UC Irvine
UC Irvine Previously Published Works

Title
REPORT on the First International Workshop on Chromosome 9 held at Girton College Cambridge, UK, 22–24 March, 1992

Permalink
https://escholarship.org/uc/item/5k97g95t

Journal
Annals of Human Genetics, 56(3)

ISSN
0003-4800

Authors
POVEY, S
SMITH, M
HAINES, J
et al.

Publication Date
1992-07-01

DOI
10.1111/j.1469-1809.1992.tb01145.x

REPORT on the First International Workshop on Chromosome 9

held at Girton College Cambridge, UK, 22–24 March, 1992

Prepared by: S. POVEY, M. SMITH, J. HAINES, D. KWIATKOWSKI, J. FOUNTAIN,
A. BALE, C. ABBOTT, I. JACKSON, M. LAWRIE and M. HULTÉN

The meeting was attended by 70 participants whose names and addresses are included in an appendix to this report. Fifty-four abstracts were received and the data presented on posters. The main role of the meeting was seen as the construction of a consensus map of chromosome 9, together with a sharing of knowledge about resources such as hybrids, libraries and new polymorphisms. The group divided into separate working parties to consider 9p, 9cen–9q32, 9q33–9qter, global problems and comparative mapping. The findings of each of these groups are included in this report. There was a separate discussion of resources which is also summarized. Two databases were discussed and demonstrated (GDB by Bonnie Maidak and ldb by Andy Collins). The chromosome 9 workshop was preceded on the afternoon of Sunday, 22 March by a workshop on Tuberous Sclerosis. Because of the relevance of this to chromosome 9q34 a report on this workshop is included in that section. A further subgroup met on 24 March to discuss the CEPH chromosome 9 consortium map and a brief report on their progress was produced.

In accordance with the recommendation of the Global group an attempt has been made to reference information in the maps but it is recognized that this is incomplete. 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 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 the reader should consult GDB. It is also planned to enter information into ldb so that in future it may be possible to compare a map produced by artificial intelligence with that produced by a human consensus view! It was decided to hold a further workshop on chromosome 9 in April or May 1993 and David Kwiatkowski kindly agreed to organize this in Boston.

CHROMOSOME 9p

A number of groups co-ordinated by Jane Fountain combined to produce an ordered map of 9p (Figs 1, 2). This incorporates a partial map of 9p supported by multipoint linkage analysis, pulsed field gels and FISH (Fountain *et al.* and Fountain *et al.* 1992). Most of the detailed information on 9p comes from intensive effort by several workers to investigate the position of a potential tumour suppressor gene or genes in gliomas, leukaemias, non-small cell lung carcinomas (NSCLCs) and melanomas. Deletion mapping combined with isolation of the region on a 900 kb YAC contig has led to the determination of the physical position of 27 human interferon genes (Diaz *et al.*, Olopade *et al.*). The position of WP4 remains uncertain. From the minimal region of overlap of an extensive series of deletions in leukaemias and gliomas Olopade *et al.* suggested the existence of a tumour suppressor gene between the proximal end of IFNA and the gene MTAP. Other groups also reported results consistent with this (Nobori *et al.*, Middleton *et al.*, Heyman *et al.*).
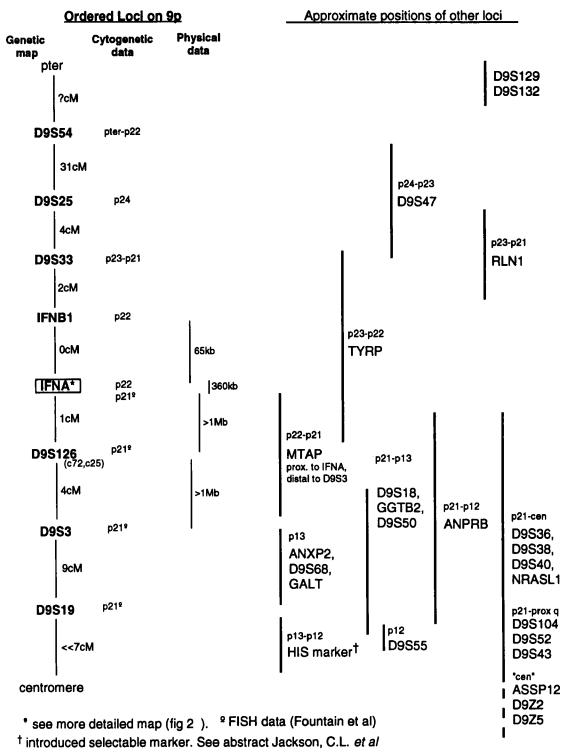
Ordered Loci on 9p

Approximate positions of other loci

Genetic map · Cytogenetic data · Physical data

```
pter
  |
  | ?cM
  |
D9S54        pter-p22
  |
  | 31cM
  |
D9S25        p24
  |
  | 4cM
  |
D9S33        p23-p21
  |
  | 2cM
  |
IFNB1        p22
  |
  | 0cM              65kb
  |
[IFNA*]      p22
             p21⁹    |360kb
  |
  | 1cM             >1Mb
  |
D9S126       p21⁹
(c72,c25)
  |
  | 4cM             >1Mb
  |
D9S3         p21⁹
  |
  | 9cM
  |
D9S19        p21⁹
  |
  | <<7cM
  |
centromere
```

D9S129
D9S132

p24-p23
D9S47

p23-p21
RLN1

p23-p22
TYRP

p22-p21
MTAP
prox. to IFNA,
distal to D9S3

p21-p13

D9S18,
GGTB2,
D9S50

p21-p12
ANPRB

p21-cen
D9S36,
D9S38,
D9S40,
NRASL1

p13
ANXP2,
D9S68,
GALT

p12
D9S55

p21-prox q
D9S104
D9S52
D9S43

p13-p12
HIS marker†

"cen"
ASSP12
D9Z2
D9Z5

* see more detailed map (fig 2).   ⁹ FISH data (Fountain et al)
† introduced selectable marker. See abstract Jackson, C.L. *et al*

Fig. 1. Consensus map of human chromosome 9p. Genetic distances shown on the left are in sex-averaged centimorgans. Where no cytogenetic regional assigment is given the position has been inferred from genetic data (see text).

