Review

A Phenotype Map of the Mouse X Chromosome: Models for Human X-linked Disease

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The identification of many of the transcribed genes in man and mouse is being achieved by large scale sequencing of expressed sequence tags (ESTs). Attention is now being turned to elucidating gene function and many laboratories are looking to the mouse as a model system for this phase of the genome project. Mouse mutants have long been used as a means of investigating gene function and disease pathogenesis, and recently, several large mutagenesis programs have been initiated to fulfill the burgeoning demand of functional genomics research. Nevertheless, there is a substantial existing mouse mutant resource that can be used immediately. This review summarizes the available information about the loci encoding X-linked phenotypic mutants and variants, including 40 classical mutants and 40 that have arisen from gene targeting.

Mammalian X-linked traits are easily recognized by their inheritance patterns and their mode of expression. Whereas hemizygous males carry one copy of X-linked loci and suffer from the full effect of any mutation, heterozygous females carry two copies and have a phenotype that reflects the relative expression, as determined by X-inactivation status, of the mutated and normal copies of the gene (Lyon 1999). The X chromosome is also unusual in that X linkage of genes is almost totally conserved in eutherian mammals (Ohno 1973). Therefore, disorders that are X linked in man are also X linked in the mouse, which leads to the ready identification of mouse models of human X-linked disease. The existing mouse mutant resource, which comprises well over 1000 different stocks and strains, has been exploited to investigate gene function and disease pathogenesis associated with X-linked and autosomal loci (Paigen 1995; Bedell et al. 1997)[1]. The past decade has seen a revolution in the ability to deliberately introduce mutations into mouse genes by homologous recombination (Fisher 1997; Müller 1999; Roths et al. 1999) and, as a result, the number of mouse X-linked traits has doubled. Although there are earlier reviews (Davisson 1987; Miller 1990), no comprehensive summary of existing mouse X-linked phenotypes has been published recently. The primary aim of this review is to describe the current status of the phenotype map of the mouse X chromosome for those working in the field of genome research with an interest in X-linked disease.

Analyzing mouse mutants at the molecular and phenotypic level is one of the most powerful ways of understanding gene function in mammals. Apart from a few notable exceptions, in which mutations exist in mouse genes whose homologs are known to be responsible for human disease, there are considerable phenotypic similarities between the mouse and human disorders, and the mutant mouse provides an animal model for understanding disease pathogenesis and for assessing therapeutic regimes. Therefore, it is likely that most of the remaining mouse phenotypes will provide a valuable resource for identifying the molecular basis of a homologous human disease.

Comparative Map of the Human and Mouse X Chromosomes

The initial stage of assessing and identifying mouse models for human disease from the existing mouse mutant resources involves careful characterization of the phenotype associated with the mutant locus and predicting the position of its human homolog on the man–mouse comparative map.

The mapping of >130 conserved loci on the X chromosomes of both mouse and man (Boyd et al. 1998, 1999) has confirmed the prediction that X linkage of genes is preserved in mammals (Ohno 1973). However, when the relative positions of loci on the human and mouse X chromosomes are compared, it can be seen that subchromosomal blocks of homologous loci have been rearranged with respect to each other during the 80 million years of evolutionary time that separate the two species. It is important to under-

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[1]A comprehensive list of international mouse strain resources, developed jointly by the UK MRC laboratory at Harwell and the USA Jackson Laboratory (Eppig and Strivens 1999), and a list of strains available at the newly established European Mouse Mutant Archive (EMMA) in Italy, can be accessed via the World Wide Web at http://ismr.har.mrc.ac.uk; http://www.emma.cnr.it.

stand these rearrangements fully, because an identical comparative map position is an important criterion for identifying and confirming mouse models for human genetic disease. More than a decade ago, five distinct homologous blocks of loci or conserved segments were acknowledged as sharing homology on both the human and mouse X chromosomes (Searle et al. 1987, 1989; Amar et al. 1988; see Fig.1 and Table 1 for the current status of the comparative map). The human X chromosome long arm (Xq) was recognized as being split into two major blocks on the mouse X chromosome. There are only two minor modifications to this Xq comparative map, the identification of a 600-kb inversion around *Xist* (Rougelle and Avner 1996) and the mapping of the synaptobrevin like locus (*Sybl1*) to the proximal region of the mouse X chromosome (D'Esposito et al. 1997). In contrast, it soon became apparent that the three conserved segments thought to comprise the human X chromosome short arm (Xp) could be apportioned into five major and four minor conserved segments on the mouse X chromosome (Laval and Boyd 1993; Blair et al. 1994, 1995, 1998b; Blaschke and Rappold 1997). Twelve conserved segments have now been identified on the man–mouse X chromosome comparative map (Fig.1), and additional regions of homology may be defined as conserved genes are mapped to a higher resolution (Ehrmann et al. 1998). Nevertheless, for most of the X chromosome, once the position of a locus is known on the human X chromosome, its position on the mouse X chromosome can be predicted with reasonable accuracy and vice versa. The evolutionary breakpoint regions remain the only areas of uncertainty and these, because they have been subjected to multiple rearrangements during evolution, can be expected to have a complex structure and this has been borne out by recent mapping data (Dinulos et al. 1996; Blair et al. 1998b; Disteche et al. 1998). Over 130 genes and conserved loci have been regionally mapped on both the human and mouse X chromosomes and form the framework for constructing the comparative map (Table 1). This map has been invaluable in identifying human diseases and candidate gene loci for many of the classical mutants that have been recovered from mouse colonies over the years.

Spontaneous and Induced X-Linked Mouse Mutants and Variant Traits

Thirty-eight X-linked mouse-independent visible phenotypes covering a wide range of traits are reported in the literature (Table 2; Fig. 2). Most of these phenotypes have arisen spontaneously in mouse colonies or among the large numbers of mice used in mutagenesis experiments (George et al. 1994). The paucity of induced X-linked mutations is probably due to that fact that most novel mutations have been sought in the F_1 progeny of mutagenized males and as a result, only those X-linked mutations that have a phenotypic ef-

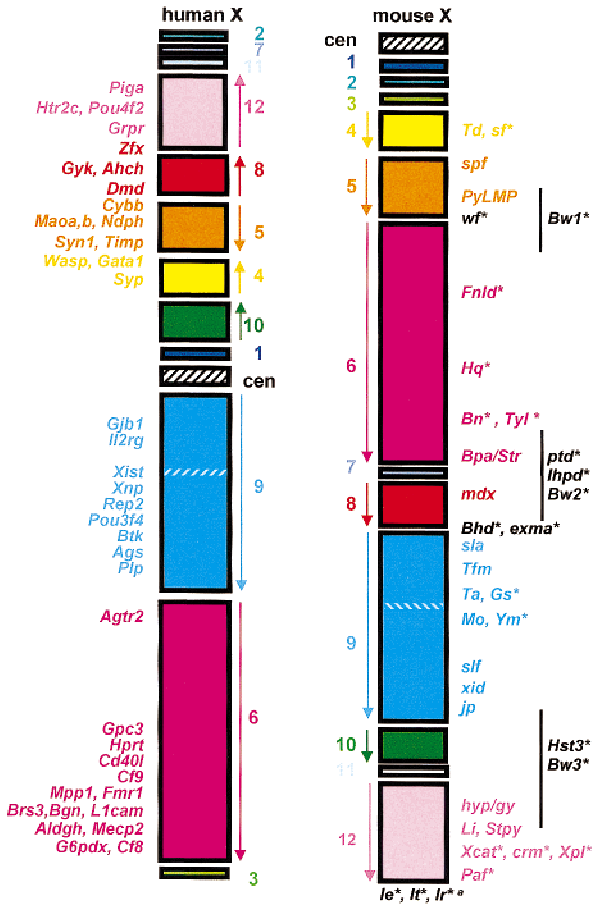

Figure 1 The comparative phenotype map of the human and mouse X chromosomes. Each conserved segment, in which the order of loci is the same in mouse and man, is indicated by a colored rectangle. The loci that define each segment are given in Table 1; note that the order of segments *1*, *2*, and *3* has not been established and is arbitrary. The segments are numbered from *1–12* from the centromere to the telomere on the mouse X chromosome and the order of loci indicated by an arrow alongside each block. The hatched region within segment *9* represents the 600-kb region that is inverted around the *Xist* locus (see text). The centromeric regions are indicated by black and white hatched rectangles; there is, as yet, no known evidence for evolutionary conservation of centromeric sequences between mouse and man. The Xp pseudoautosomal region, which has a complex evolutionary history (Blaschke and Rappold 1997), is not included because it is outside the scope of this review, as loci in this region do not exhibit X-linked inheritance. Classical mutants carrrying spontaneous and induced mutations and variants (Table 2) are indicated on the mouse X chromosome, and targeted mutations (Table 3) are positioned on the human X chromosome for clarity. Names in black text are (1) known to have an X-linked inheritance pattern but have not been positioned on the X (e.g., *Ie, It*), or (2) have not been subjected to high-resolution mapping (e.g., *Bw1*, the black line indicates the probable region in which the locus lies), or (3) have been mapped to evolutionary breakpoint positions and therefore the position of the human homolog cannot be defined (e.g., *exma, Bhd, wf*). For those traits marked with an asterisk (*), the gene responsible is not known; for all other traits the underlying lesion has been defined. [a](*Ir*) Immune response genes that are X linked (see Table 2 footnote).

