



Review

Analogues of human genetic skin disease in domesticated animals[☆]Justin Finch, MD^{a,*}, Stephanie Abrams, DVM^b, Amy Finch, MBA^a Department of Dermatology, University of Connecticut School of Medicine, Farmington, CT^b The Ohio State University Veterinary Medical Center, Columbus, OH

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ABSTRACT

Genetic skin diseases encompass a vast, complex, and ever expanding field. Recognition of the features of these diseases is important to ascertain a correct diagnosis, initiate treatment, consider genetic counseling, and refer patients to specialists when the disease may impact other areas. Because genodermatoses may present with a vast array of features, it can be bewildering to memorize them. This manuscript will explain and depict some genetic skin diseases that occur in both humans and domestic animals and offer a connection and memorization aid for physicians. In addition, we will explore how animal diseases serve as a model to uncover the mechanisms of human disease.

The genetic skin diseases we will review are pigmentary mosaicism, piebaldism, albinism, Griscelli syndrome, ectodermal dysplasias, Waardenburg syndrome, and mucinosis in both humans and domesticated animals.

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Introduction

Human genetics is a vast, complicated, and rapidly expanding field. Many genetic diseases affect the integumentary system; therefore, afflicted patients present first to a dermatologist. The dermatologist's ability to recognize the features of a genodermatosis and their capability to group salient features together to ascertain a diagnosis is unique among medical specialists. It is rare for a dermatologist to encounter undiagnosed genetic skin diseases in daily practice, thus making it difficult to memorize these genodermatoses. Any connections we can draw between the work we do in our own clinic and other areas of life will aid in the remembrance of genetic skin disease.

Many of the genetic skin diseases that doctors encounter in their patients occur in animal species as well and the expression of gene mutations in animals is at times much more apparent than in human patients.

This manuscript will explore genetic skin diseases that occur both in humans and domesticated animals. Recognition of the genetic underpinnings of pigmentary variations in animals can reinforce the memorization of features of gene mutations that are important in diagnosing human disease. Furthermore, for those outside of the medical profession, knowledge of the outcome of genetic variation in

animals makes the complicated topic of human genodermatoses more accessible and relatable.

Connections between human genetic disease and phenotype of domesticated animals

In domesticated animals, genetic skin diseases and particularly those that affect pigmentation may have a striking phenotypic expression. For millennia, humans have bred animals for specific desirable traits and historically, domesticated animals were bred primarily for function. For example, terriers were bred to control the population of rabbits and rats in Europe and oxen for their strength as a plow animal. More recently, domesticated animals have been bred for appearance, sometimes to the detriment of their health.

The interest in and emphasis on the appearance of purebred dogs and the popularity of dog showing was initially noted in North America in the 1870s with the establishment of the National American Kennel Club in 1876 and the Westminster Dog show in 1877. Subsequently, the National American Kennel Club developed a studbook in 1879 to help regulate breed standards and breeders started selecting dogs on the basis of beauty points instead of working talent. This trend has been notably criticized in the German Shepherd dog breed. The German Shepherd was originally bred to protect and herd flocks of sheep because of its well-muscled hind quarter and strong hind limbs. Recently, a sloping back conformation has become

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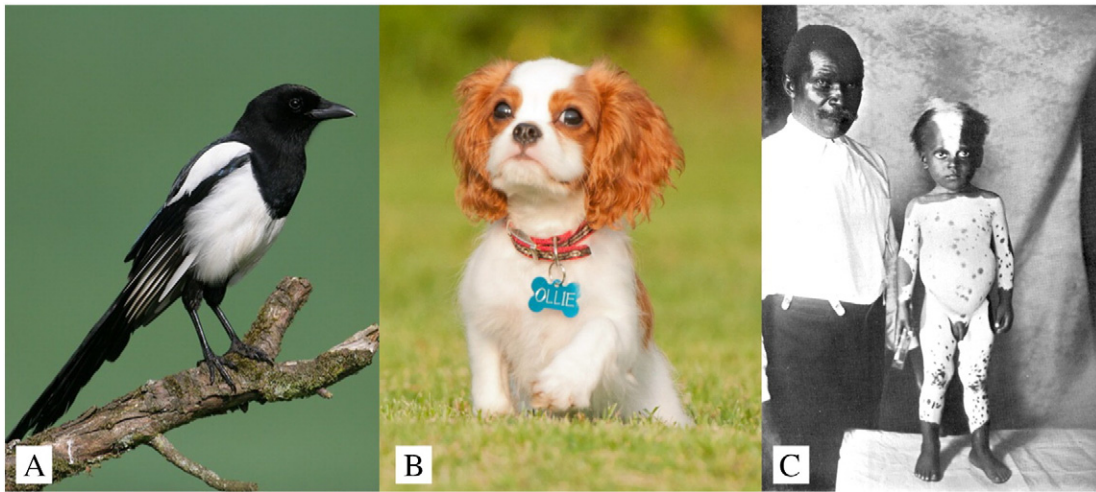


