Melanin and Melanocyte Molecular Biology

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The purpose for writing this section was to provide the cell physiology, molecular and biochemical context for producing melanin in multicellular animals. I wanted to have access to relevant genes in order to use the web to quickly get more information on those genes. I wanted to describe what was known about relevant genes, so that I could place the *E* locus (*MC1R*) into a functional context. If I could do this I believe that I can do a better job of describing how the *MC1R* gene fits into melanogenesis, and how it may be associated with the various feather colors and patterns that various *E* locus alleles are associated with. It was baffling that for a topic so well studied due to melanocyte association with melanoma that I could not find a recent review that provided the information about the genes and what was known about them that I was looking for. I ended up going through multiple review articles, and the references that they cited as well as looking up the old mouse work and what had been discovered about the genes associated with the classic color loci. I ended up creating my own list of genes before finding Baxter et al., 2018. Baxter et al., 2018 came up with a gene list of around 650 genes associated with pigmentation in mouse, human and zebrafish databases (supplementary Table S7), but they missed some genes associated with fur color loci in other animals like horses, dogs, and cats. I have decided to stick with my list of around 140 genes because I have some idea of what those genes are doing, and it will take a lot of work to check out what each of the Baxter et al., 2018 genes may be doing, and what evidence there is for them having some function in melanin production.

Bennett and Lamoreux, 2003 placed the mouse genes that they were working with into 6 categories: Melanocyte Development (MD), Components of Melanosomes and their Precursors (CMP), Melanosome Construction/Protein Routing (MCPR), Melanosome Transport (MT), Eumelanin and Pheomelanin (EP), and Systemic Effects (SE). In their uncloned list of genes they also had the category of dark skin (DSK). When I tracked down the genes associated with the uncloned loci most of them turned out to fit into the MT category, but two of them were ribosomal proteins that were part of the ribosomal protein synthesis complex, but also can bind to other proteins. Two others were involved in MD. My Table 1 has these designations for the genes that they were working with, and I have tried to maintain the same categories for the pigmentation genes identified since their 2003 publication.

Melanin has been of interest to animal science and genetics since the rediscovery of Mendel’s research. Melanin produces an observable phenotype, and at the beginning of genetics phenotypes were the only genetic “markers” that we could use to identify what scientists started to call genes. No one knew what genes were or that the genetic material was DNA, but it didn’t take long (only a couple decades) before it was understood that genes resided on chromosomes, that the phenotypic markers (distinct color variants) could tag a location on a chromosome, and that linear maps could be constructed ordering the loci that were determined to be linked on any chromosome. Before we knew what a gene was the genes location in the genome (locus) could be associated with a specific variant phenotype, given a locus designation, and assumed to be somewhere on an existing chromosome. I have tried to identify the original locus designations for the pigmentation genes in my Table 1. We can now sequence whole genomes and are attempting to classify over 15,000 coding genes of an average terrestrial vertebrate genome, but we still do not understand what most of those genes do. It turns out that a good way to begin to figure out what a gene does is to go back to the old genetic research and associate the old loci phenotypes with genes located at those positions of the chromosomes.

There are multiple review papers on the genes and cellular processes involved in the development of melanocytes, melanin biosynthesis, and transfer of melanosomes to keratinocytes that form the pigmented skin, hair, and feathers. I tried to make up a list of genes involved and their function using the reviews, but all the reviews that I found were inadequate. There have been claims for decades that on the order of 100 genes have been shown to be involved in melanin production, but I could not find a modern list, and Bennett and Lamoreux, 2003 listed 60 known genes in their Table 1. I began to construct my own table of genes based on genes identified in half a dozen recent reviews, and the mouse database. I also used the OMIA (Online Mendelian Inheritance in Animals) database to identify genes associated with pigmentation in animals. It was likely a lucky break that I did not find Baxter et al., 2018 because it would have been a lot more work sifting through their list of 650 genes to get enough genes in the relevant categories to aid my research of the published literature.

