Mouse models of human disease. Part II: Recent progress and future directions

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The development of new methods for manipulating the mouse genome, including transgenic and embryonic stem (ES) cell knockout technology, combined with greatly improved genetic and physical maps for mouse has revolutionized our ability to generate new mouse models of human disease. In Part I of this review (Bedell et al., this issue), we described in detail the various techniques and genetic resources that have facilitated mouse model development. In Part II of this review we highlight some of the recent progress that has been made in mouse model development and discuss areas where these mouse models are likely to contribute in the future. We have focused in part II only on those models where the homologous gene is mutated in both the human and mouse disease. A total of ~100 such genes are listed in seven tables according to the primary tissue or organ system they affect. The chromosomal location of each mapped disease gene in the mouse can be found in Figure 1. Detailed information about each mouse model can be obtained by entering the corresponding gene symbol into the Mouse Genome Database (MGD), maintained by the Jackson Laboratory at http://www.informatics.jax.org/mgd.html. Detailed information about each human disease can be obtained using the Mendelian Inheritance in Man (MIM) accession nos. that are provided (McKusick et al. 1994). Each MIM entry may be accessed over the Internet at http://www3.ncbi.nlm.nih.gov/omim/, a site maintained by the National Center for Biotechnology Information. MIM accession nos. from 100050-195002 are for dominant traits; 200100-280000 are for recessive traits; and 300010-315000 are for X-linked traits.

Although we have tried to be as inclusive as possible, our list of mouse models is unlikely to be complete. In addition, space limitations have precluded a complete description of all mouse models we have listed; instead, we discuss only a few models in each section where significant progress in either identifying or utilizing a mouse model has been made recently. Much of the success in developing mouse models has been with mono- genic traits; however, great potential lies in modeling polygenic diseases. In the last section, we review some of the recent progress in this area. Throughout the text and tables, we have cited only the most recent papers and refer to reviews whenever possible. Interested readers are encouraged to read the primary papers on each model and associated disease.

Disorders of neural crest derivatives

Cells from the neural crest differentiate into many different cell types including melanocytes of the skin and inner ear, neuronal and glial components of the peripheral nervous system, neuroendocrine cells of the adrenal medulla and thyroid, and cartilaginous and membranous bones of the skull. Mutations that affect melanocyte development and cause visible effects on pigmentation have been arguably one of the most important phenotypic classes of mutations used in classical mouse genetics. The study of these mutants has revealed many aspects of melanocyte development, including the identification of factors controlling their survival and migration during embryogenesis, as well as pathways for pigment biosynthesis and transport. In Table 1, we have listed 11 genes in which mutations have been identified in mouse and human homologs that cause deficiencies in cells derived from the neural crest. All of these models share at least some aspect of the mutant phenotype with the corresponding human disease.

Excellent reviews of mouse and human pigmentation mutants have been published recently (Jackson 1994; Spritz 1994a, b; Barsh 1996). Here we will limit our discussion to three disorders of the neural crest: Hirschsprung’s disease [HSCR; MIM 142623], Waardenburg syndrome [WS; MIM 193500, 193510], and piebald trait [PT; MIM 172800], for which cloning of each of the human disease genes was aided by the identification of mutations in the homologous mouse gene. All three syndromes display dominant inheritance, although some forms of HSCR and WS are recessive. HSCR patients have deficiencies in enteric ganglia resulting in megacolon, intestinal blockage, and chronic constipation. WS and PT patients have deficiencies in melanocytes of the skin and inner ear leading to pigment defects in the hair and hypopigmentation on the forehead, chest, and abdomen in PT patients, and pigment defects in the hair and eye and sensorineural deafness in WS patients.

Hirschsprung’s disease

Mutations in the RET proto-oncogene cause dominant
forms of HSCR, whereas mutations in endothelin B receptor (EDNRB) and its cognate ligand, endothelin 3 (EDN3), cause recessive forms of HSCR [van Heyningen 1994; Chakravarti 1996; Edery et al. 1996; Hofstra et al. 1996]. Curiously, patients with Shah–Waardenburg syndrome (a disease phenotypically similar to combined HSCR and WS) have mutations in EDNRB or EDN3, but not RET. HSCR is thus a prime example of a complex disease in which mutations in several different genes can produce the same disease and mutations in one gene can produce many different, albeit related, phenotypes.

A direct role for Ret in development of the enteric nervous system was demonstrated by use of knockout mice (Schuchardt et al. 1994). In mice homozygous for Ret null mutations, the intestines lack ganglia, have defective peristalsis, and are distended. This phenotype is similar to that caused by RET mutations in HSCR patients and provides a useful model for understanding the pathogenesis of this disease. There are some differences, however, between mice carrying Ret null mutations and HSCR patients. Ret mutations are completely recessive in mice but cause haploinsufficiency in humans. In addition, homozygous Ret null mice display renal agenesis, a phenotype not observed in HSCR patients. These phenotypic differences suggest that some tissues of mice and humans may respond differently to alterations in Ret signaling or to levels of Ret protein.

Knockout mutations in the mouse Ednrb and Edn3 genes were shown recently to be allelic with the spontaneous mutations piebald (s) and lethal spotting (ls),
Table 1. Disorders of neural crest derivatives

<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>Mendelian inheritance in Man (MIM) no.</th>
<th>Selected references</th>
</tr>
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<tbody>
<tr>
<td>Edn3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Endothelin 3</td>
<td>K,S</td>
<td>Waardenburg-Shah syndrome</td>
<td>277580</td>
<td>Baynash et al. (1994); Edery et al. (1996); Hofstra et al. (1996)</td>
</tr>
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<td>Ednrb&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Endothelin receptor type B</td>
<td>C,K,R,S</td>
<td>Hirschsprung's disease, Waardenburg-Shah syndrome</td>
<td>142623, 277580</td>
<td>Hosoda et al. (1994); Puffenberger et al. (1994); *Chakravarti (1996); *Besmer et al. (1993); *Fleischman (1993); *Spritz (1994a)</td>
</tr>
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<td>Kit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Kit oncogene</td>
<td>C,R,S</td>
<td>Piebald trait</td>
<td>172800</td>
<td>*Barsh (1996)</td>
</tr>
<tr>
<td>Mc1r&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Melanocortin 1 receptor</td>
<td>S</td>
<td>Red hair color</td>
<td>266300</td>
<td>*Barsh (1996)</td>
</tr>
<tr>
<td>Msnx2&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Homeo box, msh-like 2</td>
<td>TE</td>
<td>Craniosynostosis type 2</td>
<td>123101</td>
<td>Jabs et al. (1993); Liu et al. (1995b)</td>
</tr>
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<td>Pax3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Paired box protein-3</td>
<td>R,S</td>
<td>Waardenburg syndrome type 1</td>
<td>193500</td>
<td>*Jackson (1994); *Spritz (1994b); *Barsch (1996)</td>
</tr>
<tr>
<td>Ret&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ret proto-oncogene</td>
<td>K</td>
<td>Hirschsprung's disease</td>
<td>142623</td>
<td>Schuchardt et al. (1994); *van Heyningen (1994); *Chakravarti (1996)</td>
</tr>
<tr>
<td>Tyr&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Tyrosinase</td>
<td>C,R,S</td>
<td>Oculocutaneous albinism type I</td>
<td>203100</td>
<td>*Jackson (1994); *Spritz (1994b); *Barsch (1996)</td>
</tr>
<tr>
<td>Tyrpl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Tyrosinase related protein</td>
<td>C,R,S</td>
<td>Oculocutaneous albinism type III</td>
<td>203290</td>
<td>*Jackson (1994); *Barsch (1996)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Abbreviations for creation of mouse mutations: (C) chemically induced; (K) knockout; (R) radiation-induced; (TI) transgene insertion; (TE) transgene expression; (S) spontaneous.

<sup>b</sup>Reviews are indicated with an asterisk.

<sup>c</sup>Also called Waardenburg syndrome, type 3.

<sup>d</sup>Also associated with multiple endocrine neoplasia (Table 5).

Although Ret, Ednrb, and Edn3 are clearly implicated in intestinal aganglionosis in humans and mice, evidence from both species suggests that these are not the only genes involved in this disease. Mice that lack glial cell line-derived neurotrophic factor (Gdnf), the recently identified ligand for Ret, display an identical phenotype to Ret knockout mice (for review, see Massague 1996). In addition, Puffenberger et al. (1994) have reported a genetic modifier of HSCR that maps to chromosome 21q22. Likewise, Pavan et al. (1995) have mapped six genetic modifiers of the s phenotype. Whether these genes directly modify the incidence or severity of megacolon remains to be determined.

**Piebald trait**

Mutations in Kit, a receptor tyrosine kinase, cause PT in humans and Dominant spotting (W) in mice (for review,
see Besmer et al. 1993; Fleischman 1993]. At least 57 different W alleles have been identified. In heterozygous mice, most W mutants have spots of hypopigmentation on the head and ventrum, a phenotype strikingly similar to PT. In homozygous mice, the severe W mutations cause embryonic lethality [resulting from severe effects on erythropoiesis] while milder mutations allow viability but the mice are anemic, sterile, and deaf, and have extensive hypopigmentation and reduced muscle contractions in the gut [Besmer et al. 1993; Huizinga et al. 1995]. In both humans and mice [Fig. 2], all point mutations in Kit that produce a phenotype localize to the tyrosine kinase domain. In general, mutations in the mouse that abolish Kit activity are homozygous lethal, whereas mutations that reduce, but don’t abolish, tyrosine kinase activity are homozygous viable. Interestingly, mice heterozygous for a dominant negative W allele [W178, see Fig. 2] have severe defects in pigmentation and are anemic, but a human with an identical mutation is hypopigmented but is not anemic [Fleischman 1992]. Additionally, W homozygous mice are deaf because of a reduction or absence of melanocytes of the inner ear [for review, see Steel 1995] whereas humans with PT display no apparent defects in hearing, nor are they sterile or anemic.

The phenotype of W mutant mice is identical to that of mice carrying mutations at the Steel [Sl] locus, which encodes mast cell growth factor (Mgf), the ligand for Kit [for review, see Besmer et al. 1993]. Surprisingly, Mgf mutations have not been identified in humans with PT [Ezoe et al. 1995]. Whether this reflects different functions of Mgf in mice versus humans has not been determined.

**Figure 2.** Mutations in Kit that have been identified in humans with PT [top] and in mice with different W alleles [bottom]. The different domains of the protein are as follows: the extracellular domain is shaded, the transmembrane domain is black, and the split kinase domains are hatched. For point mutations, the amino acid residue affected by each mutation is indicated with the one-letter abbreviation for the normal and mutant residue; e.g., M318G is a mutation that replaces methionine with glycine at amino acid 318. Stop is a termination codon created by a frameshift mutation. The W7 allele is semidominant and the less severe alleles are recessive and the mutations in each class localize to specific domains. Interestingly, a mutation identical to that seen in W mice is hypomorphic but is not anemic [Fleischman 1992]. Additionally, W homozygous mice are deaf because of a reduction or absence of melanocytes of the inner ear [for review, see Steel 1995] whereas humans with PT display no apparent defects in hearing, nor are they sterile or anemic.

**Waardenburg syndrome**

WS is a dominant pigmentation disorder that occurs with congenital deafness. Three types of WS have been described. WS1 [MIM 193500] is distinguished from WS2 [MIM 193510] by dystopia canthorum, a lateral displacement of the inner canthi of the eye, whereas WS3 [MIM 148820, also called Klein-Waardenburg syndrome] is a severe form of WS1 that involves WS1 symptoms plus upper limb anomalies. Like HSCR, WS is genetically heterogeneous. Mutations in two transcription factors, paired box gene-3 (PAX3) and microphthalmia transcription factor (MITF), cause each of the different types of WS. More than 30 PAX3 mutations that affect virtually every domain of the protein have been found in WS1 and WS3 patients [Baldwin et al. 1995; Tassabehji et al. 1995]. Strikingly, each of these mutations, whether a point mutation or a deletion of the entire gene, results in a very similar phenotype that may be explained by b- p-loinsufficiency. Approximately 20% of WS2 patients contain mutations in MITF [Tassabehji et al. 1995]. For both PAX3 and MITF, humans appear to be more sensitive than mice to gene dosage effects [Jackson and Raymond 1994; Tassabehji et al. 1995]; however, the reasons for these differences are not known.

In mice, PAX3 is encoded by the splotch (Sp) locus [for review, see Strachan and Read 1994]. At least six Sp alleles are available for study and all cause white spotting in the abdomen, tail, and feet in the heterozygous condition. The Sp homozygous phenotype varies with different alleles. Mice homozygous for Sp null alleles (Sp and Sp7) die midway through gestation with defects in the neural tube and spinal ganglia, whereas mice homozygous for a hypomorphic Sp allele (Sp?) may survive to birth but have spina bifida and absent or abnormal spinal ganglia. Mutations analogous to these Sp alleles have been described in humans [Tassabehji et al. 1994]; however, there is an important interspecies difference in phenotype: All WS patients that are heterozygous for PAX3 mutations have hearing loss, whereas Sp heterozygous mice have normal hearing and no anatomical or physiological defects in the inner ear [Steel and Smith 1992]. In addition, an individual homozygous for a severe PAX3 mutation has lived at least 3 months and did not display any neural tube defects [Zlotogora et al. 1995].

