1

Introduction to the Pigmentary System

1.1 Introduction

The colors of mice, horses, dogs, rabbits, humans, and other animals – yellow, black, brown, cream, orange, chocolate, blue, beige, white – result from mutations in genes that influence some of the most basic genetically controlled processes of life. These include specification of cell lineage, migration and homing of specialized cells, tissues, and organs, interactions of cells with surrounding tissues and their differentiation, and maintenance throughout life. Because defects in pigment cells are usually not lethal to the organism, pigmentation is an unusually accessible system in which to study these basic processes of vertebrate life.

In addition to these useful qualities of the pigmentary system, the availability of inbred mice with genetic defects in pigmentation that can be studied using modern techniques of genetics and cell biology – and comparative genetics at the level of sequenced genomes – has resulted in an unprecedented explosion of information about pigmentation.

The pigmentary system of the inbred laboratory mouse is a uniquely useful model of phenotype-based genetics, both basic and applied (Lauber 1971; Morse 1978; Barsh 2007). With the inbred mouse, the sequenced genome, modern technologies, and the pigmentary model we have the necessary tools to unravel the complex web of interacting genic functions that lead from a change in a gene through the multiple communicating processes that result in a specific phenotypic outcome.

Study of pigmentary genetics began, at the turn of the last century, with yellow mice and albino mice (Cuénot 1902; Castle & Allen 1903; Little 1913a; Wright 1917). A few books serve as landmarks of the progress of our studies of the genetic control over murine and comparative phenotypes; prominent among them are Green's (1966) *Biology of the Laboratory Mouse*, Searle's (1968) *Comparative Coat Color Genetics in Mammals*, Silvers' (1979) *The Coat Colors of Mice*, and Nordlund et al.'s (2006) *The Pigmentary System*. See also Foster (1965). More recent technological advances have given us the tools to take a closer look at the interacting processes that generate specific pigmentary phenotypes of the mouse, our most valuable genetically controlled animal model (Fig. 1.2).

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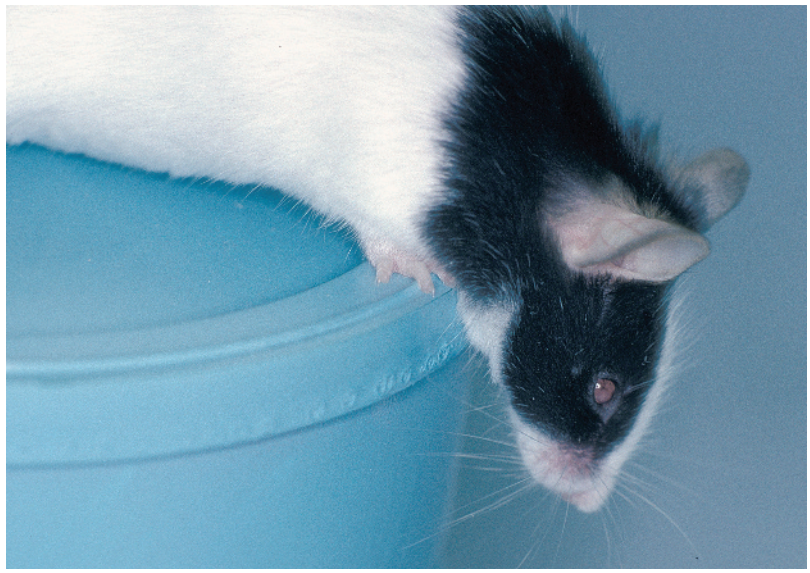


Figure 1.2 White spotted mouse, *red-eyed-white*, genotype $Mitf^{rw}/Mitf^{rw}$.

1.2 Colors of vertebrate animals

The function of melanocytes is to deposit melanin pigment within their cell-specific organelles (melanosomes). In the skin and/or growing hairs (feathers, scales) these melanosomes are often delivered to neighboring keratinocytes. Pigment cells of the eye arise *in situ* and retain their melanosomes; pigment cells of other organs may also retain their melanosomes. The *colors* of the native pigment – but not all the phenotypes of mice and other mammals – are red/yellow pheomelanin and black or brown eumelanin. Yellow, black, and chocolate brown are the three basic colors of pigment produced in mammalian melanocytes (see Chapter 4 on melanogenesis and Chapter 5 on pigment-type switching). Additionally, some colors are affected by the blood in the tissues, as for example in the comb and wattles of chickens, and other colors are influenced primarily by the structures of skin and hair (Quevedo & Holstein 2006), but most color variables, especially in animals that are covered with hair or feathers, are created by genetically controlled modification of the amount and distribution of the three basic colors of melanin pigment and of the melanocytes themselves (Searle 1968; Silvers 1979).

Pheomelanin is yellow/red melanin pigment found, for example in the hairs of Golden Retriever and Irish Setter breeds of dogs; yellow mice, rabbits and guinea pigs, orange or red cats, sorrel or chestnut horses, 'red' chickens (Fig. 1.3), 'brown' cattle (Fig. 1.4), and the bright red hair of humans (Little 1957; Searle 1968; Robinson 1971; Bowling & Ruvinsky 2000; Ostrander et al. 2005; Pontius et al. 2007; Schmutz & Berryere 2007; Barsh 2007; see Chapter 5). Eumelanic pigment is of two varieties: black eumelanin, as in the hairs of black Labrador Retriever dogs, and brown eumelanin, as in brown (chocolate) Labrador Retrievers, as well as chestnut Oriental Shorthair cats (see the picture under Statement regarding the use of pictures at the front of the book), brown mice (Fig. 1.5), and others.

Some of the phenotypes that we think of as 'brown' actually are not brown at the level of pigment color, and this is also true of 'red' or 'yellow.' It's not always easy to tell the difference visually, and

Figure 1.3 Pheomelanic chicken, genotype unknown.

Figure 1.4 Pheomelanic calf/cow, *Mc1r*^{e}/*Mc1r*^{e} (original name *e*/*e*); genotype name *Recessive yellow*. The common name is 'red' or 'brown'; however, brown is technically incorrect as *Brown* is an allele of the black/brown *Tyrp1* locus (Chapter 4).

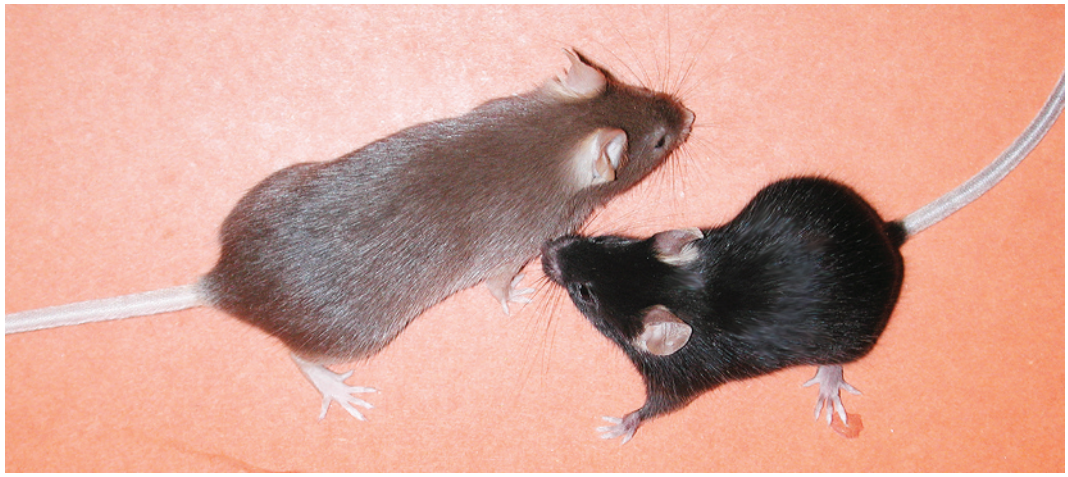


Figure 1.5 Eumelanic mice, one brown, one black; *Tyrp1*^{b}/*Tyrp1*^{b} (former name *b*/*b*), phenotype brown; *Tyrp1*^{B}/*Tyrp1*^{B} (formerly *B*/*B*), phenotype black.

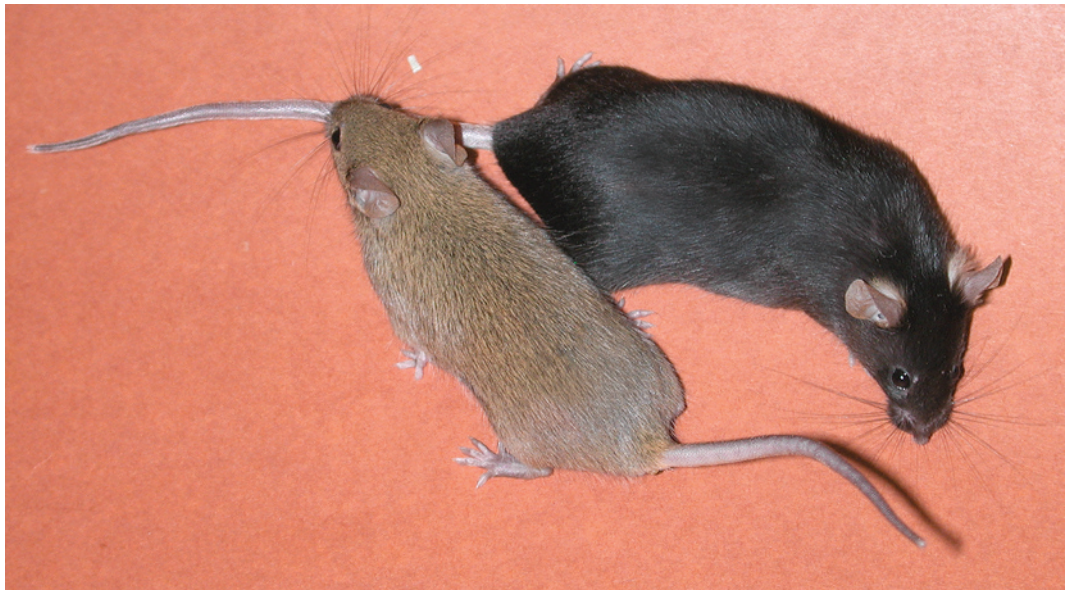


Figure 1.6 Agouti black mouse and nonagouti black mouse; *A*/*A Tyrp1*^{B}/*Tyrp1*^{B} (former name *A*/*A B*/*B*); *a*/*a Tyrp1*^{B}/*Tyrp1*^{B} (former name *a*/*a B*/*B*). The hairs of the agouti mouse are banded with yellow pigment and nonyellow pigment as determined by the *Agouti* locus. The color of the nonyellow pigment is black, as determined at the black/brown (*Tyrp1*) locus.

the common names for color phenotypes are not based on science. Sometimes the word brown is used to describe animals that are pheomelanic, like the cow and calf in Figure 1.4, that may be called brown or red; sometimes the word brown is used instead of the more accurate term agouti for phenotypes such as the mouse in Figure 1.6 and the cat in Figure 1.7. Agouti coloration – such as

Figure 1.7 An *Agouti* (*A*/*A*) cat of the Abyssinian breed. The name of a breed of animal does not relate to the genetics of its pigmentation.

the wild type in the mouse, rabbit, cat, guinea pig, and squirrel (Fig. 2.5), actually most mammals – consists of patterns (bands) of eumelanin and pheomelanin within individual hairs. These are produced by pigment-type switching, with switching between the deposition of eumelanic and pheomelanic pigment, into the growing hair at different times in its creation, as discussed in Chapter 5. We will reserve the word 'brown' for phenotypes that are based on brown eumelanin.

Mammals may produce eumelanin or pheomelanin in the same or different melanocytes. This choice is under direct genetic control. In mice, pheomelanin may be produced in the skin of tail and ears; otherwise pheomelanin is not normally produced outside the hair follicles. Other mammals, however, do produce pheomelanin in the skin; for example, humans, rabbits, and guinea pigs.

Color of pigment is not the only cause of variability in phenotypes. Banding patterns of hairs have already been described. Pheomelanin and eumelanin may also be distributed in specific patterns over the body surface. Normal black (or brown) and yellow color patterns such as those of tigers and ocelots, black (or brown)-and-tan patterns of mice or dogs (Fig. 1.8), brindle dogs (Fig. 1.9) and cows (Fig. 5.11), and tabby cats, as well as the agouti pattern of hair banding (Fig. 5.8), are exquisitely controlled and are caused by pigment-type switching as discussed in Chapter 5.

