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Review – Pigment Gene Focus

The Color Loci of Mice – A Genetic Century

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Color loci in mammals are those genetic loci in which mutations can affect pigmentation of the hair, skin, and/or eyes. In the mouse, over 800 phenotypic alleles are now known, at 127 identified color loci. As the number of color loci passed 100 only recently, we celebrate this 'century' with an overview of these loci, especially the 59 that have been cloned and sequenced. These fall into a number of functional groups representing melanocyte development and differentiation, melanosomal components, organelle biogenesis, organelle transport, control of pigment-type switching, and some systemic effects. A human ortholog has been identified in all cases, and the majority of these human genes are found to be loci for human disorders, often affecting other body systems as well as pigmentation. We expect that a significant number of color loci remain to be identified. Nonetheless, the large number known already provide a treasury of resources for reconstruction of the mechanisms, at the subcellular, cellular and tissue levels, that produce a functional pigmentary system and contribute to the normal development and functioning of many other organ systems. The mutant mice also provide valuable models for the study of human disease.

Key words: Color genes, Mouse genetics, Human genetics, Pigmentary disorder, Melanocyte development, Melanosomal proteins, Protein routing

INTRODUCTION

In 1979, WK Silvers made the remark, while introducing his invaluable and influential book 'The Coat Colors of Mice' (1), that the known mouse coat color mutations then included over 130 determinants (phenotypic alleles) at over 50 loci. These figures were impressive enough and were much quoted, yet the numbers have risen progressively since then. In 2003, by our estimate, the number of published mouse color loci has passed 100. Accordingly, this seems an ideal moment to take stock of our current knowledge of this 'century' of mouse color loci, or at least a snapshot of the rapidly changing landscape. The number of loci, indeed, has now leaped up to 127, partly through results emerging from the large-scale chemical mutagenesis screens now under analysis in several countries (2, 3). The total number of alleles at these loci has now exceeded 800 (2, 4). Clearly, this short review can give only the briefest summary of this now massive field. We will concentrate on an overview, and on some of the most recent developments. We will be selective with literature citations, as the main references on each mouse and human locus can be found readily in Mouse Genome Informatics (2) and OMIM (5), respectively.

By color loci, we mean genetic loci affecting the pigmentation of an animal, more specifically of the hair, skin and/or eyes. This excludes effects that do not involve the pigmentary system, for example pale skin color because of anemia. It does not exclude genes that affect pigmentation only incidentally, because their mutations damage skin or hair growth. This is because in general one can only guess that that is the case, and it is hard to prove that there is no regulatory effect on pigmentation. As frequently remarked,

Abbreviations – AP3, adaptor protein 3; ASP, agouti signal protein; BLOC, biogenesis of lysosome-related organelle complex; CHS, Chediak–Higashi syndrome; HPS, Hermansky–Pudlak syndrome; MSH, melanocyte-stimulating hormone; POMC, pro-opiomelanocortin; RPE, retinal pigment epithelium

pigment cells make an ideal system for genetic analysis, because pigmentary mutations are readily identified in living animals, and are frequently non-lethal and thus easy to select and breed. (The only color genes that may be harder to identify are those involved solely in pigmentary responses to a stimulus, such as ultraviolet light. These would not be found in screens without applying the relevant stimulus.) It is possible that we will attain a complete description of the molecular-genetic control of this lineage and its development and function before any other mammalian lineage. Progress in our molecular understanding has surged ahead since 1979. None of Silvers 50 loci were cloned, whereas now 59 or nearly half of the known genes have been cloned (2; Table 1). This number is rising with increasing speed, a rise now facilitated by the extensive mouse and human genome sequence databases. In that connection, all of the color genes cloned in either the mouse or the human to date have proved to have an ortholog in the other species (2, 4, 5), and we can expect that most of them will be common to all mammals. The correspondence with other vertebrate families such as fish is lower, although extensive (6).

The cloned color loci fall into functional sets (Fig. 1; Table 1), partly anticipated by Silvers, reflecting the several discrete processes required to generate pigment cells and their pigment. By discussing these sets in turn, we will analyze what this wealth of information can tell us to date about these different processes, and also about how these may go wrong in human pigmentary disorders (see 7 for a recent review). Table 1 summarizes all of these cloned color loci, and the functional sets discussed below. The table gives 'old' symbols and names as well as current ones. This is because the name is frequently changed when the gene is cloned, to reflect the discovered function or gene product (e.g. *Edn3*) or to follow human terminology (e.g. *Hps1*); but the old name is often useful in relating the newer to the older literature. There also remain a large number, 68, of uncloned color loci (Table 2), many of which have been reported in the last few years, although others such as *misty* have been long-standing mysteries. We have attempted to categorize these too according to putative function, using the mutant phenotypes, although these categories must be taken as provisional. We have also assembled brief summaries of the more specific apparent function or effect of each of these loci, for reference. For reasons of space, we will not consider these uncloned loci in any more detail here, but we are confident that they will progressively be transferred to the cloned category, becoming in turn the topical genes of future years.

MELANOCYTE DEVELOPMENT AND DIFFERENTIATION – THE SPOTTING LOCI

The first step toward making melanin (in mammals) is development of the relevant cells. These are melanocytes and retinal pigment epithelium (RPE) cells, not usually called melanocytes, although they make very similar melanosomes (pigment granules) and share many of the same gene products. All mammalian melanocytes other than RPE cells are derived from the neural crest in the early embryo (Fig. 1). From there, they normally migrate to all of the epidermis and hair follicles, and also to the iris and choroid of the eye, the inner ear and to other internal organs in some mammals (1, 8–10). [As an aside, melanocytes are required for normal hearing, and a recent report may explain this. In the inner ear, only melanocytes express the Kir4.1 potassium channel, required for establishment of the endocochlear potential (11).]

Many, perhaps all, of the loci required for development of integumental melanocytes are spotting loci (12) (Tables 1a, 2a). In other words, their mutations produce congenital patches of white hair and skin (piebaldism) when either homozygous or heterozygous. Melanocytes appear absent from the white areas. This may result from a failure of migration, division or differentiation, but most commonly seems to reflect death of melanoblasts, at a specific time of development when the specific gene product is required (1, 8, 12). Some spotting genes also affect melanocyte survival after birth. Gene action may be within the melanoblast or melanocyte, or in its environment (for example growth-factor and ligand pairs; Table 1a). Some genes seem to be required for pigmentation of a specific region or compartment of the skin such as a lumbar 'belt' – for example *bt* or belted (Fig. 2M), now *Adamts20*^{bt} (see below). Different loci affect different regions (see 1, 8 for discussion). Other genes affect the entire skin or coat. In some cases (depending on the mutation), some melanoblasts in the affected areas seem to survive randomly and then proliferate to produce pigmented patches, as seen with *Ednrb*^{s} or *Edn3*^{ls} (7, 13) and others (Fig. 2J,L,M). At the *Kit* and *Mitf* loci (more below), some mutant alleles will produce such spotting when heterozygous, and a complete absence of any neural crest-derived melanocytes when homozygous (Fig. 2I) (1, 2). The phenotypes produced by a given genotype can vary widely with mouse genetic background (Fig. 2J–L), showing the importance of congenesis with a consistent background in the description of phenotypes, and also revealing the existence of modifying genes that vary between strains (12). These genes can be mapped and eventually identified, and may prove to act in similar pathways to the color genes that they interact with.

