Review article

Mouse homologues of human hereditary disease

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Abstract

Details are given of 214 loci known to be associated with human hereditary disease, which have been mapped on both human and mouse chromosomes. Forty two of these have pathological variants in both species; in general the mouse variants are similar in their effects to the corresponding human ones, but exceptions include the *Dmd/DMD* and *Hprt/HPRT* mutations which cause little, if any, harm in mice. Possible reasons for phenotypic differences are discussed. In most pathological variants the gene product seems to be absent or greatly reduced in both species. The extensive data on conserved segments between human and mouse chromosomes are used to predict locations in the mouse of over 50 loci of medical interest which are mapped so far only on human chromosomes. In about 80% of these a fairly confident prediction can be made. Some likely homologies between mapped mouse loci and unmapped human ones are also given. Sixty six human and mouse proto-oncogene and growth factor gene homologies are also listed; those of confirmed location are all in known conserved segments. A survey of 18 mapped human disease loci and chromosome regions in which the manifestation or severity of pathological effects is thought to be the result of genomic imprinting shows that most of the homologous regions in the mouse are also associated with imprinting, especially those with homologues on human chromosomes 11p and 15q. Useful methods of accelerating the production of mouse models of human hereditary disease include (1) use of a supermutagen, such as ethylnitrosourea (ENU), (2) targeted mutagenesis involving ES cells, and (3) use of gene transfer techniques, with production of 'knockout mutations'.

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The need to develop good animal models of human hereditary disease has been recognised ever since the subject was first reviewed^{1,2} but, until recently, progress in this field has been slow. It is clear that the most relevant models are likely to emerge when the comparable human and animal conditions are known to

involve homologous loci. In this respect our genetic knowledge of the laboratory mouse outstrips that for all other non-human mammals. The 829 loci recently assigned to both human and mouse chromosomes³ has now risen to 900, well above comparable figures for other laboratory or farm animals. In a previous publication,⁴ 102 loci were listed which were associated with specific human disease, had mouse homologues, and had been located in both species. The number has now more than doubled (table 1A). Of particular interest are those which have pathological variants in both the mouse and humans: these are listed in table 2. Many other pathological mutations have been detected and located in the mouse; about half these appear to lie in conserved chromosomal segments. Thus the likely position of their human homologues can be predicted with some confidence.

Homologous loci

Table 1A lists 187 autosomal and 27 sex linked loci associated with pathological effects, which have been located on both human and mouse chromosomes.³ They are ordered in terms of the associated human disease(s), sometimes with two entries for particular loci. For ease of reference, table 1B has a tabulation of the same set in alphabetical order of human gene symbols.⁵ The MIM number, location, etc come from McKusick's catalogue⁶ and other work,⁷ which also gives details of the disorders. Schinzel *et al*⁸ also list human clinical disorders with chromosomal localisations of the genes concerned. Information on corresponding mouse genes is given in several publications,^{9,10} while the latest locus map of the mouse¹¹ has been used to show mouse gene locations as distances in centimorgans from the centromere (figures after the full stop). When there is a double zero after the full stop the gene concerned has not yet been localised on the linkage map. Positions of mouse loci on the G banded map are derived from the *Mouse Chromosome Atlas*.¹² References given in table 1 are for recently reported disease homologues; for earlier ones please consult *Human Gene Mapping 11*.¹³

With reference to polycystic kidney disease⁵¹ it should be noted that the mouse *Pkd-1* locus has not been identified but two flanking DNA markers to the human PKD1 locus were used to show that the region concerned mapped to mouse chromosome 17. Some unconfirmed

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Table 1A Mapping and other data on loci for human hereditary diseases which have been assigned to human and mouse chromosomes. In Disease name, a dash signifies deficiency and + an excess. A variant which may not be harmful is indicated by (v) after the name. Some loci associated with more than one disease are entered twice. For further information see text

Disease name	MIM No	Human symbol	Human location	Mouse symbol	Mouse location†	Mouse G band	Ref
Acatalsasaemia	115500	CAT	11p13	Cas-1*	2.40	C1-D	
Acid phosphatase –	171650	ACP2	11p11	Acp-2	2.00		
Adenomatosis, colorectal	190070	KRAS2	12p12.1	Kras-2	6.70	G1-G3	
Adrenal hyperplasia III	201910	CYP21	6p21.3	Cyp21-ps	17.19	B-C	
Adrenal hyperplasia IV	202010	CYP11B1	8q21	Cyp11b	15.24	C-D2	14
Adrenal hyperplasia V	202110	CYP17	10q24-q25	Cyp17	19.37	D1-D2	
Adrenocorticotrophin (ACTH) –	176830	POMC	2p23	Pomc-1	12.01	Cen-F1	
Albinism, oculocutaneous type II	203200	OCA2	15q11.2-q12	p*	7.27	B3-C	15
Albinism, partial	172800	KIT	4q12	Kit*	5.37	D-E1	
Albinism, tyrosinase negative	203100	TYR	11q14-q21	Tyr(c)*	7.41	D3	
Alphafetoprotein persistence (v)	104140	AFP	4q11-q13	Afp	5.46	E2-F	
Alzheimer, type I	104760	APP	21q21.2	App	16.49	B5-C4	
Amelogenesis imperfecta	301200	AMELX	Xp22.3-22.1	Amel	X.73	F2-ter	
Amyloid in fam Med fever	104750	SAA1	11p15.1	Saa	7.24	B3-C	
Amyloid neuropathy	176300	TTR	18q11.2-q12.1	Ttr	18.04	Cen-B2	16
Amyloidosis IV, Iowa type	105100	APOA1	11q23-q24	Apoa-1	9.25	Cen-A4	
Amyloidosis V, Finnish type	105120	GSN	9q33	Gsn	2.26	C1-D	
Amyloidosis, B2M deposition	109700	B2M	15q21-q22	B2m	2.46	E3-E4	
Amyloidosis, cerebral, Dutch type	104760	APP	21q21.2	App	16.49	B5-C4	
Amyloidosis, secondary, susceptibility to	104770	APCS	1q21-q23	Sap	1.72	H5-ter	
Amyotrophic lateral sclerosis-1	105400	ALS1	21q22.1-q22.2	Sod-1	16.51	B5-C4	17
Anaemia, haemolytic (AK1-)	103000	AK1	9q34.1	Ak-1	2.24	B-D	
Anaemia, haemolytic (G6PD-)	305900	G6PD	Xq28	G6pd	X.35	B-C	
Anaemia, haemolytic (GPI-)	172400	GPI	19q13.1	Gpi-1	7.12	A3-B1	
Anaemia, haemolytic (GSR-)	138300	GSR	8p21.1	Gr-1	8.10	A1-A4	
Anaemia, haemolytic (HK1-)	142600	HK1	10q22	Hk-1	10.30	Cen-B4	
Anaemia, haemolytic (PFKL-)	171860	PFKL	21q22.3	Pfkl	10.51	B3-C1	18,19
Anaemia, haemolytic (PGK-)	311800	PGK1	Xq13	Pgk-1	X.48	D-F1	
Anaemia, haemolytic (TPI-)	190450	TPI1	12p13	Tpi-1	6.61	F-G3	
Anaemia, macrocytic (TCN2-)	275350	TCN2	22q11.2-qter	Tcn-2	11.01	Cen-A2	
Anaemia, megaloblastic (DHFR-)	126060	DHFR	5q11.2-q13.2	Dhfr	13.52	C1-D2	
Analbuminaemia	103600	ALB	4q11-q13	Alb-1	5.46	E2-F	
Aniridia-2	106210	PAX6	11p13	Sey(Pax-6)*	2.49	E3-E4	
Antitrypsin, alpha 1 –	107400	PI	14q32.1	Aat	12.49	E-F1	
Apolipoprotein AI and CIII –	107680	APOA1	11q23-q24	Apoa-1	9.25	Cen-A4	
Apolipoprotein AII –	107670	APOA2	1q21-q23	Apoa-2	1.71	H5-ter	
Apolipoprotein H –	138700	APOH	17q23-qter	Apoh	11.58	D-E1	20
Argininosuccinicaciduria	207900	ASL	7cen-q11.2	Asl	5.00		
Atransferrinaemia	190000	TF	3q21	Trf	9.52	E3-ter	16
Cancer, colorectal	159350	MCC	5q21	Mcc	18.24	Cen-B2	21,22
Cancer, mammary, one form	176705	PHB	17q21	Phb	11.00	D	
Cardiomyopathy, hypertrophic	192600	MYH6	14q11.2-q13	Mhyc-a	14.19	D1-E1	
Cardiomyopathy, one form	125660	DES	2q35	Des	1.00	C3	
Cataract, Coppock-like	123660	CRYG1	2q33-q35	Cryg	1.31	C2-C4	
Cerebrotendinous xanthomatosis	213700	CYP27	2q33-qter	Cyp27	1.00		
Charcot-Marie-Tooth neuropathy 1	118220	CMT1A	17p12-p11.2	T*	11.35	B1-B5	23,24
Chondrodysplasia punctata, X	302960	CDPX2	Xq27-q28	Bpa*	X.33	B-C	
Citrullinaemia	215700	ASS	9q34.1	Ass-1	2.21	B	
Colourblindness, deutan/protan (v)	303900	RCP	Xq28	Rsvp	X.37	B-C	
Complement 3 –	120700	C3	19p13.3-p13.2	C3	17.28	D-E1	
Complement 4 –	120810	C4A,C4B	6p21.3	C4	17.19	B-C	
Cortisol resistance	231570	GRL	5q31-q32	Grl-1	18.21	Cen-B2	
Creutzfeldt-Jakob, predisposing	176640	PRNP	20pter-p12	Prn-p	2.55	F1-G	
Crigler-Najjar, type I	197140	UGT1A1	2q37	Ugt1a1	1.37	C3-C4	25,26
Cystic fibrosis	219700	CFTR	7q31	Cftr*	6.07	Cen-B1	
Debrisoquine sensitivity	236850	CYP2D	22q13.1-q13.2	Cyp2d	15.34	D3-E	
Diabetes insipidus, neurohypophyseal	192340	ARVP	20pter-p12.2	Arvp	2.71	H1-H4	27
Diabetes mellitus, MODY type II	138079	GCK	7p15-p13	Gk	11.03	Cen-A2	28
Diabetes mellitus, rare form, MODY	176730	INS	11p15.5	Ins-2	7.72	F1-F4	
Diabetes mellitus, type II	147940	IAPP	12p12.3-p11.2	Iapp	6.60	F-G3	
Dopamine-beta-hydroxylase –	223360	DBH	9q34	Dbh	2.20	C1-D	29
Duchenne muscular dystrophy	310200	DMD	Xp21.2	mdx(Dmd)*	X.37	B-C	
Dwarfism (pygmy)	147440	IGF1	12q23	Igf-1	10.54	C1-D1	
Dwarfism, Laron	262500	GHR	5p14-p12	Ghr	15.02	A2-B1	
Dysfibrinogenemia, gamma chain	134850	FGG	4q28	Fgg	3.59	D-F3	
Ectodermal dysplasia, anhidrotic	305100	EDA	Xq13	Ta*	X.41	C-D	
Ehlers-Danlos, type IV	120180	COL3A1	2q31	Col3a-1	1.24	A4-B	
Ehlers-Danlos, type X	135600	FN1	2q34-q36	Fn-1	1.33	C2-C4	
Elliptocytosis-1	130500	EL1	1p36.2-p34	Elp-1	4.58	D2	30
Elliptocytosis-2, spherocytosis 3	182860	SPTA1	1q21	Spna-1*	1.73	H5-ter	
Elliptocytosis-3, spherocytosis 1	182870	SPTB	14q24.1-q24.2	Spnb-1*	12.31	Cen-F1	
Enolase deficiency	172430	ENO1	1p36	Eno-1	4.73	D3-ter	
Epidermolysis bullosa simplex	131900	KRT14	17q11-q22	Krt-1.14	11.00	D	31,32
Epidermolysis bullosa simplex, generalised	131900	KRT1	12q11-q13	Krt-2	15.45	E-F1	33
Fabry	301500	GLA	Xq22	Ags	X.58	F1	
Factor V –	227400	F5	1q23	Cf-5	1.68	H3-H5	
Fetal hydatoin syndrome	132810	EPHX	1p11-qter	Eph-1	1.76	H5-ter	
Fletcher factor –	229000	KLK3	4q34-q35	Kal3	8.00	B2-B3	
Fucosidosis	230000	FUCA1	1p34	Fuca	4.58	D2	
Galactokinase –	230200	GALK1	17q21-q22	Glk	11.77	E1-E2	
Galactosaemia	230400	GALT	9p13	Galt	4.19	A1-A5	
Gangliosidosis, generalised GM1	230500	GLB1	3p23-p22	Bgl	9.62	E3-ter	
Gaucher	230800	GBA	1q21	Gba*	3.60	D-F3	
Gerstmann-Straussler, predisposing	137440	PRNP	20pter-p12	Prn-p	2.55	F1-G	
Glomerulonephritis (HF1-)	134370	HF1	1q32	Cfh	1.56	C4-H3	
Glycogen storage II (Pompe)	232300	GAA	17q23	Gaa	11.74	E1-E2	34,35
Glycogen storage VI (Hers)	232700	PYGL	14q11.2-q24.3	Pygl	12.28	Cen-F1	
Glycogen storage VIIa	311870	PHKA1	Xq13.1	Phka	X.45	D	
Glyoxylase –	138750	GLO1	6p21.3-p21.1	Glo-1	17.17	A3-B	
Gonadal dysgenesis, XY type	480000	TDF	Yp11.3	Tdy	Y.00	A1	
Granulomatous, chronic X linked	306400	CYBB	Xp21.1	Cybb	X.01	A1-A2	
Granulomatous, chronic autosomal	233710	NCF2	1q25	Ncf-2	1.52	C4-H3	
Greig's cephalopolysyndactyly	175700	GCPS	7p13	Xr* (Gli3)	13.18	A2-A3	
Growth hormone –, Illig type	139250	GH1	17q22-q24	Gh	11.68	E1-E2	
Gynaecomastia (aromatase +)	107910	CYP19	15q21	Cyp19	9.27	A4-E	
Haemoglobinuria, paroxysmal	107271	CD59	11p14-p13	Ly-6	15.20	C-D2	
Haemophilia A	306700	F8C	Xq28	Cf-8	X.38	B-C	
Haemophilia B, Christmas disease	306900	F9	Xq27.1-27.2	Cf-9	X.26	A6-A7	
Histidinaemia	235800	HAL	12q22-q23	Hal*	10.59	C1-D1	36
Homocystinuria, B6 responsive and non-responsive	236200	CBS	21q22.3	Cbs	17.18	A3-B	
Hypercholesterolaemia, familial	143890	LDLR	19p13.3	Ldlr	9.04	Cen-A4	