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I had issues interpreting Wang et al., 2024, and though it is the most recent review I ended up using their references to figure out what they were describing. Their citations are good, and support what Wang et al., 2024 are reviewing, but I did find one or two miscitations, but other papers on the topics supported their claims. In order to associate genes with their old loci designations and gene functions I utilized the mouse MGI database, NIH gene search page, and GeneCards database. I describe how to utilize these databases in the Appendix. I came up with my Table 1. As previously noted Bennett and Lamoreux, 2003 placed the genes into categories such as MT (melanosome transport) and I tried to group genes that I added to their list into these same categories. Whenever possible I identified the original animal loci designation so that the phenotype produced by variation involving these genes could be looked up in the literature. I had nearly completed this list, of around 140 genes, when I found Baxter et al., 2018. These authors had manually searched for genes associated with pigmentation in humans mice and fish, and had come up with a list of 650 genes (supplementary Table 7) associated with pigmentation in the animals that they included in their search results. There was not a complete overlap between my shorter list and theirs and I note them in Table 1 in the column labeled “Baxter”. They seemed to have missed some genes associated with pigmentation in other animals (identified using OMIA) like dogs and horses. I had also assumed that all the genes known to be associated with the BLOC and other transport complexes were associated with pigmentation even though mutations in those genes had not been identified to produce pigmentation phenotypes.

The sections that follow are classification of the genes in the order that they occur in the Bennett and Lamoreux, 2003 Table 1. The Bennett and Lamoreux, 2003 designations are used in my Table 1 as gene classification. My Table 1 also has the designations used in their Table 2 of “uncloned mouse color genes” if I was able to identify the genes associated with those mice loci.

**Melanocyte Development (MD):**

Bennett and Lamoreux, 2003 placed genes involved with differentiating melanocyte stem cells and melanocytes from other neural crest cells into their MD category. Melanocytes cells, also called melanophores, are cells that produce melanin containing organelles called melanosomes. Melanin is synthesized and organized inside melanosomes. Melanosomes are membrane bound organelles that share components with lysosomes, but they are derived from the early endosomal membrane. Melanosomes are transferred from melanocytes to keratinocytes for pigmentation of skin, hair, scutes, and feathers. Melanocytes are derived from a region of the early developing embryo called the neural crest. Cells that separate early from the neural crest become neurons and glia cells of the peripheral nervous system while melanocyte stem cells migrate away from the neural crest later in embryo development. As the embryo develops the melanocytes migrate out of the neural crest to parts of the developing embryo where they will produce melanin in tissues such as the epidermis and iris of the eye. Melanocyte stem cells are claimed to be multipotent and can be highly prolific in producing functional melanocytes. Retinal pigment epithelium (RPE) cells also produce melanosomes and require many of the same genes as melanocytes, but they are not considered to be melanocytes and are derived from the neural ectoderm. The neural crest develops between the neural ectoderm and the surface ectoderm of the embryo. Cells derived from both the neural ectoderm and neural crest can develop melanosomes, but the neural crest produces melanocytes.

Table 1 has 38 genes in the MD category. These are genes that are needed to create a melanocyte from neural crest cells. Bennett and Lamoreux, 2003 note that homozygous mutations in important pigmentation genes such as *KIT* (KIT proto-oncogene, receptor tyrosine kinase) and *MITF* (Melanocyte inducing transcription factor) can result in no melanocytes being generated by the neural crest. Bennett and Lamoreux, 2003 noted that most of the genes in the MD category are associated with the mouse spotting loci, and disrupting the normal function of these genes results in a nonuniform distribution of functional melanocytes. The *KIT* gene codes for a growth factor receptor. Growth factors were identified by their effects on cell proliferation. Receptors like KIT are activated by growth factors like KITLG (KIT ligand). Receptor activation usually results in the phosphorylation activation of gene protein products involved in cell proliferation and cell survival. Among the functions of KIT is the activation of growth factors associated with making melanocytes. MITF is a transcription factor that binds DNA sequences associated with the regulation of the transcription of specific genes. MITF is involved in transcribing genes essential for the differentiation of melanocytes from neural crest cells, but it is also one of the transcription factors regulated by the activation of the MC1R (E locus, melanocortin 1 receptor) G protein coupled receptor involved in melanosome maturation and melanin production. MITF is essential for the development of melanocytes from neural crest cells, and it is also essential for the production of melanosomes by melanocytes.

The genes in the MD category are primarily growth factors and transcription factors needed to regulate the expression of genes and activation or inactivation of the activity of the gene products needed to produce melanocytes and the development of mature melanocytes with functional melanosomes. These genes have usually been associated with cell proliferation and cancer biology (e.g., *BRCA1*, breast cancer 1, tumor suppressor gene). They are genes that need to be functional in the neural crest for cells to differentiate into melanocyte stem cells.

