Everything you need to know about Genetics...

You can learn from your Cat!

PART FIVE – BLUE DILUTION

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VARIATIONS ON A THEME AND FIFTY SHADES OF GREY
VARIABLE EXPRESSION AND GENETIC HETEROGENEITY

The domestication of the cat led to the propagation of novelty colorations, which are not prevalent or unknown in the progenitor wildcat population. Blue dilution (*Dilute* or *Dense*) (a.k.a. Maltese dilution) is a simple autosomal recessive trait (*d*), meaning a cat must have two copies of the mutation (*dd*) to express the trait (phenotype blue) [1].

The blue trait in cats helped to prove the accuracy of Mendel's laws in the early 1900's[2]. Other species, including mice, rabbits and guinea pigs were soon recognized to have the same coloration and inheritance pattern[3,4].

Although genetically simple, the blue dilution trait of cats can help explain the complex genetic concepts of *"variable expression"* and *"disease heterogeneity"*. All research studies in genetics must be aware of these phenomena and control for their occurrence when developing a new investigative project.

In cats, blue dilution is caused by one, and only one, specific DNA mutation (c.83delT) in the gene called *melanophilin* (*MLPH*)[5]. Because this same single mutation causes blue in all breeds and in all cat populations around the world, the mutation is likely fairly ancient and occurred before the development of breeds and before cats were distributed around the world!

The one missing base of DNA, which occurs early in the gene (exon 2), changes nearly the entire translation of the protein, thereby gravely disrupting the protein formation and function. The melanophilin protein helps to transport the pigment-producing organelles (melanosomes), which are in the color producing cells (melanocytes), into the developing hair shaft[6-8].

Animals with *MLPH* mutations make black pigment (eumelanin) but, the deposition of the black pigment in the hair shaft is uneven and clumping. Thus, the refraction of the light through the air spaces of the hair shaft causes the black pigment to appear blue – an optical illusion. This pigment clumping has been demonstrated in mice[6-8] and in the domestic cat[9-10] and can be viewed with a light microscope.

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CHARTREUX CATS - Left: IC Foxycats Figaro (Italy) owned and photo by Katia Pocci
Right: IC Mayrit de la Chabanade (France) owned and photographed by Claire Luciano
These cats display the diversity of light and dark shades naturally occurring in the Chartreux Breed

KORAT CATS – GC, BW, RW. Sezerp's Frangelica of Rebkor owned and photographed by Becky Mullen and Right: CCCA GC, & Gd.Db.GC, Doklao Luuk Chai, owned and photographed by Eva Krynda.
Korats have a close-lying coat with silver tipping on the hairs that gives the cat a 'halo' effect.

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This is the Fifth in a series of articles based on feline genetics by Dr Leslie Lyons being published in FELIS HISTORICA over the ensuing months

But why then – when you look at a Russian Blue, a Chartreux, and a Korat, which all are **fixed** and each cat has **two copies of the *MLPH* mutation** (*dd*), as well as blue British shorthairs or a common blue tabby - ***why then - do these cats all have different shades of blue?***

This is the concept of *variable expression*!

Even though a trait may have very simple, autosomal recessive, Mendelian genetics, the overall resulting phenotype and physiological effects on the animal is a summation of the interactions of all the other genes in the pigment pathway, as well as the external and internal environment (i.e., nutrition) of the animal.

The breeds fixed for blue (Russian blue, Chartreux, and Korat) have very consistent but very different shades of blue, implying the rest of each breeds' genetic background tweaks the final presentation of the coloration.

Therefore, by inspecting these cat breeds, *variable expression* can be clearly witnessed by the average cat owner and breeder.

This same concept is true for other traits and diseases – in all species. Sometimes, a disease mutation can be present in an individual cat, but the cat may never get sick, or, have very mild disease.

Most cats with polycystic kidney disease live a long life, but clearly have a severe disease mutation in *PKD1*[11]. Some cats with the known retinal degeneration (blindness) mutations (*CEP290*) don't seem to go blind[12]!

This is variable expression and currently, no one knows the second most influential gene(s) or mutation(s) in the genome that affect the variation of the trait or disease.

Why are some *Dominant White* cats deaf, why do some have blue eyes or are odd-eyed, - these are all examples of *variable expression*.

Thus, the genetic tests for DNA mutations are not necessarily incorrect when a disease or trait is not present, or does not "appear" to be present!

The major mutation causing the coloration or disease is known, but not the genes and mutations causing the variations of the theme.

Blue dilution is a common phenotype identified in many other species, such as mice, rabbits, mink, cattle, and dogs[13-19].

However, at least three different DNA mutations cause blue dilution in dogs, all in the same gene, *MLPH*[17-19].

In mice, at least three different genes (*RAB27*, *MLPH and MYO5A*), cause the same blue dilution phenotype, the traits known as *Ashen*, *Leaden*, and *Dilution*[20,21,13]

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BRITISH SH CATS - Left: GC, NW Kitties Land Kratos and Right: GC, NW Kitties Land Main Event owned and photo by Allen Shi. The plush coat of the British Blue is the same shade of Blue from the root to the tip, with lighter shades preferred.