IFNB	W1	A21	WP15	A4	WP9	A7	A10	WP18	A16	A17	WP5
0	65	85	98	105	110	120	125	127	135	145	147

A14	A22	P23	A5	P20	A6	A13	A2	P11	P12	A8	WP2
162	218	222	240	270	280	293	305	312	316	322	335

P24	A1	WP19
408	412	424

Fig. 2. Detailed map of the human Interferon A cluster (IFNA). Data from Diaz *et al.*, Olopade *et al.* Distances are given in kb from IFNB. The estimates are ±5 kb.

Table 1. *Useful primers for new polymorphisms on Chromosome 9*

Locus	Probable position	Sequence	Source
9cmP3	9p	CCAAAAATGATGACTACATCC GCAACAACAAAAATGAACACT	Dr R. Furlong/ Jon Lyall
9cmP4	9p	AAATATTATAGCAAGTTAATTACTGAA GGATAAATACACTGGAAAAGAGAT	Dr R. Furlong
Cosmid 80	9p21–9q21	GCATTTCACAGGAAATAATCTAAGG CCTCTCTGCATGCCCCAG	Dr S. Graw
Cosmid 103	9p21–9q21	ATCAGAGATAGAAACAGGGTCTGG ATAAGCTTGATCTTGGGTATCAGG	Dr S. Graw
D9S126	9p21	Available for collaboration	Dr J. Fountain
Cosmid 123	9q11–9q23	ATTTGTCCTTGGAAGTGGCA CGGTTTTGCTGCTCTATTC	Dr S. Graw
cmP5	9cen–9q12	ACCAGTCTCTATGGGATTCC AAAATTACTTGAATTAAGGACATC	Dr R. Furlong/ Jon Lyall
cmP6	9cen–9q12	TGCAATCAAATTCCCAGC GAGGTGACATCTGGAATT	Dr R. Furlong/ Jon Lyall
ALDOB	9q22.3–q32	AGGGTGAACCAAGCATTCTG ACTGTACTCCAGCCTGGGTG	Yuille *et al.* (at this meeting)
Cosmid EB2	proximal 9q	TCCCTTCCTGGGCTGCTAGG GAGGGTGCAGGGGCACTGCC	Armour *et al.* (at this meeting)
D9S125 D9S113 D9S122 D9S114	 9q34.1 	 Available on enquiry 	Contact Dr D. Kwiatkowski for sequence
DBH		GCAAAAGTCAGGCACATGCACC GTCAGCGAGATGGGGAGGTGGA	Nahmias *et al.* 1992 (submitted)

A large number of other GT repeats published since HGM 11 (Kwiatkowski *et al.* 1992; Wilkie *et al.* 1992; Kwiatkowski & Gusella, 1992; Furlong *et al.* 1992; Lyall *et al.* 1992) can be found in GDB.

Existing YAC clones include a YAC extending 220 kb centromeric to IFNA (Nobori *et al.*) which must lie close to the tumour suppressor region. The tumour suppressor for melanoma has been mapped to the same general area of p21 (Fountain *et al.*). A direct test of the existence of a tumour suppressor gene was reported by Porterfield *et al.* who used MTAP as a selective
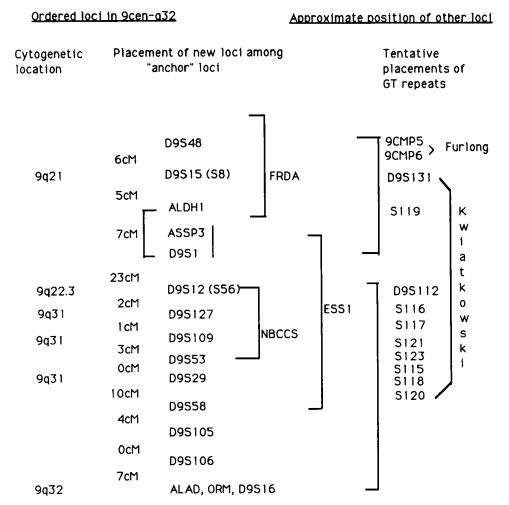
Fig. 3. Consensus map of human chromosome 9cen–9q32. Genetic distances shown are in sex-averaged centimorgans. Details of 29 cosmids from the region 9q21.1 to 9q23 (Graw *et al.*) are not included.

system to introduce copies of chromosome 9 originally derived either from normal tissues or tumours with deletions of 9 (other than those deleted for MTAP) into tumorigenic cell lines to investigate the effect on tumorigenicity. The results supported the existence of a tumour suppressor gene in the region.

There is still a shortage of markers on 9p distal to D9S54. Two new highly polymorphic CA repeats at loci D9S129 and D9S132 thought to lie in this region (Kwiatkowski, personal communication) were described (Hudson, personal communication to GDB; primers listed in GDB). Two other useful CA repeats mapped to 9p by translocation breakpoints were described by Yuille *et al.* and the primers are in Table 1. New regional assignments include 1GHEP2 to 9p (Yuille *et al.*). A YAC recognized by D9S50 was found to hybridize to 9p21-p13 even though the distance between D9S50 and D9S15 is about 9 cM and D9S15 has previously been shown to lie in 9q13–21.1 (Shaw *et al.*). Useful resources on 9p include a well characterized radiation hybrid panel derived using the selectable marker histinol-resistance – integrated into the region p13–p12 (Jackson, C. *et al.*). Cosmids mapped against this panel of radiation hybrids include a

number in p24–p23 (c 132, c 165, c 198, c 219, c 238, c 101, c 77), some in p23–p21 (c 79, c 129, c 23) and a large number in the more centromeric region (p21-q11) (c 3, c 76, c 69, c 80, c 65, c 43, c 49, c 87, c 29, c 30, c 31, c 109, c 100, c 148, c 103 (Graw *et al.*)). Many of these have been mapped more precisely by FISH, and the order in which they have been listed gives some rough indication of the most likely order. Three cosmids have already been found to have useful CA repeat polymorphisms (c 80, c 103 and c 123) and the primers are in Table 1.

