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REPORT on the Third International Workshop on Chromosome 9

held at Queens' College, Cambridge, UK, 9–11 April, 1994

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The Third International Workshop on human chromosome 9 was held at Queens' College, Cambridge 9–11 April, 1994. The meeting was attended by 74 participants from 12 countries. On the morning of 12 April a satellite meeting was held on Tuberous Sclerosis, and because of its relevance to chromosome 9 a summary of this meeting is also presented within this report. Sixty-four abstracts were received and the data presented on posters.

As before after a brief presentation of interests and highlighted results the workshop divided into several groups, each with the task of producing a report. The division consisted of a group with global interests, four regional groups 9p, 9q11–q21, 9q22–q33 and 9q33–qter, a group interested in mapping putative suppressor genes in ovarian and bladder cancer and a comparative mapping group. There was also discussion of resources, both physical and informatic.

The amount of information on chromosome 9 has increased greatly in the past two years and it is clear that the integration of different types of information and the display of such information is an urgent problem. At this meeting two possible systems were explored, SIGMA and ldb. As described in the global group report an attempt was made to enter all mapping information into SIGMA, a program developed by Michael Cinkosky at Los Alamos. 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 in general confined 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

and also for all primer sequences (except a few actually listed in the abstracts) the reader should consult GDB. The proceedings of the two previous workshops have been published and are listed in the references (Povey *et al.* 1992, Kwiatkowski *et al.* 1993*a*). It was decided that a fourth workshop would be held in about a year's time. Dr Margaret Pericak-Vance offered to host this at Duke University, North Carolina.

As in previous years there was considerable debate about the importance of producing sex-specific genetic maps. It is recognized that a sex-averaged chromosome does not exist and several individual workers had indeed considered the sexes separately but it was not practical to attempt integration of sex-specific data into the consensus over the time of the workshop. Collins *et al.* presented a comprehensive integrated map of chromosome 9 generated by ldb including over 220 loci which estimated the genetic length (D9S143–D9S11) as 117 cM in males and 160 cM in females, with a marked increase in male recombination near pter. This map together with the relevant datafiles will be available on the chromosome 9 file-server (see section on resources). Hultén has previously reported a male chiasma map of 9 suggesting a genetic length of 116 cM with very strong interference, a finding which has been borne out by recent publications (Kwiatkowski *et al.* 1993*b*, Attwood *et al.* 1994) and at the meeting (Farndon *et al.*). Female chiasmata maps would now be possible if suitable material can be obtained (Hulten *et al.*). There is some suggestion that recombination is determined by position rather than sequence, since increased recombination was shown within the interstitial segments of two male carriers of translocations involving 9 (Armstrong & Hulten).

Haines & Kwiatkowski presented an analysis of CEPH families showing that the average number of recombinants per chromosome 9 per individual parent followed a normal distribution, with a range of 0·43 to 1·86 in males and 0·88 to 2·67 in females. In males a decrease in recombination was seen over the age of 40 years.

GLOBAL MAPPING GROUP

This group included John Armour, David Kwiatkowski, Julia White, John Attwood, Sue Povey, Maj Hultén and Andy Collins. Although the two major groups involved in global mapping projects did not attend they both contributed data. J. Weissenbach contributed unpublished primary data on 35 new Genethon markers in the CEPH families. J. Murray contributed the latest map from CHLC.

The global group concerned itself primarily with the production of maps of the whole chromosome, centred on two approaches:

(*a*) *SIGMA*

The group encouraged and facilitated the transfer of new mapping information into SIGMA, a UNIX-based mapping and display tool written by Michael Cinkosky at Los Alamos. These data were used to produce an updated SIGMA map of chromosome 9. It should be emphasized that SIGMA uses information from both genetic and physical mapping to give an integrated map; the linkage data are mainly used to provide an initial framework, and on a smaller scale to interpolate between flanking markers of known relationship. Its main function for this workshop was to provide an overall 'best guess' relative location for as many markers as possible. The amount of data which can be entered into SIGMA is constrained only by time and

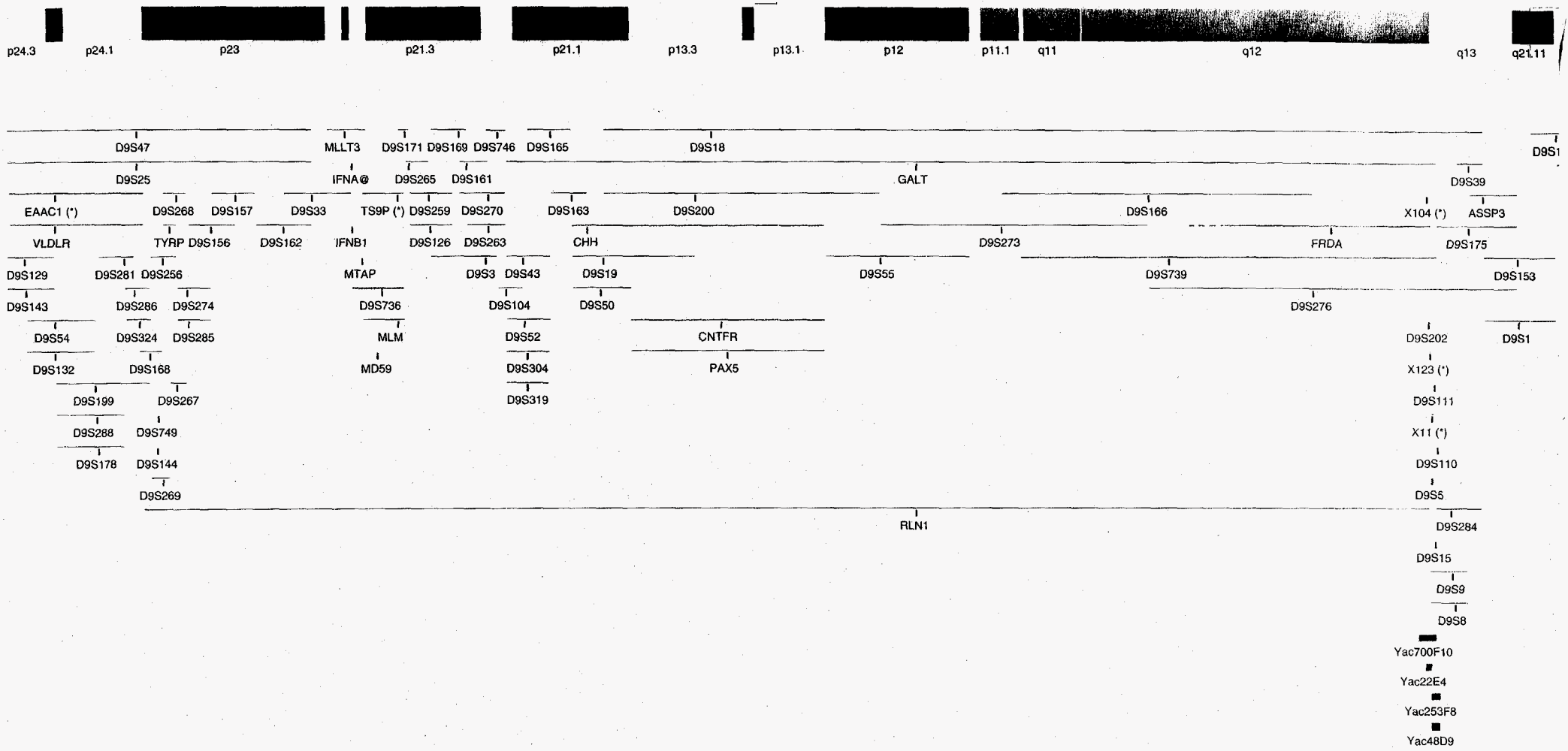
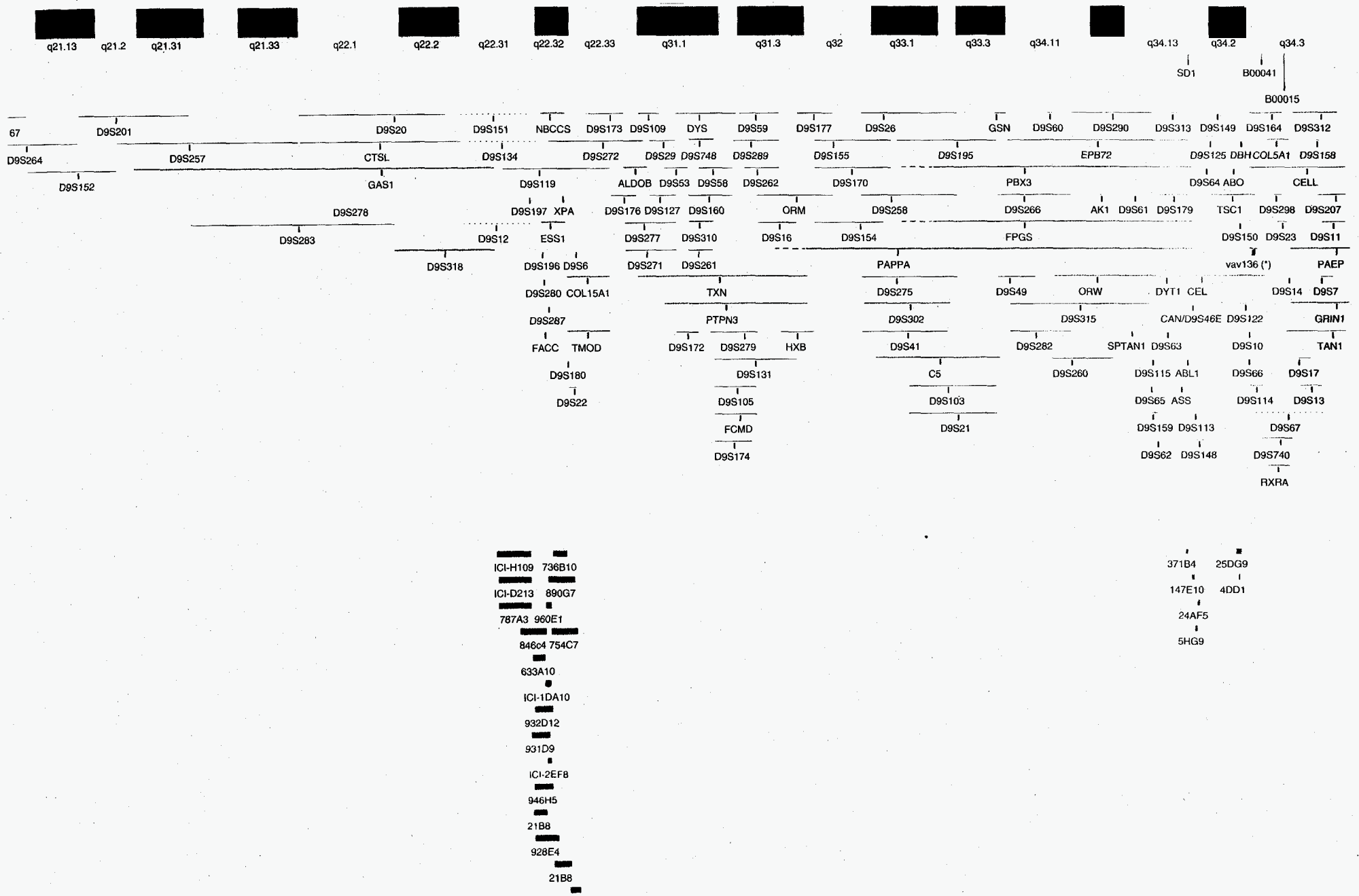