Table 1A—contd

Disease name	MIM No	Human symbol	Human location	Mouse symbol	Mouse location†	Mouse G band	Ref
Hyperlipoproteinaemia	238600	LPL	8p22	<i>Lpl</i>	8.26	C1-C3	
Hyperlipoproteinaemia, type III	107741	APOE	19q13.2	<i>Apoe</i>	7.06	Cen-A3	
Hyperproglucagonaemia	138030	GCG	2q36-q37	<i>Gcg</i>	2.34	C1-D	
Hypertension, essential, susceptibility	106150	AGT	1q42-q43	<i>Agt</i>	8.48	C3-E1	37
Hypobetalipoproteinaemia	107730	APOB	2p24-p23	<i>Apob*</i>	12.03	Cen-F1	
Hypoceruloplasminaemia	117700	CP	3q23-q25	<i>Cp</i>	9.00	D	
Hypogonadism, hypogonadotrophic	227200	LHRH	8p21-p11.2	<i>Gnrh(hpg)*</i>	14.29	D3-E3	38
Hypoparathyroidism, familial	168450	PTH	11p15.2-p15.1	<i>Pth</i>	7.48	E1-E3	
Hypophosphataemia	307800	HYP	Xp22	<i>Hyp*</i>	X.69	F2-ter	
Hypophosphataemia II, with deafness	307810	GY	Xp22	<i>Gy*</i>	X.70	F2-ter	
Hypophosphatasia, infantile	146300	ALPL	1p36.1-p34	<i>Akp-2</i>	4.60	D2-D3	
Hypopituitarism	173110	PIT1	3q	<i>Pit-1(dw)*</i>	16.39	A-B5	
Hypoprothrombinaemia	176930	F2	11p11-q12	<i>Cf-2</i>	2.46	E3-E4	
Hypothyroidism, goitrous	188450	TG	8q24	<i>Tgn*</i>	15.17	C	
Hypothyroidism, non-goitrous, TSH -	188540	TSHB	1p13	<i>Tshb</i>	3.67	F3-H1	
Ichthyosis, sex linked	308100	STS	Xp22.32	<i>Sts</i>	X.88	F3-ter	
Immunodeficiency due to CD3Z	186780	CD3Z	1q22-q25	<i>Cd3z</i>	1.68	H1-H5	39
Immunodeficiency due to NP -	164050	NP	14q11.2	<i>Np-1</i>	14.16	B-C1	
Immunodeficiency, severe combined	102700	ADA	20q12-q13.11	<i>Ada</i>	2.74	H3-H4	
Immunodeficiency, severe combined	147680	IL2	4q26-q27	<i>Il-2</i>	3.39	C-D	
Immunoglobulin heavy chain -	146900	IGH	14q32.33	<i>Igh</i>	12.65	E-F1	
Infections, recurrent	217050	C6	5p13	<i>C6</i>	15.01	A2-B1	
Infections, recurrent	217070	C7	5p13	<i>C7</i>	15.01	A2-B1	
Infections, recurrent	120960	C8B	1p32	<i>C8b</i>	4.44	C7	
Infections, recurrent pyogenic	120650	CR2	1q32	<i>Cr-2</i>	1.83	H5-ter	
Infections, recurrent (candidiasis)	254600	MPO	17q21.3-q23	<i>Mpo</i>	11.49	D	
Infertility, male, one form	136530	FSHB	11p13	<i>Fshb</i>	2.42	C1-D3	
Infertility, male, one form	102480	ACR	22q13-qter	<i>Acr</i>	15.33	D3-E	
Interferon, alpha -	147660	IFNA	9p22	<i>Ifa</i>	4.39	C3-C6	
Interferon, gamma -	147570	IFNG	12q24.1	<i>Ifg</i>	10.69	C1-D1	
Krabbe	245200	GALC	14q21-q31	<i>twi*</i>	12.29	Cen-F1	
Lactoferrin- neutrophils	245480	LTF	3q21-q23	<i>Ltf</i>	9.00		
Leprechaunism	147670	INSR	19p13.3-p13.2	<i>Insr</i>	8.01	A1-A4	
Lesch-Nyhan	308000	HPRT	Xq26	<i>Hprt</i>	X.30	A6-B	
Leucocyte adhesion -	116920	ITGB2	21q22.3	<i>Itgb2</i>	10.51	B3-C1	40
Leucodystrophy, metachromatic	250100	ARSA	22q13.31-qter	<i>As-2</i>	15.00	E	
Lipoid adrenal hyperplasia	201710	CYP11A	15q23-q24	<i>Cyp11a</i>	9.27	Cen-A4	
Li-Fraumeni (familial cancer)	191170	TP53	17p13.1	<i>Trp53</i>	11.42	B4-B5	
Lupus C2-, predisposing	217000	C2	6p21.3	<i>C2</i>	17.19	B-C	
Lupus C5-, predisposing	120900	C5	9q34.1	<i>Hc*</i>	2.18	C1-D	
Lymphoma, Burkitt's	190080	MYC	8q24	<i>Myc</i>	15.15	A2-C	
Malignant hyperthermia, one form	145600	RYR1	19q13.1	<i>Ryr</i>	7.08	Cen-A3	
McArdle	232600	PYGM	11q12-q13.2	<i>Pygm</i>	19.03	B	
Menkes	309400	MNK	Xq13.2-q13.3	<i>Mo*</i>	X.45	D	
Mental retardation, X linked, one form	309550	FRAXA	Xq27.3	<i>Fmr-1</i>	X.38	B-C	
Methaemoglobinemia, enzymopathic	250800	DIA1	22q13.31-qter	<i>Dia-1</i>	15.00	E	
Methylmalonicaciduria, mutase -	251000	MUT	6p21	<i>Mut</i>	17.23	D	
Miller-Dieker (lissencephaly)	247200	MDCR	17p13.3	<i>D11Bay1</i>	11.00		
Mucopolysaccharidosis I	252800	IDUA	4p16.3	<i>Idua</i>	5.33	B-E1	
Mucopolysaccharidosis II	309900	IDS	Xq27.3-q28	<i>Ids</i>	X.30	A6-B	
Mucopolysaccharidosis VI	253200	ARSB	5p11-q13	<i>As-1s</i>	13.65	C1-D2	
Mucopolysaccharidosis VII	253220	GUSB	7q22	<i>Gus*</i>	5.63	F-G3	
Mullerian, persistent duct	261550	AMH	19p13.3	<i>Amh</i>	10.49	B3-C1	41
Myoadenylate deaminase -	102770	AMPD1	1p13	<i>Ampd-1</i>	3.67	F3-H1	
Myoglobinuria, exertional (LDHA -)	150000	LDHA	11p15.1-p14	<i>Ldh-1</i>	7.23	B3-C	
Myopathy, lipid storage	201470	ACADS	12q22-qter	<i>Bcd-1</i>	5.49	E2-F	
Myotonia congenita	118425	CLCN1	7q35	<i>Cle-1</i>	6.20	B1-B3	42
Nance-Horan	302350	NHS	Xp22.3-p21.1	<i>Xcat*</i>	X.64	F1-F2	
Niemann-Pick	257200	SMPD1	11p15.4-p15.1	<i>spm*</i>	18.12	Cen-B2	
Norum	245900	LCAT	16q22.1	<i>Lcat</i>	8.42	C3-E1	
Ornithinaemia, gyrate retinal atrophy	258870	OAT	10q26	<i>Oat</i>	7.64	F1-F4	
Ornithine transcarbamylase -	311250	OTC	Xp21.1	<i>Otc(spf)*</i>	X.02	A1-A2	
Osteodystrophy, Albright	139320	GNAS1	20q13.2	<i>Gnas</i>	2.86	H3-H4	
Osteogenesis imperfecta, one type	120160	COL1A2	7q21.3-q22.1	<i>Cola-2*</i>	6.04	Cen-B1	
Osteogenesis imperfecta, one type	120150	COL1A1	17q21.3-q22	<i>Cola-1</i>	11.54	D	
Osteoporosis due to renal acidosis	259730	CA2	8q22	<i>Car-2</i>	3.04	Cen-A2	
Opalotodigital syndrome	311300	OPD1	Xq28	<i>ptd*</i>	X.30	A6-B	43,44
Paralysis, hyperkalaemic periodic	170500	SCN4A	17q23.1-q25.3	<i>Scn4a</i>	11.52	D	45,46
Paramyotonia congenita	170500	SCN4A	17q23.1-q25.3	<i>Scn4a</i>	11.52	D	45,46
Pelizaeus-Mersbacher	312080	PLP	Xq21.3-q22	<i>Plp(jp)*</i>	X.56	F1	
Phenylketonuria due to QDPR -	261630	QDPR	4p15.3	<i>Qdpr</i>	5.28	B-E1	
Phenylketonuria, common form	261600	PAH	12q22-q24.2	<i>Pah*</i>	10.53	C1	47
Piebaldism	172800	KIT	4q12	<i>Kit*</i>	5.37	D-E1	48,49
Placental lactogen -	150200	CSH1	17q22-q24	<i>Pl-1</i>	13.00		
Plasminogen Tochigi	173350	PLG	6q26-q27	<i>Plg</i>	17.08	A2-A3	
Plasminogen activator -	173370	PLAT	8p12	<i>Plat</i>	8.07	A1-A4	
Platelet alpha/delta storage pool -	173610	GRMP	1q21-q24	<i>Grmp</i>	1.68	H3-H5	
Polycystic kidney disease, adult	173900	PKD1	16p13.3	<i>Pkd-1</i>	17.00		50,51
Polyposis coli, adenomatous	175100	APC	5q21-q22	<i>Min*</i>	18.15	Cen-B2	52,53
Porphyria, acute intermittent	125270	ALAD	9q32-q34	<i>Lv</i>	4.30	A5-C2	
Porphyria, acute intermittent	176000	PBGD	11q23.2-qter	<i>Ups</i>	9.24	Cen-A4	
Porphyria, hepatocerythropoietic	176100	UROD	1p34	<i>Urod</i>	4.49	C7-D1	54
Prolidase -	170100	PEPD	19q12-q13.2	<i>Pep-4</i>	7.15	A3-B1	
Properdin -	312060	PF	Xp21-p11	<i>Pfc</i>	X.03	A3	
Protoporphyrria, erythroid	177000	FECH	18q21.3	<i>Fech*</i>	18.40	C-D	55
Pseudohermaphroditism, LH derived	152780	LHB	19q13.32	<i>Lhb</i>	7.22	C	
Pseudohermaphroditism, SRD5A1 derived	264600	SRD5A1	5p15	<i>Srd5a-1</i>	13.51	C1-D2	56
Pseudohermaphroditism type Ia	103580	GNAS1	20q13.2	<i>Gnas</i>	2.86	H3-H4	
Pyridoxine dependency with seizures	266100	GAD1	2q31	<i>Gad-1</i>	2.38	C1-D	
Pyruvate dehydrogenase -	312170	PDHA1	Xp22.1	<i>Pdha-1</i>	X.00	F3-F4	
Retinal degeneration, slow	179605	RDS	6p12	<i>rd*</i>	17.24	D-E1	57,58
Retinitis pigmentosa 4, rhodopsin	180380	RHO	3q21-q24	<i>Rho</i>	6.49	F	
Retinoblastoma	180200	RB1	13q14.2	<i>Rb-1*</i>	14.27	D3-E2	
Retinol binding protein-1 -	180260	RBP1	3q21-q22	<i>Crbp</i>	9.46	E3-ter	
Retinol binding protein-3 -	180290	RBP3	10q11.2	<i>Rbp-3</i>	14.14	B	
Retinol binding protein-4 -	180250	RBP4	10q23-q24	<i>Rbp-4</i>	19.19	D1-D2	
Sandhoff	268800	HEXB	5q13	<i>Hexb</i>	13.53	C1-D2	
Sialidosis I and II	162050	NEU	6p21.3	<i>Neu-1</i>	17.19	B-C	
Sly	253220	GUSB	7q22	<i>Gus</i>	5.63	F-G3	
Spherocytosis-2	182900	ANK1	8p21.1-p11.2	<i>Ank-1*</i>	8.07	A1-A4	
Spherocytosis, Japanese type	177070	EPB42	15q15	<i>pa*</i>	2.53	F1-F3	59
Stickler	108300	COL2A1	12q13.11-13.2	<i>Col2a-1</i>	15.33	D3-E	60
Tay-Sachs (GM2-gangliosidosis I)	272800	HEXA	15q22	<i>Hexa</i>	9.29	A4-E	
Testicular feminisation	313700	AR	Xq12	<i>Tfm(Ar)*</i>	X.40	B-D	