RUSSIAN SH CATS - Left: GC, Tsar Blu's Zcarlet and Right: GC, RW Tsar Blu's Zanzibar as a kitten bred, owned and photographed by Donna Fuller. Lighter shades are also preferred in the Russian Blue, while the tips of the hairs appear to sparkle with silver.

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In mice, each of these genes actually has several mutations causing variations in the blue coloration (*variable expression*) and also the mutations affect other tissues (plieotrophic effects).

In humans, Griscelli syndromes are rare autosomal recessive disorders resulting in pigmentary dilution of the skin and hair, the presence of large clumps of pigment in hair shafts, silvery-gray hair and accumulation of melanosomes in melanocytes.

Griscelli syndrome patients can also show developmental delay, hypotonia and mental retardation, as well as immune abnormalities, and have mutations in the same dilutions genes as found in mice[22]

The recently published Chediak-Higashi Syndrome mutation in the cat gene called *lysosomal trafficking enzyme* (*LYST*) is also a Griscelli - like syndrome and causes a different pigment dilution in cats[23].

These different genes and different mutations cause the same phenotype – blue dilution, this phenomenon is known as *disease (genetic) heterogeneity*.

Genetic studies are often unsuccessful because investigators are lumping individuals with the same clinical presentation together, but, actually, the different individuals are a mixture of similar phenotypes caused by different genes or mutations within the same gene.

Usually, information from the mouse is used to help find mutations in other species, like the cat, causing the same phenotype, implying the same gene becomes the top candidate, i.e. the candidate gene approach.

The same phenotype for *Agouti*, *Brown*, and *Color* (Siamese, albino) were known in mice and the cat versions of the mouse genes were directly investigated to find the cat-specific mutations.

Mice actually have several other genes that cause blue dilution - type phenotypes such as, *Slaty*, *Pewter*, and *Steel*[24].

The first recognized dilute mouse is actually caused by mutations in *MYO5A* – not in *MLPH*, thus, the direct candidate gene approach would have failed when looking for the cat blue dilution mutation.

Therefore, although the candidate gene approach is always the first consideration for genetic studies that search for new mutations in new traits and diseases, **other genetic approaches** need to available to help localize genes to a specific chromosomal region to further prioritize the potential candidate genes.

New technologies, **such as DNA arrays** and **whole genome** and **whole exome sequencing**, are the current, state-of-the-art techniques that support the identification of DNA mutations for new traits and diseases.

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PERSIAN CATS - Left: GC, PassionFelin Squeaky Smurf, and Right: GC, RW PassionFelin Paddington Bred, owned and photographed by Isabelle Beaulieu

Shades of Blue also vary in Persians, but evenness and soundness of colour throughout is paramount

References

1. Bateson W., Saunders E.R., Punnett R.C. Report III to the Evolution Committee of the Royal Society. pp 53 London, 1906.
2. Doncaster L. Proc. Camb. Phil. Soc.13:35-38, 1904.
3. Bateson W. *Mendel's principles of heredity*. University Press, Cambridge, UK., 1909.
4. Castle W.E., *et al*. Studies of Inheritance in Rabbits. *Carnegie Institute Washington Publication*, Washington. Series no. 114, 1909.
5. Ishida Y., *et al*. Genomics. 88:698–705, 2006.
6. Orlow S.J. J Invest Dermatol. 105:3–7, 1995.
7. Provance D.W., Jr, Wei M., Ipe V. Proc Natl Acad Sci USA. 93:14554–14558, 1996.
8. Wu X., *et al*. J Cell Sci.110:847–859, 1997.
9. Prieur D.J., Collier L.L. J Hered. 75:41-44, 1984.
10. Prieur D.J., Collier L.L. Hered. 72:178-182,1981.
11. Lyons L.A., *et al*. J Am Soc Nephrol. 15(10):2548-55, 2004.
12. Menotti-Raymond M., *et al*. Hered. 98(3):211-20, 2007.
13. Mercer J.A., *et al*. Nature. 349:709–713, 1991.
14. Lehner S., *et al*. PLoS One. 8:e84525, 2013.
15. Cirera S., *et al*. Gene. 527:48–54, 2013.
16. Li W., *et al*. Anim. Genet. 47:110–113, 2016.
17. Drögemüller C., *et al*. Hered. 98:468–473, 2007.
18. Welle M., *et al*. Hered. 100: S75–S79, 2009.
19. Van Buren S.L., *et al*. Genes.11(6):639, 2020.
20. Wilson S.M., *et al*. Proc. Natl. Acad. Sci. USA. 97:7933–7938, 2000.
21. Matesic L.E., *et al*. Proc. Natl. Acad. Sci. USA. 98:10238–10243, 2001.
22. Ménasché G., Fischer A., Basile G.D. Am. J. Hum. Genet. 71:1237–1238, 2002.
23. Buckley R.M., *et al*. Sci Rep. 10(1):64, 2020.
24. http://www.informatics.jax.org/allele (Accessed 12 October 2020)