Of the genes required for melanocyte development, the first few to be cloned were found to consist of growth or survival factors, receptors for such factors, and transcription factors (Table 1a). This revealed the first nodal points at which this cell lineage and its differentiation can be controlled: transcription and cell–cell signaling. This was perhaps not surprising, but still illuminating. The first spotting gene to be cloned, the stem cell factor receptor and proto-oncogene *Kit*, formerly *W* (white spotting), has now accumulated 75 mutant alleles (2) (for example Fig. 2J–L). Human *KIT* mutations have been identified in piebald syndrome (14). See (10) for a review of the spotting genes and their molecular interactions up to 2000, with emphasis on the key transcription factor Mitf. Here we will highlight more recent work. The spotting genes cloned most recently do include further transcription factor genes – *Lmx1a* (formerly *dr*, dreher, with a phenotype resembling belted) (15), *Sox18* (*rg*, ragged or *dcc1*, dark coat color 1) (3, 16), and *Snai2* (Snail 2 or Slug), recently reported as a new locus for Waardenburg syndrome 2 in humans (similar effects to *MITF* mutations) (17). Snai2 also interacts with Kit signaling (18). Other new members in this group have expanded the repertoire of types of function,

to include for example genes for a membrane carrier protein, *Sfxn1 f*, flexed-tail) (19); the (apparent) cation channel mucolipin 3 (*Mcoln3*, formerly *Va*, varitint-waddler) (20), and two metalloproteases of the ADAM family. One is the cell-surface disintegrin and protease Adam17 (2, 21). Adam17 protease activates several other interesting molecules including tumor necrosis factor, transforming growth factor α and Notch1 (2, 5, 21). This suggests several possible routes for its requirement in melanocyte development, although Adam17 also acts in epidermal development, so its effect may instead be indirect. The other ADAM protein is the novel family member Adamts20, site of the *belted* mutation (Fig. 2M). This metalloprotease appears to be secreted by cells other than melanoblasts, and to act in melanoblast migration, possibly by modifying extracellular matrix (22). The requirement for Adamts20 may be specific to the lumbar (belt) region, or may be more extensive, depending whether the known mutations prove to be null or hypomorphic.

Another interesting addition is the signaling kinase inhibitor *Ikbkg* (inhibitor of κB kinase γ), or NEMO (NFκB essential modulator), required for NFκB signaling. Mutations in the X-linked human *IKBKG* gene are generally prenatally lethal in males, attributed to high rates of cell apoptosis, and cause incontinentia pigmenti in heterozygous females (23). This disorder affects the CNS and the skin and its appendages, with inflammation, rash and 'incontinent' spread of melanin into the dermis, in stripes where the mutant X-chromosome is active. Knockout of mouse *Ikbkg* can produce similar symptoms in mice (24). The dermal melanin is found in phagocytic cells (24), suggesting either death of melanocytes or incorrect routing of melanosomes. This seems to implicate NFκB signaling in melanocyte survival or function. The requirement may however be either direct, or mediated through the observed skin inflammation and excessive proliferation and apoptosis of keratinocytes, or both. The reported correspondence of the striping pattern in humans to the lines of Blaschko (25) is more consistent with the expected distribution of epidermal clones (in the X-inactivation mosaic) than melanocytic clones, and supports an indirect effect via the epidermis.

Intensive study is beginning to illuminate the developmental actions and interactions of all these spotting genes (9). Nonetheless, much work remains to be carried out to complete our functional understanding even of what seems to be the 'master control gene' activating melanocyte differentiation, *Mitf* or microphthalmia-related transcription factor (9, 26, 27). For example, there is evidence that Mitf expression does not require Kit expression (26), that Kit signaling can nonetheless activate Mitf by phosphorylation (27), and that Mitf expression is required, not for minimal Kit expression but for up-regulation beyond that [literature cited in (26)]. If the latter two are correct, it gives a positive feedback loop, a known general mechanism for stabilizing cell differentiation. This gives a potential basic framework, but we still need to fit many other molecular interactions (9, Table 1a) into this framework, and identify the key extracellular signals, to achieve an integrated understanding of how the whole program of melanocyte differentiation is normally initiated and stabilized.

MELANOSOMAL COMPONENTS

Some of the best-known color genes are among those encoding components of the melanosome or pigment organelle (Fig. 1B; Table 1b; Fig. 2D–H; Fig. 3F–H). Most of these gene products are found only in eumelanosomes, containing eumelanin (black to brown melanin), although tyrosinase is also in pheomelanosomes, which make pheomelanin (red to yellow melanins). The investigation of other proteins in pheomelanosomes is one of the field's current challenges. Genetic analysis has clarified the distinctions between the known (eu)melanosomal enzymes, although there are still some debates about their functions in different mammals. *Tyrp1* (tyrosinase-related protein 1, originally TRP1) was the first of all the color genes to be cloned, by Shibahara et al. (28) in 1986, initially as a candidate for tyrosinase itself, the rate-limiting enzyme for melanin synthesis. The identity of *Tyrp1* was clarified soon afterward, with the cloning of authentic human and mouse tyrosinase (*TYR, Tyr*) sequences (29, 30). Completion of these sequences was followed rapidly by the identification of tyrosinase mutations in human oculocutaneous albinism type 1 (31, 32) and the common albino mouse (33). This was another landmark, the identification of the first color mutation in human and mouse. Among the color genes, mouse *Tyr* holds the current record for the highest number of reported phenotypic alleles, at 102 (2) (e.g. Fig. 2F–H), closely followed by *a* (non-agouti or agouti, see below) at 97, and exceeded among all mouse loci only by the t-complex with 124 alleles. Moreover the t-complex is a large chromosomal region rather than a single gene. If the t-complex is excluded, then the nine mouse loci with the most known phenotypic alleles are color genes (2; P. Szauter, Jackson Laboratory, personal communication). Tyrp1 was identified as a protein related to Tyr, proving to be the product of the mouse *b* or brown locus, mutated in brown mice (Fig. 3G), and thus needed for the production of black pigment. It has been identified as a DHICA oxidase in the mouse (34), although its role may be different in humans (35).