Table 1A—contd

Disease name	MIM No	Human symbol	Human location	Mouse symbol	Mouse location†	Mouse G band	Ref
Thalassaemia, alpha	141800	HBA1	16p13.3	Hba*	11.14	A1-B1	
Thalassaemia, beta	141900	HBB	11p15.5	Hbb*	7.49	E3	
Thrombophilia	107300	AT3	1q23-q25	At-3	1.66	H3-H5	
Thyroid hormone defect	274500	TPO	2p13	Tpo	12.09	Cen-F1	
Thyroid hormone unresponsiveness	190120	THRA1	17q11.2-q12	Erba	11.56	D-E1	
Thyrotropin unresponsiveness	275200	TSHR	14q24-q31	Tshr	12.48	E-F1	
Trypsinogen -	276000	TRY1	7q32-qter	Try-1	6.20	B1-B3	
Tyrosinaemia I	276700	FAH	15q23-q25	Fah	7.41	D3	61
Tyrosinaemia II	276600	TAT	16q22.1	Tat	8.46	C3-E1	
Urolithiasis, 2,8-dihydroxyadenine	102600	APRT	16q24	Aprt	8.63	E1-ter	
Waardenburg, PAX3 related	193500	PAX3	2q35	Sp(Pax-3)*	1.36	C3	62
Wilms's tumour	194070	WT1	11p13	Wt-1	2.41	C1-D	
Wolf-Hirschhorn	142983	HOX7	4p16.1	Hox-7	5.14	B-E1	
Wolman	278000	LIPA	10q24-q25	Lip-1	19.00		
Xeroderma pigmentosum IX	278700	XPA	9q32-q34.1	Xpa	4.00	C2	
Xeroderma pigmentosum, group D	126340	ERCC2	19q13.2-q13.3	Ercc-2	7.06	Cen-A3	63

* Mouse gene with pathological allele.

† Given as chromosome number, followed after full stop by estimated distance of locus from centromere in cM. A double zero indicates that regional location is unknown.

Table 1B Data from table 1A shown in alphabetical order of human locus symbols with associated diseases

