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Human chromosome 8

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SUMMARY The role of human chromosome 8 in genetic disease together with the current status of the genetic linkage map for this chromosome is reviewed. Both hereditary genetic disease attributed to mutant alleles at gene loci on chromosome 8 and neoplastic disease owing to somatic mutation, particularly chromosomal translocations, are discussed.

Human chromosome 8 is perhaps best known for its involvement in Burkitt's lymphoma and as the location of the tissue plasminogen activator gene, PLAT, which has been genetically engineered to provide a natural fibrinolytic product for emergency use in cardiac disease. Since chromosome 8 represents about 5% of the human genome, we may expect it to carry about 5% of human gene loci. This would correspond to about 90 of the fully validated phenotypes in the MIM7 catalogue.[1] The 27 genes assigned to chromosome 8 at the Ninth Human Gene Mapping Workshop (Paris, September 1987) thus represent a third of the expected number. In addition, six loci corresponding to fragile sites, three pseudogenes, and four gene-like sequences were reported.[2] Nevertheless, this is but a small fraction of the 500 to 5000 gene loci expected from a genome that contains between 10 000 and 100 000 genes.

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In an era when complete sequencing of the human genome is being proposed, it is appropriate for medical geneticists to accept the challenge of defining the set of loci that have mutant alleles causing hereditary disease. The fundamental genetic tool of linkage mapping can now be applied, owing largely to progress in defining RFLP markers.[3 4] This review will focus on genetic disease associated with chromosome 8 loci and the status of the chromosome 8 linkage map.

Disease loci

Inherited diseases that are thought to result from mutant alleles at defined gene loci on chromosome 8 are shown in table 1. Loci that have been regionally localised are shown in the figure. The *EBS1*, *SPH1*, and *VMD1* loci are defined by the disease associated alleles, while the *LGCR* locus, which is deleted in Langer-Giedion syndrome, is cytogenetically defined.

TABLE 1 *Chromosome 8 loci that may have disease-causing alleles.*

Disease	*Locus symbol*	*McKusick No*	*Localisation*	*Cloned DNA*	*RFLP*
Dominant disorders					
Epidermolysis bullosa	*EBS1*	13195	8q		
Hereditary thrombotic disease	*PLAT*	17337	8p12–q11·2	+	+
Langer-Giedion syndrome	*LGCR*	15023	8q24·11–q24·12		
Hereditary spherocytosis	*SPH1*	18290	8p21·1–p11·22		
Congenital goitre	*TG*	18845	8q24·2–q24·3	+	+
Vitelliform macular dystrophy	*VMD1*	15370	8q		
Recessive disorders					
Osteopetrosis with renal tubular acidosis	*CA2*	25973	8q22	+	+
Congenital adrenal hyperplasia 11B	*CYP11B*	20201	8q21	+	
Haemolytic anaemia	*GSR*	23180	8p21		
Hyperlipoproteinaemia	*LIPD*	23860	8p22	+	+