Mitf is encoded by the mouse microphthalmia (mi) locus [for review, see Jackson and Raymond 1994; Moore 1995]. The mi locus is particularly fascinating because there are many alleles available for study and the various alleles display a plethora of phenotypic consequences and complex inheritance patterns. All mi alleles cause defects in melanocytes that lead to pigmentation and deafness in homozygotes, yet certain alleles affect other cell types including the retinal pigmented epithelium, mast cells, basophils, natural killer cells, macrophages, and osteoclast precursors. In general, the more severe alleles are semidominant and the less severe alleles are recessive and the mutations in each class localize to specific domains. Interestingly, a mutation identical to that
of the original mutation at this locus, the mi allele, was found in a WS2 family [see Fig. 3]. Heterozygous mi/+ mice display coat pigmentation defects and have normal hearing; however, humans with the analogous mutation have a phenotype that resembles albinism–deafness rather than classical WS2 [Tassabehji et al. 1995]. Similarly, patients heterozygous for mutations that would be expected to be recessive [such as functional nulls] have hearing deficiencies, whereas the only heterozygous hearing deficiencies observed in mice are caused by a severe, dominant negative allele of mi [Mrw+] [for review, see Steel and Brown 1994; Steel 1995] and are described elsewhere in this review [see Tables 1, 3, and 4].

Disorders of retinal development

Aniridia is a developmental defect of the eye that results from hypoplasia of the iris [MIM 106210]. The human aniridia gene was shown to be Pax6, a paired domain transcription factor, and subsequent studies revealed that the homologous gene is affected in small eye (Sey) mice [for review, see Hanson and van Heyningen 1995]. Since these initial reports, Pax6 mutations have also been associated with anterior segment malformations, such as Peter’s anomaly [MIM 261540; Hanson et al. 1994] and a range of other ocular defects [Glaser et al. 1994].

Gene dosage appears to be critical to Pax6 function in both mice and humans as deletions and null point mutations are semidominant and homozygosity results in an even more severe phenotype [for review, see Hanson and Van Heyningen 1995]. Interestingly, eye development is sensitive to increased, as well as decreased, expression of Pax6. This was demonstrated elegantly by Schedl et al. [1996], who used YAC transgenic experiments to investigate gene dosage effects of Pax6. Although YACs containing wild-type Pax6 were able to rescue the Sey mutant phenotype, they caused severe microphthalmia and cataracts when present in the wild-type background. Furthermore, by analyzing Sey/+ chimeras, Quinn et al. [1996] have provided evidence that normal eye development requires a threshold number of normal cells. Thus, somatically acquired rearrangements that affect Pax6 expression, either positively or negatively, could have dramatic effects on eye development.

Degenerative disorders of the retina

The stimulation of photoreceptors in the retina by light results in electrical signals that are transmitted to the brain. Mutations in three components of this phototransduction system cause degeneration of the photoreceptor cells that ultimately leads to blindness: Rhodopsin (Rho) is a G protein-coupled photoreceptor that mediates vision at low light levels; peripherin (Prph2) is a transmembrane glycoprotein that may be important for the assembly and stability of membranous disks of the outer segment of photoreceptors; and the β-subunit of rod CGMP phosphodiesterase (Pdeβ) is a component of the key regulator of cGMP-gated cation channels that are involved in phototransduction.

Retinitis pigmentosa (RP; MIM 268000) is a heterogeneous group of disorders that are the most common causes of blindness in middle-aged individuals. X-linked, autosomal recessive [ar] and autosomal dominant [ad] forms of RP have been reported. Mutations in RHO have been associated with both arRP and adRP [for review, see McInnes and Bascom 1992]. Because null alleles cause arRP and point mutations cause adRP, it has been proposed that the latter mutations cause gain of function.
Myo7a ~*hl
Pdeb rdl
photoreceptor degeneration. Huang et al. (1993) showed

gene Mouse

Pax6 s~v
Pax2 Krd
mutations in
Rho
Prph2 ~d2
(review, see Steel and Brown 1994; Steel 1995).

Table 2. Disorders of vision and hearing

<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references</th>
</tr>
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<tbody>
<tr>
<td>Myo7a&lt;sup&gt;vt&lt;/sup&gt;</td>
<td>Myosin VIIA</td>
<td>C,S</td>
<td>Ushers syndrome type IB</td>
<td>276903</td>
<td>Gibson et al. (1995); Weil et al. (1995)</td>
</tr>
<tr>
<td>Oat</td>
<td>Ornithine amino transferase</td>
<td>K</td>
<td>Hypo-ornithinemia with gyrate atrophy of choroid and retina</td>
<td>258870</td>
<td>*Valle and Simell (1995); Wang et al. (1995)</td>
</tr>
<tr>
<td>Pax2&lt;sup&gt;Krd&lt;/sup&gt;</td>
<td>Paired box homeotic gene 2</td>
<td>TI</td>
<td>Optic nerve coloboma w/renal disease</td>
<td>120330</td>
<td>Keller et al. (1994); Sanyanusin et al. (1995)</td>
</tr>
<tr>
<td>Pax6&lt;sup&gt;Sev&lt;/sup&gt;</td>
<td>Paired box homeotic gene 6</td>
<td>C,R,S</td>
<td>Aniridia type II</td>
<td>106210</td>
<td>*Hanson and Van Heyningen (1995)</td>
</tr>
<tr>
<td>Pdeb&lt;sup&gt;rd2&lt;/sup&gt;</td>
<td>Phosphodiesterase, cGMP, rod receptor, beta</td>
<td>S</td>
<td>Autosomal recessive retinitis pigmentosa</td>
<td>180072</td>
<td>Bowes et al. (1990); McLaughlin et al. (1993, 1995); Gal et al. (1994)</td>
</tr>
<tr>
<td>Prph2&lt;sup&gt;rd2&lt;/sup&gt;</td>
<td>Peripherin 2</td>
<td>S</td>
<td>Retinal degeneration, slow</td>
<td>179605</td>
<td>*Travis and Hepler (1993); Ma et al. (1995)</td>
</tr>
<tr>
<td>Rho</td>
<td>Rhodopsin</td>
<td>TE</td>
<td>Retinitis pigmentosa-4</td>
<td>180380</td>
<td>*McInnes and Bascom (1992), Naash et al. (1993), Sung et al. (1994)</td>
</tr>
</tbody>
</table>

Mutations in Pax3<sup>vt</sup> and Mitf<sup>mi</sup> (Table 1), Cola1<sup>Mov13</sup> (Table 3), Pmp22<sup>Tr</sup> (Table 4), and Gus<sup>mr+</sup> (Table 7) also cause hearing defects (for review, see Steel and Brown 1994; Steel 1995).

aSee Table 1 for footnote.

[GOF] that in some way induces degeneration of photoreceptor cells. In support of this hypothesis, various mouse models that express mutant Rho proteins induce similar photoreceptor degeneration. These transgenic mouse models also have been used to examine the mechanism of and possible environmental effects on photoreceptor degeneration. Huang et al. (1993) showed that the Rho phenotype is non cell-autonomous in mice that are chimeric for nontransgenic and transgenic cells. Thus, some form of interaction must be occurring between wild-type and mutant cells that induces cellular death in both populations.

By comparing the rate of photoreceptor degeneration in mice containing mutant Rho transgenes that were raised in the dark or in alternating light/dark cycles, Naash et al. (1996) have proposed that the vision of RP patients may be prolonged by minimizing light exposure.

The first mutations in Prph2 were identified in retinal degeneration-2 [Rd2, previously called retinal degeneration slow, rds] mice (Travis et al. 1989). Rd2 is a semidominant trait that causes degeneration of both rod and cone photoreceptors. As the only allele at this locus appears to be null as a result of the insertion of a repetitive element (Ma et al. 1995), the semidominant inheritance of Rds is thought to result from haploinsufficiency. In humans, PRPH2 mutations have been associated with a variety of phenotypes that are each caused by different types of mutations (for review, see Travis and Hepler 1993). Because adRP has been associated with null PRPH2 alleles, the rds mouse is a good model for this form of retinopathy. Surprisingly, a large amount of phenotypic variation has been seen in humans with different PRPH2 mutations. Construction of mice with analogous mutations in Prph2, either through ES cell technology or through transgene engineering, and the introduction of these mutations into different genetic backgrounds, will be useful to sort out the effects of potential modifying factors on the function of this gene.

One of the most important models for the study of RP is the retinal degeneration-1 [rd1] mouse, in which all photoreceptor cells have degenerated in homozygous mice by four weeks of age. Many of the commonly used inbred strains, including C3H and its derivatives and CBA/J, are homozygous for rd1. Mutations in the Pdeb gene were first identified in rd1 mice (Bowes et al. 1990; Pittler et al. 1991) and subsequently in humans with arRP (McLaughlin et al. 1993, 1995) and a dominant form of night blindness (Gal et al. 1994). Two mutations in the Pdeb gene of rd1 mice have been identified: a nonsense mutation that causes truncation of the protein (Bowes et al. 1990) and intronic insertion of an endogenous mouse leukemia virus [Xmv28] that causes a transcriptional defect (Bowes et al. 1993). Xmv28 has also been found in strains derived from wild mice, as well as from inbred laboratory strains that are not known to have recent common origins (Bowes et al. 1993). This suggests a surprisingly high degree of evolutionary stability for a mutation that causes loss of vision in the mice.

A potentially useful treatment for retinal degeneration has been tested in rd1 mice (Bennett et al. 1996). Recombinant defective adenoviruses that carry the wild-type Pdeb gene were introduced into the retinas of rd1 mice before the onset of photoreceptor degeneration and found to significantly delay photoreceptor cell death. These mouse models are thus proving to be very useful for testing various treatment vehicles and regimens for retinal degeneration.

Recent evidence obtained by gene targeting in mice...
has revealed the importance of the gamma subunit of rod cGMP phosphodiesterase (Pdeg) to retinal disease. Tsang et al. [1996] have disrupted the Pdeg gene and found that homozygous mice display a phenotype of retinal degeneration virtually identical to that of rd1 mice and arRP. Unlike other mouse models, introduction of the Pdeg mutation into a variety of different genetic backgrounds did not affect the mutant phenotype. A possible role for this gene in human retinal diseases should be investigated.

**Hearing disorders**

Deafness may be grouped into several categories, depending on the primary site of the defect in the auditory system [Steel and Brown 1994; Steel 1995]. In humans, the most common type of hearing abnormality is caused by defects in the sensory neuroepithelium, particularly in the organ of Corti, that is responsible for normal auditory transduction. Because the majority of these cases are recessive and nonsyndromic and involve numerous genes, linkage analysis of this form of hearing defect has been difficult to perform in humans.

A landmark in our understanding of hearing disorders was the cloning in 1995 of the first gene involved in auditory transduction and the mouse played an integral role in this endeavor. Comparative mapping and phenotypic similarities had suggested that the mouse shaker 1 (sh1) deafness mutation is homologous to Usher syndrome type IB (USH1B; MIM 276903), the most common form of deaf-blindness in humans. Gibson et al. [1995] used a positional cloning strategy to show that an unconventional myosin (Myo7a) is encoded at the sh1 locus. Once the mouse gene was cloned, it was then fairly straightforward to analyze and find MYO7A mutations in USH1B patients [Weil et al. 1995]. Although degeneration of the organ of Corti occurs in both sh1 mice and USH1B patients, only the latter display retinal degeneration. Currently it is unclear whether these interspecies differences are attributable to the nature of the mutations or to differences in function or compensation of defective Myo7a. Recently, a second unconventional myosin (Myo6) has been shown to be mutated in Snell's waltzer mice, which also have defects in the sensory neuroepithelium of the ear [Avraham et al. 1995]. Unconventional myosins, as well as the numerous accessory proteins that interact with these cytoskeletal proteins, are thus likely candidate genes for other loci involved in neuroepithelial deafness.

**Disorders of bone, cartilage, and skin**

In the mouse, there are >100 genetically defined loci and transgenic models that affect skeletal development (MGD). A wide range of skeletal abnormalities have been found in mice and humans that result from patterning defects during embryogenesis, failure to establish the correct proportions of bone growth, and alterations in the biomechanical properties of bone. In Table 3, 13 genes are listed in which alterations in both human and mouse homologs disrupt skeletal development. In addition, three keratin genes are listed in this table that cause skin disorders. With the exception of mutants in alkaline phosphatase-2 (Akp2), all of the mouse models have phenotypic consequences that closely mimic or explain some aspect of the corresponding human disease.