<div align="center">CHROMOSOME 9cen to 9q32</div>

The report of the working party on this region was prepared by Allen Bale.

Linkage mapping

Based on the published data of Kwiatkowski *et al.* (1992) and Wilkie, P. J. *et al.* (1992) with data presented at this meeting from Goudie, D. *et al.*, Shaw, J. *et al.*, Furlong, R. A. and Slaugenhaupt, S., a consensus map was generated showing the locations of new polymorphic markers among established loci anchored by physical localization (Fig. 3). Where distances did not agree, an average was taken. There were no discrepancies with regard to order, although there were corrections since HGM11 based on new typing and physical mapping by PFGE and contigs.

Physical localization of markers in this region

D9S50, although closely linked to D9S15, has been mapped by *in situ* hybridization to 9p13–p21 (Shaw *et al.*). ANX1 has been assigned to 9q12–q21.2, CTSL to 9q22.1–q22.2, ALDB2 and C8G to 9q22.3–q32, GSN and HXB to 9q32–q33, GRP78 to 9q33–q34 (Yuille *et al.*), refining the previous localization (Fig. 3). These data were generated by PCR from flow-sorted translocation chromosomes.

D9S15 and D9S8 identify the same restriction fragments and are likely to be identical loci (Shaw, personal communication).
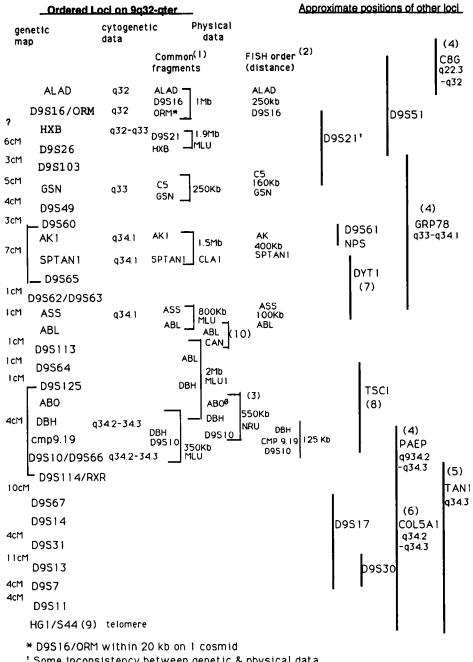
PFGE and Contig mapping

D9S15, S110, S111, S5 and probe GS1 are within 460 kb (Shaw, J., personal communication) by PFGE and YAC contigs. Primers D9S12 and D9S56 identify the same polymorphism (David Goudie, personal communication) confirmed by construction of cosmid contigs and by sequencing. D9S16, ORM and ALAD all lie within 1 Mb (Harris, 1991, and David Goudie, personal communication) by PFGE and cosmid contigs.

Disease loci on chromosome 9cen to 9q32

The gene for Friedreich's Ataxia (FRDA) is located on proximal 9q13–21.1. Conservative estimates of the map location would include the region between D9S48 and ALDH1 but the gene probably lies very close to D9S15 ($Z > 70$, $\theta = 0.0$) (Shaw, J. *et al.*, personal communication).

ESS1 (multiple self-healing squamous epithelioma) shows linkage disequilibrium with markers in the 9q31 region. The most likely location is between D9S29 and D9S1 based on

Ordered Loci on 9q32-qter   **Approximate positions of other loci**

genetic   cytogenetic   Physical
map   data   data

                 Common[1]   FISH order[2]   (4)
                 fragments   (distance)   C8G
                                                                                    q22.3
ALAD   q32   ALAD ┐   ALAD   -q32
                     D9S16 │1Mb   250kb
D9S16/ORM   q32   ORM* ┘   D9S16   D9S51
?
                                                          D9S21'
HXB   q32-q33 D9S21 ┐1.9Mb
6cM   HXB ┘ MLU
D9S26
3cM
D9S103
5cM   C5
GSN   q33   C5 ┐   160Kb
                     GSN ┘250Kb   GSN
4cM
D9S49
3cM ┌ D9S60   (4)
     │ AK1   q34.1   AK1 ┐   AK   GRP78
7cM │   │1.5Mb   400Kb   D9S61   q33-q34.1
     │ SPTAN1 q34.1   SPTAN1┘ CLA1   SPTANI   NPS
     └ D9S65
1cM   DYT1
D9S62/D9S63   (7)
1cM ASS   q34.1   ASS ┐800Kb   ASS
                    ABL ┘ MLU   100Kb
ABL   ABL ┐   ABL
1cM   CAN ┘ (10)
D9S113
1cM   ABL
D9S64   ┐2Mb
1cM   DBH ┘ MLU1   TSC1
   ┌ D9S125   ABOø ┐ (3)   (8)
   │ ABO   │550Kb
4cM│ DBH   q34.2-34.3   DBH ┘   NRU   DBH   (4)
   │ cmp9.19   DBH   D9S10 CMP 9.19 125 Kb   PAEP
   │   q34.2-34.3 D9S10 ┐350Kb   D9S10   q934.2
   │ D9S10/D9S66   MLU ┘   -q34.3   (5)
   └ D9S114/RXR   TAN1
10cM   q34.3
D9S67   (6)
D9S14   D9S17   COL5A1
4cM   q34.2
D9S31   -q34.3
11cM
D9S13   D9S30
4cM D9S7
4cM
D9S11

HG1/S44 (9) telomere

* D9S16/ORM within 20 kb on 1 cosmid
' Some inconsistency between genetic & physical data
ø ABO and DBH on common 350 MLU and 305 NRU fragments (3)

Fig. 4. Consensus map of human chromosome 9q32–9qter. Genetic distances shown are in sex-averaged centimorgans. Where no cytogenetic regional assignment is given the position has been inferred from genetic data (see text). References: (1) Harris *et al.* 1991 and Affara, personal communication. (2) Leversha *et al.* (3) Handa *et al.* (4) Yuille *et al.* (5) Ellisen *et al.* 1992. (6) Greenspan *et al.* 1992. (7) Ozelius *et al.* (8) Several contributors, see section in report. (9) Guerrini *et al.* 1990. (10) Von Lindern *et al.* 1990.

linkage disequilibrium. Formal linkage places the gene between D9S58 and ASSP3 (Goudie *et al.*, personal communication).