A number of other melanosomal components have been well characterized to date, as reviewed by Hearing (36). We will pick out only one or two threads here. One is the apparent approach of an answer to a long-running puzzle. This is the function of silver protein (si, SILV), also known as Pmel17, gp100 (human)/gp87 (mouse), and tumor antigens ME20, HMB45, HMB50, and NKI-beteb (37, 38). The silver mutation in mice, which causes hair silvering through melanocyte loss in vivo (1), is predicted to misdirect the silver protein away from the melanosomes (37). Mutation appears to darken cultured melanocytes, and reduce their growth and viability (39). There is now evidence that this protein is required to generate the striations or matrix seen in normal eumelanosomes (40). These 'striations' (which in three dimensions probably take the form of rolled, pleated or stacked sheets, as judged by the appearance of transverse sections of immature melanosomes) appear to provide a binding surface for melanin accumulation, and may play a part in both stabilizing and trapping melanin intermediates as they are produced. Silver protein is proposed to control the formation of the striations, and perhaps to be a major

Table 1. Summary of the cloned mouse color genes

Symbol (old symbol)	Name (old name)	Chromosome	Function	Human symbol	Human chr'some	Syndrome
(a) Melanocyte development						
Adam17	A disintegrin and metalloprotease domain 17	12	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	Metalloprotease. Melanoblast migration?	*ADAMTS20*	12q12	N
Brca1	Breast cancer 1	11	Development of various organs; tumor suppressor	*BRCA1*	17q21	BC
Eda (Ta)	Ectodysplasin-A (tabby)	X	Sweat gland, tooth and hair morphogenesis	*ED1*	Xq12-q13	EDA/HED
Edn3 (ls)	Endothelin 3 (lethal spotting)	2	Growth and differentiation factor	*EDN3*	20q13	HD, WSS
Ednrb (s)	Endothelin receptor type B (piebald spotting)	14	Growth factor receptor	*EDNRB*	13q22	HD, WSS
Egfr (Dsk5)	Epidermal growth factor receptor (dark skin 5)	11	Growth factor receptor	*EGFR*	7p12.3	N
Fgfr2	Fibroblast growth factor receptor 2	7	Growth factor receptor	*FGFR2*	10q26	CrS, PfS
Ikbkg	Inhibitor of κB kinase, γ subunit (NEMO)	X	IκB kinase. Required for NFκB signaling	*IKBKG*	Xq28	IP, HED-ID, EDA-ID
Kit (W)	Kit oncogene (white spotting)	5	Growth factor receptor	*KIT*	4q11-q12	PS
Kitl (Sl)	Kit ligand (steel)	10	Growth and differentiation factor	*KITLG*	12q22	N
Krt2–17 (Dsk2)	Keratin 2–17 (dark skin 2)	15	Cytoskeleton	*KRT2A*	12q11-q13	IBS
Lmx1a (dr)	LIM homeobox transcription factor 1α (dreher)	1	Transcription factor	*LMX1A*	1q22–23	N
Mcoln3 (Va)	Mucolipin 3 (varitint-waddler)	3	Cation channel	*MCOLN3*	1p22.3	N
Mitf (mi)	Microphthalmia-associated transcription factor (microphthalmia)	6	Transcription factor	*MITF*	3p12–14	WS2
Pax3 (Sp)	Paired box gene 3 (splotch)	1	Transcription factor	*PAX3*	2q35	WS1, WS3
Sfxn1 (f)	Sideroflexin 1 (flexed tail)	13	Tricarboxylate carrier	*SFXN1*	5q35.3	N
Snai2	Snail homolog 2/Slug	16	Transcription factor	*SNAI2*	8q11	WS2
Sox10 (Dom)	SRY-box containing gene 10 (dominant megacolon)	15	Transcription factor	*SOX10*	22q13.1	WSS
Sox18 (rg, Dcc1)	SRY-box containing gene 18 (ragged, dark coat color 1)	2	Transcription factor	*SOX18*	20q13.33	N
Wnt1	Wingless-related MMTV integration site 1	15	Growth factor/morphogen	*WNT1*	12q13	N
Wnt3a	Wingless-related MMTV integration site 3A	11	Growth factor/morphogen	*WNT3A*	1q42	N
(b) Components of melanosomes and their precursors						
Dct (slt)	Dopachrome tautomerase (slt)	14	Melanosomal enzyme	*DCT*	13q31-q32	N
Gpnmb	Glycoprotein (transmembrane) NMB	6	Apparent melanosomal component	*GPNMB*	7p15	N
Matp (uw)	Membrane-associated transporter protein (underwhite)	15	Apparent transporter	*MATP*	5p	OCA4
Rab38 (cht)	RAB38, member RAS oncogene family (chocolate).	7	Targeting of Tyrp1	*RAB38*	11q14	N
Si (si)	Silver (silver)	10	Melanosome matrix	*SILV*	12q13-q14	N
Tyr (c)	Tyrosinase (color, albino)	7	Melanosomal enzyme	*TYR*	11q21	OCA1
Tyrp1 (b)	Tyrosinase-related protein 1 (brown)	4	Melanosomal protein	*TYRP1*	9p23	OCA3
(c) Melanosome construction/protein routing (HPS-related)						
Ap3b1 (pe)	Adaptor-related protein complex AP-3, β 1 subunit (pearl)	13	Organellar protein routing	*AP3B1* [HPS2]	15q15	HPS
Ap3d (mh)	Adaptor-related protein complex AP-3, δ subunit (mocha)	10	Organellar protein routing	*AP3D1*	19p13.3	N
Vps33a (bf)	Vacuolar protein sorting 33a (buff)	5	Organellar protein routing	*VPS33A*	12q24.31	N
cno (cno)	Cappuccino	5	Organelle biogenesis	*CNO*	4p16-p15	N
Hps1 (ep)	Hermansky-Pudlak syndrome 1 homolog (pale ear)	19	Organelle biogenesis and size	*HPS1*	10q24	HPS
Hps3 (coa)	Hermansky-Pudlak syndrome 3 homolog (cocoa)	3	Organelle biogenesis	*HPS3*	3q24	HPS
Hps4 (le)	Hermansky–Pudlak syndrome 4 homolog (light ear)	5	Organelle biogenesis and size	*HPS4*	22q11-q12	HPS
Hps5 (ru2)	Hermansky–Pudlak syndrome 5 homolog (ruby-eye 2)	7	Organelle biogenesis	*HPS5*	11p14	HPS
Hps6 (ru)	Hermansky–Pudlak syndrome 6 homolog (ruby-eye)	19	Organelle biogenesis	*HPS6*	10q24.31	HPS
Lyst (bg)	Lysosomal trafficking regulator (beige)	13	Organelle biogenesis and size	*LYST*	1q42	CHS