Fig. 1. Piebaldism. (A) A magpie that exhibits midline depigmentation (Available from: <https://upload.wikimedia.org/wikipedia/commons/5/50/01-Magpie.jpg> User: diginatur [own work], CC BY-SA 3.0). (B) Cavalier King Charles Spaniel dog that demonstrates axial depigmentation (Justin Finch, MD). (C) Human with piebaldism who lives in El Cayo, British Honduras (Available from: https://commons.wikimedia.org/wiki/File:ALBINISM;_Human_Piebald_living_in_El_Cayo_Wellcome_L0032353.jpg Credit: Wellcome Library, London. Originally published in Karl Pearson and C. H. Usher. London: 1913. Plate BB).

en vogue and breeding for the sloped back has weakened the integrity of the breed's hips and limited their use as a working dog.

Piebaldism

Piebaldism is a rare, autosomal dominant (AD) disorder of melanocyte migration that results from a mutation in the *KIT* gene and can occur in nearly every species of mammal. Unlike many of the genodermatoses we will discuss, piebaldism is notable because it is solely a pigmentary skin disorder and lacks any systemic findings. Therefore, it is not surprising that when the unique pigmentary alteration was identified in domesticated animals, humans selected the gene for propagation to create new breeds of animals.

KIT gene mutations that cause piebaldism result in axial depigmentation, which usually spares the hands, feet, and back. Humans present with poliosis at birth, of which the most characteristic feature is a white forelock in 80% to 90% of cases. A piebald or pied animal has an analogous pigmentary pattern. The term *piebald* is a portmanteau of the words magpie and bald and originated as a reference to the distinctive black and white plumage of a magpie (Fig. 1; Skeat, 1882). Other notable examples include a black-and-white spotted Holstein cow and the Cavalier King Charles Spaniel dog breed.

Pigmentary mosaicism and lyonization

Pigmentary mosaicism is the occurrence of multiple colors or tonal variations of the skin or hair as a result of a mosaic gene mutation (Fig. 2). The exact genetic underpinnings of pigmentary mosaicism in humans remain elusive. Pigmentary mosaicism is a phenotypic endpoint that likely results from a vast array of genes. Although it is likely highly genetically heterogeneous, there are many cases of phylloid hypomelanosis among the known genes that are due to mosaic trisomy 13 (Faletra et al., 2012; González-Enseñat et al., 2009).

In cats, hair color is a manifestation of different types of melanin much like in humans, with areas of pheomelanin-producing orange or red hair and eumelanin-producing black hair. Tortoiseshell cats have coat coloration that comprises of brindled swirls and stripes of red and black colored fur (Fig. 2). The orange coat color in cats is coded on the X chromosome and the tortoiseshell phenotype is

produced by lyonization or X-inactivation. Therefore, tortoiseshell cats are female (or in rare cases, XXY male cats). When the tortoiseshell phenotype is combined with piebaldism, the result is a calico cat, which is also female. As the amount of piebalding increases in a calico cat, the areas of color become more distinct from one another and produce a phylloid tricolor pattern of white, orange, and brown.

Albinism

Oculocutaneous albinism is a group of pigmentary dilution disorders that affect the pigment-containing structures of the skin and eyes. Oculocutaneous albinism type 1 exhibits the greatest degree of pigmentary dilution and is characterized by very pale skin, white hair, and pink- or light-colored irises (Fig. 3). Types 2, 3, and 4 have lesser degrees of pigmentary dilution. Causative genes and their protein products include tyrosinase (*TYR*), *OCA2* gene (a P protein), tyrosinase-related protein (*TYRP*), and the membrane-associated transporter protein, which is also known as solute carrier family 45 member 2 (Finch and Payette, 2016).

Among domesticated animals, albinism in rats is noteworthy because the rat was the first mammalian species that was domesticated for scientific research. Work with albino rats dates back to the first half of the nineteenth century (Kuramoto et al., 2012). The albino rat was used as a model to confirm that Gregor Mendel's famous laws on Mendelian Inheritance held true in the animal kingdom and it continues to be a popular exotic house pet today.

