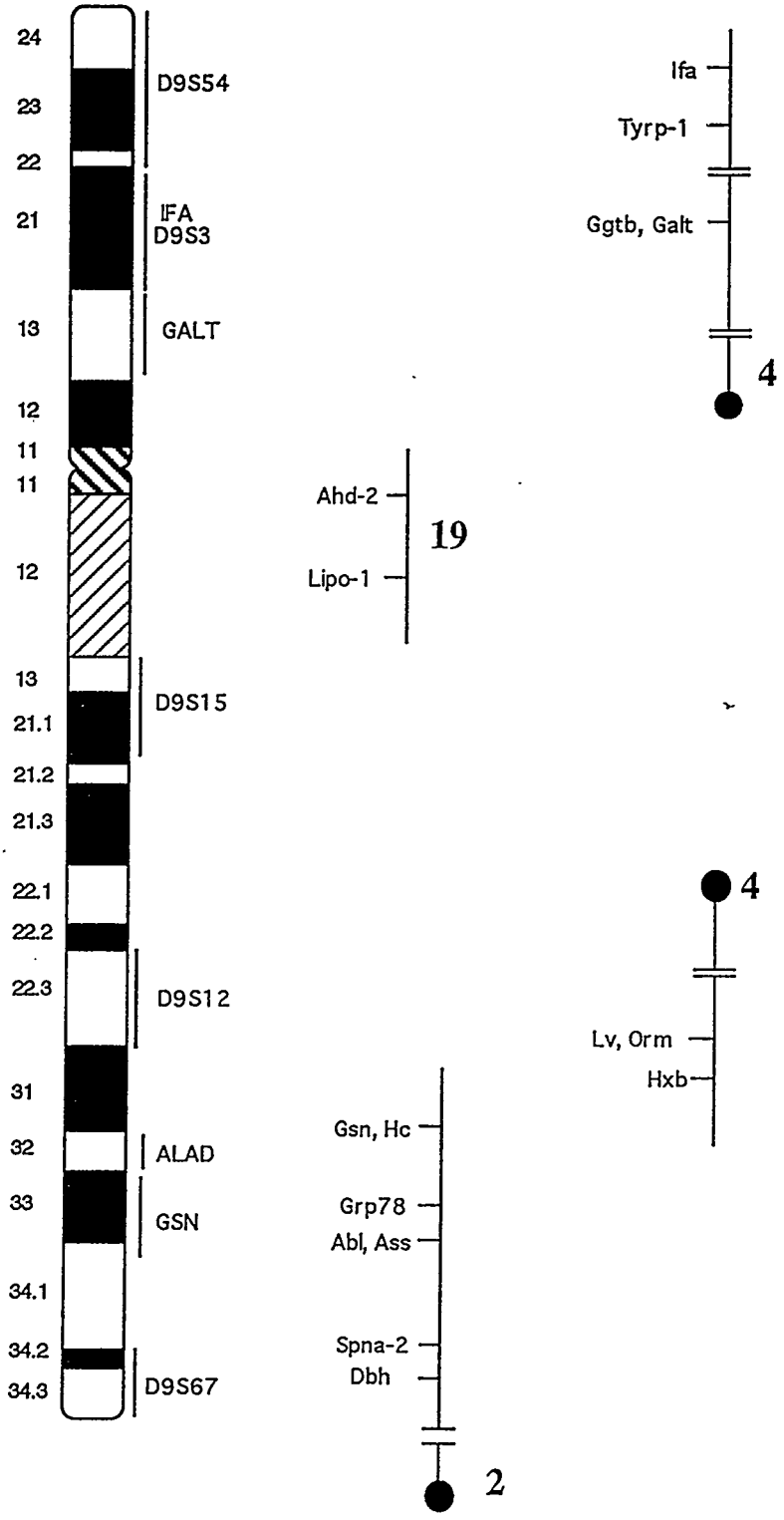

Figure 5. Conserved mouse homologies aligned to human chromosome 9. The centromere of the mouse chromosomes where orientation is known, is shown by a filled circle. Chromosome 4 is displayed twice in order to make comparison easier. Hc is the mouse homologue of C5; Lv is the mouse homologue of ALAD.