Figure 1.8 Black-and-tan dog with white spotting; a^t/a^t $Tyrp1^B/Tyrp1^B$ (former name a^t/a^t, B/B). The specific white-spotting genotype is unknown, but it does not relate to the *Agouti* gene locus or the *Tyrp1* locus. This is another example of the patterning function of the *Agouti* locus. The *Agouti* locus regulates patterns of yellow pheomelanin and nonyellow eumelanin on individual hairs, as in Figures 1.6 and 1.7, or patterns of pheomelanin and eumelanin over the surface of the body. The so-called tan portion of the pattern is actually pheomelanic (yellow) pigment. The black color of the eumelanic portion is determined by the *Black/brown* locus (Kerns et al. 2004).

Pigment-type switching describes the ability of pigment cells to switch between the production of eumelanin and pheomelanin, under the control of the *Agouti* (*A*) and/or *Extension* (*Mc1r*) loci and modifying genes. The *Agouti* locus regulates the pattern of distribution of eumelanin and pheomelanin on each hair and over the surface of the body. So, agouti is not so much a color as a pattern of pheomelanogenesis that may or may not occur. That the pigment switch is between eumelanin and pheomelanin is illustrated, for example, in the Doberman Pinscher dog (or the similarly pigmented dog in Fig. 1.8). These may display yellow and black pigment patterns, or yellow and brown patterns in chocolate brown (incorrectly named 'red') Doberman Pinscher dogs.

Black and brown combinations do not occur. The type of eumelanin pigment, black versus brown, is genetically determined at birth, by the genotype at the *B* (*Tyrp1*, black/brown) locus, and there is no mechanism for switching between them. Color switching is exclusively a phenomenon involving eumelanin and pheomelanin.

In the mouse and other mammals, the three basic colors of melanin pigment, and their patterns of distribution over the body or within individual hairs, are regulated by the *Agouti* (*A*), *Extension* (*Recessive yellow*, *E*, or *Mc1r*), and black/brown (*B* or *Tyrp1*) loci (see Chapter 4).

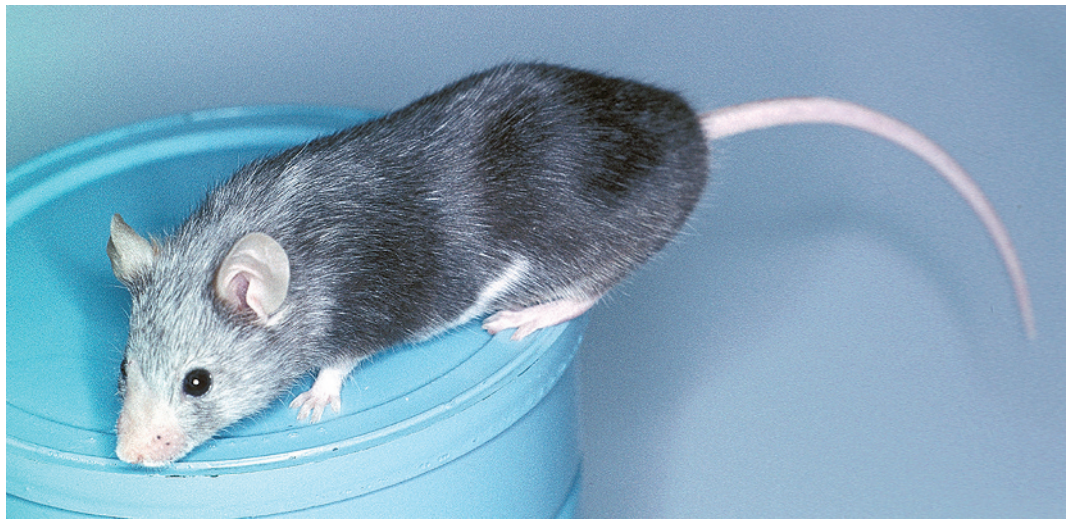
Two basic types of pigment pattern exist that involve the death of melanocytes or their failure to differentiate or survive. White spotting is defined as the congenital absence of pigment cells from portions of the body or from the entire body, and we will use the term progressive graying to

Figure 1.9 Franny and Bitsy, a white-spotted dog of the Border Collie breed and brindle-colored Catahoula Hound. Both dogs have white spotting of unknown genotype that is not associated with the other color genotypes. Both dogs are *Black* at the *Black/brown* locus; therefore, eumelanic areas are black. The brindle phenotype is associated with mutation at a third locus that regulates the eumelanin/pheomelanin alternative in dogs (the *K*, *Canine β-defensin 103* locus).

describe ongoing loss of melanocytes in mice. Everyone has seen progressive graying with age, caused by loss or death of pigment cells from the hair follicles. Premature graying or patterned graying may be termed vitiligo or hypopigmentation; these are discussed in Chapter 3 (see also Fig. 1.10). Here we will use vitiligo and avoid the term hypopigmentation because it is not specific to an etiology.

Examples of white spotting include Paint horses, Hereford cattle, white forelock in humans, and the white areas of white-spotted cats, dogs, and mice, many of which are pictured throughout this book, especially in Chapter 3. The terms partial albinism and hypopigmentation are sometimes substituted for white spotting, especially in older publications. However, these are not appropriate to specifically describe white spotting, because hypopigmentation is a term also applied to albinism, which is a fundamentally different process. White-spotting and progressive-graying phenotypes result from pigment cell death or failure to survive, whereas albinism is the failure of deposition of pigment in living pigment cells, as discussed in Chapter 4.

The final step in cutaneous pigmentation occurs when the pigment cell transfers its melanosomes into keratinocytes of the adjacent skin, or the keratinocytes of a growing hair or feather as discussed in Chapter 4. The distribution of melanosomes in hairs is precise, and is an



(a)

(b)

Figure 1.10 Vitiligo; (a) *Mitf*^{vit}/*Mitf*$^{mi\text{-}rw}$; (b) *Mitf*$^{mi\text{-}vit}$/*Mitf*$^{mi\text{-}or}$. The *Vitiligo* mouse has both white spotting and vitiligo. (a) This mouse is in the process of molting to a lighter color. (b) The older mouse is shown at the rear.

important component of how we perceive the color. When this pattern of distribution is modified by mutation, if the change causes the fur coat or feathers to reflect light differently to our eyes, the animal may appear to be quite a different color. In mammals, the most common example of this type of genetically controlled color difference is found in the 'dilute' phenotypes that are variously referred to as gray or blue, lavender, or cream (there are yet more names for this phenotype in various species) colors of cats, dogs, and other mammals (see Fig. 1.11). These may be caused by mutation at several different loci. We discuss melanosomal transfer briefly below in section 1.8 and in more detail in Chapter 4.

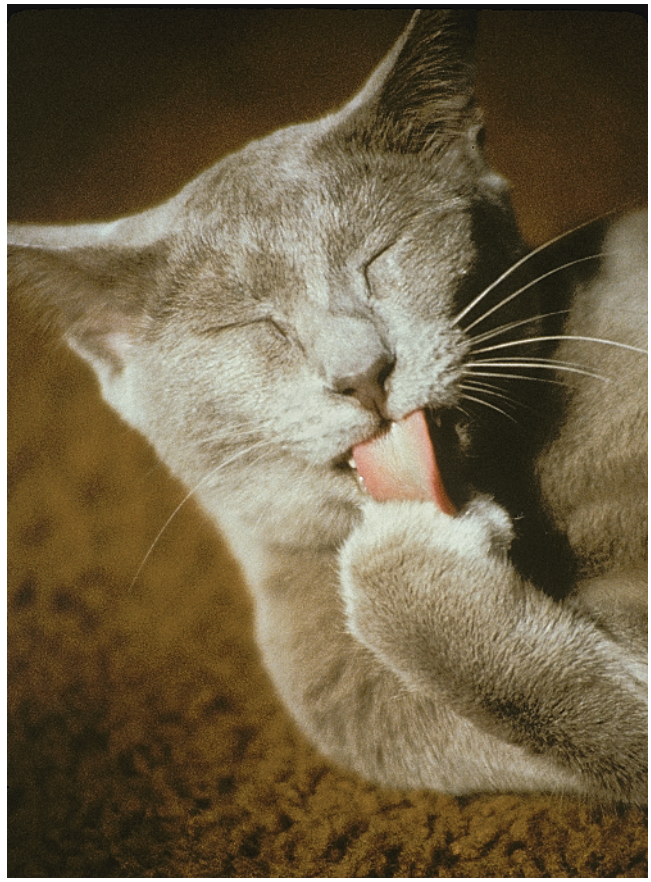


Figure 1.11 Mini Mizzle, lavender color, oriental shorthair. Oriental shorthair is the name of a breed of cat, and is therefore not a color. 'Lavender' is a cat fancier's term for 'nonagouti, brown, dilute' Unfortunately, 'dilute' is the cat breeder's term for the mouse gene known as *Leaden* (*Melanophilin*). The mouse *Dilute* gene identifies the *Myo5a* locus. The genotype of this cat is *a*/*a Tyrp1*^{b}/*Tyrp1*^{b} *Mlph*^{ln}/*Mlph*^{ln}, which cat fanciers would refer to as *a*/*a b*/*b d*/*d*; however, the correct original nomenclature is *a*/*a b*/*b ln*/*ln*.

To summarize, the complexity of pigmentation phenotypes results primarily from four basic processes:

1. development of the melanocyte (Chapter 3);
2. differentiation of the melanocyte as it generates melanosomes (Chapter 4);
3. regulation of the type of melanin that is deposited upon the melanosome (pheomelanin, black eumelanin, or brown eumelanin) (Chapter 5);
4. transport of the melanosome within the pigment cell and transfer to the neighboring keratinocytes (Chapter 4).

These four basic functions are regulated by over 300 gene loci in the laboratory mouse (see the Appendix to this chapter). In the mouse, any of these genes can be evaluated using natural or

created mutations against an inbred background genome and using advanced genetic techniques (see Chapter 6). The mutant mice, or their cells, are usually viable and can be evaluated at every level of gene function, from transcription to the final mouse phenotype. This makes the pigment system of mice uniquely valuable to our understanding of basic biological processes, including cell and tissue communication networks within the developing embryo and the adult body, and specific medical conditions, including melanoma.

1.3 Other pigment cells

Chromatophores or chromatocytes (colored cells) are general terms for pigment cells, which in some vertebrates may produce pigments other than melanin. Chromatophores of vertebrates – fish, amphibians, reptiles, birds, and mammals – provide protection from the environment as well as adaptive and/or disruptive coloration, through the colors of their pigments and the movement of their pigmented organelles (chromatosomes) within the pigment cells (Bagnara & Matsumoto 2006; Logan et al. 2006). The chromatophores of fishes, amphibians, and some reptiles are more varied in content and function than those of birds and mammals, and generally retain their pigment rather than transferring it to other cells. Colors of lower vertebrates thus result from the distribution of dermal and epidermal pigment cells (Lamoreux et al. 2005; Parichy et al. 2006). Fish chromatophores are primarily melanophores/melanocytes that produce black or brown melanin pigment; leucophores (white) and iridophores (shiny silvery colors), both of which use purines to create their pigments; and the yellow-red xanthophores. The yellow colors of fish xanthophores, unlike the pheomelanocytes of birds and mammals, are based in pteridine pigments (Ziegler 2003). Color changes in the dermal melanophores of fishes, amphibians, and reptiles may be rapid and varied, because the pigment cells can quickly disperse or aggregate their chromatosomes within the dermal chromatophores in response to neuronal and hormonal controls.

The pigmentation repertoire of mammals and birds is more limited. Mammals and birds do not have so many types of chromatophores; for the most part, they are limited to epidermal melanophores. Furthermore, rapid changes in the hair/feather pigmentation pattern of birds and mammals are not possible, except through behaviors such as the tail flagging of deer or courtship displays of birds. There are two reasons for this. First, the hairs of mammals (and feathers of birds) are not living tissue and so cannot change biologically. Secondly, the epidermal melanocytes of mammals do not normally translocate their melanosomes in response to direct neuronal and hormonal cues, as do the dermal melanophores of amphibians and fishes. Their primary function is to transfer melanosomes into neighboring keratinocytes. They accomplish this function slowly, responding to the environment via the epidermal melanin unit (Klaus 2006; Quevedo & Holstein 2006).

1.4 The epidermal melanin unit

The epidermal melanin unit (also called the EMU) of human skin (Fitzpatrick & Breathnach 1963; Quevedo & Holstein 2006) is a subunit of epidermal tissue, in humans consisting of a melanocyte and its 30–40 associated keratinocytes, that together are responsible for the production of melanosomes, and their subsequent transport, metabolism, and degradation. As they mature, the melanosomes, which are members of the lysosomal family of organelles, are transferred to adjacent keratinocytes of a growing hair or, in pigmented skin of humans and some other mammals, to

the adjacent keratinocytes of the epidermal melanin unit in the basal layer of the epidermis, where they are sequestered within lysosomes. Because the epidermis grows continually from the basal layer, the cells of the epidermal melanin unit are pushed upward, gradually cornified as the normal protective layer of skin, and then lost/shed as new epidermal tissue replaces them from below.