**Polydactyly**

Mutations in Hoxd13 and Cli3, which are members of the homeodomain and zinc-finger families of transcription factors, respectively, cause pattern deformities of the skeleton of mice and humans. Mice that are homozygous for null Hoxd13 mutations display mild skeletal abnormalities along all body axes and reduced loss of phalanges, bone fusions, and duplications in the limbs [Dolle et al. 1993]. In humans, the candidate gene approach was used to identify mutations in HOXD13 that cosegregated with synpolydactyly trait [MIM 186000], an autosomal dominant trait characterized by both webbing between fingers and duplication of fingers. The mutation in these patients involves expansion of a polyalanine tract near the amino terminus of the protein [Murakagi et al. 1996b]. Although the homozygous phenotype of Hoxd13 mice is milder than that of synpolydactyly patients, some aspects of the mutant phenotype overlap in the two species. However, unlike humans with synpolydactyly, the Hoxd13 heterozygous mice do not have an apparent phenotype.

**Skeletal dysplasia: Fgfr mutations**

Cell–cell signaling via fibroblast growth factor receptors (FGFRs) has been shown recently to be involved in coordinating the growth of endochondral and intramembranous bones. Disruption of the proportional growth of the radial and longitudinal axes of endochondral bones results in skeletal dysplasias. In the skull, bone deposition and growth of intramembranous bones is coordinated temporally with suture closure, and various abnormalities, known as craniosynostoses, result from premature suture closure.

Point mutations in FGFR1 and FGFR2 have been associated with Pfeiffer, Jackson–Weiss, and Crouzon syndromes: All three syndromes are autosomal dominant craniosynostosis syndromes that also exhibit variable degrees of limb abnormalities (for review, see Muenke and Schell 1995). Because mice heterozygous for Fgr1 null mutations are normal, and homozygosity causes early embryonic lethality [Deng et al. 1994; Yamaguchi et al. 1994], the human mutations have been postulated to express GOF gene products. Mouse transgenics that recapitulate the human mutations will be useful models for the human diseases.

Although FGFR1 and FGFR2 mutations affect intramembranous bones, mutations in FGFR3 generally affect endochondral bones [for review, see Muenke and Schell 1995]. Three dominant skeletal dysplasias that represent a graded series of phenotypic severity have been associated with FGFR3 mutations [Bellus et al.
<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references</th>
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</thead>
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<tr>
<td><strong>Akp2</strong></td>
<td>Alkaline phosphatase-2, liver</td>
<td>K</td>
<td>Hypophosphatasia</td>
<td>171760</td>
<td>Henthorn et al. (1992); Waymire et al. (1995)</td>
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<td><strong>Cola1Mor</strong></td>
<td>Procollagen type 1, alpha 1</td>
<td>K,RI,TE</td>
<td>Osteogenesis imperfecta; Ehlers-Danlos type VII</td>
<td>130060; 166200</td>
<td>Liu et al. (1995a); *Prockop and Kivirikko (1995)</td>
</tr>
<tr>
<td><strong>Cola2vom</strong></td>
<td>Procollagen type 1, alpha 2</td>
<td>S</td>
<td>Osteogenesis imperfecta; Ehlers-Danlos type VII</td>
<td>130060; 166200</td>
<td>Chipman et al. (1993); *Prockop and Kivirikko (1995)</td>
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<tr>
<td><strong>Col2a1</strong></td>
<td>Procollagen type 2, alpha 1</td>
<td>K,TE</td>
<td>Spondyloepiphyseal dysplasia; achondrogenesis type 3; spondyloepimetaetal dysplasia</td>
<td>183900; 200610; 184250</td>
<td>Hiltonen et al. (1994); *Vikkula et al. (1994); Li et al. (1995a)</td>
</tr>
<tr>
<td><strong>Col5a2</strong></td>
<td>Procollagen type 5, alpha 2</td>
<td>K</td>
<td>Ehlers-Danlos type c</td>
<td>130000</td>
<td>Andriopolous et al. (1995); Toriello et al. (1996)</td>
</tr>
<tr>
<td><strong>Col9a1</strong></td>
<td>Procollagen type 9, alpha 1</td>
<td>K,TE</td>
<td>Multiple epiphyseal dysplasia 2</td>
<td>600204</td>
<td>Nakata et al. (1993); Fassler et al. (1994); Muragaki et al. (1996a)</td>
</tr>
<tr>
<td><strong>Col11a1</strong></td>
<td>Procollagen type 10, alpha 1</td>
<td>K,TE</td>
<td>Schmid metaphyseal chondrodysplasia</td>
<td>156500</td>
<td><em>Olsen (1995);</em> Prockop and Kivirikko (1995)</td>
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<tr>
<td><strong>Col11a1vcho</strong></td>
<td>Procollagen type 11, alpha 1</td>
<td>K,S</td>
<td>Stickler syndrome type II</td>
<td>184840</td>
<td>Li et al. (1995b); *Olsen (1995); Vikkula et al. (1995)</td>
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<tr>
<td><strong>Fgfr1</strong></td>
<td>Fibroblast growth factor receptor 1</td>
<td>K</td>
<td>Acocephalopolysyndactyly type V</td>
<td>101600</td>
<td>Bellus et al. (1995); *Muenke and Schell (1995)</td>
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<tr>
<td><strong>Fgfr3</strong></td>
<td>Fibroblast growth factor receptor 3</td>
<td>K</td>
<td>Achondroplasia; hypochondroplasia, thanatophoric dwarfism</td>
<td>134934</td>
<td>Bellus et al. (1995); *Muenke and Schell (1995); Colvin et al. (1996); Deng et al. (1996); Nakai et al. (1995)</td>
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<td><strong>Fbn1Tsk</strong></td>
<td>Fibrillin</td>
<td>S</td>
<td>Marfans syndrome</td>
<td>154700</td>
<td>Ramirez et al. (1996); Siracusa et al. (1996)</td>
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<td><strong>Gli3xt</strong></td>
<td>GLI-Kruppel family member</td>
<td>R,S</td>
<td>Greig cephalopolysyndactyly syndrome</td>
<td>175700</td>
<td>Vortkamp et al. (1991); Hui and Joyner (1993)</td>
</tr>
<tr>
<td><strong>Hoxd13</strong></td>
<td>Homeo box D13</td>
<td>K</td>
<td>Syndactyly type II</td>
<td>186000</td>
<td>Dolle et al. (1993); Hui and Joyner (1993); Muragaki et al. (1996b)</td>
</tr>
<tr>
<td><strong>Krt1-10</strong></td>
<td>Keratin complex-1, acidic, gene 10</td>
<td>K,TE</td>
<td>Bullous erythoderma icthyosiformis congenita</td>
<td>113800</td>
<td>*Fuchs (1995); Porter et al. (1996)</td>
</tr>
<tr>
<td><strong>Krt1-14</strong></td>
<td>Keratin complex-1, acidic, gene 14</td>
<td>K,TE</td>
<td>Epidermolysis bullosa simplex</td>
<td>148066</td>
<td>*Fuchs (1995); Lloyd et al. (1995)</td>
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<tr>
<td><strong>Krt1-16</strong></td>
<td>Keratin complex-1, acidic, gene 16</td>
<td>TE</td>
<td>Nonpeidermolytic palmoplantar keratoderma; pachyonychia congenita</td>
<td>148067</td>
<td>Takahashi et al. (1994a); *Fuchs (1995)</td>
</tr>
</tbody>
</table>

*aSee Table 1 for footnotes.
*bMutations are in COL1A1 or COL1A2 gene.
*cMutations are in COL5A1 gene.
*dMutations are in COL9A2 gene.
*eMutations are in COL11A1 or COL11A2 gene.
*fAlso called Pfeiffer syndrome.

Compelling genetic evidence that all of the human FGFR3 mutations result in the constitutive activation of FGFR3 comes from studies of mice. Mice heterozygous for null mutations in Fgfr3 are normal, yet homozygous mice show a phenotype that is the opposite of human FGFR3 mutations (Colvin et al. 1996; Deng et al. 1996); that is, the Fgfr3-deficient mice exhibit overgrowth of the long bones rather than decreased growth. These results have suggested that Fgfr3 is a negative regulator of bone growth. Furthermore, Fgfr3-deficient mice are profoundly deaf owing to abnormalities in the organ of Corti.
humans may be associated with hearing loss as well as skeletal abnormalities.

**Skeletal dysplasia: Collagen mutants**

Collagens are the main fibrous proteins of connective tissue and are the most abundant proteins of the extracellular matrix. There are at least 19 different collagens [Prockop and Kivirikko 1995] that are formed into a triple helix of three pro-α polypeptide chains; some collagens are comprised of three of the same pro-α chains while other collagens are heterotrimers, composed of two or more different pro-α chains. Thus, mutations in different collagen genes may disrupt the same collagen fibril. In humans, mutations in 13 different collagen genes have been associated with disease phenotypes (Olsen 1995; Prockop and Kivirikko 1995). Different human diseases can also result from mutations in the same collagen gene. For example, at least five different forms of chondrodysplasia and cartilage degeneration result from mutations in the COL2A1 gene (Vikkula et al. 1994).

In one case, a mouse collagen mutant was instrumental in identifying the corresponding human disease gene. Using a candidate gene approach, Li et al. (1995b) showed that mutations in the gene encoding procollagen type 11, α 1 (Col11a1) are responsible for the skeletal defects in chondrodysplasia (cho) mice. The phenotypic similarity between cho mice and certain human chondrodysplasias, such as Stickler syndrome (MIM 184840), and the close linkage between COL11A2 and autosomal dominant Stickler syndrome led to the identification of COL11A2 mutations in Stickler syndrome patients [Vikkula et al. 1995]. In addition to cho mice, mouse models for mutations in six other human collagen genes have been reported (see Table 3). The localization of the defects in the developing bone caused by each of these mutations, as well as for Fgfr3, is illustrated in Figure 4. These models were derived in a variety of ways including disruption by a retroviral provirus [Cola1], spontaneously occurring mutations [osteogenesis imperfecta (Col1a2)] and transgenic and/or knockout models [Cola1, Col2a1, Col5a2, Col9a1, and Col10a1].

**Neurological and neuromuscular disorders**

There are at least 150 different mutant loci in the mouse that cause neurological, neuromuscular or behavioral defects [MGD]. Twenty-two of these mutant loci are models for human disease and are shown in Table 4. Sixteen of these models cause neurological phenotypes and the remaining six cause neuromuscular or muscular abnormalities. With the exception of the Hdh deficient mouse, all of the mouse models described in Table 4 share many phenotypic similarities with corresponding human disease.

**Neurodegenerative disorders: Alzheimer’s**

The fourth leading cause of death in developed countries is Alzheimer’s disease [AD; MIM 104300], a progressive dementia that can be caused by mutations in at least four genes (for review, see Pericak-Vance and Haines 1995). In the central nervous system (CNS) of AD patients, neuronal degeneration in specific regions of the brain leads to loss of memory and cognitive abilities. Two histopathological hallmarks of AD are the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles, which consist primarily of Aβ protein (also called β-amyloid) and abnormally phosphorylated tau protein, respectively. Aβ is derived from amyloid beta precursor protein (APP), and both increased gene dosage and intragenic mutations in the APP gene have been associated with AD (Pericak-Vance and Haines 1995). A second major risk factor for AD is apolipoprotein E [APOE]. Of three different APOE isoforms found in humans, one [APOE*E4] is associated with increased risk and decreased age of onset of AD [for review, see Strittmatter and Roses 1995]. Although there is evidence that APP mutations may lead to abnormal processing and higher levels of Aβ, and that the APOE isoforms differ with respect to binding to tau protein and Aβ, the mechanisms by which these proteins contribute to AD pathogenesis are currently obscure.