Temperature-sensitive albinism

Temperature-sensitive albinism is a variant of oculocutaneous albinism type 1B and is caused by an autosomal recessive (AR) mutation in the *TYR* gene. The temperature-sensitive variant *TYR* gene encodes a thermolabile tyrosinase enzyme that is inactivated at temperatures that exceed 35°C. The mutation results in decreased tyrosinase levels but with enough residual tyrosinase activity to produce some pheomelanin. As a result, cutaneous structures in warm sites of the body (eg, axilla, groin) are depigmented but normal coloration persists in cool acral sites (eg, arms, legs). Intermediate areas may have red hair (Wang et al., 2005).

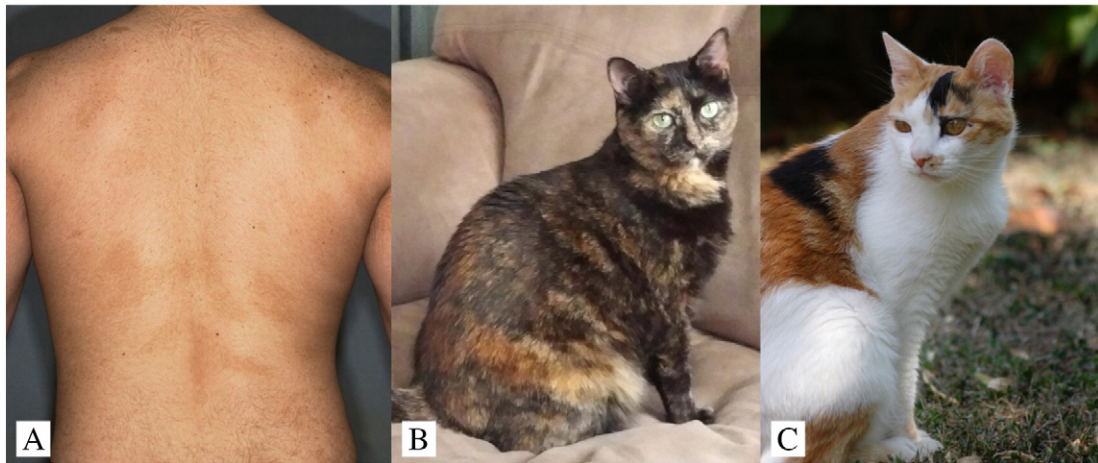


Fig. 2. Variations in pigmentary mosaicism. (A) Pigmentary mosaicism in a human (Justin Finch, MD). (B) Pigmentary mosaicism in a tortoiseshell cat (Stephanie Abrams, DVM). (C) Pigmentary mosaicism in a calico cat (photo courtesy of Tatiana Chessa; under CC-BY SA 3.0 license).



Fig. 3. Albinism. (A) Pet rat with albinism (Available from: <http://dir.niehs.nih.gov/dirlep/Webpages/clinpath.html>, public domain). (B) An albino girl from Papua New Guinea (Available from: https://commons.wikimedia.org/wiki/File:Albinistic_girl_papua_new_guinea.jpg, public domain).

These variations may be difficult to detect in humans but are striking in fur-bearing animals. The most notable example is the Siamese cat (Fig. 4).

Griscelli syndrome

Griscelli syndrome type 1, often classified as one of the silver hair syndromes (Finch and Payette, 2016), is a pigmentary dilution disorder that is caused by an AR mutation in Myosin Va (*MYO5A*). Myosin Va binds melanophilin to the actin cytoskeleton. Myosin Va is abundant in neurons of the central nervous system, cephalic ganglia, and spinal ganglia (Mercer et al., 1991) and controls oligodendrocyte morphogenesis and myelination (Sloane and Vartanian, 2007). Therefore, mutations result in profound neurologic defects and disordered melanosome trafficking. Affected humans have silvery-colored skin and hair, quadraparesis, mental retardation, and seizures.

Mutated *MYO5A* is present in approximately 10% of Arabian horses and homozygous transmission of the gene results in a lethal disorder known as Lavender Foal Syndrome, also known as Coat Color Dilution Lethal (Brooks et al., 2010). Affected foals are born with a coat color that is described as silver, pewter, lavender, or pink (Webb and Cullen, 2010). Afflicted foals are typically euthanized because of a constellation of severe neurologic abnormalities including opisthotonos and an inability to stand (Fig. 5).

Ectodermal dysplasia

Ectodermal dysplasias are a group of disorders in which there is abnormal development of the skin, nails, hair, teeth, or other adnexal structures such as sweat glands. Dozens of causative genes have been identified in humans. It is beyond the scope of this article to cover all the associated genes; however, it is worth discussing some specific phenotypes.