Fig. 1. Integrated map of human chromosome 9 produced with the SIGMA software. Markers added at this workshop are shown in red. Individual YACs are indicated as solid red bars below the main map.


q21.13
q21.2
q21.31
q21.33
q22.1
q22.2
q22.31
q22.32
q22.33
q31.1
q31.3
q32
q33.1
q33.3
q34.11
q34.13
q34.2
q34.3
SD1
B00041
B00015
67
D9S201
D9S20
D9S151
NBCCS
D9S173
D9S109
DYS
D9S59
D9S177
D9S26
GSN
D9S60
D9S290
D9S313
D9S149
D9S164
D9S312
D9S264
D9S257
CTSL
D9S134
D9S272
D9S29
D9S748
D9S289
D9S155
D9S195
EPB72
D9S125
DBH
COL5A1
D9S158
D9S152
GAS1
D9S119
ALDOB
D9S53
D9S58
D9S262
D9S170
PBX3
D9S64
ABO
CELL
D9S278
D9S197
XPA
D9S176
D9S127
D9S160
ORM
D9S258
D9S266
AK1
D9S61
D9S179
TSC1
D9S298
D9S207
D9S283
D9S12
ESS1
D9S277
D9S310
D9S16
D9S154
FPGS
D9S150
D9S23
D9S11
D9S318
D9S196
D9S6
D9S271
D9S261
PAPPA
vav136 (*)
PAEP
D9S280
COL15A1
TXN
D9S275
D9S49
ORW
DYT1
CEL
D9S14
D9S7
D9S287
PTPN3
D9S302
D9S315
CAN/D9S46E
D9S122
GRIN1
FACC
TMOD
D9S172
D9S279
HXB
D9S41
D9S282
SPTAN1
D9S63
D9S10
TAN1
D9S180
D9S131
C5
D9S260
D9S115
ABL1
D9S66
D9S17
D9S22
D9S105
D9S103
D9S65
ASS
D9S114
D9S13
FCMD
D9S21
D9S159
D9S113
D9S67
D9S174
D9S62
D9S148
D9S740
RXRA
ICI-H109
736B10
ICI-D213
890G7
787A3
960E1
846c4
754C7
633A10
ICI-1DA10
932D12
931D9
ICI-2EF8
946H5
21B8
928E4
21B8
ICI-8AD8
371B4
25DG9
147E10
4DD1
24AF5
5HG9

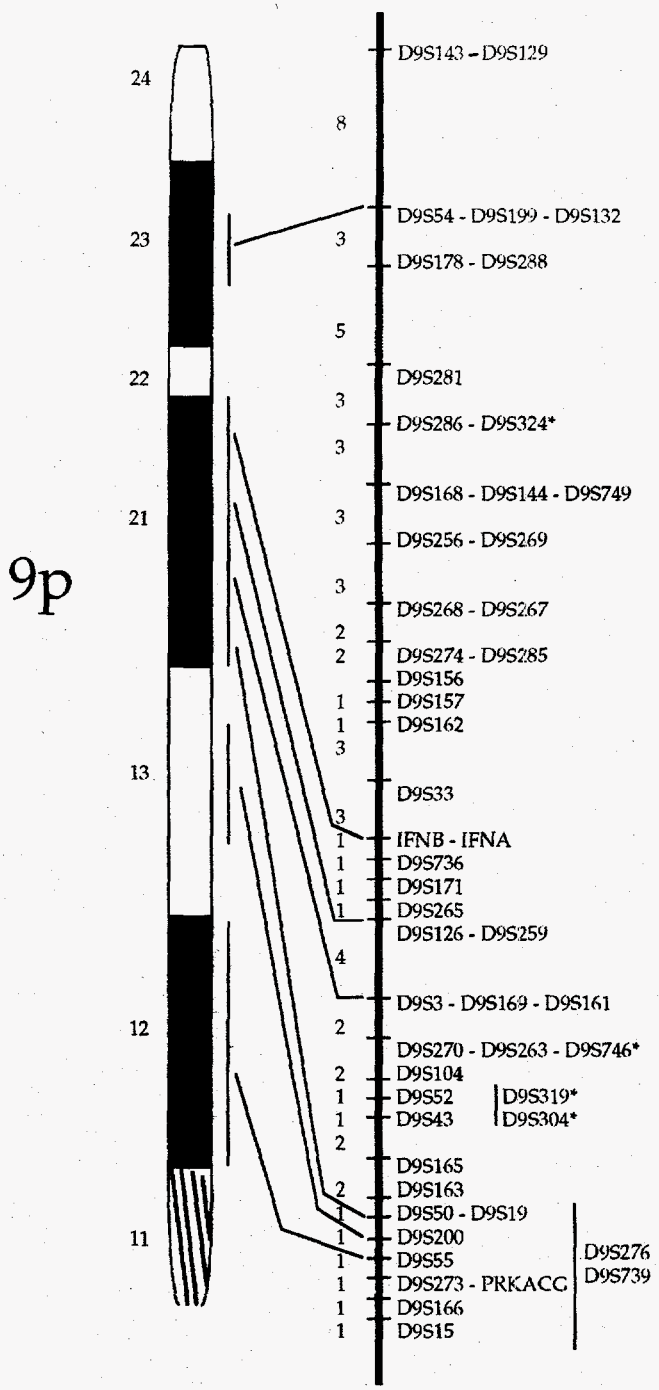


Fig. 2. The composite genetic linkage map of human chromosome 9p (sex-average). The map represents a consensus linkage map based upon a variety of information, both published and unpublished. The intent is to incorporate as many markers as possible, and to use physical information when available. * denotes marker is of the tetranucleotide repeat type. The majority of markers with S numbers less than 50 are RFLPs. Nearly all markers with S numbers greater than 50 are the STR type, the majority of which are GT/CA repeats. Numbers shown are consensus intermarker distances in cM, sex-average. Additional STR markers together with relevant mapping information have been provided by the Utah Genome Center Genetic Marker and Mapping Group (Tables 4–5), but are not shown in this figure.

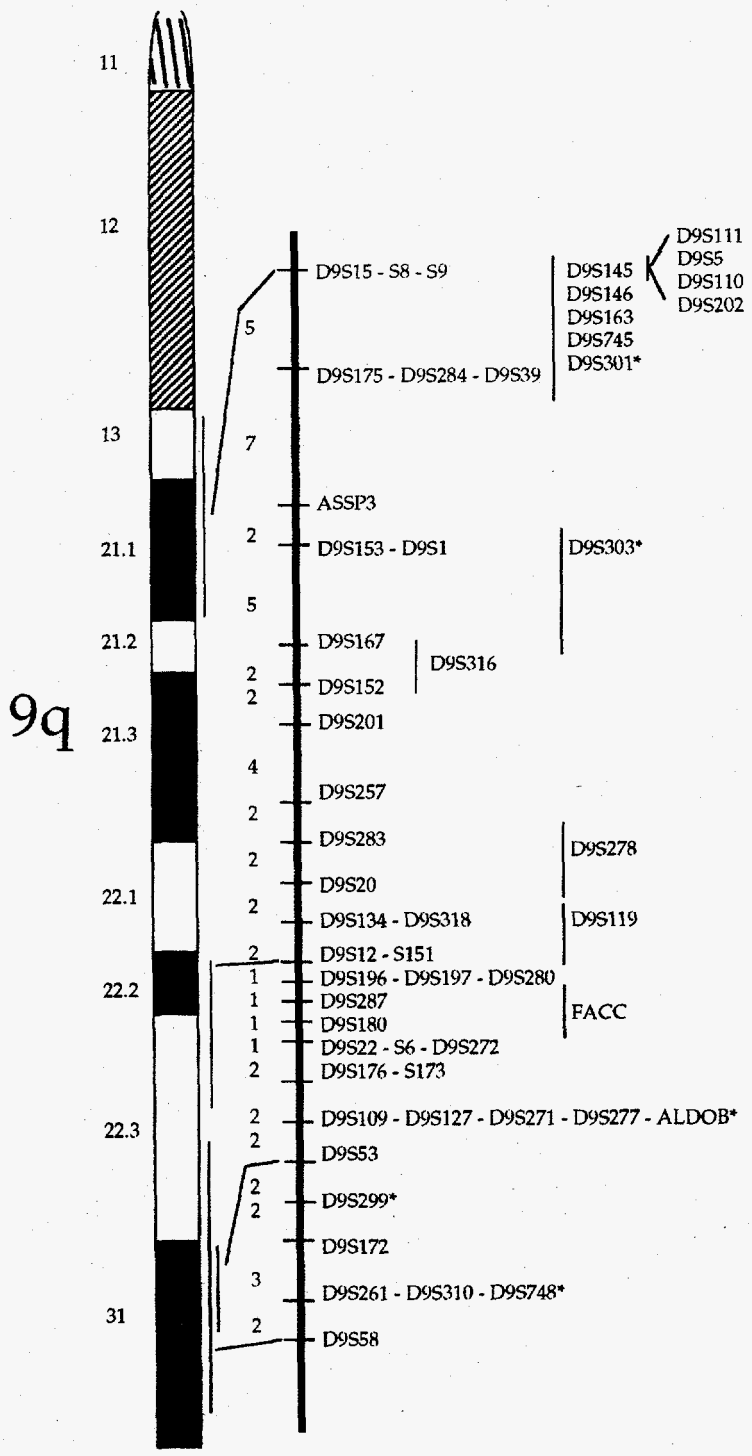


Fig. 3. The composite genetic linkage map of human chromosome 9qcen–q31 (sex-average). See legend to Fig. 2.

resources and it should be possible to keep a 'main' version updated so that older information is never lost. The printout supplied in this report (Fig. 1) has had to be selective, concentrating especially on new data which are shown in red. The scale used does not allow fine detail so for some regions additional diagrams are needed.

