BY
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Everything you need to know about Genetics...

You can learn from your Cat!

PART FOUR

THE SIAMESE
PHENOTYPIC VARIATION = GENETICS + ENVIRONMENT

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A basic concept of genetics is - the interaction between genes and the environment (GxE) produces the variation seen in the phenotype of an individual. Although someone may have "good genes", we do have to remember "you are what you eat". Siamese, Burmese and Tonkinese cats are a perfect example of the interaction between a gene and its environment.

The *Color* locus (*C*) in mammals encodes for the gene called *tyrosinase* (*TYR*).[1] Cats have *TYR* DNA variants causing the temperature-sensitive colorations of the sable Burmese (c^bc^b) and the "points" of the Siamese (c^sc^s)[2,3] (OMIA 000202-9685) and recently, the mocha colored Burmese (c^mc^m).[4]

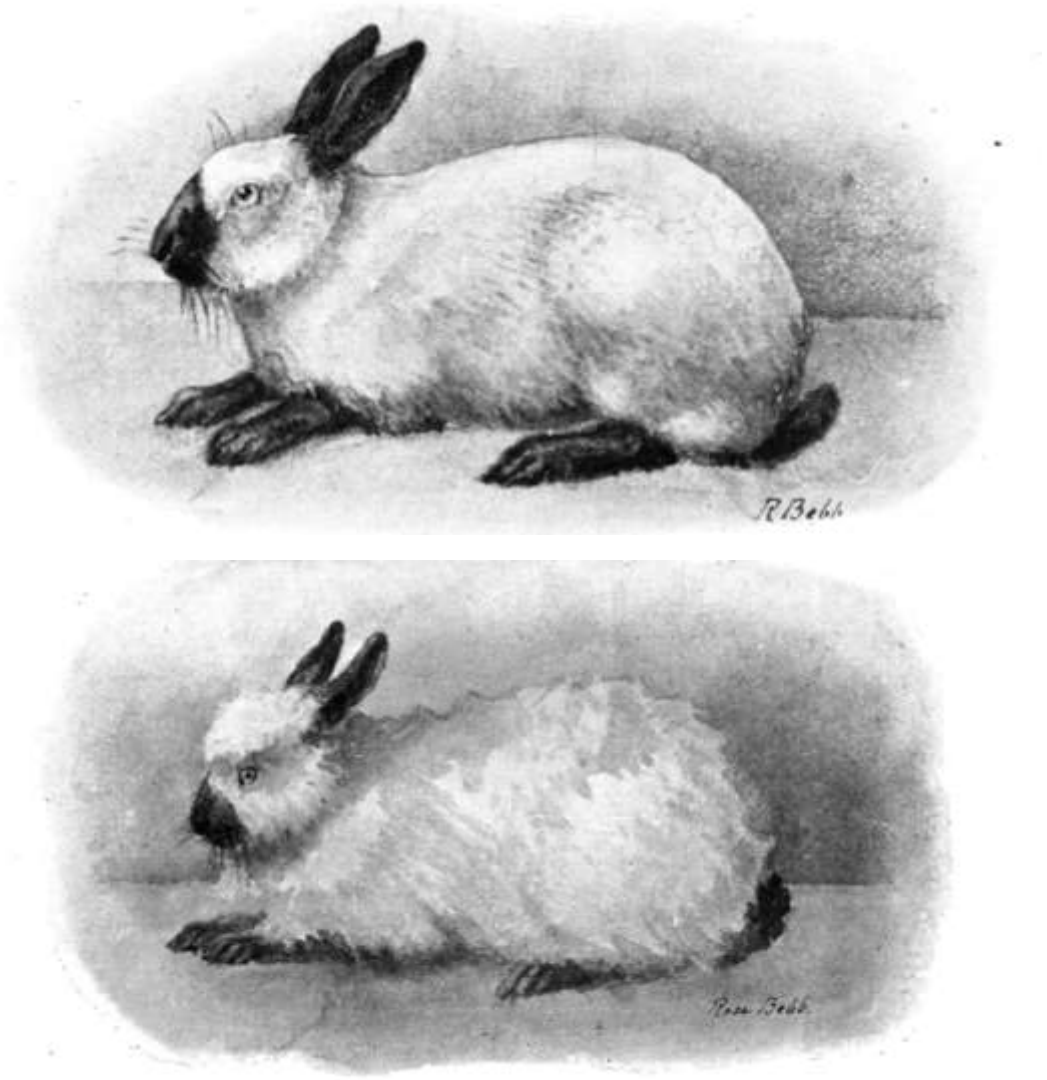
These breeds originated in Thailand and are known as the Suphalak (Burmese), Wichien-maat (Siamese) and Wila Krung Thep is suggested for the name of the Si Mai Thong (mocha) colored cats.[5] Two complete albino variants (c, c^2) are also known in *TYR* for cats (OMIA 000202-9685).[6,7]

For the well-known Siamese 'pointed' phenotype is c^sc^s; the fur is pigmented only at the extremities (tail, paws and a 'mask' on the face), the torso coloration is very light to white, and the lack of pigmentation produces blue eye color.[8-11] Burmese is an allelic variant (c^b) that is less temperature-sensitive, producing more pigment throughout the torso.[12]

The sable Burmese (c^bc^b) also has "points", which are less noticeable because of the overall greater color production on the body.