Symbol	Name of disease	Symbol	Name of disease	Symbol	Name of disease
ACADS	Myopathy, lipid storage	EPB42	Spherocytosis, Japanese type	LTF	Lactoferrin- neutrophils
ACP2	Acid phosphatase -	EPHX	Fetal hydnantoin syndrome	MCC	Cancer, colorectal
ACR	Infertility, male, one form	ERCC2	Xeroderma pigmentosum, group D	MDCR	Miller-Dieker (lissencephaly)
ADA	Immunodeficiency, severe combined	F2	Hypoprothrombinaemia	MNK	Menkes
AFP	Alphafetoprotein persistence (v)	F5	Factor V -	MPO	Infections, recurrent (candidiasis)
AGT	Hypertension, essential, susceptibility	F8C	Haemophilia A	MUT	Methylmalonicaciduria, mutase -
AK1	Anaemia, haemolytic (AK1-)	F9	Haemophilia B, Christmas disease	MYC	Lymphoma, Burkitt's
ALAD	Porphyria, acute hepatic	FAH	Tyrosinaemia I	MYH6	Cardiomyopathy, hypertrophic
ALB	Analbuminaemia	FECH	Protoporphyrria, erythroid	NCF2	Granulomatous, chronic autosomal
ALPL	Hypophosphatasia, infantile	FGG	Dysfibrinogenaemia, gamma chain	NEU	Sialidosis I and II
ALS1	Amyotrophic lateral sclerosis-1	FN1	Ehlers-Danlos, type X	NHS	Nance-Horan
AMELX	Amelogenesis imperfecta	FRAXA	Mental retardation, X linked, one form	NP	Immunodeficiency due to NP -
AMH	Mullerian, persistent duct			OAT	Ornithinaemia, gyrate retinal atrophy
AMPD1	Myoadenylate deaminase -	FSHB	Infertility, male, one form	OCA2	Albinism, oculocutaneous type II
ANK1	Spherocytosis-2	FUCA1	Fucosidosis	OPD1	Otopalatodigital syndrome
APC	Polyposis coli, adenomatous	G6PD	Anaemia, haemolytic (G6PD-)	OTC	Ornithine transcarbamylase -
APCS	Amyloidosis, secondary, susceptibility to	GAA	Glycogen storage II (Pompe)	PAH	Phenylketonuria, common form
APOA1	Apolipoprotein AI and CIII -	GAD1	Pyridoxine dependency with seizures	PAX3	Waardenburg, PAX3 related
APOA1	Amyloidosis IV, Iowa type	GALC	Krabbe	PAX6	Aniridia-2
APOA2	Apolipoprotein AII -	GALK1	Galactokinase -	PBGD	Porphyria, acute intermittent
APOB	Hypobetalipoproteinaemia	GALT	Galactosaemia	PDHA1	Pyruvate dehydrogenase -
APOE	Hyperlipoproteinaemia, type III	GBA	Gaucher	PEPD	Prolidase -
APOH	Apolipoprotein H -	GCG	Hyperproglucagonaemia	PFD	Properdin -
APP	Amyloidosis, cerebral, Dutch type	GCK	Diabetes mellitus, MODY type II	PFKL	Anaemia, haemolytic (PFKL-)
APP	Alzheimer, type I	GCP5	Greig's cephalopolysyndactyly	PGK1	Anaemia, haemolytic (PGK-)
APRT	Urolithiasis, 2,8-dihydroxyadenine	GH1	Growth hormone -, Illig type	PHB	Cancer, mammary, one form
AR	Testicular feminisation	GHR	Dwarfism, Laron	PHKA1	Glycogen storage VIIIA
ARSA	Leucodystrophy, metachromatic	GLA	Fabry	PI	Antitrypsin, alpha 1 -
ARSB	Mucopolysaccharidosis VI	GLB1	Gangliosidosis, generalised GM1	PIT1	Hypopituitarism
ARVP	Diabetes insipidus, neurohypophyseal	GLO1	Glyoxylase -	PKD1	Polycystic kidney disease, adult
ASL	Argininosuccinicaciduria	GNAS1	Osteodystrophy, Albright	PLAT	Plasminogen activator -
ASS	Citrullinaemia	GNAS1	Pseudohypoparathyroidism type Ia	PLG	Plasminogen Tochigi
AT3	Thrombophilia	GPI	Anaemia, haemolytic (GPI-)	PLP	Pelizaeus-Mersbacher
B2M	Amyloidosis, B2M deposition	GRL	Cortisol resistance	POMC	Adrenocorticotrophin (ACTH) -
C2	Lupus C2 -, predisposing	GRMP	Platelet alpha/delta storage pool -	PRNP	Creutzfeldt-Jakob, predisposing
C3	Complement 3 -	GSN	Amyloidosis V, Finnish type	PRNP	Gerstmann-Straussler, predisposing
C4A,C4B	Complement 4 -	GSR	Anaemia, haemolytic (GSR-)	PTH	Hypoparathyroidism, familial
C5	Lupus C5 -, predisposing	GUSB	Mucopolysaccharidosis VII	PYGL	Glycogen storage VI (Hers)
C6	Infections, recurrent	GUSB	Sly	PYGM	McArdle
C7	Infections, recurrent	GY	Hypophosphataemia II, with deafness	QDPR	Phenylketonuria due to QDPR -
C8B	Infections, recurrent	HAL	Histidinaemia	RB1	Retinoblastoma
CA2	Osteoporosis due to renal acidosis	HBA1	Thalassaemia, alpha	RBP1	Retinol binding protein-1 -
CAT	Acatalsaemia	HBB	Thalassaemia, beta	RBP3	Retinol binding protein-3 -
CBS	Homocystinuria, B6 responsive and non-responsive	HEXA	Tay-Sachs (GM2-gangliosidosis I)	RBP4	Retinol binding protein-4 -
		HEXB	Sandhoff	RCP	Colourblindness, deutan/protan (v)
CD3Z	Immunodeficiency due to CD3Z	HF1	Glomerulonephritis (HF1-)	RDS	Retinal degeneration, slow
CD59	Haemoglobinuria, paroxysmal	HK1	Anaemia, haemolytic (HK1-)	RHO	Retinitis pigmentosa 4, rhodopsin
CDPX2	Chondrodysplasia punctata, X	HOX7	Wolf-Hirschhorn	RYR1	Malignant hyperthermia, one form
CFTR	Cystic fibrosis	HPRT	Lesch-Nyhan	SAA1	Amyloid in fam Med fever
CLCN1	Myotonia congenita	HYP	Hypophosphataemia	SCN4A	Paralysis, hyperkalaemic periodic
CMT1A	Charcot-Marie-Tooth neuropathy 1	IAPP	Diabetes mellitus, type II	SCN4A	Paramyotonia congenita
COL1A1	Osteogenesis imperfecta, one type	IDS	Mucopolysaccharidosis II	SMPD1	Niemann-Pick
COL1A2	Osteogenesis imperfecta, one type	IDUA	Mucopolysaccharidosis I	SPTA1	Elliptocytosis-2, spherocytosis 3
COL2A1	Stickler	IFNA	Interferon, alpha -	SPTB	Elliptocytosis-3, spherocytosis 1
COL3A1	Ehlers-Danlos, type IV	IFNG	Interferon, gamma -	SRD5A1	Pseudohermaphroditism, SRD5A1 derived
CP	Hypoceruloplasminaemia	IGF1	Dwarfism (pygmy)		
CR2	Infections, recurrent pyogenic	IGH	Immunoglobulin heavy chain -	STS	Ichthyosis, sex linked
CRYG1	Cataract, Coppock-like	IL2	Immunodeficiency, severe combined	TAT	Tyrosinaemia II
CSH1	Placental lactogen -	INS	Diabetes mellitus, rare form, MODY	TCN2	Anaemia, macrocytic (TCN2-)
CYBB	Granulomatous, chronic X linked	INSR	Leprechaunism	TDF	Gonadal dysgenesis, XY type
CYP11A	Lipoid adrenal hyperplasia	ITGB2	Leucocyte adhesion -	TF	Atransferrinaemia
CYP11B1	Adrenal hyperplasia IV	KIT	Albinism, partial	TG	Hypothyroidism, goitrous
CYP17	Adrenal hyperplasia V	KIT	Piebaldism	THRA1	Thyroid hormone unresponsiveness
CYP19	Gynaecomastia (aromatase +)	KLK3	Fletcher factor -	TP53	Li-Fraumeni (familial cancer)
CYP21	Adrenal hyperplasia III	KRAS2	Adenomatosis, colorectal	TPI1	Anaemia, haemolytic (TPI-)
CYP27	Cerebrotendinous xanthomatosis	KRT1	Epidermolysis bullosa simplex, generalised	TPO	Thyroid hormone defect
CYP2D	Debrisoquine sensitivity			TRY1	Trypsinogen
DBH	Dopamine-beta-hydroxylase -	KRT14	Epidermolysis bullosa simplex	TSHB	Hypothyroidism, non-goitrous, TSH-
DES	Cardiomyopathy, one form	LCAT	Norum	TSHR	Thyrotropin unresponsiveness
DHFR	Anaemia, megaloblastic (DHFR-)	LDHA	Myoglobinuria, exertional (LDHA -)	TTR	Amyloid neuropathy
DIA1	Methaemoglobinemia, enzymopathic	LDLR	Hypercholesterolaemia, familial	TYR	Albinism, tyrosinase negative
DMD	Duchenne muscular dystrophy	LHB	Pseudohermaphroditism, LH derived	UGT1A1	Crigler-Najjar, type I
EDA	Ectodermal dysplasia, anhidrotic	LHRH	Hypogonadism, hypogonadotrophic	URD1	Porphyria, hepaterythropoietic
EL1	Elliptocytosis-1	LIPA	Wolman	WT1	Wilms's tumour
ENO1	Enolase deficiency	LPL	Hyperlipoproteinaemia	XPA	Xeroderma pigmentosum IX

Table 2 Listing of pathological variants in presumptive mouse homologues of human disease loci.^{69 10} See also table 1A and B. McKusick's classification of human phenotypes as dominant (D), recessive (R), or sex linked (X) is given in parentheses after locus symbol

Locus symbol		Name of disease/mutant		Phenotypic effects in mice
Human	Mouse	Human	Mouse	
AN2(D)* = PAX6	<i>Sey</i>	Aniridia-2	Small eye	Small eyes, colobomata, homozygous lethal Jaundiced young, splenomegaly etc, gallstones Adenoma along intestinal tract Decreased concentrations of lipoproteins, cholesterol. Some with hydro- and exencephalus
ANK1(D)*	<i>nb</i>	Spherocytosis-2	Normoblastic anaemia	
APC(D)	<i>Min</i>	Polyposis coli, adenomatous	Multiple intestinal neoplasia	
APOB(D)	<i>Apob</i>	Hypobetalipoproteinaemia	<i>Apob</i> deficient	
AR(X)*	<i>Tfm</i>	Testicular feminisation	Testicular feminisation	Hemizygous males look female with minute testes, androgen insensitivity
C5(D)*	<i>Hc</i>	Lupus C5, predisposing	Haemolytic complement null	Lowered resistance to infection
CAT(D)*	<i>Cas-1</i>	Acatalasaemia	Acatalasaemia	Increased susceptibility to liver tumours
CDPX2(X)	<i>Bpa</i>	Chondrodysplasia punctata, dominant	Bare patches	Skin and skeletal lesions, hemizygous lethal
CFTR(R)	<i>Cftr</i>	Cystic fibrosis	<i>Cftr</i> deficient	Intestinal obstruction, homozygous lethal
CMT1A(D)	<i>Tr</i>	Charcot-Marie-Tooth neuropathy	Trembler	Tremor, convulsions, defective myelination
COL1A2(R)	<i>oim</i>	Osteogenesis imperfecta	Osteogenesis imperfecta	Multiple fractures, bone thinning, etc
DMD(X)*†	<i>mdx</i>	Duchenne muscular dystrophy	Muscular dystrophy	Tremors, incoordination in old mice, muscle fibre degeneration
EDA(X)	<i>Ta</i>	Ectodermal dysplasia, anhidrotic	Tabby	Defective teeth, skin, hairs
EPB42(D)	<i>pa</i>	Spherocytosis	Pallid	Prolonged bleeding time, depigmentation, inner ear defects
FECH(D)*	<i>Fech</i>	Protoporphyrria, erythropoietic	Ferrochelatase deficient	Anaemia, photosensitivity, liver disease
GALC(R)*	<i>tui</i>	Krabbe	Twitcher	Tremor, wasting, early death, psychosine accumulation
GBA(R)*	<i>Gba</i>	Gaucher	<i>Gba</i> deficient	Homozygous lethality, lysosomal storage of glucocerebroside
GCPS(D) = GLI3	<i>Xt</i>	Greig cephalopolysyndactyly	Extra toes	Polydactyly etc, homozygous lethality
GUSB(R)*	<i>gus</i>	Mucopolysaccharidosis VII	Mucopolysaccharidosis VII	Small, male sterile, lack of adipose tissue
GY(X)	<i>Gy</i>	Hypophosphataemia with deafness	Gyro, phosphate transport defect	Rickets, inner ear anomalies, hemizygous sterility
HAL(R)	<i>his</i>	Histidinaemia	Histidinaemia	Balance defect
HBA1(D)*	<i>Hba</i>	Thalassaemia, alpha	Thalassaemia, alpha	Thalassaemia, homozygous lethal
HBB(D)	<i>Hbb</i>	Thalassaemia, beta	Thalassaemia, beta, polycythaemia	Thalassaemia, polycythaemia
HYP(X)	<i>Hyp</i>	Hypophosphataemia	Hypophosphataemia, phosphate transport defect	Skeletal changes like rickets
KIT(D)	<i>W</i>	Piebaldism	Dominant spotting	White spotting, macrocytic anaemia, sterility
LHRH(D)* = GNRH	<i>hpg</i>	Hypogonadism, hypogonadotrophic	Hypogonadal	Underdeveloped reproductive tracts
MNK(X)	<i>Mo</i>	Menkes kinky hair disease	Mottled, copper transport defect	Defective collagen, keratin, pigmentation, and behaviour; some alleles male lethal
NHS(X)	<i>Xcat</i>	Nance-Horan cataract-dental syndrome	X linked cataract	Total lens opacity in hemi/homozygote
OCA2(R)	<i>p</i>	Albinism, oculocutaneous type 2	Pink eyed dilution	Homozygotes with much reduced pigmentation, ocular albinism in <i>p</i>
OPD1(X)	<i>ptd</i>	Otopalatodigital	Palate-tail-digits anomaly	Frequent hemizygous lethality with cleft palate; survivors with crooked tail, polydactyly, etc
OTC(X)*	<i>spf</i>	Ornithine transcarbamylase deficiency	Sparse fur	Small, wrinkled skin, lack of hair, bladder stones
PAH(R)	<i>Pah</i>	Phenylketonuria	Hyperphenylalaninemia	Homozygotes with hyperphenylalaninemia
PIT1(D)*	<i>dw</i>	Hypopituitarism	Dwarf	Homozygotes small, sterile
PLP(X)*	<i>jp</i>	Pelizaeus-Merzbacher	Jimmy	Lethal, convulsions, myelin deficiency, etc
RB1(D)	<i>Rb-1</i>	Retinoblastoma	<i>Rb-1</i> deficient	Heterozygotes associated with pituitary tumours. Homozygotes lethal in utero
RDS(D)	<i>rds</i>	Retinal degeneration, slow	Retinal degeneration, slow	Early onset retinal degeneration
SMPD1(R)* = NPD	<i>spm</i>	Niemann-Pick disease	Sphingomyelinosis	Tremor, ataxia, death. Foam cells invade liver, spleen. Purkinje cell depletion
SPTA1(D)*	<i>sph</i>	Elliptocytosis-2, spherocytosis-3	Spherocytosis	Lethal spherocytic anaemia, no alpha spectrin
SPTB(D)*	<i>ja</i> ‡	Elliptocytosis-3, spherocytosis-1	Jaundiced	Severe microcytic anaemia, no beta spectrin
TG(D)*	<i>cog</i> ‡	Hypothyroidism, goitrous	Congenital goitre	Small, enlarged thyroid
TYR(R)*	<i>c</i>	Albinism, tyrosinase negative	Albinism	Absence of melanin, defective vision
WS1, WS3(D) = PAX3	<i>Sp (Pax-3)</i>	Waardenburg I and III	Spotch	Depigmentation, homozygous lethal with neural tube defects