Table 1. List of X-Linked Genes and Conserved Sequences

Seg.	Mouse location	Mouse symbol	Locus name	Human symbol	Human location
1	(A1-A2) 0.2	*DXHXF34*	DNA segment, Chr X, human DXF34	DXF34E	Xp11.21
2	0.5	*Sybl1*	synaptobrevin like gene 1	SYBL1	Xq28
3	(A-B) 0.7	*Pkare*	cAMP-dependent protein kinase	PRKX	Xp22.3
4	0.8	*Clcn5*	chloride channel 5	CLCN5	Xp11.2
	1.7	*Syp*	synaptophysin	SYP	Xp11.23-p11.22
	(A2) 1.8	*Tcfe3*	transcription factor E3	TFE3	Xp11.23-p11.22
	1.9	*Gata1*	GATA-binding protein 1	GATA1	Xp11.23
	1.95	*Suv39h1*	supressor of variegation 3-9, human like	DXS7466E	Xp11.23
	2.0	*Wasp*	Wiskott-Aldrich syndrome protein	WASP	Xp11.23
	2.05	*DXHXS7467e*	DNA segment, ChrX, human DXS7467E	DXS7467E	Xp11.23
	2.1	*Rbm3*	RNA binding motif protein 3	RBM3	Xp11.23
	2.1	*Ebp*	emopamil binding protein (*Tcf*)	EBP	Xp11.23
	2.1	*DXHXS7927e*	DNA segment, ChrX, human DXS7927E	DXS7927E	Xp11.23
	2.15	*DXHXS7465e*	DNA segment, ChrX, human DXS7465E	DXS7465E	Xp11.23
5	2.6	*Xkh*	McLeod syndrome gene homologue	XK	Xp21.1-Xp11.4
	2.8	*Cybb*	cytochrome b-245, beta polypeptide	CYBB	Xp21.1
	(A1) 3.0	*Otc*	ornithine transcarbamylase (*spf*)	OTC	Xp21.1
	3.5	*DXHXS676*	DNA segment, Chr X, human DXS676	DXS676	Xp21.1-p11.3
	4.0	*DXHXS32*	DNA segment, Chr X, human DXS32	DXS32	Xp22-p11
	5.2	*Maoa*	monoamine oxidase A	MAOA	Xp11.4-p11.3
	5.3	*Ndph*	Norrie disease homologue	NDPH	Xp11.4-p11.3
	5.5	*Utx*	ubiquitously transcribed sequence, ChrX	UTX	Xp11.4-Xp11.3
	(A2-A3) 5.7	*Ube1x*	ubiquitin-activating enzyme E, Chr X	UBE1	Xp11.3-p11.23
	6.2	*Elk1*	ELK1, member of ETS oncogene family	ELK1	Xp11.3-p11.23
	(A3) 6.2	*Pfc*	properdin factor, complement	PFC	Xp11.3-p11.23
	6.2	*Araf*	raf-related oncogene	ARAF1	Xp11.3-p11.23
	(A1-A4) 6.2	*Syn1*	synapsin I	SYN1	Xp11.23
	6.2	*Timp*	tissue inhibitor of metalloproteinase	TIMP1	Xp11.3-p11.23
6	12.5	*Agtr2*	angiotensin II receptor, type 2	AGTR2	Xq22-q23
	12.5	*Lamp2*	lysosomal membrane glycoprotein-2	LAMP2	Xq24
	13.0	*Ant2*	adenine nucleotide translocator 2 (fibroblast)	ANT2	Xq24-q25
	(A6) 17.0	*Hprt*	hypoxanthine-guanine phosphoribosyl transferase	HPRT1	Xq26.1
	18.0	*Cd40l*	CD40 antigen ligand	CD40LG	Xq26
	18.0	*Fgf13*	fibroblast growth factor 13	FHF-2	Xq26
	21.0	*DXHXS144E*	DNA segment, Chr X, human DXS144E	DXS144E	Xq26.2
	(A6-A7) 22.0	*F9*	coagulation factor IX	F9	Xq26.3-q27.1
	(A6-A7) 22.5	*Mcf2*	mcf.2 transforming sequence	MCF2	Xq26.3-q27.1
	23.5	*Cdr*	cerebellar degeneration-related antigen	CDR1	Xq27.1-q27.2
	24.5	*DXHXS296*	DNA segment, Chr X, human DXS296	DXS296	Xq27.3-q28
	24.5	*Fmr1*	fragile X mental retardation syndrome1 homologue	FMR1	Xq27.3
	24.5	*Sox3*	SRY-box containing gene-3	SOX3	Xq26-q27
	27.0	*Ids*	iduronate 2-sulfatase	IDS	Xq27.3-q28
	(A7) 27.5	*Brs3*	bombesin receptor sub-type 3	BRS3	Xq26-q28
	27.8	*Mtm1*	myotubular myopathy gene 1	MTM1	Xq28
	28.5	*Gabra3*	gamma-aminobutyric acid (GABA-A) receptor, subunit alpha-3	GABRA3	Xq28
	28.8	*DXHXS1104*	DNA segment, Chr X, human DXS1104	DXS1104	Xq28
	28.82	*Atp6s1*	ATPase, H+ transporting,lysosomal (vpp)subunit1	VATPS1	Xq28
	28.85	*Calt*	calltractin, 20 kD calcium-binding protein	CALT	Xq28
	28.9	*Nsdhl*	NAD(P) dependent steroid dehydrogenase-like (*Bpa/Str*)	XAP104	Xq28
	29.1	*F8a*	factor 8-associated gene A	F8A	Xq28
	29.25	*DXHXS52*	DNA segment, Chr X, human DXS52	DXS52	Xq28
	29.3	*Bgn*	biglycan	BGN	Xq28
	29.5	*Creat*	creatine transporter	CREAT	Xq28
	29.5	*Idh3g*	isocitrate dehydrogenase (NAD+),gamma subunit	IDH3G	Xq28
	29.5	*Ssr4*	signal sequence receptor, delta	SSR4	Xq28
	(A6-B) 29.51	*L1cam*	L1 cell adhesion molecule	L1CAM	Xq28
	29.52	*Avpr2*	arginine vasopressin receptor 2	AVPR2	Xq28
	29.53	*Renbp*	renin-binding protein	RENBP	Xq28
	29.54	*Hcfc1*	host cell factor C1	HCFC1	Xq28
	29.6	*Il1rak*	interleukin 1 receptor associated kinase	IRAK	Xq28
	29.6	*Mecp2*	methyl CpG binding protein 2	MECP2	Xq28
	29.7	*Rsvp*	red sensitive visual pigment	RCP	Xq28
	29.8	*Fln1*	filamin 1	FLN1	Xq28
	29.81	*Emd*	emerin	EMD	Xq28
	29.83	*Gdi1*	GDP dissociation inhibitor 1	GD1	Xq28
	29.86	*Plxn3*	plexin 3	PLEX	Xq28
	30.01	*DXHXS253E*	DNA segment, Chr X, human DXS253E	DXS253E	Xq28
	(A2-3) 30.02	*G6pdx*	glucose-6-phosphate dehydrogenase X-linked	G6PD	Xq28
	30.48	*Mpp1*	membrane protein, palmitoylated (55kD)	MPP1	Xq28
	(A7-B) 30.5	*Cf8*	coagulation factor VIII	F8C	Xq28

Table 1. (*Continued*)

7		31.0	*Tbl1*	transducin beta like-1	TBL1	Xp22.3
8	(C)	32.0	*Dmd*	dystrophin, muscular dystrophy (***mdx***)	DMD	Xp21.3-p21.2
		33.0	*Ahch*	adrenal hypoplasia (AHC) gene homologue	AHC	Xp21.3
	(C-D)	33.0	*Gyk*	glycerol kinase	GYK	Xp21.2
	(C-D)	34.0	*Pola1*	DNA polymerase alpha 1, 180-kDa	POLA	Xp22.1-p21.3
	(C-D)	34.5	*Zfx*	zinc finger protein, X-linked	ZFX	Xp22.1-p21.3
9		36.0	*Ar*	androgen receptor (***Tfm***)	AR	Xq11.2-q12
		37.0	*Efnb1*	ephrin B1	EPLG2	Xq12
		37.0	*Eda*	ectodysplasin A (***Ta***)	EDA	Xq12-q13.1
		38.0	*Ccg1*	cell cycle, G1 phase defect	CCG1	Xq13.1
		38.0	*DXHXS393*	DNA segment, Chr X, human DXS393	DXS393	Xq13-q24
		38.0	*Gjb1*	gap junction membrane channel protein beta-1	GJB1	Xq13.1
		38.0	*Il2rg*	interleukin 2 receptor, gamma chain	IL2RG	Xq13.1
		39.0	*Abc7*	ATP-binding cassette transporter, ABC7	ABC7	Xq12-13
		39.0	*Phka1*	phosphorylase kinase alpha-1	PHKA1	Xq13.1
		39.0	*Rps4x*	ribosomal protein S4, X-linked	RPS4X	Xq13.1
		40.0	*Msg1*	melanocyte specific gene	MSG1	Xq13.1
		42.0	*Xist*	inactive X specific transcripts	XIST	Xq13.2
		42.0	*Nap1l2*	nucleosome assembly protein 1-like 2	NAP1L2	Xq13
		42.5	*Cdx4*	caudal type homeo box-4	CDX4	Xq13.2
		43.9	*DXHXS1608e*	DNA segment, Chr X, human DXS1068E	DXS1068E	Xq13.3
		44.0	*Atp7a*	ATPase, Cu++ transporting, type 7a(***Mo***)	ATP7A	Xq13.2-q13.3
	(C-D)	45.0	*Pgk1*	phosphoglycerate kinase-1	PGK1	Xq13.3
		48.4	*Pou3f4*	POU domain, class 3, transcription factor 4 (***slf***)	POU3F4	Xq21.3-q22
		51.0	*Btk*	Bruton agammaglobulinemia tyrosine kinase(***xid***)	BTK	Xq21.3-q22
	(E-F1)	53.0	*Ags*	alpha-galactosidase	GLA	Xq21.3-q22
		55.0	*DXHXS101*	DNA segment, Chr X, human DXS101	DXS101	Xq22
		56.0	*Plp*	myelin proteolipid protein (***jp***)	PLP	Xq21.33-q22
		57.0	*DXHXS178*	DNA segment, Chr X, human DXS178	DXS178	Xq21.33-q22
	(F1-F2)	60.0	*Prps1*	phosphoribosyl pyrophosphate synthetase-1	PRPS1	Xq21-q27
		62.0	*Gucy2f*	guanylyl cyclase 2f	GUC2F	Xq22
		62.4	*Col4a5*	procollagen, type IV, alpha 5	COL4A5	Xq22
10		63.0	*Alas2*	aminolevulinic acid synthase-2, erythroid	ALAS2	Xp11.21
		63.0	*DXHXS674*	DNA segment, Chr X, human DXS674	DXS674	Xp11.22-p11.21
		63.0	*DXHXS679*	DNA segment, Chr X, human DXS679	DXS679	Xp11.22-p11.21
	(F)	64.0	*DXHXS423*	DNA segment, Chr X, human DXS423	DXS423	Xp11.21
		64.0	*Fgd1*	faciogenital dysplasia homologue	FGDY	Xp11.21
	(F2-F4)	64.0	*Smcx*	selected mouse cDNA on the X	DXS1272E	Xp11.22-p11.21
11	(F2-F3)	65.0	*Apxl*	apical protein Xenopus laevis like	APXL	Xp22.3
	(F2-F3)	65.0	*Oa1*	ocular albinism 1	OA1	Xp22.3
12		65.2	*Sat*	spermine/spermidine N(1) acetyl transferase	SAT	Xp22.1
		65.4	*Phex*	phosphate regulating neutral endopeptidase on the X chromosome(***hyp, gy***)	PHEX	Xp22.1
		65.5	*Sms*	spermine synthase(***gy***)	SMS	Xp22.1
		65.6	*Rps6ka3*	ribosomal S6 kinase(***Li, Stpy***)	RSK2	Xp22.1
	(F3-F4)	66.5	*Pdha1*	pyruvate dehydrogenase E1alpha subunit(***Stpy***)	PDHA1	Xp22.1
	(F3-F4)	67.0	*Piga*	phosphatidylinositol glycan, class A	PIGA	Xp22.1
		67.5	*Ppef*	protein phosphatase, EF hand calcium binding domain	PPEF	Xp22.2
		70.0	*Grpr*	gastrin releasing peptide receptor	GRPR	Xp22.2-p22.13
		72.0	*Glra2*	glycine receptor, alpha 2 subunit	GLRA2	Xp22.1-p21.3
	(F2-F3)	72.0	*Prps2*	phosphoribosyl pyrophosphate synthetase-2	PRPS2	Xp22.3-p22.2
		72.0	*Phka2*	phosphorylase kinase alpha-2	PHKA2	Xp22.2-p22.1
		73.0	*Amel*	amelogenin	AMELX	Xp22.31-p22.1
		73.8	*Mid1*	midline defect, 1 (***Paf?***)	MID1	Xp22.3
		74.0	*Clcn4-1*	chloride channel 4-1	CLCN4-1	Xp22.3

Included are only those loci that have been regionally mapped on both the human and mouse X chromosomes with sufficient resolution to contribute to the man–mouse comparative map (see Fig. 1). This list is given in order of loci from the mouse centromere to the telomere. The rectangles encase conserved segments, in which locus order is preserved in man and mouse, with the exception of a small inversion around *Xist* (see text). Note that the relative order of segments 1–3 has not been established, and *eIF2γ* (Ehrman et al. 1998) has not been sufficiently well positioned in the mouse to include here, although it might represent a novel conserved segment. The location of each locus on the mouse X chromosome is given in column 1 and indicates the distance in cM from the centromere. When a locus also has been mapped by in situ hybridization, the cytogenetic location on the mouse X chromosome is given in brackets before the genetic map position. Mapping data are taken from the literature (Boyd et al. 1998), except for the *Sat* locus (H.J. Blair, unpubl.). The cytogenetic position of each locus is given for its location on the human X chromosome as, because of the large number of translocation breakpoints and rearrangements affecting the human X chromosome, this provides a more useful reference than a genetic map position. For a visual appreciation of the relative physical size of the conserved segments and their locations on the human and mouse chromosomes, see Fig. 1.

