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Authors

Povey, S
Attwood, J
Chadwick, B
[et al.](#)

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REPORT on the Fifth International Workshop on Chromosome 9

held at Eynsham, Oxfordshire, UK, September 4–6, 1996

Report compiled by: S. POVEY¹, J. ATTWOOD¹, B. CHADWICK², J. FREZAL³, J. L. HAINES⁴, M. KNOWLES⁵, D. J. KWIATKOWSKI⁶, O. I. OLOPADE⁷, S. SLAUGENHAUPT⁴, N. K. SPURR⁸, M. SMITH⁹, K. STEEL¹⁰, J. A. WHITE¹ AND M. A. PERICAK-VANCE¹¹

¹*MRC Human Biochemical Genetics Unit, Galton laboratory, University College London, Wolfson house, 4 Stephenson Way, London, NW1 2HE UK*

²*Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London, WC2A 3PX UK*

³*GENATLAS, Service de Genetique Medicale Hopital des Enfants Malades, 149, rue de Sevres, 75743 Paris, Cedex 15, France*

⁴*Massachusetts General Hospital, Molecular Neurogenetics Unit, Building 149, 6th Floor, 13th Street, Charlestown, MA 02129, USA*

⁵*Marie Curie Research Institute, The Chart, Oxted, Surrey, RH8 0TL, UK*

⁶*Experimental Medicine Division, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, USA*

⁷*University of Chicago Medical Center, 5841 S. Maryland Avenue, MC 2115 Chicago, IL 60637-1470, USA*

⁸*Smithkline Beecham Pharmaceuticals, New Frontiers, Science Park (North), Third Avenue, Harlow, Essex, CM19 5AW, UK*

⁹*Center for Medical Genetics, Johns Hopkins, Hospital Blalock Building Room 1007, 600N Wolfe Street, Baltimore MD 21287-4922, USA*

¹⁰*MRC Institute of Hearing Research, University Park, Nottingham, NG7 2RD*

¹¹*Division of Neurology, Duke University Medical Center, Box 2900, Durham, NC 27710, USA*

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SUMMARY

The Fifth International workshop on chromosome 9 comprised a gathering of 36 scientists from seven countries and included a fairly even distribution of interests along chromosome 9 as well as a strong input from more global activities and from comparative mapping. At least eight groups had participated in the goal set at the previous workshop which was to improve the fine genetic mapping in different regions of chromosome 9 by meiotic breakpoint mapping in allocated regions and this has resulted in some greatly improved order information. Excellent computing facilities were available and all contributed maps were entered not only into SIGMA (and thence submitted to GDB) but also into a dedicated version of *ACEDB* which can be accessed on the Web in the form of one of 28 slices into which the chromosome has been arbitrarily divided. It was generally agreed that the amount of data is now overwhelming and that the integration and validation of all data is not only unrealistic in a short meeting but probably impossible until the whole chromosome has been sequenced and fully annotated. Sequence-ready contigs presented at the meeting totalled about 3 MB which is about one fiftieth of the estimated length. The single biggest barrier to integration of maps is the problem of non-standard nomenclature of loci. In the past 2 workshops efforts have been made to compare traditional 'consensus' maps made by human insight (still probably best for small specific regions) with those generated with some computer assistance (such as SIGMA) and those generated objectively by defined computer algorithms such as *ldb*. Since no single form of map or representation is entirely satisfactory for all purposes the maps reproduced in the published version of the report are confined to one of the genetic maps, in which Genethon and older markers have been incorporated, a Sigma map of the genes as symbols together with a listing of known 'disease' genes

on chromosome 9, and a revised assessment of the mouse map together with a list of mouse loci predicted to be on human chromosome 9. One of the 28 *ACEDB* slices is also shown to illustrate strengths and weaknesses of this approach. Workshop files include not only all maps available at the time but also details of loci and details of the meiotic breakpoints in the CEPH families (<http://www.gene.ucl.ac.uk/scw9db.shtml>).

This report and other information on chromosome 9 can be found on the chromosome 9 homepage at the URL: <http://www.gene.ucl.ac.uk/chr9/>

INTRODUCTION

The format of this report reflects the working groups at the meeting and co-ordinators of each group are identified. The groups included 9p, proximal 9q, 9q34, global, computing and informatics, comparative mapping and disease genes. Disease data have been placed in the relevant chromosomal region and in addition a summary of all known disease-causing genes on chromosome 9 is shown in Table 1. As previously, a name with a date in the text report refers to a publication listed in the reference section. All other references refer to abstracts at this workshop. The proceedings of the fourth workshop were published and listed in the references (Pericak-Vance *et al.* 1995).

The Whitehead Institute have been producing whole genome maps based on a combination of YAC and radiation hybrid mapping. The RH maps have been built using the whole genome radiation hybrids panels Genbridge 4 and Stanford. These maps consist of a framework map taken from the genetic linkage map generated at Genethon. These are then populated with STSs from known genes and ESTs and any other markers amenable to analysis by PCR amplification. There was nobody from this group at the meeting, but all publicly-available maps were available and considered by subgroups. In addition, information from RHDB was extracted for the use of individual researchers at the meeting. However, these data (now available as the Science map, Schuler *et al.* 1996) do not form part of this publication.

THE 9P GROUP

Group co-ordinators: Olufunmilayo Olopade and Nigel K Spurr

Mapping of the short arm of chromosome 9 has until recently always been in the shadow of the efforts undertaken to map the long arm. However, this situation is changing and the report from this workshop reflects the rapid increase in knowledge in this region.

Total 9p mapping

Several groups reported or had supplied partial or whole arm maps of 9p. These included accurate assignments for many genes and ESTs. More than 145 markers were placed on the SIGMA map. The group refined the localization of some markers with a combination of data generated from genetic and physical mapping using radiation hybrids, YAC clones and meiotic mapping in CEPH families (Bouzyk *et al.*; Rebello *et al.*; Ridanpää *et al.*). Nigel Spurr presented an integrated radiation hybrid YAC map of chromosome 9p. Eighty-nine STS markers were used in the construction of the RH map and these were used to isolate and order a minimal tiling path of YAC clones identified from the CEPH mega-YAC library. This contig is 88 individual YACs in length with an average size of 1 Mb giving about 90% coverage of the short arm. A few minor gaps remain mainly towards the centromere and telomere. Additionally, two major gaps (~ 3 cM each) occur between D9S269 and D9S1039E and between CNTFR and D9S962 and these are also identified by

the maps generated by the Whitehead Institute. These two gaps flank the gene CDKN2 which is commonly deleted in several tumour types. Many of the YAC clones were tested for integrity by FISH mapping. This map reduces the average physical distance between markers to 0.75 Mb on the integrated map.

The distal portion of 9p has always been poorly mapped. At the meeting Rebello and colleagues presented a new genetic map of 9p24 which included several new Genethon markers. In addition, a meiotic breakpoint map of 9p as well as a full length genetic linkage map were presented.

A cosmid in the sub-telomeric region of 9p has been identified and will be used to anchor the telomere of 9p. The marker D9S1779 was identified as the most telomeric genetic marker on 9p. The marker D9S163, shown as telomeric on the Whitehead map is placed by genetic mapping and also by FISH much more proximally in p21 (see Fig. 4.)

9p regional maps

Several detailed maps of specific sub-regions of 9p were presented. These included a 1 Mb region around RPS6 (Illison *et al.*). RPS6 codes for the ribosomal protein S6. The gene lies in a 9p22–p23 region telomeric of the IFN gene cluster. Further mapping is underway to construct a cosmid contig of the region. A transcript map of 9p13–p21 (Lynch *et al.*) and a 2.8 Mb region around the tumour suppressor gene CDKN2 (Olopade *et al.*) were presented. These regions have cosmid contigs ready for DNA sequencing; three cosmids around CDKN2 have already been sequenced completely (Olopade, personal communication.)

Gene localization on 9p

The localization of the following genes were refined: VLDLR, AK3, RPS6, CNTFR, PAX5, CHH, RLN1, TYRP1, MLLT3. In addition, numerous ESTs coding for genes of unknown function were located on the RH and YAC maps. Lynch and co-workers reported on the isolation of several new ESTs from around the CDKN2 locus. They used exon trapping to isolate novel sequences from 200 to 250 cosmids which span approximately 3.5–4.0 Mb of this region.

No further information was available on the location of NRASL1. This gene was placed on 9p in 1987 following in situ hybridisation with a probe specific for NRAS1. A secondary signal was detected on 9p leading to the assignment of NRASL1. It is questionable whether this localization should be retained or should be archived until DNA sequencing of this chromosome takes place.

Disease genes on 9p

Considerable progress has been made in mapping and localizing disease genes on 9p and several reports were presented at the meeting.