Recently, several laboratories have produced transgenic mice that exhibit many of the pathological changes associated with AD. This occurs with transgenes that express high levels of wild-type Aβ [LaFerla et al. 1995] or APP that has a point mutation found in AD patients [Games et al. 1995]. Both models share striking similarities to AD patients; however, senile plaques were observed only in the latter model and neither model developed neurofibrillary tangles. Although the reasons for this are not known and warrant further investigation, these results in mice suggest that the plaques and tangles...
<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alzheimer disease</td>
<td>104300</td>
<td>Müller et al. (1994); Games et al. (1995); LaFerla et al. (1995); *Pericak-Vance and Haines (1995); Zheng et al. (1995)</td>
</tr>
<tr>
<td>Atm</td>
<td>Ataxia telangiectasia</td>
<td>K</td>
<td>Ataxia telangiectasia</td>
<td>208900</td>
<td>Savitsky et al. (1995); Barlow et al. (1996)</td>
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<tr>
<td>Cchlla3mdx</td>
<td>Calcium channel, L type, 1A3 subunit</td>
<td>S</td>
<td>Periodic paralysis I</td>
<td>170400</td>
<td>Chaudhari (1992); Ptacek et al. (1994)</td>
</tr>
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<td>DM15</td>
<td>Dystrophin myotonica kinase, B15</td>
<td>K,TE</td>
<td>Dystrophia myotonica</td>
<td>160900</td>
<td>*Campbell (1995); *Harper (1995); Jansen et al. (1996); Reddy et al. (1996)</td>
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<tr>
<td>Dma-mdx</td>
<td>Dystrophia, muscular dystrophy</td>
<td>C,S</td>
<td>Muscular dystrophy, Duchenne and Becker types</td>
<td>310200</td>
<td>Cox et al. (1993a); *Campbell (1995); *Worton and Brooke (1995); *Nawrotzki et al. (1996)</td>
</tr>
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<td>Fmr1</td>
<td>Fragile X mental retardation syndrome 1</td>
<td>K</td>
<td>Fragile X syndrome</td>
<td>309550</td>
<td>Bakker et al. (1994); *Oostra and Willems (1995)</td>
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<tr>
<td>Galctsw</td>
<td>Galactosylceramidase</td>
<td>S</td>
<td>Krabbe disease</td>
<td>245200</td>
<td>*Suzuki et al. (1995)</td>
</tr>
<tr>
<td>GlrAlpsd</td>
<td>Glycine receptor, alpha 1 subunit</td>
<td>S</td>
<td>Kok disease(^c)</td>
<td>149400</td>
<td>Shiang et al. (1993); Ryan et al. (1994)</td>
</tr>
<tr>
<td>Hdh</td>
<td>Huntington disease gene homolog</td>
<td>K</td>
<td>Huntington disease</td>
<td>143100</td>
<td>Duyao et al. (1995); Nasir et al. (1995); Zeitlin et al. (1995)</td>
</tr>
<tr>
<td>Lama2(^by)</td>
<td>Laminin, alpha 2</td>
<td>S</td>
<td>Congenital muscular dystrophy</td>
<td>156225</td>
<td>Sunada et al. (1994); Xu et al. (1994); Helbling-Leclere et al. (1995)</td>
</tr>
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<td>Mjdl</td>
<td>Machado-Joseph disease</td>
<td>TE</td>
<td>Machado-Joseph disease</td>
<td>109150</td>
<td>Kawaguchi et al. (1994); Ikeda et al. (1996)</td>
</tr>
<tr>
<td>Mpz</td>
<td>Myelin protein zero</td>
<td>K</td>
<td>Charcot-Marie Tooth neuropathy, type 1B, Dejerine-Sottas syndrome</td>
<td>118200</td>
<td>Martini et al. (1995); *Suter and Snipes (1995)</td>
</tr>
<tr>
<td>Nfh</td>
<td>Neurofilament, heavy polypeptide</td>
<td>TE</td>
<td>Amyotrophic lateral sclerosis</td>
<td>162230</td>
<td>*Brady (1993); Figlewicz et al. (1994); *Brown (1995)</td>
</tr>
<tr>
<td>Pbgd</td>
<td>Porphobilinogen deaminase</td>
<td>K</td>
<td>Acute intermittent porphyria</td>
<td>176000</td>
<td>*Kappas et al. (1995); Lindberg et al. (1996)</td>
</tr>
<tr>
<td>Phk</td>
<td>Phosphorylase kinase, alpha subunit</td>
<td>S</td>
<td>Muscle glycogenosis, X-linked</td>
<td>311870</td>
<td>Schneider et al. (1993); Wehner et al. (1994)</td>
</tr>
<tr>
<td>Plpy(^p)</td>
<td>Proteolipid protein</td>
<td>K,TE,S</td>
<td>Pelizaeus-Merzbacher disease, spastic paraplegia type 2, Charcot-Marie Tooth neuropathy type 1A, hereditary neuropathy with liability to pressure palsies</td>
<td>312080; 312920; 118220; 162550</td>
<td>*Griffiths et al. (1995); Adlkofer et al. (1995); *Suter and Snipes (1995)</td>
</tr>
<tr>
<td>Pmp22(^Tm)</td>
<td>Peripheral myelin protein, 22 kDa</td>
<td>K,S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prnp</td>
<td>Prion protein</td>
<td>K,TE</td>
<td>Familial fatal insomnia, Creutzfeldt-Jacob and Gerstmann-Straussler disease</td>
<td>176640</td>
<td>*Prusiner (1996)</td>
</tr>
<tr>
<td>Ryr1</td>
<td>Ryanodine receptor 1, skeletal muscle</td>
<td>K</td>
<td>Hyperthermia of anesthesia</td>
<td>145600</td>
<td>MacLennan and Phillips (1992); Takeshima et al. (1994)</td>
</tr>
<tr>
<td>Sca1</td>
<td>Spinocerebellar ataxia 1</td>
<td>TE</td>
<td>Spinocerebellar ataxia type 1</td>
<td>164400</td>
<td>Burright et al. (1995); *Zoghbi and Orr (1995)</td>
</tr>
<tr>
<td>Sod1</td>
<td>Superoxide dismutase-1, soluble</td>
<td>K,TE</td>
<td>Amyotrophic lateral sclerosis</td>
<td>105400</td>
<td>*Brown (1995); Collard et al. (1995); Wong et al. (1995); Reaume et al. (1996); Tu et al. (1996)</td>
</tr>
</tbody>
</table>

\(^a\)See Table 1 for footnote.

\(^b\)Also associated with hyperlipoproteinemia (Table 7).

\(^c\)Also called hyperekplexia.
may be the consequence, rather than the cause, of neurodegeneration. Others have documented age-dependent alterations in the brains of APP-transgenic mice (Higgins and Cordell 1995; Hsiao et al. 1995; Moran et al. 1995). Significantly, Moran et al. [1995] have shown that these transgenic mice display learning deficits and Hsiao et al. [1995] have demonstrated that genetic background has a dramatic effect on the phenotype. All of these models will be very useful for understanding the role of APP in AD, for testing models that may either reduce Aβ production or its toxicity, and for identifying modifiers that then may be used to develop effective therapies for AD.

The normal function of APP is not known; however, recent studies in mice indicate that it may be required for neuronal function. Mice homozygous for a "leaky" App mutation show defects in spatial learning and an increased incidence of agenesis of the corpus callosum [Müller et al. 1994]. In addition, mice homozygous for a null App mutation, while not exhibiting any abnormalities in the corpus callosum [Zheng et al. 1995], showed decreased locomotor activity and reactive gliosis in the brain indicative of impaired neuronal function. These App-deficient mice will be useful to assess the effects of mutant App transgenes in the absence of possible interference by wild-type App encoded by the endogenous gene.

Mouse models may also prove useful for elucidating the role of APOE in AD. Although mice homozygous for null mutations in Apoe were reported originally to be neurologically normal [Popko et al. 1993], more recent studies have identified synaptic alterations and neurodegeneration in the CNS of Apoe null mice [Masliah et al. 1995]. It will be very interesting to determine whether the neurological defects are exacerbated or alleviated in Apoe mutant mice that express mutant App transgenes. Transgenic mice that express the different human APOE isoforms individually have been generated already [Bowman et al. 1995] and should provide an excellent background in which to test interactions between the different APOE isoforms and mutant App peptides.

Neurodegenerative disorders: Prion diseases

The only diseases known to occur as sporadic, genetic, and transmissible forms are caused by nonviral infectious particles, called prions, whose sole component is prion protein [PrP; see Prusiner 1996]. Either prion infection or mutation of the PrP gene causes neurodegeneration in sheep and cattle [scrapie and bovine spongiform encephalopathy (BSE), respectively], and in humans [kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Schinkler disease (GSS), and fatal familial insomnia (FFI) [MIM 176640]]. In humans, prion diseases cause progressive decline in cognitive and motor functions and pathological features in the CNS include spongiform degeneration, gliosis, neuronal loss, and amyloid plaques. Recently much attention has focused on these diseases as an epidemic of BSE occurred in Britain and other European countries, and the risk of transmission of the disease to humans via ingestion of contaminated beef is not known conclusively. Studies with mouse models have been instrumental not only for beginning to understand the pathogenesis of prion disease but also for quelling some of the concerns about possible interspecies transmission [see Collinge et al. 1995; Hope 1995].

The development of neuropathological alterations and transmissibility of disease in transgenic mice that express wild-type and mutant forms of PrP has provided conclusive evidence that this protein causes prion diseases [see Prusiner 1996]. Although the initial analysis of mice homozygous for null Prn-p mutations did not reveal any significant developmental, behavioral, or neurological abnormalities, the mutant mice were resistant to prion infection and were unable to generate infectious particles. Subsequently, Collinge et al. [1994] reported that Prn-p-deficient mice have abnormalities in synaptic inhibition in the hippocampus. In contradiction, others reported no abnormalities in hippocampal electrophysiology in Prn-p-deficient mice and suggested that differences in genetic background may explain these discrepancies [Lledo et al. 1996]. Further support for a role for PrP in the nervous system has been provided by two recent reports of Prn-p-deficient mice: Homozygous mutants display abnormalities of circadian activity rhythm and sleep [Tobler et al. 1996] and aged homozygous mice exhibit ataxia, impaired motor coordination, and extensive loss of Purkinje cells [Sakaguchi et al. 1996]. The former phenotype is similar to that of FFI patients and suggests that this disease may result from loss-of-function (LOF) in PrP. Clearly, further studies on the mutant mice will be needed to clarify the role of PrP and its derivatives in neural function.

Two problems associated with a transgenic model of human GSS, in which the mice express Prn-p with a point mutation identical to a human mutant, are the wide variability in age of onset of the disease and the lack of amyloid plaques. Telling et al. [1996] have overcome these problems by crossing the transgene into the Prn-p null background, and the new model faithfully recapitulates virtually all features of human GSS. In addition, they clearly demonstrate that the wild-type Prn-p gene has a suppressive effect on the phenotype. Furthermore, mice that express human/mouse chimeric Prn-p transgenes in a wild-type Prn-p background are resistant to infection by human prions, whereas susceptibility occurred when the transgene was expressed in a Prn-p null background [Telling et al. 1995]. To explain these observations, Prusiner and colleagues have proposed that prion formation requires the action of another host protein, perhaps analogous to a molecular chaperone [Telling et al. 1995, 1996]. Identification of this protein and the mechanism by which it affects prion susceptibility could have important implications for prion, as well as other, diseases.

Neuromuscular disorders

The neuromuscular abnormalities described in Table 4 result from failure of the excitation–contraction coupling of skeletal muscle (Ryr1 and Cch11a3 mutants),
defects in muscle metabolism (Phk mutants), and degeneration and/or weakness of muscle (Dmd, Dm15, and Lama 2 mutants). Here we will discuss recent results on mouse models of the latter type of disorders. Each of the corresponding human disorders has been reviewed recently [Campbell 1995; Nawrotzki et al. 1996].

Two X-linked traits in humans, Duchenne and Becker muscular dystrophies (DMD and BMD, MIM 310200), are attributable to mutations in dystrophin, a large cytoskeletal protein that localizes to the sarcolemma of normal skeletal muscle [Worton and Brooke 1995]. DMD is the first major human disease gene to be discovered through positional cloning. Comparative mapping and phenotypic similarities had suggested that the mouse homolog of DMD might be the X-linked muscular dystrophy (mdx) locus, and Sicinski et al. [1989] reported a point mutation in the Dmd gene of these mice. Several other alleles of mdx have been generated by chemical mutagenesis [Chapman et al. 1989] and one of these has been characterized at the molecular level [Cox et al. 1993]. In both DMD patients and mdx mice, extensive necrosis of skeletal muscle fibers occurs. In DMD patients, significant muscle impairment occurs owing to the replacement of muscle tissue with fibrotic tissue and adipocytes. However, in mdx mice, a high rate of muscle regeneration occurs and allows the mice to be relatively asymptomatic until ~1 year of age. The one exception to this is the diaphragm, which displays severe myopathy. Nonetheless, these mice serve as important models for DMD and BMD and several laboratories have used them to test various models for gene therapy [Cox et al. 1993a; Vincent et al. 1993; Wells et al. 1995; Deconinck et al. 1996]. Recently, a mouse model that more closely resembles the muscle pathology of DMD patients was generated [Megeney et al. 1996]. In this model, mice that contain mutations in both mdx and Myod, which encodes a myogenic transcription factor, were generated and the double mutants exhibit a much more pronounced myopathy resulting from lack of muscle regeneration.

Recent studies with mdx mice have been used to test the hypothesis that the secondary loss of dystrophin-associated proteins (DAPs) contributes to muscle degeneration. DAPs form a complex with dystrophin and together are thought to play a structural role in skeletal muscle [for review, see Campbell 1995]. In both humans and mice, DAPs are reduced as the result of dystrophin deficiency. To determine directly whether DAP loss plays a role in muscle disease, two groups have introduced transgenes that express a truncated version of Dmd into mdx mice [Cox et al. 1994; Greenberg et al. 1994]. The truncated Dmd protein (Dp71) was able to localize to the membrane and restored normal levels of DAP. Significantly, however, the up-regulation of DAPs did not prevent myofiber degeneration in the mdx mice, suggesting that other mechanisms must operate to cause the muscular degeneration.

