BY
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Everything you need to know about Genetics...

You can learn from your Cat!

PART SIX

DOMINANT WHITE – *not as clear as you think!*

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Dominant *White (W,w)* is a coat color trait recognized in cats since their domestication. The book "*Siamese Cats: Legend and Reality*", recognized the completely white cat (Khao Manee) in ancient times.[1]

Many domesticated or fancied species, such as, mice, alpaca, donkey fox, and pig have versions of completely white individuals.[2-7] All white and white spotting phenotypes are actually associated with the domestication process.[8] Rarely do animals in the wild have and maintain all white (albino) colorations as these colors are not supportive of the camouflage necessary for tracking and hunting prey or eluding predators in most ecological niches.

SAME GENE – DIFFERENT MUTATION

Early breeding studies suggested a completely white cat may be an accumulation of white spotting (piebald spotting), however, focused breeding studies proved dominant *White* was a separate "entity" from *Spotting*, but potentially an allele (different DNA mutation) at the same gene.[9-11] *Spotting* was genetically mapped to cat chromosome B1 near the *KIT* locus, suggesting the involvement of this gene known to cause white in other species.[12]

Although white spotting and all white coat colors have historically been represented as two different loci, hence, two different genes, *Spotting* (*S, s*) and *White* (*W,w*), the early genetic suggestions are accurate, both white spotting and completely white cats are controlled by different mutations in the same gene.[13,14]

THE PROTO-ONCOGENE *(KIT)*

Not considering *Spotting* phenotypes, a completely white cat can occur by three different genetic means – they can be homozygous for two different recessive mutations in the gene called *Tyrosinase* (*TYR*) or have a dominant mutation in the gene called *v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog* (*KIT*).[13,14] Notice the gene name has the word "oncogene". Because cancer studies are so prominent, many genes are first identified via their associations with cancers. Oncogenes are a mutated version of a normal gene (a.k.a. proto-oncogene) that contribute to the development of cancer. The normal cells and DNA of a cat have the proto-oncogene called *KIT*.

HEART STEALER WHITE KNIGHT (Odd-Eyed White Maine Coon Male)
Owner: Adrienn Cripper (Hungary) Photographs © Helmi Flick Cat Photography

FIFe SC. GENASAQUA'S PRINCE OF WHITE'R'US (Blue-Eyed Persian Male)
Breeder: Lisa Monical (USA) Owner/Photograph: Jose Dias (Portugal)

KIT is also known as *c-kit*, meaning the cellular, i.e. the normal version of the gene. Two researchers, William Hardy and Evelyn Zuckerman, identified *KIT* is a type of skin cancer, fibrosarcoma, but it was a mutated version and known as viral (*v-kit*).[15] This version of the gene had a specific DNA domain sequence called a ***ki***nase inser***t***, hence was called kit (nothing to do with cats really). But since that early discovery, the *KIT* gene has been shown to play many other roles in cat development.

KIT plays a major role in normal cell migration during the development of the body – in all species.[16] Particularly involved with melanocyte (the cells that produce pigment) migration, *KIT* mutations alter the normal flow of melanocytes in the skin.[17] During development, as an early embryo, the precursor cells to melanocytes – melanoblasts - migrate from basically the backbone area (i.e. the neural crest) and move from dorsal to ventral – on both sides of the body. The melanoblast cells meet in the middle of the body (i.e. the midline) on the belly side (ventral) of the cat. Little white spots, including lockets and belly spots, are actually very mild midline closure defects, similar to a cleft palate, cleft lip, or umbilical herniations of the intestines.

If a melanoblast does not finish its migration to a certain part of the body, such as the midline, the paws, the underside of the cat, then no cells will be present that can make color, thus, the cat will be white in these areas. A cat that is all white has a severe mutation that basically disrupts all melanoblasts, so no melanocyts are produced, therefore no color is produced. Sometimes just a tiny number of melanocytes are present, which will lead to a pigmented spot in the middle of the top of the head (i.e. a skull cap).

ODD-EYED WHITES

Melanoblasts are very important cells and also migrate to the iris and the reflective layer in the back of the eye – the tapetum lucidum.[18-20] The more melanocytes in the iris, the darker the eye color. Hence, when the *KIT White* mutation is present, cats can often have blue or odd-eyed coloration as they do not have enough melanocytes to produce more pigment. The blue eye will also have red eye shine since the melanoblasts did not migrate to the tapetum lucidum as well. In this layer of cells in the back of the eye, the melanoblasts specialize and uptake zinc, which then helps with light reflection. Light comes into the eye through the pupil, passes through the retina, which has the photoreceptors that read the photons of light, light hits the tapetum lucidum, then bounces back the other way to the photoreceptors again, thereby improving the light signal. Cats with red eye shine likely have a lower ability to see well in the dark, although this has never been proven to my knowledge.