In mice, the outermost protective layer is the hair coat. The transfer of melanosomes from the pigment cell into the growing hair is precisely controlled in its distribution within the cortex and the medulla of the hair and differentially according to the type of hair and its location on the body. In mice, control over the amount, distribution, and color of melanosomes is specific to the age of mouse, stage of the hair growth cycle, and position on the body (Galbraith 1964).

Mammalian pigment cells are also delivered to the inner ear, iris, choroid, heart, and other extracutaneous locations (Quevedo & Holstein 2006). The retinal pigment epithelium (see Chapter 3) is produced *in situ*.

1.5 Mammalian hair

In mice, overall pigment phenotype is predominantly a reflection of the hair (fur) that covers the body. Most of the melanocytes are located in the hair rather than in the interfollicular epidermis. Each hair grows from an epidermal hair follicle (Fig. 1.12). The hair follicle is an ingrowth of the epidermis that pushes deep into the dermis and the hypodermis. The hair follicle, where most of the activity takes place during a hair growth cycle, consists of the hair bulb, the dermal papilla, and the bulge area. The dermal papilla pushes up into the root of the hair bulb and provides a blood supply to the hair bulb cells, which generate the keratinocytes that become cornified as hair. The bulge area, at least in mice, sequesters melanocyte stem cells between hair cycles. At the beginning of a hair cycle, melanoblasts (unpigmented melanocyte precursor cells; sometimes called melanocyte

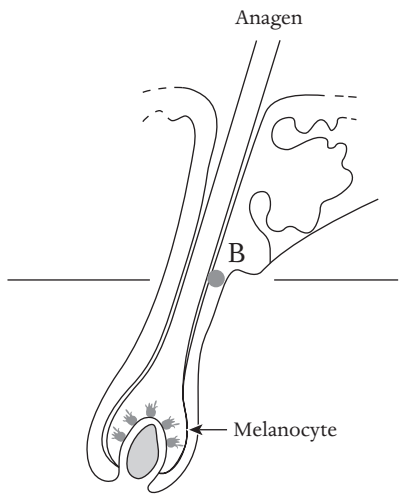


Figure 1.12 A mature hair follicle. B indicates the bulge region of the hair follicle and the gray spot shows where the melanocyte stem cells reside. The horizontal line represents the level to which the follicle regresses after the growth phase is complete. Diagram courtesy of Nishimura et al. (2002).

stem cells in this context) migrate from the bulge area into the hair bulb, around the dermal hair papilla, where they proliferate, differentiate, and initiate melanogenesis.

1.6 Melanosome biogenesis and translocation

The epidermal melanocyte (Fig. 1.13) is dendritic and contains an abundant endoplasmic reticulum and active Golgi region where melanosomal proteins are processed before being carried to their specific locations in stage I, II, III, and the mature stage IV melanosomes, as described in Chapter 4 (Fig. 4.8). Correct processing of the melanosomal proteins and their appropriate transport to the developing melanosome are necessary for normal pigmentation. Pigmentary defects associated with processing and transport are discussed in Chapter 4.

The melanosome is a member of the family of lysosome-related organelles that also includes platelet dense granules, lamellar bodies of type II alveolar epithelial cells, and lytic granules of cytotoxic T lymphocytes and natural killer cells. Premelanosomes appear to derive as 'saccules' that bud from the smooth endoplasmic reticulum (Orlow 1995). In eumelanosomes an internal matrix condenses from amorphous filamentous material to an organized internal structure. This material is largely the protein product of the *Silver* gene locus, as discussed in Chapter 4 (Boissy et al. 2006).

When assembled into a stage II melanosome (lacking pigment) the structure appears in section as highly organized spirals that apparently represent three-dimensional sheets that are rolled or

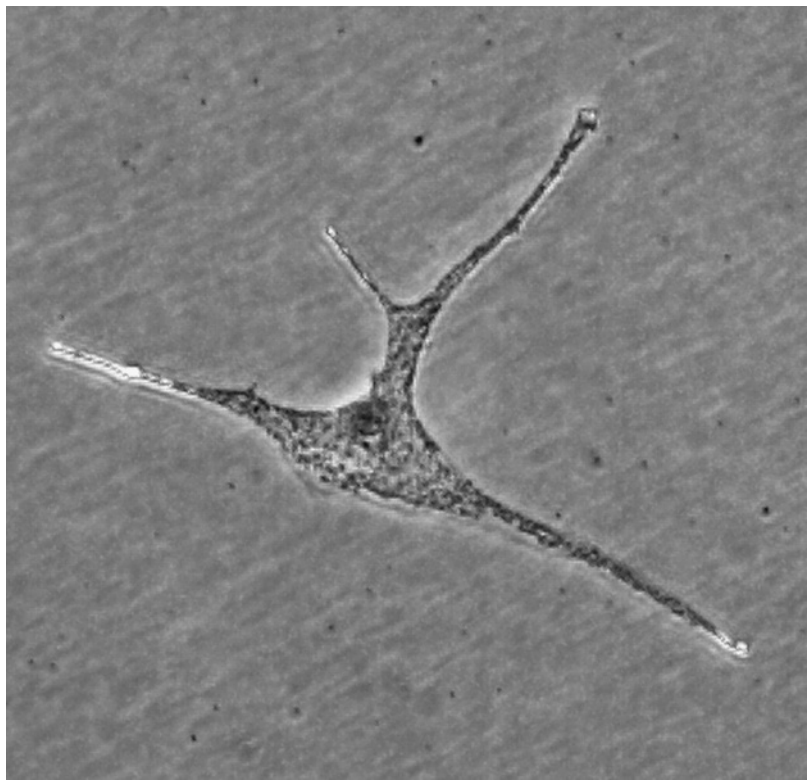


Figure 1.13 A eumelanocyte in cell culture.

pleated to form the basic structure upon which pigment is deposited in later stage melanosomes (Fig. 4.8). As the melanosome matures beyond stage II to stage III, catalytic enzymes are delivered to it and initiate deposition of melanin upon and within the matrix of the melanosome until it finally matures as the fully pigmented, chemically inert stage IV melanosome. In the living cell, the catalytic enzymes are active only briefly in the controlled environment of the melanosome, when they are needed for pigment deposition. During other stages of the cycle, their locations and functions are controlled tightly by other molecules in the pigment cell, as discussed in Chapter 4. Stage IV melanosomes are transported to the periphery of the melanocyte and transferred to keratinocytes as discussed in Chapter 4 (Scott 2007; Byers 2006).

1.7 Melanin

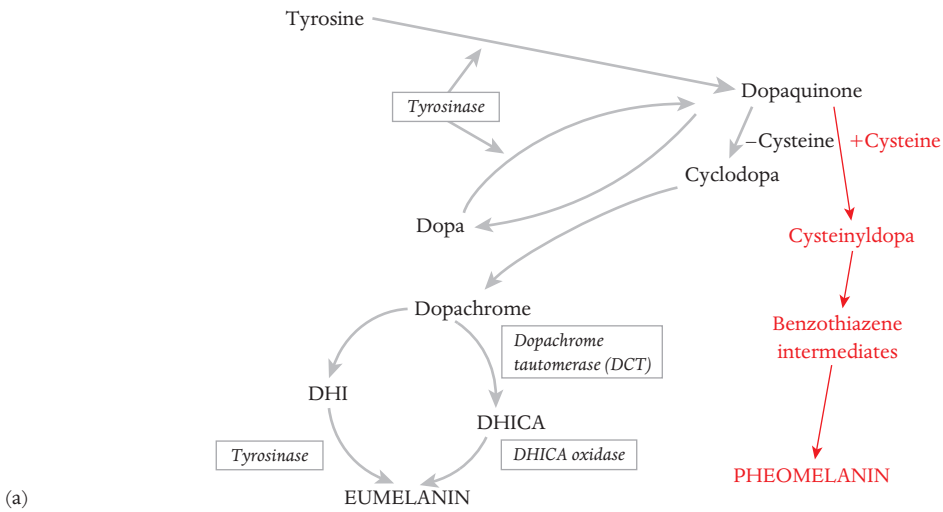
Melanogenesis occurs within the melanosome. Failure of melanogenesis results in albinism. The substrate molecule required for initiation of melanogenesis, tyrosine, is found in all cells; it is not a limiting factor. The enzyme tyrosinase is normally the rate-limiting factor, and is sufficient to catalyze melanogenesis *in vitro*. The biochemical pathway is relatively simple, as shown in Figure 1.14. To prevent premature activity of tyrosinase *in vivo*, the cell maintains tight control over its processing and routing to the melanosome, as described in Chapter 4. Genetic defects in tyrosinase itself, encoded at the *Albino* or *Color* (*Tyr*, *c*) locus, constitute one class of albinism. Other causes of albinism most often relate to the loci involved with processing and routing. As mentioned, mammals are able to produce two chemically distinct types of melanin pigment: (1) black or brown eumelanin and (2) pheomelanin in shades ranging from yellow to red (Chapter 4; Brilliant 2006; Hearing 2006; Oetting & Setaluri 2006; Solano & García-Borrón 2006; Figure 1.15).

Pheomelanosomes differ from eumelanosomes in structure, as well as color and the chemical nature of the pigment (Ito & Wakamatsu 2006; Sarna & Swartz 2006). These differences result at least in part from the switching off of several of the gene loci that are responsible for the production of eumelanosomes, as discussed in Chapter 5, pigment-type switching (and see Barsh 2006), and probably also in the availability of cysteine substrate.

1.8 Hair growth

As melanosomes mature, they are carried to the outer perimeter of the pigment cell and normally are transferred into neighboring keratinocytes of the growing hair or feathers in mammals (described in Chapter 4) or birds, and within the skin of humans. In the hair follicle, melanogenesis occurs during the growth of a new hair. During anagen, the first stage of hair follicle development, which lasts about 17 days in mice, the hair follicle extends deeper into and below the dermis, while melanocytes in the bulb area of the follicle (Figure 1.12) transfer melanosomes into the growing hair. Catagen, which lasts about a day, is a transitional second stage of the cycle, after the hair is fully grown, when a basal club is formed that anchors the hair in the upper part of the hair follicle. Telogen is the resting stage between cycles of hair growth. The length of telogen varies between a month and several months, depending upon the age of the mouse and other factors such as genetics, nutrition, or damage to the hair.

During the anagen or growth stage of the hair follicle, keratinocytes flow upward in the hair shaft from the lower hair bulb where they are generated, while melanocytes in the upper hair bulb synthesize melanosomes and deposit them from their long dendritic processes into the living



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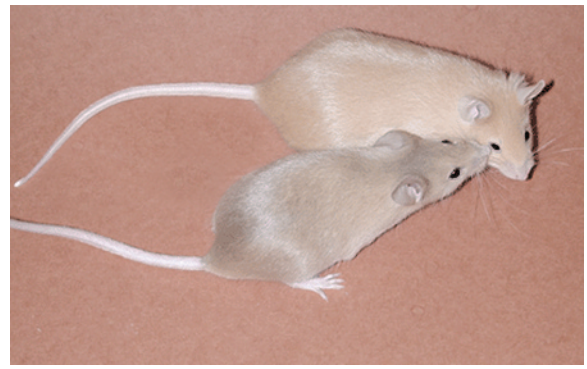

(c)

Figure 1.14 (a) The melanogenic pathway functions in the pigment granule (pathway simplified from Ito & Wakamatsu 2008; reproduced with permission of Wiley-Blackwell). Enzymes are shown in boxes. The rate-limiting enzyme is tyrosinase; mutation at the *Tyr* (*Albino*) locus reduces the amount of melanin that the pigment cell can make. In nonagouti mice that are otherwise wild type at pigment loci, mutation of the gene that encodes dopachrome tautomerase (DCT) results in slaty mice (below left, the one on the lower right is Slaty, that is, mutant at *Dct*). Mutation of the gene with 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidase activity (*Tyrp1*) results in brown mice (b, rear) (see also Chapter 4). The mouse on the left in this picture is wild type. Pheomelanogenesis is primarily regulated by a cell-surface receptor (MC1R) and its ligand, melanocyte-stimulating hormone (MSH), that control whether or not the cell will make yellow pigment. Pheomelanogenesis is epistatic to eumelanogenesis. The two pheomelanic mice (c) are (front) *Recessive yellow*, in which the MC1R is mutant, and (back) *Lethal yellow*, in which the *Agouti* locus that encodes MSH is mutant (see also Chapter 5).

keratinocytes. The hairs become pigmented in an exquisitely reproducible fashion that reflects the genotype of the mouse, type of hair, and its location on the body. The resulting hair consists of variations on the theme of medullary segments, within which the melanosomes are arranged in a ladder-like formation, surrounded by a cortex in which the melanosomes are more or less evenly

Figure 1.15 Pheomelanic cat (known by some as 'red' and others as 'orange' and even others as 'marmalade'). Notice that the darker markings on this yellow cat are pheomelanic, whereas the darker markings on the agouti cat in Figure 1.7 are eumelanic.

distributed (Montagna & Ellis 1958; Searle 1968; Quevedo & Holstein 2006). By the time the hair emerges from the shaft of the hair follicle, the keratinocytes are pigmented, cornified, nonliving appendages to the skin.