The nevoid basal cell carcinoma syndrome gene (Gorlin Syndrome, gene symbol: NBCCS) has been mapped to 9q22.3–q31 by three groups (Farndon *et al.* 1992; Gailani *et al.* 1992; Reis *et al.* 1992). Six recombinants place the gene proximal to D9S53 and two recombinants place the gene distal to D9S12 (Reis *et al.*, Farndon *et al.*). The maximum lod score with marker D9S53, is 19.4 at $\theta = 0.05$. The majority of basal cell carcinomas, both sporadic and hereditary, show allelic loss at this location and little or no allelic loss elsewhere in the genome (Gailani *et al.* 1992; Wainwright *et al.*).

Two groups provided evidence for a tumour suppressor gene on 9q important in bladder carcinoma. Cairns, P. *et al.* studied 252 patients and found allelic loss in 59% including both high and low grade tumours. The exact localization of the necessary region of allelic loss was not clear. Most tumours showed allelic loss for all chromosome 9 markers. The few tumours with loss of portions of 9 suggested that the critical region was proximal to 9q34. Jones, P. A. *et al.* described similar findings in 33 tumours and have also been unable to map the putative tumour suppressor gene on chromosome 9q.

CHROMOSOME 9q32–qter

The report of the working party on chromosome 9q32–qter was co-ordinated by Jonathan Haines.

Extensive data on genetic order and distances in a reference set of Venezuelan families were contributed by Kwiatkowski *et al.* (1992) and Kwiatkowski *et al.* (two abstracts) and Ozelius *et al.* with some small amounts of genetic data from CEPH pedigrees and Tuberous Sclerosis families contributed by other participants (Attwood *et al.*, Burley *et al.*, Haines *et al.*, Nellist *et al.*). Information was also obtained from Wilkie *et al.* (1992). The consensus map produced also contains information previously reported at HGM 11 with additional physical mapping data from PCR analysis of flow-sorted chromosome 9 translocation chromosomes (Zhou *et al.*), metaphase and interphase fluorescent *in situ* hybridization (Leversha *et al.*), deletion mapping from radiation hybrids (Fitzgibbon *et al.*), pulsed field gel electrophoresis (Handa *et al.* and Affara, personal communication). There was remarkable agreement in the consensus order which is shown on the left side of Fig. 4. The position of SPTANI was, however, not that expected from mouse homology (see report of comparative subgroup). The genetic distances shown are only very approximate and are sex averaged. Attwood *et al.* presented a sex specific map in which the distance from D9S49 to D9S10 was 20.5 cM in females and 14.5 cM in males.

Loci whose position is less clearly defined are shown on the right-hand side of Fig. 4. Yuille *et al.* provided new regional localization for C8G, GRP78 and PAEP. Walter *et al.* confirmed the long-standing provisional assignment of FPGS to 9q by using this locus as a selection system in somatic cell hybrids.

Disease loci on 9q34

One form of Torsion dystonia has been previously mapped to the region between AK1 and ASS, with a strong allelic association between the Torsion dystonia gene and ASS/ABL (Ozelius, 1991 and 1991*b*). Data presented at this meeting from 25 small families with

idiopathic Torsion dystonia (4 Jewish, 21 non-Jewish) suggested heterogeneity. When three clearly non-linked families were excluded, the remaining families give a lod score with ASS of 2.64 at $\theta = 0.01$ (Warner *et al.*).

Tuberous sclerosis

Progress has been made in refining estimations of the map position of the Tuberous sclerosis gene on chromosome 9q34. Progress is due to extensive analysis of haplotypes for a series of highly informative markers in the 9q34 region in several large families considered to map to chromosome 9 on the basis of linkage analysis. Families were considered most likely to map to chromosome 9 if the two-point lod score (Z_{max}) between TSC and a chromosome 9q34 marker was above 2.0.

At this meeting Haines presented results of re-analysis of the data from Boston TSC families, using an affecteds-only analysis. This revised analysis revealed a higher proportion of 9 linked TSC families (50 %) than was obtained in data analysis which utilized information from affected and unaffecteds. This finding indicates that penetrance is an important factor to consider in Tuberous sclerosis. It is therefore important to concentrate primarily on recombination events in affected individuals in defining the position of the TSC gene.

Key recombinants were considered to be those in affected individuals in families in whom two-point lod scores between TSC and a chromosome 9q34 marker were above 2.0.

In the Hou4 family described by Northrup in which the two-point lod score between TSC and a chromosome 9q34 marker was greater than 3, a recombination event in an affected individual placed the TSC gene below GSN. In the same family another recombination event also in an affected individual placed TSC proximal to D9S14. A recombination event which placed TSC below D9S62 was described in an affected individual (Haines and Kwiatkowski); the chromosome 9q34 TSC two-point lod score in this family was 2.1. A recombination event which placed TSC below D9S64 occurred in Duke family 507 (Kandt and Pericak-Vance). In this family the chromosome 9q34 TSC two-point lod score was 2.0.

A recombination event which placed TSC below D9S125 was described in an affected individual in Irvine family TS 26 (Smith, Kwiatkowski, personal communication). The maximum lod score between TSC and chromosome 9q34 markers in this family was 2.4. A recombination event in an affected individual which placed TSC below D9S64 in a family with a TSC 9q34 maximum lod score of 1.2 was described by Pitiot (personal communication).

Recombination events in unaffected individuals (Nellist *et al.*) were consistent with assignment of TSC to the region between GSN and DBH in a family with a 3.9 lodscore between TSC and chromosome 9 markers. A recombination event in an unaffected individual in a family with a lodscore of 1.9 would place TSC above D9S66 (Haines *et al.*).

Burley *et al.*, Haines *et al.* and Jannssen *et al.* described additional recombination in affected individuals in families with maximum lod scores between TSC and 9q34 markers which ranged between 0.9 and 1.5. These were consistent with analysis reported in larger families. Haplotype analysis indicated that the TSC1 gene was positioned below ABL (Janssen *et al.*), below ALAD and below D9S49 (Burley *et al.*) and below D9S64 (Haines *et al.*).