The Tonkinese (c^bc^s), is termed a compound heterozygote, having once copy of the Siamese allele and one copy of the Burmese allele and has an intermediate color gradient phenotype to Burmese and Siamese.[12]

Several cat breeds are fixed for the thermolabile albinism alleles, including Burmese and Singapura for the c^b allele, and Siamese, Birman,



Two early examples of Himalayan pattern Rabbits, dating from 1903.
Above: HIMALAYAN, Challenge Cup, Crystal Palace. Owner, F Avard. Below: SIBERIAN RABBIT.
'Rabbits, Cats & Cavies' (1903) by Charles H. Lane. Illustrations by Rosa Bebb.

Colorpoints, and Himalayan (pointed Persians) for the c^s allele. Over 13 cat breeds have desired segregation for the c^s and/or c^b alleles.[13,14]

Animals with this thermolabile type of "albinism" are called acromelanistic – Greek (akro – meaning top or point). The Himalayan rabbit phenotype was first published in 1857 in Europe, also known as the Black Nosed Rabbit from China[15] and was also described by Charles Darwin and others[16,17]. The inheritance of the pattern was determined as recessive by several early geneticists studying cats[8-12], Himalayan rabbits[18-20] and guinea pigs.[17,21,22] Likely, the Himalayan cat breed (pointed Persians) borrowed the name from the Himalayan rabbits.

The DNA variants causing similar temperature-sensitive acromelanism phenotypes have been identified in the Himalayan mouse[23], rabbit[24], gerbil[25], mink[26], and human.[27] The Siamese 'pointed' phenotype was demonstrated to be associated with (linked) to hemoglobin (HBB) protein variants in the cat.[28] *TYR* is on the same chromosome in cats as *HBB*, thus, *TYR* was suggested as the gene causing the Siamese phenotype. After this discovery, all other animals with the same "points" or "Himalayan" phenotype investigated the *TYR* gene and found the causal DNA variant!

EDITOR:
This is the Fourth in a series of articles based on feline genetics by Dr Leslie Lyons that will be published in FELIS HISTORICA in the ensuing months

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The trait locus was originally designated the *Color* locus (*C*). The *C* allele is completely dominant with normal color presentation. Breeding data from cats suggested an allelic series with at least three alleles, $C > c^b > c^s$.[29]

The DNA variant associated with the Siamese phenotype is an exon 2 guanine to adenine nucleotide transition changing the glycine to an arginine amino acid (G302R) in the protein. [2,3]

The DNA variant associated with the Burmese phenotype (c.679G>T; p.Gly227Trp) is an exon 1 guanine to thymidine nucleotide transversion changing the glycine to a tryptophan amino acid.

The mocha variant appears to interact with the temperature-sensitive alleles but also produces a more even, lighter coloration and is less thermally labile when homozygous. This variant introduces two novel amino acids and deletes 39 amino acids of exon 2, which causes a 37-amino-acid deletion (c.820_936delinsAATCTC (p.Ile274_Leu312delinsAsnLeu).

The current allelic series is consider *C* (*full color*) > c^b (*Burmese*) = c^s (*Siamese*) > *c*, c^2 (*albinos*), but, not all allelic combinations have been produced, thus, the complete interactions and the amount of dominance is not entirely understood.[4]

TYR is an enzyme, implying it causes (catalyzes) a chemical reaction. *TYR* uses a non-essential amino acid called tyrosine, which itself is made from the essential amino acid phenyalanine, which is commonly found in many high-protein food products, such as, chicken, turkey, fish, and milk.

TYR is a copper-containing enzyme present in plant and animal tissues that catalyzes the production of melanin and other pigments from tyrosine by oxidation. This enzyme is found inside a small organelle called a melanosome, which are synthesized in the skin cells that make pigment - melanocytes.[1] Melanocytes are also found in the iris and the tapetum of the eye, thus, the color variation affects these cells – a plieotrophic effect.

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Siamese cats have blue eyes and red eye-shine, Burmese and Tonkinese are more intermediate to full eye color and full eye shine. The optic nerves are also affected, the variants interfering with the normal development of the optic chiasma, which can lead to cross-eyes (strabismus) and shaking eyes (nystagmus).[30,31]

Studies in Himalayan mice demonstrated the environmental effects of the *TYR* DNA variants.[32] Pigment synthesis only occurs in actively growing hair. Housing adult and juvenile mice at 15°C (59°F) produced pigment in growing hair follicles whereas mice housed at 30°C (86°F) were absence of pigment granules in the growing hair follicles.