Table 2. Spontaneous and Induced X-Linked Mouse Traits

Symbol	Mutant name	Origin	Map position	No. of alleles	Phenotype details and gene mutated if known	References
Bhd	broad-headed	R	35	1	broad heads and snouts in heterozygous females, males die at birth, have aberrant ossification and may have cleft palate	Phillips and Fisher (1978); Reed and Boyd in prep. (1999)
Bn	bent-tail	S	central X	1	shortened and kinked tails	Carger (1952)
Bpa and *Str* (*Nsdh*$^{Bpa/Str}$)	bare patches or striated	SRC	29	4	hyperkeratosis, punctate calcification in the epiphyses of vertebrae, and long bones in heterozygous females, males die in utero; mutations have been found in *Nsdhl* [NAD(P)-dependent steroid dehydrogenase], an enzyme involved in sterol biosynthesis	Liu et al. (1999)
Bw1	body weight marker 1	V	proximal X	1	increased body weight in males	Dragani et al. (1995)
Bw2	body weight marker 2	V	central X	1	increased body weight in males	Dragani et al. (1995)
Bw3	body weight marker 3	V	distal X	1	increased body weight in males	Dragani et al. (1995); York et al. (1997)
crm	cream	S	distal X	1	pale yellow coat that is fluorescent in long-wave UV light, in hemizygous males and homozygous females	Hetherington (1977)
Fnld	faint-lined	R	15	1	faint dorsal stripes on heterozygous females, which are also small, males die in utero	Cormally and Boyd (1998)
Gs	greasy	S?	38	1	shiny fur in homozygous females and males	Larsen et al. (1964)
gy	gyro #	R	65.4	1	hypophosphatemia, rickets, sterility, and inner ear abnormalities in males; the 5′ end of *Phex*, the endopeptidase mutated in HYP patients and *Sms* (spermine synthase) are deleted	Lyon et al. (1986); Strom et al. (1997); Lorenz et al. (1999)
Hq	harlequin	S	17	1	small, almost totally bald, homozygous females and males	Barber (1971)
Hst3	hybrid sterility 3	V	distal X	1	sterility in F_1 males from crosses between *Mus spretus* and laboratory strains of mice	Guenet et al. (1990)
hyp	hypophosphatemia #, X-linked	S	65.4	1	hypophosphatemia and rickets seen in males; the 3′ end of *Phex*, the endopeptidase mutated in HYP patients is deleted	Eicher et al. (1976); Strom et al. (1997); Strom et al. (1998)
Ie	eye–ear reduction	R	syntenic	1	anopthalmia, small external ears in homozygous females and males	Hunsicker et al. (1974)
Ihpd	interspecific hybrid dysplasia	V	central X	1	abnormal development of the spongiotrophoblast, influenced by the sex of the conceptus, with a resultant effect on fetal growth	Zechner et al. (1996)
Ir	irregular teeth	S?	syntenic	1	incisors absent in heterozygous females, males die in utero	Phipps (1969)
jp, msd, or *rsh* (*Plp*$^{jp/msd/rsh}$)	jimpy, myelin synthesis deficiency or rumpshaker #	S	56	3	tremor of hindquarters and convulsions with early death in males caused by mutations in *Plp* (myelin proteolipid protein); models for Pelizaeus–Merzbacher disease	Meier and MacPike (1970); Dautigny et al. (1986); Griffiths et al. (1990)
Li	lined #	S?	65.6	1	transverse dorsal stripes in heterozygous females, males die in utero; ribosomal S6 kinase (*Rps6ka3*), which is mutated in Coffin–Lowry syndrome, and possibly other genes are deleted	Blair et al. (1998a)

Table 2. (*Continued*)

Symbol	Mutant name	Origin	Map position	No. of alleles	Phenotype details and gene mutated if known	References
mdx or *(Dmd^{mdx})*	muscular dystrophy #, X-linked	SC	32	4	tremors and mild inco-ordination, elevated creatine and pyruvate kinase in males; mutations have been found in *Dmd* (dystrophin), models for Duchenne muscular dystrophy	Bulfield et al. (1984); Chapman et al. (1989)
Mo or *(Atp7a^{Mo})*	mottled #	SRC	44	>20	Defective pigmentation, wavy vibrissae/coat, connective tissue, and neurological abnormalities, males have allele-dependent time of death, from in utero to adulthood; mutations have been found in *Atp7a* (ATPase, Cu^{2+} transporting, type 7a), models for Menkes disease	Hunt (1974); Danks (1986); Das et al. (1995); Cecchi et al. (1997); Reed and Boyd (1997); Cunliffe (1999)
Paf	patchy fur	S	73	1	missing fur with hemizygous males more severely affected than homozygous females, male carriers have delayed disjunction at meiotic metaphase I; associated with rearrangements at *Mid1* locus (midline 1), which is associated with Opitz syndrome	Lane and Davisson (1990); Quaderi et al. (1998)
ptd	palate-tail-digits abnormality	S	central X	1	tail malformations, hind feet polydactyly and frequent cleft palate in homozygous females and males	Barra (1990)
PyLMP	transgenic insertion of LMP	I	5.0	1	secondary cleft palate and craniofacial malformation, males die shortly after birth; transgenic insertion in *Cask* (calcium/calmodulin) dependent serine protein kinase	Laverty and Wilson (1998)
Rv3	Rauscher leukemia virus susceptibility-3	V	syntenic	1	CBA strain variant which results in susceptibility to spleen focus formation by Rauscher leukemia virus in males	Heller and Pluznik (1984)
sf	scurfy	S	2.1	1	scaly and tight skins, hypogonadism, thrombocytopenia with death before weaning in males	Lyon et al. (1990)
sla	sex-linked anemia	R?	36.4	1	severe hypochromic anemia, defective intestinal iron transport; mutation in hephaestin (*Heph*) a ceruloplasmin homologue	Kingston et al. (1978); Vulpe et al. (1999)
slf	sex-linked fidget #	R	In8H (A7-E1)	1	slight vertical head shaking in homozygous females and males; *Pou3f4* expression abolished in embryonic ear, model for DFN3	Phillips and Fisher (1978); Phippard et al. (2000)
spf (Otc^{spf})	sparse-fur #	S?	3	2	wrinkled skin, paucity of fur and bladder stones in males; mutations found in *Otc* (ornithine transcarbamylase)	Rosenberg et al. (1983); Veres et al. (1987)
Stpy	stripey	S	65.6	1	transverse dorsal stripes in heterozygous females, males die in utero; ribosomal S kinase (*Rps6ka3*, also known as *Rsk2*) and pyruvate dehydrogenase E1α (*Pdha1*), which is mutated in lactic acidosis, and possibly other genes are deleted	Blair et al. (1998a)
Ta (Eda^{Ta})	tabby #	SRC	37	>15	hair defects, tooth abnormalities and aberrant eccrine sweat glands in males and heterozygous females; mutations found in *Eda* (ectodysplasin-A), model for anhidrotic ectodermal dysplasia	Srivasta et al. (1997)
Td (Ebp^{Td})	tattered #	R	2.1	2	hyperkeratosis and craniofacial malformations in heterozygous females, males die in utero with skeletal and developmental defects; mutation in the sterol isomerase *Ebp* (emopamil-binding protein); model for chondrodysplasia punctata	Derry et al. (1999)

Table 2. (*Continued*)

Symbol	Mutant name	Origin	Map position	No. of alleles	Phenotype details and gene mutated if known	References
Tfm (Ar^{Tfm})	testicular feminization #	S	36	2	external female genitalia and insensitivity to androgens in males; mutations in *Ar* (androgen receptor), model for testicular feminization	Lyon et al. (1981a); Charest et al. (1991); Gaspar et al. (1993); Tanaka et al. (1993)
Tyl	trembly-like	S	central X	1	tremors, seizures and paralysis with death before weaning in males	Sweet et al. (1990)
wf	wide-faced	S	12.7	1	craniofacial malformations in homozygous females and males, males have an increased body weight with age	Boyd et al., (in prep.)
Xcat	X-linked cataract	R	68	1	total lens opacity in homozygous females and males, suggested model for Nance-Horan syndrome	Favor and Pretsch (1990); Zhou et al. (1995)
Xid (Btk^{xid})	X-linked immunodeficiency #	S	51	1	defective and impaired immune responses; mutations in *Btk* (Bruton agammaglobulinemia tyrosine kinase)	Rawlings et al. (1993); Thomas et al. (1993)
Xpl	X-linked polydactyly	S	distal X	1	preaxial polydactyly and tibial hemimelia in carrier and homozygous females and males	Sweet and Lane (1980)
Ym	yellow mottled	S?	44	1	yellowish mottling of heterozygous females, males die in utero, lies close to, but recombines with *Mo*	Hunsicker (1969)

Mutants that carry lesions at genes associated with human genetics disease are indicated by a pound sign (#) after the mutant name. Mouse mutants are generally given a name and symbol when they are first identified; these are used throughout this review for clarity, and the mutants described here are arranged in the alphabetical order of the symbol. Once the gene responsible for a mutant has been cloned, current nomenclature rules dictate that the official name for the mutant is (*gene symbol*$^{mutant\ name}$) and this is given in parentheses beside the original symbol, where appropriate. Mutants with small deletions that remove several genes, e.g., *gy*, which has a deletion that removes both *Phex* and *Sms*, retain their original mutant symbol. The origin of the mutation, if known, is indicated : (C) chemical mutagenesis; (I) insertional mutagenesis; (R) radiation mutagenesis; (S) spontaneous; (V) natural variant. Several reports of X-linked loci affecting various aspects of immune responsive have also been published. These include regulation of the secondary immune response to LDH-C_4 (Marsh et al. 1977), to thymus-independent antigens (Zeicher et al. 1977), to spleen focus formation by Rauscher leukemia virus (Heller and Pluznik 1984), and to denatured DNA (Mozes and Fuchs 1974). These have not been included here, as their relationship to each other and to X-linked loci known to be involved in immune regulation, e.g., *xid*, is unclear. They are indicated by *Ir* below the mouse X chromosome on Fig. 1.

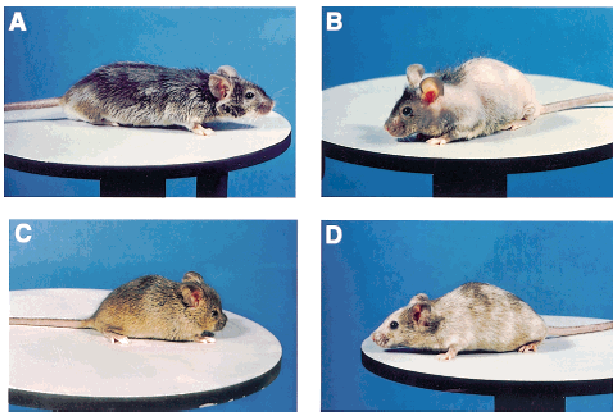

Figure 2 Examples of spontaneous and induced X-linked traits in the mouse. (*A*,*B*) Males carrying the greasy (*Gs*) (*A*) and harlequin (*Hq*) (*B*) mutations; neither of the genes responsible has been cloned. (*C*) A heterozygous female carrying the broad-headed (*Bhd*) mutation, which is associated with a craniofacial anomaly, note the unusually short and broad snout. Comparative mapping has shown that *Bhd* cannot be a model for FGD1 or ATRX, but it remains an interesting skeletal mutant in which males have multiple ossification anomalies and die shortly after birth (V. Reed and Y. Boyd, in prep.). (*D*) A heterozygous female carrying a mutation at one of the mottled (*Mo*) alleles associated with death between birth and weaning of affected males ($Atp7a^{Mo\text{-}10H}$). The mosaic coat can be clearly seen, in which hypopigmented areas represent populations of cells carrying the mutant allele and the normally pigmented (brown) areas represent areas of cells carrying the wild-type allele. Details of the phenotypes and references describing each of these mutants are given in Table 2.

fect in heterozygous females are identified. Some attempts were made to obtain sex-linked recessive lethals by identifying abnormal sex ratios in the offspring of F_1 females produced in classical mutagenesis experiments (Searle et al. 1964). Recessive mutations, such as sex-linked fidget, arose in experiments like these (Lyon et al. 1981b; Phippard et al. 2000).

For most of the recovered mutations, only a single mutant allele is available for analysis, limiting the value of the mouse as a model for X-linked human disease, which is often associated with a high number of different new mutations (Rossiter and Caskey 1991). However, where several alleles exist, the mouse provides an ideal tool for studying the phenotypic effects of different mutations in the same gene on an identical genetic background. Over 20 alleles, associated with differing phenotypes have been recovered at the mouse mottled locus and these provide a useful paradigm for using the mouse to study human disease (Cunliffe 1999).