In summary, a conservative definition of the position of the TSC1 gene would be distal to D9S64 and proximal to D9S66 (or proximal to D9S14 if considering affecteds only). There is some evidence which will need to be substantiated, that the TSC1 gene may be between D9S125

and DBH, i.e. within a region that is less than 4 centimorgans and less than 2 Mb (see Fig. 4 for estimates of genetic and physical distances in this region). It will, however, be important to identify additional recombinants in affected individuals in families which are clearly chromosome 9 linked.

Other TSC loci

It is clear that genetic heterogeneity occurs in Tuberous sclerosis. Other TSC loci are not definitively assigned at this time.

Analysis of a collaborative data-set (Janssen and the TS collaborative group, this meeting) provided no support for a locus on chromosome 11 and very little (non-significant) support for a locus on chromosome 12. Analysis of the same data by John Edwards, using a different approach, also found definite evidence only for a locus on chromosome 9 and for heterogeneity.

There was some support for a locus on chromosome 11 in three studies presented at this meeting. Studies by Haines *et al.* revealed a maximum lod score of 2.0 between TSC and tyrosinase in families where linkage to chromosome 9 was excluded. Data in two families analysed by Smith *et al.* provided evidence for linkage to markers on chromosome 11. Multipoint analysis of TSC using stromolysin, D11S84 and tyrosinase revealed a Z_{max} of 3.51 with a peak at tyrosinase.

Data presented by Benham *et al.* also provided some support for a locus on chromosome 11 in a small number of families. Their analysis would suggest location of a putative TSC gene below DRD2.

It was generally agreed that there must be another locus determining TSC which has not yet been found. Dr Pericak-Vance presented preliminary results on analysis of 95 additional markers scattered through the genome which have been tested on several large non-9-linked families contributed by a number of US groups. So far no clear positive results are reported and an agreement was made to extend the number of families to be tested and the coverage of the genome by sharing DNA between all willing participants and allocating each laboratory a piece of the genome not yet excluded.

NEW GENES ON CHROMOSOME 9

New assignments to distal 9q from the literature since HGM 11 included a collagen gene COL5A1 to 9q34.2–9q34.3 (Greenspan *et al.* 1992). A homologue of the *Drosophila* notch gene, thought to function in cell lineage determination during embryonic development, has been cloned from a series of leukaemia breakpoints in 9q34.3 and named TAN1 (Ellisen *et al.* 1991). A new homeobox gene PBX3 has been mapped to 9q33–q34 (Monica *et al.* 1991).

Two other loci assigned to chromosome 9 but without regional assignment include a new form of aldehyde dehydrogenase ALDH5 (Hsu & Chang, 1991) and platelet erythroleukemia cell PGG/H synthase (Funk *et al.* 1991). A gene previously mapped to chromosome 9, HSPBL2, has been excluded from 9 by more recent work (Yuille *et al.*).

GLOBAL GROUP

This group consisted of: M. Hultén (Chairman), N. Morton (Co-Chair), J. Armour, J. Attwood, S. Graw, M. Lawrie, S. Slaugenhaupt and L. Wang.

Discussions mainly concerned the relationship between and integration of the different types of maps: (1) *the physical map* including chromosome bands, the ordering of markers along the length of the chromosome arms and their location in relation to chromosome bands; (2) *the genetic map* derived from family linkage analysis and (3) *the chiasma maps.*

(1) *Documentation on generation of maps.* It would be helpful if the consensus physical and genetic maps produced as a result of specific chromosome meetings would document the generation of any specific changes and additions to current maps.

(2) *Sex-specific genetic maps.* Genetic maps, illustrating density of meiotic crossing-over/recombination along the length of the chromosome arms are unlikely to be identical in the two sexes in the human. Sex specific mouse chiasma density and interference maps (ChiDI maps), presented at this meeting (M. Lawrie *et al.*, personal communication, Fig. 5) indicate differences in the location of hot-spots of meiotic recombination between sexes. It would be valuable if the family linkage data are analysed for each sex separately so that eventually human sex specific rather than sex averaged linkage based genetic maps may be produced. This would: (1) allow an adequate comparison with the human male chiasma map presented at this meeting (M. Hultén and M. Lawrie, personal communication, Fig. 6) which in turn (2) may indicate more precisely the physical distance to any gene locus in the segment concerned and thus the amount of work required to identify the gene, and (3) be useful for genetic counselling in situations where disease status is still dependent on family linkage analysis.

(3) *Genetic interference.* It is evident that genetic interference may preclude the formation of double recombinants over quite large chromosome segments. The human male chromosome 9 chiasma density and interference map (Fig. 6) indicates that double recombinants should normally be rare within 9p, as well as over the segments 9cen–9q32 and 9q31–9qter. Within these segments male recombination fractions, obtained by family linkage, would be additive and numerically correspond to genetic distance. Any double recombinants retrieved by family linkage analysis within these segments should therefore be regarded with caution and checked for typing errors, for example. It was recognized that the information on genetic interference provided by the chiasma maps cannot be readily incorporated into currently available linkage programs. Computer programs using null interference would tend to inflate genetic distances. Therefore any program taking account of genetic interference would be an improvement over those based on null interference.

(4) *Computer analysis.* A discussion took place regarding the potential advantage of simplified linkage analysis, using personal computers. No consensus was reached whether or not efforts should now be made in this direction.

CEPH CHROMOSOME 9 CONSORTIUM MAP

Previous to this meeting some identification of possible errors in the original data-set had been carried out by Mark Lathrop and, after communication with various contributors and some corrections, a revised data-set had been distributed in February 1992. Preliminary maps were produced by J. Haines, J. Attwood, S. Slaugenhaupt, N. Morton, J. Yates and C. Falk (C. Falk not present). It was encouraging that there was substantial agreement between the maps. After agreement on a working framework order it was decided to re-examine those remaining unlikely double recombinants which could be tested by PCR before distribution of

the final data-set within the next two months. This data-set will be used for the definitive CEPH Consortium map.

COMPARATIVE MAPPING BETWEEN CHROMOSOME 9 AND THE MOUSE

This report was prepared by Cathy Abbott and Ian Jackson.