(*b*) *Genetic maps*

Complementing the SIGMA map, a consensus genetic map was produced using the CEPH consortium map (Attwood *et al.* 1994) as a starting point. This was updated using data from Genethon (which had been subjected to preliminary analysis by John Attwood) and data from CHLC (Murray *et al.*). Also incorporated were new index markers provided by David Kwiatkowski (Zahn *et al.*) and by John Armour (Armour *et al.*) and further work on some markers in 9q34 (Jeremiah *et al.*). The genetic map shown in Figs 2, 3 and 4 is based on typing in CEPH families. Several groups have also deduced detailed regional maps from other sources and some of those results are included in the regional reports.

Relatively few new markers could be placed conservatively and without ambiguity on the linkage map, but the updated version contains a high density of markers, the largest (sex-average) interval being 10·5 cM, between D9S157 and IFN. The map, however, includes many additional markers which could not be placed unambiguously. The updated linkage map is presented as three figures, corresponding to 9p, proximal 9q and distal 9q (Figs 2, 3 and 4 respectively).

THE 9p GROUP

The report on 9p was co-ordinated by Olufunmilayo Olopade, who also presented data in an abstract (Bohlander *et al.*). Contributors to the discussion whose data are also presented as abstracts (as first authors unless indicated) were Paul Cairns, Cathryn Lewis (Cannon-Albright *et al.*), Jayne Devlin, Magali Williamson, Alison Keen, Margaret Knowles (Devlin & Knowles, Williams & Knowles, Keen & Knowles), Rob Furlong, Dan Grander, Pali Kaur, K. Ichimura, Michael Lynch, Charles Spruck, Joseph Wagstaff and T. Sulisalo. Other contributors included Nigel Spurr.

The 9p region has generated a lot of interest because of the localization of putative tumour suppressor genes in the region. Several groups have reported homozygous deletions of 9p sequences in ALL, glioma, melanoma, lung cancer, mesothelioma, head and neck cancer, and bladder cancer. Moreover, familial melanoma has been linked to this region in some families. Therefore, most of the new information came from groups interested in the tumour suppressor gene region.

A 3·0 megabase YAC contig has been constructed around the IFN gene cluster. The MTAP gene has been localized 500 kb from IFNA8/A1 and within the same 1400 kb Not1 fragment as the IFN gene cluster (Bohlander *et al.*, Stadler *et al.*, 1994). An STS MD59 has been mapped approximately 800 kb from IFNA1. This YAC contig spanning the IFN gene cluster and including at least 2 megabases centromeric to IFNA1 does not contain D9S171. Therefore, D9S171 is at least 2 megabases from the IFN gene cluster. The TS9P locus was refined to the region between MTAP and MD59, i.e. proximal to MTAP. A new marker D9S736 has been mapped 2 cM distal to D9S171 and proximal to IFNA. MLM maps between D9S736 and D9S171 based on recombination information in 2 Utah families (Cannon-Albright *et al.*). In one

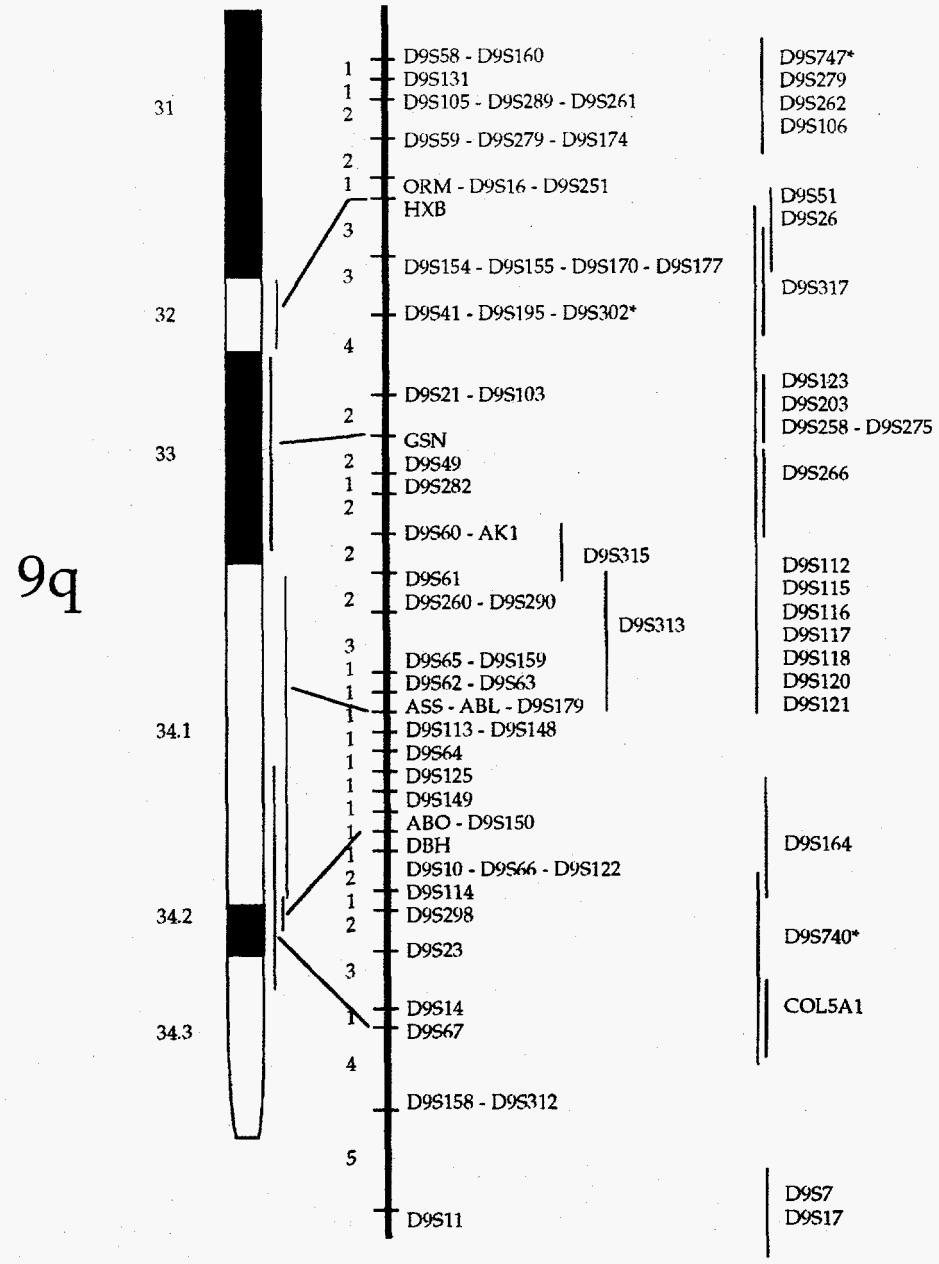


Fig. 4. The composite genetic linkage map of human chromosome 9q31–qter (sex-average). See legend to Fig. 2.

UK family MLM was mapped proximal to D9S169 (N. Spurr, personal communication). It is not clear if TS9P is the same as the MLM gene or if there are other tumour suppressor genes in the region. D9S265 has been placed in the interval between D9S171/D9S126 and MLLT3. The gene MLLT3 has been placed between D9S171 and D9S156 and has been shown to contain an unstable polymorphic trinucleotide repeat (Walker *et al.* 1994).

$9p^-$ syndrome, characterized by craniosynostosis and mental retardation, has been defined to a region bordered by D9S162 and D9S286 (Wagstaff *et al.*). TYRP has been localized within a

600 kb YAC which also contains the marker D9S267, and TYRP is proximal to D9S269 (J. Wagstaff, personal communication).

The genetic mapping of the gene for cartilage hair hypoplasia (CHH) has been refined by high resolution linkage disequilibrium analysis (in uniplex families) as well as by 8-point linkage analysis. Both methods suggest CHH is very slightly proximal to D9S163 (Sulisalo *et al.*). Two new genes assigned to 9p24 are very low density lipoprotein receptor, VLDLR (Oka *et al.* 1994; Sakai *et al.* 1994) and a high affinity glutamate transporter provisionally designated EAAC1 (official symbol now SLC1A1) (Smith *et al.* 1994). A new CA repeat marker D9S749 has been mapped close to D9S144 (Furlong *et al.*).

A few days after the workshop, two independent groups reported the identification of mutations, deletions and rearrangements in a gene found on 9p21 previously unmapped but already described as an inhibitor of cyclin-kinase 4, in cell lines derived from a variety of tumours in which deletions of 9p21 have been found as described above (Kamb *et al.* 1994, Nobori *et al.* 1994). It is not yet clear whether cases of familial melanoma have germline mutations in the same gene.

9q11–q21

Recent work in the region of the locus for Friedreich's ataxia, FRDA, has placed this gene proximal to the D9S5/D9S15 linkage group with the most probable order being FRDA-D9S5-D9S15-qter (Doudney, St Mary's Hereditary Ataxia Group). Several markers have been added giving the order FRDA-D9S202-D9S5-D9S111-D9S15-D9S110 (Rodius *et al.* 1994). Three additional new markers FR7, FR8 and FR5 are thought to be proximal to FRDA (Rodius *et al.* 1994). Three new coding sequences have been reported, X11 and X123 between D9S111 and D9S202, and X104, approximately 40 kb proximal to D9S202 and probably distal to FRDA (Duclos *et al.* 1994). This would narrow the critical region for FRDA to about 300 kb (Duclos *et al.* 1994). There has been a suggestion from Japan of another locus determining a form of ataxia similar to Friedreich's but with some additional features including early onset and hypoalbuminaemia. This disorder showed linkage to D9S15 with a maximum lodscore of 3·4 although three recombinant events with D9S15 suggest it may not be allelic with FRDA (Tanaka *et al.* 1993).