DEAFNESS

Deafness has been associated with White cats and documented in 1959.[21] Pigmentation cells are also important in the development of the inner ear. Melanocytes are contained within a blood vessel–rich zone of the cochlea known as the stria vascularis.[22-24] Disruption of the stria vascularis is known to cause deafness in many species, included mice and man, which will also have white spotting (hypopigmentation) phenotypes as well. Like eye color, a cat can have poor migration of the melanoblasts to the inner ear and some completely white cats may have unilateral or bilateral deafness. A BAER (brainstem auditory evoked response) test is required to determine if a cat has unilateral or bilateral deafness, since, you may think the cat can hear – but the cat may be using only one ear. Since cats can sense vibrations extremely well, deaf cats often go unnoticed.

The genes and mutations that produce alterations in many tissues have what is called “plieotrophic effects”. The migration of the melanoblasts can be somewhat random and may be disturbed by other factors.[25-26] Thus, although a cat may have a mutation for dominant *White*, prediction of eye color and hearing is very difficult. Likely, other genetic factors are important and interplay with *KIT* as some lines of cats never have hearing problems, while other lines and breeds more commonly have blue, odd-eyed and hearing issues. Since white cats with blue eyes clearly did not have sufficient melanoblast migration during development, the correlation is strong that the cat may also have a hearing deficit, or on the same side as the blue eye for odd-eyed colored cats.

EDITOR:

This is the sixth in a series of articles based on feline genetics by Dr Leslie Lyons to be published in FELIS HISTORICA

ASSOL DeMAUNTIFUL (Odd-Eyed White Oriental Shorthair)
Breeder/Owner: Ivan Menshenin 'cattery DeMauntiful' /Photograph: E.Lisenkova

In study of 84 cats from 10 breeds, overall deafness prevalence was 20.2%; 9 cats (10.7%) were bilaterally deaf and 8 cats (9.5%) were unilaterally deaf. Deafness status was associated with iris color.[28] In a second study, deafness was diagnosed only in solid white kittens of the breed cats examined, with a prevalence of 30.3% (15.9% bilateral, 14.4% unilateral). The prevalence of deafness was significantly higher in white kittens with one (44.4%) or two (50%) blue eyes than kittens with normal eye color (22.2%). Kittens with at least one blue iris were 3.2 times more likely to have deafness than kittens without blue eyes. Considering the breeds, deafness was diagnosed in 7 of 15 (46.7%) Turkish Vankedisi, 8 of 18 (44.0%) Maine Coon, 18 of 41 (43.9%) Norwegian Forest, three of 11 (27.3%) British Shorthair, two of 12 (16.7%) Devon Rex, two of 12 (8.3%) Persian, one of 21 (4.8%) Russian, and neither of two Sphynx.[29] Therefore, breed differences may be a result of different genetic factors influencing the major *KIT* mutation. More studies need to focus on the genetic differences between breeds and lineages within breeds.

WHITE SPOTTING

Other interesting facets regarding the mutations causing *White* and *Spotting* are the placement, size and types of the *KIT* mutations. The *White* and *Spotting* phenotypes are caused by a feline endogenous retrovirus (FERV1) in the first intron of the KIT gene. [13,14] A full-length (7125 bp) FERV1 element, a big mutation is associated with the lesser white spotting, whereas a smaller FERV1 long terminal repeat of ~ 700 bp (LTR) is associated with cats with a greater amount of white, all white cats.

Firstly, the bigger mutation causes the lesser phenotype and vice versa. Secondly, the mutations are in an intron, which do not code for the protein. Thus, the functions of these mutations are still unknown but must play a role in gene control, regulation and expression. Thirdly, the mutations are parts of an endogenous retrovirus.

These are sequences of an inactive historical virus that are highly repeated and inserted all through-out the cat genome – junk DNA. Now we are finding that accidental insertions of this junk DNA into a gene or near a gene can cause a disruption in the gene's regulation and function. Many more mutations are now being identified that affect the regulation of genes and not the production and function of the gene's protein. These mutations are much harder to confirm and to understand.

Overall, most white phenotypes in cats are caused by mutations in the *KIT* gene, including *White*, *Spotting* and *Gloves*,[30] however, other genes and variants may cause other white phenotypes as well, such as mitted in the Ragdoll.

KIT has many functions in development and its function is affected by sporadic chance occurrences and likely other genes and mutations. Although the cats are white, the interactions of the *KIT* gene and its mutations are not exactly clear!

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