One gene that doesn’t seem to fit into this category is the *KRT2A* gene. KRT2A is associated with keratinocyte activation. Keratin may be a minor structural component of melanocytes, but I do not know how important it is for melanocyte development and differentiation. Bennett and Lamoreux, 2003 list the KRT2A gene as part of the cytoskeleton (internal structural component of a cell).

I have 7 genes on my MD list that were not on the Baxter et al., 2018 list of 650 pigmentation genes. The transcription factor E2F1 (E2F transcription factor 1) is an odd one to be missing. It is known to be over expressed in melanoma, and I found it associated with melanocytes in Bandyopadhyay and Medrano, 2000. I found that paper when I was looking for other evidence that CDKN2A/B (sex-linked barring locus in chickens) was associated with pigmentation. CDKN2A/B made Baxter’s list, but E2F1 did not. Three genes made the Bennett and Lamareux, 2003 list, but not the Baxter et al., 2018 list: Fibroblast growth factor receptor 2, LIM homeobox transcription factor 1 alpha, and Sideroflexin 1 (*FGFR2*, *LMX1A*, and *SFXN1*, respectively). FGFR2 (mouse hobby horse *hob* locus) is activated by multiple FGF (Fibroblast growth factor) ligands and has been associated with melanoma, melanocyte development, proliferation and viability, and is listed in the MD category by Bennett and Lamareux, 2003, LMX1A (mouse dreher *dr* locus) is a transcription factor associated with white belly spots, and SFXN1 (mouse flexed tail *f* locus) is known to transport amino acids into the mitochondria, and Bennett and Lamareux have it associated with melanocyte development. *HINF1A* (HNF1 Homeobox A) was left off Baxter’s list, but I found multiple papers associating it with regulation of pigmentation genes and it’s function was reviewed in Wang et al., 2024. *PSMB7* (Proteasome 20S subunit beta 7, dog harlequin *H* locus) is a pigmentation related gene that I found at the OMIA web site associated with coat color in dogs. It is one subunit of a protease complex involved in protein recycling in the cell. It may affect melanocyte development by removing proteins that are no longer needed in order to allow melanocyte development to proceed. I also obtained *DKK4* (Dickkopf WNT signaling pathway inhibitor 4, cat ticked *Ti* locus) from OMIA. DKK4 is an antagonist of WNT signalling. WNT signalling is required for early embryo development and is needed for stem cell maintenance and maintaining tissue homeostasis. The dominant variant results in the loss of the wild-type tabby pattern and replaces it with the ticked (hair with alternating coloration) phenotype.

**Components of Melanosomes and their Precursors (CMP):**

Melanosomes are organelles found inside melanocytes that contain the melanin pigment that determines the color generated by the melanocyte. Eumelanin and pheomelanin are synthesized within the melanosomes. Genes categorized as CMP in Table 1 have their gene products as physical components found in melanosomes, are involved in the structure of the melanosome and/or have something to do with melanin biosynthesis. Genes such *PMEL17* (Premelanosome protein 17, mouse silver locus, dominant white locus in chicken) codes for a structural component in eumelanosomes that is associated with the scaffold structure that produces the elongated elliptical and bar shaped structure of eumelanosomes. APOE (Apolipoprotein E) is another structural protein associated with the scaffold structure (D’Alba and Shawkey, 2019). Enzymes such as TYR (Tyrosinase, chicken *C* locus), TYRP1 (Tyrosinase related protein 1, chicken sex-linked *choc* locus) and TYRP2 (Tyrosinase related protein 2/Dopachrome tautomerase, mouse slaty *slt* locus) are integrated into this protein scaffold and are involved in the biosynthesis of eumelanin. TYR is also required for the synthesis of pheomelanin, but TYRP1 and TYRP2 are not required for pheomelanin synthesis. Eumelanin is incorporated into the scaffold structure as it is synthesized, but how eumelanin is incorporated and the final physical structure is unknown (What is known is reviewed in D’Alba and Shawkey 2019 and Raposo and Marks, 2007). It is believed that both eumelanin and pheomelanin are synthesized in eumelanosomes with eumelanin associated with the scaffold forming a shell eumelanin, within the melanosomal membrane, with pheomelanin synthesized inside this eumelanin shell. Pheomelanosomes are less structured, have little PMEL17 and associated scaffold structure. Pheomelanosomes are usually observed in a more rounded less elongated shape, so there are differences in the physical make up of eumelanosomes and pheomelanosomes. Pheomelanosomes do not form a full scaffold structure and do not contain enough eumelanin and PMEL17 to form the eumelanin protein scaffold shell.