* Gene product absent or greatly reduced in pathological variants of both species.
† Homology based on absence of dystrophin in both DMD and *mdx* variants.^{69 70}
‡ *ja* is thought to be a mutant at the *Spnb-1* locus, homologous with SPTB, but this has yet to be confirmed. The same situation applies to *cog* and the *Tgn* locus, homologous with human TG.

homologies, based mainly on phenotypic resemblances, have been omitted from these listings, for example, those between human WAS (Wiskott-Aldrich syndrome) and mouse *sf*,⁶⁴ also IP (incontinentia pigmenti) and mouse *Td* (tattered).⁶⁵ However, the findings of Laval and Boyd⁶⁶ have made these homologies more likely. Homology between the X linked agammaglobulinaemia locus (AGMX1) and X linked immune deficiency (*xid*) also needs clarification, as there are several human X linked immunodeficiencies. However, the X linked loci for human otopalatodigital syndrome (OPD1) and mouse palate-tail-digits anomaly (*ptd*) have been included in the tables because of their unique and similar phenotypes and equivalent position on the map.^{43 44}

Chromosome maps of disease homologies

Fig 1 is a synthesis of the data on chromosomal locations of disease genes (given in table 1) and of their mouse homologues, arranged in order of human chromosomes. Chromosomal locations of mouse homologues are shown under the human map, so as to indicate conserved segments. These can be used to predict the likely position in one species of a disease gene located to a conserved segment in the other. Since the mouse locus positions of fig 1 are arranged in order of increasing distance from the centromere, the slope of the result (if discernible) indicates whether orientations with respect to the centromere are the same in both species (as in human chromosome 1p and

Figure 1 Positions of hereditary disease homologues on human and mouse chromosomes. Horizontal diagrams of banded human chromosomes are shown above and below, with p and q positions read vertically. Sandwiched between them are shown the band positions of homologous loci (indicated by their human gene symbols) by means of parallel lines under the human bands concerned, as well as chromosomal and regional locations (in terms of cM from the centromere) of homologues on the mouse map in parentheses. If only the chromosome number is shown the mouse gene has not been regionally located. Asterisks show centromere positions on the human chromosomes while horizontal dotted lines separate mouse loci on different chromosomes.

Human chromosome 4

Human chromosome 5

Human chromosome 6

Human chromosome 10

Human chromosome 7

Human chromosome 8

Human chromosome 9

Human chromosome 11

Human chromosome 12

Human chromosome 19

Human chromosome 22

Human chromosome 20

Human chromosome X

Human chromosome 21

Human chromosome Y

Figure 2 Oxford grid⁶⁷ which shows numbers of loci associated with hereditary disease which have been assigned to different pairs of human and mouse autosomes. Small triangles refer to individual loci, large triangles to groups of five. Where triangles point downwards loci are in the short arm (p), where upwards they are in q. Small circles represent a single locus unassigned to p or q.

mouse 4) or opposite (as in human 1q and mouse 1). However, this point of evolutionary importance can be analysed with greater precision by use of the whole database (now comprising more than 900 pairs of assignments) rather than just the disease homologies, so is not considered further here.

Oxford grid

The Oxford grid⁶⁷ is designed to show the distribution of homologous loci and conserved segments among human and mouse autosomal arms. In the grid for all the assigned loci⁴⁶ there is a general tendency for conserved regions to be found in chromosomes of similar relative size in the two species. This same tendency is found in the present grid (fig 2) for loci associated with hereditary diseases, since entries around the top-left to bottom-right diagonal are much more numerous than around the opposite diagonal. Homologous disease loci have been assigned on all human and mouse chromosomes, but human 13 is only represented once and human 18 twice. The X chromosome has more homologous disease loci than any others (12% of the total) with human chromosomes 1 (10%) and 11 (9%) next. However, when all known human-mouse assignments are considered, human chromosome 1 has 68% more homologous loci than chromosome 11.

Nature of variation in mouse homologues

We list 214 loci associated with human hereditary disease which have homologues

located in the mouse. These should provide useful and valid mouse models for such diseases, once suitable mutants have been obtained.

For 32 of the mouse loci (15%) no variants have been reported. There are 143 loci (67%) associated with restriction fragment length variants,⁶⁸ much used in mapping, but pathological variants have been reported so far from only 42 (20%). These are marked with an asterisk in table 1A and their characteristics are summarised in table 2. They include examples of the successful production of pathological variants by targeted mutagenesis, such as the mouse models for cystic fibrosis (CFTR),^{71 72} for Gaucher disease (GBA),⁷³ and for retinoblastoma (RB1).^{74 75} Non-pathological variants other than RFLVs are known from 49 loci (23%).

Homologies given in table 2 are based mainly on molecular and other biochemical criteria, apart from certain X linked loci (for example, human CDPX2, EDA, NHS) where they are based on phenotypic resemblance and expected location. Mouse symbols are as given in the standard listing¹⁰ but some alternatives, based on recent research throwing light on homology, are also given in parentheses. At several mouse loci multiple pathological alleles are known; only the most relevant one (or two in the case of *Hbb*) are given in table 2. McKusick⁶ tabulates human phenotypes under autosomal dominant, autosomal recessive, and X linked; these are indicated in table 2. For the mouse dominants, heterozygous effects are indicated in the table although homozygous ones (often lethality) may also be shown. For mouse recessives, homozygous effects are shown and both hemi- and heterozygous ones as a rule with the X linked variants. From a comparative point of view the most useful homologies are those in which the pathological effects seem to result from lack of the same gene product, for example, inactivation of the same enzyme in both species. The basis for homology has been marked with an asterisk in table 2 where this appears to be the case. It should be noted, however, that if the enzyme deficiency is the result of a chromosome deletion involving the gene concerned (as may frequently happen with radiation induced mutations), adjacent loci will often be affected also.

Among the 49 loci for which only non-pathological variants other than RFLVs have been described in the mouse are those associated with Fabry disease (GLA), gangliosidosis (GLB1), haemolytic anaemia resulting from G6PD deficiency (G6PD), Lesch-Nyhan disease (HPRT), Creutzfeldt-Jakob disease (PRNP), and X linked ichthyosis (STS). In general, these variants determine different forms of the enzyme concerned (often found in different mouse strains, races, or species) rather than enzyme deficiencies. An exception is the HPRT homology. A mouse mutant cell with loss of HPRT activity was selected in cultured embryonic stem (ES) cells and then incorporated into embryos to give mouse chimeras, from which mutant mice having the

same genetic defect as Lesch-Nyhan patients were generated.^{76,77} These were viable and apparently normal at birth and still appeared normal on later examination although they had abnormal dopamine levels, as expected with HPRT deficiency. It has now been reported⁷⁸ that if *Hprt* deficient mice are given an APRT inhibitor they develop a Lesch-Nyhan type of self-injurious behaviour. Thus, mice seem more reliant on APRT than HPRT for their purine salvage, in contrast to humans.

Thus HPRT deficiency cannot be included among the pathological variants of the mouse, despite its severe effects in human hemizygotes. Another locus with contrasting effects in human and mouse deficiencies is that for Duchenne muscular dystrophy (DMD). This has been included among the mouse pathological variants (table 2) because affected mice develop tremors and mild incoordination when 'old',⁷⁹ but effects in human victims of this disease are much more severe and do not involve incoordination beyond that secondary to weakness.

The most appropriate comparisons of pathological effects at human and mouse homologous loci are those between those having the same mutant gene dosage, whether homozygotes, hemizygotes, or heterozygotes. A problem arises with some recessive pathological variants in the mouse since the nature of a mutant homozygote may be unknown at the homologous human locus. One probable example is myelin basic protein (MBP) deficiency, which leads to the shiverer (*shi*) condition in mice, with a much shortened lifespan, violent shivering, and locomotor difficulties.⁹ Heterozygotes have normal behaviour but only half the normal amount of MBP. Effects of human homozygosity for MBP deficiency seem to be unknown.⁶ Another example involves colony stimulating factor 1 (CSF1). This protein gene is absent in the macrophage deficient osteopetrotic (*op/op*) mouse,⁸⁰ but the phenotype of human homozygotes for CSF1 deficiency is unknown.⁶

In general, scrutiny of table 2 together with information on the relevant human homologues⁶ suggests that effects of pathological mutants are similar in both species. Of course this would be expected for those loci for which homologies have been postulated mainly on the basis of phenotypic effects (as well as appropriate chromosomal location), but it also seems to be true for those in which the homology is based on knowledge of proteins or DNA sequences involved.