Sex determination

Monosomy of distal 9p is frequently associated with abnormal development of external genitalia in 46, XY boys. A gene involved in sex determination has been located at the tip of 9p. It has been refined between SNF2L2 and D9S144 in the region 9p24.1–qter (Guioli *et al.*; Veitia *et al.*).

9p⁻ Syndrome

The constitutional 9p⁻ syndrome was mapped to the region between D9S267 and D9S286 (Schwartz *et al.*). This syndrome includes facial dysmorphism and mental retardation. The majority of patients have a breakpoint in 9p22 with breakpoints clustering in two regions, between D9S1659 and D9S285

and also between D9S1709 and D9S162. These were mapped with high resolution FISH using 40 YACs and PCR with 25 different STSs. The minimal region covers approximately 2–3 Mb in the region 9p22–p23.

Tumour suppressor loci

The most well characterized tumour suppressor locus on 9p involves the gene CDKN2 of which germline mutations have been described in melanoma and pancreatic cancer families. This region has been frequently reported as being the target for high frequency deletions in a wide range of somatic tumours in cell lines and primary tissue.

In addition, other data were presented at the workshop supporting other regions of deletion on 9p. Terminal deletions of 9p were reported in several breast cancer cell lines using FISH mapping with a panel of YACs from 9p (Savelyeva *et al.*). Every marker tested distal to D9S1813 was hemizygotously deleted in the majority of cell lines; two homozygous deletions of the region distal to D9S1813 and between D9S263 and D9S1845 were identified. Campell and co-workers presented data on LOH in lung cancer cell lines that peaked around the locus D9S259. However, there continue to be significant data in support of CDKN2 as the target gene involved in 9p deletions. Olopade *et al.* presented a genomic map of the MTAP gene in relation to CDKN2 and CDKN2B including the comparative map of the rat map and CDKN2 loci.

CDKN2 appears to be the target locus in multiple tumour types. In addition to several families segregating melanoma having mutations in CDKN2, several have been reported with mutations in another gene, CDK4, which interacts with the CDKN2 gene product, p16. Although CDKN2 has been reported to be inactivated by homozygous deletions, methylation of the promoter region or by point mutations, there remain some 9p-linked families that do not have detectable mutations in CDKN2. The group decided to keep the designation of MLM on the map alongside CDKN2 until the issue of mutations in all the melanoma families could be resolved. The group also decided not to assign a name for p19ARF, the alternate transcript from Exon 1B of CDKN2 until a human protein corresponding to the p19ARF is characterized. No mutations in Exon 1B have been described in melanoma kindreds thus far.

Lymphatic leukaemias and PAX5 on chromosome 9p

The 9p13 region is involved in t(9;13) (p13;q32), and Ohno *et al.* (1990) showed that in a diffuse large cell lymphoma (KIS1) with this translocation the IgH locus on chromosome 14 was translocated to 9p13 sequences of unknown function. Busslinger *et al.* (1996) showed that in the KIS1 translocation the E mu enhancer of IgH is brought into proximity with the PAX5 promoters and that PAX5 gene transcription is involved in the pathogenesis of lymphatic lymphomas with plasmacytoid differentiation.

Cartilage hair hypoplasia (CHH)

The gene for CHH has previously been shown to be 0.3 cM proximal to D9S163 between the PAX5 and CNTFR genes. Radiation hybrid mapping in this region has refined the localization of PAX5, TPM2, GALT and CNTFR and has excluded IL11RA and HA2337 as candidate genes (Ridanpää *et al.*).

TYRP1 Tyrosinase related protein 1 in OCA3

Boissy *et al.* (1996) reported mutation in and lack of expression of tyrosinase related protein-1 (TRP-1) in brown oculocutaneous albinism, a new sub-type of albinism classified as OCA3. One member of a set of African American twins was found to have light brown skin and blue-grey irides

with a red reflex consistent with brown oculocutaneous albinism. The other twin had dark hair and dark skin pigment. The affected twin was homozygous for a single basepair deletion in exon 6 of TYRP1. The deletion of an A in codon 368 led to a premature stop at codon 384.

REPORT ON 9CEN-9Q31

Group co-ordinators: Brian P. Chadwick, Susan A. Slaughaupt

Physical and genetic mapping on 9cen-9q31

Two regions of proximal 9q have been the centre of attention for physical mapping over the past year around the nevoid basal cell carcinoma syndrome (NBCCS) on 9q22 and familial dysautonomia (DYS) on 9q31.

A YAC contig spanning the genetically defined NBCCS region of 9q22 between D9S196 and D9S180 suggests a physical distance of greater than 2 Mb (Hahn *et al.* 1996). A second YAC contig spanning D9S197 and D9S287 implies this region is approximately 5.5 Mb (Johnson *et al.* 1996). A further map presented at this meeting spanning FACC and D9S173 agreed with a physical estimate previously described by Hahn *et al.* Four independent YAC maps covering 9q22 exist (Hahn *et al.* 1996, Johnson *et al.* 1996, Morris *et al.* 1994; Lench *et al.* unpublished). Fig. 1 shows the conflicting results for the order of the markers. The precise ordering of D9S280, PTCH, FACC, FBP1 and D9S287 remains unresolved. Although the order of these markers shows discrepancies on the YAC maps, data from the CEPH breakpoint map in two phase known recombinants give the order Cen-D9S196-D9S280-FACC-D9S287-Tel. This is in agreement with other previously published maps (Povey *et al.* 1994).

The YAC contig surrounding the DYS gene has been expanded to 1.3 Mb in distal 9q31 (Slaughaupt *et al.*). An 800 Kb cosmid contig begins 300 Kb proximal to D9S1677 and extends through D9S311. Recently a BAC contig has been constructed that spans the interval D9S261 through D9S310. In addition to this 13 new markers were added to the existing breakpoint map between D9S180 and D9S59 (Slaughaupt *et al.*).

Disease genes in 9cen-9q31

Hereditary sensory neuropathy type I (HSNI)

HSNI was mapped to an 8 cM region flanked by D9S318 and D9S176 on 9q22.1-22.3. Multipoint analysis gave the most likely location at D9S287 (Nicholson *et al.* 1996). This dominant disorder causes loss of sensation, especially to pain and temperature, and is the most common of a group of degenerative disorders of sensory neurons.

Familial dilated cardiomyopathy (CMDIB)

A large kindred with autosomal dominant familial dilated cardiomyopathy (CMDIB) was assigned to 9q13-q22 by linkage analysis between D9S153 and D9S152 (Krajcinovic *et al.* 1995). FDC is characterised by impaired myocardial contractility and ventricular dilatation.

Hearing loss

Neurosensory nonsyndromic hearing impairment (DFNB7) was mapped in two consanguineous families from India to 9q13-q21 (Jain *et al.* 1995). A second autosomal recessive nonsyndromic hearing loss was mapped to 9q13-q21 in two inbred Bedouin kindreds from Israel by Scott *et al.* (1996). Scott and colleagues show linkage to D9S922 and D9S301 on 9q. The disease locus lies between the markers D9S915 and D9S927. Haplotype analysis shows segregation with a common

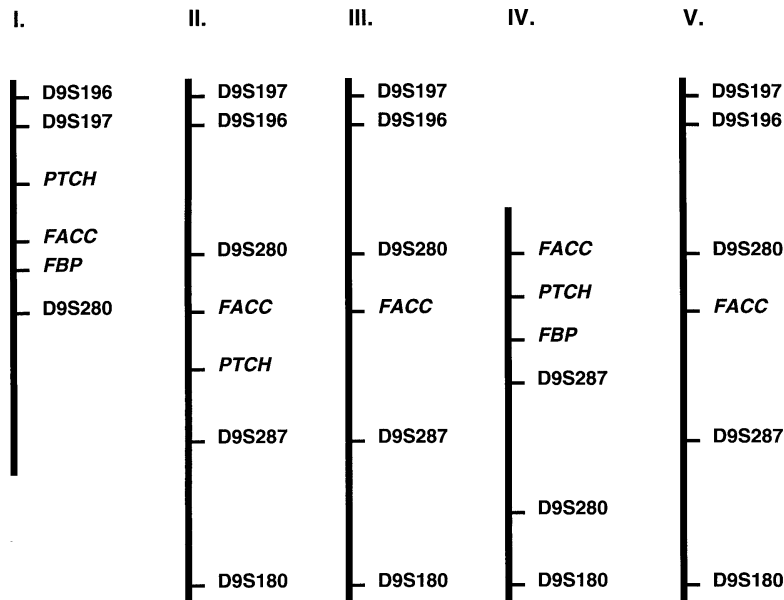


Fig. 1. Schematic map showing the conflicting results for the relative order of markers from 9q22. **I-IV** show physical results from YAC maps, while **V** shows the CEPH breakpoint map order (**I.** Johnson *et al.*, 1996; **II.** Hahn *et al.*, 1996; **III.** Morris and Reis, 1994; **IV.** Lench *et al.*, this meeting). Not shown to scale.

haplotype in two kindreds at markers D9S927, D9S175 and D9S284, supporting the belief that both families inherited the disease gene from a common ancestor. The positioning of this locus is distal to that described for DFNB7. Either this represents a novel form of neurosensory non-syndromic hearing loss, or it positions the DFNB7 locus to a more telomeric region. There is a deafness (dn) locus in the mouse which maps to mouse chromosome 19 with flanking loci syntenic to 9q11-q21.