Mottled: A Paradigm for Mouse Models for Human X-Linked Disease

For many years, the mottled mouse has been recognized as a model for Menkes disease (MD), and in both species, a range of mutations has been found in the gene encoding the copper transporter *ATP7A* (Cecchi et al. 1997; Reed and Boyd 1997; Tümer et al. 1997). Affected mice and human patients show a similar and variable course of disease with the main features being growth retardation, neurological and connective tissue abnormalities, peculiar hair and hypopigmentation (Danks 1986; Tümer and Horn 1997; Fig. 2D). Mutations that have a mild phenotypic effect in the mouse, such as the splice-site lesion leading to the production of both normal and aberrant transcripts in mottled blotchy, seem to be of a similar type to those associated with occipital horn syndrome (OHS, a mild allele of MD). In both man and mouse, this type of mutation is associated mainly with connective tissue problems (Das et al. 1995). However, there are significant differences between man and mice in the type of molecular lesions associated with the more severe phenotypes. The classical MD phenotype is mainly associated with nonsense or frameshift mutations and there is also a substantial proportion (~20%) of patients with gross deletions covering varying proportions of the ATP7A-coding region. In the mouse, the largest known deletion, which covers exons 11–14 (Cunliffe 1999), is in frame, and no nonsense or frameshift mutations have been reported to date. This fact demonstrates that caution must be taken when assessing potential therapies with mottled mice as animal models. The most striking phenotypic difference is that MD patients, with what might be expected to be null mutations at ATP7A, survive until birth, whereas over half of the mottled alleles are associated with prenatal lethality of males sometime after mid gestation. It has long been thought that the mottled mutations causing early postnatal death are the most appropriate model for classical MD in which affected boys die in the first few years of life. However, recent evidence has shown that in the mouse, Atp7a mutations most similar to those seen in classical MD cause prenatal death (Cunliffe 1999; P. Cunliffe, V. Reed, and Y. Boyd, in prep.). Therefore, at the level of cellular copper processing, mottled alleles associated with prenatal lethality may provide a better model. This is particularly important in light of the varied response of MD patients to copper histidine treatment (Tümer and Horn 1997).

Using the Mouse to Identify the Genes Responsible in X-Linked Dominants Associated with Intrauterine Male Lethality

A further interesting picture has emerged from studies on mouse mutants as possible models for X-linked dominant disease, which, because they are associated with prenatal lethality of males, are difficult to position accurately on the human X chromosome. Disorders associated with the lethality of males in utero are probably caused by lesions in genes that have impor-

tant developmental roles and that may be conserved in man and mouse. In the mouse, the relative ease of high-resolution mapping renders the genes responsible amenable to positional cloning. Recently, an interesting association between sterol biosynthesis and skeletal defects has been revealed by the identification of the underlying molecular lesions in the *Bpa*, *Str*, and *Td* mutants, which are all associated with skeletal and skin anomalies in heterozygous females (Table 2). Mutations in the 3β-hydroxysteroid dehydrogenase *Nsdhl* were first found in several independently derived *Bpa* and *Str* mutants, which were shown to be allelic, although there are differences in the severity of the phenotype (Liu et al. 1999). The *Bpa* mouse was suggested originally as a mouse homolog of CPDX2 as both display-striated hyperkeratosis and skeletal abnormalities including short stature, rhizomelic shortening of the limbs, epipyhseal stippling, and craniofacial anomalies (Happle 1983). However, a more detailed phenotypic analysis of *Td* has revealed that it also has many of these features and *Td* was discovered to be a model for CPDX2 when mutations in the sterol isomerase Ebp were discovered in *Td* and CPDX2 patients (Braverman et al. 1999; Derry et al. 1999). Thus, the *Bpa/Str* alleles and *Td* mice provide tools to investigate the relationship between sterol biosynthesis, intrauterine death of males, and the skin and skeletal defects seen in heterozygous females.

X-Linked Phenotypes Associated with Mutations Introduced by Gene Targeting

There are now as many mouse X-linked phenotypes introduced deliberately by gene targeting than have been recovered over the years in mouse colonies. Approximately one-half of the targeted genes are implicated in overt human disease and have been ablated to create models for understanding gene function and disease pathogenesis (Table 3). Some of these genes have shown comparable phenotypes in the mouse, such as the targeted disruption of genes encoding factor VIII and IX, which have provided excellent mouse models for studies on haemophilia A and B (Bi et al. 1995; Wang et al. 1997). Others exhibit some, but not all, aspects of the corresponding human disease; for example, there is an impaired humoral immune response in CD40 ligand-deficient mice, but they do not develop full-blown hyperIgM syndrome (Renshaw et al. 1994). In the future, mouse models carrying defined molecular lesions identical to those found in human disease can be provided by gene-targeting technology. In conjunction with the production of a series of different mutations in the same target gene, as has been done at the autosomal *Fgf8* locus by Meyers et al. (1998), the availability of engineered mouse models relevant to human disease can only increase.

Other mutants have been created to investigate the potential functions and the phenotypic consequence of a deficiency in the targeted gene. Some of these studies have revealed interesting clinical effects in mice with potential applications for studying complex human disorders, for example the demonstration that a lack of biglycan leads to osteoporosis (Xu et al. 1998). Other gene disruptions have also proven to be highly informative in understanding gene function, for example, the targeting of the *Xist* locus demonstrated its vital role in the X-inactivation process (Penny et al. 1996; Marahens et al. 1997).

Until stable female embryonic stem cell lines are widely available and can be transmitted to the germ line with a high frequency, one problem that remains with the targeted disruption of X-linked genes is the study of those genes that are potentially lethal in males. Genes may be dispensable in stem cells but essential for embryonic development, as is the case with the methyl-CpG-binding protein Mecp2 (Tate et al. 1996). The Mecp2 knockout mice are particularly interesting in light of the recent revelation that the X-linked dominant neurological disorder Rett syndrome is associated with *MECP2* mutations (Amir et al. 1999). The problem of early lethality preventing the recovery of mice carrying targeted mutations of X-linked genes can be partially circumvented by the production of conditional knockouts, in which ablation or modification of the gene of interest is engineered on a temporal or tissue-specific basis (for review, see Müller 1999; Roths et al. 1999). Tarutani et al. (1997) used this approach to demonstrate that the X-linked *Piga* gene plays an important role in skin development.

X Inactivation and Analysis of the Phenotypic Variation Associated with Heterozygous Females

Mice carrying X-linked mutations can also be used as tools to investigate the influence of cellular mosaicism associated with X-inactivation patterns in different tissues on the phenotype. X inactivation occurs early in mammalian female development and results in the transcriptional silencing of one of the two X chromosomes, at random, in every somatic cell (Lyon 1999). As a consequence, females heterozygous for X-linked coat mutations such as mottled have a variegated coat pattern resulting from the two cell populations, one expressing the mutant allele and the other expressing the wild-type allele (Fig. 2D). Because the number of cells at the time of X inactivation is small, and the choice of which X chromosome is inactivated is usually random, considerable differences are seen between females in the relative sizes of the two cell populations; this manifests as a variation in the severity of the phenotype between female mice carrying the same mutation. For some X-linked mutations, cellular mosaicism is a benefit with the population of cells expressing the normal allele, providing enough of the normal gene

Table 3. Targeted Mutations at Mouse X-Linked Loci

Symbol	Targeted gene	Phenotype details	References
Ags	α-galactosidase, mutated in Fabry disease #	phenotypically normal at 10 weeks, liver and kidney pathophysiology similar to human Fabry disease	Ohshima et al. (1997)
Agtr2	angiotensin II receptor, type 2	blood pressure increase, increased sensitivity to pressor action of angiotensin II, lowered body temperature, reduced exploratory behavior, anxiety-like behavior	Hein et al. (1995); Ichiki et al. (1995); Okuyama et al. (1999)
Abcd1	ATP-binding cassette, subfamily D, member 1, mutated in adrenoleukodystrophy #	reduced β-oxidation of very long chain fatty acids (VLCFAs) with consequent elevation of saturated VLCFAs in total lipids of all tissues and cholesterol esters in adrenocortical cells, no neurological involvement seen in mice up to 6 months	ForssPetter et al. (1997); Lu et al. (1997)
Bgn	biglycan	skeletal phenotype marked by progressive lowering of bone mass, suggested model for role of ECM proteins in osteoporosis	Xu et al. (1998)
Brs3	Bombesin receptor subtype-3	mild obesity, hypertension, impaired glucose metabolism, reduced metabolic rate, increased feeding efficiency and subsequent hyperphagia	Ohki-Hamazaki et al. (1997)
Btk	Bruton agammaglobulinemia tyrosine kinase #	mild X-linked immunodeficiency, with additional compromise of B cell precursor expansion	Kerner et al. (1995); Khan et al. (1997)
CD40l	CD40 antigen ligand, mutated in hyper-IgM syndrome #	failure to undergo isotype switching to T-cell-dependent antigens, normal response to T-cell-independent antigens	Renshaw et al. (1994); Xu et al. (1994); Castigli et al. (1995)
Cf8	coagulation factor VIII, mutated in hemophilia A #	<1% factor VIII clotting activity, significant bleeding after tail biopsy, which may be lethal, no spontaneous bleeding	Bi et al. (1995)
Cf9	coagulation factor IX, mutated in hemophilia B #	absence of factor IX antigen in plasma, <5% factor IX clotting activity	Wang et al. (1997)
Cybb	subunit of NADPH-oxidase complex, mutated in chronic granulomatous disease #	chronic granulomatous disease, lack of phagocyte superoxide production, increased susceptibility to infection and altered inflammatory response to thioglycollate peritonitis	Pollock et al. (1995); Morgenstern et al. (1997)
Dmd	dystrophin, mutated in Duchenne muscular dystrophy #	hypertrophic skeletal muscles, fibre size variations with necrosis and regeneration	Araki et al. (1997)
Fmr1	fragile X mental retardation syndrome 1 homolog #	macro-orchidism, learning deficits	Bakker et al. (1994); Oostra and Hoogeveen et al. (1997)
G6pdx	glucose-6-phosphate dehydrogenase	at ES cell level only, clones with undetectable levels of the enzyme are extremely sensitive to hydrogen peroxide and diamide	Pandolfi et al. (1995)
Gata1	GATA-binding protein 1	male neonatal lethal, mid-gestation embryos pallid with arrest of erythroid development	Pevny et al. (1991); Fujiwara et al. (1996); Takahashi et al. (1997)
Gjb1	gap junction protein connexin32, mutated in X-linked Charcot-Marie-Tooth disease #	from 3 months progressive demyelinating neuropathy, motor fibers more affected than sensory fibers	Scherer et al. (1998)
Gpc3	glypican 3, mutated in, Simpson–Golabi–Behmel syndrome #	overgrowth, cystic kidneys	Li et al. (1998)
Grpr	gastrin releasing peptide receptor	no gross phenotypic abnormalities, loss of bombesin-induced feeding suppression	Hampton et al. (1998)
Gyk	glycerol kinase #	males normal at birth but exhibit growth retardation, altered fat metabolism with profound hypoglycerolemia and elevated free fatty acids, autonomous glucocorticoid synthesis and death by 3–4 days; heterozygous females are healthy and biochemically normal	Huq et al. (1997)
Hprt	hypoxanthine phosphoribosyl transferase #	overgrooming in older mice, increased locomotor activity after amphetamine administration; self-injurious behavior only when inhibitor of *Aprt* also present (Wu and Melton 1993), model for Lesch–Nyhan disease	Hooper et al. (1987); Kuehn et al. (1987); Nehls et al. (1994); Tsuda et al. (1997)
Htr2c	5-hydroxytryptamine (serotonin) receptor 2C	overweight because of abnormal feeding behavior, spontaneous death from seizures	Tecott et al. (1995)
Il2rg	interleukin 2 receptor, γ chain, mutated in X-linked severe combined immunodeficiency #	similar phenotype to human XSCID, decrease in lymphocyte numbers but increase in monocytes, few T cells in young mice and no natural killer cells	Leonard et al. (1995); Ohbo et al. (1996); Sugamura et al. (1996)

Table 3. (*Continued*)