Positional predictions for loci without known homologies

Many human or mouse pathological loci have been mapped in the one species but are unknown in the other. However, our knowledge of conserved regions in the two species is now so extensive that it is often possible to predict the likely map position of the undiscovered human or mouse locus from its known position in the other species, thus facilitating any search for the locus concerned.

A list of mouse loci, in alphabetical order of gene symbols, was scanned for pathological mutants. Data from the first 50 which had been regionally mapped but had as yet no human homologues (from *asebia ab* to grey lethal *gl*) were analysed in relation to any neighbouring loci which had regionally assigned human homologues. It was found that for 26 of the loci (that is, over 50%) the position of a human homologue could be confidently predicted because the mouse locus concerned lay within or very close to a known conserved region.

Even higher rates of prediction were obtained when a series of mapped human disease loci without known mouse homologues was analysed. Table 3 shows that for about 80% of these it was possible to predict regional locations of a mouse homologue with a fair degree of confidence. Only future mapping studies will show whether this confidence is justified.

Table 4 deals with the opposite situation, in which loci with pathological effects in the mouse have been located accurately but their possible human homologues have not. There are, of course, many other similar syndromes in the two species^{81,82} for which genetic information is more limited.

Proto-oncogenes

Another group of genes of considerable medical interest, besides those directly responsible for human hereditary disease, are the proto-oncogenes. An increasing number are now known to control various aspects of cell growth and differentiation when in their normal form. If, however, their essential functions are disrupted through mutation, structural change or other mechanisms, they may become oncogenic. Table 5 lists those proto-oncogene loci which have been mapped on both human and mouse chromosomes, as well as growth factor loci, many known to have oncogenic effects. These and other neoplasia related loci, including those for endogenous mouse mammary tumour and leukaemia viruses as well as genes controlling viral replication, viral and tumour specific antigens, etc, are listed by Kozak⁸³ and by Roderick *et al.*⁸⁴ The recently discovered family of *Wnt* genes is included as members are clearly oncogenic and seem to have an important role in intercellular signalling and other aspects of developmental regulation.⁸⁵

Of the 69 loci listed here, 67 are in conserved segments of human-mouse homology, often of considerable length. The two apparent exceptions are REL and RET, but the human locations of both are regarded as provisional.⁶ The three oncogene loci JUNB, JUND, and MEL, together with the lymphoblastic leukaemia locus LYL1 and the insulin resistance gene INSR, form a medically interesting conserved (but disrupted) segment between human 19p and mouse 8, with no other known members.⁸⁶ The oncogene/growth factor group of loci seem to be fairly evenly spread over human and mouse chromosomes, with highest numbers on human 1 (7) and mouse 7 (9).

Table 3 Probable location on mouse autosomes of homologues for mapped human disease loci

Name of disorder	Symbol	Human location	Predicted mouse location	
			Chromosome No	Map units (cM) from centromere
Acetyl-CoA carboxylase deficiency	ACAC	17q21	11	49-62
Acoustic neuroma	NF2	22q11.21-q13.1	15 or 16	25-27 or 12-18
Adrenal hyperplasia II	HSDB3	1p13.1	3	63-67
Alagille syndrome	AGS	20p11.2	2	55-65
Alcohol intolerance, acute	ALDH2	12q24.2	10	56-70
Alpha-1-antichymotrypsin deficiency	AACT	14q32.1	12	49-ter
Angiodema	C1NH	11q11-q13.1	19	Cen-16
Ataxia telangiectasia	ATA	11q22-q23	9	14-25
Basal cell naevus syndrome	BCNS	9q31	2 or 4	10-30 or 25-35
Beckwith-Wiedemann syndrome	BWS	11pter-p15.4	7	23-26
Cardiomyopathy, hypertrophic	MYH7	14q12	12	20-31
Cerebrotendinous xanthomatosis	CYP27	2q33-qter	1	25-32
Deafness, low tone	LFHL1	5q31-q33	11	23-30
Dentinogenesis imperfecta 1	DGI1	4q13-q21	4	36-50
Diabetes mellitus, MODY type I	MODY1	20q13	2	74-ter
Diastrophic dysplasia	DTD	5q31-q34	11	23-30
DiGeorge syndrome	DGCR	22q11	16	12-18
Epidermolysis bullosa	COL7A1	3p21	9	54-70
Epilepsy, juvenile myoclonal	EJM1	6p21.3	17	17-23
Fanconi anaemia 1	FA	20q	2	—
Friedreich ataxia	FRDA	9q13-q21.1	19?	—
Haemochromatosis	HFE	6p21.3	17	17-23
Huntington's disease	HD	4p16.3	5	13-31
Langer-Giedion syndrome	LGCR	8q24.11-q24.13	15	15-28
Long QT syndrome	LQT	11p15.5	7	23-50
Marfan syndrome	FBN1	15q21.1	2 or 9	51-56 or 26-27
Maroteaux-Lamy syndrome	ARSB	5q11-q13	13	52-65
Multiple endocrine neoplasia I	MEN1	11q13	19	Cen-16
Muscular dystrophy, facioscapulohumeral	FMD	4q34-qter	8?	~ 30?
Muscular dystrophy, limb-girdle	LGMD1	5q31.3-q33.5	11	23-30
Myotonic dystrophy	DM	19q13.2-q13.3	7	Cen-22
Nail-patella syndrome	NPS1	9q34	2	14-26
Nemaline myopathy	NEM1	1q21-q23	1	71-73
Neurofibromatosis, von Recklinghausen	NF1	17q11.2	11	44-50
Oroticaciduria	UMPS	3q13	9?	45-52
Paraganglioma	PGL	11q22-q23	9	14-25
Plasmin inhibitor deficiency	PLI	17pter-p12	11	37-43
Polycystic ovarian disease	EDH17B1	17q11-q12	11	44-50
Prader-Willi syndrome	PWCR	15q11	7	26-33
Rubinstein-Taybi syndrome	RSTS	16p13.3	16	Cen-12
Sanfilippo syndrome	GNS	12q14	10	71-73
Smith-Magenis syndrome	SMCR	17p11.2	11	37-43
Spinal muscular atrophy	SMA	5q12.2-q13.3	13	52-66
Spinocerebellar ataxia 1	SCA1	6p21.3-p21.2	17	17-25
Split hand/foot deformity type 1	SHFD1	7q21.2-q21.3	5	53-69
Torsion dystonia	DYT1	9q32-q34	2	14-26
Treacher-Collins mandibulofacial dysostosis	TCOF1	5q31.3-q33.3	18	17-35
Trichorhinophalangeal syndrome	TRPS1	8q24.12	15	15-28
Tuberous sclerosis 1	TSC1	9q33-q34	2	14-26
Usher syndrome, type 1	USH1	14q	12 or 14	—
van der Woude syndrome	VWS	1q32	1	47-56
von Hippel-Lindau syndrome	VHL	3p24-p25	6 or 14	35-45 or cen-10
von Willebrand disease	VWF	12pter-p12	6	50-71
Werner syndrome	WRN	8p12-p11	8	5-10
Wilson disease	WND	13q14-q21	14	28-ter
Xeroderma pigmentosum, group B	ERCC3	2q21	2	27-56
Zellweger syndrome 1	ZWS1	7q11.23	5 or 6	—

Table 4 Genetically unassigned human syndromes suspected of homology with mouse genes of known regional location, thus allowing tentative predictions of likely human gene location

Name of human syndrome	MIM No	Mouse mutant(s)	Locations	
			Mouse	Human (predicted)
Acromesomelic dysplasia	201250	Ulnaless (<i>Ul</i>)	2.35	2q31-q37
Cenani-Lenz (syndactylism)	212780	Limb deformity (<i>ld</i>)	2.53	15q15
Chediak-Higashi (lysosomal)	214500	Beige (<i>bg</i>)	13.17	1q43/7p
Epilepsy, temporal lobe	—	Epilepsy (<i>El-1</i>)	9.51	3q21
Fraser (cryptophthalmos)	219000	Blebs (<i>my</i>) or Blebbed (<i>bl</i>)	3.39 or 5.44	4q26-q27 or 4q11-q13
Fryns	229850	Short ear (<i>se</i>)	9.38	6p12/15q
Hermansky-Pudlak	203300	Cocoa (<i>coa</i>) or pearl (<i>pe</i>)	3.07 or 13.62	8q or 5q
Pituitary dwarfism III	262600	Miniature (<i>mn</i>)	15.26	22q12/8q24
Osteopetrosis (Albers-Schonberg)	259700	Grey lethal (<i>gl</i>)	10.25	6q21
Restrictive dermopathy	275210	Pupoid fetus (<i>pf</i>) or tight skin (<i>Tsk</i>)	4.61 or 2.56	1p36 or 2q/15q/20p
Situs inversus viscerum	270100	Situs inversus viscerum (<i>iv</i>)	12.63	14q32
Spondylocostal dysplasia	277300	Rachiterata (<i>rh</i>)	2.35	2q31-q37

Their regional location shows no marked signs of a proximal or distal bias.

Genomic imprinting

In recent years it has been realised that the route of inheritance of a gene, that is, the parent of origin, can influence its phenotypic effects and expression in various tissues as well

as those of any mutation which it carries. Normally, of course, an autosomal gene is inherited from both parents but a deletion of the locus concerned, or such phenomena as non-disjunction or meiotic segregation in translocation heterozygotes, can lead to transmission from one parent only, that is, to uniparental disomy or monosomy. For certain

Table 5 Proto-oncogene (O) and growth factor (GF) homologies in human and mouse chromosomes