Muted (mu)	Muted (muted)	13	Organelle biogenesis	*MU*	6p25-p24	N
Oa1	Mouse homolog of human ocular albinism 1 (Nettleship-Falls)	X	Melanosome biogenesis and size	*OA1*	Xp22.3	OA
p	Pink-eyed dilution	7	?Glutathione transport in ER. Melanosomal protein processing and routing.	*P*	15q11-q12	OCA2
Pldn (pa)	Pallidin (pallid)	2	Organelle biogenesis	*PLDN*	15q15.1	N
Rabggta (gm)	Rab geranylgeranyl transferase, α subunit (gunmetal)	14	Organelle biogenesis	*RABGGTA*	14q11.2	Ch
(d) Melanosome transport						
Mlph (ln)	Melanophilin (leaden)	1	Melanosome transport	*MLPH*	2q37	N
Myo5a (d)	Myosin Va (dilute)	9	Melanosome transport	*MYO5A*	15q21	GS
Myo7a (sh-1)	Myosin VIIa (shaker-1)	7	Melanosome transport (pigmented retina)	*MYO7A*	11q13.5	US 1B
Rab27a (ash)	RAB27A, member RAS oncogene family (ashen)	9	Melanosome transport	*RAB27A*	15q15-q21	GS
(e) Eumelanin and pheomelanin						
a	Non-agouti	2	Eumelanin/pheomelanin switch	*ASIP*	20q11.2	N
Atrn (mg)	Attractin (mahogany)	2	Eumelanin/pheomelanin switch (among others)	*ATRN*	20p13	N
Ggt1	γ Glutamyltranspeptidase 1	10	Glutathione metabolism (pheomelanin synthesis)	*GGT loci* (several)	22q11	GU
Gl	Grey-lethal	10	Pheomelanin and osteoclast function	*GL*	6q21	SRO
Mc1r (e)	Melanocortin 1 receptor (extension)	8	Eumelanin/pheomelanin switch (among others)	*MC1R*	16q24.3	RH
Mgrn1 (md)	Mahogunin, ring finger 1 (mahoganoid)	16	Melanin color, CNS role. E3 ubiquitin ligase	*MGRN1*	16p13.3	N
Pomc1	Pro-opiomelanocortin-α	12	Eumelanin/pheomelanin (and endocrine)	*POMC*	2p23.3	O and RH
(f) Systemic effects						
Atp7a (Mo)	ATPase, Cu^{2+} transporting, α polypeptide (mottled)	X	Copper transport	*ATP7A*	Xq13.2-q13.3	MD
Atp7b (tx)	ATPase, Cu^{2+} transporting, β polypeptide (toxic milk)	8	Copper transport	*ATP7B*	13q14-q21	WD
Bcl2	B-cell leukemia/lymphoma 2	1	Inhibitor of apoptosis	*BCL2*	18q21.3	BCL
Ercc2	Excision repair cross-complementing rodent repair deficiency, complementation group 2	7	DNA excision repair	*ERCC2*	19q13	XPD, TTD, CS

See refs (2, 5) for more information on any locus.
N: none known, BC: breast cancer, BCL: B-cell lymphoma, Ch: choroideremia, CHS: Chediak–Higashi syndrome, CS: Cockayne syndrome, CrS: Crouzon syndrome, EDA: ectodermal dysplasia, anhidrotic, EDA-ID: EDA with immune deficiency, GS: Griscelli syndrome, GU: Glutathionuria, HED: hypohidrotic ectodermal dysplasia, HED-ID: HED with immune deficiency, HPS: Hermansky–Pudlak syndrome, HD: Hirschsprung disease, HSS: Hirschsprung–Shah syndrome, IBS: ichthyosis bullosa of Siemens, IP: incontinentia pigmenti, MD: Menke's disease, O: obesity, OA: ocular albinism, OCA1-4: oculocutaneous albinism types 1–4, PfS: Pfeiffer syndrome, PS: piebald syndrome, RH: red hair (included although not a defect), SRO: severe recessive osteopetrosis, TTD: trichothiodystrophy, US 1B: Usher syndrome, type 1B, WD: Wilson disease, WS1-3: Waardenburg syndrome types 1–3, WSS: Waardenburg–Shah syndrome (Waardenburg syndrome type 4), XPD: xeroderma pigmentosum, group D.

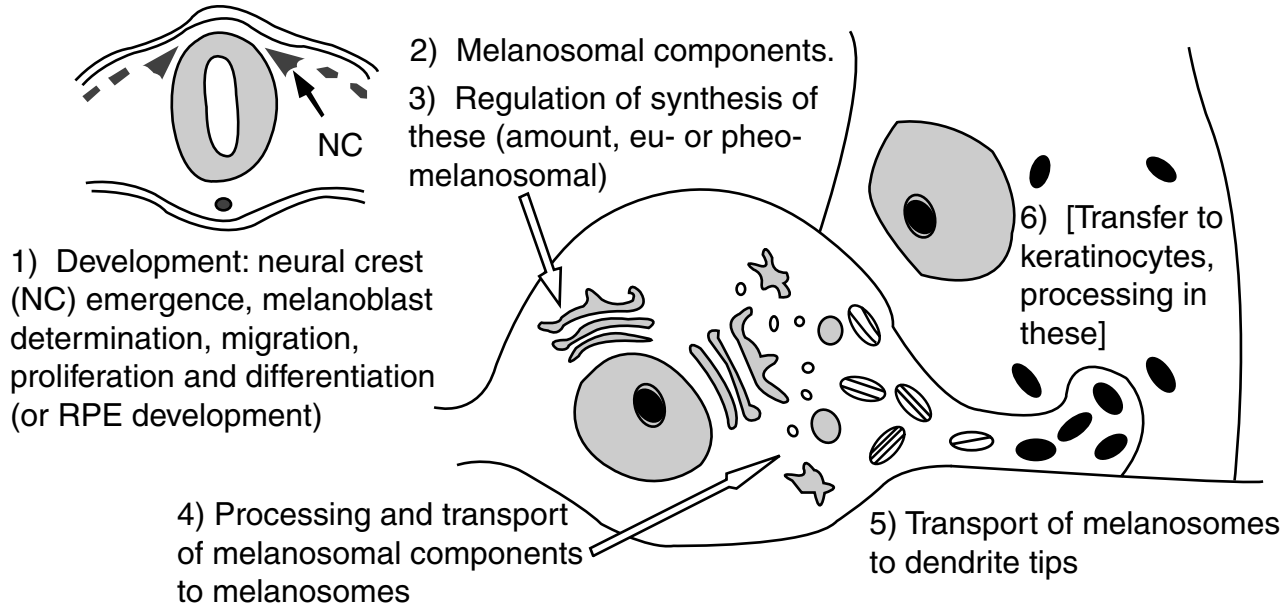

Fig. 1. Main processes affected by color genes. The processes shown have approximate correspondence with the divisions of this review. Also illustrated is the transfer of melanosomes to the keratinocytes of hairs and epidermis, and processing in keratinocytes, which are likely to be under genetic control, although no specific genes of this type have been identified as yet. Some genes determining skin color differences between human populations are likely to fall into this set.

component of them (40), recalling that the bovine SILV ortholog was known initially as melanosomal matrix protein (MMP) 115 (2). This proposed structural function could account for the apparently conflicting reports of roles for silver protein in accelerating or retarding various steps in melanin production (37, 39–41).