The CMP category includes membrane bound ion and solute transporter proteins such as SLC45A2 (sex-linked silver locus in chicken) that is a membrane associated component of the melanosome, but SLC45A2 is also involved in the differential synthesis of eumelanin and pheomelanin (EP) category. I added quite a few genes to the CMP category, and if they were involved in the differential synthesis of pheomelanin I labeled them CMP/EP. The pH inside of the melanosome is very important for the differential synthesis of eumelanin and pheomelanin. Pheomelanin synthesis is favored under acidic conditions, while eumelanin synthesis becomes favored as the pH increases. At neutral to more basic pH pheomelanin synthesis is inhibited. SLC45A2 is involved in pumping hydrogen ions out of the melanosome. Dysregulation of SLC45A2 with a resulting higher level of removing H+ ions from the melanosome would increase the pH (more basic) and may result in the dominant sex-linked silver phenotype observed in chicken. A more basic pH would inhibit pheomelanin synthesis. There are many carrier or transport proteins in Table 1 that will affect the pH of the melanosome, and I have labeled them CMP/EP because they are components of the melanosome, and they could be involved in the differential synthesis of eumelanin and pheomelanin. ATP6V0 is not a single gene, but it is the name of a protein complex made up of multiple subunits. I did not list all the genes known to be associated with the ATP6V0 complex. ATP6V0 is likely the main proton pump that acidifies the melanosome. Table 1 notes that other CMP/EP gene products that transport hydrogen ions, pump them out of the melanosome and would make the melanosome less acidic. Transporters like MFSD12 import cysteine into the melanosome, while CTNS can transport cystine (cysteine dimer) out of the melanosome, and so are involved in regulating pheomelanin synthesis that requires cysteine.

Bennett and Lamoreux, 2003 had *RAB38* in the CMP category, but the gene is also involved in Melanosome Construction/Protein Routing (MCPR), so I labeled *RAB38* as CMP/MCPR. *RAB32* also has this double designation. They are part of the melansome and are associated with trafficking enzymes such as TYR and TYRP1 into the melanosome. RAB27A is a physical part of the melanosome and is used to interface the melanosome with the intracellular motor transport system of the melanocyte in order to move the melanosome around inside the cell, so I gave it a double designation of CMP/MT (Melanosome Transport).

On Table 1 there are 9 genes that are components of melanosomes that Baxter et al., 2018 did not have on their list of genes associated with melanogenesis. *APOE* has been noted to be part of the melanosomal scaffold attached to the inner membrane of the melanosome. Genes such as *GSS* (Glutathione Synthetase), *TH* (Tyrosine Hydroxylase 1), and *TPH1* (Tryptophan Hydroxylase 1) are enzymes involved in tyrosine metabolism. Tyrosine is required to make both pheomelanin and eumelanin. *QDPR* (Dihydroptern Reductase) and *PCBD2* (Pterin-4A-cabinolamine dehydratase 2) are enzymes that produce cofactors important for tyrosine metabolism. Zhou et al., 2024 claimed that Solute Carrier Family 9 members A3 and A7 (*SLC9A3* and *SLC9A7*) have been localized to the melanosome and both are sodium and hydrogen transporters involved in maintaining the pH of the melanosome. Gaudel et al., 2020 found *SLC7A4* (Solute Carrier Family 7 member A4) had it’s gene product localized to the melanosome and it was found to be involved in melanin biosynthesis. SLC7A4 can transport large neutral amino acids when it is a heterodimer with SLC3A2, but I could not find other evidence that SLC3A2 was also found in the melanosome (*SLC3A2* is not included in Table 1 but may be CMP). The SLC7A4/SLC3A2 heterodimer would transport tyrosine, phenylalanine and tryptophan (all involved in melanin biosynthesis) into the melanosome. Tyrosinase, Tyrosine Hydroxylase, Tryptophan Hydroxylase 1, and Phenylalanine Hydroxylase (*TYR*, *TH*, *TPH1*, and *PAH*, respectively) are enzymes found in the melanosome that would use those amino acids to supply the tyrosine needed to make melanin.