A new gene GAS1, growth arresting factor, has been mapped to the region 9q21.3–q22 (Evdokiou *et al.* 1993, Del Sal *et al.* 1994) and was also localized by two colour FISH proximal to D9S12 (B. Wainwright, personal communication).

9q22–q33

The report on this region was co-ordinated by Peter Farndon. The consensus map of this area as entered into SIGMA is shown in Fig. 1. This incorporates information from physical and genetic mapping techniques. A more detailed map of 9q22.3 is shown in Fig. 5.

New assignments

COL15A1 and TMOD have both been mapped to the interval bounded by D9S180 and D9S173 (Dean *et al.*). Gailani *et al.* also presented data localizing COL15A1 distal to D9S180. TMOD (tropomodulin) is a protein which modulates the association of tropomyosin with the

spectrin-actin complex in the membrane skeleton of erythrocytes. PTPH1, the first identified third class protein tyrosine phosphatase, whose structure suggests that it may play an important role in the regulation of cell to cell or cell to substratum interactions, has been localized distal to D9S29 (Dean *et al.*).

Multipoint linkage analysis has placed the gene for Fukuyama congenital muscular dystrophy (FCMD) in the interval D9S58–D9S59, homozygosity mapping in consanguineous families supporting this location (Toda *et al.* 1993).

Refinement of locations of disease genes

Nevoid basal cell carcinoma syndrome (NBCCS, Gorlin Syndrome)

Four groups (Bare *et al.*, Dean *et al.*, Farndon *et al.*, Wainwright *et al.*), presented information about markers proximal to NBCCS. One recombinant was reported with D9S12, and three recombinants with D9S196. There were three recombinants with D9S176 (Bare *et al.*, Farndon *et al.*) and one recombinant with a closer distal marker D9S180 (Wicking *et al.*). NBCCS therefore maps in the interval D9S196–D9S180.

GAS1, COL15A1, TMOD, and PTPH1 were possible candidate genes for the Gorlin syndrome, but their localizations exclude them.

Multiple self healing squamous epithelioma (ESS1, Ferguson-Smith Syndrome)

Linkage analysis and haplotype data give odds of 100:1 that the gene for this syndrome also lies between D9S196 and D9S180 (Goudie *et al.*), a genetic distance of about 4 cM.

Fanconi anaemia complementation group C (FACC)

Linkage data place the gene between D9S12/D9S196 and D9S287 (Jeremiah *et al.*, Dean *et al.*, Farndon *et al.*). Physical mapping (Morris *et al.*) places the gene between D9S280 and D9S287. Mutations in the FACC gene have been found in patients with Fanconi anaemia (Whitney *et al.* 1993; Verlander *et al.* 1994).

Xeroderma pigmentosum complementation group A (XPAC)

Barroso *et al.* and Morris *et al.* place XPAC on the physical map in the interval D9S287–D9S180. The distance between XPAC and D9S180 is estimated to be about 250 kb by using FISH on interphase cells (Leversha *et al.*).

Order of markers and physical distances

The consensus order of markers is as shown in Fig. 5. The linkage data are consensus data based on published data and data from Kwiatkowski *et al.* and Farndon *et al.*

Fluorescent *in situ* hybridization on interphase nuclei prepared from normal male fibroblast cultures gave a distance between D9S12 and D9S180 of about 1 Mb (Leversha *et al.*). Distances between ALAD and HXB, and between HXB and GSN were 1·6 Mb and 1·5 Mb respectively. Molecular distance estimates from FISH are in broad agreement with currently available physical mapping data. A comparison of measured distances and precise molecular distances will provide valuable insight into the conformation of the interphase chromosome.

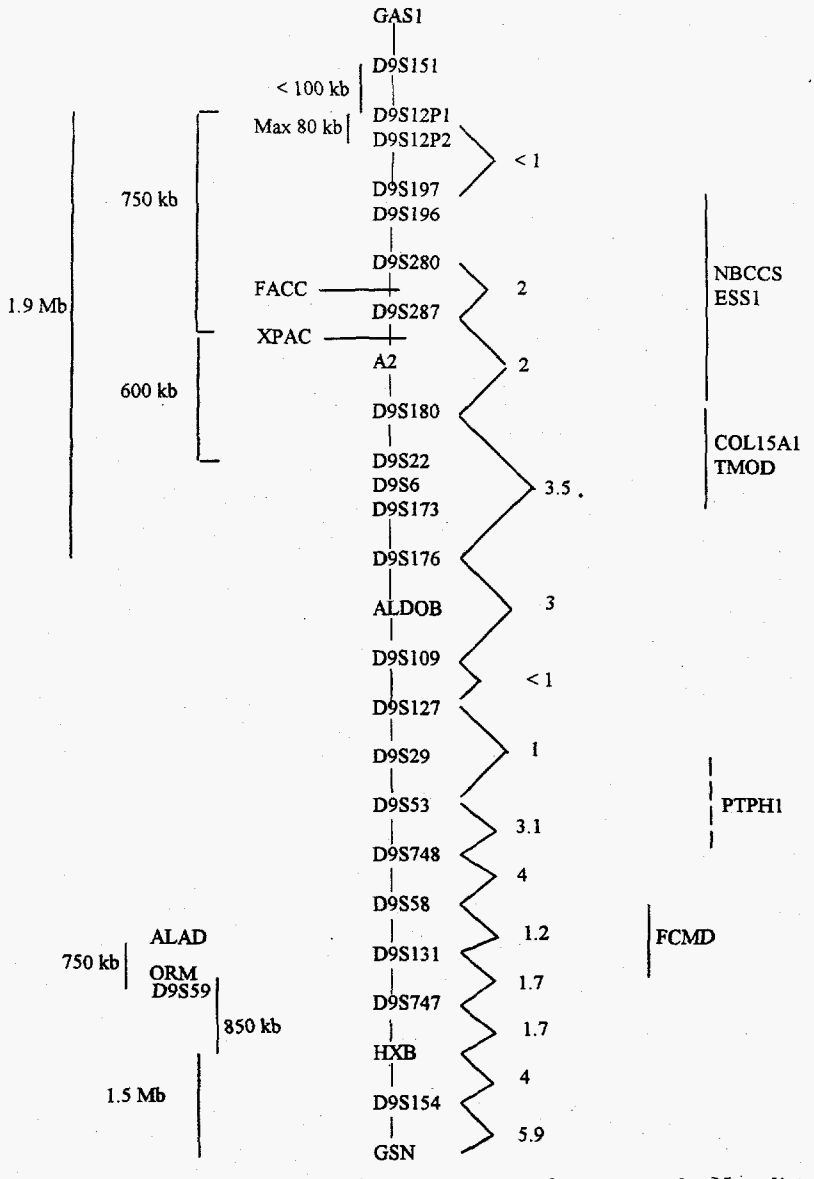


Fig. 5. High resolution map of 9q22.3–q33. Distances are not drawn to scale. Map distances shown to the right of the markers are in cM. These are consensus distances from data presented at the workshop, and may vary slightly from the distances on Figs 3–4 which include previously published data. Physical distances to the left of the markers are mostly from FISH data on interphase cells.

Physical data from YAC studies give a distance between D9S12 and D9S176 of about 1·9 Mb (Morris *et al.*).

YAC contigs

Several groups (Barroso *et al.*, Dean *et al.*, Morris *et al.*, Wicking *et al.*) presented YAC contigs of the region between D9S151 and D9S176 (and formed a small committee to share information). The sources of the YAC clones and their chromosome contents are shown in Table 1. There was variation in both the size of the YACs, and typing of markers (Table 2). However,

Table 1. *YAC source and physical information*

YAC	Source	Size (Mb) *G*	*F*	*B*	*C*	*Br*	Chromosome content
846c4	G	1·1		1·4	1·5	1·6	
H109	ICRF						
D213	ICRF						
787a3	G	1·8		1·9	1·0		9q22, 11, 20
931d9	G	0·9		0·95	1·0	1·1	9q22, Xp
21b8	G (F)	1·5	1·5				
633a10	G	1·5		1·0			9q22, 9q34, 16p, 13q
928e4	G	1·4				1·4	
946h5	G	1·1				1·0	9q22
960e1	G	1·3	0·3	0·3			
932d12	G	1·0					
890g7	G	1·5				1·4	9q22
1da10	ICI				0·3		9q22
2ef8	ICI						9q22
736b10	G	0·8			0·8		9q22, 1, 19, 5
754c7	G				1·5		9q22
8ad8	ICI			0·65	0·65		9q22

YAC clones containing markers in the NBCCS region were obtained from Genethon (G), ICI, and ICRF libraries, were obtained by groups in Frederick (Dean), Cambridge (Barroso), Berlin (Morris), and Brisbane (Wicking). These YAC clones were sized, and typed for the markers indicated in Table 1. Markers are displayed in the order most supported by the typing data. Results are displayed as PCR positive (+), negative (−), or untested (N) (see Table 2).

the physical marker order supported by the YAC typing data was consistent between laboratories, and consistent with genetic linkage data, where these were available.

Uncertainty of ordering

Conflicting information was presented over the orientation and order of D9S134, D9S151 and D9S12. Data from fluorescent *in situ* hybridization on interphase cells, linkage data and the order from YACs favoured cen-D9S151–D9S12. Information from radiation hybrids (Obermayr *et al.*) favoured the order cen-D9S12–D9S151. Interphase FISH (Leversha *et al.*) places D9S134 distal to D9S12, but the CEPH map places D9S134 proximal to D9S12 (Attwood *et al.* 1994). Kwiatkowski *et al.* placed D9S151 proximal to D9S12 at odds of 1000:1.

Genetic interference

Linkage data was presented to support complete positive genetic interference in 9q22 as predicted by the male chiasmata maps of Lawrie and Hultén (First International Chromosome 9 Workshop). By direct counting of recombinant haplotypes between D9S12 and D9S53, the sex averaged distance between these markers was 10·5 cM and the male to female ratio was 1:1·6 (Farndon *et al.*). Apparently complete interference was also found on analysis of data from CEPH families (Kwiatkowski *et al.* 1993). Family studies using flanking markers for a disease in this region are therefore expected to give a high level of accuracy in predicting clinical status.