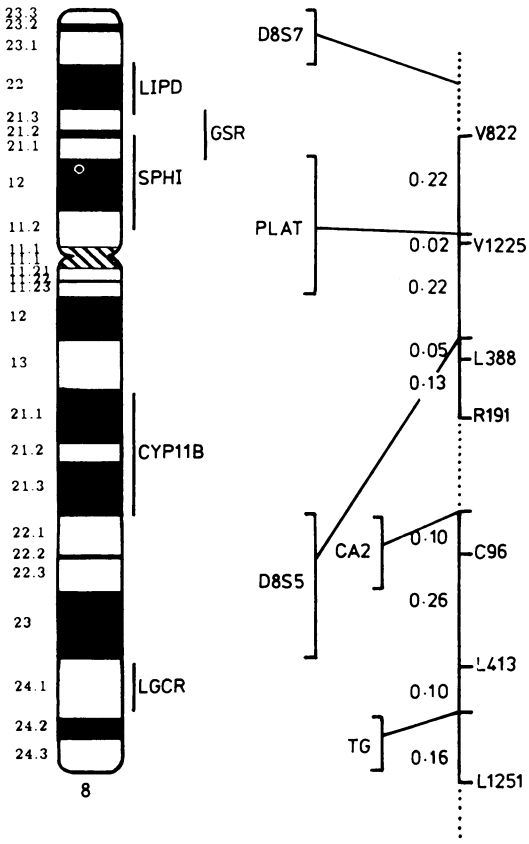

FIGURE *Regional localisation of disease loci and linkage map for human chromosome 8. Both the physical and linkage relationships are shown for the loci D8S7, PLAT, D8S5, CA2, and TG. The remaining linked loci are defined by proprietary probes of Collaborative Research Incorporated[161] (for clarity the CRI prefix is not indicated in this figure). The numbers indicate sex average recombination between adjacent loci. A broken line is used to indicate unknown linkage distance.*

The remaining loci are defined by their biochemical gene product which is abnormal or absent in the associated disease. Most of these structural gene loci have been cloned and RFLP markers defined, so that it is possible to show cosegregation of the disease with the structural gene locus. For most disorders this preliminary step towards defining the nature of the mutant allele(s) has not yet been accomplished.

EPIDERMOLYSIS BULLOSA SIMPLEX, OGNA TYPE (EBS1)

Dominantly inherited EBS, characterised by a generalised bruising tendency of the skin and hence considered to be a distinct variant from the EBS Koebner or EBS Weber-Cockayne type, was reported in a single, large Norwegian family.[5] The mutation was thought to originate in the community of Ogna in south-western Norway.[5] Among 246 family members, 93 cases were identified and close linkage to *GPT* established[6] (θ=0·05, Z=10·98). The recent placement of *GPT* and the chromosome 8 locus *TG*[7] on the same linkage group enables the *EBS1* locus to be assigned to chromosome 8. The possibility that these three dominant forms of EBS are allelic can now be evaluated by linkage analysis with DNA markers.

PLASMINOGEN ACTIVATOR DEFICIENCY AND THE PLAT GENE

Three families have been reported where defective release of vascular plasminogen activator, inherited as a dominant trait, was associated with a history of deep venous thromboses.[8–10] The deficient fibrinolytic activity in these families may reflect a primary defect of the PLAT structural gene.

The Bowes melanoma cell line which produces plasminogen activator has been used for isolation of cDNA clones.[11 12] Subsequently, phage[13] and cosmid[13 14] clones have been isolated and expressed in L cells.[15] The entire gene, which exceeds 32 kb encompassing 14 exons, has been sequenced.[16] The gene has been assigned to chromosome 8 using cell hybrids[17–19] and sublocalised to the pericentromeric[20] region 8p12–q11·2[21] by in situ hybridisation. A common RFLP has been reported.[17]

LANGER-GIEDION SYNDROME CHROMOSOME REGION (LGCR)

The Langer-Giedion syndrome (LGS) has features which include characteristic facies, sparse hair, and cone shaped epiphyses that resemble trichorhinophalangeal syndrome type I (TRP I). LGS, which is sometimes called TRP II, includes additional features of mental retardation, microcephaly, and multiple exostoses that are generally not seen in TRP I. Recently 36 cases of LGS were reviewed.[22]

Since the initial report[23] of an 8q terminal deletion in LGS, various deletions[24–35] as well as complex rearrangements[36 37] have been described in affected patients. Cytogenetic review[38] suggested that apparent non-deletion cases[39] might exhibit subtle features of asymmetry between chromosome homologues. The minimum critical region of deletion that is involved in LGS has been the subject of many reports.[29 36 38] Recently, deletion of 8q24·11–q24·12 has been suggested as the critical region for LGS[33] consistent with a reported patient in whom the *TG* locus (at 8q24·2–q24·3) was not involved.[40]

It has been suggested that the only consistent

clinical feature that distinguishes LGS from TRP I is the presence of cartilaginous exostoses in the former condition.[38] Furthermore, interstitial deletions of chromosome 8,[41–43] including two cases with deletion of 8q24·12,[42 43] have been reported in patients with TRP I. This suggests that the larger LGS deletion may uncover an exostosis gene. Dominantly inherited multiple exostoses may involve this same locus, although no cytogenetically apparent deletion of chromosome 8 has been found.[44]

Most cases of LGS are sporadic, resulting from de novo deletions or presumed deletions. One case report concerned a patient whose father had an inversion, inv(8)(q22·3q24·13).[35] Although this may be a chance observation, the suggestion that inversions may predispose to unequal recombination[45] is of general interest and concern[46] to medical geneticists. A familial syndrome with features of LGS cosegregating with an 8q inversion has been reported.[47] An affected father and daughter have been reported although cytogenetic findings were not available.[48] Finally, a patient reported with normal intelligence and a minimal deletion[33] could be expected to transmit LGS as a dominant trait.