**Melanosome Construction/Protein Routing (HPS-related) (MCPR):**

Bennett and Lamareux, 2003 placed genes involved in getting the components of the melanosome from where they were synthesized (often passed to the golgi apparatus, and then routed to and incorporated within the melanosome) into their MCPR category. Raposo and Marks, 2007 devoted a section of their review to protein routing within the melanocyte to get proteins such as PMEL17, TYR, TYRP1, and TYRP2 into the melanosomes. Wang et al., 2024 also has a section on protein routing and melanosome transport.

Components of the melanosome have to get into the melanosome in their functional state. Structural proteins such as PMEL17 (gp100 antigen, Chicken dominant white locus) need to be synthesized and transported to where they can be processed correctly and integrated into the inner melanosomal membrane. Some proteins may be melanocyte specific such as PMEL17 whose transcripts are found in many different cell types, but antigenic protein is only observed in melanocytes (Brouwenstjn et al., 1997). The functional PMEL17 protein has to be routed correctly into the premelanosome or melanosome. Berson et al., 2001 found that if *PMEL17* was expressed in cell types other than melanocytes, that it could be found associated with intralumenal membrane vesicles and multivesicular bodies within those cells. In melanocytes the *PMEL17* mRNA is translated into the golgi, and PMEL17 is transported and processed in such a way that the functional product can interact correctly with the intraluminal membranes of the melanosome and form the melanosomal protein scaffold associated with the elongated structure of eumelanosomes and eumelanin shell inside the melanosomal membrane. Somehow the components of the melanosome are tagged, and or identified, and correctly routed to the melanosomes within the melanocyte.

Hermansky-Pudlak Syndrome (HPS) is caused by disruption of protein transport within lysosome-related organelles like melanosomes. There are four intracellular transport complexes that have been associated with HPS and responsible for getting melanosomal components to the melanosome (Adapator related protein complex 3 (AP-3) and biogenesis of lysosomal organelles complexes 1, 2, and 3 (BLOC1, BLOC2, and BLOC3). Genes associated with all four are identified in Table 1. 12 of the genes that are part of these four transport complexes have loci designations in mice (noted in Table 1). Structural variants in these transport complexes are associated with various phenotypes in mice. Disruption of the complexes seems to mostly reduce melanosome production (fewer melanosomes are produced).

Three other MCPR category genes have loci designations in mice (Lysosomal trafficking regulator (*LYST*, mouse sandy, *sdy* locus), Vacuolar protein sorting 33a (*VPS33A*, mouse buff, *bf* locus) and Ocular albinism 1/G Protein coupled receptor 143 (*OA1*/*GPR143*, mouse and human *OA1* locus). LYST is involved in intracellular protein trafficking in endosomes. VPS33A is a core subunit of the homotypic fusion and sorting protein (HOPS) complex. GPR143 binds heterotrimeric G proteins and is involved in intracellular signaling. GPR143 is stabilized by MLANA (Melan-A) and the two are found together in melanosomes.

There are 8 genes in the MCPR category that were not found in the Baxter et al., 2018 list. 7 of them are subunits of one of the transport complexes. I put these seven on the list because they were known to be part of one of the transport complexes even though they had not yet been associated with pigmentation phenotypes. I put *PIK4II*/*PI4K2A* on the list because Wang et al., 2024 claimed that PIK4II interacted with the BLOC1 complex, and their reference (Zhu et al., 2022) confirmed PIK4II association with transport to melanosomes.

**Melanosome Transport (MT):**

An important function within melanocytes and melanophores is the movement of melanosomes within the cell. Melanosomes also need to be transported out of the melanosomes into keratinocytes to form melanin pigmented structures such as hair and feathers. Wang et al., 2024 has a section on the biochemistry of melanosome transport. These transport genes may also be associated with getting components to and into the melanosome. Many of these transport proteins are likely also components of melanosomes and their precurors (CMP) in Table 1, but I did not double label (CMP/MT) them unless I found that they were a part of the melanosomal membrane.