An early study on Siamese also demonstrated cats that were raised outside at 3°C (37°F) – 13°C (55°F) and never above 16°C (61°F) had very dark coats.[33] All pointed / Himalayan animals are born all white at birth.

In cats, the kittens are developing at the mother's body temperature, which is ~38°C (101°F), no pigment is produced in the fur and kittens are born all white. However, as kittens mature and they molt and regrow their fur, they begin to develop their point coloration. As cats age, circulation gets poorer, skin gets thinner, more coloration develops beyond the points. Areas of the fur that have been shaved or damaged will often grow in a different color and remain until a full mottling of the fur.

The Siamese cat is another example of how the domestic cat helped to develop and understand the basic concepts of genetics. The cat's variants in tyrosinase explain, co-dominance, recessive, plieotrophic effects, environmental effects and variable expression. They also demonstrate how a simple coat color can be important to understanding the biology of all mammals and the diverse roles of pigment genes of other physiology of the organism.

References

1. Ohbayashi N, Fukuda M. (2020) F1000Res. 9:F1000 Faculty Rev-608.
2. Lyons LA, *et al.* (2005) *Animal Genetics* 36:119– 26.
3. Schmidt-Küntzel A, *et al.* (2005) *Journal of Heredity* 96:289– 301.
4. Yu Y, Grahn RA, Lyons LA. (2019) *Animal Genetics* 50(2):182-186.
5. Clutterbuck MR. (2004) *Siamese Cats: Legends and Reality*, White Lotus, Bangkok, Thailand.
6. Imes DL, *et al.* (2006) *Animal Genetics* 37:175–8.
7. Abitbol M, *et al.* (2017) *Animal Genetics* 48:127–8.
8. Whiting PW. (1918) *Journal Experimental Zoology* 25:539.
9. Castle WE. (1919). *American Naturalist* 53:265–268.
10. Tjebbes K. (1924) *Journal of Genetics* 14:355-366.
11. Bamber RC. (1927) *Bibliographie Genetica* 3:1-83.
12. Thompson JC, *et al.* (1943) *Journal of Heredity* 34(4):119-123.
13. Cat Fanciers' Association (1993a) In: *The Cat Fanciers' Association Cat Encyclopedia* (Ed. Cat Fanciers' Association), pp. 128– 36. Simon & Schuster, New York.
14. Cat Fanciers' Association (1993b) In: *The Cat Fanciers' Association Cat Encyclopedia* (Ed. Cat Fanciers' Association), pp. 155– 94. Simon & Schuster, New York.
15. https://www.himalayanrabbit.com/copy-of-archived-breed-history
16. Darwin C. (1868) The Variation of Animals and Plants under Domestication (1st ed.) London: John Murray
17. Lane CH. (1903) In: *Rabbits, Cats and Cavies*. p.77 J.M. Dent & Co., London.
18. Castle WE, Allen GM. 1903. *Proceedings of the American Academy of Arts and Sciences* 38(21):603.
19. Castle WE. (1907) *Science*, 26(661):287-291.
20. Punnett RC. (1912) *Journal of Genetics* 2:2.
21. Castle WE. (1905) *Carnegie Institution of Washington* No. 23.
22. Wright, S. (1915). *American Naturalist* 49:140–148.
23. Kwon BS, Halaban R, Chintamaneni C. (1989) *Biochemical and Biophysical Research Communications* 161:252– 60.
24. Aigner B, *et al.* (2000) *Mammalian Genome* 11:700–2.
25. Petrij F, *et al.* (2001) *Journal of Heredity* 92:74–8.
26. Benkel BF, *et al*. (2009) *Mammalian Genome* 20:256– 9.
27. Giebel LB, *et al.* (1991) *Journal of Clinical Investigation* 87:1119–22.
28. O'Brien SJ, *et al.* (1986) *Journal of Heredity* 77(6):374-8.
29. Robinson R. *Genetics for Cat Breeders.* International Series of Monographs in Puer and Applied Biology Zoology Division, Vol 45: Pergamon Press, London, UK. 1971, 1977, 1991.
30. Hubel DH, Wiesel TN. (1971) *Journal of Physiology* 218(1):33-62.
31. Kalil RE, Jhaveri SR, Richards W. (1971) *Science* 174(4006):302-5.
32. Kidson S, Fabian B. (1979) *Journal of Experimental Zoology* 210(1):145-52.
33. Iljin NA, Iljin VN. (1930) *Journal of Heredity* 21(7):309-318.

A SAMPLING OF BREEDS THAT ARE THE INHERITORS OF THE HIMALAYAN POINTED COAT PATTERN

Left: Seal-Point Siamese, bred by Jenny Thomsen. Right: Blue-Point Bi-Colour Ragdoll, bred by Carolyn Littlejohns

Left: Blue-Point Exotic Shorthair, bred by Alex Luk Chun Lap. Right: Seal-Point Templecat, bred by Cheryl Davies-Crook

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