No new disease loci have been added to the 9q33-ter region since the last meeting. Some progress has been made in the elucidation of heterogeneity in torsion dystonia (ITD) in that a distinctive haplotype in the ASS region is found in more than 90% of Jewish cases with early limb onset. Those non-Jewish families with the same phenotype, appear to map to the same region (Ozelius et al.). The allelic association between DYT1 and ASS and also with D9S63 was confirmed in UK Jewish families. In non-Jewish families with DYT1 there was no overall allelic association but for other cases with early limb onset significant allelic association with ASS was found (Warner et al.).

Bladder carcinoma gene

A discussion of the location of a probable tumor suppressor involved in the early steps of the pathogenesis of bladder cancer was led by M. A. Knowles. In total, 430 sporadic bladder tumors have been studied for allele loss on chromosome 9 (Cairns et al., Miyao et al., Ruppert and Sidransky). The majority have loss of heterozygosity at all informative loci along the chromosome. Only 15 tumors have been identified with partial deletions of chromosome 9. Thirteen of these are well characterized and all appear to represent large terminal deletions. No interstitial deletions have been found. Two alternative interpretations may be considered. 1) There is a single target within a large common region of deletion between D9S18 (9p12-p13) and D9S22 (9q22.3). This would exclude the melanoma locus at 9p21 but may include the Nevoid Basal Cell Carcinoma Syndrome (NBCCS) locus. 2) Two or more separate targets exist and all deletions may not involve the same target gene.

Comparative mapping between human chromosome 9 and mouse chromosomes
(prepared by Alison Pilz).

Genes mapping to human chromosome 9 have homologues which map to three different mouse chromosomes; namely mouse chromosomes 2, 4, and 19 (Fig. 5). The homology on chromosome 4 is in three segments - two regions of synteny with human chromosome 9p are separated physically by a region syntenic with 9q. The figure shows the conserved mouse syntenies aligned with the chromosome 9 map. A number of predictions may be made based on a comparison of the human and mouse maps. First, the inter-a-inhibitor a1-microglobulin/ bikunin precursor (AMBP) gene most likely maps to 9q32, since its mouse homologue (Itil) maps close to ORM and Lv (the mouse homologue of ALAD). Secondly, PAX5 will probably map centromeric to GALT. Third, the mapping of the mouse homologue of ALDOB confirms the human mapping of the ALDOB gene centromeric to ALAD and ORM, (as expected from its broad assignment to 9q22.3-q32). Last, GRP78 is probably telomeric of C5 and centromeric of ABL.

The data also predict the occurrence of human homologues for several mouse genes whose mutations have the following phenotypes.

Table I. Mouse mutants whose causative genes are predicted to map to human chromosome 9

Mouse chrom. loc	Abbrev	Name	Phenotype	Chr 9
MMU2	Sd	Danforth's short tail	Kidney/notchord development	9q31-34
MMU2	Stb	Stubby	Mild achondoplasia	9q31-34
MMU2	Lh	Lethargic	Neurological/ immunological	9q31-34
MMU4	An	Hertwig's anaemia	Hematologic	9p/9q
MMU4	Vc	Vacillans	Neurological	9p/9q
MMU4	Cy	Crinkly tail	Tail	9p/9q
MMU4	Dep	Deplillated	Hair	9p
MMU4	Pt	Pintail	Tail	9p
MMU4	Wi	Whirler	Deafness/inner ear	9q

Informatics

Jamie Cuticchia demonstrated version 5.0 of GDB and there was considerable discussion about the submission of YAC data which is so far poorly represented for chromosome 9. Collins et al. presented an integrated summary map of chromosome 9 generated by the program ldb from partial maps. This contains 166 loci of which 112 have genetic locations. Many of the markers are approximately placed with groups of loci locally unordered. There was no serious conflict with the human consensus view which contains many fewer loci. It is planned to add data from this meeting to ldb and workers are encouraged to submit new partial physical or genetic maps for incorporation into future versions.

An anonymous ftp server has been established at diamond.gene.ucl.ac.uk (128.40.82.1). This will be used initially as a means of electronic distribution of the workshop abstracts and this report. In the longer term it will be used to distribute items of general interest such as the summary maps of ldb and news of interest to the chromosome 9 community. A tutorial on how to access the server was presented at the meeting and copies are obtainable from John Attwood (see list of participants). This server is available to all laboratories with access to a computer connected to the Internet. Workers in the field are invited to submit items of general interest.