HEREDITARY SPHEROCYTOSIS (SPH1)

Hereditary spherocytosis is a common, usually dominantly inherited, haemolytic anaemia caused by defects in the red cell cytoskeleton.[49] The prevalence has been estimated to be about 1 in 5000 Caucasians.[50] Both biochemical and genetic studies indicate that hereditary spherocytosis is heterogeneous. A specific abnormality of β spectrin has been reported in three of 10 kindreds with dominantly inherited spherocytosis.[51 52] The defect involves the interaction of spectrin and actin, which is enhanced by protein 4·1. In affected kindreds, the binding of normal protein 4·1 by spectrin is reduced to about 60% of controls.[51 52] The defective spectrin can be chromatographically separated into two populations.[52] One population, comprising about 40% of the total, fails to bind protein 4·1,[52] consistent with this molecule being the product of a defective allele. Kindreds with this spectrin defect have been termed type I hereditary spherocytosis, while the remaining kindreds have been designated type II hereditary spherocytosis.[51]

Genetic studies also show heterogeneity. A large kindred was described where hereditary spherocytosis was cosegregating with a reciprocal translocation t(8;12)(p11;p13) in 11 family members.[53] The lod score for linkage between hereditary spherocytosis and the translocation breakpoint was 5·12 at $\theta=0{\cdot}0$.[54] A subsequent report of a mother and son with hereditary spherocytosis and a reciprocal translocation t(3;8)(p21;p11) suggested a location close to 8p11 for the SPH1 gene.[55] A family has been reported where hereditary spherocytosis and glutathione reductase deficiency segregated independently[56] suggesting that these genes are not closely linked, although the type of hereditary spherocytosis was not determined.

More recently, two dysmorphic sibs affected with congenital spherocytosis were found to share a deletion of chromosome 8, del(8)(p11·1p21·1). The parents were both haematologically and chromosomally normal.[57] This interesting case presumably represents an example of chromosomal germ line mosaicism.[57] An additional case of interstitial deletion of chromosome 8, del(8)(p11·22p21·1), associated with spherocytosis has been reported.[58] Spherocytosis in these deletion patients is probably the result of uniplex (that is, single copy) gene expression. This indicates that hereditary spherocytosis owing to the SPH1 locus is likely to be an amorph or null allele and not the type I hereditary spherocytosis associated with a neomorph of β spectrin.

Recently, cDNA clones for β spectrin have been isolated.[59] This has allowed localisation of this gene to chromosome 14 by hybridisation to dot blots of flow sorted chromosomes.[59] Linkage between hereditary spherocytosis and *Gm* has been reported[54] with a lod score of 3·42 at $\theta=0{\cdot}22$. While the odds of heterogeneity to homogeneity of 1:2·04 neither favoured nor excluded heterogeneity, the largest four families of the 11 families studied made the major contribution to the lod score. A subsequent study of 19 families gave no evidence for linkage between spherocytosis and *Gm*.[60] Thus, it seems likely that type I hereditary spherocytosis, associated with abnormal spectrin, is an allele of the structural gene for β spectrin and is located on chromosome 14 within measurable distance of the immunoglobulin heavy chain gene that carries the Gm marker. The presence of RFLP markers within the β spectrin gene[59] should allow genetic discrimination between type I and type II hereditary spherocytosis and facilitate mapping of the chromosome 8 *SPH1* locus.

HEREDITARY GOITRE AND THYROGLOBULIN (TG)

Familial goitre is a heterogeneous group of disorders. Most are autosomal recessive traits with frequent parental consanguinity.[61] Congenital hypothyroidism has a frequency of about 1 in 3700,[62] and defects in the structure or synthesis of thyroglobulin may account for 14% of these patients.