Mouse homology

The consensus view from data presented at the workshop was that the fusion between mouse chromosome 4 and 13 should be found between FACC and XPAC. Fleming *et al.* predicted that

Table 2. *NBCCS region YAC STS typing data*

YAC	S151 FBCBr	S12.1 FBCBr	S12.2 FBCBr	S197 FBCbr	S196 FBCBr	S280 FBCBr	FAC FBCBr
846c4	+ − − N	+ − − −	N − N N	+ + + +	+ + + +	− − + +	N − N −
ICI-H109	− N N N	+ N N N	N N N N	+ N N N	− N N N	− N N N	N N N N
ICI-D213	− N N N	+ N N N	N N N N	+ N N N	− N N N	− N N N	N N N N
787A3	− − − N	+ − − N	N + N N	+ + + N	− − + N	− + − N	N − N N
931D9	− − − N	− − − N	N N N N	+ + + +	+ + + +	+ + + +	− + N N
21B8	N N N N	N N N N	N N N N	+ N N −	+ N N −	N N N −	− N N −
633A10	N − − N	N − − N	N − N N	− − − N	+ + + N	− + − N	− + N N
928E4	N N N N	N N N −	N N N N	− N N N	+ N N +	+ N N +	+ N N +
946H5	N N N N	N N N −	N N N N	N N N N	− N N +	− N N +	N N N N
960E1	N N N N	N − N N	N − N N	− − N N	− − N N	+ + N N	+ + N N
932D12	N N N N	N N N N	N N N N	N N N N	+ N N N	+ N N N	N N N N
890G7	N N N N	N N N N	N N N N	N N N N	− N N N	− N N +	− N N N
ICI-1DA10	N N N N	N N N N	N N N N	N N N N	N N + N	N N + N	N N N N
ICI-2EF8	N N N N	N N N N	N N N N	N N − N	N N − N	N N + N	N N N N
736B10	N N N N	N N N N	N N N N	N N − N	N N − N	N N − N	N N N N
754C7	N N N N	N N N N	N N N N	N N − N	N N − N	N N − N	N N N N
ICI-8AD8	N N N N	N − − N	N N N N	N − − N	N − − N	N − − N	N + N N

YAC	S287 FBCBr	A2 FBCBr	XPAC FBCBr	S180 FBCBr	S22 FBCBr	S6 FBCBr	S176 FBCBr
846c4	− − − −	N N − N	N − − N	− − − −	N N − N	N − − N	N − − N
ICI-H109	N N N N	N N N N	N N N N	− N N N	N N N N	N N N N	N N N N
ICI-D213	N N N N	N N N N	N N N N	N N N N	N N N N	N N N N	N N N N
787A3	N − − N	N N − N	N − − N	− − − N	N N − N	N − − N	N − − N
931D9	− − − −	N N − N	N − − N	− − − N	N N − N	N − − N	N − − N
21B8	+ N N −	N N N N	+ N N N	+ N N −	N N N N	N N N N	N N N N
633A10	+ − − N	N N − N	− − − N	N − − N	− N − N	− − − N	N − − N
928E4	− N N +	N N N N	− N N N	N N N N	N N N N	− N N N	N N N N
946H5	+ N N +	N N N N	− N N N	N N N −	− N N N	− N N N	N N N N
960E1	+ + N N	N N N N	− + N N	N − N N	N N N N	− − N N	N − N N
932D12	+ N N N	N N N N	− N N N	N N N N	N N N N	− N N N	N N N N
890G7	− N N +	N N N N	+ N N N	+ N N +	N N N N	N N N N	N N N N
ICI-1DA10	N N + N	N N + N	N N − N	N N − N	N N N N	N N N N	N N N N
ICI-2EF8	N N + N	N N + N	N N − N	N N − N	N N N N	N N N N	N N N N
736B10	N N − N	N N + N	N N + N	N N − N	N N − N	N N − N	N N N N
754C7	N N − N	N N + N	N N + N	N N + N	N N + N	N N − N	N N N N
ICI-8AD8	N + − N	N N + N	N + + N	N + + N	N N + N	N + + N	N + − N

Key: F, Frederick; B, Berlin; C, Cambridge, UK; Br, Brisbane. +, PCR positive; −, PCR negative; N, untested.

a human homologue to a mouse autosomal recessive deafness gene should be located in the interval between ALAD and HXB. This on FISH interphase is a distance of about 1·7 megabases. This is certainly an area which should be included in studies of deafness by homozygosity mapping.

9q34–qter

Newly mapped genes

Several genes have been given more refined map positions since the last meeting. These include COL5A1 (Northrup *et al.*, Zahn *et al.*), AK1, SPTAN1, CEL, PAEP, TAN1 (now designated NOTOH1) (Woodward *et al.*, Leversha *et al.*) and GRIN1 (Brett *et al.* 1994 (see Fig. 6)). A new disease gene, ORW (Haemorrhagic telangiectasia, Osler Rendu Weber

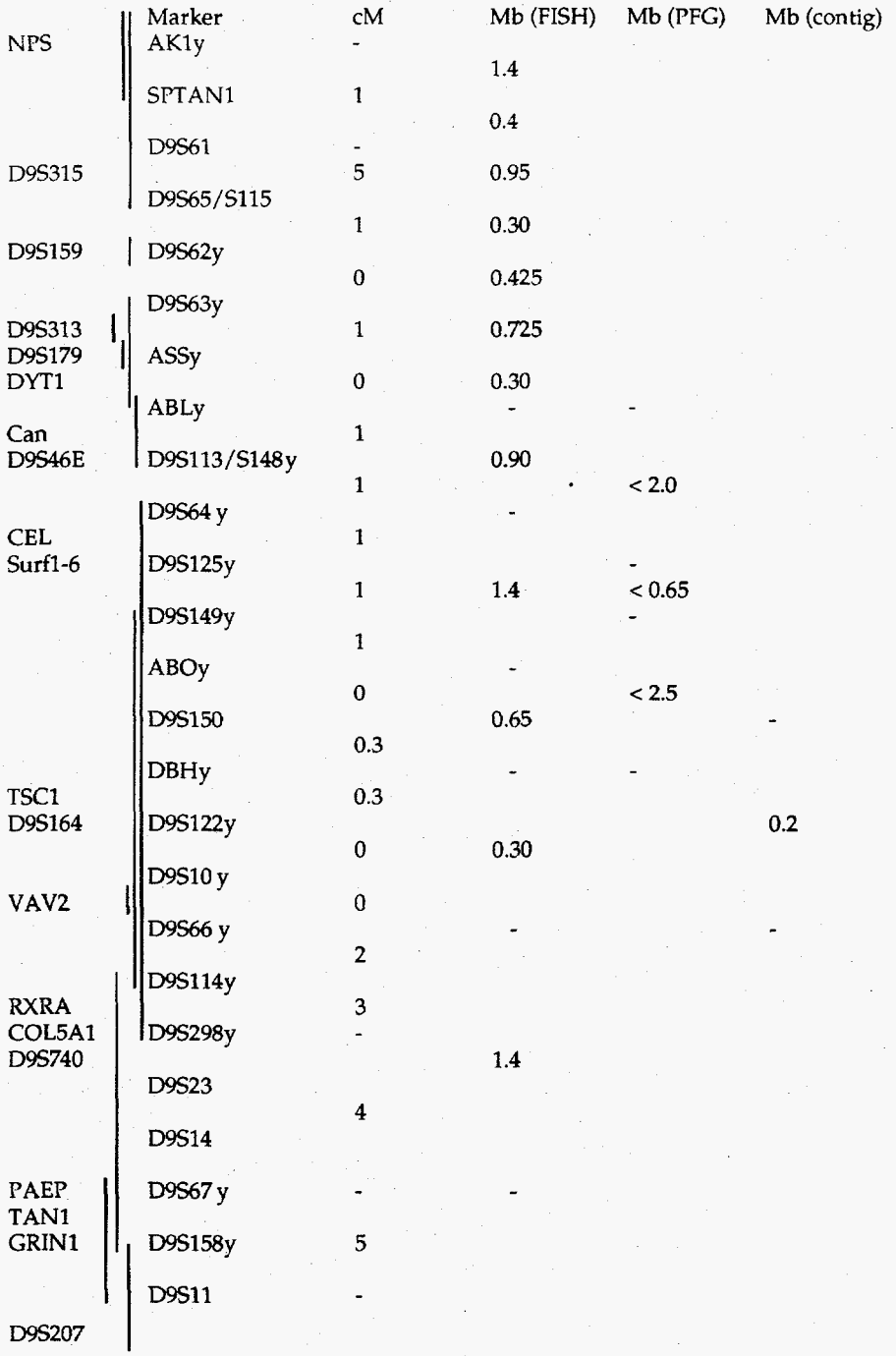


Fig. 6. High resolution map of 9q34. Distances are not drawn to scale. The cM and Mb distances between markers are shown. Dashes indicate the endpoints of measured distance when the markers are not adjacent in the listing from top to bottom. y indicates that a yac clone has been identified

syndrome), has been mapped between D9S60 and D9S159 by linkage analysis (Marchuk *et al.*). There is some evidence for existence of a new gene with homology to the VAV oncogene very close to D9S66 (Smith *et al.*, Woodward *et al.*).

Genetic mapping

Several polymorphisms received refined positions, including D9S298, D9S158 and D9S207. The primary genetic map has been modified slightly, with the replacement of the VNTR markers D9S17 and D9S7 with D9S158. The data for D9S158 and D9S11 have been extensively checked and results in a shrinkage in sex-averaged map distance of 6 cM; the distance from S67 to the most distal marker D9S11 now estimated as 5·5 cM in females and 12·2 cM in males (Jeremiah *et al.*). Two groups described polymorphisms of COL5A1, placing the gene distal to D9S114 (Northrup *et al.*, Zahn *et al.*).

Physical mapping

Two regions have been subject to extensive physical mapping (see Fig. 6). The region between GSN-D9S61 has been mapped by interphase FISH, ordering the markers GSN-D9S60-AK1-SPTAN1-D9S61. Leversha *et al.* have generated an extended interphase FISH map from GSN to DBH, spanning an estimated 14 Mb. The second region is ABO to D9S67. Cosmid, YAC and P1 contigs exist for D9S150-DBH-D9S122-D9S10-D9S66, and these markers span approximately 350 kb. Cosmid or YAC contigs exist around many genes and markers in a more extended region (Janssen *et al.*, Jobert *et al.*, Kumar *et al.*, Hornigold *et al.*, Murrell *et al.*, Zhou *et al.*) some of which are described in detail (Hornigold *et al.*) but there are several gaps in the region proximal to ABO. A gap also exists between D9S66 and D9S114, but a YAC contig exists spanning D9S114–D9S23–D9S14–D9S67. A pulsed field map of genomic DNA extending from ABL to D9S114 was presented (Henske & Kwiatkowski) with these markers lying between 4·5 and 6·7 Mb apart.