CMSF Human homolog of rat NOR1 gene.

A segment on chromosome 9q22 is fused to the EWS (Ewing sarcoma gene) on chromosome 22 in a recurrent translocation 9;22 which is observed in extraskeletal myxoid chondrosarcomas (Gill *et al.* 1995). The segment on chromosome 9 which gives rise to the fusion gene with EWS was reported to be a homolog of the rat NOR1 gene (Clark *et al.* 1996), who noted further that it is a member of the steroid/thyroid receptor gene super family. In the EWS-CMSF fusion protein the C terminal RNA binding domain of EWS is replaced by the entire CMSF protein.

Friedreich's ataxia (FRDA)

The gene for the autosomal recessive condition Friedreich's ataxia (FRDA) was identified by Campuzano *et al.* (1996) to be X25 on 9q13. A few FRDA patients were found to have point mutations in X25 but the majority were homozygous for an unstable (GAA)_n trinucleotide expansion in the first X25 intron. A severely reduced X25 mature mRNA (expected to result in a low level of frataxin) in the spinal cord, heart and pancreas is probably the primary cause of neuronal degeneration, cardiomyopathy and increased risk of diabetes. Carvajal *et al.* (1996) reported that the X25 (frataxin encoding gene) described by Campuzano *et al.* (1996) comprises part of a gene that they described as STM7. They reported that the STM7.1 transcript has phosphatidyl inositol-4-phosphate 5-kinase activity, similar to the catalytic domain of the ataxia telangiectasia gene. Durr *et al.* (1996) analysed 187 patients with autosomal recessive ataxia. They reported that larger GAA expansions correlated with earlier age of onset, with the frequency of cardiomyopathy

and with loss of reflexes. They concluded that test of the GAA repeat expansion is useful for diagnosis, prognosis, and counselling.

Nevoid basal cell carcinoma syndrome (NBCCS)

The gene for NBCCS was identified by mutations in a gene with strong homology to the drosophila segment polarity gene *patched* (Hahn *et al.* 1996; Johnson *et al.* 1996). NBCCS is characterised by multiple basal cell carcinomas of the skin, jaw cysts, other tumours and skeletal abnormalities. Hahn *et al.* found that four unrelated patients had deletions and insertions in *patched* (PTCH) that resulted in frameshifts and two had mutations leading to premature stop codons. Johnson *et al.* reported one patient with a 9bp insertion while another had an 11bp deletion. Both groups investigated the possibility of PTCH involvement in the more common sporadic BCC in patients not affected by NBCCS. Hahn *et al.* show that in two sporadic cases of BCC with allelic loss of the NBCCS region had inactivating mutations in the other allele. Johnson *et al.* found a C-T transition that changed a Leu, conserved in drosophila, chicken, mouse and humans to a Phe.

Other work on tumour suppressor loci in 9cen-9q31

Previously allelic loss of proximal 9q was reported in basal cell carcinomata, ovarian cancer and bladder cancer (Pericak-Vance *et al.* 1995). Lench *et al.* (1996) report the loss of DNA markers in odontogenic keratocysts on 9q22.3-q31 in three sporadic cases where the patients had no family history or symptoms of NBCCS. Odontogenic keratocysts of the jaw are a common symptom of NBCCS (Gorlin, 1987). The presence of inactivating mutations in the human PTCH gene for sporadic forms of odontogenic keratocysts has not been shown.

Further allele loss of 9q22.3 in human non-melanoma skin cancer was reported by Holmberg *et al.* (1996). In eight sporadic cases of basal cell carcinoma loss of markers between D9S196 and D9S180 was observed. For squamous cell carcinoma a frequency of 50% LOH was observed for D9S180 and suggest the presence of a tumour suppressor gene important in development of squamous cell cancer within the D9S196-D9S180 interval or distal of it. Others have shown loss of 9q31-q32 distal of D9S180 in squamous cell carcinomas of the oesophagus (Miura *et al.* 1996). Miura and colleagues isolated six new microsatellite markers at 9q31-32 and narrow a region commonly deleted in squamous cell cancer to 200 Kb between KM9.1 and D9S177.

Devlin *et al.* (1996) present evidence for three possible tumour suppressor loci involved in ovarian cancer on chromosome 9. Thirty-three ovarian tumours were investigated for LOH on 9 and it was detected in 26 cases. The region commonly deleted on 9p was shown to be between D9S126 and D9S736 at 9p21. Large regions of 9q were also shown to be deleted.

Fukuyama congenital muscular dystrophy (FCMD)

Toda *et al.* (1996) utilized linkage disequilibrium mapping to further refine the map location of FCMD in the Japanese population. They determined that the markers D9S2105, D9S2107, and D9S172 are closest to the FCMD locus. Haplotype analysis carried out using these markers revealed that most FCMD bearing chromosomes are derived from a single ancestral founder. Toda *et al.* (1996) reported that these markers can be used for the diagnosis of sporadic cases of FCMD in the Japanese population. They reported further that the FCMD gene most likely lies within a 100 Kb region containing D9S2107. Toda *et al.* (1996) considered that the receptor tyrosine kinase, MuSK, described by Valenzuela *et al.* (1995), is a possible candidate for the FCMD gene, since this gene is expressed in muscle and brain and it maps to chromosome 9q31.3-9q32.

A mild form of the brain malformation Cobblestone Lissencephaly (CL) is present in FCMD. Patients with Walker-Warburg syndrome (WWS) suffer from a severe form of CL. FCMD and WWS consist of congenital muscular dystrophy and complex malformations of the brain and eye.

Both disorders have been shown to inherit the same 9q31–32 alleles in two Japanese families and could be genetically identical. Northrup *et al.* investigated the possibility of WWS being allelic to FCMD by testing several markers from the 9q31–32 region on seven families with one or more children affected by WWS. Linkage of FCMD to WWS was not excluded.

New and refined placements of other genes on 9cen–9q31

The gene for the human nuclear cap binding protein, NCBP, was mapped by somatic cell hybrids and cosmid hybridization to 9q22 adjacent to the human gene for xeroderma pigmentosum complementation group A (XPA) and is conserved adjacent to mouse xpa on MMU4 (Chadwick *et al.* 1996). NCBP is important for the pre-mRNA splicing and the transport of RNA from the nucleus to the cytoplasm (Ohno *et al.* 1990).

The gene for cyclin dependent kinases regulatory subunit 2 (CKS2) was mapped to 9q22 by FISH (Demetrick *et al.* 1996). CKS2 binds to the catalytic subunit of cyclin dependent kinases, and is essential for their biological function (Nigg, 1993).

Lench *et al.* and Chadwick *et al.* placed the human tropomodulin gene (TMOD) adjacent to the STS D9S780 close to the NCBP gene. TMOD is a tropomyosin binding protein that regulates the elongation and depolymerization of tropomyosin coated actin filaments (Weber *et al.* 1994).

Lench *et al.* mapped the human p57 gene which codes for the Coronin protein to 9q22. Coronin binds to F-Actin and is required for normal motility and participates in cytokinesis (Hostos *et al.* 1991).

Chadwick *et al.* presented data for the mapping of the Keratin-18-like3 gene (KRT18L3). KRT18L3 was mapped to chromosome 9 by somatic cell hybrids (Romano *et al.* 1988). KRT18L3 is located less than 1 Kb upstream of the XPA gene on 9q22. Comparisons of the KRT18L3 genomic sequence to human KRT18 showed loss of the AUG start codon and premature stop codons suggesting that KRT18L3 is a pseudogene (Chadwick *et al.* submitted).

Two novel genes GRC-7 and GRC-14 were mapped downstream of the FACC gene (Chadwick *et al.* unpublished). A third novel gene GRC-3 was mapped close to the D9S180 marker.

Isoleucyl-tRNA synthetase (IARS) was localised to 9q21 by FISH (Nichols *et al.* 1996). This is in agreement with Whitworth *et al.* (unpublished) who fine mapped an EST for IARS (Acc.No. d28473.gb_pr) by PCR across a set of radiation hybrids with well defined breaks in 9q to 9q21. The 17- β -hydroxysteroid dehydrogenase 3 (HSD17B3) gene was fine mapped by Lench *et al.* close to the D9S1809 marker. HSD17B3 when mutated causes pseudohermaphroditism (Geissler *et al.* 1994).