The Ras superfamily of small GTPases have a prominent role in melanosome transport. Ras members are membrane bound due to having a lipid attached to them post translation. They can bind proteins and ligands and signal using their GTP binding and hydrolysis ability. They have evolved to perform many different tasks required by the cell. Raposo and Marks, 2007 and Wang et al., 2024 have sections on the Rab members of the Ras superfamily associated with melanosomes. They are involved in vesicle transport and also protein transport. One example that seems to have been worked out fairly well is *RAB27A* (mouse ashen, *ash* locus). RAB27A is bound to the melanosomal membrane on the external surface, and forms a trinary complex with MLPH (mouse leaden, *ln* locus and chicken lavender, *lav* locus) and MYO5A (mouse dilute, *d* locus). MYO5A binds to the actin filaments that act as roadways within the cell. MYO5A can move in large steps along the actin filament and is associated with moving the melanosome around inside of the melanocyte.

Wang et al., 2024 also has a section on the Rho subfamily of the Ras superfamily, but I did not include these genes in Table 1. The MGI (Mouse Genome Informatics) database does claim a pigmentation phenotype for *Rac1*, but none of the genes seem to be listed in the Bennett and Lamoreux, 2003 lists of pigmentation genes, or their list of loci whose genes had not yet been identified. The Rho subfamily is associated with creating cell structures and may be involved with melanosome distribution within the melanocyte and export of melanosomes to keratinocytes.

There were 6 MT genes on my list that did not appear on the Baxter et al., 2018 list. Four of them are Rab related that I picked up from Wang et al., 2024 or by checking their references. MYO7A (Myosin VIIA mouse shaker-1 *sh-1* locus) is listed in the MT category by Bennett and Lamoreux, 2003, and has a similar function as MYO5A in transporting membranous vesicles within the cell. *PLIN3* (Perilipin 3 also known as *M6PRBP1*) came from Wang et al., 2024 as being associated with BLOC3 functions.

**Eumelanin and Pheomelanin (EP):**

Genes that appeared to be associated with differential synthesis of eumelanin or pheomelanin were categorized as eumelanin and pheomelanin (EP) by Bennett and Lamoreux, 2003. Among the EP genes listed in Table 1 the Melanocortin 1 receptor (*MC1R*, extension *E* locus in chickens and *e* locus in mice) is a central player among several EP genes (Wolf Horrell et al., 2016). Proopiomelanocortin (*POMC*) is post translationally processed into a number of peptide ligands including melanocortin stimulating hormone (MSH) that is a ligand for MC1R. Binding of MSH to MC1R activates the receptor and results in stimulation of eumelanin synthesis. Agouti signal protein (ASIP) and agouti related neuropeptide (AGRP) binding to MC1R inhibits the binding of MSH and so keeps the receptor from being stimulated and signaling to produce eumelanin and results in the production of pheomelanin. Beta-defensin 103 (CBD103) is an antimicrobial peptide, but the *KB* allele of *CBD103* produces a peptide that likely binds to MC1R and blocks ASIP binding so that the cAMP signaling is not impeded by the binding of ASIP to MC1R (Candille et al., 2007). CBD103 competitively inhibits the binding of ASIP to MC1R. Brancalion et al., 2022 in their review of dog genetics correctly describes the work of Candille et al., 2007, but two web sites (animalgenetics.com and vgl.ucdavis.edu/test/dominant-black) incorrectly describe the causative phenotype as being the repression of expression of the ASIP gene. In molecular genetics “expression” of the gene refers to production of mRNA, but the peptide product of the *KB* allele of the *CBD103* locus competitively blocks binding of the ASIP peptide to MC1R so that MC1R signaling is not antagonized by ASIP. This has nothing to do with the expression of the ASIP gene. I should note that there were multiple errors in the Brancalion et al., 2022 review, but the description of the results of Candille et al., 2007 was not one of the corrections that needed to be made.

Many of the CMP genes that are involved in pH regulation or transport of solutes into and out of the melanosome are also associated with differential synthesis of eumelanin and pheomelanin in the melanocytes. The ATP6V0 complex decreases the pH of the melanosomes. Under acidic conditions pheomelanin production is favored over the production of eumelanin. SLC45A2 (chicken silver *S* locus) transports H+ ions out of the melanosome and would be associated with higher pH within the melanosome that would be expected to inhibit pheomelanin synthesis. CTNS (mouse cystinosis *ctns* locus) and SLC7A11 (mouse subtle gray *sut* locus) are involved in cystine melanosomal transport. Cystine is a dimer of cysteine and cysteine is required for pheomelanin synthesis but is not involved in the synthesis of eumelanin.