New unresolved difficulties

Three major inconsistencies have arisen in this region. D9S179, D9S125 and D9S164 span a minimum of 4 cM by linkage analysis covering an estimated 3 Mb. However, all three markers have been found within a single 200 kb YAC (Murrell pers. comm.). The second controversy surrounds the order of D9S67 and D9S14. Genetic mapping data suggest that D9S14 is distal (Attwood *et al.* & global group) while YAC maps suggest the reverse. Finally, D9S298 maps between D9S114 and D9S67 by genetic mapping (Jeremiah *et al.*, Attwood *et al.* 1993) and physical mapping confirms that it is distal to D9S114 (Woodward *et al.*, Nahmias *et al.*) but is not found within the YAC-contig which spans this region.

Location of bladder and ovarian carcinoma genes

LOH studies of bladder tumours now define two regions of deletion on chromosome 9 which may be deleted independently or concurrently in individual bladder tumours (Keen & Knowles). Homozygous deletions in the region 9p21–22 have been found and a region of deletion between D9S162 and D9S171 has been delineated (Cairns *et al.*, Devlin & Knowles). The common region on 9q is large (D9S15–D9S60). This may suggest that more than one

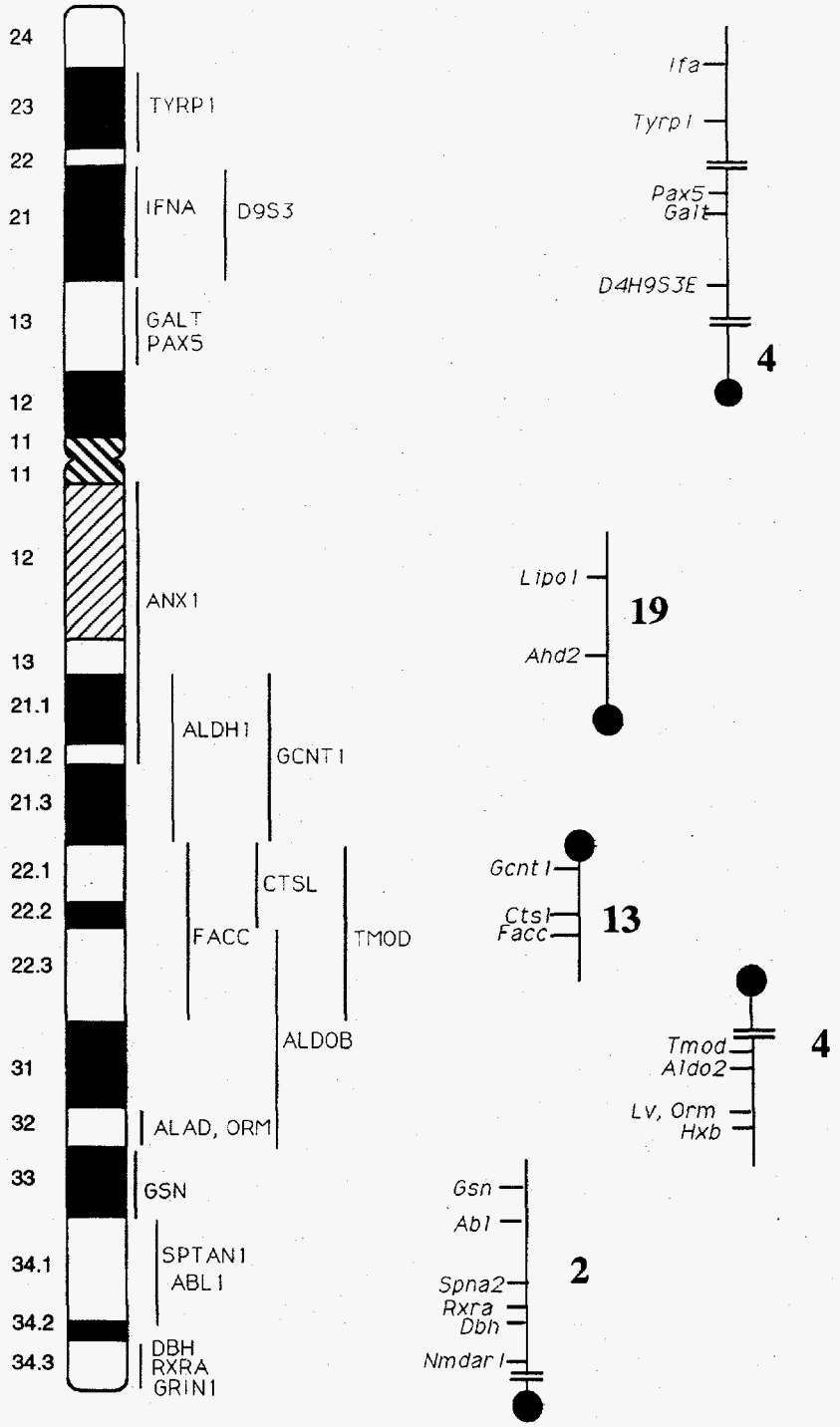


Fig. 7. Human chromosome 9 aligned with the homologous regions of mouse chromosomes 2, 4, 13 and 19. Not all markers from this study are shown for simplicity. The centromere of the mouse chromosomes is shown by a filled circle. Chromosome 4 is shown twice to make comparison easier. *Ahd2*, *Lipo1*, *Lv*, *Aldo2*, *Spna2* and *Nmdar1* are the mouse homologues of ALDH1, ANX1, ALAD, ALDOB, SPTAN1 and GRIN1 respectively.

relevant suppressor locus for bladder cancer exists on 9q. LOH studies of 9q in ovarian tumours (Osborne *et al.*) define a common region of deletion within that defined for bladder tumours between D9S160 and D9S115.

COMPARATIVE MAPPING RELEVANT TO HUMAN CHROMOSOME 9

The report on comparative mapping in the mouse was prepared by Alison Pilz and is summarized in Fig. 7. A summary of data from many other species, the unpublished data of J. Graves and M. Wakefield, was generously provided to the workshop and is shown in Fig. 8. Any queries about the data in Fig. 8 should go to the contributors at gemap@genome.latrobe.edu.au.

A high resolution genetic linkage map of the mouse facilitates the establishment of gene order on human chromosomes. Comparative mapping enables the identification of mouse mutations which are potential models of human genetic disease.

Genes mapping to human chromosome 9 have homologues which map to four different mouse chromosomes; namely mouse chromosomes 2, 4, 13 and 19. The homology group with mouse chromosome 13 (MMU13) has been defined since last year's report. The distal portion of the long arm of human chromosome 9 (HSA9) shows homology with mouse chromosomes 2 and 4. Loci in the distal region of 9q34 (e.g. ABL and C5) have homologues on proximal MMU2, and genes mapping more proximally (e.g. ORM and ALAD) have homologues on MMU4. The homology on mouse chromosome 4 (MMU4) is in three segments – two regions of synteny with human chromosome 9p are separated physically by a region syntenic with 9q. Genes mapping to HSA 9q21–q22 map to mouse chromosome 13 whilst genes which map to HSA9q12–q21 map to mouse chromosome 19. Presumably therefore an evolutionary breakpoint has occurred in HSA9q21. The mouse homologue of Gorlin's syndrome would be predicted to map on MMU13. Figure 7 shows the conserved mouse syntenies aligned with the chromosome 9 map.

A number of predictions for gene order in human may be made based on a comparison of the human and mouse maps. Genes which have not been genetically separated in reasonably large crosses in the mouse would be predicted to map close to each other in human. When comparing the gene order for MMU2 to the consensus gene order for HSA9q34 (taken from Kwiatkowski *et al.* 1993) the conserved segment appears to be inverted in one species compared to the other. Within the segment gene order is the same except for two loci, *Rxra* (RXRA) and *Spna2* (SPTAN1). In mouse *Spna2* maps proximal to *Abl*, and *Rxra* maps distal to *Dbh*. These differences between the mouse and human gene maps probably indicate real evolutionary differences, although the possibility of errors in mapping cannot be excluded. For the mouse, there is a considerable degree of confidence in the proposed gene order of *Spna2* in relation to *Abl* and *Hc* as the order has been derived from four independent crosses in which all three loci have been mapped. If both maps are an accurate reflection of gene order in the two species, then the simplest explanation of the evolutionary change would be that there have been two small inversions (in mouse with respect to human or *vice versa*) within this syntenic group, one involving RXRA and DBH, and the other involving SPTAN1 and ABL. Further studies are required to determine whether the apparent difference in gene order between mouse and human represents a true evolutionary divergence.