Symbol	Targeted gene	Phenotype details	References
L1cam	L1 cell adhesion molecule, mutated in CRASH syndrome #	smaller than wild type animals, uncoordinated hind legs, hypoplasia of corticospinal tract, abnormal brain pathology, and impaired exploratory behavior	Dahme et al. (1997); Fransen et al. (1998)
Maoa	monoamine oxidase a #	pups have elevated serotonin levels, trembling, difficulty in righting, fearfulness; adults have distinct behavioral syndrome with enhanced aggression in males	Cases et al. (1995)
Maob	monoamine oxidase b	increased reactivity to stress, increased levels of beta-phenylethylamine, resistance to neurodegenerative effects of MPTP toxin (which induces a Parkinson's-like condition)	Grimsby et al. (1997)
Mecp2	methyl CpG binding protein 2, mutated in Rett syndrome #	chimeric embryos exhibit developmental defects with severity proportional to mutant cell contributions	Tate et al. (1996); Amir et al. (1999)
Ndph	Norrie disease homolog #	development of retrolental structures in vitreous body, disorganization of retinal ganglion cell layer, occasional loss of outer plexiform layer with resultant interchange of inner/outer nuclear layer, absence of outer segments of photoreceptor cell layer	Berger et al. (1996)
Ocrl	oculocerebrorenal syndrome of Lowe #	no abnormal phenotype, with postulated compensation by the autosomal gene inositol polyphosphate 5-phosphatase (Inpp5b) as explanation	Janne et al. (1998)
Piga	phosphatidylinositol glycan, class A	wrinkled and scaly skin, death a few days after birth	Tarutani et al. (1997)
Plp	myelin proteolipid protein, mutated in Pelizaeus–Merzbacher disease #	no gross effect, assembly and maintenance of normal amounts of myelin, progressive tract-specific axonopathy	Boison and Stoffel (1994); Griffiths et al. (1995); Klugmann et al. (1997); Griffiths et al. (1998)
Pou3f4	Pou domain, class 3, transcription factor 4, mutated in DFN3 #	vertical head bobbing and hearing loss, dysplastic bony compartment of the inner ear	Minowa et al. (1999); Phippard et al. (1999)
Pou4f2	POU domain, class 4, transcription factor 2	selective loss of 70% of retinal ganglion cells, other neurons in the retina and brain essentially unaffected	Erkman et al. (1996); Gan et al. (1996)
Rep1	Rab escort protein 1, mutated in choroideremia #	embryonic male lethal; heterozygous females and chimeras have a variable number of photoreceptor cells	van den Hurk et al. (1997)
Syn1	synapsin 2	no gross abnormalities, mossy fibre giant terminals reduced, fewer synaptic vesicles, presynaptic structures altered	Rosahl et al. (1993); Takei et al (1995)
Syp	synaptophysin	indistinguishable from normal littermates, predendritic neurites and axon outgrowth retarded in hippocampal neurons, with delayed synapse formation; homozygotes die prior to 10.5 dpc	Chin et al. (1995); Erhkind and Leube (1995); Arrandale et al. (1996); McMahon et al. (1996)
Timp	tissue inhibitor of metalloproteinase	no effect on steroidogenesis, reduced ovarian TIMP2 and TIMP3, at ES cell level only, more invasive than normal cells	Alexander and Werb (1992); Nothnick et al. (1997)
Wasp	Wiskott–Aldrich syndrome protein #	decreased peripheral blood lymphocyte and platelet numbers, chronic colitis	Snapper et al. (1998)
Xist	inactive X specific transcripts	mutant males unaffected, females inheriting mutant paternal X chromosome severely retarded and die in utero	Penny et al. (1996); Marahens et al. (1997)
Xnp	X-linked nuclear protein, mutated in α-thalassemia mental retardation syndrome #	at cellular level, increased sensitivity to ionizing radiation, mitomycin C, and MMS	Essers et al. (1997)
Zfx	X-linked zinc finger protein	male and female mutants smaller, with lower viability and fewer germ cells, hemizygotes had reduced sperm count and homozygotes a reduced number of oocytes	Luoh et al. (1997)

Genes associated with known human disease are indicated by a pound sign (#) after the gene name; where the disease has a different name, it is given in the same column. Targeted genes are given in alphabetical order of gene symbol. Note that a meeting abstract also mentions the targeting of the mouse p55 gene *Mpp1* (A.C. Kim, C.D. Southgate, B.J. Mitchell, and A.H. Chistiti, unpubl.), but as no details of the resulting phenotype are provided this locus is not included in the table.

product to permit a normal phenotype to develop, for example, in the *sf* or *spf* mutations (DeMars et al. 1976; Lyon et al. 1990). Another possibility is that growth competition between the two cell populations may result in the virtual elimination of the cells expressing the mutant allele (Ogura et al. 1998). In this situation, the resultant skewed X-inactivation pattern provides heterozygous females with a normal, or mild, phenotype.

Traditionally, X-inactivation patterns in mice have been investigated in the coat by the observation of doubly heterozygous female mice produced when the mutation is bred to well-characterized coat mutants, such as the mottled blotchy or tabby mutants. In humans, approaches that exploit the differences in DNA methylation between the inactive and active X chromosomes are most widely used to study X-inactivation patterns in heterozygous females (Belmont 1996). In the mouse, extensive studies of the X-inactivation patterns can be achieved because of the availability of tissues from several replica heterozygotes at a range of times in development on a constant genetic background. Techniques such as the single nucleotide primer extension (SNuPE) assay have been used to quantitatively measure the relative expression from the two X chromosomes in females heterozygous for X-linked mutations (Greenwood et al. 1997; Ogura et al. 1998). Further, the X-linked *LacZ* transgenic mice created by Tam and Tan (1992) have great potential for the study of X-inactivation patterns in heterozygous females as the transgene is subject to the inactivation process. When the *lacZ* reporter is present on only one of the X chromosomes of a female heterozygous for an X-linked mutation, the β-galactosidase activity is limited to cells with only that X chromosome active. Therefore, the distribution of cells expressing the mutant allele in a heterozygous female can be studied and insights into the mode of action of the normal X-linked gene product can be provided by the analysis of the phenotype and the X-inactivation pattern of heterozygous females. In our laboratory, such studies are under way on the *Li*, *Stpy*, and *Td* mutants.

Future Progress

The 80 X-linked phenotypes that have been reported in the laboratory mouse correspond to mutations in approximately half of the cloned X chromosomal genes. Most of these traits are associated with mutations in known genes and are of immediate value as animal models for human X-linked diseases. However, they represent <5% of the probable number of X-linked genes and the phenotype map of the mouse X chromosome is still sparse. Alternative methods will be needed to provide the detailed phenotype maps worthy of complementing the encyclopedias of mouse genes that are being developed (Marra et al. 1999). Although several laboratories are attempting to increase the size of the mouse mutant resource (Justice et al. 1997; You et al. 1997; deAngelis and Balling 1998; Schimenti and Bucan 1998; Zheng et al. 1999), no plans appear to have been made to screen systematically the progeny of F_1 females carrying mutagenized X chromosomes for X-linked traits. Without such a specific effort, it will be interesting to see whether the number of X-linked mutant stocks will increase to meet the needs and interests of groups trying to understand the roles of X-linked genes in health and disease.

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REFERENCES

Alexander, C.M. and Z. Werb. 1992. Targeted disruption of the tissue inhibitor of metalloproteinases gene increases invasive behaviour of primitive mesenchymal cells derived from embryonic cells in vitro. *J. Cell Biol.* **118:** 727–739.

Amar, L.C., L. Dandalo, A. Hanauer, A. Ryder-Cook, D. Arnaud, J-L. Mandel, and P. Avner. 1988. Conservation and re-organisation of loci on the mammalian X chromosome; a molecular framework for the identification of homologous regions in man and mouse. *Genomics* **22:** 220–230.

Amir, R.E., I.B. Van den Veyver, M. Wanm, C.Q. Tran, U. Francke, and H.Y. Zhogbi. 1999. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat. Genet.* **23:** 185–188.

Araki, E., K. Nakamura, K. Nakao, S. Kameya, O. Kobayashi, I. Nonaka, T. Kobayashi, and M. Katsuki. 1997. Targeted disruption of exon 52 in the mouse dystrophin gene induced muscle degeneration similar to that observed in Duchenne muscular dystrophy. *Biochem. Biophys. Res. Comm.* **238:** 492–497.

Arrandale, J.M., A. Gore-Willse, S. Rocks, J.M. Ren, J. Zhu, A. Davis, J.N. Livingston, and D.U. Rabin. 1996. Insulin signaling in mice expressing reduced levels of *Syp*. *J. Biol. Chem.* **271:** 21353–21358.

Bakker, C.E., C. Verheij, R. Willemsen, R. van der Helm, F. Oerlemans, M. Vermey, A. Bygrave, A.T. Hoogeveen, B.A. Oostra, E. Reyniers et al. 1994. FMR1 knockout mice—A model to study fragile-X mental retardation. *Cell* **78:** 23–33.

Barber, B.R. 1971. Research News. *Mouse NewsLett.* **45:** 34–35.

Barra, J. 1990. An X-linked recessive mutation producing cleft palate, crooked tail, and polydactyly in mice. *J. Hered.* **81:** 388–392.

Bedell, M.A., N.A. Jenkins, and N.G. Copeland. 1997. Mouse models of human disease. *Genes & Dev.* **11:** 1–43.

Belmont, J.W. 1996. Genetic control of X inactivation and processes leading to X-inactivation skewing. *Am. J. Hum. Genet.* **58:** 1101–1108.

Berger, W., D. van de Pol, D. Bachner, F. Oerlemans, H. Winkens, H. Hameister, B. Wieringa, W. Hendriks, and H.-H. Ropers. 1996. An animal model for Norrie disease (ND); gene targeting of the mouse ND gene. *Hum. Mol. Genet.* **5:** 51–59.

Bi, L., A.M. Lawler, S.E. Antonarakis, K.A. High, J.D. Gearhart, and H.H. Kazazian. 1995. Targeted disruption of the mouse factor VIII gene produces a model of haemophilia A. *Nat. Genet.* **10:** 119–121.

Blair, H.J., V. Reed, S.H. Laval, and Y. Boyd. 1994. New insights into the man-mouse comparative map of the X chromosome. *Genomics* **19:** 215–220.

Blair, H.J., M. Ho, A.P. Monaco, S. Fisher, I.W. Craig, and Y. Boyd. 1995. High resolution comparative mapping of the proximal region of the mouse X chromosome. *Genomics* **28:** 305–310.

Blair, H.J., E. Gormally, I.C. Uwechue, and Y. Boyd. 1998a. Mouse mutants carrying deletions that encompass the genes deleted in Coffin-Lowry syndrome and lactic acidosis. *Hum. Mol. Genet.* **7:** 549–555.

Blair, H.J., I.C. Uwechue, G.S. Barsh, P.S.N. Rowe, and Y. Boyd. 1998b. An integrated genetic and man-mouse comparative map of the *DXHXS674-Pdha1* region of the mouse X chromosome. *Genomics* **48:** 128–131.

Blaschke, R.J. and G.A. Rappold. 1997. Man to mouse—lessons learned from the distal end of the human X chromosome. *Genome Res.* **7:** 1114–1117.

Boison, D. and W. Stoffel. 1994. Disruption of the compacted myelin sheath of axons of the central nervous system in proteolipid-deficient mice. *Proc. Natl. Acad. Sci.* **91:** 11709–11713.

Boyd, Y., H.J. Blair, P. Cunliffe, P. Denny. E. Gormally, and G.E. Herman. 1998. Mouse Chromosome X. *Mamm. Genome* **8:** S361–S377.

Boyd, Y., P. Denny, W.K. Masson, V. Reed, and R. Elliott. 1999. Mouse X chromosome. *Mamm. Genome* **10:** 961.

Bravermann N., P. Lin, F.F. Moebius, C. Obie, A. Moser, H. Glossman, W.R. Wilcox, D.L. Rimoin, M. Smith, L. Kratz et al. 1999. Mutations in the gene encoding 3β-hydroxysteroid-Δ^8,Δ^7-isomerase cause X-linked dominant Conradi-Hünerman syndrome. *Nat. Genet.* **22:** 291–294.

Bulfield, G., W.G. Siller, P.A.L. Wight, and K.J. Moore. 1984. X chromosome-linked muscular dystrophy (*mdx*) in the mouse. *Proc. Natl. Acad. Sci.* **81:** 1189–1192.