To complement the ftp server an electronic mailing list has been established based initially on the e-mail addresses of participants. This will be used to inform people of changes and additions to the ftp server but can also be used by anyone as a means of asking questions or notifying the community of new resources. Electronic mail addressed to chr9@mrc-hbgu.ucl.ac.uk will automatically be forwarded to everyone on the list. Anyone wishing to be added to the list should contact

John Attwood.

Global mapping issues

A subgroup met to discuss global mapping issues with respect to chromosome 9, and was coordinated by John Armour. The discussion focussed on three main points.

First, the analysis of the data by John Attwood and Sue Povey for the forthcoming CEPH consortium map of chromosome 9 included the specification of meiotic breakpoints within CEPH kindreds. The results of this analysis within a family can be presented as a table detailing the grandparental origins of paternal and maternal chromosomes over particular map intervals. It was agreed that such tables would provide a valuable resource for the rapid approximate placement of new polymorphisms. At the subsequent meeting of the CEPH collaborative mapping group it was agreed that tables from two or three CEPH families, particularly those pedigrees available indepedently of CEPH, would be included in the CEPH consortium map manuscript.

Second, the current practice of using only the results of primary data within GDB may be unduly restrictive, and lead to the absence of useful information. For example, D9S104 appears on the CEPH consortium map between D9S129 and D9S50, each of which have been localized to 9p21. While it may appear a safe extrapolation to infer that D9S104 maps to 9p21, it currently appears in GDB as mapping simply to chromosome 9. The group recommended that such practice, if adopted, should be strictly rule-based, if possible implemented by GDB itself, and that inferred placements should be flagged as such to preserve a distinction from placements based on primary experimental data. The consensus of the mapping community was to improve the effective informativeness of GDB's physical localizations, by allowing conservative extrapolations from linkage maps, under the supervision of the editors. The existence and basis of any such inferences should be made plain within GDB.

Third, the group discussed ways in which the input of mapping information into GDB might be facilitated. There is understandable reluctance to make public very recent data concerning disease gene regions; however, the availability of "timelocked" data submissions should allow a more relaxed attitude towards early submission. This group also encouraged the reclamation of "orphan" data, such as resources or detailed maps which were no longer considered central to one group's research goals, but which might prove invaluable to researchers engaged in other work. A specific example of this are the numerous STR polymorphisms identified in recent years from the hamster by many, many investigators which could usefully be collected as a resource for mapping in that species.

Resources

Hybrids

Three hybrid resources were described at the meeting. A series of hybrids presented by Allen Bale (Bale et al.) were made with 4 different cell lines carrying naturally occurring deletions of 9q. These provide a panel with deletions of 9q22, 9q31, 9q22-32 and 9q22-q33. An extensive series of radiation hybrids defining different regions of 9p, previously described (Jackson et al., 1992) has now been more extensively characterised by Cynthia Jackson's group (Britt et al.). A new series of radiation hybrids from the whole of chromosome 9 was also described (MacGeogh et al.).

Cell Lines

A number of lymphoid lines with well defined translocation breakpoints, collected by Malcolm Ferguson-Smith's group in Cambridge have been deposited at the European Cell Bank as described in the 1992 Workshop Report. Nigel Carter (not present at the meeting but same address and fax as Rob Furlong) has a resource of flow sorted chromosomes from these translocations with which he is willing to map any PCR-able markers on a collaborative basis.

Cloned Resources

A flow-sorted chromosome 9 cosmid library (LL09NC01"P") has been prepared by Pieter de Jong (de Jong et al.) using as starting material a chromosome from a somatic cell hybrid. This library of 29,000 clones (72% human, 23% hamster, 5% non-recombinant) has been gridded out and distributed to eleven groups worldwide. Good results from this library have already been reported (for example Nellist et al.). Pieter de Jong also described construction of a lambda library (LL09NL01) from the same batch of flow-sorted chromosomes and available from the American Tissue Type Collection. These workers also described the development of a total genomic library in P1 derived artificial chromosomes. Randomly selected clones from this library have inserts of approximately 130 -150 kb with no obvious rearrangements. This library as yet consists of less than one genome equivalent of clones and is not ready for distribution.

A chromosome 9 flow sorted YAC library has been constructed at Los Alamos by Mary McCormick (Murrell et al.), and is available on a collaborative basis. A number of YACs and small YAC contigs have been identified (see consensus maps, individual abstracts Fountain et al., Murrell et al., Nellist et al., Zhou et al. and GDB).