Lawrie and Hultén investigated whether the genetic length of segments is conserved between

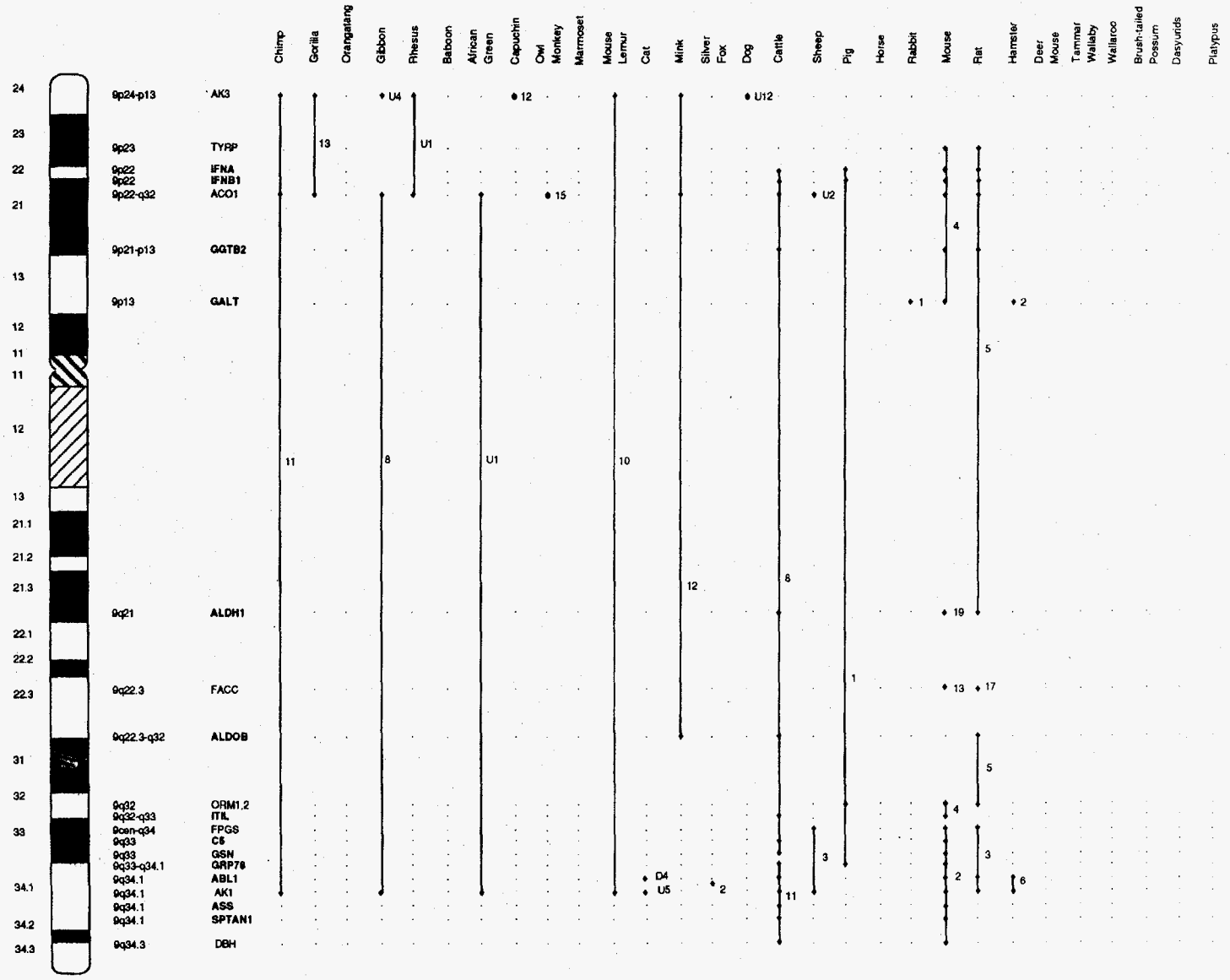


Fig. 8. Comparisons of gene locations in other mammals, of loci which map to human chromosome 9. Markers are plotted with reference to their physical location on the human chromosome, and have been included only if mapped in species other than human and mouse. (Unpublished data of Graves and Wakefield.)

Table 3. *Mouse mutants whose human homologues would be expected to map to human chromosome 9*

Mouse chrom.	Gene symbol	Mutation	Phenotype	Predicted HSA9 location
MMU2	*Sd*	Danforth's short tail	Kidney/notochord development	9q33–q34
MMU2	*stb*	stubby	Achondroplasia	9q33–q34
MMU2	*lh*	lethargic	Neurological/immunological	9q33–q34
MMU2	*us*	urogenital syndrome	Skeletal/urogenital abnormalities	9q34.1–q34
MMU4	*an*	Hertwig's anaemia	Haematological	9p/9q
MMU4	*vc*	vacillans	Neurological	9p/9q
MMU4	*cy*	crinkly tail	Tail	9p
MMU4	*dep*	depilated	Hair	9p
MMU4	*Pt*	Pintail	Tail	9p
MMU4	*wi*	whirler	Deafness/inner ear	9q32–q34
MMU13	*sdy*	sandy	Coat	9q21–q22
MMU13	*mu*	muted	Balance/ear	9q21–q22
MMU13	*jd*	juvenile depilation	Hair	9q21–q22
MMU13	*dpy*	dumpy	Skeletal	9q21–q22
MMU13	*f*	flexed-tail	Tail	9q21–q22
MMU19	*bm*	brachymorphic	Achondroplasia	9q12–q21

species. They compared male chiasma maps of the relevant segments of MMU2 and MMU4 and HSA9, and concluded that there was no apparent conservation of meiotic recombination for the segments.

The comparative mapping data also predict the occurrence of human homologues of several mouse mutations the phenotypes of which are listed in Table 3 (data taken from mouse chromosome committee reports in Mammalian Genome Special Issue 4, 1993, and Fleming *et al.*, this meeting).

RESOURCES

Physical resources

Cellular resources on chromosome 9 include a number of lymphoblastoid lines with balanced translocations, described in the report of the First International Workshop on chromosome 9 and which have been useful to several workers (e.g. Woodward *et al.*). A new compilation of constitutive rearrangements involving chromosome 9 was presented at this meeting (Edwards & Mercer, see abstract for details). A hybrid containing a t6/9 (9pter–q22.3:6pter–p23) as its only human chromosome apart from a small part of the X has recently been generated by Dr Mike Dixon (Department of Cell and Structural Biology, University of Manchester, UK. fax 44 61 275 3915) and anyone interested should contact him.

Apart from previously described irradiation hybrids (Nahmias *et al.*; Britt *et al.*) five other sets of radiation hybrids were presented at this meeting. Radiation hybrids for chromosome 9 now include four sets of hybrids made from an original hybrid containing a whole chromosome 9, three of these characterized mostly for 9p markers (Britt *et al.*, Kaur & Athwal and personal communication from Nigel Spurr), and one useful for 9q (Kaur & Athwal). Three groups have used a hybrid containing 9q as its only human component to generate radiation hybrids, two concentrating on 9q22–q31 (Obermayr *et al.*, Wicking *et al.*) and one on 9q34 (Nahmias *et al.*). These hybrids are mostly available to others on a collaborative basis although this is sometimes

Table 4. *Human chromosome 9 loci containing microsatellite repeats*

(*a*) Estimates of heterozygosity are determined from four CEPH families. (*b*) The number of alleles observed in eight unrelated individuals

Loci assigned to chromosome 9 by two-point linkage analysis with Genethon microsatellite markers

Name	GDB#	GenBank#	Het(a)	Motif
UT1220	D9S762	L31161	0·50	GATA
UT1228	D9S249	L15543	0·50	GATA
UT1231	D9S250	L18540	0·50	GATA/GA/AAAG
UT1277	D9S763	L17788	0·50	GATA/CA
UT1416	D9S764	L17814	1·00	AAAG
UT1531	D9S765	L30884	0·57	GA/GGGA
UT1892	D9S766	L17918	0·83	GGAA/GA
UT2100	D9S251	L18726	0·50	GATA
UT2103	D9S252	L17974	0·88	GATA
UT2163	D9S767	L17984	0·33	AGC
UT2372	D9S255	L18736	0·38	AAAG/GGAA
UT2399	D9S253	L18027	0·75	GATA
UT2420	D9S254	L18050	0·62	GATA
UT457	D9S225	L18282	0·50	CA
UT458	D9S226	L18283	0·62	AAAG
UT5024	D9S245	L18515	0·50	GATA
UT5110	D9S761	L17697	0·62	AAAG
UT5132	D9S248	L16438	0·75	AAAG
UT535	D9S755	L31701	0·50	AAAT
UT5494	D9S768	L18114	0·67	GATA
UT6023	D9S769	L30683	0·86	AAAG
UT6068	D9S752	L30703	0·88	GATA
UT6090	D9S737	L18104	0·88	AAAG
UT6185	D9S771	L30755	0·38	AAAG
UT6211	D9S770	L30747	1·00	AAAG/GA
UT6405	D9S773	L30619	0·75	AAT
UT6556	D9S772	L30569	1·00	GGAA/GA
UT683	D9S229	L18370	0·83	AAAG/GGAA
UT685	D9S230	L16312	0·67	CA
UT724	D9S232	L18384	0·62	AAAG
UT726	D9S234	L16322	1·00	AAAG
UT727	D9S236	L18386	0·62	CA
UT739	D9S237	L16324	0·62	AAAG/GGAA
UT7422	D9S774	L30444	0·88	GATA
UT7622	D9S775	L30528	0·75	GATA
UT764	D9S757	L31180	0·67	AAAG
UT7655	D9S776	L30291	0·83	GATA
UT7939	D9S777	L30395	0·86	AAAG
UT7968	D9S778	L30161	0·88	AAAG/GA
UT801	D9S238	L18422	0·83	AAAT
UT8063	D9S753	L30185	1·00	AAAG
UT8065	D9S779	L30188	0·50	AAAG
UT808	ND	L16335	0·33	AAAT
UT840	D9S758	L31235	0·75	AAAG/AG
UT844	D9S750	L31239	0·88	GA/AAAG
UT873	D9S759	L31258	0·62	GGAA/GAAA
UT913	D9S241	L18466	0·75	AAAG
UT914	D9S242	L18467	0·88	AAAG
UT915	D9S243	L18468	0·88	GGAA/AAAG
UT917	D9S244	L18469	1·00	AAAG

Table 4 (*cont.*)

Assigned to chromosome 9 by results of PCR-amplification of Coriel somatic cell hybrid mapping panel

Name	GDB#	GenBank#	# alleles (b)	Motif
UT536	D9S227	L18321	1	CA
UT537	D9S228	L18322	3	CA
UT684	D9S756	L30078	6	AAAG
UT725	D9S233	L18385	2	AAAG
UT728	D9S236	L18387	1	CA
UT911	D9S239	L18464	1	AAAG
UT912	D9S240	L18465	1	AAAT
UT916	D9S760	L31287	2	AAAG

limited by the tendency of these hybrids to lose fragments when regrown. It is hoped to put more details of the hybrids on the chromosome 9 file-server.

Cosmids

At least eight groups present at the meeting had been working with the Laurence Livermore chromosome 9 flow sorted gridded cosmid library made by Pieter de Jong, and all reported it to be of high quality and extremely useful. The library has been distributed in two formats (300 normal density microtitre plates or 75 high density plates) and Dr de Jong made a request that publication should identify clones using the 300 plate nomenclature (see abstract by Hornigold *et al.* for contigs with clones identified in this way). The only gap identified so far in this library is that it appears to lack clones for the ABO blood group in 9q34.1.

Another cosmid resource which has been described in the past year is a flow sorted chromosome 9 library produced in Dr Nakamura's lab and for which 203 cosmids have already been mapped by FISH (Takahashi *et al.* 1994). The distribution of these cosmids again shows 9q34 to be over represented. Dr Nakamura has already shared some of these cosmids with other workers.