Cases, O., I. Seif, J. Grimsby, P. Gaspar, K. Chen, S. Pournin, U. Müller, M. Auguet, C. Babinet, J.C. Shih et al. 1995. Aggressive behaviour and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* **268:** 1763–1766.

Castigli, E., R. Fuleihan, N. Ramesh, E. Tsitsikov, A. Tsytsykov, and R.S. Geha. 1995. CD40 ligand/CD40 deficiency. *Int. Arch. Allergy Immunol.* **107:** 37–39.

Cecchi, C., M. Biasotto, M. Tosi, and P. Avner. 1997. The mottled mouse as a model for human Menkes disease: Identification of mutations in the *Atp7a* gene. *Hum. Mol. Genet.* **6:** 425–433.

Chapman, V.M., D.R. Miller, D. Armstrong, and C.T. Caskey. 1989. Recovery of induced mutations for X chromosome-linked muscular dystrophy in mice. *Proc. Natl. Acad. Sci.* **86:** 1292–1296.

Charest, N.J., Z. Zhou, D.B. Lubahn, K.E. Olsen, E.M. Wilson, and F.S. French. 1991. A frameshift mutation destablizes androgen receptor RNA in the *Tfm* mouse. *Mol. Endocrinol.* **5:** 573–581.

Chin, L.S., L. Li, A. Ferreira, K.S. Kosik, and P. Greengard. 1995. Impairment of axonal development and of synaptogenesis in hippocampal neurons of synapsin I-deficient mice. *Proc. Natl. Acad. Sci.* **92:** 9230–9234.

Cunliffe, P. 1999. "Molecular genetic analysis of mottled mice", Ph. D. thesis. University of Oxford, Oxford, UK.

Dahme, M., U. Bartsch, R. Martini, B. Anliker, M. Schachner, and N. Mantei. 1997. Disruption of the mouse L1 gene leads to malformations of the nervous system. *Nat. Genet.* **17:** 346–349.

Danks, D.M. 1986. Of mice and men, metals and mutations. *J. Med .Genet.* **23:** 99–106.

Das, S., B. Levinson, C. Vulpe, S. Whitney, J. Gitschier, and S. Packman. 1995. Similar splicing mutations of the Menkes/mottled copper-transporting ATPase gene in occipital horn syndrome and the blotchy mouse. *Am. J. Hum. Genet.* **56:** 570–576.

Dautigny, A., M.-G. Mattei, D. Morello, P. M. Alliel, D. Pham-Dinh, L. Amar, D. Arnaud, D. Simon, J.-F. Mattei, J.-L. Guenet et al. 1986. The structural gene coding for mylein-associated proteolipid protein is mutated in *jimpy* mice. *Nature* **321:** 867–868.

Davisson, M.T. 1987. X-linked homologies between mouse and man. *Genomics* **1:** 213–227.

De Angelis, M.H. and R. Balling. 1998. Large scale ENU screens in the mouse: Genetics meets genomics. *Mutat. Res.* **400:** 25–32.

De Mars, R., S.L. LeVan, B.L. Trend, and L.B. Russell. 1976. Abnormal ornithine carbamoyltransferase in mice having the sparse-fur mutation. *Proc. Natl. Acad. Sci.* **73:** 1693–1697.

Derry, J.M.J., E. Gormally, G.D. Means, W. Zhao, A. Meindl, R.I. Kelley, Y. Boyd, and G.E. Herman. 1999. Mutations in a Δ^8-Δ^7 sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasia punctata. *Nat. Genet.* **22:** 286–290.

D'Esposito, M., M.R. Matarazzo, A. Ciccodicola, M. Strazzullo, R. Mazzarella, N.A. Quaderi, H. Fujiwara, M.S.H. Ko, L.B. Rowe, A. Ricco et al. 1997. Differential expression pattern of XqPAR-linked genes *SYBL1* and *IL9R* correlates with the structure and evolution of the region. *Hum. Mol. Genet.* **6:** 1917–1923.

Dinulos, M.B., M.T. Bassi, E.I. Rugarli, V. Chapman, A. Ballabio, and C. Disteche. 1996. A new region of conservation is defined between the human and mouse X chromosomes. *Genomics* **35:** 244–247.

Disteche, C.M., M.B. Dinulos, M.T. Bassi, R.W. Elliott, and E.I. Rugarli. 1998. Mapping of the murine *Tbl1* gene reveals a new rearrangement between mouse and human X chromosomes. *Mamm. Genome* **9:** 1062–1064.

Dragani, T.A., Z.-B. Zeng, F. Canzian, M. Garibaldi, M.T. Ghilarducci, G. Manento, and M.A. Pierotti. 1995. Mapping of body weight loci on mouse chromosome X. *Mamm. Genome* **6:** 778–781.

Ehrman, I.E., P.S. Ellis, S. Mazeyrat, S. Duthie, N. Brockdorff, M.G. Mattei, M.A. Gavin, N.A. Affara, G.M. Brown, E. Simpson et al. 1998. Characterization of genes encoding translation initiation factor eIF-2γ in mouse and human: Sex chromosome localization, escape from X-inactivation and evolution. *Hum. Mol. Genet.* **7:** 1725–1737.

Eicher, E.M., J.L. Southard, C.R. Scriver, and F.H. Glorieux. 1976. Hypophosphatemia: Mouse model for human familial hypospho sphatemic (vitamin D-resistant) rickets. *Proc. Natl. Acad. Sci.* **73:** 4667–4671.

Eppig, J.T. and M. Strivens. 1999. Finding a mouse: The International Mouse Strain Resource (IMSR). *Trends Genet.* **15:** 81–82.

Erkman, L., R.J. McEvilly, L. Luo, A.K. Ryan, F. Hooshmand, S.M. O'Connell, E.M. Keithley, D.H. Rapaport, A.F. Ryan, and M.G. Rosenfeld. 1996. Role of transcription factors Brn-3.1 and Brn-3.2 in auditory and visual system development. *Nature* **381:** 603–606.

Eshkind, L.G. and R.E. Leube. 1995. Mice lacking synaptophysin reproduce and form typical synaptic vesicles. *Cell Tiss. Res.* **3:** 423–433.

Essers, J., R.W. Hendriks, S.M.A. Swagemakers, C. Troelstra, J. de Wit, D. Bootsma, J.H.J. Hoeijmakers, and R. Kanaar. 1997. Disruption of mouse RAD54 reduces ionizing radiation resistance. *Cell* **89:** 195–204.

Favor, J. and W. Pretsch. 1990. Genetic localization and phenotypic expression of X-linked cataract (Xcat) in *Mus musculus*. *Genet. Res.* **56:** 157–162.

Fisher, E.M.C. 1997. The contribution of the mouse to advances in human genetics. *Adv. Genet.* **35:** 155–205.

ForssPetter, S., H. Werner, J. Berger, H. Lassmann, B. Molzer, M.H. Schwab, H. Bernheimer, F. Zimmermann, and K.A. Nave. 1997. Targeted inactivation of the X-linked adrenoleukodystrophy gene in mice. *J. Neurosci. Res.* **50:** 829–843.

Fransen, E.R., Dhooge, G. van Camp, M. Verhoye, J. Sijbers, E. Reyniers, P. Soriano, H. Kamiguchi, R. Willemsen, S.K.E. Koekkoek et al. 1998. L1 knockout mice show dilated ventricles, vernis hypoplasia and impaired exploration patterns. *Hum. Mol. Genet.* **7:** 999–1009.

Fujiwara, Y., C.P. Browne, K. Cunniff, S.C. Goff, and S.H. Orkin. 1996. Arrested development of embryonic red cell precursors in mouse embryos lacking transcription factor GATA-1. *Proc. Natl. Acad. Sci.* **93:** 12355–12358.

Gan, L., M. Xiang, L. Zhou, D.S. Wagner, W.H. Klein, and J. Nathans. 1996. POU domain factor Brn-3b is required for the development of a large set of retinal ganglion cells. *Proc. Natl. Acad. Sci.* **93:** 3920–3925.

Garber, E.D. 1952. "Bent-tail", a dominant sex-linked mutation in the mouse. *Proc. Natl. Acad. Sci.* **38:** 8786–8789.

Gaspar, M.-L., T. Meo, P. Bourgarel, J.-L.Guenet, and M. Tosi. 1991. A single base deletion in the *Tfm* androgen receptor gene creates