Hypothyroidism owing to inherited thyroglobulin deficiency has been recognised as a recessive trait in sheep,[63] cattle,[64] goats,[65] and mice[66] as well as man. The caprine[67] and murine[68] defects have been

localised to the TG gene while the bovine mutation has been defined as a TG nonsense mutation.[69]

A family with dominantly inherited congenital goitre owing to defective thyroglobulin synthesis and structure showed cosegregation with a TG RFLP.[70] Thyroglobulin is a dimeric, major storage protein. Mutant TG alleles may confer either recessive or dominant inheritance depending upon whether the mutant is a null allele or produces a structurally abnormal subunit.[71]

The TG gene is at least 300 kb, comprises at least 37 exons,[72] and codes for an 8448 bp message.[73] The gene has been assigned to chromosome 8 using cell hybrids[74] and flow sorted chromosomes.[75] It has been localised by in situ hybridisation to the distal long arm,[74 76 77] 8q24·2–q24·3. The size of the gene has been exploited for developing fluorescent in situ hybridisation methods.[78 79] Marker RFLPs have been found in the 5′ region of the gene,[74 80] although the 3′ region is surprisingly devoid of useful RFLPs.[81]

VITELLIFORM MACULAR DYSTROPHY (VMD1)

A single kindred with dominantly inherited, atypical vitelliform macular dystrophy (VMD1), with affected subjects in at least five generations, has provided significant linkage data.[82] Blood samples from 128 subjects were collected and the data from 93 persons over the age of 14 were analysed for linkage using 13 serological and biochemical markers. Close linkage to soluble *GPT1* was found (θ=0·05, Z=4·34). *VMD1* may now be assigned to the long arm of chromosome 8 since *GPT* has been linked to *TG*.[7]

OSTEOPETROSIS WITH RENAL TUBULAR ACIDOSIS AND CARBONIC ANHYDRASE II DEFICIENCY (ca2)

The association of osteopetrosis and renal tubular acidosis has been recognised as a rare recessive disorder.[83–85] Cerebral calcifications are a feature of this disease,[86 87] while some cases show mental retardation. The primary enzyme defect has been identified as a deficiency of carbonic anhydrase II.[88] Carbonic anhydrase II is the only carbonic anhydrase isozyme found in kidney. Red cell carbonic anhydrase II is deficient in affected subjects and shows intermediate levels in heterozygotes.[88] The majority of cases originate from Kuwait, Saudi Arabia, and North Africa.[89] Consanguinity is common. The CA2 gene has been assigned to chromosome 8 using somatic cell hybrids[90] and localised to 8q22 by in situ hybridisation.[91] A frequent RFLP has been described[92] and the coding sequence reported.[93 94] Cosegregation of the disease with RFLP markers in the CA2 structural gene has not been reported nor has the molecular defect been defined. CA2 is part of a contiguous gene cluster that includes CA1 and CA3.

CONGENITAL ADRENAL HYPERPLASIA AND CYTOCHROME P450, STEROID 11β-HYDROXYLASE (CYP11B)

Congenital adrenal hyperplasia has an incidence between 1 in 5000 and 1 in 15 000.[95] Deficiency of steroid 11β-hydroxylase is the second most frequent form accounting for 5 to 8% of cases.[96] In addition to virilisation, hypertension owing to accumulation of 11-deoxycorticosterone is a feature of 11β-hydroxylase deficiency. In contrast to the 21-hydroxylase defect, no patients have been found with deletions or rearrangements of the gene,[97] CYP11B.

DNA probes for 11β-hydroxylase have been isolated from a human fetal adrenal cDNA library.[96] The sequence predicts a mature protein of 479 amino acids with a mitochondrial signal sequence of 24 amino acids. The gene was assigned to chromosome 8 using somatic cell hybrids and localised to 8q21 by in situ hybridisation.[96]

HAEMOLYTIC ANAEMIA WITH GLUTATHIONE REDUCTASE DEFICIENCY (GSR)

Haemolytic anaemia owing to an inherited defect in glutathione reductase is extremely rare. One well documented family indicates that this condition is inherited as a recessive trait. The consanguineous parents had intermediate levels, while the three affected children showed a virtual absence of glutathione reductase enzyme activity.[98] This red cell defect did not respond to riboflavin supplementation, thereby excluding a nutritional basis for the disease.