Woolly hair is an abnormal variant of hair growth in which the hair shaft is tightly coiled and imparts a woolly appearance. It is frequently



Fig. 4. Siamese cat (Stephanie Abrams, DVM).



Fig. 5. Foal with Lavender Foal Syndrome demonstrating pigimentary dilution and opisthotonos, one cardinal neurological sign of the disorder (PLoS Genet 2010;6, CC-BY 3.0).

associated with hypotrichosis and considered a hair growth deficiency. Keratins are a major structural component of the hair follicle and type II keratins 71, 72, 73, and 74 have been shown to localize to the inner root sheath of the hair follicle (Langbein et al., 2003). Keratin 74 mutations have been shown to underlie some pedigrees of AD woolly hair and hypotrichosis (Shimomura et al., 2010; Wasif et al., 2011), and more recently a keratin 71 mutation has been shown to cause the same phenotype (Fig. 6; Fujimoto et al., 2012).

Interestingly, in cats the *KRT71* gene is responsible for two distinct breeds: woolly-haired and hypotrichotic. The woolly-haired Selkirk Rex (Gandolfi et al., 2013) carries a *KRT71* mutation (Fig. 6). Likewise, the very distinctive phenotype of the profoundly hypotrichotic hairless Sphinx cat is the result of a *KRT71* mutation that was bred into the feline to create this notable breed (Fig. 6; Gandolfi et al., 2010). These cats, like affected humans, do not appear to have any systemic deficits.

Interest in hairless pets is not limited to cats. Among dogs, the Chinese Crested and Xoloitzcuintli dogs (commonly known as the Mexican hairless dog) are also bred for their hairlessness. Mutations in the *FOXI3* gene that encode a forkhead box (FOX) protein are responsible for ectodermal dysplasia in both the Chinese Crested and Xoloitzcuintli dog breeds (Drögemüller et al., 2008; Wiener et al., 2013). Forkhead box proteins are a family of transcription factors that are important in regulating the expression of genes that are involved in cell growth, proliferation, and differentiation.

Today, we have not implicated forkhead box proteins in ectodermal dysplasias in humans but this discovery in dogs may prompt an investigation for new paths of human disease. Among human genodermatoses, FOX gene mutations that are worthy of a mention include *FOXP3*, which is responsible for IPEX Syndrome, and *FOXC2*, which is responsible for a range of disorders that exhibit lymphedema as a prominent feature including Meige Lymphedema, Lymphedema-Distichiasis, and Lymphedema-Yellow Nail Syndrome. But again, ectodermal dysplasia is not a feature of these disorders.

Waardenburg syndrome

Waardenburg syndrome is a group of heterogeneous disorders that are caused by mutations in at least half a dozen genes (Table 1). In humans, characteristic phenotypic features include poliosis that resembles piebaldism, synophrys (ie, medial eyebrow hyperplasia), and sensorineural deafness. Waardenburg syndrome commonly results in ophthalmic findings and most notably dystopia canthorum (ie, increased intercanthal distance and a broad nasal root with normal interpupillary distance) and heterochromia iridis. Affected patients have normal vision. Mutations in the endothelin-B receptor (*ENDRB*), endothelin-3, or SRY box 10 underlie type 4 Waardenburg Syndrome in which affected patients also exhibit Hirschsprung's disease.

Waardenburg syndrome has several corollaries in the animal kingdom. For example, among horses, the unique pigmentation of the American Paint Horse breed Frame Overo results from an AD mutation in *ENDRB* (Fig. 7A; Magdesian et al., 2009). Like affected humans, these horses are deaf. Foals homozygous for this mutation suffer from a fatal condition known as Lethal White Overo, with lethality that results from severe Hirschsprung's disease. Among ferrets, the blaze coloration is a ferret with a white stripe down its forehead (Fig. 7B). One hundred percent of ferrets with a white blaze are deaf (Piazza et al., 2014) and between 20% to 40% of white odd-eyed (heterochromic) cats are deaf (Cvejic et al., 2009). The association between deafness and dappled coat color also extends to llamas, alpacas, and dogs (Gauly et al., 2005; Strain et al., 1992).