Lastly in this section, we will mention Gpnmb (glycoprotein NMB, or non-metastatic [B]). This sequence was originally isolated from a non-metastatic melanoma. It has some homology to SILV, including a conserved ExxPLL motif similar to the (E)(E)xxPLL consensus sequence seen in Tyr, Tyrp1 and other melanosomal proteins. This motif has adaptor protein 3 (AP3)-binding activity (42), suggesting a role in protein routing (see next section). A mutation in *Gpnmb* is associated with pigmentary glaucoma in mice, as is the *b* mutation of *Tyrp1* (43). These findings suggest that Gpnmb is a melanosomal protein. Its function if so is unknown, but the homology with SILV raises the possibility that it could be another matrix component.

MAKING THE MELANOSOME (AND OTHER ORGANELLES)

There have been rapid advances recently in the genetics of melanosome biogenesis. This field is relevant to human Hermansky–Pudlak syndrome (HPS) and the related Chediak–Higashi syndrome (CHS). These are disorders of organelle biogenesis, typically affecting melanosomes, lysosomes and platelet dense granules, and accordingly producing symptoms of hypopigmentation, hemophilia and kidney and lung disease, with varying effects on leukocyte lineages (44–48). There are 16 separate mouse loci, where mutations cause both light pigmentation and prolonged bleeding which are therefore at least partial models for HPS (Table 1c and 2c). An example is the recently cloned *cappuccino* (Fig. 2B). This count of 16 does not include $Lyst^{bg}$ (beige), the accepted single model for CHS (47), nor the related $Rab38^{cht}$ (chocolate), which apparently affects the targeting of Tyrp1 protein (49), and is included under components of melanosomes (Table 1b). It does include misty (*m*), although this is also not a typical member of the set because it seems to act through adenine nucleotide metabolism (50). Only four of these 16 loci remain uncloned, including misty (Table 2c).

The best understood genes in this set are *Ap3b1* and *Ap3d*, encoding the β1 and δ subunits of the adaptor protein 3 (AP3) complex, involved in routing of proteins to organelles including melanosomes (42, 45, 46). These have provided a clue for the other 13 or 14 HPS-related loci, suggesting protein routing as a possible common factor. We do know that mutations in *Hps1* and *Hps4*, as with *Lyst*/*CHS1*, result in the presence of giant melanosomes (48), indicating another common factor, shared with the ocular albinism 1 product Oa1. (*Oa1* is in set A in Table 1 because mutations do not affect platelets, etc., but Oa1 deficiency also results in giant melanosomes). There are various theories as to how such giant melanosomes are formed, for example a failure to export melanosomal proteins from late endosomes to melanosomes, a proposed stage in the routing (51). The giant 'melanosomes' here would in fact be late endosomes that had swollen by accumulation of melanosomal proteins and melanin. For other mutations there is some evidence for fusion of normal melanosomes (48). Not all HPS-like mutations lead to giant melanosomes; for example, $Hps3^{coa}$ does not (52). A first step toward understanding the functions of these proteins has been the recent identification of a series of cytoplasmic complexes containing them,

Table 2. Summary of the uncloned mouse color genes (Categories and functions are generally provisional or speculative)

Symbol	Name	Chromosome	Possible function (or effect, in parentheses)
(a) Development?			
Alm	Anterior lenticonus with microphthalmia	?	Eye, coat, others
baln2	Balance 2	?	Eye, coat, neurological
Bst	Belly spot and tail	16	Eye, coat, skeletal
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.
Dc	Dancer	19	Head pigment, ear, palate, neural
dds	Dorsal dark stripe	15	Dorsal pigment
dwg	Dwarf grey	?	Multiple, including pheomelanin, osteoclasts
fc	Flecking	2	(Head and belly spot)
Fk	Fleck	?	(White on belly, tail, feet)
gr	Grizzled	10	Pheomelanin, tail
gt	Gray tremor	15	Pheomelanin, spotting, neurological
hs	Head spot	?	(Head spot)
Ku	Kumba	14	(Belly spot, curly tail)
Ph	Patch deletion region (patch)	5	(White spotting. Responsible gene in deletion unknown. Not *Pdgfra*.)
pwk	Patchwork	10	Autocrine growth of melanocytes?
rg	Rotating	?	Ear development, neural, sometimes belly spot
rn	Roan	14	(Micro-spotting, whole coat)
rs	Recessive spotting	5	Melanocyte numbers. Interacts with Kit
smk	Smoky	?	Pigment color, reproductive system
tp	Taupe	7	Pigment color, female reproductive system
vl	Vacuolated lens	1	Lens, spine development, sometimes belly spot
vs	Variable spotting	9	(White on belly, head, tail, feet)
Whto	White toes	7	Color, digit development
wn	White nose	15	(White nose, ventral streak)
Xs	Extra-toes spotting	7	Color, digit development
ysb	Yellow submarine	3	Ear, neural, eumelanin
(b) Melanocyte function only?			
brwd	Brownoid	?	Melanin color (brown)
da	Dark	7	Pheomelanin
dp	Dilution-Peru	15	(Pale coat)
dsu	Dilute suppressor	1	Melanosome transport?
gdn	Golden	?	Eumelanin
rmy	Rimy	11	Pheomelanin
sea	Sepia	1	(Coat color dilution)
U	Umbrous	?	Pheomelanin
Up	Umbrous-patterned	?	Pheomelanin (patchy)
(c) Melanocytes and platelets (HPS-related?)			
m	Misty	4	Adenine nucleotide metabolism
rp	Reduced pigmentation	7	Organelle biogenesis
sdy	Sandy	13	Organelle biogenesis
sut	Subtle grey	3	Organelle biogenesis
(d) Systemic effects			
acd	Adrenocortical dysplasia	8	Adrenal cortex development
(e) Dark skin			
Dfp	Dark foot pads	?	Skin color
Dfp2	Dark foot pads 2	4	Skin color
Dsk1	Dark skin 1	19	Skin color
Dsk3	Dark skin 2	7	Skin color
Dsk4	Dark skin 4	4	Skin color
Dsk6	Dark skin 6	3	Skin color
Dsk7	Dark skin 7	10	Skin color
Dsk8	Dark skin 8	3	Skin color
Dsk9	Dark skin 9	11	Skin color
Dsk10	Dark skin 10	19	Skin color
soo	Sooty foot	2	Skin color
(f) Unknown			
fe	Faded	6	(Progressive coat fading; skin lesions)
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)
gri	Grey intense	11	?Pigment color
lgr	London grey	?	(Grey coat, later patchy, systemic effects)
Li	Lined	X	Hemizygous lethal. Fine striping. Deletion that includes *Rsk2*
Mch	Modifier of chinchilla	?	Tyr^{c-ch} mice look browner
Mcm1	Modifier of chinchilla-mottled 1	?	Lightens Tyr^{c-m} mice
Mcm2	Modifier of chinchilla-mottled 2	?	Lightens Tyr^{c-m} mice
Och	Ochre	4	Eumelanin, balance, other
Sta	Autosomal striping	X	(Striping in both sexes)
Strg	Striped greasy	X	Hair texture and color
wuf	White under fur (extinct?)	?	(Underfur white)
Ym	Yellow mottled	X	(Yellow mottling, hemizygous lethal)