The GSR gene has been assigned to chromosome 8 using somatic cell hybrids.[99] Enzyme activity has been assayed in a variety of patients with chromosome 8 anomalies. These dosage studies showed raised activity in mosaic trisomy[100] and reduced activity in a patient with a terminal deletion, 8p21–pter.[101] Three unrelated patients with different partial duplications involving 8p were all found to have raised GSR activity, indicating that the gene was located within the region 8p21–p23.[102] This assignment was subsequently refined to 8p21.[103–105]

FAMILIAL LIPOPROTEIN LIPASE DEFICIENCY (LIPD)

Most patients with lipoprotein lipase deficiency are classified as type 1 hyperlipoproteinaemia (pure hyperchylomicronaemia).[106] This rare recessive disorder, which has an incidence of less than 1 in a million, is genetically heterogeneous. Lipoprotein

lipase (LPL) deficiency may result from a primary defect in the LIPD gene itself or from a defect in the APOC2 gene (on chromosome 19)[107] which produces the apolipoprotein CII cofactor required for LPL activity. The latter variant is distinguished by a complete deficiency of apo CII. LPL hydrolyses the triglycerides of chylomicrons which show massive accumulation in the plasma of patients. The disorder is characterised by recurrent pancreatitis, eruptive cutaneous xanthomas, and hepatosplenomegaly, but not atherosclerotic vascular disease.[106]

Human LPL cDNA clones have been isolated from adipose tissue and the complete sequence determined.[108] Analysis of the sequence indicates that LIPD codes for a mature protein of 448 amino acids preceded by a 27 amino acid signal peptide.[108] Comparisons with bovine hepatic lipase and porcine pancreatic lipase indicate that these lipases are members of a gene family.[109] This gene family seems to be dispersed, since the human hepatic lipase has been assigned to chromosome 15q21–q23,[110] whereas the LIPD gene has been localised to 8p22 by in situ hybridisation.[110] A number of RFLPs have been identified using oligonucleotide,[111 112] cDNA,[113–115] and genomic[116] probes.

Oncogenes

The *MYC* locus, which carries the cellular proto-oncogene homologue of the avian myelocytomatosis viral oncogene, has been extensively investigated.

The 'activation' mechanisms of chromosome translocation, proviral insertion, and gene amplification first discovered for this oncogene locus have been recently reviewed.[117] Among these gene rearrangements, chromosomal translocations are of direct interest with regard to gene mapping. The involvement of such translocations in malignancy has been recently reviewed.[118 119]

Burkitt's lymphoma, a B cell malignancy, is predominantly associated with an 8;14 translocation and less often with 2;8 or 8;22 translocations (table 2). These translocations all involve breakpoints in the 8q24 region, where the MYC gene resides.[120] The major or common rearrangement, t(8;14)(q24;q32), involves a translocation of the *MYC* locus to chromosome 14[121] directly into the immunoglobulin μ heavy chain locus.[122] The breakpoints involved are within the class switch region of the *IGH* locus and either 5′ to *MYC*, within the first exon, or within the first intron. These translocations show the transcriptional orientation of *MYC* to be telomeric and of *IGH* to be centromeric. The fusion thus occurs with opposite transcriptional orientation, that is, head to head.

TABLE 2 *Characteristics of translocation chromosomes in Burkitt's lymphoma.*

Translocation	*Derivative chromosome carrying MYC locus and immunoglobulin constant region*	*MYC rearranged*
Major		
t(8;14)(q24;q32)	14q+	Yes
Variant		
t(2;8)(p11;q24)	8q+	No
t(8;22)(q24;q12)	8q+	No

The less frequent or variant 2p11 and 22q12 breakpoints involve those chromosome segments that carry the immunoglobulin κ[123] and λ[124] light chain loci respectively. In these variants the chromosome 8 breakpoint is distal and hence 3′ to *MYC*, so that an unrearranged *MYC* locus is retained by the derivative chromosome 8 to which the immunoglobulin κ or λ chain is translocated.[123 124]