YACs

Eleven abstracts at this meeting described work with YACs, but this has in general been concentrated on a limited number of areas, in particular 9p21, 9q11–q21, q22.3–31 (four groups) and q34 (five groups). The most useful sharing of information came from 9q22.3–q31 and the results of all groups working in this region are shown in the appropriate regional report. In 9q34 two groups reported a YAC for ABO, (Jobert *et al.*, Zhou *et al.* presumably the same clone) from one of the CEPH libraries, suggesting that this region is clonable in YACs if not in cosmids. Jill Murrell reported that the chromosome 9 YAC library made by Mary K. McCormack is now available on a collaborative basis.

The greatest number of YACs added to chromosome 9 in the past year is of course from Genethon. Information on these YACs can be obtained from GDB or the Genethon file server and the YACs themselves are obtainable from the ICRF. It was agreed that notification of YACs found to be chimeric or mapping completely to an unexpected chromosome, would be a useful addition to the information on the chromosome 9 fileserver. Any information on this topic should go to John Attwood.

Other cloned resources

Ioannou, Kroisel *et al.* described a micro-dissection library from 9q12–21 of 50000 clones in Bluescript. Ioannou P. de Jong *et al.* described a currently available genomic PI library which has already been used successfully on chromosome 9 (Kumar *et al.*, Zhou *et al.*, Ioannou, Frenger *et al.*). This library has four fold redundancy and exists as 312 high density (384 well) microtitre plates. A new generation of PAC vectors especially appropriate for expression studies in mammalian cells locus was also described.

In GDB 109 entries are expressed sequences on chromosome 9 (other than those designated as genes): these include 70 trapped exons some of which have regional mapping information (Church *et al.* 1993).

Polymorphisms

Six new tetranucleotide repeats on chromosome 9 were reported at this meeting; D9S739 and D9S740 (J. Armour) and D9S745, D9S746, D9S747 and D9S748 (Zahn *et al.*). Since the primers for these and for all the new Genethon and CHLC markers are in GDB they are not repeated here. Table 4 shows details of 59 new polymorphisms on chromosome 9 mostly tetranucleotide repeats, described by the Utah Genome Center, Genetic Marker and Mapping group, which includes Linda Ballard, Hans Albertsen, Paige Bradley, Steve Gerken, Pilar Holik, Norisada Matsnami, Elisabeth Lawrence, Robert Melis, Mary Moore, Shanon Odelberg, Margaret Robertson, Rosemarie Plaetke, Xuyn Zhao and Ray White. For 45 of these markers pairwise lodscores indicating a close Genethon marker on chromosome 9 are shown in Table 5. Most of the other polymorphisms were assigned to chromosome 9 by somatic cell hybrids. The primer sequences for all these polymorphisms are in GDB.

Informatics

In addition to the SIGMA program being used to construct the map, other programs demonstrated at the Workshop included ldb (Collins *et al.*) and a comparative mapping database (Edwards). Jamie Cuticchia demonstrated various new features of GDB, especially a user-friendly version accessible via any Mac on a network. An internet connection was established through a modem connection to the Cambridge University Computer Centre and quite a number of participants learned something of the art of accessing an anonymous file-server and downloading files either from Genethon, Chromosome 9 at UCL or CHLC. The vast majority of participants now have email addresses and this should really improve communication in the future. Information about chromosome 9, including the current SIGMA map and database, the ldb map and database, this report plus the abstracts and participant list, the HGM93 report and EST reports for chromosome 9 are currently available by anonymous FTP from *ftp.gene.ucl.ac.uk* (128.40.82.1), in the sub-directory /pub/c9workshop/1994. Wherever possible, plain ASCII text files have been made available as well as PostScript versions for high-quality printout. Hopefully, in the future, details of YAC and FISH results and radiation hybrids on Chromosome 9 will also be available by the same means. Everyone on the Chromosome 9 electronic mail list receives information about future meetings and is also notified when new information is placed on the FTP server. Anyone wishing to join the electronic mail list should contact John Attwood (john@mrc-hbgu.ucl.ac.uk).

Table 5. *Pairwise analysis of linkage between Utah markers and Genethon markers. lod score* (Z_{max}) at recombination fraction (theta)

Utah marker	Genethon marker	Z_{max}	Theta
D9S762	D9S155	10·6	0·024
D9S249	D9S152	5·4	0·097
D9S250	D9S170	7·7	0·031
D9S763	D9S176	5·4	0·001
D9S764	D9S152	12·0	0·038
D9S765	D9S176	8·5	0·024
D9S766	D9S159	14·4	0·001
D9S251	D9S161	4·6	0·048
D9S252	D9S152	8·4	0·082
D9S767	D9S176/ D9S174/ D9S155	6·3	0·001
D9S255	D9S196	7·8	0·001
D9S253	D9S196	7·8	0·001
D9S254	D9S157	12·0	0·020
D9S225	D9S165	6·3	0·001
D9S226	D9S175	12·3	0·001
D9S245	D9S153	6·6	0·001
D9S761	D9S175	8·8	0·095
D9S248	D9S175	10·9	0·057
D9S755	D9S167	6·0	0·001
D9S768	D9S153	9·0	0·001
D9S769	D9S175	15·9	0·001
D9S752	D9S159	17·0	0·015
D9S737	D9S170	19·5	0·001
D9S771	D9S196	7·9	0·001
D9S770	D9S157	6·4	0·086
D9S773	D9S175	10·2	0·080
D9S772	D9S166	4·8	0·001
D9S229	D9S166	6·9	0·001
D9S230	D9S178	6·3	0·001
D9S232	D9S168	7·7	0·073
D9S234	D9S175	9·3	0·068
D9S236	D9S157	12·6	0·001
D9S237	D9S175	12·6	0·001
D9S774	D9S172	11·4	0·001
D9S775	D9S168	15·3	0·001
D9S757	D9S176	22·3	0·001
D9S776	D9S167	11·7	0·039
D9S777	D9S152	6·4	0·159
D9S778	D9S177	12·5	0·038
D9S238	D9S175	12·0	0·039
D9S753	D9S196	14·4	0·001
D9S779	D9S174	9·6	0·001
UT808	D9S167	4·6	0·048
D9S758	D9S166	9·6	0·001
D9S750	D9S176	22·3	0·001
D9S759	D9S168	10·8	0·001
D9S241	D9S177	12·9	0·020
D9S242	D9S177	14·8	0·032
D9S243	D9S177	18·5	0·014
D9S244	D9S153	14·0	0·033

Anyone with data they wish to share with the Chromosome 9 Community can up-load it to the anonymous FTP server to the sub-directory /pub/incoming (please also send electronic mail to John Attwood explaining what you have up-loaded).

It is hoped that the SIGMA map will be modified on an ongoing basis, and that updated versions will be made available on the FTP server throughout the year. This of course relies on the Chromosome 9 Community checking the existing map and contributing new map information to the general pool. It should be noted that it is not yet simple to merge SIGMA maps. Thus, although it is possible to download the SIGMA map database file, view and edit it using a local version of SIGMA (available from atlas.lanl.gov or 128.165.24.191) it will not necessarily be possible to merge this edited version back into the original map. Anyone wishing to contribute information, should contact Julia White (julia@mrc-hbgu.ucl.ac.uk) to find out the most efficient way of doing it. The best ways of entering large amounts of data (e.g. extensive cosmid contigs) are currently being explored, as are ways of interchanging data between GDB, AceDB and SIGMA.

Tuberous Sclerosis Meeting

Associated With Chromosome 9 Workshop, 12 April, 1994

Approximately 50 individuals attended the tuberous sclerosis meeting held after the chromosome 9 meeting, on the morning of 12 April, 1994. The first subject to be discussed was the cloning and characterization of the chromosome 16 (TSC2) gene. A round of congratulations was given to Drs Julian Sampson (Cardiff, UK) and Bart Janssen (Rotterdam, The Netherlands) for leading the European Consortium in cloning this gene. Dr Sampson reported that over half the genomic structure of the gene is now known (it has at least 26 exons) and he is now making the cDNA clones available to all interested individuals. More deletion mutations have been identified by the Welsh and Dutch groups; groups in Cambridge (UK), Boston (USA), and Houston (USA) have also identified mutations. Approximately 10% of patients studied so far have deletion mutations. No point mutations have been identified. Anna-Marie Frischauf (London, UK) reported on the cloning of the mouse homolog of the TSC2 gene (on mouse chromosome 17).

Efforts to clone the chromosome 9 gene are underway in many laboratories. A list of critical recombinants was compiled, and as has been the case before, several are in conflict with each other. A recombination in an affected individual placed TSC1 distal to D9S10 (Pitiot *et al.*), while in another study TSC1 was placed between ABL and ABO (Janssen *et al.*). The most consistent localization of the TSC1 gene is between D9S149 and D9S114, a genetic distance of approximately 3 cM and a physical distance of approximately 1500 kb. Moyra Smith (Irvine, USA) reported an apparent duplication of D9S66 in a sporadic case of TS, which was seen both by polymorphism studies and FISH. Sue Povey (London, UK) also saw evidence of a duplication for DBH in one small family. However, not all affected individuals in the family showed the duplication, and it was seen with only one DBH polymorphism. Andrew Green (Cambridge, UK) reported a deletion between D9S149 and D9S67 in one tumor, and Nicola Migone (Turin, Italy) reported deletions between ASS and D9S158 in another tumor. Moyra Smith also reported a candidate gene which spans D9S10 and D9S66 and which was homology

to the mouse VAV gene. A list of six families apparently genetically linked to chromosome 9. but including a person who excludes the consensus candidate region, was compiled.

A study of 21 families which had been assigned either as TSC1 or TSC2 found no consistent clinical differences between TSC1 and TSC2 patients and also found no evidence for genomic imprinting (Povey *et al.*). Antonia Clarke reported that there is an increased rate of mental retardation in males, and that this is not related to the number of brain lesions.

Also discussed was the impact of the TSC2 gene cloning on patients and families. Ann Hunt (TSA, UK) reported that many families have contacted the TSC associations with questions about testing, and the most appropriate course of action was debated. It was generally agreed that although testing for TSC2 mutations could be done, only a minority would be identified, and that until much more is known about the mutations few people can yet be offered practical help.

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