1.9 Hair growth cycles

In mice, new hairs replace the old in more or less predictable cycles of growth. The first hairs begin to grow around the time of birth. After the first coat has grown, hair growth cycles can be induced artificially by plucking or shaving. Normally, the second cycle of hair growth begins at about 7–9 weeks of age. Thereafter, cycles of hair growth occur every few months. It may take about 2 weeks to fully replace the coat of hair. The process begins at the head of the mouse and proceeds caudad as a wave of new growth. During this time a continually changing pattern of pigmentation is usually more or less obvious, depending upon how much the newer hairs differ in appearance from the old.

Natural molt patterns may be caused by age-related genetic changes in the new hairs, or simple wear and tear of the old. In some mutant phenotypes or strain backgrounds, it is normal for pigmentation to change with age, sometimes resulting in rather dramatic molt patterns, especially at first molt (for example, Lamoreux & Galbraith 1986, and Fig. 5.4). Even if there are no developmental differences, the black or brown hairs can become rusty-looking with age, presumably because of the bleaching effect of saliva through grooming, and urine in the cage, so that a mouse in the middle of a hair cycle may have a pattern of shiny black or brown new hairs that contrast with the rusty-looking hairs, farther back on the body, that are yet to be shed. Similar patterns can be

created artificially by injection (during the hair growth cycle) of substances that alter pigment phenotype (Chapter 5). The artificially created pattern will be maintained until the subsequent natural molt, when the mouse returns to its genetically determined phenotype. Patterns created by hair growth cycles are secondary to the hair cycle itself. Therefore, strictly speaking, they are not primarily the result of action of 'pigmentary genes,' but are nevertheless important to interpretation of pigmentary genetics for a couple of reasons. First, it is important to recognize the difference between phenotypes that are under direct genetic control, and those such as the hair cycle patterns that may not be directly relevant. Second, the hair cycle pattern of mice illustrates the need to be aware of differences between the physiology of humans and of mice that must be taken into consideration when interpreting data. The molt cycle of mice differs significantly from the condition in humans.

1.10 Embryonic development of the pigment cell lineage

Development has no beginning, and we hope it will have no end, technology notwithstanding. For an individual organism, development begins with the zygote, product of the fusion of a haploid sperm with an egg that carries a haploid set of chromosomes plus the extensive egg cytoplasm that is rich in nutrients and proteins. These proteins, encoded in the genome of the mother, make possible the maturation of offspring by providing enzymes and cellular biochemical structures that support development, from organizing the zygote to mitotic cell divisions and the early steps of cleavage, with the formation of the primary germ layers.

The pigment cell lineage of melanoblasts that mature into melanocytes arises after these earliest events, during the transient emergence of the neural crest as described in Chapter 3. The odyssey of neural-crest-derived pigment cells begins when neural-crest cells delaminate from the dorsolateral portion of the neural tube, in the mouse just before or as the neural tube closes. Melanoblasts (immature pigment cells) migrate, while replicating rapidly, along complex pathways. In mice, as the hair follicles develop concurrently with pigment-cell migration, the melanoblasts home to the follicles, leaving the interfollicular areas nearly devoid of pigment cells. Some melanoblasts then enter the bulge area of the follicle and others differentiate in the bulb region to pigment the growing hair as described above. Melanoblasts also migrate through the head and to the nose, eyes, ears, and even the heart following equally specific migratory pathways. The retinal pigment epithelium (see Chapter 3) is exceptional because it is not neural-crest-derived, but is induced directly in the neural tube.

1.11 Pigment cells in culture

Pigment cells of course develop normally in the tissue environment, not in cell culture, and there are differences between the cell culture requirements and biochemical properties of mouse and human melanocytes. Additionally, the mature pigment system of mice differs somewhat from the human pigment system *in vivo*, as do some of its functions and associated functional genetics (Sundberg 1994; Green 1966; Boissy et al. 2006; Montoliu et al. 2009). Therefore, it is wise to fully define the genetics of biological materials, human or murine, and to use caution when attributing results across species or genomic lines. That said, the unparalleled availability of murine pigmentary tissues and melanocytes that are inbred and genetically controlled provides a powerful tool for dissecting the basic mechanisms of melanogenesis at all levels, from the cell to the organism (Nordlund et al. 2006). Comparative mammalian genetics, especially at the molecular and

phenotypic levels, has become highly sophisticated; information from the human and other species is informing mouse studies, and vice versa.

1.12 Conclusion

The remarkably choreographed accomplishments that result in development and differentiation of pigment phenotypes are made possible by an intricate web of tissue interactions and cellular signaling pathways that direct the functions of the pigment cells at every level of organization from the gene to the whole organism. Through chemical messages received from the environment and recognized by its own information-processing pathways, the pigment cell regulates the genes that direct the necessary cellular processes. Because pigment cells are easily observed, and their absence is not lethal, the pigment phenotypes provide an unparalleled model for the study of cellular communications and interacting signaling pathways as they function to bring about observable phenotypes summarized above. With the genomes of several species now sequenced, and others rapidly joining the databases, we are in a position to evaluate the pigmentary system using reductionist, phenotypic, and comparative methods in parallel.

Figure 1.16 Two dogs that are mutant at different loci influencing the choice between eumelanic and pheomelanic pigmentation (discussed in Chapter 5). The dog to the rear (but leading the pack) is a chimeric mix of eumelanic and pheomelanic pigmentation resulting from mutation at the *K* (*Canine β-defensin 103*) locus. In this case the eumelanin/pheomelanin switch is regulated via the keratinocytes. See also Figure 5.13 for a better view of the pattern. The dog in the foreground is mutant at the *Agouti* (*A*) locus that regulates the eumelanin/pheomelanin switch over the body and on each hair via the genotype of the mesoderm. Other loci that influence the switch are listed in the Appendix of this chapter, and in Chapter 5. Photograph courtesy of TheOneCreation.

Appendix: color loci of the mouse

Introduction

This appendix lists all of the loci that have been reported to contribute to pigmentation to date. For further information and updates we refer you to:

- the Mouse Genome Informatics (MGI) database maintained by The Jackson Laboratory (JAX), www.informatics.jax.org/;
- the International Federation of Pigment Cell Societies (IFPCS) Color Genes initiative, www.espcr.org/micemut/, maintained by the European Society for Pigment Cell Research (ESPCR) (Montoliu et al. 2009).

Specific (mostly classical) mutant loci are discussed throughout the book in the context of their contribution to phenotype. These sections can be identified in the text because they have headings that look like the one shown here (e.g. see Chapter 4), and they are listed below in alphabetical order by locus name.

***Silver* (*Si*, *Pmel17*, *Gp100*)**
MGI lists one spontaneous phenotypic allele
Availability: JAX, CMMR, MMRRC

In such headings, 'Availability' refers to the facilities where various resources (mice, frozen embryos, etc.) are available. We use abbreviations for the facilities, and these are listed below. Besides the main ones (JAX, HAR, ORNL, MMRRC), quite a few other centers that have proliferated internationally with the availability of modern genetic technology (see Chapter 6). These are listed in full by the International Mouse Strain Resource (IMSR), sponsored by the MGI: www.findmice.org/fetch?page=imsrStrainRepositories.

CARD	Center for Animal Resources and Development
CFG	Consortium for Functional Glycomics
CMMR	Canadian Mouse Mutant Repository
EMMA	European Mouse Mutant Archive
HAR	Mammalian Genetics Unit, Harwell
JAX	The Jackson Laboratory
KOMP Repository	Knockout Mouse Repository
MMRRC	Mutant Mouse Regional Resource Centers
ORNL	Oak Ridge National Laboratories
RBRC	RIKEN BioResource Center
TAC	Taconic
TIGM	Texas A&M Institute for Genomic Medicine

Following is an index to the specific mutant loci, listed by phenotype-based name, that are discussed in the text of this book.

Index of mutant loci discussed in text

Cloned and uncloned loci

Table A1.1 shows a summary of the cloned mouse color genes and Table A1.2 gives a summary of the uncloned mouse color genes.

Table A1.1 Summary of the cloned mouse color genes

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
(A) Melanocyte development – involving integument							
Acd	adrenocortical dysplasia	8	Hyperpigmented skin, adrenal hyperplasia, other organ disorders	Telomere capping; may affect pigmentation through excess ACTH	*ACD*	16q22.1	N
Adam17	a disintegrin and metalloprotease domain 17	12	Irregular pigmentation in hairs	Protease, processing various bioactive proteins	*ADAM17*	2p25	N
Adamts20 (*bt*)	a disintegrin and metalloprotease domain (reprolysin type) with thrombospondin type 1 motif, 20 (belted)	15	Lumbar white belt	Metalloprotease, melanoblast migration?	*ADAMTS20*	12q12	N
Apc	adenomatous polyposis coli, allele *tm2Rak*	18	Prenatal dorsal dark stripe and head patch	Wnt pathway mediator; transcription factor	*APC*	5q22.2	Adenomatous polyposis coli
Brca1	breast cancer 1, allele *tm2Arge*	11	Abnormal skin pigmentation	DNA repair; tumor suppressor	*BRCA1*	17q21	Breast cancer
Dock7 (*m*, *mnlt*)	dedicator of cytokinesis 7 (misty, moonlight)	4	Distal white spotting, hypopigmented fur, but melanocytes *in vitro* hyperpigmented	widely expressed Rho-family guanine nucleotide exchange factor	*DOCK7*	1p31.3	N
Ece1	endothelin converting enzyme 1, allele *tm1Reh*	4	No melanocytes in uvea nor dorsal skin at birth (perinatal lethal)	Endothelin synthesis	*ECE1*	1p36.12	N
Edn3 (*ls*)	endothelin 3 (lethal spotting)	2	White spotting, megacolon and other neural crest defects	Melanoblast/neuroblast growth and differentiation factor	*EDN3*	20q13	Hirschsprung disease, Waardenburg–Shah syndrome
Ednrb (*s*)	endothelin receptor type B (piebald spotting)	14	White spotting, megacolon and other neural crest defects	EDN3 receptor	*EDNRB*	13q22	Hirschsprung disease, Waardenburg–Shah syndrome

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Egfr (*Dsk5*)	epidermal growth factor receptor (dark skin 5)	11	Dark skin	Growth factor receptor	*EGFR*	7p12.3	N
En1	engrailed 1	1	Hyperpigmentation of digits (polydactyly etc)	Transcription factor	*EN1*	2q14.2	N
Fgfr2	fibroblast growth factor receptor 2	7	Lighter skin (many other defects)	Growth factor receptor	*FGFR2*	10q26	Crouzon syndrome, Pfeiffer syndrome
Foxn1 (*tw*)	forkhead box N1, allele *tw* (traveling wave)	11	Hairless. Waves of dark/light travel slowly over skin (poss. normal hair cycle + very short hairs)	Transcription factor	*FOXN1*	17q11.2	N
Frem2	Fras1 related extracellular matrix protein 2, allele my-F11	3	Microphthalmia/anophthalmia, patches of discolored or white fur	Extracellular protein; possibly epithelial–mesenchymal interactions at basement membrane	*FREM2*	13q13.3	Fraser syndrome
Fzd4	frizzled homolog 4 (*Drosophila*), allele *tm1Nat*	7	Many abnormalities including light or silvered coat	WNT receptor, putatively for WNT5A and/or NDP (see *Ndp*)	*FZD4*	11q14.2	Exudative vitreoretinopathy 1
Gata3	GATA binding protein 3, allele *tm3Gsv*	2	Extra stem-like cells in hair follicles; abnormal hair, irregular pigment deposition	Transcription factor	*GATA3*	10p14	Hypoparathyroidism, sensorineural deafness, and renal disease syndrome, Barakat syndrome
Gli3	GLI-Kruppel family member GLI3	13	White belly patch or lumbar belt; nervous system defects (homozygous postnatal lethal)	Signaling in hedgehog pathway; modifies SOX10 expression	*GLI3*	7p14.1	Pallister–Hall syndrome and others
Gnaq (*Dsk1*, *Dsk10*)	guanine nucleotide-binding protein subunit Gaq (dark skin 1, dark skin 10)	19	Dark skin (hyperproliferation of melanocytes)	Signal transduction, possibly from an EDNR(s) to PLCβ	*GNAQ*	9q21	Possible platelet defect