Genes mapping to human chromosome 9 have homologues mapping to three different mouse chromosomes; 2, 4 and 19. The homology on chromosome 4 falls into three segments. The simplest explanation by which the three segments are related is that there has been an insertion/deletion event and an inversion with respect to the ancestral chromosome. Figure 7 shows the conserved mouse linkages and syntenies aligned to the chromosome 9 map. The comparison allows a number of predictions to be made:

(A) *Predictions for chromosome 9, based on mouse data*

(i) TYRP (human designation) would be expected to be centromeric of IFN (mapping telomeric would require an additional rearrangement to be invoked).

(ii) ACO1 most likely maps to 9p, since it maps close to *Galt* in the mouse.

(iii) SPTAN1 is probably telomeric of ABL, and centromeric of DBH (based on mapping data from three independent, large backcrosses, all of which put *Spna-2* proximal of *Abl*).

(iv) SURF is probably telomeric to ABL (again based on good backcross data).

(B) *Prediction for the mouse map, based on chromosome 9 data*

(i) *Ifb* would be expected to be telomeric to *Ifa* in the mouse, based on physical mapping in human.

(ii) The mouse homologue of MTAP is most likely to be on mouse chromosome 4, close to *Ifa*.

(iii) *Rmrpr* is known to be on mouse 4 and human 9p, so will map either close to *Tyrp/Ifa* or to *Ggtb/Galt* in mouse.

(iv) *Ass* will be probably telomeric of *Abl* in mouse, although they have not been genetically separated, because *ASS* is known to be centromeric of ABL in humans, based on interphase mapping and the use of the Philadelphia translocation.

(v) *Ak-1* in the mouse, which has previously only been localized using somatic cell hybrids, is probably between *Ass/Abl* and *Gsn/Hc*.

(vi) *Xpa* in the mouse will probably be in *Lv*, *Orm*, *Hxb* region of chromosome 4.

(C) *Mouse mutants whose human homologues would be predicted to lie on human chromosome 9*

MMU2: Sd   Danforth's short tail   (kidney/notochord development)
       stb   Stubby   (mild achondroplasia)
       lh   lethargic   (neurological/immunological)

---

cold region in comparison with the near-terminal hotspots. The total chromosome 9 genetic length is estimated at 116 cM. The arrows below the diagram indicate chromosome segments where there is apparently full interference and no risk of double chiasmata/recombinants. The exclusively single chiasma in the p arm means that recombination fractions are additive and numerically equivalent to genetic distances. The 9q arm is subdivided into two major interference segments within each of which recombination fractions are again additive and numerically correspond to respective genetic distances.
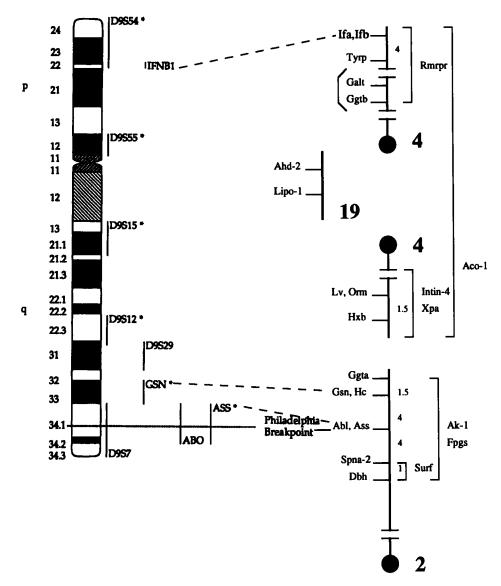
Fig. 7. Conserved mouse linkages and syntenies aligned to the human chromosome 9. The centromere, where orientation is known, is represented by a filled circle. Chromosome 4 is displayed twice in order to allow the alignment to be shown. Genes where precise localization is not known in the mouse are displayed to the side and bracketed around the limits of their location. Where human and mouse nomenclature differs markedly both names are noted at the foot. Distances on the mouse chromosomes, where known accurately from at least one large backcross pedigree, are shown in cM.

MMU4: an   Hertwig's anaemia
      vc   vacillans   (neurological)   ⎫
      wi   whirler   (deafness/inner ear) ⎬ 9p/9q
      dep depillated   (hair)   ⎫
      pt   Pintail   (tail)   ⎬ 9p

Fig. 8. Regions present in eleven chromosome 9 hybrids are indicated above. References for hybrids 1, 2, 3 (Carritt & Povey, 1979), for hybrids 4, 5 (Carritt, B., unpublished), for hybrids 6, 7, 11 (Mohandas *et al.* 1979; Taylor *et al.* 1991); for hybrid 10 (Warburton *et al.* 1990), for hybrid 8 also known as CJ9q (Jones & Kao, 1984). DNA from hybrid 640-63a12 and from GM10611 has been labelled with biotin and used to paint normal human metaphase spreads. In both cases signal was seen only on chromosome 9 (West & Povey, personal communication).

CHROMOSOME 9 RESOURCES

Somatic cell hybrids and radiation reduced hybrids

Somatic cell hybrids containing portions of chromosome 9 are listed in Fig. 8. Radiation reduced hybrid panels were described at this meeting by Fitzgibbon *et al.*, Henske *et al.*, Jackson *et al.* and Slaugenhaupt *et al.* Fitzgibbon *et al.* described a panel of radiation hybrids which contained fragments of chromosome 9q. In this panel they defined 15 deletion intervals which spanned the AK1 to D9S7 interval. Henske *et al.* produced a panel of radiation reduced

hybrids by irradiating a hybrid which contained chromosome 9q. The selection applied to the post-irradiation hybrids resulted in selection for hybrids containing the human ASS gene. One hybrid, E6B, contained 5 Mb of DNA from the region between AK1 and D9S66. Jackson *et al.* described production of a panel of radiation reduced hybrids from the MG10611 cell line. This cell line contained a human chromosome 9 which is selectively retained by culture in histidinol, since the histidinol dehydrogenase gene (HIS) was integrated into the short arm of chromosome 9 using a retroviral vector. All hybrids in this panel therefore contain the portion of chromosome 9p where the HIS gene is located and varying size fragments extending toward both 9pter and 9qter but being biased towards 9p. Slaugenhaupt *et al.* also described production of a radiation reduced hybrid panel from the hybrid PK87-9 (GM 10611).