A total of 10 ESTs were fine mapped to the D9S197–D9S180 interval (Hahn *et al.* 1996): R14225, T88697, R14413, R06574, R17127, R39928, T11435, Z43835, R16281 and yo20g05.s1. This is in agreement with Lench *et al.* (unpublished).

Montermini *et al.* (1995) identified the gene X104 as the human tight junction protein ZO-2 when characterizing 150 Kb of the FRDA critical region on 9q13. A second gene, PRKACG, encoding for the α -catalytic subunit of the cAMP-dependent protein kinase was placed between FR8 and FR6 on 9q13.

REPORT ON 9Q32–9QTER

Group co-ordinator David Kwiatkowski

Physical and genetic mapping 9q32–9qter

A subgroup of ten individuals gathered to consider the state of the map of 9q34, and to prepare an update to the consensus map of this region. The region continues to be exceptionally gene and

STR marker rich, with 59 known genes and over 200 STR markers assigned. There was little change to the map in the region of HXB. Immediately below HXB on the map there is a cluster of 18 STR markers without genetic distance separation. The physical and/or genetic basis for this clustering is unknown. The map below this region has been significantly improved (Knowles *et al.*). D9S275, D9S195, D9S258, D9S103, and AFMA239XA9 are known to be part of a 2-fold deep YAC contig, with the first four of these in the order given. GSN and D9S123 are likely to be connected on the telomeric side of this contig in a 1-fold deep extension. Considerably greater resolution has been given to the region below GSN, due to the efforts of MacIntosh *et al.* The NPS1 gene is now localized to a 1 cM interval (S60–AK1), and the following order of markers is secure, due to informative events in either CEPH or NPS1 kindreds: D9S282–(S266, S1829, S113)–S60–(S1821, S112, S315, S1798)–AK1–END–SPTAN1–S1144–S61–(S260, S121, S752)–S63–(S120, S903)–PTPA–(S65, S115)–S62–S159–S63–(ASS, ABL). Considerably greater resolution has been given to the region between S149 and S114, the consensus critical region for the TSC1 gene (Wolfe *et al.*, Kwiatkowski *et al.*, Gilbert *et al.*, Fried *et al.*). The order of markers and genes in this region is now known at the 10 Kb level: S149–S2127–S2126–S1830–S2133–S1199–CEL–S1198–S2134–ABO–SURF1–SURF6–SURF5–RPL/7A–SURF1–SURF2–SURF4–S164–S1793–S968–S150–DBH–S122–S10–S66–VAV2–S114. A sequence ready contig now covers almost all of this region, and the Whitehead Genome Center has begun sequencing of cosmids from this region: -4446_7fab-2ba_1863-5dde_5d9a – Relatively little change has occurred in the region telomeric to S114 in recent months.

Additional disease mapping in 9q32–9qter

Tuberous sclerosis

Au *et al.* (1996) reported results of analysis of chromosome 9 markers in a large TSC family where linkage to chromosome 16 (TSC2) had been excluded. Analysis of haplotypes showed a cross-over event at the A6 locus. This is a highly polymorphic locus 100Kb proximal to D9S114 and 200 Kb distal to D9S66. The cross-over event placed the TSC1 locus centromeric of A6. This cross-over event eliminated COL5A1 as a candidate gene. Henske *et al.* (1996) reported that 57% of angiomyolipomas and rhabdomyomas from 28 TSC patients showed LOH for 16p13. Out of 47 patients analyzed, LOH for chromosome 9q34 was only found in 1 patient. Carbonara studied LOH in both the TSC1 and the TSC2 loci in 20 hamartomas. Loss of heterozygosity at either locus was found in 7 out of 14 cases of sporadic TSC and in 1 out of 4 familial cases. Loss of heterozygosity at the TSC2 locus was significantly more frequent in the sporadic patients. They tested 7 other tumour suppressor gene regions in the TSC hamartomas and found no evidence of LOH in these regions.

Green *et al.* (1996) demonstrated clonality in 12 out of 13 hamartomas from females with TSC. They examined differential methylation of the HpaII restriction site adjacent to the androgen receptor repeat polymorphism on Xq11–12. Using this method they demonstrated a skewed pattern of X inactivation in 12 hamartomas.

Ehlers Danlos syndrome

Burrows *et al.* (1996) observed tight linkage of the COL5A1 locus to a mixed Ehlers Danlos syndrome type I/II phenotype in a 3 generation family; the lod score was 4.07 at theta 0. Burrows reported that the variation in expression in this family suggested that EDS1 and II are caused by mutations at one locus and linkage data supported the hypothesis that mutation in COL5A1 can cause both phenotypes. Wenstrup *et al.* (1996) examined 4 families with EDS1 and reported that EDS1 cosegregated with COL5A1 in two families. In one of these families they demonstrated that affected individuals were heterozygous for a 4 bp deletion in intron 65 and this led to a deletion of

344 basepairs of exon 65 in the processed mRNA. In two other families linkage of EDS1 and COL5A1 was excluded. Wenstrup *et al.* (1996) concluded that EDS types I and II constitute a clinical molecular spectrum which is genetically heterogeneous.

SUBGROUP ON BLADDDER CANCER GENES

Group coordinator: Margaret Knowles

Previous LOH studies have shown that there may be multiple tumour suppressor loci on 9q in addition to the locus at 9p21. Further deletion mapping studies have shown that several bladder cancers have localised deletion at 9q33 or 9q34. The deleted region at 9q33, named as Deleted in Bladder Cancer 1 (DBLC1), is considered to be near to D9S195, and the region at 9q34 may be overlapped with the TSC1 locus (Habuchi and Knowles, 1996).

Bartlett *et al.* reported that in bladder tumours from patients with known outcome, 3 hotspots for LOH could be identified at CDKN2, D9S15 and ABL. These losses were independent of tumour stage but loss at ABL was associated with high grade disease. Investigation of the pericentromeric classical satellite (9q12) by FISH showed 30% (6/20) of patients with subsequent disease recurrence demonstrated loss of chromosome 9 in their primary and all subsequent TCCs analysed. No patients with non-recurrent disease showed this loss ($p = 0.047$). In addition, LOH occurred more frequently at D9S67 (q34.3) and ABL (q34.1) in TCCs from patients with recurrent, progressive disease, indicating that loss at 9q12 may predict disease recurrence, whilst loss at q34 may predict tumour progression.

SUMMARY OF DISEASE LOCI

Group co-ordinators: Moyra Smith and Jean Frezal

Advances in understanding of disease-causing genes on chromosome 9 in the past year and at the workshop are included in the relevant sections. Table 1 shows a complete list of known disease-causing genes on chromosome 9.

BREAKPOINT MAPPING

Group co-ordinators Sue Povey and John Attwood

Six abstracts, representing in some cases more than one group (Kwiatkowski *et al.*; Ozelius *et al.*; Haines *et al.*; Slangenaupt *et al.*; Rebello *et al.* and Pericak-Vance *et al.*) present data from the concerted breakpoint mapping effort. Data have also been contributed by Hope Northrup and by Rob Furlong. These results have been incorporated into the overall map but, because of some difficulties in the data formats and the need to look at some of the data again, are not yet visible in the meiotic breakpoints displayed in *ACEDB* on the chromosome 9 home page. The program which is used to generate and draw the breakpoints has recently been described (Attwood and Povey 1996) and it is hoped to complete this analysis soon.

Fig. 2 shows a sample breakpoint obtained from the WEB version of *ACEDB*. This shows the evidence that FACC is proximal to D9287, as indicated by CEPH individual 1416-09. The haplotyped system Galton:D9S287 contains three loci (D9S287, D9S1851, D9S1809) which have not so far been found to recombine within the CEPH families. However, in this example only one member of that haplotyped system was informative (or perhaps the others were not tested). Thus FACC can be placed proximal to D9S287, but the position with respect to D9S1851 and D9S1809 cannot be deduced from these data alone.