Locus symbol		Name	Human location		Mouse location		
Man	Mouse		Chr	G band	Chr	cM*	G band
ABL1	<i>Abl</i>	Abelson leukaemia O	9	q34	2	21	B
ABL2	<i>Abll</i>	ABL-like O	1	q24-q25	1	62	C5-H3
AKT1	<i>Akt</i>	Murine thymoma viral O	14	q32.3	12	65	F1-F2
ARAF1	<i>Araf</i>	Raf related O	X	p11.4-p11.23	X	7	A2-A3
EGF	<i>Egf</i>	Epidermal GF	4	q25	3	78	F3-H1
EGFR	<i>ErbB</i>	Epidermal GF receptor	7	p13-p12	11	8	A1-A2
ERBB2	<i>ErbB-2</i>	Erythroblastosis B2 O	17	q11.2-q12	11	56	D-E1
ETS1	<i>Ets-1</i>	E26 avian leukaemia 1 O	11	q23.3	9	14	A1-A4
ETS2	<i>Ets-2</i>	E26 avian leukaemia 2 O	21	q22.3	16	57	C3-C4
FES	<i>Fes</i>	Feline sarcoma O	15	q25-qter	7	37	D1-D3
FGF1	<i>Fgf-1</i>	Fibroblast GF 1, acidic	5	q31.3-q33.2	18	19	C-D
FGF2	<i>Fgf-2</i>	Fibroblast GF 2, basic	4	q26-q27	3	18	A2-B
FGF3	<i>Fgf-3</i>	Fibroblast GF 3 (INT2 O)	11	q13	7	74	F1-ter
FGF4	<i>Fgf-4</i>	Fibroblast GF 4 (HSTF1 O)	11	q13	7	74	F1-ter
FGF5	<i>Fgf-5</i>	Fibroblast GF 5	4	q21	5	50	F
FGF6	<i>Fgf-6</i>	Fibroblast GF 6	12	p13	6	54	F3-G1
FGFR1	<i>Fgfr1</i>	Fibroblast GF receptor 1	8	p12-p11.2	8	10	A1-A4
FGR	<i>Fgr</i>	Gardner-Rasheed feline sarcoma O	1	p36.2-p36.1	4	62	D3
FOS	<i>Fos</i>	FBJ osteosarcoma O	14	q24.3-q31	12	35	Cen-F1
FYN	<i>Fyn</i>	FYN oncogene	6	q21	10	24	Cen-B4
GLI	<i>Gli</i>	Glioblastoma O	12	q13.3-14.1	10	72	D
GLI3	<i>Gli-3</i>	Glioblastoma O 3	7	p13	13	18	A2
GRO1	<i>Mgsa</i>	GRO1 O, melanoma growth stim activity	4	q21	5	45	E2-F
HRAS	<i>Hras-1</i>	Harvey rat sarcoma O	11	p15.5	7	31	C-D3
HS1	<i>His-1</i>	His-1 O	2	q14-q21	2	32	C
IGF1	<i>Igf-1</i>	Insulin-like GF 1	12	q23	10	54	C1-D1
IGF1R	<i>Igf1r</i>	Insulin-like GF 1 receptor	15	q25-qter	7	31	C-D3
IGF2	<i>Igf-2</i>	Insulin-like GF 2	11	p15.5	7	72	F1-ter
IGF2R	<i>Igf2r</i>	Insulin-like GF 2 receptor	6	q25-q27	17	11	A2-A3
INT4	<i>Int-4</i>	Mammary tumour virus integration site 4 O	17	q21-q22	11	62	E1-E2
JUN	<i>Jun</i>	Avian sarcoma virus O	1	p32	4	40	C5-C7
JUNB	<i>Junb</i>	Avian sarcoma virus B O	19	p13.2	8	29	C
JUND	<i>Jund</i>	Avian sarcoma virus D O	19	p13.2	8	22	C
KIT	<i>Kit</i>	Kit (Hardy-Zuckerman) O	4	q11-q12	5	37	D-E2
KRAS2	<i>Kras-2</i>	Kirsten rat sarcoma 2 O	12	p12.1	6	70	F3-G3
LYN	<i>Lyn</i>	Yamaguchi sarcoma, viral related O	8	q13-qter	4	6	A1-A2
MAS1	<i>Mas</i>	Mas O	6	q24-q27	17	8	A2-A3
MEL	<i>Mel</i>	NK14 derived transforming O	19	p13.2-cen	8	30	C
MET	<i>Met</i>	Met O	7	q31	6	6	Cen-B1
MGF	<i>Sl</i>	Mast cell GF	12	q14.3-qter	10	65	D1
MOS	<i>Mos</i>	Moloney sarcoma O	8	q11	4	6	A1-A2
MYB	<i>Myb</i>	Avian myeloblastosis O	6	q22-q23	10	16	Cen-B4
MYC	<i>Myc</i>	Myelocytomatosis O	8	q4.1	15	15	D2-D3
MYCL1	<i>Lmyc-1</i>	Lung carcinoma, myc related O	1	p32	4	50	C7-D1
MYCN	<i>Nmyc-1</i>	Neuroblastoma, myc related O	2	p24.1	12	4	Cen-F1
NGFB	<i>Ngfb</i>	Nerve beta GF	1	p13	3	67	F3-H1
NGFG	<i>Ngfg</i>	Nerve gamma GF	19	—	7	22	C
NGFR	<i>Ngfr</i>	Nerve growth factor receptor	17	q21-q22	11	54	D
NRAS	<i>Nras</i>	Neuroblastoma transforming O	1	p13	3	63	D-H1
PDGFA	<i>Pdgfa</i>	Platelet derived GF alpha	7	p22	5	69	G
PDGFB	<i>Pdgfb</i>	Platelet derived GF beta	22	q12.3-q13.1	15	25	E
PDGFRA	<i>Pdgfra</i>	Platelet derived GF receptor alpha	4	q11-q13	5	37	D-E2
PDGFRB	<i>Pdgfrb</i>	Platelet derived GF receptor beta	5	q33-q35	18	31	D
PIM	<i>Pim-1</i>	Proviral integration, MCF, O	6	p21	17	17	A3-B
PVT1	<i>Pvt-1</i>	Plasmacytoma variant translocation O	8	q24	15	16	D2-D3
RAF1	<i>Raf-1</i>	Murine leukaemia viral O	3	p25	6	45	C3
REL	<i>Rel</i>	Reticuloendotheliosis O	2	p13-p12	11	12	A1-B1
RET	<i>Ret</i>	Ret O	10	q11.2	6	46	C3-F3
RRAS	<i>Rras</i>	Related ras viral O	19	q13.3-qter	7	22	C
SEA	<i>Sea</i>	S13 avian erythroblastosis O	11	q13	19	5	B
SKI	<i>Ski</i>	Sloane-Kettering avian viral O	1	q22-q24	4	69	D3-ter
SRC	<i>Src</i>	Rous sarcoma O	20	q12-q13.11	2	71	H1
TGFB1	<i>Tgfb-1</i>	Transforming beta 1 GF	19	q13.1	7	7	Cen-A3
TGFB2	<i>Tgfb-2</i>	Transforming beta 2 GF	1	q41	1	79	H5-ter
TGFB3	<i>Tgfb-3</i>	Transforming beta 3 GF	14	q24	12	36	Cen-F1
THRA1	<i>Erba</i>	Thyroid hormone receptor O	17	q11.2-q12	11	56	D-E1
WNT1	<i>Wnt-1</i>	Wingless related integration site 1 O	12	q13	15	41	F1-F3
WNT2	<i>Wnt-2</i>	Wingless related MMTV integration site 2	7	q31	6	6	Cen-B1
WNT3	<i>Wnt-3</i>	Wingless related MMTV integration site 3	17	q21-q22	11	62	E1-E2

* Distance from centromere in centimorgans.

loci or chromosome regions uniparental inheritance has a detrimental effect, the nature and extent of which may depend on whether the inheritance is maternal or paternal.⁸⁷ In addition, distortion of segregation ratios, with human examples in cystic fibrosis, diabetes, neural tube defects, and allergy pedigrees,⁸⁸ may reflect a parent of origin effect.⁸⁹ Two of the most convincing examples of imprinting among human conditions concern the Angelman (AS) and Prader-Willi syndromes (PWS) with different clinical phenotypes but both often involving deletions in 15q11-q13. However, the Angelman syndrome is associated with maternal origin of the deletion^{90 91} while the Prader-Willi syndrome is

associated with its paternal origin.⁹² This deletion is in a short region of conserved synteny between parts of human 15q and mouse 7.⁹³ The latter chromosome has one imprinting region proximal to G band 7C and another distal to 7E1.⁹⁴ The deleted region in AS/PWS seems homologous to a more central region of mouse 7, but recent evidence shows that this region too is implicated in the imprinting phenomenon.⁹⁵ These two human syndromes also arise in the absence of deletions but associated with either iso- or heterodisomy of the maternal chromosome 15 (in PWS)⁹⁶ or the paternal one (in AS)⁹⁷ as would be expected if genomic imprinting is occurring in this region. It now seems likely that there are separate

Table 6 Mapped human disease loci and chromosomal regions possibly involved in genomic imprinting⁸⁷⁻⁹⁹⁻¹¹⁴ with homologous regions in the mouse.^{3,4} M,P=maternal or paternal inheritance when human anomaly is expressed. Where evidence for imprinting is described as 'slight' in last column, differential rates of recovery of maternal and paternal disomies have been reported⁸⁹

Chromosome	Human			Mouse	
	Disease/malformation	Locus symbol	Origin	Homologous region in chr(s)	Evidence for imprinting in these
4p16.3	Huntington's (severe early onset form)	HD	P	5B-F	Slight
6p21.3-21.2	Spinocerebellar ataxia	SCA1	P	17	Yes
7	Pre- and postnatal growth retardation	—	Uniparental disomy M	2,5,6,11,13	Yes on 2,6,11
9q34-qter	Chronic myeloid leukaemia	—	P	2,4	Yes on 2, none on 4
22cen-q11			M	10	None
11p15.5	Embryonal rhabdomyosarcoma	RMS	Isodisomy P	7B5-E3	Yes
11p15.5	Beckwith-Wiedemann	BWS	Duplication P*	7B5-E3	Yes
11p13	Wilms's tumour	WT1	Deletion M	2E4-F3	Yes (more distal)
11q23-qter	Paraganglioma	PGL	P	9A4-B	None
13q14.1-q14.2	Retinoblastoma 1	RB1	P	14D2-E1	Slight
14	Dysmorphism, mental defect	—	Disomy P	12,14	Unknown on 12, slight on 14
14	Short stature	—	Disomy M	12,14	Unknown on 12, slight on 14
15q11-q13	Angelman	ANCR	Deletion M	7B5-D3	Yes
15q11-q13	Prader-Willi	PWCR	Disomy P		
			Deletion P	7B5-D3	Yes
			Disomy M		
16	Intrauterine growth retardation, abortion	—	Isodisomy M†	7,8,11,16,17	Yes on 7,11,17
17q11.2	Neurofibromatosis 1 (severe form)	NF1	M	11B5-E1	Yes (more proximal)
19q13.3	Myotonic dystrophy‡ (severe form)	DM	M	7cen-A3	Yes
20q13.11	Albright's osteodystrophy	AHO	M	2H	Yes
22q11.21-q13.1	Neurofibromatosis 2 (severe form)	NF2	M	10,11,15,16	Yes for 11

* Expression also with maternal inheritance; probably two genes involved.
† Maternal disomy for chromosome 22 has also been reported but is apparently harmless,^{112,113} as is maternal disomy for chromosome 4, paternal isodisomy for chromosome 6, and paternal heterodisomy for the X and Y chromosomes.⁸
‡ Associated with unstable DNA sequence (trinucleotide repeats).¹¹⁴ As with the fragile X syndrome (FRAXA) there seems to be expansion of the repeats through an ovary but not through a testis.

unique critical regions or even single genes responsible for the Angelman and Prader-Willi syndromes.⁹⁸

Genomic imprinting has been suspected as the mechanism behind a number of other instances of differential parental transmission of human hereditary diseases.⁸⁷⁻⁹⁹⁻¹⁰¹ Those of known human location are listed in table 6, together with information on presumptive homologous regions in the mouse. Only two of the 18 entries show a clear cut discrepancy between findings in the two species. It should be remembered, however, that little is known about the actual size of imprinted regions in the mouse since those shown as such on the map¹¹⁵ have been identified mainly by the aberrant behaviour of marked chromosome segments which are proximal or distal to translocation breakpoints, when heterozygotes for such translocations are intercrossed. Recent data on this point for mouse 7 concern the closely linked genes *Igf2* and *H19*, both mapping to a distal region which is known to show imprinting effects with both maternal and paternal duplication.⁹⁴ Both genes are imprinted, with only the paternal gene active in *Igf2*^{116,117} and the maternal one in *H19*.¹¹⁸ This suggests that imprinting signals are unlikely to act over large chromosomal regions. Indeed, single genes or small critical regions may be responsible for these parent of origin effects. Confirmatory evidence comes from *Igf2r*, which codes for the *Igf2* receptor gene on mouse 17. This is expressed only from the maternally inherited chromosome (that is, not from paternal disomy/maternal nullosomy) but some very closely linked genes are not subject to imprinting.¹¹⁹

In general, imprinting phenomena involve major effects on growth and behaviour, including overgrowth, hyperactivity, and tumours.