a short-lived messenger RNA that directs internal translation initiation. *Proc. Natl. Acad. Sci.* **88:** 8606–8610.
George, A.M., V. Reed, P. Glenister, Z. Tümer, N. Horn, J. Chelly, A.P. Monaco, and Y. Boyd. 1994. Analysis of *Mnk*, the murine homologue of the locus for Menkes disease, in normal and mottled (*Mo*) mice. *Genomics* **37:** 96–104.
Gormally E. and Y. Boyd. 1998. Faint lined (*Fnl*): A novel X-linked coat mutant in the mouse. *Genet. Res.* **72:** 211–216.
Greenwood, A.D., E.M. Southard-Smith, A.T.J. Galecki, and D.T. Burke. 1997. Coordinate control and variation in X-linked gene expression among female mice. *Mamm. Genome* **8:** 818–822.
Griffiths, I.R., I. Scott, M.C. McCulloch, J.A. Barrie, K. McPhilemy, and B.M. Cattanach. 1990. Rumpshaker mouse: A new X-linked mutation affecting myelination: Evidence for a defect in PLP expression. *J. Neurocytol.* **19:** 273–283.
Griffiths, I.R., A. Schneider, J. Anderson, and K.A. Knave. 1995. Transgenic and natural mouse models of proteolipid (PLP)-related dysmyelination and demyelination. *Brain Pathol.* **5:** 275–281.
Griffiths, I.R., M. Klugmann, T. Anderson, C. Thomson, D. Vouyiouklis, and K.A. Nave. 1998. Current concepts of PLP and its role in the nervous system. *Microscop. Res. Technique* **41:** 344–358.
Grimsby, J., M. Toth, K. Chen, T. Kumazawa, L. Klaidman, J.D. Adams, F. Karoum, J. Gal, and J.C. Shih. 1997. Increased stress response and β-phenylethylamine in *MAOB*-deficient mice. *Nat. Genet.* **17:** 206–210.
Guenet, J.-L., C. Nagamine, D. Simon-Chazettes, X. Montagutelli, and F. Bonhomme. 1990. *Hst-3*: And X-linked hybrid sterility gene. *Genet. Res.* **56:** 163–165.
Hampton, L.L., E.E. Ladenheim , M. Akeson, J.M. Way, H.C. Weber, V.E. Sutliff, R.T. Jensen, L.J. Wine, H. Arnheiter, and J.F. Battey. 1998. Loss of bombesin-induced feeding suppression in gastrin-releasing peptide receptor-deficient mice. *Proc. Natl. Acad. Sci.* **6:** 3188–3192.
Happle, R. 1983. Homologous genes for X-linked dominant chondrodysplasia punctata in man and mouse. *Hum. Genet.* **63:** 24–27.
Hein, L., G.S. Barsh, R.E. Pratt, V.J. Dzau, and B.K. Kobilka. 1995. Behavioural and cardiovascular effects of disrupting the angiotensin II type-2 receptor in mice. *Nature* **377:** 744–747.
Heller, E. and D.H. Pluznik. 1984. Chromosomal assignment of two murine genes controlling susceptibility to spleen focus formation by Rauscher leukemia virus. *Exp. Hematol.* **12:** 645–649.
Hetherington, C. 1977. Research News. *Mouse NewsLett.* **56:** 35.
Hooper, M., K. Hardy, A. Handyside, S. Hunter, and M. Monk. 1987. HPRT-deficient (Lesch-Nyhan) mouse embryos derived from germline colonization by cultured cells. *Nature* **326:** 292–295.
Hunsicker, P.R. 1969. Research News. *Mouse NewsLett.* **40:** 42.
Hunsicker, P.R. 1974. New mutants: Eye-ear reduction *Ie*. *Mouse NewsLett.* **50:** 51–52.
Hunt, D.M. 1974. Primary defect in copper transport underlies mottled mutants in the mouse. *Nature* **249:** 852–854.
Huq, A.H.M.M., R.S. Lovell, C.N. Ou, A.L. Beaudet, and W.J. Craigen. 1997. X-linked glycerol kinase deficiency in the mouse leads to growth retardation, altered fat metabolism, autonomous glucocorticoid secretion and neonatal death. *Hum. Mol. Genet.* **6:** 1803–1809.
Ichiki, T., P.A. Labosky, C. Shiota, S. Okuyama, Y. Imagawa, A. Fogo, F. Niimura, I. Ichikawa, B.L.M. Hogan, and T. Inagami. 1995. Effects on blood pressure and exploratory behaviour of mice lacking angiotensin II type-2 receptor. *Nature* **377:** 748–750.
Janne, P.A., S.F. Suchy, D. Bernard, M. MacDonald, J. Crawley, A. Grinberg. A. Wynshaw-Boris, H. Westphal, and R.L. Nussbaum. 1998. Functional overlap between murine Inpp5b and Ocrl1 may explain why deficiency of the murine ortholog for OCRL1 does not cause Lowe syndrome in mice. *J. Clin. Invest.* **101:** 2042–2053.
Justice, M.J., B. Zheng, R.P. Woychik, and A. Bradley. 1997. Using targeted large deletions and high efficiency N-ethyl-N-nitrosourea mutagenesis for functional analyses of the mammalian genome. *Methods*: *Companion Methods Enzymol.* **13:** 423–436.
Kerner, J.D., M.W. Appleby, R.N. Mohr, S. Chien, D.J. Rawlings, C.R. Maliszewski, O.N. Witte, and R.M. Perlmutter. 1995. Impaired expansion of mouse B cell progenitors lacking *Btk*. *Immunity* **3:** 301–312.
Khan, W.N., A. Nilsson, E. Mizoguchi, E. Castigli, J. Forsell, A.K. Bhan, R. Geha, P. Sideras, and F.W. Alt. 1997. Impaired B cell maturation in mice lacking Bruton's tyrosine kinase (*Btk*) and CD40. *Int. Immunol.* **9:** 395–405.
Kingston, P.J., C.E.M. Bannerman, and R.M. Bannerman. 1978. Iron deficiency anaemia in newborn *sla* mice: A genetic defect of placental iron transport. *Br. J. Haematol.* **40:** 265–276.
Klugman, M., M.H. Schwab, A. Pulhofer, A. Schneider, F. Zimmerman, I.R. Griffiths, and K.A. Knave. 1997. Assembly of CNS melin in the absence of proteolipid protein. *Neuron* **18:** 59–70.
Kuehn, M.R., A. Bradley, E.J. Robertson, and M.J. Evans. 1987. A potential animal model for Lesch-Nyhan syndrome through introduction of HPRT mutations into mice. *Nature* **326:** 295–298.
Lane, P.W. and M.T. Davisson. 1990. Patchy fur (*Paf*), a semidominant X-linked gene associated with a high level of X-Y nondisjunction in male mice. *J. Hered.* **81:** 43–50.
Larsen, M.M. 1964. Research news: Greasy. *Mouse NewsLett.* **30:** 47.
Laval, S.H. and Y. Boyd. 1993. Partial inversion of gene order within an homologous segment on the X chromosome. *Mamm. Genome* **4:** 119–123.
Laverty, H.G. and J.B. Wilson. 1998. Murine CASK is disrupted in a sex-linked cleft palate mouse mutant. *Genomics* **53:** 29–41.
Leonard, W.J., E.W. Shores, and P.E. Love. 1995. Role of common cytokine receptor gamma chain in cytokine signaling and lymphoid development. *Immunol. Rev.* **148:** 97–114.
Li, M., J.A. Squire, and R. Weksberg. 1998. Overgrowth syndromes and genomic imprinting: From mouse to man. *Clin. Genet.* **53:** 165–170.
Liu, X.Y., A.W. Dangel, R.I. Kelley, W. Zheo, P. Denny, M. Botcherby, B. Cattanach, J. Peters, P.R. Hunsicker, A.-M. Mallon et al. 1999. The mouse bare patches and striated gene encodes a novel 3β-hydroxysteroid dehydrogenase. *Nat. Genet.* **22:** 182–187.
Lorenz, B., F. Francis, K. Gempel, A. Boddrich, M. Josten, W. Schmahl, J. Schmidt, H. Lehrach, T. Meitinger, and T.M. Strom. 1999. Spermine deficiency in Gy mice caused by deletion of the spermine synthase gene. *Hum. Mol. Genet.* **7:** 541–547.
Lu, J.F., A.M. Lawler, P.A. Watkins, J.M. Powers, A.B. Moser, H.W. Moser, and K.D. Smith. 1997. A mouse model of X-linked adrenoleukodystrophy. *Proc. Natl. Acad. Sci.* **94:** 9366–9371.
Luoh, S.W., P.A. Bain, R.D. Polakiewicz, M.L. Goodheart, H. Gardner, R. Jaenisch, and D.C. Page. 1997. ZFX mutation results in small animal size and reduced germ cell number in male and female mice. *Development* **124:** 2275–2284.
Lyon, M.F. 1999. X-inactivation. *Curr. Biol.* **9:** R235–R237.
Lyon, M.F., B.M. Cattanach, and H.M. Charlton. 1981a. Genes affecting sex differentiation in mammals. In *Mechanisms of sex differentiation in animals and man* (ed. C.R. Austin and R.G. Edwards), pp. 329–386, Academic Press, New York, NY.
Lyon, M.F., R.J.S. Phillips, and G. Fisher. 1981b. Use of an inversion to test for induced X-linked lethals in mice. *Mutat. Res.* **92:** 217–228.
Lyon, M.F., C.R. Scriver, L.R.I. Baker, H.S. Tenenhouse, J. Kronick, and S. Mandla. 1986. The *Gy* mutation: Another cause of X-linked hypophosphatemia in mouse. *Proc. Natl. Acad. Sci.* **43:** 4899–4903.
Lyon, M.F., J. Peters, P.H. Glenister, S. Ball, and E. Wright. 1990. The scurfy mouse has previously unrecognized hematological abnormalities and resembles Wiskott-Aldrich syndrome. *Proc. Natl. Acad. Sci.* **87:** 2433–2437.
Marra, M., L.-D. Hillier, T. Kucaba, M. Allen, R. Barstead, C. Beck, A. Blistain, M. Bonaldi, Y. Bowers, L. Bowles et al. 1999. An encylopedia of mouse genes. *Nat. Genet.* **21:** 191–194.
Marahens, Y., B. Panning, J. Dausman, W. Strauss, and R. Jaenisch.

1997. *Xist*-deficient mice are defective in dosage compensation but not spermatogenesis. *Genes & Dev.* **11:** 156–166.
Marsh, J.A., T.E. Wheat, and E. Goldberg. 1977. Temporal regulation of the immune response to LDH-C_4 by an X-linked gene in C3H/HeJ and SJl/J mice. *J. Immunol.* **118:** 2293–2295.
McMahon, H.T., V.Y. Bolshakov, R. Janz, R.E. Hammer, S.A. Siegelbaum, and T.C. Sudhof. 1996. Synaptophysin, a major synaptic vesicle protein is not essential for neurotransmitter release. *Proc. Natl. Acad. Sci.* **10:** 4760–4764.
Meier, H. and A.D. MacPike. 1970. A neurological mutation (*msd*) of the mouse causing a deficiency of myelin synthesis. *Exp. Brain Res.* **10:** 510–525.
Meyers, E.N., M. Lewandoski, and G.R. Martin. 1998. An *Fgf8* mutant allelic series generated by Cre- and Flp-mediated recombination. *Nat. Genet.* **18:** 136–141.
Miller, J.R. 1990. *X-linked traits: A catalog of loci in non-human mammals.* Cambridge University Press, Cambridge, UK.
Minowa, O., K. Ikeda, Y. Sugitani, T. Oshima, S. Nakai, Y. Katori, M. Suzuki, M. Furukawa, T. Kawase, Y. Zheng et al. 1999. Altered cochlear fibrocytes in a mouse model of DFN3 nonsyndromic deafness. *Science* **285:** 1408–1411.
Morgenstern, D.E., M.A. Gifford, L.L. Li, C.M. Doerschuk, and M.C. Dinauer. 1997. Absence of respiratory burst in X-linked chronic granulomatous disease mice leads to abnormalities in both host defence and inflammatory response to *Aspergillus fumigatus*. *J. Exp. Med.* **185:** 207–218.
Mozes, E. and S. Fuchs. 1974. Linkage between iummune response potential to DNA and X chromosome. *Nature* **249:** 167–168.
Müller, U. 1999. Ten years of gene targeting: Targeted mouse mutants, from vector design to phenotype analysis. *Mech. Dev.* **82:** 3–21.
Nehls, M., M. Messerle, A. Sirulnik, A.J. Smith, and T. Boehm. 1994. Two large insert vectors lambda PS and lambda Ko, facilitate rapid mapping and targeted disruption of mammalian genes. *BioTechniques* **17:** 770–775.
Nothnick, W.B., P. Soloway, and T.E. Curry. 1997. Assessment of the role of tissue inhibitor of metalloproteinase-1 (TIMP-1) during the periovulatory period in female mice lacking a functional TIMP-1 gene. *Biol. Reprod.* **56:** 1181–1188.
Ogura, H., S. Takada, N. Mise, M. Sugimoto, S.-S. Tan, and N. Takagi. 1998. Translocation breakpoint possibly predisposes to nonrandom X-chromosome inactivation in mouse embryos bearing Searle's T(X;16)16H translocation. *Cytogenet. Cell Genet.* **80:** 173–178.
Ohbo, K., T. Suda, M. Hashiyama, A. Mantani, M. Ikebe, K. Miyakawa, M. Moriyama, M. Nakamura, M. Katsuki, K. Takahashi et al. 1996. Modulation of haematopoiesis in mice with a truncated mutant of the interleukin-2 receptor gamma chain. *Blood* **87:** 956–967.
Ohki-Hamazaki, H., E. Wada, K. Matsui, and K. Wada. 1997. Cloning and expression of the neuromedin B receptor and the third type of bombesin receptor genes in the mouse. *Brain Res.* **762:** 165–172.
Ohno, S. 1973. Ancient linkage groups and frozen accidents. *Nature* **244:** 259–262.
Ohshima T., G.J. Murray, W.D. Swaim, G. Longenecker, J.M. Quirk, C.O. Cardarelli, Y. Sugimoto, I. Pastan, M.M. Gottesman, R.O. Brady et al. 1997. Alpha-galactosidase deficient mice: A model of Fabry disease. *Proc. Natl. Acad. Sci.* **94:** 2540–2544.
Okuyama, S., T. Sakagawa, S. Chaki, Y. Imagawi, and T. Ichiki. 1999. Anxiety-like behaviour in mice lacking the angiotensin II type-2 receptor. *Brain Res.* **821:** 150–159.
Oostra, B.A. and A.T. Hoogeveen. 1997. Animal model for fragile X syndrome. *Ann. Med.* **29:** 563–567.
Paigen, K. 1995. A miracle enough: The power of mice. *Nat. Med.* **1:** 215–220.
Pandolfi, P.P., F. Sonati, R. Rivi, P. Mason, F. Grosveld, and L. Luzzatto. 1995. Targeted disruption of the housekeeping gene encoding glucose 6-phosphate dehydrogenase (G6PD): G6PD is dispensable for pentose synthesis but essential for defence against oxidative stress. *EMBO J.* **14:** 5209–5215.
Penny, G.D., G.F. Kay, S.A. Sheardown, S. Rastan, and N. Brockdorff. 1996. Requirement for *Xist* in X chromosome inactivation. *Nature* **379:** 131–137.
Pevny, L., M.C. Simon, E. Robertson, W.H. Klein, S.F. Tsai, V. D'Agati, S.H. Orkin, and F. Constantini. 1991. Erythroid differentiation in chimaeric mice blocked by a targeted mutation in the gene for transcription factor GATA-1. *Nature* **349:** 257–260.
Phillips, R.J.S. and G. Fisher. 1978. New mutants. *Mouse NewsLett.* **58:** 43–44.
Phippard, D., L. Lu, D. Lee, J.C. Saunders, and E.B. Crenshaw. 1999. Targeted mutagenesis of the POU domain gene *Brn4/Pou3f4* causes developmental defects in the inner ear. *J. Neurosci.* **19:** 5980–5989.
Phippard, D., Y. Boyd, V. Reed, G. Fisher, W.K. Masson, E.P. Evans, J.C. Saunders, and E.B Crenshaw. 2000. The sex-linked fidget mutation abolishes *Brn4/Pou3f4* expression in the embryonic inner ear. *Hum. Mol. Genet.* **9:** 79-85.
Phipps, E.L. 1969. New mutants: Irregular teeth *It. Mouse NewsLett.* **40:** 41–42.
Pollock, J.D., D.A. Williams, M.A. Gifford, L.L. Li, X. Du, J. Fisherman, S.H. Orkin, C.M. Doerschuk, and M.C. Dinauer. 1995. Mouse model of X-linked chronic granulomatous disease, an inherited defect in superoxide production. *Nat. Genet.* **9:** 202–209.
Quaderi, N.A., S. Messali, S. Cainarca, A. Ballabio, G. Meroni, and E. Rugarli. 1998. Possible involvement of Mid1 in the patchy fur (*Paf*) mutant. *In Twelfth International Mouse Genome Conference*, Garmisch-Partenkirchen, Bavaria.
Rawlings, D.J., D.C. Saffran, S. Tsukada, D.A. Largasepada, J.C. Grimaldi, L. Cohen, R.N. Mohr, J.F. Bazan, M. Howard, N.G. Copeland et al. 1993. Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. *Science* **261:** 358–361.
Reed, V. and Y. Boyd. 1997. Mutation analysis provides additional proof that mottled is the mouse homologue of Menkes disease. *Hum. Mol. Genet.* **6:** 417–423.
Renshaw, B.R., W.C. Fanslow, R.J. Armitage, K.A. Campbell, D. Liggitt, B. Wright, B.L. Davison, and C.R. Maliszewski. 1994. Humoral responses in CD40-ligand deficient mice. *J. Exp. Med.* **180:** 1889–1900.
Rosahl, T.W., M. Geppert, D. Spillane, J. Herz, R.E. Hammer, R.C. Malenka and T.C. Sudhof. 1993. Short-term plasticity is altered in mice lacking synapsin-1. *Cell* **75:** 661–670.
Rosenberg, L.E., F. Kalousek, and M.D. Orsulak. 1983. Biogenesis of ornithine transcarbamylase in *spf^{ash}* mutant mice: Two cytoplasmic precursors, one mitochondrial enzyme. *Science* **222:** 426–428.
Rossiter, B.J.F. and C.T. Caskey. 1991. Molecular studies of human genetic disease. *FASEB J.* **5:** 21–27.
Roths, J.B., W.B. Foxworth, M.J. McArthur, C.A. Montgomery, and A.B. Kier. 1999. Spontaneous and engineered mutant mice as models for experimental and comparative pathology: History, comparison, and developmental technology. *Lab. Anim. Sci.* **49:** 12–29.
Rougelle, C. and P. Avner. 1996. Cloning and characterisation of a murine brain specific gene *Bpx* and its human homologue lying within the *Xic* candidate region. *Hum. Mol. Genet.* **5:** 41–49.
Scherer, S.S., Y.T. Xu, E. Nelles, K. Fischbeck, K. Willeke, and L.J. Bone. 1998. Connexin32-null mice develop demyelinating peripheral neuropathy. *Glia* **24:** 8–20.
Schimenti, J. and M. Bucan. 1998. Functional genomics in the mouse: Phenotype based mutagenesis screens. *Genome Res.* **8:** 698–710.
Searle, A.G. 1964. Genetic effects of spermatogonial X-irradiation on the productivity of F1 female mice. *Mutat. Res.* **1:** 99–108.
Searle, A.G., J. Peters, M.F. Lyon, E.P. Evans, J.H. Edwards, and V.J. Buckle. 1987. Chromosome maps of man and mouse III. *Genomics* **1:** 3–18.
Searle, A.G., J. Peters, M.F. Lyon, J.G. Hall, E.P. Evans, J.H. Edwards, and V.J. Buckle. 1989. Chromosome maps of man and mouse IV.