416-09-P-1

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Person      1416:09
Map         Galton BP      Ends      Left      93
           KcM           1.5      Right     94.5
Flanked_by FACC          D9S287
Gap         Map_intervals      1
Score      Best      1090
           Worst      880
Chrompic    p<11i-11-11---1i1-11-i1111111-1--1-111--1
           11-1111-i-iii11111111--1-1i--11i1i111--
           11i1i1111//0-0000o00--o000-00-00o00o--o0
           0?00o-00
Above      D9S1781      3      Galton:D9S1781      [11-] D9S1781ge D9S1841ge
           D9S151      3
           D9S134      1.5      Galton:D9S134      [1-1i11] D9S134 S12A D9S197ge D9S1803ge
           D9S196      1.5      Galton:D9S196      (D9S12K)
           D9S280      0.8      Galton:D9S280      [11] D9S196ge 289wh1
           FACC      0          Galton:D9S280      [1-] D9S280ge
Below      D9S287      0      Galton:D9S287      [0--] D9S287ge
           D9S272      0.7      Galton:D9S272      [-]
           D9S180      1.4      Galton:D9S180      [00--000] D9S180ge S22A D9S176ge
           D9S1690      4.7      Galton:D9S127      D9S1857ge D9S1783ge
           D9S127      4.7
    