Mouse *Igf2* imprinting effects involve growth, so it is interesting to note that both this gene and *H19* have homologues in the short arm of human chromosome 11, at 11p15.5.¹²⁰ This region seems to contain a locus for the fetal overgrowth anomaly which leads to Beckwith-Wiedemann syndrome (BWS) and at least two genes which predispose to Wilms's tumour, rhabdomyosarcoma, hepatoblastoma, etc. It is now clear that parent of origin effects, including paternal duplication of this region, can be found in BWS and in associated tumours as well as in *Igf2* related growth anomalies.¹²¹⁻¹²³

The amount of human imprinting information derived from the detection of uniparental de novo disomies is increasing rapidly, as table 6 shows. In its nature it closely resembles that provided by heterozygotes for Robertsonian translocations in the mouse when intercrossed and is particularly useful in its scanning of a whole chromosome for effects of imprinting. Prenatal lethality because of isodisomy may be difficult to pick up in humans. Nevertheless, it may play an important role in predicting the outcome after chorionic villus sampling where mosaicism is restricted to the placenta. It has particular importance for translocation carriers. The outcome for these and the transmission of single genes which manifest imprinting will have important ramifications for genetic counselling.⁸⁸ It seems clear that explanations based on genomic imprinting will play an important part in our future understanding of the origins of human hereditary disease.

Discussion

We list 214 mapped human loci with known pathological variants in which the position of the corresponding mouse locus has also been mapped. Forty two of these mouse loci (20%)

also have pathological variants, many of which resemble the human condition and are thus actually or potentially useful mouse models of human disease. These can throw light on the causes of the disease but can also help in developing therapies for various conditions not only at the genetic level but also in studying effects of diet changes, medication, etc.⁸² Gene therapy trials in humans are already being approved.¹²⁴ In general, the guidelines for these suggest that animal models are developed for trials before human use. Many models are currently in use,^{125 126} but at present only a small proportion of human hereditary disease loci have mouse models. The situation will not improve if we wait for relevant spontaneous mutations to turn up. Among alternative strategies are the following.

(1) Mutation induction with a supermutagen, such as ethylnitrosourea (ENU).¹²⁷ This has already been used successfully in mice to induce a mutant deficient in phenylalanine hydroxylase at the *Pah* locus,⁴⁷ a dominant mutant at the *Min* (multiple intestinal neoplasia) locus which develops numerous adenomata and seems to be a homologue of the gene for familial adenomatous polyposis coli (APC),⁵³ and a ferrochelatase deficiency at the *Fech* locus which leads to anaemia, photosensitivity, and liver dysfunction when homozygous.⁵⁵

(2) Targeted mutagenesis, in which a mutant cloned DNA sequence from the locus concerned is introduced into mouse pluripotent embryonal stem (ES) cells by the process of homologous recombination. The altered ES cells are then injected into mouse eight cell embryos or blastocysts, in the hope that some of these progeny will become part of the germ cell lineage and thus make the mutation heritable.^{128 129} As described earlier, this method has been used to generate a mutation at the *Hprt* locus in mice, while further gene targeting has led to the correction of an HPRT deficiency in an embryonic stem cell line¹³⁰ and generation of growth deficient *Igf2* mice.⁹⁸ An extension of the targeting technique has allowed the creation of a large deletion at the *Tcrb* (T cell receptor β subunit) locus on mouse chromosome 6.¹³¹ The successful production of mouse models of cystic fibrosis^{71 72} and Gaucher disease⁷³ are other examples.

(3) Use of gene transfer techniques, with the introduction of foreign DNA, either by microinjection into the pronuclei of fertilised eggs or by retroviral infection of a specific organ. This technique has been used to remove the pathological effects of a mutant gene, for example, in shiverer (*shi*) mice, the locus being homologous with human MBP. The injection of normal DNA at this locus led to the production of mice with normal behaviour.¹³² Meisler¹³³ has listed 13 insertional mutations at established mouse loci generated by the integration of foreign DNA within a functional gene, as well as pathological mutations at 16 previously unknown loci. Undoubtedly some of these will become mouse models of human disease. A steady flow of such models can be expected from the random insertion of micro-

injected transgenes and resultant 'accidental knockouts' of genes at medically important loci.

At least 670 disease loci have now been mapped on human chromosomes,⁶⁷ as compared with 214 on both human and mouse. Since many other loci have been mapped in the mouse it seems likely that a large number of human/mouse homologies for mapped loci remain to be discovered. Because so much is now known about conserved segments in the two species, the 'positional cloning' approach¹³⁴ to gene identification is likely to become increasingly useful in unmasking these hidden homologies. With the development of new in situ techniques, localising the human or mouse homologue on its chromosome should become relatively simple. Once the location of the human disease gene has been mapped by pedigree analysis, then perusal of both human and mouse chromosome maps may be useful in showing 'candidate genes' if the locus lies within a conserved segment. Thus Waardenburg syndrome type I (WS1) was mapped to a region of human chromosome 2 which shares a long conserved segment with proximal mouse 1. The similar mouse gene *splotch* (*Sp*) was located here at the appropriate spot and was subsequently shown to be one of the paired box genes *Pax-3*. Affected WS1 families have been found to contain mutations in the human homologue of this gene, PAX3. These have now been found associated with Waardenburg syndrome type 3 (WS3) also.⁶² Similarly, human aniridia (AN2) and mouse small eye (*Sey*) are located in homologous regions on chromosomes 11 and 2 respectively and both are the result of mutations in *Pax-6*. In addition, *Pax-1* is mutated in the chromosome 2 mouse mutant undulated (*un*), with vertebral and other skeletal anomalies. Thus, this set of paired box containing genes clearly comprise a vital component of the molecular mechanisms of mammalian development.¹³⁵

Another recent example of a candidate gene for a human hereditary disease is PMP22 (peripheral myelin protein 22), for the Charcot-Marie-Tooth neuropathy type 1A (CMT1A). This maps to 17p11.2, with a mouse model trembler (*Tr*) in a conserved segment on chromosome 11. *Tr* and another allele have now been found to be mutant for *Pmp22*, which maps very close to this locus.¹³⁶ CMT1A is associated with a DNA duplication and it has now been shown that PMP22 maps within this duplication.^{137 138} A similar condition results from partial trisomy of human 17 including the 17p segment concerned.

It is not really surprising that mouse mutants at homologous loci to those responsible for human disease sometimes fail to resemble the human phenotype at all closely, since so many factors can lead to differences. Of course it is most important to be sure that the genes are truly homologous. As Darling and Abbott⁸² have pointed out, even if both mutate to give the same enzyme deficiency, this may affect the structural gene in one species but a regulatory gene in the other, switching off gene transcription. Introduction of a wild type structural

gene into the latter would not correct the gene defect. Thus evidence at the DNA level is very desirable. This may well show mutations in each lineage since the common ancestral form. In view of our substantial knowledge of conserved segments, accurate location of a suspected homologue is also of great value, especially where several 'mimic genes' are rival candidates.

Even where homology is not in doubt the actual nature of the mutation may be very different in the two species, with divergent effects on development as a result. Thus in the PMP22 homology described above, the Charcot-Marie-Tooth neuropathy is the result of duplication of part of the gene while the trembler alleles in the mouse stem from base pair mutation. As mentioned earlier, even if both mutant phenotypes are deficiencies which inactivate the gene, one or both may not be entirely intragenic, so that neighbouring loci may be affected also, complicating the analysis. It should also be remembered that many mouse loci have a whole series of multiple alleles, which may have surprisingly different pleiotropic effects. Thus, at the microphthalmia (*mi*) locus on chromosome 6 the 11 mutant alleles have a mixture of effects which involve pigmentation, size of eye, and capacity for secondary bone absorption. Pigmentation is abnormal in all, in a variety of ways, but each of the other traits is only found with some of the alleles, the most extreme of which (*mi*) is lethal.⁹ The degree of dominance also varies greatly. Where homology detection is based on mutants with partial gene inactivation, therefore, comparison with a single allele may not be sufficient. Thus, one *mi* allele (*mi*^{vi}) has been thought a possible homologue of human vitiligo because of its effects on pigmentation.¹³⁹ However, other effects of *mi* alleles may need consideration before the true homology can be established.

The genetic backgrounds to homologous genes cannot be the same for human and mouse chromosomes and this fact alone may lead to different phenotypic effects in the two species. It is known in the mouse that modifying genes can have a marked effect on gene expression, so placing the mouse model on a different genetic background (for example, an unrelated inbred strain) may be useful. Presumably human ethnic differences may have a similar effect. Sometimes a completely different species than the mouse may provide a more suitable model. Thus, the very slight deleterious effect of X linked muscular dystrophy in the mouse contrasts with the homologous canine condition (DMD) which is a progressive degenerative myopathy "clinically and pathologically similar to Duchenne muscular dystrophy in man".¹⁴⁰ This seems to be a better animal model, possibly because dogs live longer than mice.

These marked interspecific differences may arise because of evolutionary changes in metabolic pathways which may, for instance, allow a toxic product to accumulate in one species but to be efficiently removed in another. Time related effects should also be considered, es-

pecially when comparing species with life spans as divergent as the human 70+ years and the mouse 2+ years, with phenotypic classification of the latter often taking place soon after weaning age (20 to 50 weeks and 3 to 4 weeks respectively). Thus, homologues of some human hereditary diseases of late onset may not show up well in the mouse, even if they are kept until old. However, the loci concerned may still be discovered by positional cloning and other methods, as with Alzheimer disease (APP) (table 1).

Summing up, the philosophy encapsulated by Bateson's injunction: "Treasure your exceptions!" is now bearing fruit, as more and more of the mouse variants which were kept, bred, studied, and placed on the linkage and then the chromosome map are proving to be homologues of human disease loci. Thus, they can be used as models of human hereditary conditions, as appropriate subjects for gene therapy tests, and as aids to the demarcation of conserved segments and therefore to the localisation of human genes. In this respect human and mouse genetic advances can truly be called symbiotic.

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