Ann. Hum. Genet. **53:** 89–140.
Snapper, S.B., F.S. Rosen, E. Mizoguchi, P. Cohen, W. Khan, C.H. Liu, T.L. Hagemann, S.P. Kwanm, R. Ferrini, L. Davidson et al. 1998. Wiskott-Aldrich syndrome protein-deficient mice reveal a role for WASP in T but not B cell activation. *Immunity* **9:** 81–91.
Srivastava, A.K., J. Pispa, A.J. Hartung, Y. Du, S. Ezer, T. Jenks, T. Shimada, M. Pekkanen, M.L. Mikkola, M.S.H. Ko et al. 1997. The Tabby phenotype is caused by mutation in a mouse homologue of the EDA gene that reveals novel mouse and human exons and encodes a protein (ectodysplasin-A) with collagenous domains. *Proc. Natl. Acad. Sci.* **94:** 13069–13074.
Strom, T.M., F. Francis, B. Lorenz, A. Böddrich, M.J. Econs, H. Lehrach, and T. Meitinger. 1997. Pex gene deletions in *Gy* and *Hyp* mice provide mouse models for X-linked hypophosphatemia. *Hum. Mol. Genet.* **6:** 165–171.
Sugamura, K., H. Asao, M. Kondo, N. Tanaka, N. Ishii, K. Ohbo, M. Nakamura, and T. Takeshita. 1996. The interleukin-2 receptor gamma chain: Its role in the multiple cytokine receptor complexes and T cell development in XSCID. *Annu. Rev. Immunol.* **14:** 179–205.
Sweet, H.O. and P.W. Lane. 1980. X-linked polydactyly (*Xpl*), a new mutation in the mouse. *J. Hered.* **71:** 207–209.
Sweet, H.O., R.T. Bronson, B.S. Harris, and M.T. Davisson. 1990. Trembly-like (*Tyl*)—a new X-linked mutation in the mouse. *Mouse Genome* **87:** 112.
Takahashi, S., K. Onodera, H. Motohashi, N. Suwabe, N. Hayashi, N. Yanai, Y. Nabesima, and M. Yamamoto. 1997. Arrest in primitive erythroid cell development caused by promoter-specific disruption of the GATA-1 gene. *J. Biol. Chem.* **272:** 12611–12615.
Takei, Y., A. Harada, S. Takeda, K. Kobayashi, S. Terada, T. Noda, T. Takahashi, and N. Hirokawa. 1995. Synapsin I deficiency results in the structural change in the presynaptic terminals in the murine nervous system. *J. Cell Biol.* **131:** 1789–17880.
Tam, P.L.P. and S.-S. Tan. 1992. The somitogenic potential of cells in the primitive streak and the tail bud of the organogenesis-stage mouse embryo. *Development* **115:** 703–715.
Tanaka, S., T. Kaneko, T. Moriyama, and A. Matsuzawa. 1993. A new testicular feminization mutation found in C57BL/6J mice. *Lab. Anim.* **28:** 262–264.
Tarutani, M., S. Itami, M. Okabe, M. Ikawa. T. Tezuka, K. Yoshikawa, T. Kinoshita, and J. Takeda. 1997. Tissue-specific knockout of the mouse Pig-a gene reveals important roles for GPI-anchored proteins in skin development. *Proc. Natl. Acad. Sci.* **94:** 7400–7405.
Tate, P., W. Skarnes, and A. Bird. 1996. The methyl-CpG binding protein MeCP2 is essential for embryonic development in the mouse. *Nat. Genet.* **12:** 205–208.
Tecott, L.H., L.M. Sun, S.F. Akana, A.M. Strack, D.H. Lowenstein, M.F. Dallman, and D. Julius. 1995. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. *Nature* **374:** 542–546.
Thomas, J.D., P. Sideras, C.I.E. Smith, I. Vorechovský, V. Chapman, and W.E. Paul. 1993. Colocalization of X-linked agammalobulinemia and X-linked immunodeficiency genes. *Science* **261:** 355–358.
Tsuda, H., C.E. Maynard-Currie, L.H. Reid, T. Yoshida, K. Edamura, N. Maeda, O. Smithies, and A. Jakobivits. 1997. Inactivation of the mouse HPRT locus by a 203-bp retroposon insertion and a 55-kb gene-targeted deletion: Establishment of new HPRT-deficient mouse embryonic stem cell lines. *Genomics* **42:** 413–421.
Tümer, Z. and N. Horn. 1997. Menkes disease: Recent advances and new aspects. *J. Med. Genet.* **34:** 265–274.
Tümer Z., C. Lund, J. Tolshave, B. Vural, T. Tønnesen, and N. Horn. 1997. Identification of point mutations in 41 unrelated patients affected with Menkes disease. *Am. J. Hum. Genet.* **60:** 63–71.
van den Hurk, J.A., W. Hendriks, D.J. van de Pol, F. Oerlemans, G. Jaissle, K. Ruther, K. Kohler, J. Hartmann, E. Zrenner, H. van Bokhoven et al. 1997. Mouse choroideremia gene mutation causes photoreceptor cell degeneration and is not transmitted through the female germline. *Hum. Mol. Genet.* **6:** 851–858.
Veres, G., R.A. Gibbs, S.E. Schere, and C.T. Caskey. 1987. The molecular basis of the sparse fur mutation. *Science* **237:** 415–417.
Vulpe, C.D., Y-M. Kuo, T.I. Murphy, L. Cowley, C. Askwith, N. Libina, J. Gitschier, and G.J. Anderson. 1999. Hephaestin, a ceruloplasmin homologue implicated in intestinal ion transport, is defective in the *sla* mouse. *Nat. Genet.* **21:** 195–199.
Wang, L., M. Zoppe, T.M. Hackeng, J.H. Griffin, K.F. Lee, and I.M. Verma. 1997. A factor IX deficient mouse model for hemophila B gene therapy. *Proc. Natl. Acad. Sci.* **94:** 11563–115636.
Xu, J., T.M. Foy, J.D. laman, E.A. Elliott, J.J. Dunn, T.J. Waldschmidt, J. Elsemore, R.J. Noelle, and R.A. Flavell. 1994. Mice deficient for the CD40l ligand immunity. *Immunity* **1:** 423–431.
Xu, T.S., P. Bianco, L.W. Fisher, G. Longnecker, E. Smith, S. Goldstein, J. Bonadio, A. Boskey, A.M. Heegard, B. Sommer et al. 1998. Targeted disruption of the biglycan gene leads to an osteoporosis-like phenotype in mice. *Nat. Genet.* **20:** 78–82.
York B., K. Lei, and D.B. West. 1997. Inherited non-autosomal effects on body fat in F_2 mice derived from am AKR/J x SWR/J cross. *Mamm. Genome* **8:** 726–730.
You, Y., R. Bergstrom, M. Klemm, B. Lederman, H. Nelson, C. Ticknor, R. Jaenisch, and J. Schimenti. 1997. Chromosomal deletion complexes in mice by radiation of embryonic stem cells. *Nat. Genet.* **15:** 285–288.
Zechner, U., M. Reule, A. Orth, F. Bonhomme, B. Strack, J.-L. Guenet, H. Hameister, and R. Fundele. 1996. An X-chromosome linked locus contributes to abnormal placental development in the mouse. *Nat. Genet.* **4:** 398–403.
Zeicher, M., E. Mozes, and P. Lonai. 1977. Lymphocyte alloantigens associated with X-chromosome-linked immune response genes. *Proc. Natl. Acad. Sci.* **74:** 721–724.
Zheng, B.H., A.A. Mills, and A. Bradley. 1999. A system for rapid generation of coat color-tagged knock-outs and defined chromosomal rearrangements in mice. *Nucleic Acids Res.* **27:** 2354–2360.
Zhou, E., J. Favor, W. Dilvers, and D. Stamboulian. 1995. Exclusion of the candidate genes, *Grpr*, *Cxn33* and *Pdha1*, for X-linked cataract gene on the distal region of mouse chromosome X. *Mamm. Genome* **6:** 357–359.

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