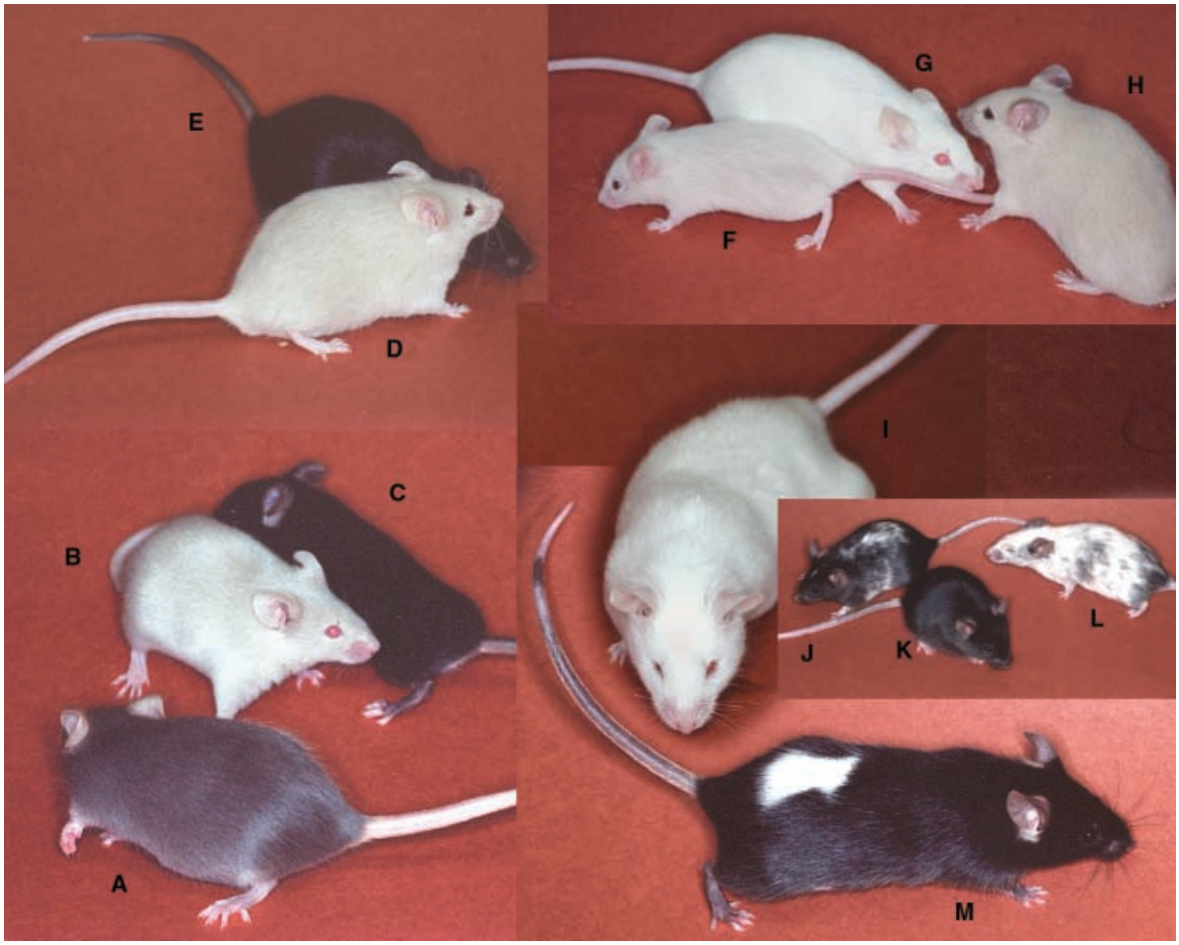

Fig. 2. Illustrative examples of mouse color mutations. All mice are of strain C57BL/6J except (**L**). (**A**) *Rab27a*^{ash}/*Rab27a*^{ash}, ashen. (**B**) *cno*/*cno*, cappuccino. (**C**) C57BL/6J control. (**D**) *Matp*^{uw}*Matp*^{uw}, underwhite. (**E**) C57BL/6J control. (**F**) *Tyr*$^{c-bew}$/*Tyr*$^{c-bew}$ (black-eyed white). This *Tyr* mutant is almost entirely unpigmented in skin and hair, but has pigmented eyes, thus superficially resembling some spotting mutants, but lacking pigment rather than melanocytes in the integument. (**G**) *Tyr*$^{c-2J}$/*Tyr*$^{c-2J}$, albino/tyrosinase null. (**H**) *Tyr*$^{c-a}$/*Tyr*$^{c-a}$, acromelanic. Acromelanic mice appear similar to the temperature-sensitive Himalayan mice, but are slightly darker. (**I**) *Mitf*$^{mi-VGA9}$/*Mitf*$^{mi-VGA9}$. The many *Mitf* alleles generate phenotypes ranging from apparently normal to completely unpigmented with microphthalmia and defects impacting many other systems of the body. (**J**) *Kit*$^{W-2J}$/*Kit*$^{W-2J}$. In this stock there are apparent reversion events producing mice as shown in (**K**). (**K**) *Kit*$^{W-2J}$/*Kit*$^{W-2J}$, the same nominal strain and genotype as (**J**) but a stock selected for minimum spotting. This low level of spotting breeds true without reversion events. (**L**) JU/CtLm-*Kit*$^{W-2J}$/*Kit*$^{W-2J}$. Here the allele has been backcrossed onto another inbred strain, JU/CtLm, giving a more severe phenotype. Strain pairs like (**J**) and (**L**) provide models for study of the influence of background genome, and for the identification of modifying genes that do not cause white spotting alone but do modify the effects of other color genes. (**M**) *Adamts20*^{bt}/*Adamts20*^{bt}, belted. The belted genotype is consistent and not responsive to background genome.

perhaps reminiscent of the heterotetrameric AP3. These complexes have been termed biogenesis of lysosome-related organelles complex (BLOCs). There are reports of BLOC1, containing the pallid, muted and cappuccino gene products (53); BLOC2 containing the Hps5 and Hps6 proteins (54), and BLOC3, 4 and 5 containing Hps1 and/or Hps4 in different combinations with other unidentified components (55). These complexes show some association with vesicular fractions of cytosol, and are proposed to be involved in protein routing to nascent organelles (55). However, their exact roles remain to be determined.