The most frequent autosomal muscular dystrophy in humans is dystrophia myotonica (DM, MIM 160900), which is characterized by neuromuscular disturbances that affect skeletal muscle, smooth muscle of various organs, and a host of extramuscular features [Harper 1995]. After nearly a decade of mapping and positional cloning, three laboratories reported in 1992 that the DM gene encodes a protein kinase, called DM15 (see Harper 1995). The causative mutation in DM15 is the instability of trinucleotide repeats in the 3' untranslated region of the gene. Two groups recently have created targeted mutations in the Dm15 gene of mice [Jansen et al. 1996; Reddy et al. 1996]. Both groups reported that the absence of Dm15 causes progressive skeletal myopathy, but the two reports differ with respect to the severity of the alterations. Because both alleles are thought to be null mutations, and the mice are of similar genetic backgrounds, the reasons for these phenotypic differences are not known. In addition, Jansen et al. [1996] generated transgenic mice that overexpress normal human DMPK from a 14-kb genomic fragment. The expression pattern of this transgene faithfully reproduced that of the endogenous gene; however, myopathy of cardiac muscle was observed with the highest level of transgene expression and no abnormalities of skeletal muscle were noted. Although these mouse models do not clarify whether the DM15 alterations cause GOF or LOF mutations in humans, they will be useful for understanding the biological role of this gene product.

Cancer

The creation of inbred strains of mice, which began in the early part of this century, was in large part an attempt to develop better models for cancer research. Early experiments with these inbred strains of mice demonstrate clearly that cancer susceptibility behaved as a Mendelian trait and could be influenced by genetic background. The subsequent discovery of familial clustering of cancer susceptibility in humans suggested that cancer susceptibility could also be inherited as a Mendelian trait in humans [for review, see Knudson 1988]. These "cancer family" syndromes show a dominant mode of inheritance with affected individuals usually developing a relatively broad but defined spectrum of cancers. We now know that many of these inherited cancer predisposition syndromes result from germ-line mutations in tumor suppressor genes [for review, see Hooper 1994]. Most of the mouse models for these human cancer syndromes have been created by making knockout or transgenic mice (Table 5). These models have many advantages compared with human primary tumors or tumor cell lines because it is possible to study the effect of mutations on a uniform genetic background and in the absence of any other contributing somatic mutations. All of the mouse mutants described in Table 5, except for the knockouts of Brea1, Rbl1, and Wt1, have phenotypes that closely parallel those of the corresponding human disease genes.

**Li-Fraumeni syndrome**

One well-studied cancer family syndrome is Li-Frau-
### Table 5. Neoplastic diseases

<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apc&lt;sup&gt;Mink&lt;/sup&gt;</td>
<td>Adenomatous polyposis cell</td>
<td>C,K</td>
<td>Adenomatous polyposis of the colon</td>
<td>175100</td>
<td>Groden et al. (1991); *Moser et al. (1995); *Peifer (1996)</td>
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<tr>
<td>Brca1</td>
<td>Breast cancer 1</td>
<td>K</td>
<td>Breast cancer type 1</td>
<td>114480</td>
<td>*Cannon-Albright and Skolnick (1996); Gowen et al. (1996); Hakem et al. (1996)</td>
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<tr>
<td>Cdkn2a</td>
<td>Cyclin dependent kinase inhibitor 2a</td>
<td>K</td>
<td>Malignant melanoma</td>
<td>155600</td>
<td>Hussussian et al. (1994); Serrano et al. (1996)</td>
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<td>Mlh1</td>
<td>MutL [E. coli] homolog 1</td>
<td>K</td>
<td>Familial colon cancer, nonpolyposis type 1</td>
<td>120435</td>
<td>*Jass et al. (1994); de Wind et al. (1995); Reitmair et al. (1995)</td>
</tr>
<tr>
<td>Msh2</td>
<td>MutS [E. coli] homolog 2</td>
<td>K</td>
<td>Familial colon cancer, nonpolyposis type 1</td>
<td>120435</td>
<td>*Jass et al. (1994); Nicolaides et al. (1994); Baker et al. (1995)</td>
</tr>
<tr>
<td>Pms2</td>
<td>Postmeiotic segregation increased 2 (S. cerevisiae)</td>
<td>K</td>
<td>Familial colon cancer, nonpolyposis type 3</td>
<td>600259</td>
<td></td>
</tr>
<tr>
<td>Nf1</td>
<td>Neurofibromatosis type 1</td>
<td>K</td>
<td>Neurofibromatosis type 1</td>
<td>162200</td>
<td>*Gutmann and Collins (1993); Brannan et al. (1994); Jacks et al. (1994)</td>
</tr>
<tr>
<td>Rb1</td>
<td>Retinoblastoma-1</td>
<td>K</td>
<td>Familial retinoblastoma</td>
<td>180200</td>
<td>*Hooper (1994); *Clarke (1995)</td>
</tr>
<tr>
<td>Ret&lt;sup&gt;1b&lt;/sup&gt;</td>
<td>Receptor tyrosine kinase</td>
<td>TE</td>
<td>Multiple endocrine neoplasia type 2 familial medullary thyroid carcinoma</td>
<td>171400</td>
<td>*Goodfellow (1994); Jhiang et al. (1996); Santoro et al. (1996)</td>
</tr>
<tr>
<td>Wt1</td>
<td>Wilms’ tumor homolog</td>
<td>K</td>
<td>Wilm’s tumor; Denys-Drash syndrome</td>
<td>194070; 194080</td>
<td>Kreidberg et al. (1993); *Mueller (1994); *Hastie (1994)</td>
</tr>
</tbody>
</table>

<sup>a</sup>See Table 1 for footnote.

<sup>b</sup>Also associated with Hirschsprung’s disease (Table 1).

Meni syndrome (LFS; MIM 151623). LFS is a rare autosomal dominant disorder caused by germ-line mutations in the p53 (TRP53) tumor suppressor gene (for review, see Malkin 1994). LFS patients develop a variety of cancers, notably soft tissue sarcoma, breast carcinoma, brain tumors, osteosarcoma, leukemia, and adrenocortical carcinoma. Sporadic mutations in TRP53 also occur in approximately half of all primary human tumors making it one of the most commonly mutated human cancer genes (Nigro et al. 1989; Hollstein et al. 1991; for review, see Levine et al. 1991). The majority of tumors with TRP53 mutations contain a missense mutation in one allele and a loss of the second allele. When expressed as transgenes in mice, these mutant forms of TRP53 give rise to a variety of tumor types showing significant overlap with those often seen in LFS patients [Lavigueur et al. 1989]. In addition, there is considerable evidence that many of these TRP53 missense mutant proteins possess dominant-negative activity compared to wild-type [Harvey et al. 1995]. Like LFS patients, mice heterozygous for Trp53 null mutations develop tumors, but with a longer latent period than homozygous mutant animals [for review, see Hooper 1994; Malkin 1994; Clarke 1995; Jacks 1996]. Interestingly, the spectrum of tumor types in these strains is influenced strongly by strain background [for review, see Hooper 1994]. Modifier genes affecting tumor incidence might thus be identifiable in these strains.

**Multiple endocrine neoplasia type 2**

Mutations in proto-oncogenes are also found in sporadic tumors, yet they are involved less frequently in hereditary human cancers. One exception is the RET proto-oncogene. Activating GOF mutations in the RET receptor tyrosine kinase have been found in multiple endocrine neoplasia type 2 (MEN2; MIM 171400) and familial medullary thyroid carcinoma (FMTC; MIM 155240) (Donis-Keller et al. 1993; Mulligan et al. 1993, for review, see Goodfellow 1994). MEN2 is a dominantly inherited cancer syndrome characterized by the development of medullary thyroid carcinoma and pheochromocytoma in the type 2A form as well as ganglioneuromas of the gastrointestinal tract and skeletal and opthalmic abnormalities in the type 2B form. Transgenic mice expressing an activated form of RET under the control of a bovine or rat thyroglobulin gene promoter develop papillary thyroid...
carcinoma and are a promising model for RET-induced malignancies [Jhiang et al. 1996; Santoro et al. 1996].

Colorectal cancer

In the last several years, it has become apparent that genetic predisposition to cancer can also result from mutations in DNA repair genes. For example, individuals heterozygous for mutations in the human MutS homolog 2 (Msh2) gene develop familial colon cancer, nonpolyposis type 1 [MIM 120435] and tumors show microsatellite length instability [Fishel et al. 1993; Leach et al. 1993]. Mutations in other DNA repair genes, MutL homolog 1 (MLH1) and postmeiotic segregation increased 2 (PMS2), are responsible for familial colon cancer, nonpolyposis, types 2 [MIM 120436] and 3 [MIM 276300, 600259], respectively [Bronner et al. 1994; Hemminki et al. 1994; Nicolaides et al. 1994]. Mice homozygous for an inactivating mutation in the Msh2 gene are fully viable and fertile. However, beginning at two months of age homozygous Msh2 mice develop a high frequency of lymphomas that show microsatellite instability [deWind et al. 1995; Reitmair et al. 1995]. As a general regulator of DNA repair, it might be expected that a Msh2 mutation would uncover underlying tumor susceptibility in an organism. This may explain why Msh2-deficient mice, as well as Pms2 and likely Mlh1-deficient mice, develop lymphomas and sometimes sarcomas [Baker et al. 1995, 1996], whereas humans who have inherited mutations in these genes develop colorectal, endometrial, and gastric tumors.

The genetic predisposition to most human cancers is not associated with single-gene mutations but rather results from complex interactions involving mutations in many different genes. A good example of this in mice is provided by the recent identification of a candidate gene for a modifier of a mutation that causes intestinal adenoma formation [Dietrich et al. 1993; MacPhee et al. 1995]. Multiple intestinal neoplasia (Min) mice develop intestinal adenomas and adenocarcinomas resulting from a missense mutation in the adenomatous polyposis coli (Apc) gene [Su et al. 1992]. Mutations in the human homolog of this tumor suppressor gene cause a very similar disease in humans [Groden et al. 1991]. APC is a large protein associated with the plasma membrane that binds to β-catenin, an adherins junction protein, and regulates signaling through the Wnt/Wingless pathway [for review, see Peifer 1996]. In Apc mice, the number of intestinal adenomas is strongly affected by a modifier of Min, called Mom1, that is carried by various inbred strains of mice [Deitrich et al. 1993]. An excellent candidate for Mom1 was identified by MacPhee et al. [1995] as the secretory phospholipase A2 (Pla2s) gene. All strains sensitive to high incidence of adenomas express very low Pla2s mRNA levels and have a frameshift mutation in Pla2s [MacPhee et al. 1995]. Although PLA2S mutations have not yet been identified in humans with intestinal neoplasms or in patients predisposed to these cancers, it remains possible that mutations in this or other genes in the PLA2S biochemical pathway may influence polypl formation in humans.

Immunological and hematological disorders

There are many well-known inherited human blood cell diseases such as the X-linked hemophilias and immunodeficiencies, and the anemias associated with defects in adult α- and β-globin genes. Many of these disorders have been modeled in mice (Table 6), and all of the models listed, with the exception of adenosine deaminase (Ada)-deficient mice, have many phenotypic similarities to their human counterparts. The mouse models for hematological and immunological diseases are being used to test new therapeutic approaches. As the hematopoietic system is a relatively accessible tissue from which stem cells can be isolated, much work has focused on gene therapy. In addition, new insights into the physiological significance of these gene products are being acquired.

Sickle cell anemia

Sickle cell anemia (MIM 141900) was one of the first diseases demonstrated to be a molecular disease when Linus Pauling and colleagues showed that an altered β-globin was inherited in a Mendelian fashion that cosegregated with the disorder [for review, see Weatherall et al. 1995]. The creation of a mouse model for sickle cell anemia provides a good example of the level of sophistication with which the mouse germ line can be manipulated to create a mouse disease model. Most transgenic mice expressing a normal human α-globin gene in addition to the sickle cell mutant human β-globin gene, βS(6Val), did not develop sickle cell anemia as hoped because the endogenous mouse major β-globin polypeptide interferes with the polymerization of the human α- and β-globins [for review, see Fabry 1993]. This problem was partially overcome by introducing the α-and β-globin transgenes into mice hemizygous for a chemically induced germ-line mutation in the major endogenous mouse β-globin gene. In addition to the classic human βS(6Val) sickle cell mutation, other mutations that enhance the sickling phenotype also have been introduced into the human β-globin transgene together with the βS(6Val) mutation [Trudel et al. 1991, 1994; Fabry et al. 1995]. The net result of these studies is that researchers now have a variety of sickle cell disease models in the mouse with phenotypes ranging from mild to severe, which respond to clinically utilized antisickling agents [Trudel et al. 1994], and which will be useful for testing new therapeutic approaches.