Gna11 (*Dsk7*)	guanine nucleotide-binding protein subunit Ga11 (dark skin 7)	10	Dark skin (hyperproliferation of melanocytes)	Signal transduction, possibly from an EDNR(s)	*GNA11*	19p13	N
Gpc3	glypican 3, allele *tm1Arge*	X	Dominant distal and belly spotting	GPI-linked extracellular membrane protein; putative SHH-binding (competitive with PTCH)	*GPC3*	Xq26.2	Simpson-Golabi-Behmel syndrome type 1
Gpr161 (*vl*)	G protein-coupled receptor 161 (vacuolated lens)	1	Vacuolated lens, occasional belly spot, spina bifida, others	Signal transduction	*GPR161*	1q24.2	N
Hells	helicase, lymphoid specific	19	Early ageing includes graying by 15d old. p16 overexpression	DNA methylation, gene silencing	*HELLS*	10q23.33	N
Itgb1	integrin β1, allele *tm1Ref*	8	Transient patchy hypopigmentation, crest migration defect	Fibronectin receptor–cell attachment, migration	*ITGB1*	10p11.22	N
Kit (*W*)	Kit oncogene (white spotting)	5	White spotting, anemia and germ-cell deficiency	Receptor for KIT ligand/stem cell factor; required for melanoblast survival	*KIT*	4q11–q12	Piebald syndrome
Kitl (*Sl*)	Kit ligand (steel)	10	White spotting, anemia and germ-cell deficiency	Growth and differentiation factor	*KITLG*	12q22	N
Krt1 (*Dsk12*)	keratin 1 (dark skin 12)	15	Dark skin	Cytoskeleton	*KRT1*	12q13	Epidermolytic hyperkeratosis
Krt2 (*Krt2-17*, *Dsk2*)	keratin 2 (Keratin 2-17, dark skin 2)	15	Dark skin	Cytoskeleton	*KRT2A*	12q11–q13	Ichthyosis bullosa of Siemens
Krt4	keratin 4	15	'Bright' diluted coat color	Cytoskeleton	*KRT4*	12q13.13	White Sponge Nevus of Cannon
Krt17	keratin 17, allele *tm1Cou*	11	Abnormal hairs with clustered melanin granules	Cytoskeleton	*KRT17*	17q1.2	Pachyonychia congenita type 2 Steatocystoma multiplex
Krt75	keratin 75, allele *tm1Der*	15	Hair defects with variable pigment clumping	Cytoskeleton	*KRT75*	12q13.13	N

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Lef1	lymphoid enhancer binding factor 1, allele *tm1Rug*	3	Underdeveloped hair follicles lacking melanin	Transcription factor; Wnt/β-catenin mediator	*LEF1*	4q25	Sebaceous adenomas
Lmx1a (*dr*)	LIM homeobox transcription factor 1α (dreher)	1	Partial or complete white belt and/or belly spot	Transcription factor	*LMX1A*	1q22-23	N
Mbtps1	membrane-bound transcription factor peptidase, site 1, allele wrt	8	Diluted hair with white base (melanocyte death?)	Peptidase involved in regulation of membrane lipid composition	*MBTPS1*	16q23.3–q24.1	N
Mcoln3 (*Va*)	mucolipin 3 (varitint-waddler)	3	Patches of normal, diluted and white hair (and behavioral defects)	Cation channel	*MCOLN3*	1p22.3	N
Mitf (*mi*)	microphthalmia-associated transcription factor (microphthalmia)	6	White spotting and small or absent eyes	Transcription factor: master regulator of melanocyte lineage	*MITF*	3p12-14	Waardenburg syndrome type 2
Mpzl3 (*rc*)	myelin protein zero-like 3 (allele rough coat)	9	Hair follicle loss, black pigment changes to light brown	Putative adhesion protein, expressed in keratinocytes	*MPZL3*	11q23.3	N
Myc	myelocytomatosis oncogene (when KO targeted by Wnt1 promoter-Cre)	15	Pigmentary spotting, not head	Transcription factor, regulator of cell proliferation	*MYC*	8q24.21	
Notch1	Notch gene homolog 1 (*Drosophila*)	2	Scattered gray hairs, when KO targeted to melanocytes	Receptor for ligands in Delta and Jagged families	*NOTCH1*	9q34.3	N
Notch2	Notch gene homolog 2 (*Drosophila*)	3	Scattered gray hairs, when KO targeted to melanocytes; all gray with Notch1 KO, eventually white	Receptor for ligands in Delta and Jagged families	*NOTCH2*	1p12	Alagille Syndrome 1

Ntrk1 (*TrkA*)	neurotrophic tyrosine kinase, receptor, type 1	3	Mottled coat (also neural defects, skin lesions)	Coreceptor for nerve growth factor	*NTRK1*	1q23.1	Insensitivity to pain, congenital, with anhidrosis
Pax3 (*Sp*)	paired box gene 3 (splotch)	1	White belly splotch, neural crest defects	Transcription factor	*PAX3*	2q35	Waardenburg syndrome type 1, Waardenburg syndrome type 3
Pax6 (*Sey*)	paired box gene 6 (small eye)	2	Eye abnormalities can include reduced RPE, also distal/ventral white spotting	Transcription factor	*PAX6*	11p13	Aniridia Other eye disorders
Pcbd1	pterin 4α carbinolamine dehydratase/ dimerization cofactor of hepatocyte nuclear factor 1α (TCF1)	10	Mild hypopigmentation, belly spot, mild microphthalmia	Both phenylalanine metabolism and binding partner of TCF1 (HNF1), hence WNT pathway interaction	*PCBD1*	10q22.1	Hyperphenylalaninemia with primapterinuria
Rb1	retinoblastoma 1 (targeted deletion)	14	Melanocyte hyperproliferation in culture	Growth-inhibitor, suppresses E2F transactivation activity	*RB1*	13q14.2	Retinoblastoma
Rbpj (*RBP-JK*)	recombination signal binding protein for immunoglobulin κ J region (Tyr targeted KO)	5	Hair whitening; other melanocytes not affected	Transcription factor, mediator of Notch signaling and cell fate	*RBPJ* (*RBPSUH*)	4p15.2	N
Sema3c	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	5	Some skin hypopigmentation, ectopic pigment in internal organs	Secreted signaling factor, can mediate axon repulsion	*SEMA3C*	7q21.11	N
Sfxn1 (*f*)	Sideroflexin 1 (flexed tail)	13	Belly spot (and flexed tail, anemia etc)	Tricarboxylate carrier	*SFXN1*	5q35.3	N
Snai2	Snail homolog 2/Slug	16	Spotting, head blaze, pale hair and skin, neural crest and other organ defects	Transcription factor	*SNAI2*	8q11	Waardenburg syndrome type 2
Sox10 (*Dom*)	SRY-box-containing gene 10 (dominant megacolon)	15	White spotting, megacolon and other neural crest defects	Transcription factor	*SOX10*	22q13.1	Waardenburg syndrome types 2E, 4

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Sufu	suppressor of fused homolog (*Drosophila*)	19	CNS, dark hair, basal cell lesions on skin. (hedgehog pathway suppressor)	Cytoplasmic signaling intermediate	*SUFU*	10q24.32	Medulloblastoma
Tbx10 (*Dc*)	T-box 10 (Dancer)	19	Head spot (variable); ear, palate and neural defects	Transcription factor (ectopic expression in Dc)	*TBX10*	11q13.2	N
Tbx15 (*de*)	T-box 15 (droopy ear)	3	Ear shape; skeletal, altered dorsoventral color pattern with A^t, a^e	Transcription factor	*TBX15*	1p13	N
Tcfap2a	transcription factor AP-2α	13	Wnt1-targeted KO gives neural crest defects including pigmentary	Transcription factor	*TFAP2A*	6p24	N
Traf6	Tnf receptor-associated factor 6	2	Many effects including pale skin, few/delayed hair follicles; postnatal lethal	Signaling from IL1A to NF-κB	*TRAF6*	11p12	Ectodermal dysplasia, anhidrotic
Wnt1	Wingless-related MMTV integration site 1	15	Defects of neural crest including melanoblasts in mice lacking both Wnt1 and Wnt3a	Growth factor/morphogen	*WNT1*	12q13	N
Wnt3a	Wingless-related MMTV integration site 3A	11	Defects of neural crest including melanoblasts in mice lacking both Wnt1 and Wnt3a	Growth factor/morphogen	*WNT3A*	1q42	N
Zbtb17	zinc finger and BTB domain containing 17	4	Darkened coat (mixed strain background); dark skin, dark dermis around hairs. Abnormal follicles	Transcription factor	*ZBTB17*	1p36.13	N
Zfp53	zinc finger protein 53	17	Abnormal skin pigmentation	Resembles transcription factor	*?*	?	N
Zic2 (*Ku*)	Zinc finger protein of the cerebellum 2 (Kumba)	14	Belly spot, curly tail, hindbrain	Transcription factor	*ZIC2*	13q32	Holoprosencephaly 5

(B) Development: predominantly eye and/or ear

Bmpr1a	bone morphogenetic protein receptor, type 1A, allele *tm1Bh*	14	Abnormal prenatal RPE with discontinuity in pigmentation	Receptor	*BMPR1A*	10q22.3	Juvenile polyposis syndrome
Bmpr1b	bone morphogenetic protein receptor, type 1B, allele *tm1Kml*	3	Abnormal prenatal RPE with discontinuity in pigmentation	Receptor	*BMPR1B*	4q23–q24	Brachydactyly, types A2, C; chondrodysplasia
Fkbp8	FK506 binding protein 8, allele *tm1Tili*	8	Microphthalmia/ anophthalmia	Endogenous calcineurin inhibitor; can inhibit apoptosis	*FKBP8*	19p13.11	N
Gas1	growth arrest specific 1, allele *tm1Fan*	13	RPE transdifferentiates to neural retina	Can enhance hedgehog signaling, inhibit growth	*GAS1*	9q21.33	Holoprosencephaly
Gnpat	glyceronephosphate O-acyltransferase, allele *tm1Just*	8	Abnormal RPE morphology, microphthalmia	Enzyme	*GNPAT*	1q42.2	Rhizomelic chondrodysplasia punctata, Type 2
Grlf1	glucocorticoid receptor DNA binding factor 1 (p190 RhoGAP)	7	RPE hyperplasia, microphthalmia	Transcriptional repressor	*GRLF1*	19q13.32	N
Jmjd6	Jumonji domain containing 6, allele *tm1Gbf*	11	Lack of one/both eyes, ectopic RPE in nose	Demethylates histones; transcriptional regulator	*JMJD6*	17q25.2	N
Mab21l2	Mab-21-like 2 (*Caenorhabditis elegans*), allele *tm1Nao*	3	lack of RPE by time of embryonic lethality	Cell fate determination, TGFβ signaling	*MAB21L2*	4q31.3	N
Med1	mediator complex subunit 1	11	Low retinal pigmentation (before embryonic lethality)	Binds methylated DNA; DNA repair	*MBD4*	17q12	N
Ndp	Norrie disease homolog (allele *tm1Wbrg*)	X	Many defects including hyperpigmentation of RPE and overgrowth of strial melanocytes	TGFβ-like extracellular factor; FZD4 and LRP5 also associated with human Norrie disease	*NDP*	Xp11.4	Norrie disease
Nf1	neurofibromatosis 1	11	Small, unpigmented eyes, microphthalmia (Ras pathway)	Ras GTPase-activating protein (neurofibromin)	*NF1*	17q11.2	Neurofibromatosis 1