New Strategies

John Armour described a strategy for the efficient isolation of arrays of tri- and tetranucleotide repeats from whole genome PCR libraries. It is planned to extend this procedure to material isolated from a hybrid containing 9q as its only human material (Armour and Gobert).

Rutter et al. described a strategy for the isolation of genes on human chromosome 9 using exon amplification, with further improvements in the vector and method originally described by Buckler et al. Starting with a collection of cosmids from a 9-only hybrid, 71 putative exons have been cloned. By the end of 1993 it is hoped to have identified 1000 exons from chromosome 9 by this approach.

New Polymorphisms

The largest contribution of new markers to chromosome 9 in the past year has been that of Genethon (Weissenbach, et al., 1992). Several new polymorphisms were also described at this meeting by David Kwiatkowski (Henske et al.), Sue Slaugenhaupt (Leibert et al.), Allen Bale et al., and Joseph Nahmias (Attwood et al.).

Table II. New polymorphisms on chromosome 9. Oligonucleotide primer sequences are shown, when publicly available.

Locus/ local name	hetero- zygosity	size range	location	source
D9S62 2BH10	.85	156-188	9q34.1	Kwiatkowski
TGGTCTCTTTTCTGTTGGGG, CACCCTTTCCTATAGAGGAG				
D9S113 5B1	.82	118-132	9q34.1	"
TCCTTCTAAAAGCAAGGAACC, GGGATAAGACACAGCAGGGA				
D9S148 C10	.61	99-123	9q34.1	"
TGGGCAACATAGTGAGACCA, AGCCAGGAGCTGTGGATG				
D9S125 3AB12	.85	113-155	9q34.1	"
AGCAAGAACGCTCCATGGG, AACCTGGGTAAGAATCTGGC				
D9S149 D3	.88	146-176	9q34.1	"
GATTGACCTGTGAATTTGTACAGC, TGTTATGCCTTGCTGTTGCT				
D9S150 B1	.72	87-99	9q34.1	"
GGAATGTGGTCTGTGTGCA, TGCTCTTCATCCACTCTCAGC				
D9S122 10G11	.78	146-160	9q34.1	"
CTGGGATGGCTGCAGACTG, TTCTGGATGGAATCCTCAGC				
D9S114 5B11	.79	93-111	9q34.1	"
CTCTCTCTCTCTGTCTGCC, CGGGGAATGCGAATGAG				
CBL2			9q34.1	Slaugenhaupt
CBL6			9q31-32	"
CBL3			"	"
CBL1			9q34	"
CBL4			9q34.1	"
CBL5			9q21	"
F2-5			9q34.1	Nahmias
TTATTCCGGATAACTGTCCA, TATTACAATTTGCTGAGCCC				
15.5-6			9q22.1	"
TGGCAGTTACAAGCACGTTTAC, GGGAACTGGGTGGACATCTC				
JDS19n			9q31-32	Bale
JDS15n			9q32	"
JDS4n			9q31-32	"

Tuberous sclerosis satellite meeting

A satellite meeting on tuberous sclerosis was held in association with the chromosome 9 meeting. The primary focus of the discussions was on refining the locations of the TSC genes. The location of the chromosome 9 gene (TSC1) is problematic. Various groups reported recombinants with ASS, ABL, D9S64, D9S125, and D9S149, all consistent in suggesting that the gene is distal to these markers. As well, numerous recombinants with D9S14 and D9S67 were reported, as were several recombinants with D9S114, all indicating the gene lies proximal to these loci. More problematic was one cross in an affected individual reported by Margaret Pericak-Vance placing the gene distal to DBH, while one unaffected individual reported by Bart Janssen places the gene proximal to D9S150 (which is proximal to DBH). In addition, 5 individuals from apparently 9-linked families excluded regions spanning at least D9S64 to D9S114. It was suggested by many that these apparent inconsistencies are similar to those seen in Huntington's disease, in which the apparent genetic event has recently been identified as a trinucleotide repeat mutation. Although less well characterized, the localization of the chromosome 16 locus (TSC2) is consistent. Several groups reported crosses with D16S85, placing TSC proximal, and two crosses (from Pericak-Vance and Povey) place the gene distal to D16S291. Sue Povey also reported that two of her D16S85 crosses also crossed with D16S309 (probe MS205), narrowing the candidate region to the region between D16S309 and D16S291. An informal collation of data suggested that the split between chromosome 9 and 16 families is almost 50/50. Placing raw linkage data from TS pedigrees on an anonymous FTP server was also discussed.