Also included in this group is the p protein, formerly considered to be melanosomal but now found to be located largely in the ER (56). p differs from the HPS proteins in having a function apparently specific to melanocytes; *P* mutations in human being cause not HPS but OCA2 (oculocutaneous albinism 2) is the most common form of albinism. Many functions have been proposed for p (56), but recent evidence suggests a role in the transport of glutathione into the ER, where glutathione is required for the correct folding and subsequent routing of tyrosinase (56).

It seems possible that we may achieve a reasonably complete reconstruction of the cellular machinery for making melanosomes, with the cloning of the last few known genes in this class, over the next few years. This topic also has a broad and fundamental importance in cell biology, as the phenotypes of this set of mutants indicate that the cellular mechanisms for making lysosomes and platelets have many components in common with those for melanosomes.

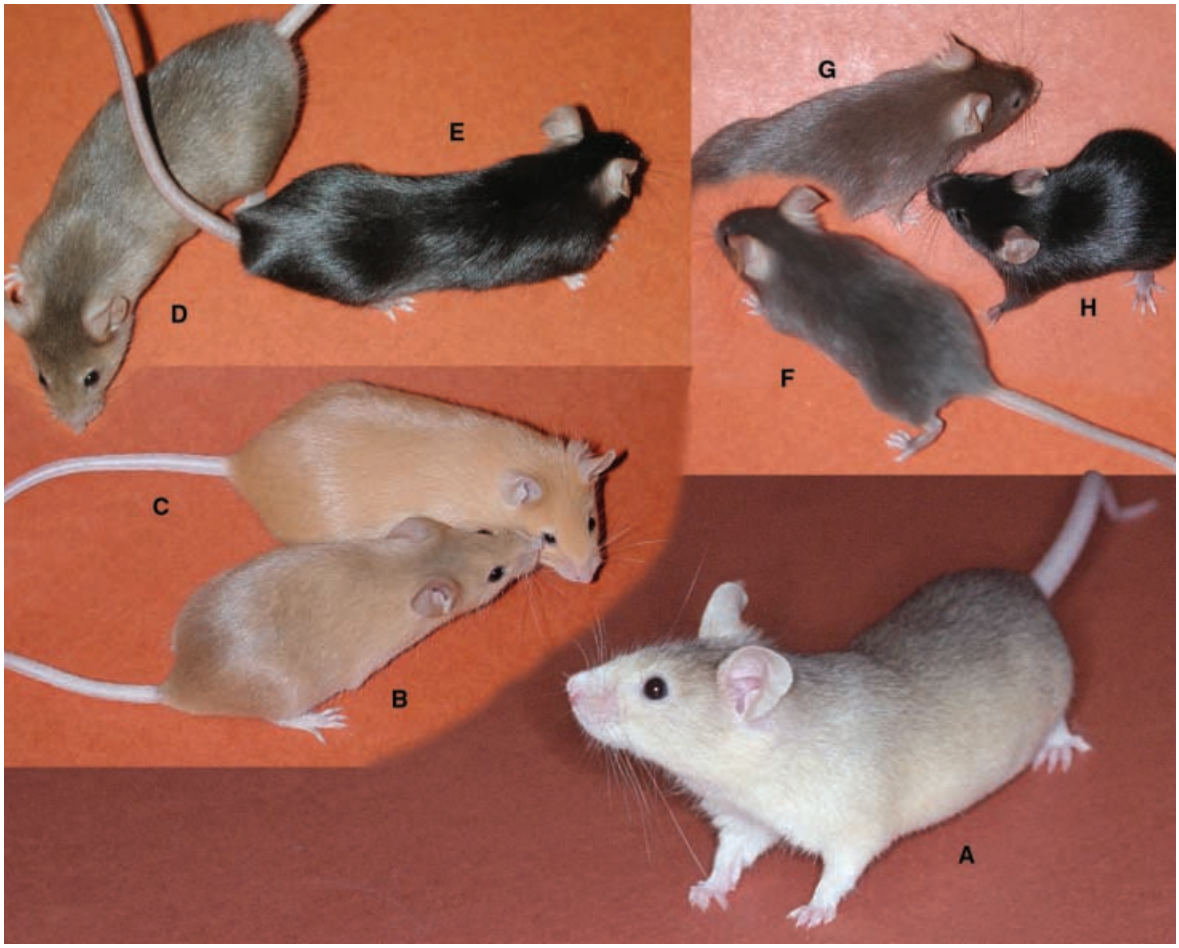

Fig. 3. Further illustrative examples of mouse color mutations. All mice are of strain C57BL/6J except (**A**). (**A**) JU/CtLm-A^y/a, for comparison with (**C**). On the C57BL/6J background the A^y/a mouse is clear yellow, whereas on the JU/CtLm background it is paler clear yellow until the first molt, when it becomes umbrous (darker dorsally). Mice older than about 6 months again become pale yellow. (**B**) $Mc1r^e/Mc1r^e$ (recessive yellow). The tips of the dorsal hairs have slight dark ticking, invariant with background genome. (**C**) C57BL/6J-A^y/a. See (**A**). (**D**) A^y/a,$Atrn^{mg}/Atrn^{mg}$ (mahogany). Much of the pheomelanic pigmentation because of $A^y/-$ is replaced by eumelanin. Even $Atrn^{mg}/+$ slightly darkens $A^y/-$ mice. (**E**) a/a,$Atrn^{mg}/Atrn^{mg}$. (**F**) Dct^{slt}/Dct^{slt}, slaty. (**G**) $Tyrp1^b/Tyrp1^b$, brown. (**H**) C57BL/6J, wild-type control mice.