Immune deficiencies

Many models of human immune deficiency exist in the mouse and generally show good correlation with the human disease. These models also have allowed detailed studies of many of the proteins required for such processes as cellular adhesion [integrin β 2, Itgb2], T/B cell...
**Table 6. Immunological and hematological diseases**

<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ada</td>
<td>Adenosine deaminase</td>
<td>K</td>
<td>Severe combined immunodeficiency</td>
<td>102700</td>
<td>*Markert (1994); Migchielsen et al. (1995)</td>
</tr>
<tr>
<td>Ank1&lt;sup&gt;nb&lt;/sup&gt;</td>
<td>Ankyrin 1, erythroid</td>
<td>S&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hereditary spherocytosis</td>
<td>182900</td>
<td>White et al. (1990); Peters et al. (1991); Jarolim et al. (1995); Eber et al. (1996)</td>
</tr>
<tr>
<td>Btk&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>Bruton's tyrosine kinase</td>
<td>S</td>
<td>X-linked agammaglobulinemia</td>
<td>300300</td>
<td>*Rawlings and Witte (1994)</td>
</tr>
<tr>
<td>Cd40l</td>
<td>CD40 ligand</td>
<td>K</td>
<td>Hyper-IgM immunodeficiency; common variable immunodeficiency</td>
<td>308230</td>
<td>Renshaw et al. (1994); Farrington et al. (1994); *Ramesh et al. (1994)</td>
</tr>
<tr>
<td>C/8</td>
<td>Coagulation factor VIII</td>
<td>K</td>
<td>Hemophilia A</td>
<td>306700</td>
<td>Bi et al. (1995); *Kazazian et al. (1995)</td>
</tr>
<tr>
<td>Cybb</td>
<td>Cytochrome b-245, beta</td>
<td>K</td>
<td>Chronic granulomatous disease</td>
<td>306400</td>
<td>*Roos et al. (1994); Pollock et al. (1995)</td>
</tr>
<tr>
<td>Ebp4.2&lt;sup&gt;ra&lt;/sup&gt;</td>
<td>Erythrocyte protein band 4.2</td>
<td>S</td>
<td>Hereditary hemolytic anemia</td>
<td>177070</td>
<td>White et al. (1992); *Becker and Lux (1995)</td>
</tr>
<tr>
<td>Fasl&lt;sup&gt;le&lt;/sup&gt;</td>
<td>Fas antigen 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S</td>
<td>Autoimmune lymphoproliferative syndrome</td>
<td>134637</td>
<td>*Singer et al. (1994); Fisher et al. (1995); Rieux-Laucat et al. (1995)</td>
</tr>
<tr>
<td>Hba</td>
<td>Hemoglobin alpha gene cluster</td>
<td>C,K,R</td>
<td>Alpha-thalassemia</td>
<td>141800</td>
<td>Russell et al. (1976); Whitney et al. (1980); Pászty et al. (1995); *Weatherall (1995)</td>
</tr>
<tr>
<td>Hbb</td>
<td>Hemoglobin beta gene cluster</td>
<td>C,K</td>
<td>Beta-thalassemia</td>
<td>141900&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Skow et al. (1983); Shehee et al. (1993); Clavatta et al. (1995); *Weatherall (1995)</td>
</tr>
<tr>
<td>Hbb&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>Hemoglobin beta gene cluster</td>
<td>C + TE</td>
<td>Sickle cell anemia</td>
<td>141900&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Trudel et al. (1991); Fabry et al. (1995); *Weatherall (1995)</td>
</tr>
<tr>
<td>Itgb2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Integrin beta 2</td>
<td>K</td>
<td>Leukocyte adhesion deficiency, Type 1</td>
<td>116920</td>
<td>*Anderson and Springer (1987); Wilson et al. (1993); Bullard et al. (1996)</td>
</tr>
<tr>
<td>I12r&lt;sup&gt;g&lt;/sup&gt;</td>
<td>IL-2 receptor gamma chain</td>
<td>K</td>
<td>Severe combined immunodeficiency, X-linked</td>
<td>300400</td>
<td>*Leonard et al. (1994); DiSanto et al. (1995)</td>
</tr>
<tr>
<td>Lyst&lt;sup&gt;ex&lt;/sup&gt;</td>
<td>Lysosomal trafficking</td>
<td>S</td>
<td>Chediak-Higashi syndrome</td>
<td>214500</td>
<td>Barbosa et al. (1996); Perou et al. (1992)</td>
</tr>
<tr>
<td>Rag1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Recombination activating gene-1</td>
<td>K</td>
<td>Severe combined immunodeficiency, B-cell negative</td>
<td>601457</td>
<td>Mombaerts et al. (1992); Shinkai et al. (1992); Schwartz et al. (1996)</td>
</tr>
<tr>
<td>Snpa1&lt;sup&gt;oh&lt;/sup&gt;</td>
<td>Alpha-spectrin-1, erythroid</td>
<td>TI,S</td>
<td>Elliptocytosis-2</td>
<td>130600</td>
<td>Grimber et al. (1992); *Gallagher and Forget (1993)</td>
</tr>
<tr>
<td>Snpb1&lt;sup&gt;ao&lt;/sup&gt;</td>
<td>Beta-spectrin-1</td>
<td>S</td>
<td>Elliptocytosis-3</td>
<td>182870</td>
<td>*Gallagher and Forget (1993); Bloom et al. (1994)</td>
</tr>
</tbody>
</table>

<sup>a</sup>See Table 1 for footnote.

<sup>b</sup>Although a mutation in the Ank1 gene of nb mice has not been identified, nb/nb mice express lower levels of ankyrin mRNA and protein and express a truncated ankyrin protein [White et al. 1990; Peters et al. 1991].

<sup>c</sup>Also called Apoptosis antigen-1 [APT-1], APO-1, and CD95.

<sup>d</sup>All hemoglobin beta locus (HBB) mutations and phenotypic data can be accessed at MIM no. 141900.

<sup>e</sup>Also called CD18 antigen, macrophage antigen-1 beta, and LFA-1.

<sup>f</sup>Both the RAG1 and RAG2 genes, which are closely linked in both mouse and human, have been shown to be mutated in some patients with B cell-negative SCID. Inactivation of these genes in mice gives a very similar phenotype [Mombaerts et al. 1992; Shinkai et al. 1992].

Communication (CD40 ligand, Cd40l), and signal transduction by tyrosine kinases (Bruton's tyrosine kinase, Btk). In several cases, the identification of a mutant gene product in a human disease was followed by the creation of knockout mutations in the mouse.

The recent identification of the gene affected in Chediak-Higashi syndrome (CHS; MIM 214500) was preceded by and depended on the cloning of the mouse beige (bg) gene [Barbosa et al. 1996; Perou et al. 1992]. It had been suggested that bg mice and CHS patients may have...
mutations in homologous genes based on comparative mapping, somatic cell complementation analysis, and phenotypic similarities (Justice et al. 1990; Perou and Kaplan 1993; Barrat et al. 1996). Cells from both CHS patients and bg mice show lysosomal defects and compartmental missorting that are thought to arise from defective homotypic vesicle fusion (Perou and Kaplan 1993). These problems are manifested as a dilution of pigmentation, abnormal bleeding, natural killer cell dysfunction, and an increased susceptibility to infection. The bg gene was shown to be lysosomal trafficking regulator (Lyst) and is predicted to encode a large protein with a carboxyl-terminal prenylation motif, multiple phosphorylation sites, and an extended coiled-coil domain (Barbosa et al. 1996; Perou et al. 1996). Subsequently, the same gene was shown to be mutated in CHS patients. The cloning of Lyst has revealed a novel, apparently critical component of lysosome function that is required for normal function of a number of hematopoietic cells and melanocytes in both species.

**Autoimmune lymphoproliferative syndrome**

Many very important human diseases, such as diabetes, arthritis, lupus, and glomerulonephritis, have an autoimmune component. Studies on two mouse mutations, lymphoproliferation (lpr) and generalized lymphadenopathy (gld), have demonstrated the important role of apoptosis in the maintenance of immune self-tolerance. In addition, the cloning of the Ipr gene has led to the identification of human patients with mutations in the same gene who suffer from a strikingly similar autoimmune disease. Mice homozygous for the lpr or the gld mutation have identical phenotypes and display massive lymphoid enlargement because of T cell accumulation. This is accompanied by autoimmune vasculitis and immune complex glomerulonephritis [for review, see Singer et al. 1994]. Using a candidate gene approach, mutations in the gene encoding Fas antigen [also called apoptosis antigen (Apt) or CD95] were shown to cause the lpr phenotype [Watanabe-Fukunaga et al. 1992]. The Fas gene encodes a member of the tumor necrosis factor (TNF) receptor family, and its ligand, called Fasl, is a member of the TNF-related type II family and was subsequently shown to be mutated in gld mice [Takahashi et al. 1994b]. Patients with autoimmune lymphoproliferative syndrome (ALPS; MIM 134637) have been shown to have mutations in the FAS gene, and many of these mutant products appear to behave as dominant negative proteins [Fisher et al. 1995; Rieux-Laucat et al. 1995].

There is strong evidence that many mouse and human autoimmune diseases are influenced by modifying genes and the lpr/ALPS diseases are not exceptions. In some affected ALPS families, individuals with FAS mutations have no clinical symptoms [Fisher et al. 1995], whereas the lpr mutation causes no autoimmune disease in C57BL/6 mice and only mild disease in C3H mice. The identification of genetic modifiers of the lpr phenotype may shed light on human predisposition to autoimmune disease.

**Metabolic and hormonal disorders**

In Table 7 mouse models of metabolic and hormonal disease caused by mutations in 24 different genes are described. Although the majority of these models reproduce many of the phenotypes associated with mutations in the corresponding human homolog, the current mutants for hexokinase A (HexA), hypoxanthine guanine phosphoribosyl transferase (Hprt), and urate oxidase (Uox) in the mouse do not. Three mouse mutants thus illustrate that mice and humans, although very similar in most metabolic pathways, do have some significant differences.

**Disorders of purine metabolism**

Purine nucleotides are recycled from purine bases by the action of two phosphoribosyltransferases; adenosine phosphoribosyl transferase (APRT) catalyzes the conversion of adenosine monophosphate (AMP) from adenosine, and hypoxanthine guanine phosphoribosyl transferase (HPRT) catalyzes the conversion of inosine monophosphate (IMP) or guanosine monophosphate (GMP) from hypoxanthine or guanine, respectively (see Fig. 5). In the absence of APRT, adenine is converted to 2,8 dihydroxyadenine and the accumulation of this insoluble product causes the development of kidney stones that may progress to kidney failure [for review, see Simmonds et al. 1995; MIM 102600]. Recently, a targeted null mutation in Aprt was generated in mice that causes a phenotype identical to that of humans [Engle et al. 1996a] and thus will be a very useful model for understanding how kidney stones develop and contribute to renal disease. As the severity of the Aprt mutant phenotype is different in two different genetic backgrounds, Engle et al. [1996a] have suggested that other factors, affecting either adenine metabolism, stone formation, or kidney function, may be the basis for these phenotypic differences. Further analysis of these possible modifiers should be useful for understanding phenotypic variation seen in APRT-deficient humans.

HPRT deficiency in human causes Lesch–Nyhan syndrome (MIM 308000), an X-linked recessive disease characterized by hyperuricemia, mental retardation, and compulsive self-mutilation [for review, see Rossiter and Caskey 1995]. Several groups have attempted to generate a mouse model for Lesch–Nyhan by constructing targeted mutations in the Hprt gene [Williamson et al. 1992]. Although these were the first successful reports of germ-line transmission of targeted mutations in the mouse, the Hprt mutant mice did not exhibit any significant abnormalities. Two possible explanations for these interspecific differences have been proposed. The first possibility is that Aprt may be more important than Hprt for purine recycling in mice compared with humans. Wu and Melton [1993] have tested this by administering an inhibitor of Aprt to Hprt mice and found that these mice developed self-inflicted injuries that resulted from overgrooming. Thus, alteration of the metabolic pathways of mutant mice improved the usefulness of
Table 7. **Metabolic and hormonal diseases**