Mucinosis

Mucinoses are a diverse group of skin disorders that involve the deposition of mucopolysaccharides in the skin and most notably the jelly-like protein hyaluronic acid. Mucinoses in humans can range in severity from minor nuisances to life-threatening systemic



Fig. 6. Phenotypic variation of Keratin 71 mutations in humans and cats. (A) Autosomal dominant woolly hair and hypotrichosis that is caused by *KRT71*. Note the sparse eyebrow and woolly scalp hair (photo courtesy of Shimomura Yukata, MD). (B) Pure breed Sphinx cat. This phenotype is also caused by a *KRT71* mutation. (photo: by User: Artourp [Own work], CC BY-SA 3.0; Available from: <https://upload.wikimedia.org/wikipedia/commons/9/95/Shabbat.jpg>). (C) Selkirk Rex. The woolly hair is caused by a *KRT71* mutation. (photo: Nickolas Titkov [own work], CC BY-SA 3.0; Available from: <https://www.flickr.com/photos/titkov/5297138877/>).



Fig. 7. Pigmentary alteration in Waardenburg syndrome. (A) Deaf Frame Overo horse displayed at a show (photo: by Sandysphotos2009; licensed under CC BY 2.0). (B) Deaf blaze-color ferret. (image courtesy of John Porter and Erika Matulich, PhD, PCM). (C) Waardenburg syndrome in two siblings (image courtesy of Chirsophe Hsu, MD).

diseases that affect internal organs. Among the more severe forms of mucinosis, scleromyxedema and follicular mucinosis are notable for their propensity to extensively infiltrate the dermis and cause deep furrows in the skin, which impart a leonine appearance to the facial features of afflicted patients (Fig. 8A).

In domesticated animals, the Shar-Pei dog is a breed that is prized for its distinctive wrinkly skin (Fig. 8). Humans have bred a hereditary cutaneous mucinosis into this species to produce the characteristic wrinkled phenotype (Zanna et al., 2008, 2009). Some Shar-Pei dogs suffer from such severe mucinosis that the mucin forms papules and nodules on the surface of the skin that rupture, ooze, and become pyodermatous or infected.

It has long been known that Shar-Pei dogs are predisposed to aggressive mast cell cancers. In humans, mast cells are found also in increased numbers in skin that is affected by mucinosis (Kobayasi et al., 1976). Mast cells in other diseases are associated with increased angiogenesis but mast cells in mucinosis appear to not be associated with neovascularization (Martins et al., 2010). Much remains to be learned about mucinoses and

the Shar-Pei dog breed may serve as a model for ongoing studies of this disease.

Conclusions

Genetic skin diseases can present with a vast array of features. Because of humans' pursuit of desirable visible traits in domesticated animals, we have bred some of the same mutations that cause disease in humans into our pets. The phenotype of these genodermatoses is at times more apparent in animals than in humans and familiarization with the features can aid in the recollection of the important aspects of genodermatoses in humans. The genetics of skin disorders in animals also carries relevance to humans because animal diseases serve as a model for uncovering the mechanism of human disease. Without murine models of disease, the field of genetics probably would not exist at all. By recognizing the similarities between animal and human disease, dermatologists can better serve their patients.



Fig. 8. (A) Leonine facies due to follicular mucinosis (photo: Peter Heald, MD). (B) Shar-Pei dog with facial features that result from hereditary mucinosis (Available from: <https://www.flickr.com/photos/48685334@N00/388814720>; User: whartonds; licensed under CC BY-SA 2.0).

Table 1
Human disease and corresponding animal breed that result from the same gene mutation

Human Disease	Gene	Protein Product	Animal Breed
Piebaldism	<i>KIT</i>	ckit	Cavalier King Charles Spaniel dog Holstein cow Many others Calico cat
Phylloid Pigmentary Mosaicism	Humans: unknown, some due to mosaic trisomy 13	Unknown	
Oculocutaneous Albinism, Type 1	<i>TYR</i>	Tyrosinase	White rat Many others
Temperature-Sensitive Albinism	<i>TYR</i>	Tyrosinase	Siamese cat
Griscellii Syndrome	<i>MYO5A</i>	Myosin Va	Some Arabian horses (Lavender Foal Syndrome)
Autosomal Dominant Woolly Hair and Hypotrichosis	<i>KRT 71</i>	Keratin 71	Hairless Sphinx cat (KRT71) Selkirk Rex cat
Waardenburg Syndrome type 1	<i>PAX3</i> <i>SLUG</i>	Paired Box Gene 3 Zinc finger transcription factor	Blaze-colored ferret (exact gene unknown)
Waardenburg Syndrome type 2	<i>MITF</i>	Microphthalmia-associated transcription factor	Blue-eyed white-coat cats (exact gene unknown)
Waardenburg syndrome type 3	<i>PAX3</i>	Paired Box Gene 3	
Waardenburg Syndrome type 4	<i>SOX-10</i> <i>ENDRB</i> <i>EDN3</i>	SRY box 10 Endothelin-B receptor Endothelin-3	Frame overo horse

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