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Nr2e1 (*frc*)	nuclear receptor subfamily 2, group E, member 1 (allele fierce)	10	Brain and eye defects; asymmetrical and mottled RPE	Transcriptional repressor, recruits HDAC to DNA, stem cell maintenance	*NR2E1*	6q21	N
Otx2	orthodenticle homolog 2 (*Drosophila*)	14	Many effects including RPE hyperplasia	Hox-like transcription factor, can induce RPE identity in neural retina	*OTX2*	14q23.1	Dysgnathia complex
Pax2	paired box gene 2	19	Many effects including RPE cells extending into optic nerve	Transcription factor	*PAX2*	10q24.31	N
Pdgfb	platelet derived growth factor, B polypeptide	15	Cardiovascular and eye defects include abnormal RPE, microphthalmia	Growth factor	*PDGFB*	22q13.1	Meningioma
Pdgfc	platelet-derived growth factor, C polypeptide	3	Depigmented spots in the retina	Growth factor	*PDGFC*	4q32.1	N
Phactr4 (*humdy*)	phosphatase and actin regulator 4, allele humpty dumpty	4	Neuroblast overgrowth; outgrowths in RPE	Regulator of protein phosphatase 1 and its dephosphorylation of RB1	*PHACTR4*	1p35.3	N
Pitx3 (*ak*)	paired-like homeodomain transcription factor 3	19	Eye abnormalities including hyperpigmentation around embryonic pupil	Transcription factor; CNS neuronal differentiation	*PITX3*	10q24.32	Congenital cataract
Pygo1	pygopus 1	9	Eye and other defects including folded RPE	Cofactor for β-catenin- LEF-mediated transcription	*PYGO1*	15q21.3	N
Rs1	retinoschisis (X-linked, juvenile) 1 (human), allele *tmgc1*	X	Small patches of depigmentation in RPE	Retinal protein; homologies to cell-adhesion proteins	*RS1*	Xp22.13	Retinoschisis 1, X-linked, juvenile
S1pr2 (*Edg5*)	sphingosine-1-phosphate receptor 2	9	Ear defects include thickening and hyperpigmentation of stria vascularis	Receptor	*S1PR2* (*EDG5*)	19p13.2	N

Sema4a	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4A	3	Abnormal RPE, postnatal depigmentation of eye	Transmembrane juxtacrine signaling protein	*SEMA4A*	1q22	Retinitis pigmentosa
Timp3	tissue inhibitor of metalloproteinase 3	10	Abnormal RPE morphology	Protease inhibitor and can block VEGF binding to receptor	*TIMP3*	22q12.3	Fundus dystrophy, pseudoinflammatory, of Sorsby
Tub	tubby candidate gene	7	Obese; eye and ear abnormalities; degeneration and loss of RPE	Anti-apoptotic; downstream mediator of $G\alpha_q$ signaling	*TUB*	11p15.4	N
Unc119	unc-119 homolog (*Caenorhabditis elegans*)	11	Retinal degeneration; mottling of RPE	Proposed receptor-associated activator of SRC-family kinases	*UNC119*	17q11.2	N
Vsx2	visual system homeobox 2	12	Microphthalmia, reduced eye pigmentation	Pax-like transcription factor	*VSX2*	14q	Corneal dystrophy, keratoconus
(C) Components of melanosomes and their precursors							
Dct (*slt*)	dopachrome tautomerase (slaty, TRP2)	14	Dilution of eumelanin color	Melanosomal enzyme	*DCT*	13q31–q32	N
Gpnmb	glycoprotein (transmembrane) NMB	6	Glaucoma, iris pigment epithelium disorders, especially with *Tyrp1*$^{b/b}$	Apparent melanosomal component	*GPNMB*	7p15	N
Si (*si*)	silver (gp100, gp87, Pmel-17 etc)	10	Silvering with postnatal melanocyte loss in eumelanic animals (varying with strain background)	Melanosome matrix; trapping of melanin intermediates?	*SILV*	12q13–q14	N
Slc24a5	solute carrier family 24, member a5 (NCKX5)	2	Skin, eye color	Calcium transporter, ?melanosomal	*SLC24A5*	15q21.1	Skin, hair, eye color

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Slc45a2 (*uw*, *Matp*)	solute carrier family 45, member a2 (underwhite, membrane-associated transporter protein)	15	Severe dilution of coat and eye pigment	Solute transporter	*SLC45A2*	5p	Oculocutaneous albinism type 4
Tyr (*c*)	tyrosinase (color, albino)	7	No pigment in null mice	Melanosomal enzyme	*TYR*	11q21	Oculocutaneous albinism type 1
Tyrp1 (*b*)	tyrosinase-related protein 1 (brown, TRP1)	4	Brown eumelanin. Allele *isa* can contribute to glaucoma	Melanosomal enzyme	*TYRP1*	9p23	Oculocutaneous albinism type 3; glaucoma-related pigment dispersion syndrome
(D) Melanosome construction/protein routing (HPS-related)							
Ap3b1 (*pe*)	adaptor-related protein complex AP-3, β1 subunit (pearl)	13	Pigmentary dilution	Organellar protein routing	*AP3B1* [HPS2]	5q14.2	Hermansky–Pudlak syndrome, type 2
Ap3d (*mh*)	adaptor-related protein complex AP-3, delta subunit (mocha)	10	Pigmentary dilution	Organelle biogenesis; AP-3 component	*AP3D1*	19p13.3	N
Bloc1s3 (*rp*)	biogenesis of lysosome-related organelles complex 1, subunit 3 (reduced pigmentation)	7	Pigmentary dilution	Organelle biogenesis; BLOC1 component	*BLOC1S3*	19q13.32	Hermansky–Pudlak syndrome, type 8
Cno (*cno*)	cappuccino	5	Pigmentary dilution	Organelle biogenesis; BLOC1 component	*CNO*	4p16-p15	N

Dtnbp1 (*sdy*)	dystrobrevin binding protein 1 (sandy, dysbindin)	13	Sandy colored coat, platelet defect	Organelle biogenesis; BLOC1 component	*DTNBP1*	6p22.3	Hermansky–Pudlak syndrome, type 7
Fig4 (*plt1*)	FIG4 homolog (*Saccharomyces cerevisiae*) (pale tremor); phosphatidylinositol-(3,5)-bisphosphate 5-phosphatase	10	Pale color with tremor	Endosome-lysosome axis; clumped melanosomes (+immune effects, etc.)	*FIG4*	6q21	Charcot-Marie-Tooth disease
Gpr143 (*Oa1*)	G-protein-coupled receptor (GPR143); mouse homolog of human ocular albinism 1	X	Reduced eye pigmentation, giant melanosomes	Melanosome biogenesis and size; signal transduction	*OA1*	Xp22.3	Ocular albinism 1 (Nettleship-Falls)
Hps1 (*ep*)	Hermansky–Pudlak syndrome 1 homolog (pale ear)	19	Pale skin, slight coat dilution, giant melanosomes; platelet defect	Organelle biogenesis and size; BLOC3 component	*HPS1*	10q24	Hermansky–Pudlak syndrome, type 1
Hps3 (*coa*)	Hermansky–Pudlak syndrome 3 homolog (cocoa)	3	Hypopigmentation, platelet defect	Organelle biogenesis; BLOC2 component	*HPS3*	3q24	Hermansky–Pudlak syndrome, type 3
Hps4 (*le*)	Hermansky–Pudlak syndrome 4 homolog (light ear)	5	Pale skin, slight coat dilution, giant melanosomes; platelet defect	Organelle biogenesis and size; BLOC3 component	*HPS4*	22q11–q12	Hermansky–Pudlak syndrome, type 4
Hps5 (*ru2*)	Hermansky–Pudlak syndrome 5 homolog (ruby-eye 2)	7	Pigmentary dilution and red eyes; platelet defect	Organelle biogenesis; BLOC2 component	*HPS5*	11p14	Hermansky–Pudlak syndrome, type 5
Hps6 (*ru*)	Hermansky–Pudlak syndrome 6 homolog (ruby-eye)	19	Pigmentary dilution and red eyes; platelet defect	Organelle biogenesis; BLOC2 component	*HPS6*	10q24.31	Hermansky–Pudlak syndrome, type 6
Lyst (*bg*)	lysosomal trafficking regulator (beige)	13	Pale coat, immunodeficiency	Organelle biogenesis and size	*LYST*	1q42	Chediak-Higashi syndrome

Table A1.1 *(Cont'd)*

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Oca2 (*p*)	oculocutaneous albinism 2 (pink-eyed dilution)	7	Severe loss of eumelanin in hair, skin and eyes	?Glutathione transport in ER; melanosomal protein processing and routing	*OCA2*	15q11–q12	Oculocutaneous albinism type 2
Pldn (*pa*)	pallidin (pallid)	2	Pale coat, platelet defect	Organelle biogenesis; BLOC1 component	*PLDN*	15q15.1	N
Rab38 (*cht*)	RAB38, member RAS oncogene family (chocolate)	7	Brown eumelanin	Routing of Tyrp1 protein to melanosome	*RAB38*	11q14	N
Rabggta (*gm*)	Rab geranylgeranyl transferase, α subunit (gunmetal)	14	Coat dilution	Organelle biogenesis	*RABGGTA*	14q11.2	Choroideremia
Trappc6a	trafficking protein particle complex 6A	7	Pale patches in the coat and RPE	Protein trafficking	*TRAPPC6A*	19q13.32	N
Txndc5 (*mu*)	thioredoxin domain containing 5 (muted)	13	Pale pigment; platelet defect	Organelle biogenesis; BLOC1 component	*TXNDC5*	6p24–p25	N
Vps33a (*bf*)	vacuolar protein sorting 33a (buff)	5	Coat dilution	Organelle biogenesis	*VPS33A*	12q24.31	N
(E) Melanosome transport							
Mlph (*ln*)	melanophilin (leaden)	1	Silvery coat dilution, melanosomes cluster around nucleus	Melanosome transport	*MLPH*	2q37	N
Mreg (*dsu*, *Wdt2*)	melanoregulin (dilute suppressor, whn-dependent transcript 2)	1	Suppresses dilute phenotype (*Myo5a*$^{d/d}$)	Melanosome transport (interacts with Myo5a)	*MREG*	2q35	N
Myo5a (*d*)	myosin Va (dilute)	9	Silvery coat dilution, melanosomes cluster around nucleus	Melanosome transport	*MYO5A*	15q21	Griscelli syndrome
Myo7a (*sh-1*)	myosin VIIa (shaker-1)	7	Deafness, balance, head shaking	Melanosome transport (pigmented retina; ear?)	*MYO7A*	11q13.5	Usher syndrome, type 1B
Rab27a (*ash*)	RAB27A, member RAS oncogene family (ashen)	9	Silvery coat dilution, melanosomes cluster around nucleus	Melanosome transport	*RAB27A*	15q21	Griscelli syndrome

(F) Eumelanin and pheomelanin

a	agouti (or nonagouti)	2	Different alleles alter eumelanin/pheomelanin balance, either way	Eumelanin/pheomelanin switch	*ASIP*	20q11.2	N
Atrn (*mg*)	attractin (mahogany)	2	Pheomelanin darkened	Eumelanin/pheomelanin switch (among others)	*ATRN*	20p13	N
Drd2	dopamine receptor 2, allele *tm1mok*	9	Agouti color darkened; POMC level raised	Receptor	*DRD2*	1q23.1–23.2	N
Eda (*Ta*)	ectodysplasin-A (tabby)	X	Darkening of agouti pigment; striping in +/– females; deficient sweat gland and hair morphogenesis	Membrane-bound, ?TNF-related ligand	*ED1*	Xq12–q13	Ectodermal dysplasia, anhidrotic/hypohidrotic ectodermal dysplasia
Edaradd (*cr*)	ectodysplasin A receptor-associated death domain (crinkled)	13	Delayed hair growth, agouti coat darker dorsally, yellower laterally	Receptor	*EDARADD*	1q43	N
Ggt1	γ glutamyltranspeptidase 1	10	Reduced pheomelanin	Glutathione metabolism	*GGT loci* (several)	22q11	Glutathionuria
L1cam	L1 cell adhesion molecule, allele *tm1Sor*	X	Black fur patches on agouti	Cell adhesion	*L1CAM*	Xq28	X-linked hydrocephalus, MASA/Crash syndrome
Mc1r (*e*)	melanocortin 1 receptor (extension)	8	Different alleles alter eumelanin/pheomelanin balance, either way	Receptor	*MC1R*	16q24.3	Red hair
Mgrn1 (*md*)	mahogunin, ring finger 1 (mahoganoid)	16	Melanin color, CNS effects	E3 ubiquitin ligase	*MGRN1*	16p13.3	N
Ostm1 (*Gl*)	osteopetrosis associated transmembrane protein 1 (Grey-lethal)	10	Loss of pheomelanin; osteopetrosis	Pheomelanin and osteoclast function	*OSTM1*	6q21	Severe recessive osteopetrosis
Pomc	pro-opiomelanocortin-α	12	Minimal or no effect on phenotype in black mice	MSH precursor	*POMC*	2p23.3	Obesity and red hair