Cosmid libraries

Shaw *et al.* described a cosmid library produced from the hybrid PK87.9 (NG10611). In this cosmid library of 10 thousand colonies they identified approximately 200 human DNA containing colonies. Cosmid clones were subsequently localized to all regions of chromosome 9 but they were especially concentrated in human chromosome 9q. Henske *et al.* developed a cosmid library from a radiation hybrid which contained only the human 9q34 region. Approximately one in 1000 clones in this library were human in origin. Wolfe reported that his group had developed 160 cosmids from chromosome 9q. Armour reported the development of 80 human cosmid clones from chromosome 9q.

YACs containing regions of human chromosome 9

In the 9p region Olopade and Diaz reported isolation of a 900 kb YAC contig in the interferon gene region. Fountain described isolation of an 850 kb YAC contig in the D9S126 region. A YAC containing the D9S50 locus was isolated by Shaw and Chamberlain. A YAC contig containing the loci D9S5 and D9S15 was described previously (Chamberlain). Three YACs from the chromosome 9q34 region were described. Affara described a YAC containing the AK1 locus; Ozelius described a YAC which contained the ASS locus. Pitiot described a YAC containing the ABL locus. Details concerning a YAC HG1 which contains the 9q telomeric sequences can be found in Guerrini *et al.* (1990).

Cell lines

There was a general view that it would be useful to have a better panel of hybrids with well defined regions of chromosome 9. A large number of cell lines carrying translocations of chromosome 9 are available through the NIGMS mutant cell repository and are not listed here. Dr J. Yates has supplied a list of potentially useful lines available in Cambridge (some of these also from the EHCB at Porton) and this list is reproduced in Table 2.

Table 2. *Cambridge Chromosome 9 Breakpoint Panel*

	Type*	Karyotype	Cambridge ref. no.	EHCB acc. no.†
9p13.1	L	46XY t(5;9)(p14.2;p13.1)	9T-21	67
9p22	L	46XY t(5;9)(q22;p22)	9T-22	295
9cen	L	46XX t(9;13)(9p13q;9q13p)	9T-13	36
9cen	L	46XY t(9;19)(9p19q;9q19p)	9T-25	269
9q11	F	46XY- 9+der(9)t(9;15)(q11;q11)	9T-24	
9q12	L	46XX t(9;16)(q12;q12.1)	9T-23	83
9q12	L	t(9;22)(q12;p11)	9T-05	
9q21.2	L	46XY t(9;22)(q21.2;q11.2)	9T-26	91
9q21.2	L	46XX t(1;9)(p36.3;q21.2)	9T-15	23
9q21.2	L	46XX t(8;9)(q24.13;q21.2)	9T-27	314
9q22.1	L	46XX t(9;X)(q22.1;p21)	9T-02	
9q22.1	L	46XY t(9;22)(q22.1;q11.2)	9T-29	301
9q22.2	L	46XY t(5;9)(q33.2; q22.2)	9T-19	63
9q22.3	L	46XX t(6;9)(p23;q22.3)	9T-17	
9q22	L	t(9;12)(q22;q11)	9T-20	
9q22	L	t(9;10)(q22;p12)	9T-10	
9q22	L	46XX t(9;10)(q22;q22.1)	9T-16	54
9q22	F	47XX t(9;15)(q22;q24)+15	9T-28	
9q22	L	46XX t(9;10)(q22;p12)	9T-30	
9q32	L	t(9;20)(q32;q13.3)	9T-06	
9q32	F	46XX t(4;9)(q35;q32)	9T-11	
9q32	L	46XX t(2;9)(p25.3;q32)	9T-31	92
9q33	L	t(9;10)(q33;p11.2)	9T-08	
9q33	L	t(9;12)(q33;q22)	9T-09	
9q34.1	L	46XX t(9;22)(q34.1;p12)	9T-14	
9q34.1	L	t(9;14)(q34.1;q13)	9T-03	
9q34.1	L	t(9;22)(q34.1;q12)	9T-04	
9q34.1	L	46XY t(9;20)(q34.1;q11.2)	9T-12	41
9q34.3	L	46XX t(9;15)(q34.3;q24)	9T-01	15
9q34.3	L	46XY r(9)	9T-32	16
9q34.3	L	46XY t(9;15)(q34.3;q21.2)	9T-34	302
9q34	L	46XX t(9;13)(q34;q12)	9T-07	
9q34	A	46XX t(9;15)(q34;q15)	9T-33	
9q34	L	46XX t(2;9)(p23;q34)	9T-35	322

* L, Lymphoblastoid cell line; F, fibroblasts; A, amniotic fluid cells.

† EHCB acc. no. = European Human Cell Bank accession number for cell lines deposited by Cambridge Group (prefixed with BO)

Please contact the European Human Cell Bank for lines deposited there. Most of the other lines can be made available and enquiries should be made to Dr J. R. W. Yates, Cambridge University, Department of Pathology.

GENERAL REFERENCES

CARRITT, B. & POVEY, S. (1979). Regional assignments of the loci AK3, ACONS and ASS on human chromosome 9. *Cytogenet. Cell Genet.* 23, 171–181.

ELLISEN, L. W., BIRD, J., WEST, D. C., SORENG, A. L., REYNOLDS, T. C., SMITH, S. D. & SKLAR, J. (1991). Tan-1, the human homolog of the Drosophila *Notch* Gene, is broken by chromosomal translocations in T Lymphoblastic Neoplasms. *Cell* 66, 649–661.

FARNDON, P. A., DEL MASTRO, R. G., EVANS, D. G. R. & KILPATRICK, M. W. (1992). Location of gene for Gorlin syndrome. *Lancet* 339, 581–582.

FOUNTAIN, J. W., KARAYIORGOU, M., TARUSCIO, D., GRAW, S. L., BUCKLER, A. J., WARD, D. C., DRACOPOLI, N. C. & HOUSMAN, D. E. (1992). Genetic and physical map of the 'interferon region' on chromosome 9p. *Genomics* (in the press).