<table>
<thead>
<tr>
<th>Mouse gene symbol</th>
<th>Gene name</th>
<th>Mouse model*</th>
<th>Human disease</th>
<th>MIM no.</th>
<th>Selected references^a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apolipoprotein B</strong></td>
<td>Apob</td>
<td>K,TE</td>
<td>Hypobetalipoproteinemia</td>
<td>107730</td>
<td>*Young et al. [1994], Farese et al. [1995], *Knecht and Glass [1995]</td>
</tr>
<tr>
<td><strong>Apolipoprotein E</strong></td>
<td>Apoe</td>
<td>K,TE</td>
<td>Hyperlipoproteinemia type III</td>
<td>107741</td>
<td>*Knecht and Glass [1995], *Plumb and Breslow [1995], *Breslow [1996]</td>
</tr>
<tr>
<td><strong>Adenine phosphoribosyl transferase</strong></td>
<td>APrT</td>
<td>K</td>
<td>2,8-Dihydroxyadenine urolithiasis</td>
<td>102600</td>
<td>*Simmonds et al. [1995], Engle et al. [1996]</td>
</tr>
<tr>
<td><strong>Androgen receptor</strong></td>
<td>ArTm</td>
<td>S,TE</td>
<td>Testicular feminization syndrome, spinal and bulbar muscular atrophy</td>
<td>313700</td>
<td>Gaspar et al. [1991], La Spada et al. [1991], Bingham et al. [1995]</td>
</tr>
<tr>
<td><strong>ATPase, Cu++ transporting, alpha polypeptide</strong></td>
<td>Atp7aMo</td>
<td>C,R,S</td>
<td>Menkes syndrome; occipital horn syndrome</td>
<td>304150; 309400</td>
<td>Levinson et al. [1994], Mercer et al. [1994], Das et al. [1995], *Monaco and Chelly [1995]</td>
</tr>
<tr>
<td><strong>Calcium-sensing receptor</strong></td>
<td>Casr</td>
<td>K</td>
<td>Familial hypocalciuric hypercalcemia; neonatal severe hyperparathyroidism</td>
<td>145980; 239200</td>
<td>Pollack et al. [1993], Ho et al. [1995]</td>
</tr>
<tr>
<td><strong>Cystic fibrosis transmembrane conductance regulator homolog</strong></td>
<td>Cftt</td>
<td>K</td>
<td>Cystic fibrosis</td>
<td>219700</td>
<td>*Drumm and Collins [1993], *Dorin [1995]</td>
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<tr>
<td><strong>Fumarylacetoacetate hydrolase</strong></td>
<td>Fah</td>
<td>K,R</td>
<td>Tyrosinemia, type I</td>
<td>276700</td>
<td>Klebig et al. [1992], Grompe et al. [1993], *Mitchell et al. [1995]</td>
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<tr>
<td><strong>Ferrochelatase</strong></td>
<td>Fechmn/Pas</td>
<td>C</td>
<td>Erythropoietic protoporphyria</td>
<td>177000</td>
<td>Boulechfar et al. [1993], *Kappas et al. [1995]</td>
</tr>
<tr>
<td><strong>Glucose-6-phosphatase</strong></td>
<td>G6pt</td>
<td>K</td>
<td>Glycogen storage disease I</td>
<td>232200</td>
<td>Chen and Burchell [1995], Lei et al. [1996]</td>
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<tr>
<td><strong>Glucocerebrosidase</strong></td>
<td>Gba</td>
<td>K</td>
<td>Gaucher disease type I</td>
<td>230800</td>
<td>Tybulewicz et al. [1992], Bornstein et al. [1995]</td>
</tr>
<tr>
<td><strong>Growth hormone releasing hormone receptor</strong></td>
<td>Ghrh</td>
<td>S</td>
<td>Growth hormone deficiency</td>
<td>139191</td>
<td>Godfrey et al. [1993], Lin et al. [1993], Wajnraich et al. [1996]</td>
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<td><strong>Beta-glucuronidase</strong></td>
<td>Gas1ops</td>
<td>S</td>
<td>Mucopolysaccharidosis type VII</td>
<td>253220</td>
<td>Sands and Birkenmeier [1993], Berry et al. [1994], *Neufeld and Muenzer [1995]</td>
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<tr>
<td><strong>Hexokinase A</strong></td>
<td>Hexa</td>
<td>K</td>
<td>Tay-Sachs disease</td>
<td>272800</td>
<td>Yamanaka et al. [1994], Sango et al. [1995]</td>
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<tr>
<td><strong>Hexokinase B</strong></td>
<td>Hexb</td>
<td>K</td>
<td>Sandhoff disease</td>
<td>268800</td>
<td>Sango et al. [1995]</td>
</tr>
<tr>
<td><strong>Hypoxanthine guanine phosphoribosyl transferase</strong></td>
<td>Hprt</td>
<td>K</td>
<td>Lesch-Nyhan syndrome</td>
<td>308000</td>
<td>*Williamson et al. [1992], *Rossiter and Caskey [1995]</td>
</tr>
<tr>
<td><strong>Low density lipoprotein receptor</strong></td>
<td>Ldlr</td>
<td>K,TE</td>
<td>Familial hypercholesterolemia Hyperammononemia</td>
<td>143890</td>
<td>*Breslow [1994, 1996], *Paigen et al. [1994], *Knecht and Glass [1995]</td>
</tr>
<tr>
<td><strong>Orotidine transcarbamylase</strong></td>
<td>Otc40Tf</td>
<td>S</td>
<td>Hyperammononemia</td>
<td>311250</td>
<td>Veres et al. [1987], *Brusilow and Horwich [1995]</td>
</tr>
<tr>
<td><strong>Phenylalanine hydroxylase</strong></td>
<td>Pah</td>
<td>C</td>
<td>Phenylketonuria</td>
<td>261600</td>
<td>Sheldovsky et al. [1993], *Scrivener et al. [1995]</td>
</tr>
<tr>
<td><strong>Protective protein for beta-galactosidase</strong></td>
<td>Ppgb</td>
<td>K</td>
<td>Galactosialidosis</td>
<td>256540</td>
<td>*d’Azzo et al. [1995], Zhou et al. [1995]</td>
</tr>
<tr>
<td><strong>Pituitary specific transcription factor-1</strong></td>
<td>Pit11sw</td>
<td>S</td>
<td>Combined pituitary hormone deficiency</td>
<td>173110</td>
<td>*Voss and Rosenfeld [1992], Radovick et al. [1992]</td>
</tr>
<tr>
<td><strong>Sphingomyelin phosphodiesterase 1</strong></td>
<td>Smpd1</td>
<td>K</td>
<td>Niemann-Pick disease</td>
<td>257200</td>
<td>Horinouchi et al. [1995], Otterbach and Stoffel [1995]</td>
</tr>
<tr>
<td><strong>Thyroid stimulating hormone receptor</strong></td>
<td>Tshrnyr</td>
<td>S</td>
<td>Unresponsiveness to thyrotropin</td>
<td>275200</td>
<td>Duprez et al. [1994], Stein et al. [1994]</td>
</tr>
<tr>
<td><strong>Urate oxidase</strong></td>
<td>Uox</td>
<td>K</td>
<td>Hyperuricemia and gout</td>
<td>191540</td>
<td>Wu et al. [1994], *Becker and Roessler [1995]</td>
</tr>
</tbody>
</table>

^aSee Table 1 for footnotes.

^bAlso associated with Alzheimer disease-2 (Table 4)
Menkes disease

Copper is an essential trace element that is a cofactor for numerous enzymatic reactions. Because increased or decreased levels of copper have deleterious effects, multiple mechanisms are used to tightly regulate copper homeostasis. Menkes disease (MIM 304150) is an X-linked disorder of copper metabolism that is characterized by neurologic degeneration, connective tissue abnormalities, and brittle, depigmented hair. Mottled (Mo) mice share many genetic, biochemical and phenotypic similarities with humans with Menkes disease and have been proposed as models for this disease. Several groups identified \( \text{ATP7A} \), a gene responsible for copper efflux, as a strong candidate for Menkes disease [for review, see Hamer 1993]. Subsequent cloning of the mouse homolog (\( \text{Atp7a} \)) and identification of intragenic mutations in several alleles of \( \text{Mo} \) [Levinson et al. 1994; Mercer et al. 1994] provided conclusive evidence that Menkes patients and \( \text{Mo} \) mice are deficient in homologous genes.

Mutations at the \( \text{Mo} \) locus occur frequently and at least 16 different alleles have been reported (MGD). The hemizygous phenotypes range from prenatal lethality to relatively mild effects on hair color and texture. Two alleles, \( \text{Mo}^{br} \) and \( \text{Mo}^{brl} \), produce phenotypes that are very similar to Menkes patients. In Menkes patients and in \( \text{Mo}^{brl} \) males, copper accumulates in the intestines and is not exported to peripheral organs. Much of the copper in the intestines of \( \text{Mo}^{brl} \) mice is bound to metallothioneins [Mt], a group of low-molecular-weight polypeptides that bind to and detoxify copper and other metals. Mt is not essential for viability as \( \text{Mt} \) mutant mice have been generated by gene targeting and were shown to have normal lifespans [Masters et al. 1994].

Kelly and Palmiter (1996) have examined further the role of copper metabolism by generating mice that are homozygous for both \( \text{Mt} \) and \( \text{Mo}^{brl} \) mutations. Contrary to the expectation that the absence of \( \text{Mt} \) would prolong the survival of \( \text{Mo}^{brl} \) mice attributable to the lack of copper binding in the intestine, embryonic lethality occurred in the double mutants. Thus, the absence of \( \text{Mt} \) exacerbated the \( \text{Mo}^{brl} \) phenotype. Even more surprisingly, the absence of \( \text{Mt} \) caused embryonic lethality in females that were heterozygous for \( \text{Mo}^{brl} \), as well as in \( \text{Mo}^{brl} \) hemizygous males. Based on these results, Kelly and Palmiter (1996) have proposed that \( \text{Mt} \) normally protects the extra-embryonic tissues of the embryo from excessive copper that would accumulate in the absence of functional \( \text{Atp7a} \). A similar protective role for \( \text{Mt} \) may operate in other tissues, such as the intestine and liver, that accumulate high levels of copper in Menkes and Wilson disease [MIM 277900], a related disorder of copper metabolism. This opens the intriguing possibility that \( \text{Mt} \) mutations in humans could either act as modifiers in Menkes disease or other disorders of metal homeostasis, or be directly responsible for such metabolic disorders.

Cystic fibrosis

Cystic fibrosis (CF; MIM 219700) is the most common lethal disorder of Caucasian populations and is characterized by defective chloride transport and excess mucus production by epithelial cells. Although mortality in CF patients is attributable primarily to recurring pulmonary infections, CF patients also suffer from intestinal obstruction and inflammation in the airways, pancreas, intestine, bile duct, and vas deferens. The gene responsible for this disorder [cystic fibrosis transmembrane conductance regulator (CFTR)] was isolated in 1989 [for review, see Drumm and Collins 1993]. Since that time, several mouse models of CF have been constructed through gene targeting in ES cells [for review, see Dorin 1995]. Three different groups have constructed null mutations in \( \text{Cftr} \) that cause neonatal lethality as the result of severe in-

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**Figure 5.** Pathways for purine metabolism. Mutations in each of the genes encoding the boxed enzymes have been created by gene targeting and are models for human diseases. The abbrevi-ation and table for each of these enzymes is: \( \text{APRT} \) adenosine phosphoribosyl transferase (Table 7); \( \text{ADA} \) adenosine deami-nase (Table 6); \( \text{HPRT} \) hypoxanthine guanine phosoribosyl transferase (Table 7); \( \text{UOX} \) urate oxidase (Table 7). The asterisk denotes a pathway that is not used in humans because \( \text{UOX} \) is nonfunctional. \( \text{AMP} \) adenosine monophosphate; \( \text{IMP} \) inosine monophosphate; \( \text{GMP} \) guanosine monophosphate; \( \text{XDH} \) xanthine dehydrogenase.

Uric Acid $\rightarrow \text{Allantoin}^{\ast}$

$2,6$ Dihydroxyadenine $\rightarrow \text{Xanthine}$
testinal obstruction in homozygous mice. The intestinal pathology in these mice is similar to that seen in some CF patients, yet this disease occurs in only a small fraction of CF patients. On the other hand, nearly all CF patients develop lung disease. Although ion transport in the lungs of homozygous null mice is defective, intestinal defects do not allow most of the mice to live long enough to develop lung disease. A less severe Cftrr mutant phenotype was reported by Dorin et al. (1992), in which alternative splicing allowed a low level of residual Cftrr expression. In these mice the incidence of lethality because of intestinal blockage was greatly reduced, and subsequent analysis of these “leaky” Cftrr mutant mice revealed that they had increased susceptibility to bacte-
ria-induced lung infections, closely mimicking the pulmonary disease found in CF patients [Davidson et al. 1995].

Several approaches have been used to successfully correct the intestinal and pulmonary defects in mice carrying the severe and leaky Cftrr mutations described above [Hyde et al. 1993; Grubb et al. 1994; Zhou et al. 1994]. However, the majority of CF patients carry much more subtle CFTTR mutations, and strategies that interfere with such mutant proteins may have to be different from those required to correct defects resulting from the absence of normal protein. Recently, two mouse strains that each contain the most common CF mutations have been generated [van Doorninck et al. 1995; Delaney et al. 1996]. Importantly, these hypomorphic mutants cause phenotypes that more closely mimic the human disease than Cftrr null mutants. In addition to providing invaluable models for testing gene therapy strategies, these strains are the most appropriate models for understanding the molecular and cellular mechanisms of CF.

Recent studies have provided conclusive evidence for at least one unlinked modifier of the Cftrr phenotype. In various backcross and intercross progeny from different inbred strains, the survival of mice homozygous for null Cftrr mutations varied from within 10 days after birth to >6 weeks after birth (Rozmahel et al. 1996). A genome scan using polymorphic markers revealed that a genetic locus located in the proximal region of chromosome 7 is a strong modifier of the null CF phenotype. Within this interval are several intriguing candidate genes that encode proteins that might be expected to affect Cftrr function. Further analyses in mice should reveal the identity of the chromosome 7 modifier, and perhaps other modifiers, of the Cftrr phenotype that may be directly applicable to treatment of CF.