```

Fig. 2. Details of a breakpoint in CEPH individual 1416:09

Table 1. Table of disease genes on chromosome 9

Gene symbol	Putative gene	Location
SRA	46XY sex reversal	9pter-p22
SLC1A1(EAAC1)	Dicarboxylicaminoaciduria glutamic aciduria	9p24
OVC	Oncogene ovarian adenocarcinoma	9p24
VLDLR	Very low density lipoprotein receptor	9p24
TYRP, CAS2, OCA3	Tyrosinase related, homolog of mouse brown gene	9p23
IFNA1	Interferon deficiency	9p22
LALL	Lymphoblastic leukemia with lymphomatous features	9p22-p21
MLLT3	Acute myeloid/lymphoid or mixed lineage leukemia with 9p translocation	9p22
GLDC, HYG1, GCSP	Glycine dehydrogenase, decarboxylating isolated non-ketotic hyperglycinemia	9p22
CDKN2A, P16, MTS1	Cyclin dependent kinase inhibitor 2A (inhibits CDK4) Melanoma	9p21
CDK2B, P15, INK4B	Cyclin dependent kinase inhibitor 2B	9p21
AMCD1, DA1	Arthrogryposis multiplex congenit distal type	9p21-q21
GALT	Galactosemia	9p13
MROS	Melkerson Rosenthal facial swelling	9p11
IBM2	Inclusion body myopathy	9p1-q1
VMCM	Venous malformations multiple cutaneous and mucosal 'blue rubber bleb' syndrome	9p
MFT1	Multiple familial tricoepithelioma	9p21
CHH	Cartilage-Hair Hypoplasia	9p13
CMPD1	Cardiomyopathy familial dilated	9q13-q22
DFNB7	Deafness autosomal recessive	9q13-21.1
FRDA	Friedreich ataxia Frataxin	9q13
CSMF	Chondrosarcoma, extra-skeletal, fused to EWS, member of steroid thyroid receptor super-family	9q22
ALDOB	Aldolase B, fructose biphosphatase fructose intolerance	9q22

Table 1 (*cont.*)

Gene symbol	Putative gene	Location
FBP1	Fructose diphosphatase deficiency hypoglycaemia, metabolic acidosis	9q22.3
HSD17B3	Hydroxysteroid (17beta) dehydrogenase 3 male pseudohermaphroditism with gynecomastia	9q22
HSN1	Hereditary sensory neuropathy	9q22.1–q22.3
FACC	Fanconi anemia, complementation group C	9q22.3
PTCH, BCNS, NBCCS	Patched, drosophila Homolog, Gorlin basal cell nevus syndrome	9q22.3
ESS1, MSSE	Self-healing squamous epithelioma Ferguson–Smith type	9q31
TAL2	T cell acute leukaemia, 33 kb from breakpoint in t(7:9)	9q31
DYS	Familial dysautonomia, Riley–Day	9q31–q33
FCMD	Fukayama muscular dystrophy	9q31–q33
MUSK	Receptor tyrosine kinase, muscle specific	9q31.3–q32
AFDN	Acrofacial dysostosis, Nager type	9q32
DYT1	Torsion dystonia autosomal dominant	9q32–q34
SAR, SARD	Sarcosine dehydrogenase sarcosinemia	9q33–q34
ABL 1	Abelson oncogene, fusion with BCR1 in chronic myelogenous leukaemia	9q34.1
ALAD	delta amino levulinic acid dehydratase acute hepatic porphyria	9q34
AK1	Adenylate kinase 1, haemolytic anemia	9q34.1
ASS	Argininosuccinate synthase, Citrullinemia	9q34.1
C5	Complement, C5 deficiency	9q34.1
CRAT, CAT1	Carnitine acetyl transferase deficiency	9q34.1
CAN, CAIN (D9S46E)	Cain, fusion gene with DEK in acute myelogenous leukaemia	9q34.1
END, ENG, HHT, ORW	Hereditary haemorrhagic telangiectasia Osler–Rendu–Weber, endoglin	9q34.1
EPB72	Erythrocyte membrane band 7.2 stomatin, Stomatocytosis	9q34.1
NPS1	Nail-patella syndrome 1	9q34.1
XPA	Xeroderma pigmentosum	9q34.1
GSN	Gelsolin, amyloidosis, Finnish type	9q34
DBH	Dopamine beta hydroxylase, deficiency	9q34
TSC1	Tuberous sclerosis I	9q34
EDS I and II COL5A	Ehlers–Danlos, types I and II some families linked to COL5A with COL5A mutation	9q34
SET	SET, fused with Cain in acute undifferentiated leukaemia	9q34
ITO	Hypomelanosis of Ito	?9q33–qter

GLOBAL CONCERNS

Group co-ordinator Jonathan Haines

There was universal agreement that the vast amount of genetic (meiotic), physical (contig), and radiation hybrid (EST, STS) data being generated on a whole-genome basis is of extreme value to the community. However, integration of these various sources of data was difficult to impossible.

Two primary hurdles were identified. The first was the sheer volume of data, which makes the traditional ways of resolving order by human discussion impractical (certainly in the time available!). At this meeting the data were viewed in the Multimap facility of *ACEDB* (managed by John Attwood) and also in the Location Database (Andy Collins) as well as GDB (presented by Chris Porter), GID (presented by Jean Frezal), and the SIGMA map (curated by Julia White). Prior to the meeting some map comparisons and integrations providing graphical output were produced by

Stan Letovsky (at GDB). It was agreed that some automation is necessary to cope with the volume of data although in small regions specialist human knowledge is invaluable. It was also thought that automated tightening methods (such as refining cytogenetic locations by deductions from other information) although valuable, should remain distinct from primary data.

It was clear that use of appropriate databases could make the wealth of data available to all. However, the second problem seems more intransigent. This was the different naming systems being used. Each project has used its own designations for its probes/primers/loci, with little attention to maintaining aliases which would allow cross-referencing between databases. Any single locus, for example, might be represented in different databases as a probe name, a primer name, a D#, a GDB accession number, A WI (Whitehead Institute) number, an AFM (Genethon) number, an EST number, or a gene name. There was general dismay that the D# naming system was dropped as a primary name in GDB, and that its use seems to be in decline. There was a consensus shared by all groups (see below) that a consistent naming system be used.

INFORMATICS