FUNK, C. D., FUNK, L. B., KENNEDY, M. E., PONG, A. S. & FITZGERALD, G. A. (1991). Human platelet/erythroleukemia cell prostaglandin G/H synthase: cDNA cloning, expression, and gene chromosomal assignment. *FASEB Journal* **5**, 2304–2310.

FURLONG, R. A., LYALL, J. E. W., GOUDIE, D. R., LEVERSHA, M. A., AFFARA, N. A. & FERGUSON-SMITH, M. A. (1992). A dinucleotide repeat polymorphism at the D9S109 locus. *Nucleic Acids Research* **20**, 4, 925.

GAILANI, M., BALE, S. J., LEFFELL, D. J., DI GIOVANNA, J. J., PECK, G. L., POLIAK, S., DRUM, M. A., PASTAKIA, B., MCBRIDE, O. W., KASE, R., GREEN, M., MULVIHILL, J. J., BALE, A. E. (1922). Developmental defects in Gorlin syndrome related to a putative tumour suppressor gene on chromosome 9. *Cell* **69**, 111–117.

GREENSPAN, D. S., BYERS, M. G., EDDY, R. L., CHENG, W., JANI-SAIT, S. & SHOWS, T. B. (1992). Human collagen gene COL5A1 maps to the q34.2–q34.3 region of chromosome 9, near the locus for Nail-Patella Syndrome. *Genomics* **12**, 836–837.

GUERRINI, A. M., ASCENZIONI, F., PISANI, G., RAPPAZZO, G. DELLA VALLE, G. & DONINI, P. (1990). Cloning a fragment from the telomere of the long arm of human chromosome 9 in a YAC vector. *Chromosoma* **99**, 138–142.

HARRIS, R. M., CARTER, N. P., LEVERSHA, M., GOUDIE, D. R., SARGENT, C. A., HAMPSON, M., WARNER, J. P., YATES, J. R., AFFARA, N. A. & FERGUSON-SMITH, M. A. (1991). Physical mapping with DNA probes in the region 9q32–34 which show linkage to the Tuberous Sclerosis locus. *Cytogenet. Cell Genet.* **58**, 3–4 (HGM 11), 1940.

HSU, L. C. & CHANG, W-C. (1991). Cloning and characterization of a new functional human aldehyde dehydrogenase gene. *Journal of Biological Chemistry* **266**, 12257–12265.

JONES, C. & KAO, F. T. (1984). Regional mapping of the folypolyglutamate synthetase gene (FPGS) to 9cen-q34. *Cytogenet. Cell Genet.* **37**, 499.

KWIATKOWSKI, D. J., HENSKE, E. P., WEIMER, K., OZELIUS, L., GUSELLA, J. F. & HAINES, J. (1992). Construction of a GT polymorphism map of human 9q. *Genomics* **12**, 229–240.

KWIATKOWSKI, D. J. & GUSELLA, J. F. (1992). Dinucleotide repeat polymorphism at the D9S112, D9S115, D9S116, D9S117, D9S118, D9S119, D9S120, D9S121 and D9S123 loci. *Nucleic Acids Research* **20**, 4, 930–934. (Short Communications).

LYALL, J. E. W., FURLONG, R. A., YUILLE, M. A. R., GOUDIE, D. R., LEVERSHA, M. A., AFFARA, N. A. & FERGUSON-SMITH, M. A. (1992). A dinucleotide repeat polymorphism at the D9S127 locus. *Nucleic Acids Research* **20**, 4, 925.

MOHANDAS, T., SPARKES, R. S., SHULKIN, J. D., TOOMEY, K. E., FUNDERBURK, S. J. (1979). Regional localization of human gene loci on chromosome 9: studies of somatic cell hybrids containing human translocations. *Am. J. Hum. Genet.* **31**, 586–600.

MONICA, K., GALILI, N., NOURSE, J., SALTMAN, D. & CLEARY, M. L. (1991). *PBX2* and *PBX3*, new homeobox genes with extensive homology to the human proto-oncogene *PBX1*. *Molecular & Cellular Biology* **11**, 6149–6157.

OZELIUS, L., KRAMER, P., DE LEON, D., BRESSMAN, S., RISCH, N., SCHUBACK, D., BRIN, M., KWIATKOWSKI, D., BURKE, R., GUSELLA, J. F., FAHN, S., BREAKFIELD, X. O. (1991 and 1991b). Strong allele association between the torsion dystonia gene and loci on chromosome 9q34 in Ashkenazic Jews. *Am. J. Hum. Genet.* (suppl.) **49**, 415.

REIS, A., KUSTER, W., LINSS, G., GEBEL, E., HAMM, H., FUHRMANN, W., WOLFF, G., GROTH, W., GUSTAFSON, G., KUKLIK, M., BURGER J., WEGNER, R. D. & NEITZEL, H. (1992). Localisation of gene for the naevoid basal-cell carcinoma syndrome. *Lancet* **339**, 617.

TAYLOR, A. K., ZAMBAUX, J. L., KLISAK, I., MOHANDAS, T., SPARKES, R. S., SCHOTZ, M. C., LUSIS, A. J. (1991). Carboxyl ester lipase: A highly polymorphic locus on human chromosome 9qter. *Genomics* **10**, 425–431.

VON LINDERN, M., POUSTKA, A., LERACH, H. & GROSVELD, G. (1990). Chromosome translocation associated with a specific subtype of acute nonlymphocytic leukemia, leads to aberrant transcription of a target gene on 9q34. *Mol. Cell Biol.* **10**, 4016–26.

WARBURTON, D., GERSEN, S., YU, M.-T., JACKSON, C., HANDELIN, B. & HOUSMAN, D. (1990). Monochromosomal rodent-human hybrids from microcell fusion of human lymphoblastoid cells containing an inserted dominant selectable marker. *Genomics* **6**, 358–366.

WILKIE, P. J., KRIZMAN, D. B. & WEBER, J. L. (1992) Linkage map of human chromosome 9 microsatellite polymorphisms. *Genomics* **12**, 607–609.