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Slc7a11 (*sut*)	solute carrier family 7 (cationic amino acid transporter, y+ system), member 11 (subtle gray)	3	Required for normal pheomelanin levels	Cystine transporter	*SLC7A11*	4	N
Smarca5	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5, allele MommeD4	8	Dominant mottled coat with $A^{y}/-$	Transcriptional regulator	*SMARCA5*	4q31.1–q31.2	N
Smchd1 (*MommeD1*)	SMC hinge domain containing 1	17	Affects the percentage of female yellow pups on A^{vy} background	Modifies imprinting, X-inactivation	*SMCHD1*	18p11.32	N
Sox2 (*ysb*)	SRY-box-containing gene 2 (yellow submarine)	3	Yellow hair, neural, deafness	Transcription factor; Sox2 regulates Notch1 in eye	*SOX2*	3q26.33	Microphthalmia, anophthalmia, neural and pituitary defects
Sox18 (*rg*, *Dcc1*)	SRY-box-containing gene 18 (ragged, dark coat color 1)	2	Dark coat in agouti mice, sparse hair	Transcription factor	*SOX18*	20q13.33	N
(G) Systemic effects							
Atox1	Antioxidant protein 1 homolog 1 (yeast)	11	Hypopigmentation	Copper transport	*ATOX1*	5q32	N
Atp7a (*Mo*)	ATPase, Cu^{2+}-transporting, α polypeptide (mottled)	X	Pale fur in hemizygous males, striped in heterozygous females	Copper transport	*ATP7A*	Xq13.2–q13.3	Menke's disease
Atp7b (*tx*)	ATPase, Cu^{2+}-transporting, β polypeptide (toxic milk)	8		Copper transport	*ATP7B*	13q14.3–q21.1	Wilson disease
Bcl2	B-cell leukemia/lymphoma 2	1	Early graying, loss of melanocyte stem cells	Inhibitor of apoptosis	*BCL2*	18q21.3	B-cell lymphoma

Casp3	caspase 3, allele *tm1Flv*	8	Abnormal RPE	Effector of apoptosis	*CASP3*	4q35.1	N
Dst (*dt*, *ah*)	dystonin, allele *dt-J*; (dystonia musculorum; athetoid)	1	Pale skin		*DST*	6p12.1	N
Elovl3	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 3, allele *tm1Jaco*	19	Abnormal hairs with scattered hyperpigmentation	Enzyme: fatty acid biosynthesis	*ELOVL3*	10q24.32	N
Elovl4	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/ Elo3, yeast)-like 4	9	Abnormal retinae including RPE	Enzyme: fatty acid biosynthesis	*ELOVL4*	6q14.1	Stargardt Disease 3
Ercc2	excision repair cross-complementing rodent repair deficiency, complementation group 2	7	UV-sensitivity, graying hair, reduced lifespan	DNA excision repair	*ERCC2*	19q13	Xeroderma pigmentosum, group D trichothiodystrophy, Cockayne syndrome
Fas	Fas (TNF receptor superfamily member 6)	19	Fewer strial melanocytes on certain background	Receptor mediating apoptosis	*FAS*	10q23.31	N
Heph (*sla*)	hephaestin; sex-linked anemia	X	abnormal pigment location in RPE	Regulates iron levels, including in RPE	*HEPH*	Xq12	N
Hs2st1	heparan sulfate 2-O-sulfotransferase 1	3	Abnormal RPE differentiation	Enzyme in heparan sulfate biosynthesis	*HS2ST1*	1p22.3	N
Oat	ornithine aminotransferase	7	Abnormal RPE cell morphology	Enzyme	*OAT*	10q26.13	Gyrate atrophy
Pah	phenylalanine hydroxylase	10	Effects include hypopigmentation, worsening with age	Tyrosine synthesis	*PAH*	12q3.2	Phenylketonuria
Pdpk1	3-phosphoinositide dependent protein kinase-1, allele *tm1Bcol*	17	Abnormal eye pigmentation	Phosphorylates and activates AKT kinase	*PDPK1*	16p13.3	N
Polg	polymerase (DNA directed), γ	7	General premature ageing including coat graying	DNA polymerase γ	*POLG*	15q26.1	Alpers syndrome

Table A1.1 (*Cont'd*)

Symbol (old symbol)	Name (old name)	Mouse chromosome	Mutant phenotype	Molecular/biological functions	Human symbol	Human chromosome	Human syndrome
Polh	polymerase (DNA directed), η (RAD 30 related)	17	Pigment (melanocyte?) accumulation in ear skin following UV irradiation	DNA polymerase η	*POLH*	6p21.1	Xeroderma pigmentosum, variant type
Pts	6-pyruvoyl-tetrahydropterin synthase	9	Coat dilution (low biopterin, high Phe)	Tetrahydrobiopterin synthesis	*PTS*	11q23.1	Phenylketonuria III
Rbp1	retinol binding protein 1, cellular	9	Abnormal RPE morphology	Intracellular transport of retinol	*RBP1*	3q23	N
Rpl24 (*Bst*)	ribosomal protein L24 (Belly spot and tail)	16	Eye, coat, skeletal	Protein synthesis	*RPL24*	3q12.3	N
Rps19 (*Dsk3*)	ribosomal protein S19 (Dark skin 3)	7	Defect gives p53 stabilization and SCF [KITL] synthesis in keratinocytes, hence dark skin with extra melanocytes	Protein synthesis	*RPS19*	19q13.2	Diamond-Blackfan anemia (DBA)
Rps20 (*Dsk4*)	ribosomal protein S20 (Dark skin 4)	4	As Rps19	Protein synthesis	*RPS20*	8q12.1	N
Rxra	retinoid X receptor α	2	Premature hair graying then hair loss	Retinoid receptor Regulation of diverse pathways	*RXRA*	9q34.2	N
Slc31a1	solute carrier family 31, member 1	4	Copper deficiency, hypopigmentation	Copper uptake into cells	*SLC31A1*	9q32	N
Vldlr	very low density lipoprotein receptor	19	Thickening and disruption of RPE	Lipid uptake into cells	*VLDLR*	9p24.2	Cerebellar hypoplasia and mental retardation

ACTH, adrenocorticotrophic hormone, corticotropin; AKT, oncogene isolated from transforming murine retrovirus AKT8 found in a thymoma cell line (=RAC=protein kinase B, PKB); CNS, central nervous system; EDNR, endothelin receptor; ER, endoplasmic reticulum; GPI, glycosylphosphatidylinositol; HDAC, histone deacetylase; KO, knockout; LEF, lymphoid-enhancer-binding factor; N, none known; NF-κB, nuclear factor κB; PLC, phospholipase C; POMC, pro-opiomelanocortin; RPE, retinal pigment epithelium; SCF, stem cell factor, also known as Kit ligand; TGFβ, transforming growth factor β; TNF, tumor necrosis factor; UV, ultraviolet; VEGF, vascular endothelial growth factor. We are greatly indebted to the Mouse Genome Informatics (MGI) and Online Mendelian Inheritance in Man (OMIM) websites for much of the information presented here (www.informatics.jax.org/, www.ncbi.nlm.nih.gov/sites/entrez?db=omim). A table like this placed in a book will inevitably become outdated quite soon; however, we hope that updated information about the mouse color genes will continue to be available at the IFPCS Color Genes resource (www.espcr.org/micemut). The site also has links to human and zebrafish orthologs, and to other useful resources.

Table A1.2 Summary of the uncloned mouse color genes

Symbol	Name	Chromosome	Effect or possible function
(A) Development?			
Alm	anterior lenticonus with microphthalmia	?	Defects of eye, coat, others
ao	apampischo	?	Hair loss then regrowth of darker, sparser hair
baln2	balance 2	?	Defects of eye, coat, neurological
baw	black and white	18	White ventrum, scattered white hairs dorsally
Bswt	belly spot with white toes	1	Belly spot, white hind toes
bt2	belted 2	?	White belt
crsp	cryptorchidism with white spotting	5	Coat and skin pigment, male reproductive system
cw	curly whiskers	9	CBA mice go darker. (Some lymphoma)
dds	dorsal dark stripe	15	Dorsal dark stripe
dkd	darkened dorsal	2	Dorsal dark stripe
Dph1	DPH1 homolog	11	Delayed embryonic eye pigmentation
Dwh	dispersed white hair	2	White hairs and patches throughout coat
Ednrbm1	endothelin receptor type B modifier 1 (QTL)	10	Modifies extent of spotting with $Ednrb^{s}$
Eed	embryonic ectoderm development	7	Diluted coat (dwarfism etc)
Exma	exencephaly and severe microphthalmia or anophthalmia	X	Patchy coat pigmentation, microphthalmia
fc	flecking	2	Belly spot, head spot
Fk	fleck	?	white on belly, tail, feet
gand	gandalf	?	Diluted coat, +ataxia etc, delayed lethal
Gn	gentoo	10	Belly spot, head spot
Gsfali029	gsf abnormal limbs mutant 029	?	Belly spot, polydactyly
Gsfali19	gsf abnormal limbs mutant 019	?	Belly spot, polydactyly
Gsfali20	gsf abnormal limbs mutant 020	?	Belly spot, polydactyly
Gsfdcc2	gsf dark coat colour 2	?	Belly spot, darker coat
Gsfkta19	gsf kinked tail 19	?	Belly spot, kinked tail
Gsfsco6	gsf spotted coat 6	?	Small head blaze
Gsfsco7	gsf spotted coat 7	?	Distal depigmentation, belly spot, white vibrissae

Table A1.2 *(Cont'd)*

Symbol	Name	Chromosome	Effect or possible function
Gsfund3	gsf undefined 3	?	White ring around tail
Gsfwbs011	gsf white belly spot 011	?	Belly spot
Gsfwbs1	gsf white belly spot 1	?	Belly spot, kinked tail
Gsfwbs3	gsf white belly spot 3	?	Large belly spot
Gsfwbs5	gsf white belly spot 5	?	Belly spot
Gsfwbs9	gsf white belly spot 9	?	Belly spot
Gsfwnw	gsf white nose and whiskers	?	White nose and vibrissae
Gsfwt	gsf white tail	?	White tail
Hpt	hair patches	4	Hair patchy and skin has patches of pigment; also cardiovascular defects, etc.
hs	head spot	?	Head spot
Idc	iris dysplasia with cataract	?	Eye abnormalities, microphthalmia, belly spot
Mtu	Montu	12	Fewer neural crest cells; belly spot, curly tail
Mwfh	modifier of white forelock hypopigmentation	10	Modifies phenotype of $Sox10^{Dom}$
Pbdl	piebald-like	?	Spotting, progressive dilution, megacolon
Ph	patch deletion region (patch)	5	White spotting; responsible gene in deletion uncertain; not *Pdgfra*; but KIT expression is altered
pwk	patchwork	10	Patchwork of pigmented and unpigmented hairs; autocrine growth of melanocytes?
rg	rotating	?	Ear development, neural, sometimes belly spot
Rgsc58	RIKEN Genomic Sciences Center (GSC), 58	?	White hairs, spots or band in dorsal lumbar region, varying with genetic background
Rgsc117	RIKEN Genomic Sciences Center (GSC), 117	?	Belly spot, domed skull, dominant (not all mice)
Rgsc257	RIKEN Genomic Sciences Center (GSC), 257	?	Scattered white hairs dorsally
Rgsc269	RIKEN Genomic Sciences Center (GSC), 269	?	White digits and tail tip, some white patches on belly
Rgsc288	RIKEN Genomic Sciences Center (GSC), 288	?	Patches of paler fur
Rgsc394	RIKEN Genomic Sciences Center (GSC), 394	?	Variable white digits and tail tip
Rgsc398	RIKEN Genomic Sciences Center (GSC), 398	?	Variable white digits and tail tip
Rgsc444	RIKEN Genomic Sciences Center (GSC), 444	?	Variable number of white spots on tail