Group co-ordinators Julia White and John Attwood

An integrated map of chromosome 9 has been maintained for the past 2 years using the SIGMA software. This has proved to be a very useful tool, especially at the Single Chromosome Workshops. However the software does have some disadvantages, and the main points to be addressed for this workshop were as follows.

(1) The computing resources required to run SIGMA mean that it is not easily accessible to many of the researchers in the chromosome 9 community. This means reliance on Postscript files and printouts, with only limited views of the data, between Workshops.

(2) Order and ambiguities in placement of markers in the SIGMA map can be seen best at high magnifications, but these are difficult to produce as legible printouts. SIGMA can only easily export an order, with fractional distance information, for import into other databases (such as GDB and SCW9db), and the positional ambiguities are lost.

(3) SIGMA is a good graphical tool, but not so good as a database. Only a limited amount of related data can be linked to elements in the map.

(4) SIGMA itself is incapable of matching up new map objects with existing ones, even if the names are the same. The development of scripts for semi-automated entry of maps available in electronic form was necessary in order to be able to incorporate the increasing amount of map data available, with the minimum of effort.

These are problems which should be addressed by any future developers of graphical map tools.

The SCW9db database was developed for the Workshop by John Attwood using the *ACEDB* software package (Durbin & Thierry Mieg), and was an attempt to integrate maps and other data by consistent naming of map elements and other objects. It also contains a large number of hyperlinks to information in external databases such as GDB, OMIM, Genethon and dbEST. It can be browsed and queried remotely by means of Webace (J. Barnett, unpublished) a WWW interface for *ACEDB* databases, enabling it to be accessed from anywhere on the World Wide Web (which is widely used, with browsers available for all common computing platforms). The URL for viewing SCW9db is <http://www.gene.ucl.ac.uk/scw9db.shtml>. A number of recent genetic and physical maps were obtained in machine-readable form and converted into a common *ACEDB* format, at the same time using tables of aliases derived from GDB, Genethon and local knowledge to turn as many aliases as possible into an approved symbol so that maps and markers could be compared without the problems of the same marker having several different names. These maps

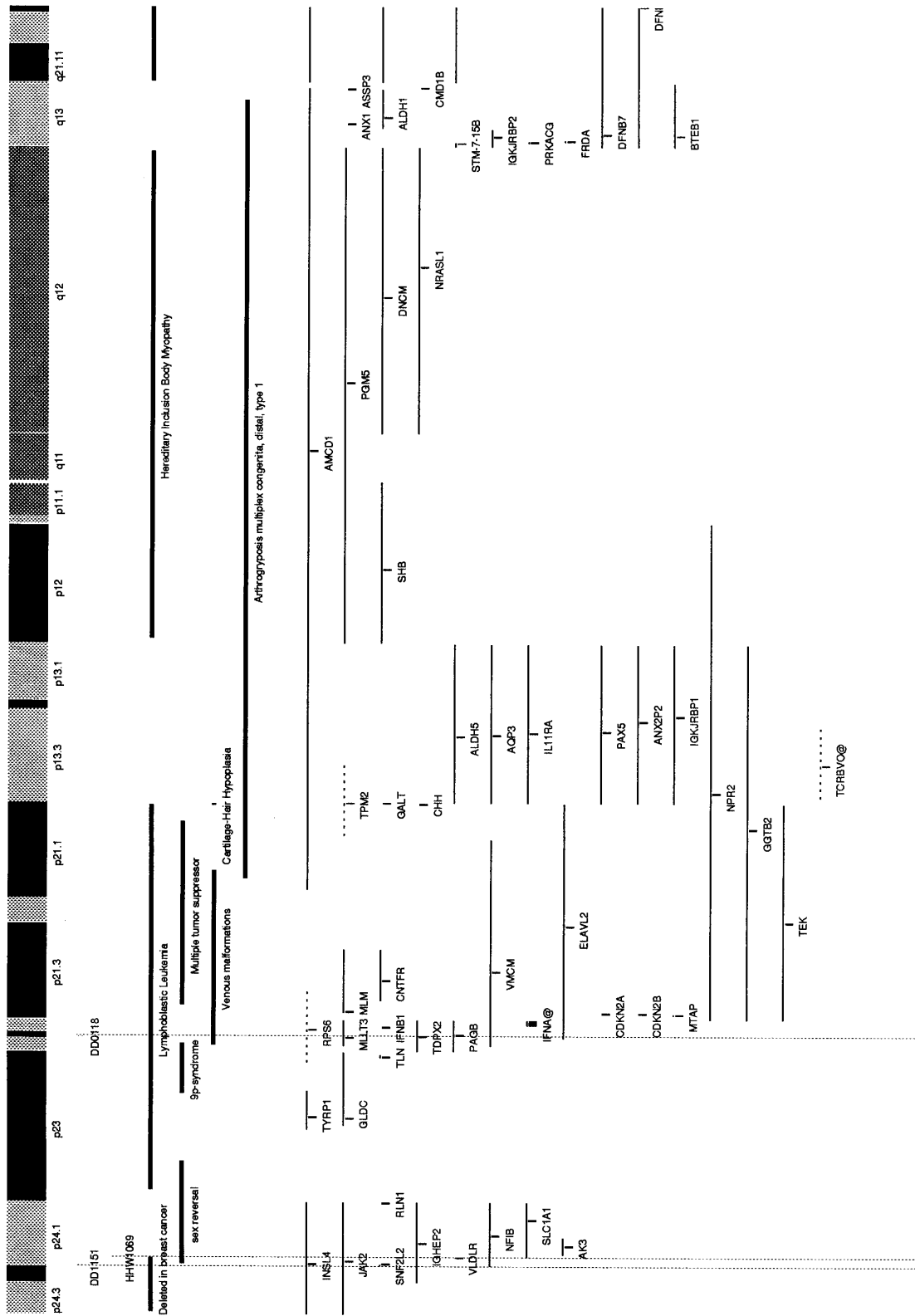


Fig. 3. For legend see facing page.

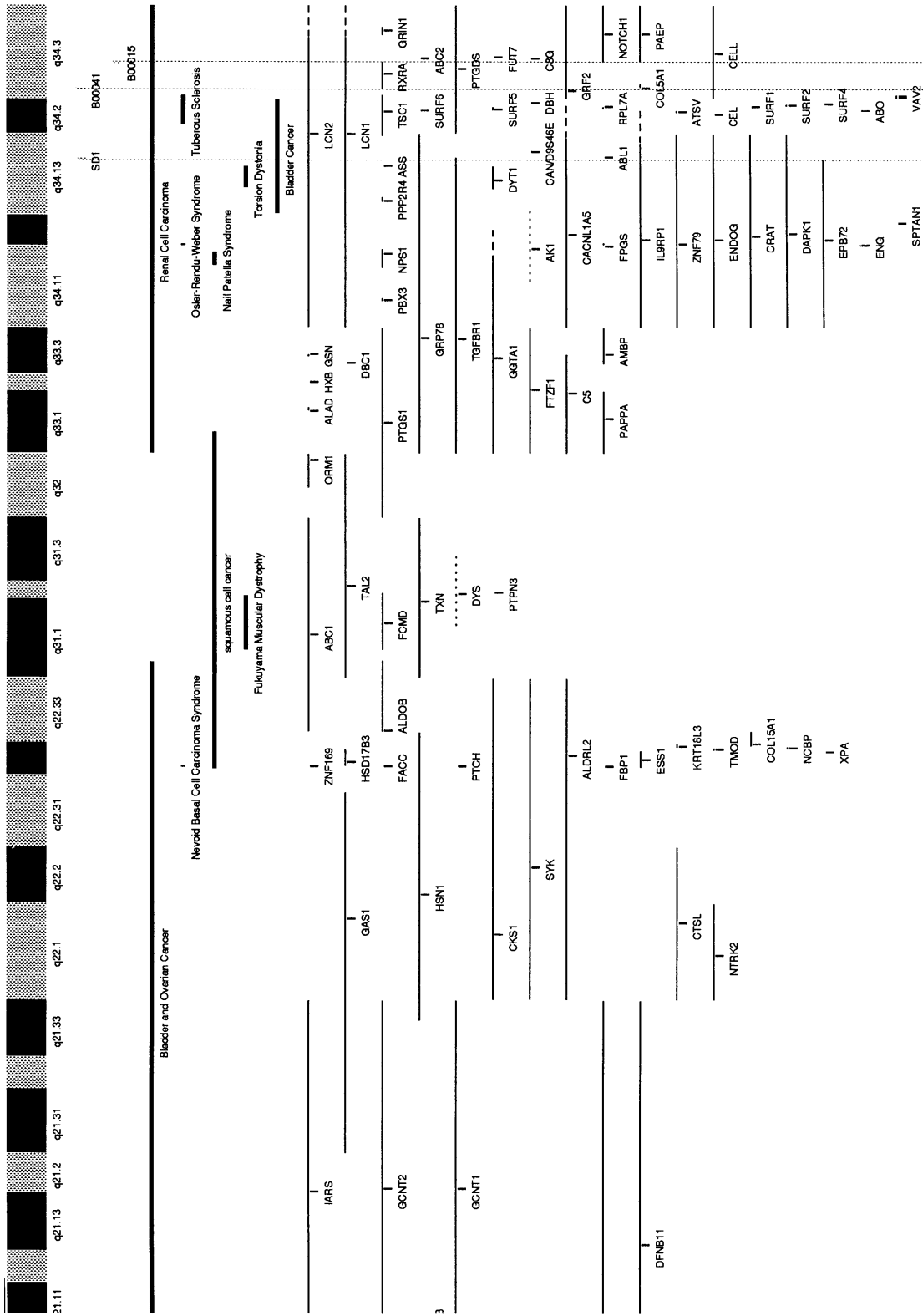


Fig. 3. SIGMA map of genes on chromosome 9.

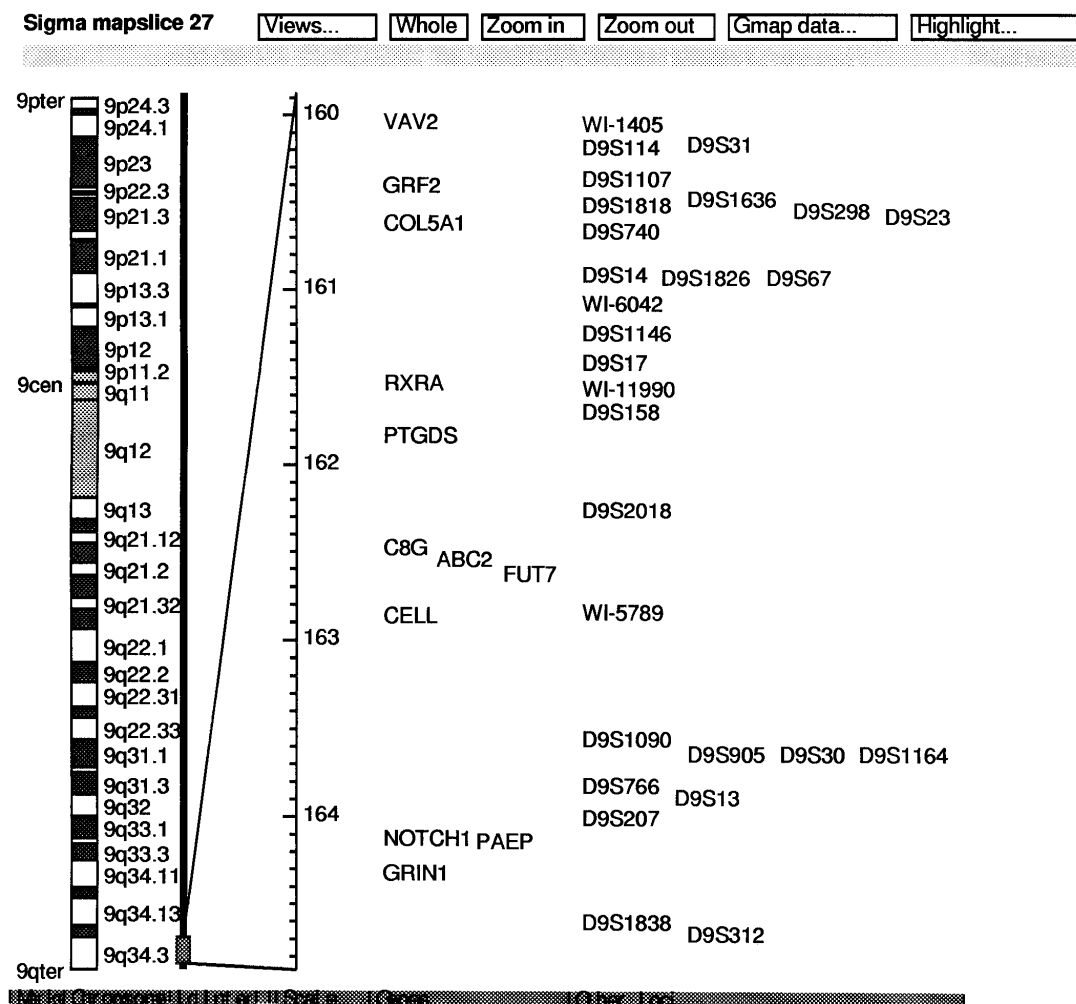


Fig. 5. Map slice No. 27 from chromosome 9 displayed in *ACEDB*.

were also used for entry in SIGMA, in order to take advantage of the standardised nomenclature. *ACEDB*'s Multimaps facility can also be used to align maps alongside each other and highlight differences in order, and this also becomes much more useful when the names have been rationalised.

A major advantage of incorporating data from diverse sources into an *ACEDB* database is that the elements automatically form links to related objects in the database. Links to external databases were obtained from IGD, GDB and RHdb and, wherever possible, were turned into live hyperlinks leading directly to the target record in the remote database. Examples of databases for which live links could be constructed are GDB, EMBL, RHdb, dbEST and TIGR. Even where live links could not be constructed, the accession numbers are shown and can be looked up manually. By means of these links, vastly more information than could be obtained and put into SCW9db has been made available, and is kept up-to-date without any additional effort.

As well as maps from GDB, the Galton Lab, Genethon, ICRF, LDB, Sanger Centre and the Whitehead Institute, all of the Galton Lab breakpoints were included, together with the genotypes from which they were derived, plus RHdb data known to be on chromosome 9. The Science96 Map was added after the workshop, as it was not available in time. It was decided to combine the map produced with SIGMA with the SCW9db database, so that the benefits of the workshop collaboration could be available on the Web.

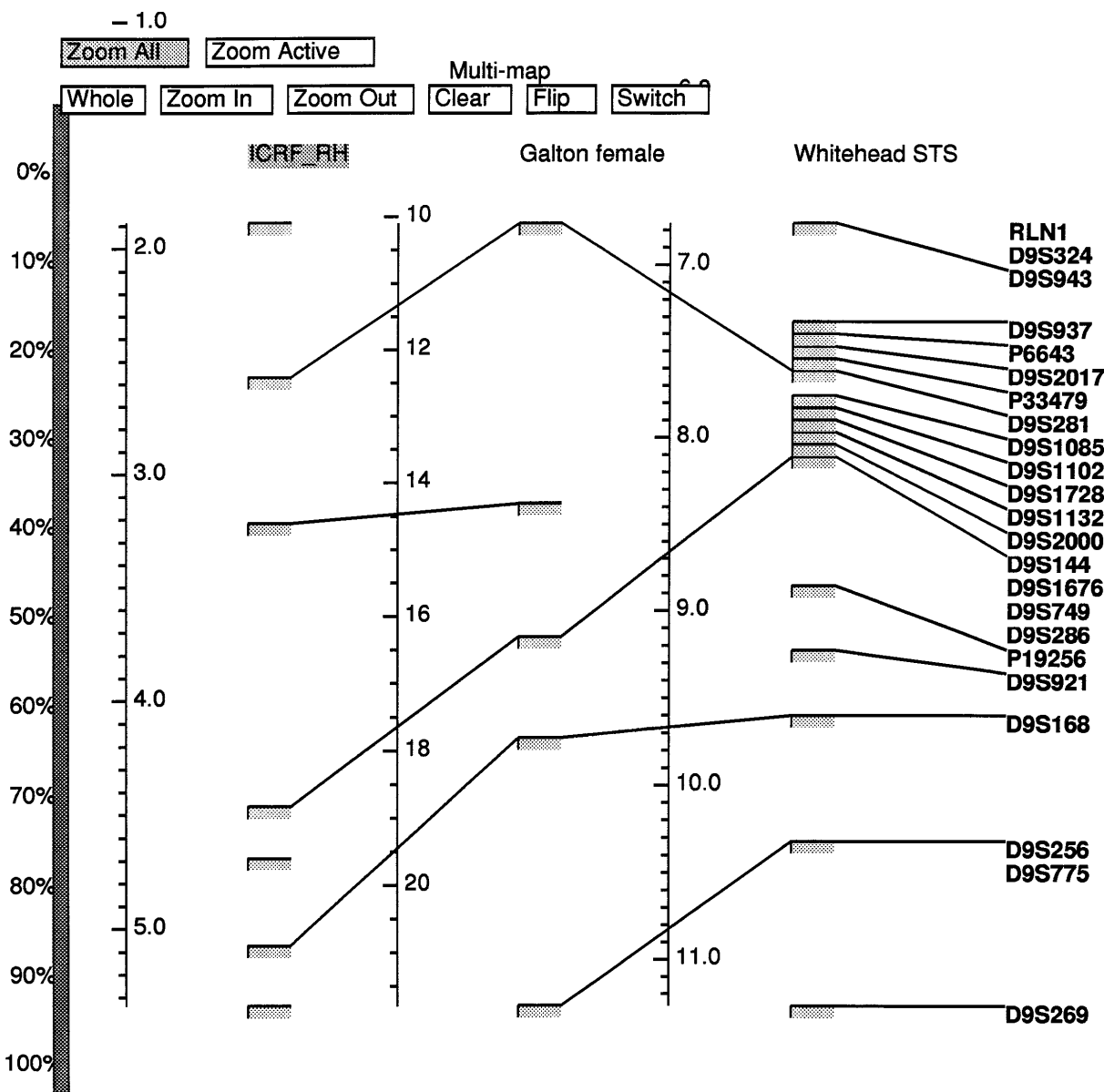


Fig. 6. Multi-Map comparison between a radiation hybrid map (Bouzyck *et al*), the female genetic map ('Galton female') and the Whitehead STS map. Note that lines connecting loci only appear when two loci are present on adjacent maps.

SCW9db can provide 'views' of all the maps in manageable 'map slices', enabling the user to look in detail at regions of interest and print these out if required. Since the current implementation of Webace does not permit the display of views, the Sigma map was broken into 28 overlapping slices, and these were added to the database so that they can be viewed over the Web. The main disadvantage to viewing the integrated SIGMA map through SCW9db is that positional ambiguities are lost and so it is no longer possible to tell how securely placed any marker is, relative to its neighbours. Also, it should be noted that the 'best' order is sometimes only plain at higher magnifications, due to space limitations when displaying many close markers.