MOVING THE MELANOSOME (AND OTHER ORGANELLES)

A smaller set of three mutations (dilute, leaden and ashen; Table 1d, Fig. 2A) cause normal melanosomes to aggregate in the center of the melanocyte rather than disperse along its dendrites (1, 44). At least two of the human orthologs are genes for Griscelli syndrome, involving prematurely graying hair, immune and neurologic deficiencies among other defects, and indicating that other organelles besides melanosomes are affected (Table 1d). We now know (not surprisingly) that all three gene products are involved in the transport of melanosomes along microtubules to the dendrite tips. All three of these gene products (now myosin 5, melanophilin, and Rab27a, respectively) have been found in a protein complex, and models have been developed for how they interact to move the organelle (57–59). A different myosin, Myo7a (shaker-1), is required in the RPE and not in integumental melanocytes, and so may play a similar transport role in the retina (60). Mutations in *MYO7A* lead to Usher syndrome type 1B in humans, involving blindness and sensorineural deafness (60).

BLACK, YELLOW AND GRAY: EUMELANIN VERSUS PHEOMELANIN

The main type of mouse hair, in the wild-type or agouti mouse, has a black tip containing eumelanin, then a yellow band containing pheomelanin, then a black base (1). These stripes are generated by a switch in the type of melanin being produced by melanocytes in the hair follicle. This switch is controlled by a number of gene products (Table 1e, Table 2, Fig. 3A–E), of which the central ones appear to be the melanocortin-1 receptor Mc1r, expressed on melanocytes, and its two ligands, melanocyte-stimulating hormone (MSH) and the competitive antagonist of MSH, agouti signal protein (ASP) (61, 62). The *Mc1r* gene is the old *e* or recessive yellow locus, in which loss-of-function

mutations give a predominantly yellow mouse (Fig. 3B), while gains of function yield a black coat. ASP is encoded by the *a* (agouti, also called non-agouti) gene in which, conversely, dominant gain-of-function mutations like A^y produce a yellow mouse (Fig. 3A, C showing effect of mouse strain background), and loss of function gives black hair, as in *a*/*a* (non-agouti, Fig. 3H) (61). MSH is one cleavage product of the peptide encoded by the pro-opiomelanocortin (*Pomc1*) gene: not a classical color locus, but one in which gene knockout produced a brownish mouse with reduced eumelanin. Interestingly this was not completely yellow (63), suggesting either some basal activity of the normal mouse Mc1r without MSH; the existence of another, separately-encoded agonist (62), or that mouse melanocytes lacking any Mc1r signaling may make some eumelanin, as also suggested by the incomplete yellowing in $Mc1r^e/Mc1r^e$ (Mc1r null) mice (Fig. 3B). In humans, pheomelanin tends to be red. While humans do not have banded hairs, both *MC1R* mutations and *POMC* mutations are likewise associated with (pheomelanic) red hair, with obesity *POMC* (associated with deficiency of other melanocortins that derive from the POMC precursor peptide) (61). No function has yet been identified for the human *a* gene ortholog, *ASIP*.

Two other mouse gene sets contribute to controlling the production of eumelanin versus pheomelanin. Mutations in one set darken agouti hair, increasing eumelanin levels. This set includes some uncloned loci together with attractin (*Atrn*, mahogany) and mahogunin (*Mgrn*, mahoganoid) (64). Attractin appears to be a co-receptor for ASP, without which its signaling through Mc1r is deficient (Fig. 3, compare C–E), while the function of the recently identified mahogunin is not clear, except that it is an intracellular protein with E3 ubiquitin ligase activity, also required for normal ASP signaling (64). The second set of loci appear to act further downstream, in the production or distribution of the pheomelanosome, an organelle about which much remains to be discovered. Mutations at these loci tend to turn agouti mice gray, the yellow band becoming white, indicating that eumelanin synthesis is successfully switched off, but there is something wrong with pheomelanin synthesis. These appear to include gray-lethal (Table 1), grizzled, gray intense, gray tremor and rimy (Table 2a,b and f). Of these, the cloning only of gray-lethal has been reported. The gene product is an intracellular transmembrane protein, without which pheomelanosomes become clumped together, while eumelanosomes are unaffected (65). The gene is also required for osteoclast development, and the human ortholog is a locus for recessive osteopetrosis (65).

THE REST

A number of other cloned color genes remain, with effects that can be described as systemic, affecting the whole body (Table 1f). These include the genes for the two subunits of the copper transporter ATP7, namely *Atp7a* (mottled) and *Atp7b* (less evocative than the former name, toxic milk). ATP7 may be a melanosomal protein, as Atp7a contains a conserved cytosolic ExxPLL sequence, a consensus AP3-binding sequence (42). Copper is required for melanin synthesis because tyrosinase contains copper. Another interesting locus in this set is that for the anti-apoptotic mitochondrial protein Bcl2, known to be highly expressed in melanocytes (66), and apparently transcriptionally activated by Mitf (67). Bcl2 knockout in mice results in graying of hair (2), suggesting melanocyte apoptosis, and high melanocytic Bcl2 levels may explain the notorious resistance of melanocytes as well as melanoma cells to drugs and other cytotoxic treatments (66).

PERSPECTIVES

How many mouse (or mammalian) color genes will eventually be identified? At the moment, potential new loci are accumulating quickly, as a result of the chemical mutagenesis programs already mentioned (2, 3). A proportion prove allelic to known loci, but it is not yet all of them. It seems likely that the number of distinct genes will rise to at least 150 and possibly 200 – another century. But even when we have all the genes, the most interesting part of the research will continue – to understand the function of each gene, and how it interacts with others (and often with crucial genes not found through mutations because deficiency is lethal) to generate a well-regulated pigmentary system. The knowledge gained here will extend to many other physiologic systems such as neuronal function, sight, hearing, blood-clotting and kidney function.

Abundant materials exist for this 'functional genomics' research in the mouse, and more are being generated. This involves on the one hand making mutations congenic – crossing them on to defined inbred mouse strains. A study of mutations in the intact animal allows reconstruction of gene actions at the tissue to organismic levels, and congenesis allows accurate reporting of phenotypes, and identification of modifying (interacting) loci that vary between strains (11, 68, 69). On the other hand, the derivation of immortal lines of melanoblasts and melanocytes, from mutant (preferably congenic) mice of interest, enables studies of gene functions and interactions at the cellular and molecular levels (as for example in refs 31, 39, 44, 46, 52, and others cited).

Our increasing understanding of the normal pigmentary system should also contribute much information about human disorders of pigmentation (Table 1). While in mice we tend to perceive these mutations as pretty coat-color effects, the orthologous human mutations are often noticed more through associated serious disorders like deafness and hemophilia. Accordingly, the mouse mutants are providing models for understanding such disorders and for developing treatments. As our understanding of color genetics continues to mushroom, we are indebted to Dr Silvers and many others who have worked together to build the extraordinary resources and knowledge that researchers in this field now enjoy.

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