The usual human translocation, t(8;14), has a counterpart in the t(12;15) translocation seen in mouse plasmacytomas, which similarly involve the loci for the immunoglobulin heavy chain (on mouse chromosome 12) and *myc* (on mouse chromosome 15). Similarly, the variant human translocation, t(2;8), has a counterpart in the mouse t(6;15) variant plasmacytoma. The mouse chromosome 15 locus involved in this *p*lasmacytoma *v*ariant *t*ranslocation has been cloned,[125] designated *pvt*-1, and found to be at least 94 kb 3′ from *myc*.[118] The levels of *myc* transcription in variant plasmacytomas are comparable with those of the usual plasmacytomas, raising the possibility of long range gene activation and a possible regulatory role for *pvt*-1. The cloned breakpoint from the human Burkitt's lymphoma cell line, JBL2, which has a variant t(2;8) translocation, is homologous with mouse *pvt*-1, indicating that a human *PVT-1* locus has the same oncogenic role.[126] The *PVT-1* locus has also been implicated in the LY91 cell line with a variant t(2;8) translocation.[127]

Recent high resolution cytogenetic analysis[128] has shown that the breakpoints in both the JBL2 and LY91 cell lines are indistinguishable from the usual 8q24·1 breakpoint found in other t(2;8) translocations and most t(8;14) translocations. However, all four t(8;22) breakpoints examined were found at an 8q24·22 divergent location,[128] raising additional questions about *myc* activation and the nature of this chromosome region. An RFLP has been reported for the *MYC* locus.[129]

The MOS gene is the human cellular homologue of the transforming gene of Moloney murine sarcoma virus.[130 131] This oncogene is located at 8q22,[120] close to the breakpoint of the t(8;21)(q22;q22) translocation associated with the M2 subtype of

acute myeloblastic leukaemia.[132] The *MOS* locus, however, does not translocate to the derivative 21 chromosome.[133]

A novel *mos EcoRI* fragment has ben observed on Southern blots of myeloid leukaemia cell lines. Whether this variant represents rearrangement of the *MOS* locus[134] or a genetic polymorphism[135] is uncertain, since Mendelian transmission has not yet been investigated.[136] Furthermore, one group[137] has sublocalised the MOS gene to 8q11 rather than 8q22 as previously reported.[120 132]

The *LYN* locus has recently been identified and localised to 8q13–qter.[138] Screening of a human cDNA library with the v-*yes* probe, derived from the Yanaguichi sarcoma virus, identified a new clone in addition to the c-*yes* homologue localised to chromosome 18. The predicted amino acid sequence of this new clone was found to be highly homologous to the kinase domains of the murine *lck* gene.[138] This member of the family of tyrosine kinase related genes was termed *lyn* (*lck*/*yes*-related *n*ovel tyrosine kinase).

Other gene loci

Other human chromosome 8 gene loci are shown in table 3. Among these loci the carbonic anhydrase genes CA1, CA2, and CA3 are members of a multigene family. The coding sequence for CA2[93 94] and CA3[139 140] have been determined. While the enzymes CAI and CAIII are essentially limited in expression to erythrocytes and skeletal muscle respectively, CAII is more widely distributed. The assignment of these loci to chromosome 8[90 139 141 142] and localisation to the 8q13–q22 region[91 143] suggests that they form a multigene cluster. This is supported by the observation that CA1 and CA3 probes both hybridised to a 175 kb *SalI* restriction fragment.[144] In addition, the mouse homologues of CA1 and CA2 are tightly linked with no recombinants being observed among 209 scored offspring.[145]

TABLE 3 *Other gene loci.*

Locus symbol	*Gene*	*Localisation*	*Cloned DNA*	*RFLP*
CA1	Carbonic anhydrase I	8q13–q22	+	
CA3	Carbonic anhydrase III	8q13–q22	+	+
CRH	Corticotrophin releasing hormone		+	
CTSB	Cathepsin B	8p22	+	
F7R	Factor VII regulator			
FNZ	Fibronectin expression			
FRV2	Full length retroviral sequence 2			
GLYB	Glycine B complementing	8q21–qter		
GPB	β glycerol phosphatase			
GPT	Glutamate pyruvate transaminase	8q23–qter		
LHRH	Luteinising hormone releasing hormone	8p21–p11	+	
LYN	v-*yes* 1 oncogene homologue	8q13–qter	+	
MOS	v-*mos* oncogene homologue	8q22(q11?)	+	+
MYC	v-*myc* oncogene homologue	8q24	+	+
NEFL	Neurofilament light polypeptide	8p22–p12	+	+
PENK	Proenkephalin		+	
POLB	Polymerase (DNA) β polypeptide	8pter–q22	+	+
PVT1	PVT1 oncogene homologue	8q24	+	