There are 4 genes in the EP category that were not on the Baxter et al., 2018 list. AGRP has been known to have a similar effect on MC1R activity as ASIP (similar peptide sequence) for several decades, and is routinely classified as an antagonist of MC1R. The issue may be that the association was found in *in vitro* studies. I do not recall any papers where a spontaneous mutation in *AGRP* altered pigmentation of an animal. AGRP is primarily expressed in hypothalamic neurons, and is not expressed in melanocytes. It would not be expected to be involved in pigmentation of the skin, hair and feathers. I obtained *ARHGAP36* (cat sex-linked orange *O* locus), *CBD103* (dog dominant black *K* locus), and *MBTPS2* (horse brindle *BR* locus) from the OMIA web site.

**Systemic Effects:**

Bennett and Lamoreux, 2003 had a category that they called systemic effects (SE). These were genes that affected pigmentation, but also affected the whole body of the animal. A lot of other pigmentation genes in other categories should also fall under this category because a lot of them are involved in the normal function of lysosomes, are transcription factors that also control genes not directly related to melanogenesis, are involved in basic intracellular transport of materials, endocytosis, and exocytosis, apoptosis, and DNA excision and repair. Copper is a cofactor in melanin biosynthesis, but it is essential for a lot of cellular processes, so that is why ATP7A and ATP7B copper transporters are listed under SE.

There is one gene in the SE category not found on the Baxter et al., 2018 list. *GPR88* (mouse striped greasy *strg* locus). Bennett and Lamoreux, 2003 had the *strg* locus in their “Unknown” category of their Table 2.

**Dark Skin:**

Dark skin (DSK) was a designation Bennett and Lamoreux, 2003 gave to 11 uncloned genes. I was able to track down 7 DSK loci whose genes had been identified since 2003. Three of them (Guanine nucleotide binding protein alpha 11, *GNA11* (*dsk7* locus), G protein subunit alpha Q, *GNAQ* (*dsk1* and *dsk10* loci are both associated with the same gene) and Neurofibromin 1 *NF1* (*dsk9* locus)) were found to be involved in melanosome transport (MT). Two (Epidermal growth factor receptor, *EGRF* (*dsk 5*) and Keratin 2A, *KRT2A* (*dsk2*)) were associated with melanosome development (MD). I left two of the loci in their own category because they turned out to be ribosomal proteins (Ribosomal protein S19 and S20 (*RPS19* (*dsk3* locus) and *RPS20* (*dsk4*) respectively). Polymorphisms in these two ribosomal protein genes are associated with activating p53 and inducing something similar to the sunburn response for activating melanocytes (Walker and Box, 2008).

**Conclusion:**

Table 1 is a list of genes that can be used to understand what is involved in melanocyte development and the production of melanosomes and their transport within and out of melanocytes that produce the pigmented tissues and structures such as hair and feathers. Anyone can use the gene names to search the web and get information. Google searches such as “chicken dominant white I locus” or “mouse brown b locus” will bring up relevant publications and other information including the gene associated with the locus if the gene has been identified. The gene symbols, such as *PMEL17*, can be used to search the GeneCards database or other gene databases such as NIH National Library of Medicine Gene database (procedures described in the Appendix) in order to learn more about the genes and what is known about them and what functions they have.

There are around 15,000 genes in terrestrial vertebrate genomes. Baxter et al., 2018 identifed 650 genes associated with pigmentation in fish, mice and humans. I have assembled a list of 142 genes that I found associated with melanocytes and melanosomes. I have the Bennett and Lamoreux, 2003 classifications for the genes, their names, and their original loci designations, if I could find them, in my Table 1 (Melanocyte Pigmentation Genes). 38 of the genes listed in my Table 1 could not be found on the Baxter et al., 2018 list.

Table 1 has the genes identified by Bennett and Lamoreux, 2003 classifications. A large array of different kinds of genes with varied functions in the cell have been associated with melanocyte pigmentation. Genes classified as MD (Melanocyte Development) are needed to develop melanocytes from embryonic neural crest cells. Bennett and Lamoreux, 2003 noted that some alleles of the *KIT* and *MITF* genes, when homozygous, resulted in the failure of melanocytes to develop from the neural crest. The KIT kinase and the MITF transcription factor are required for melanocyte development in the embryo.

There is a category of genes that are physical components of melanosomes and their precursors (CMP). These are gene products that have been found to be associated with melanosomes within the melanocytes. The enzymes involved in melanin biosynthesis, and producing the physical structure of the melanosome are in this category as are the membrane bound carrier proteins involved in solute transport and regulation of the pH of the melanosome. These components can be in other functional categories such as melanosome transport (MT).