Rgsc510	RIKEN Genomic Sciences Center (GSC), 510	?	Variable white digits and tail tip
Rgsc662	RIKEN Genomic Sciences Center (GSC), 662	?	Abnormal digit pigmentation and white tail tip
Rgsc713	RIKEN Genomic Sciences Center (GSC), 713	?	White distal feet and tail tip, sometimes belly spot
Rgsc755	RIKEN Genomic Sciences Center (GSC), 755	?	White toe tips and tail tip
Rgsc767	RIKEN Genomic Sciences Center (GSC), 767	?	White toe tips and tail tip
Rgsc990	RIKEN Genomic Sciences Center (GSC), 990	?	White toe tips and tail tip
Rgsc1246	RIKEN Genomic Sciences Center (GSC), 1246	?	Coat dilution especially ventrally; some white spotting.
Rgsc1461	RIKEN Genomic Sciences Center (GSC), 1461	?	White belly spot, skeletal changes
Rgsc1513	RIKEN Genomic Sciences Center (GSC), 1513	?	Dilution dorsally, gray fur ventrally (even in *A*/–), some belly spotting
Rgsc1520	RIKEN Genomic Sciences Center (GSC), 1520	?	White digits, tail tip, belly spot
Rgsc1545	RIKEN Genomic Sciences Center (GSC), 1545	?	Belly spot
Rgsc1554	RIKEN Genomic Sciences Center (GSC), 1554	?	Belly spot
Rgsc1658	RIKEN Genomic Sciences Center (GSC), 1658	?	Scattered white hairs, some color dilution
Rgsc1742	RIKEN Genomic Sciences Center (GSC), 1742	?	Belly spot
Rgsc1843	RIKEN Genomic Sciences Center (GSC), 1843	?	Variable scattered white spots in females
Rgsc1855	RIKEN Genomic Sciences Center (GSC), 1855	?	Belly spot
rn	roan	14	Micro-spotting, whole coat
rs	recessive spotting	5	Micro-spotting (reduced melanocyte numbers); interacts with Kit
rslk	recessive spotting-like	5	Gray coat, head and/or belly spot, white spots
Shmu	shamu	9	White feet, belly spot, head spot
Ska7	skeletal/axial 7	?	Large belly spot and skeletal defects
Skc42	skin/coat color 42	?	Sharply delineated white belly
Skc43	skin/coat color 43	?	White belly patch and tail
skc44	skin/coat color 44	?	White belt, sometimes spotting
Sls	semidominant lethal spotting	2	Semidominant spotting; may be allelic to Edn3
smk	smoky	?	Gray coat on a/a, with reproductive system defects
stn	stunted	19	Belly spot, altered facial skeleton
Stol	stripy oily	X	Stripy in heterozygote, dark in homo- and hemizygote; oily hair; microphthalmia
Strx2	striated, X-linked 2	X	Striped fur, thick skin in +/–, lethal in –/Y
Strx3	striated, X-linked 3	X	Striped fur, thick skin in +/–, lethal in –/Y
Strx4	striated, X-linked 4	X	Striped fur, scaly skin in +/–, lethal in –/Y

Table A1.2 *(Cont'd)*

Symbol	Name	Chromosome	Effect or possible function
Tcm	total cataract with microphthalmia	4	Microphthalmia, abnormal iris, lens, retina
tga	transposition of the great arteries	4	Ectopic pigmentation in heart and thoracic cavity
tmgc17	Tennessee Mouse Genome Consortium 17	X	Belly spot, syndactyly
Tmgc19	Tennessee Mouse Genome Consortium 19	?	Belly spot, other spotting, postnatal dominant lethal
Tmgc21	Tennessee Mouse Genome Consortium 21	?	Belly spot, other spotting, white feet
tp	taupe	7	Diluted color, female reproductive system
Ts	tail-short	11	Belly spot, white distal forelimbs; deficiencies of skeleton, blood, growth, etc.
vs	variable spotting	9	Spotting on belly, head, tail, feet
Vss	variable spot and size	2	Variable belly spot, small size
Wbct	white belly, claws and tail	1	Variable spotting of belly, feet, tail
Whto	white toes	7	Color, digit development
wn	white nose	15	White nose, ventral streak
Wtgr	wavy tiger	X	Coat striped and wavy; reproductive defects
Xls	*X*-linked stripe	X	Coat striping, 1 white spot on left flank
Xs	extra-toes spotting	7	Color, digit development
Xsl	extra-toes spotting-like	7	Extra toes, belly spot
(B) Melanocyte function only?			
brwd	brownoid	?	Melanin color (brown)
Cal7	caracul-like 7	15	Pale skin and eyes
dj	dilution Japan	?	Pink skin, gray coat (a/a)
dp	dilution-Peru	15	Pale coat
plto	platino	?	Off-white coat, black eyes; not Tyr
powder	powder	?	Pale coat
rgsc1820	RIKEN Genomic Sciences Center (GSC), 1820	?	No pigment, albino
Rgsc1904	RIKEN Genomic Sciences Center (GSC), 1904	?	Coat color dilution
ru2l	ruby-eye 2-like	7	Like ru2; gray coat, pale skin, red eyes

sea	sepia	1	Coat color dilution
skc14	skin/coat color 14	?	Pale coat
skc19	skin/coat color 19	?	Pale coat
skc21	skin/coat color 21	?	Pale coat when young; white guard hairs
skc22	skin/coat color 22	?	Pale coat when young; white guard hairs, red eyes
skc23	skin/coat color 23	?	Pale coat when young; dark red eyes
skc28	skin/coat color 28	?	Silver coat
skc29	skin/coat color 29	?	Silver coat
skc30	skin/coat color 30	?	Coat silvering, melanocyte death
skc31	skin/coat color 31	?	Coat silvering, melanocyte death
Skc36	skin/coat color 36	?	Mottled coat in female
titanm	titanium	?	Pale coat
tmgc14	Tennessee Mouse Genome Consortium 14	?	Diluted coat
Tmgc18	Tennessee Mouse Genome Consortium 18	?	Diluted coat, dominant
uwl	underwhite-like	15	Ruby-eyed cream; possible uw (Slc45a2) allele

(C) Eumelanin and pheomelanin?

Cdif	color difference (QTL)	15	Modifies yellow coat color
da	dark	7	Pheomelanin deficient
dal	dark-like	7	Like dark
din	dense incisors	16	Loss of pheomelanin/white belly on agouti background; loss yellow on ears
Dmyaq1	darker modification of yellow agouti QTL 1	1	Darkening of yellow and agouti coats
Dmyaq2	darker modification of yellow agouti QTL 2	1	Darkening of yellow and agouti coats
Dmyaq3	darker modification of yellow agouti QTL 3	15	Darkening of yellow and agouti coats
dwg	dwarf grey	10	Multiple effects, including deficient pheomelanin, osteoclasts
gdn	golden	?	Eumelanin deficient
gr	grizzled	10	Pheomelanin deficient; tail
gri	grey intense	11	Pheomelanin deficient
gt	gray tremor (probably extinct)	15	Pheomelanin deficient; spotting, neurological
Och	ochre	4	Deficient eumelanin, balance, other

Table A1.2 *(Cont'd)*

Symbol	Name	Chromosome	Effect or possible function
Pheo	pheomelanin (QTL)	15	Modifies color of $A^{y}/-$ mice; more eumelanic allele dominant
Reph8	reduced pheomelanin 8	?	Agouti mice darker
skc17	skin/coat color 17	?	Dark back
U	umbrous	?	Dorsal pheomelanin darkened
Up	umbrous-patterned	?	Dorsal pheomelanin darkened (patchy)
Ym	yellow mottled	X	Yellow mottling, hemizygous lethal
Yv	yellow value (QTL)	15	Modifier of eumelanin/pheomelanin ratio
(D) Organelle biogenesis or transport?			
dill	Dilute-like	?	Like dilute
rgsc80	RIKEN Genomic Sciences Center, 80	?	Diluted coat, interacts with *Myo5a*^{d}
skc6	skin/coat color 6	?	Pale coat, lysosomal storage defect, long hair
skc9	skin/coat color 9	?	Pale coat, lysosomal storage defect
skc10	skin/coat color 10	?	Pale coat, lysosomal storage defect
skc12	skin/coat color 12	?	Pale coat, lysosomal storage defect
skc15	skin/coat color 15	?	Pale skin
(E) Dark skin			
Dfp	dark foot pads	?	Dark skin
Dfp2	dark foot pads 2	4	Dark skin
Dsk6	dark skin 6	3	Dark skin
Dsk8	dark skin 8	3	Dark skin
Dsk9	dark skin 9	11	Dark skin
Rgsc45	RIKEN Genomic Sciences Center, 45	?	Gray-pigmented footpads with thickened epidermis
Rgsc63	RIKEN Genomic Sciences Center, 63	?	Slightly dark hind footpads
Rgsc150	RIKEN Genomic Sciences Center, 150	?	Dark footpads
Rgsc183	RIKEN Genomic Sciences Center, 183	?	Dark footpads

Rgsc194	RIKEN Genomic Sciences Center, 194	?	Slightly dark footpads
Rgsc207	RIKEN Genomic Sciences Center, 207	?	Pigmented dermatoglyphs of footpads
Rgsc372	RIKEN Genomic Sciences Center, 372	?	Dark footpads
Rgsc515	RIKEN Genomic Sciences Center, 515	?	Dark footpads
Rgsc526	RIKEN Genomic Sciences Center, 526	?	Dark footpads
Rgsc715	RIKEN Genomic Sciences Center, 715	?	Slightly dark footpads
Skc39	skin/coat color 39	?	Dark skin
Skc41	skin/coat color 41 (blackfoot)	?	Dark skin
soo	sooty foot	2	Dark skin

(F) Unknown

Dlp1	dominant lightened pigment 1	?	Lighter coat, sometimes slight belly spot
Dlp2	dominant lightened pigment 2	?	Lighter coat
Dlp3	dominant lightened pigment 3	?	Much lighter coat
fe	faded	6	Progressive coat fading
fnld	faint lined	X	Hemizygous lethal; fine dorsal striping
Fw	fawn	?	Lightens *Rn* mutant mice
ge	greige	1	Paler coat and skin in dilute, brown mice
Gsfbcc2	gsf bright coat colour 2	?	Complex coat color variation
lgr	London grey	?	Gray coat, systemic effects
Lgt (*Li*)	light	?	Light coat (dominant), light skin (recessive)
Li	lined	X	Hemizygous lethal; fine striping; deletion that includes *Rsk2*
Mch	modifier of chinchilla	?	$Tyr^{c\text{-}ch}$ mice look browner
Mchm1	modifier of chinchilla-mottled 1	?	Lightens $Tyr^{c\text{-}m}$ mice
Mchm2	modifier of chinchilla-mottled 2	?	Lightens $Tyr^{c\text{-}m}$ mice
Mfs	mutant fur is striped	?	'Striped fur'
nmf192	neuroscience mutagenesis facility, 192	?	Spotted or mottled retinae
nur15	neurological 15	?	Diluted coat (and neural effects, early lethal)
nur16	neurological 16	?	Diluted coat (and neural effects, early lethal)
nur17	neurological 17	?	Diluted coat (and neural effects)
Rd4	retinal degeneration 4	4	Eye defects include pigmented spots in the fundus

Table A1.2 *(Cont'd)*

Symbol	Name	Chromosome	Effect or possible function
Rd9	retinal degeneration 9	X	Retina mottled and degenerates
rdp	reduced pigment (not same as rp/Bloc1s3)	?	Marked pigment dilution, red eyes
Rgsc71	RIKEN Genomic Sciences Center, 71	?	Dilution dorsally (dominant), gray belly, sometimes belly spot
Rgsc212	RIKEN Genomic Sciences Center, 212	?	Black rostrally and brown caudally of a mid-trunk demarcation line
Rgsc547	RIKEN Genomic Sciences Center, 547	?	Patch of brown fur between the eyes, by 8 weeks old
Rgsc796	RIKEN Genomic Sciences Center, 796	?	Slight coat dilution (dominant) and behavioral changes
skc18	skin/coat color 18	?	Abnormal coat color, small size
Skc45	skin/coat color 45	?	'Shading of coat in animals expected to be white'
Sta	autosomal striping	X	Striping in both sexes
Sta2	striping, autosomal 2	?	Striped coat
Sta3	striping, autosomal 3	?	Striped coat
Strg	striped greasy	X	Hair texture and color
tmgc22	Tennessee Mouse Genome Consortium 22	7	Abnormal RPE, choroid
tmgc23	Tennessee Mouse Genome Consortium 23	7	RPE hyperpigmented around optic disk
tmgc25	Tennessee Mouse Genome Consortium 25	7	Abnormal RPE, hypopigmented fundus
tmgc29	Tennessee Mouse Genome Consortium 29	7	Like tmgc25
wuf	white under fur (extinct?)	?	Underfur white
Xmo2	X-linked mottled 2	X	Mottled coat; hemizygous lethal
Xmo3	X-linked mottled 3	X	Mottled coat; hemizygous lethal
Xmo4	X-linked mottled 4	X	Mottled coat; hemizygous postnatal lethal, pale coat
Xmo5	X-linked mottled 5	X	Mottled coat; hemizygous lethal
Xmo6	X-linked mottled 6	X	Mottled coat; hemizygous lethal

QTL, quantitative trait locus; RPE, retinal pigment epithelium. Categories and functions are generally provisional or speculative.

Figure 1.17 Studs Terkel, Mahonia, and Postdoc (left to right). Terk may have a mutation at the *Silver* locus (see Chapter 4). Mahonia is pheomelanic, often known as chestnut or sorrel (probable genotype $Mc1r^{e}/Mc1r^{e}$). Postdoc is the horse equivalent of wild type, known as bay or brown, depending on the amount of eumelanic pigment. Note that the mane, tail, and legs are eumelanic, and the pheomelanic pigmentation on the body varies from bright red/yellow to dark and nearly eumelanic, in response to modifying genes.