Atherosclerosis

The major cause of death in much of the world is attributable to cardiovascular disease induced by atherosclerosis. Although the pathogenesis of atherosclerosis is complex and results from a combination of genetic and environmental (primarily dietary) factors, the best-studied risk factor for atherosclerosis is the level of plasma lipoproteins. The first genetic disorder of cholesterol metabolism to be identified in humans is caused by muta-

tions in low density lipoprotein receptor (LDLR, for review, see Goldstein et al. 1995) that cause familial hypercholesterolemia (MIM 143890). Another risk factor for atherosclerosis is hyperlipoproteinemia type III (MIM 107741), in which different allelic forms of APOE are associated with increased incidence of the disease (Mahley and Rall 1995).

Several mouse models have been developed using transgenic and knockout technologies to investigate the role of APOE and LDLR in atherosclerosis (Table 7). Mice homozygous for Apoe null mutations develop severe hypercholesterolemia and atherosclerotic lesions at a young age, even when fed a low-fat diet [for review, see Knecht and Glass 1995; Plump and Breslow 1995]. A similar but less severe phenotype occurs in mice that have disruptions of LDLR [for review, see Knecht and Glass 1995]. These mice are very useful for understanding how atherosclerotic lesions develop and for testing possible routes of gene therapy (e.g., see Ishibashi et al. 1993; Linton et al. 1995). In addition, the Apoe and Ldlr mutant mice will be useful to test possible interactions between Apoe, Ldlr, and other factors in cholesterol metabolism and atherosclerosis. For example, it has been suggested that Apoe may bind to both Ldlr and a second receptor. Direct evidence supporting this notion has been provided by comparisons of the cholesterol levels of mice homozygous for mutations in Apoe, Ldlr, or both Apoe and Ldlr (Ishibashi et al. 1994). In addition, Smith et al. (1995) have provided evidence that macrophages play a role in development of atherosclerotic lesions by crossing Apoe mice with osteopetrotic (op) mice, which have reduced numbers of tissue macrophages as a result of a mutation in the gene encoding macrophage colony-stimulating factor. Finally, two recent papers demonstrate that atherosclerosis in mice can be affected by other genes involved in lipid metabolism. When expressed as transgenes, apolipoprotein A-IV (a constituent of plasma lipid particles) and lipoprotein lipase (involved in hydrolysis of triglyceride-rich lipoproteins) were able to protect Apoe or Ldlr mice, respectively, from developing atherosclerosis [Duverger et al. 1996; Shimada et al. 1996]. Continued studies of these and other mouse loci that affect atherosclerosis [see Table 7] should provide a wealth of information to diagnose and treat the human disease.

Gene therapy in mouse models of metabolic diseases

Mice that carry the gus<sup>mps</sup> locus and humans with mucopolysaccharidoses type VII (MPS VII; MIM 253220) have mutations in the β-glucuronidase (Gusb) gene and exhibit neural and retinal degeneration, hearing deficiencies, hepatosplenomegaly, and a shortened lifespan [Neufeld and Muenzer 1995]. Because gus<sup>mps</sup> mice so closely mimic the abnormalities found in MPS VII patients, they make excellent models to test the in vivo efficacy of different therapies. Transplantation of genetically modified bone marrow cells has been used to successfully treat many, but not all, of the symptoms of gus<sup>mps</sup> mice [Wolfe et al. 1992; Maréchal et al. 1993].
However, a major disadvantage of the transplantation procedure is the deleterious side effects of radiation treatment necessary for the transplantation. Alternative methods that obviate the need for radiation treatment have been tested in gus<sup>mps</sup> mice, including the use of autologous implants of skin fibroblasts [Moullier et al. 1993], replacement therapy with recombinant β-glucuronidase [Sands et al. 1994], intraocular injections of recombinant adenoviruses [Li and Davidson 1995], and engrafment of a neural progenitor cell line [Snyder et al. 1995]. Although each of these individual approaches alleviates symptoms only in a restricted set of tissues, it is possible that a combination of two or more of these approaches will alleviate all of the symptoms of gus<sup>mps</sup> mice and, ultimately, humans with MPS VII.

An exciting new approach for gene therapy has been used to correct a deficiency of fumarylacetoacetate hydrolase [Fah], that causes the accumulation of toxic metabolites of tyrosine in hepatocytes. Mice with Fah mutations have a phenotype very similar to that of humans with hereditary tyrosinemia type 1 [HT1; MIM 276700], and in both cases, severe hepatic dysfunction causes neonatal lethality [Klebig et al. 1992; Grompe et al. 1993]. A strategy that was based, in part, on previous observations made in a mouse model of transgene-induced liver disease [for review, see Wilson 1996] has been used in mice to correct the Fah phenotype [Overturf et al. 1996]. These authors showed that wild-type liver cells exhibited a selective growth advantage in vivo and that they could repopulate the liver of Fah mutant mice, thereby restoring liver function and viability. Although such in vivo selection may be restricted to certain types of cells and phenotypic consequences, Overturf et al. [1996] have suggested a number of diseases of the liver and other organs that may be treatable with this method.

### Diseases with polygenic etiology

Many of the most common and clinically important medical disorders in humans arise as the result of coinheritance of a number of different genes. Such polygenic traits are not inherited in a simple Mendelian manner like monogenic traits, and linkage analysis to map and identify the former traits is much more complicated. This situation is further complicated by the multifactorial nature of polygenic traits; that is, they often are influenced by environmental, as well as genetic, factors. The mouse is the most promising experimental mammal for modeling these complex diseases as well as for mapping genetic loci affecting the probability of appearance and severity of these diseases and eventually identifying the genes and allelic forms of genes involved in these diseases. In Part I of this review, we outlined some of the advantages of and methods used for analysis of polygenic traits in mice. Enough phenotypic variation exists among inbred mouse strains to find appropriate models for many of the polygenic, multifactorial human diseases. In addition, the availability of a dense set of genetic markers that are easily typed in the mouse allows the whole genome to be scanned for associations (i.e., linkage) with the disease phenotype. Lastly, environmental influences can be controlled easily and manipulated in studies with mice.

Table 8 lists some of the polygenic diseases, modeled in the mouse, for which substantial progress has been made recently. The analysis of other polygenic traits in the mouse has been reviewed recently by Frankel [1995]. Many of these complex traits are associated with extreme values for certain quantifiable traits. For example, reductions in cholesterol level are associated with protection from coronary heart disease [for review, see Marchiol et al. 1996]. Genes that contribute to these quantifiable traits are called quantitative trait loci (QTL). Mapping QTLs has been at the forefront of recent progress in mouse models of polygenic human disease.

### Asthma

In humans, linkage analysis has suggested that asthma can be inherited as a polygenic trait or as a monogenic, dominant trait with incomplete penetrance [Townley et al. 1986; Longo et al. 1987]. However, these studies are very difficult to perform in humans because asthma is affected significantly by environmental influences that are difficult to control. Such environmental influences may be minimized in mouse models by housing the mice in a controlled environment under specific pathogen-free conditions.

A critical feature of asthma is airway hyper-responsiveness, which can be measured as the amount of cholinergic agonist required to double pulmonary airway resistance [ED<sub>200</sub>R<sub>L</sub>]. Mice from the A/J strain, but not the C57BL/6J [B6] strain, have low ED<sub>200</sub>R<sub>L</sub> values similar to those seen in human asthma patients [De Sanctis et al. 1995]. This trait appears to display dominant inheritance as the F<sub>1</sub> progeny of these two strains displayed ED<sub>200</sub>R<sub>L</sub> values similar to that of A/J mice. Furthermore, a continuous distribution of ED<sub>200</sub>R<sub>L</sub> values was observed in 19 different AXB recombinant inbred strains, suggesting that airway hyper-responsiveness is under polygenic control. Individual loci that influence ED<sub>200</sub>R<sub>L</sub> values were mapped in [(B6 x A/J)[F<sub>1</sub> x B6] backcross mice using simple sequence length polymorphisms (SSLPs). These studies revealed three loci affecting airway responsiveness, called bronchial hyper-responsiveness types 1, 2, and 3 [Bhr1, Bhr2, and Bhr3] [De Sanctis et al. 1995]. Interestingly, all three of these loci lie near candidate genes implicated in the etiology or pathology of asthma. Recently, airway hyper-responsiveness was found in mice that are homozygous for a null mutation in the integrin β6 subunit gene [Itbg6] [Huang et al. 1996]. This phenotype was observed in mice of a mixed background of 129 and B6 strains. Although Itbg6 does not map near any of the Bhr loci, it will be of interest to determine whether the Itbg6 phenotype is altered when on a pure B6 or A/J background.

### Substance abuse

People with severe substance abuse problems often are
Phenotypic preferences are genetically distinct traits. Given the widespread and devastating results of addiction to alcohol and morphine, it is necessary to identify candidate genes that may now be tested directly for their effects on alcohol preference. No associations were observed in the backcrosses. Interestingly, each of these recessive loci that control alcohol preference in B6 mice; the QTLs is sex-restricted with alcohol preference cosegregating with morphine preference QTLs described by Berrettini et al. (1994). Three QTLs on mouse chromosomes 11, and each accounts for 23% of the genetic variance observed in the backcrosses. Interestingly, each of these QTLs is sex-restricted with alcohol preference cosegregating with Alcp1 in males and with Alcp2 in females. Each of the Alcp1 and Alcp2 intervals contains potential candidate genes that may now be tested directly for their effects on alcohol preference. No associations were found with the morphine preference QTLs described by Berrettini et al. (1994), suggesting that alcohol and morphine preferences are genetically distinct traits. Given the widespread and devastating results of addiction to these substances in humans, the identification of the mouse genes represented by each of these QTLs could be of tremendous importance to human health.

### Diabetes

Environmental and genetic factors contribute to the development of insulin-dependent diabetes mellitus (IDDM; MIM 222100) or type 1 diabetes, an autoimmune disease in which cells of the immune system infiltrate the pancreas, invade the islets of Langerhans, and destroy insulin-producing β cells (for review, see Tisch and McDevitt 1996). The nonobese diabetic (NOD) mouse strain spontaneously develops a disease very similar to human IDDM. NOD mice carry a diabetes-sensitivity allele at the Idd1 locus. This locus is located in the mouse major histocompatibility complex (MHC) and is analogous to human IDDM association with certain human lymphocyte antigen (HLA) haplotypes. Experimental crosses between NOD and diabetes-resistant strains such as B6, C3H, and NON have allowed the identification of a remarkable number of non-MHC loci, called Idd2–Iddl5, that affect susceptibility to type 1 diabetes (for review, see Wicker et al. 1995; Vyse and Todd 1996). The currently favored model for the action of these susceptibility genes is that no single allele is sufficient or necessary (other than Idd1) for disease to develop. The more susceptibility alleles at unlinked loci an individual has, the more likely that individual will develop type 1 diabetes.
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diabetes. Therefore, more than one combination of alleles can result in disease.

Although none of the non-MHC susceptibility genes have been identified, construction of congenic strains, with increasingly narrow chromosomal regions donated from sensitive strains, has allowed the map position of some of these loci to be refined to regions as small as a few centiMorgans. Intriguingly, some of the idd loci map within intervals associated with susceptibility to other mouse autoimmune disorders, such as systemic lupus erythematosus (e.g., Id11 and Sle2) and a multiple sclerosis-like syndrome (e.g., idd10 and eae3), as well as have human counterparts that affect susceptibility to IDDM (e.g., idd5 and IDDM7) (for review, see Vye and Todd 1996).

Concluding remarks

In reading Part II of this review it should be apparent that mouse models are having, and will continue to have, an enormous impact on human disease research. Not only do these disease models in many instances faithfully recapitulate the phenotype of the human disease, but they allow one to study the disease on a uniform genetic background. Even the few models that do not reproduce the human phenotypes exactly are still of considerable interest because they may be indicative of important interspecies differences. Alternatively, they may be attributable to mutational differences [i.e., recessive, null mutations in mice vs. dominant, GOI in humans] that are crucial for interpreting the biological function of the protein. As more and more models of monogenic traits become available, it will be possible to assess the epistatic and interactive relationships of various genes and their encoded proteins. Even more important, it is often possible to identify and map genes that modify the nature or severity of a given disease by breeding the mutated gene onto different inbred strain backgrounds. The identification and cloning of these modifier genes offers great potential for future disease gene research. Mouse models also offer an important resource for testing different treatment strategies before they are introduced into the clinic, and a number of mouse models that have been particularly useful in this regard are listed in the review. Finally, it should be apparent to everyone in the field that we are rapidly moving from an era focused largely on monogenic diseases to a more complicated, but potentially even more rewarding, era of polygenic diseases. Particularly useful in this regard are listed in the review.

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