Two releasing hormones, those for luteinising hormone[146] and corticotrophin (M Litt, 1988, personal communication), have been mapped to chromosome 8, as has the gene for proenkephalin.[147]

Human cDNA clones for the lysosomal protease cathepsin B have been isolated, the gene assigned to chromosome 8 using somatic cell hybrids,[148 149] and localised to 8p22 by in situ hybridisation.[150]

Cytosolic GPT is found in liver and erythrocytes. The enzyme exhibits two common allelic isozymes,[151] equally frequent in the population, making this locus a useful red cell genetic marker. Using expressing cell hybrids contructed from rat hepatoma cell lines, the gene has been assigned to chromosome 8.[152 153] *GPT* has been excluded from 8pter–q12[154] by exclusion linkage mapping.[155] Most recently the gene has been mapped[7] to a linkage group that includes *TG*, although linkage to *TG* itself is loose.

Other recent assignments to chromosome 8 include the genes for β glycerol phosphatase,[156] the β polypeptide chain of DNA polymerase,[157] and the gene for neurofilament light polypeptide chain.[158]

Comparative mapping

Three regions of the mouse genome carry loci homologous to those located on human chromosome 8. The human loci *LIPD* and *GSR* located on 8p (figure) have homologues on mouse chromosome 8 (A J Lusis, 1988, personal communication).[159] The human *CA1* and *CA2* loci located at 8q22 have homologues on mouse chromosome 3.[145] Finally, the cluster of loci near 8q24 of *MYC*,[160] *PVT1*,[125 126] *TG*,[66 68] and *GPT*[68] have homologues on mouse chromosome 15.

Genetic linkage map of human chromosome 8

Linkage data for RFLPs detected by 10 DNA probes from chromosome 8 were reported at HGM9.[7] Subsequently linkage data on an additional 16 chromosome 8 RFLP markers were published.[161] The locus for red cell GPT (glutamate pyruvate transaminase) was found to be linked to a chromo-

some 8 RFLP,[7] thus confirming its assignment to chromosome 8.[152 153] This enabled the disease loci *EBS1* and *VMD1*, which had been linked to *GPT*, to be assigned to chromosome 8. This represents the first assignment of disease loci to chromosome 8 based on linkage.

The preliminary linkage map shown in the figure is based upon selected loci from the published data[161] derived from a subset of CEPH families. (CEPH, the Centre d'Etude du Polymorphisme Humain, is a collaborative organisation founded by Jean Dausset for the purpose of coordinating a complete human linkage map through the provision of DNA from a common set of families. Further information is available from CEPH at 3 rue d'Ulm, 75005 Paris.) It incorporates data communicated by Dr A E Retief (*D8S5*)[162] and data collected in the author's laboratory (*CA2*, *TG*, *D8S7*). Distances between markers are shown as recombination fractions and were calculated assuming no sex differences in recombination frequency using the LINKAGE computer programs for multilocus analysis.[163 164] Two linkage groups can be positioned and oriented since they include the physically localised marker pairs *PLAT /D8S5* or *CA2 /TG*. These groups are not yet themselves linked. The extent of possible distal extension of the map on both arms is unknown. The marker *D8S7*, localised to the terminal short arm 8p23–pter,[165] cannot yet be linked to the map.

This preliminary map will hopefully soon be outdated as additional information becomes available on further marker systems. The preparation of a primary map, as a single contiguous linkage group, will enable placement of any chromosome 8 hereditary disorder by linkage analysis. This will facilitate physical localisation and cloning of such loci in order to develop a more precise understanding of hereditary disorders at the molecular level.

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