We present illustrations of the maps which can be generated. Fig. 3 shows SIGMA output of all genes (not ESTs) localised on chromosome 9. Fig. 4 shows a SIGMA genetic map of chromosome 9 which combines Genethon and some older markers. Fig. 5 shows one of the mapslices described

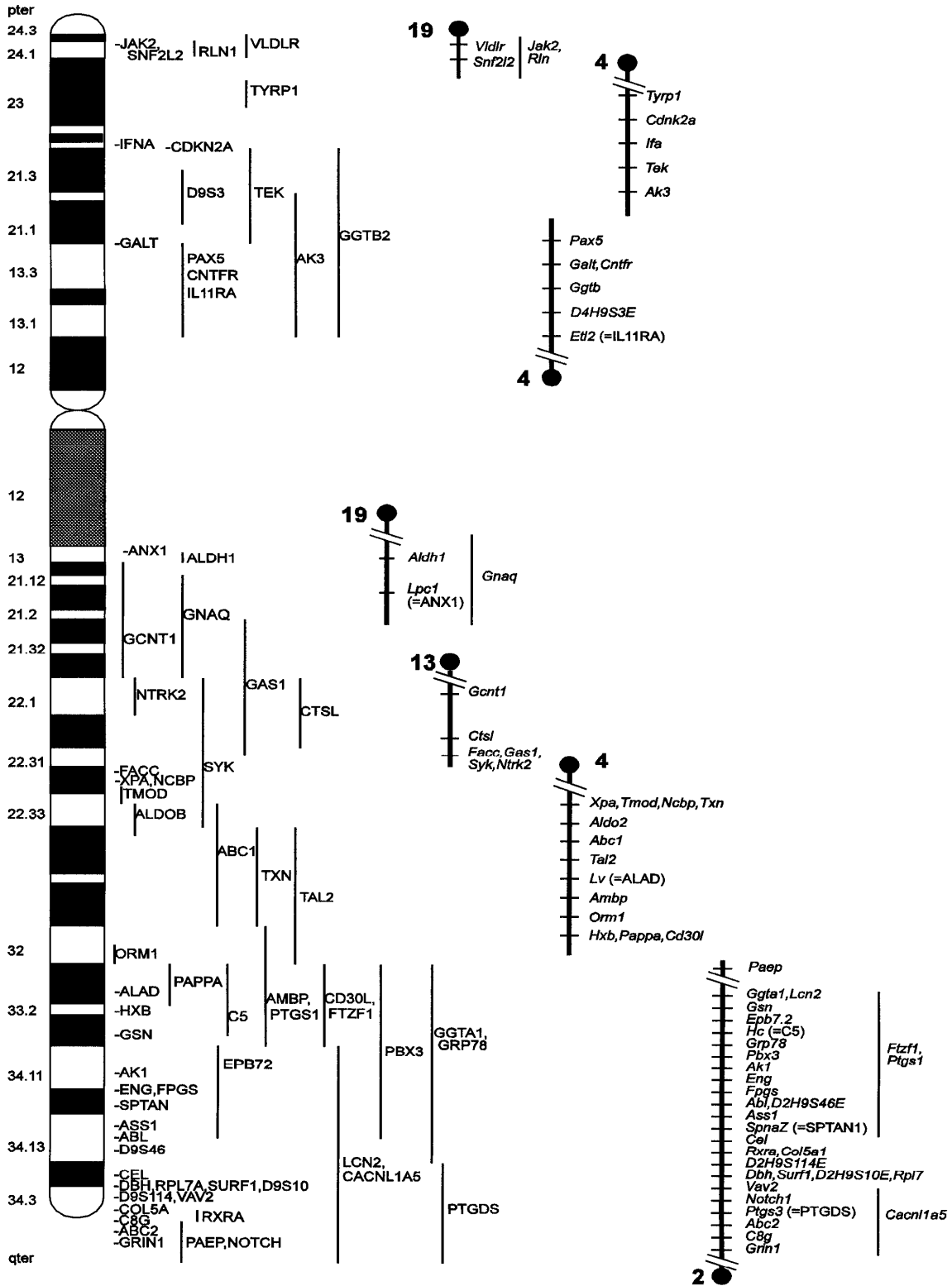


Fig. 7. Comparison of order of genes on human chromosome 9 (left) with the order on the syntenic mouse chromosomes (right). Only genes which have been localized to a reasonably limited part of a chromosome in both species have been included. The human chromosomal locations are taken from Fig. 3 of this report (sigma map), and the vertical bars represent the extent of the localization. The mouse loci are derived from a range of sources, including the relevant chromosome committee reports and many published and unpublished mapping studies (e.g. Pilz *et al.* 1995; etc). They are arranged to show order, and distances are

Table 2. *Mouse mutants in regions of synteny with HSA9*

HSA 9 syntenic region	Mouse symbol	Locus name	Pathology
9p23	<i>Tyrrp1</i>	Tyrosinase related protein-1	Brown coat colour
9p23	<i>Lyr</i>	Lymphoma resistance	Sensitivity to lymphomas
9p23	<i>dep</i>	Depilated	Skin and hair defect
9p21-p23	<i>Pt</i>	Pintail	Tail defect
9p13	<i>Cntfr</i>	Ciliary neurotrophic factor receptor	Motor neuron defects, perinatal lethality
9q13-q21	<i>dn</i>	Deafness	Deafness ^a
9q21-q22	<i>pcd</i>	Purkinje cell degeneration	Neurological degeneration, ataxia, retinal and olfactory cell degeneration, male sterility
9q21-q22	<i>mdac</i>	Modifier of <i>Dac</i>	Modifier of a second gene, <i>Dac</i> , and required for expression of digit defects
9q22-q32	<i>vc</i>	Vacillans	Tremor and gait defect, small, reduced viability
9q31-q33	<i>an</i>	Hertwig's anaemia	Anaemia, perinatal lethality
9q32-q33	<i>Och</i>	Ochre	Coat colour, mild balance defect, reduced viability
9q32-q33	<i>wi</i>	Whirler	Deafness, circling behaviour
9q32-q33	<i>Lps</i>	Lipopolysaccharide response	Immune defects
9q32-q33	<i>Dre</i>	Dominant reduced ear	Cranial and pinna defects, small
9q33-q34	<i>Lsr1</i>	Listeria resistance 1	Susceptibility to bacterial infection
9q33	<i>Hc</i>	Hemolytic component	Minor immune defects
9q33-q34	<i>stb</i>	Stubby	Skeletal defects, male sterility
9q34	<i>Notch1</i>	Drosophila notch gene homologue 1	Prenatal lethal in homozygous null mutant
9q34	<i>sar</i>	Sarcosinemia	Metabolic defect
9q34	<i>us</i>	Urogenital syndrome	Multiple skeletal defects, hair defects, urogenital defects ^b
9q34	<i>stu</i>	Stumbler	Neurological and gait defects

^a *dn* might be a homologue of DFNB7 or DFNB11, two recessive non-syndromic deafness loci.

^b *us* might be a homologue of NPS1, nail patella syndrome.

above, taken from the 9q34 region and displayed by SCW9db. Fig. 6 shows a multimap comparison of three primary maps, in a small region of 9p. The print is a poor substitute for the live version!

COMPARATIVE MAPPING :

Group co-ordinators: Karen Steel and John Edwards

Since the last report, many more genes have been mapped in both mouse and human, giving a more detailed view of the alignment of syntenic segments of mouse chromosomes to HSA9. These are shown in Fig. 7. In particular, refinement of localisations suggests that more re-arrangements during evolution have occurred than previously thought, including the following: Alignment of MMU4 markers with 9p suggests that two segments of MMU4 are represented here, but the polarity of the segment of MMU4 corresponding to 9p13-p21 is not clear. Alignment of genes on MMU19 with 9p24 and 9q13-q21, and of MMU13 with 9q21-q22 show no inconsistencies in order. Alignment of genes on a third segment of MMU4 with 9q22.32-q33 shows only one inconsistency, the

arbitrary. Vertical bars represent the approximate location of genes for which the order has not yet been clearly established. Black circles represent the positions of centromeres. The name of the human homologue is given where this is not obvious.

position of ORM1, which is placed centromeric of ALAD and HXB, while in the mouse, detailed haplotype analysis has positioned *Orm1* between *Lv* (= ALAD) and *Hxb*. Finally, the order of markers on MMU2 has been shown by detailed comparison with distal 9q to indicate at least two apparent inversions in order (Pilz *et al.*). Thus, the mouse markers *Dbh*, *Surf1*, and D2H9S10E appear to be inverted and exchanged with D2H9S114E, *Rxra* and *Col5a1*, and the order of the markers *Spna2* (= SPTAN), *Ass1* and *Abl* seem to be inverted, compared with the order of the human orthologues. Furthermore, *Paep* is located on distal MMU2, while on HSA9 it lies close to GRIN1, ABC2, CSG and NOTCH, the orthologues of which map to a more proximal region of MMU2.

Table 2 lists the mouse loci identified by visible mutations which are likely to have homologues on HSA9. Many of the genes have not yet been identified and so the human homologue has not yet been mapped, and the mouse loci may be poorly mapped in relation to known HSA9 genes, so some of the mouse mutations may eventually be found to correspond to locations on other human chromosomes. The approximate predicted position of each locus is shown in the left column.

Comparisons of chromosome 9 gene locations with positions in other species have been summarised by John Edwards in his abstract.

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