Melanosomes need to be transported to specific locations in the melanocyte or melanophore, and they need to be exported out of melanocytes into keratinocytes in order to form pigmented structures such as hair and feathers. Genes in the MT category are involved in melanosome transport.

There are genes involved in melanosome construction and routing proteins that are needed into the melanosome (MCPR). Melanosomes are derived from the endosomal membrane. These gene products are involved in making melanosomes and getting the physical components to the developing melanosome from other locations within the melanocyte.

The genes in the EP category are involved in the differential synthesis of eumelanin and pheomelanin. MC1R is an example. If the receptor is activated by binding MSH a signal is sent that results in the production of eumelanin. If ASIP binds to MC1R binding of MSH is blocked, MC1R signaling is inhibited and pheomelanin is produced. Solute carrier proteins are in the EP category because many of them alter the pH or import precursors required for melanin biosynthesis. Cysteine is required for pheomelanin biosynthesis but is not required for eumelanin biosynthesis. At acidic pH pheomelanin synthesis is enhanced while eumelanin synthesis is suppressed, but eumelanin synthesis is favored at basic pH and pheomelanin synthesis is suppressed.

Genes that affect pigmentation, but are known to be required for normal cell function are in the SE (systemic effects) category. A lot of genes in other categories can be considered SE. KIT and MITF have other functions in the cell besides regulating the development of melanocytes from neural crest cells. Enzymes such as PAH (Phenylalanine hydroxylase) and TPH1 (Tryptophan hydroxylase 1) aren’t just used for tyrosine metabolism for the production of melanin, but are enzymes involved in general cellular amino acid metabolism.

I constructed Table 1 so that I could easily identify genes in specific categories, get an idea of what function the gene is associated with, and use the table to quickly obtain more information on the genes using a web browser. I expect that others interested in melanin pigmentation can do the same. The Appendix has examples of how to utilize web resources.

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Corrections for Brancalion et al., 2022

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Animalgenetics.com canine *K* locus page with incorrect description of the causative phenotype. “The dominant black allele is actually a mutation that reduces or eliminates the expression of the agouti gene (A-Locus).”

<https://animalgenetics.com/dog-tests/canine-color-tests/8-klocus/>

UC Davis web site with the incorrect description of the causative phenotype. “Dogs with **K/K** genotype are expected to be unable to express the Agouti gene, leading to solid eumelanin pigmentation (no pigment banding in the hair shaft) in colored areas on the dog's body.”

<https://vgl.ucdavis.edu/test/dominant-black>

**Appendix:**

MGI “genes” page:

<https://www.informatics.jax.org/genes.shtml>

Type in a gene name like “MC1R” in the search box and you get:

<https://www.informatics.jax.org/quicksearch/summary?queryType=exactPhrase&query=MC1R&submit=Quick+Search>

This is the “Genome Features” page. If you click on the “Alleles” tab you get a list of known alleles for MC1R.

In the “Type” column: Spontaneous alleles often have their locus designations associated with the gene name.

“Spontaneous alleles Mc1r e Melanocortin 1 receptor; recessive yellow”

MC1R is the chicken and mouse *E* and *e* locus, respectively.

GeneCards is a human gene database:

<https://www.genecards.org/>

Search a Gene name like “MC1R” and get:

<https://www.genecards.org/Search/Keyword?queryString=MC1R>

It is a list of genes that may include an alternate gene name, but most of them are genes associated with the gene that you have searched for. If you click on the MC1R “Symbol” you get a description of what is known about that gene in humans.

NIH Gene Search page:

<https://www.ncbi.nlm.nih.gov/gene/>

If you search “Mouse MC1R” you get:

<https://www.ncbi.nlm.nih.gov/gene/?term=Mouse+MC1R>

If you click on the “melanocortin 1 receptor [*Mus musculus* (house mouse)]” search result that is provided in table format you get:

<https://www.ncbi.nlm.nih.gov/gene/17199>

You get genomic information about the gene in the description there is a category “Also known as” with “e” for *e* locus as one of the gene alternative names. NCBI does not seem to differentiate initial loci designations from gene designations. You also get genome location, transcripts, relevant publications, list of known alleles etc from each gene page. You can use this page to get information on the same gene in other animals by clicking on the links in the “Homology” section.