Color and Deafness in Dogs .

by Dr. George M. Strain

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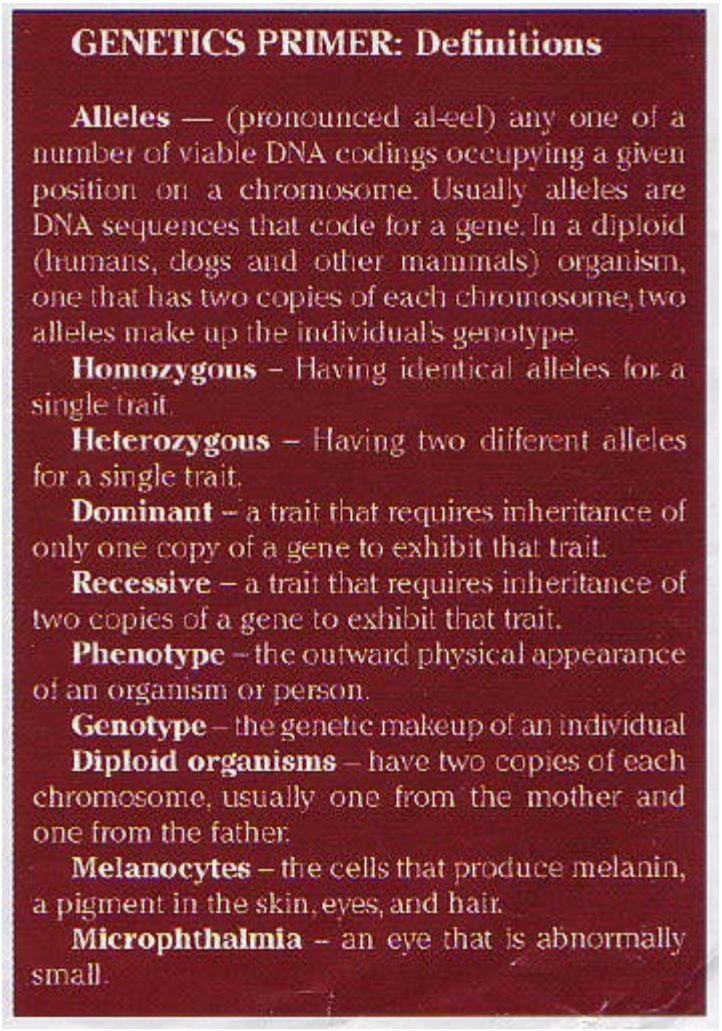
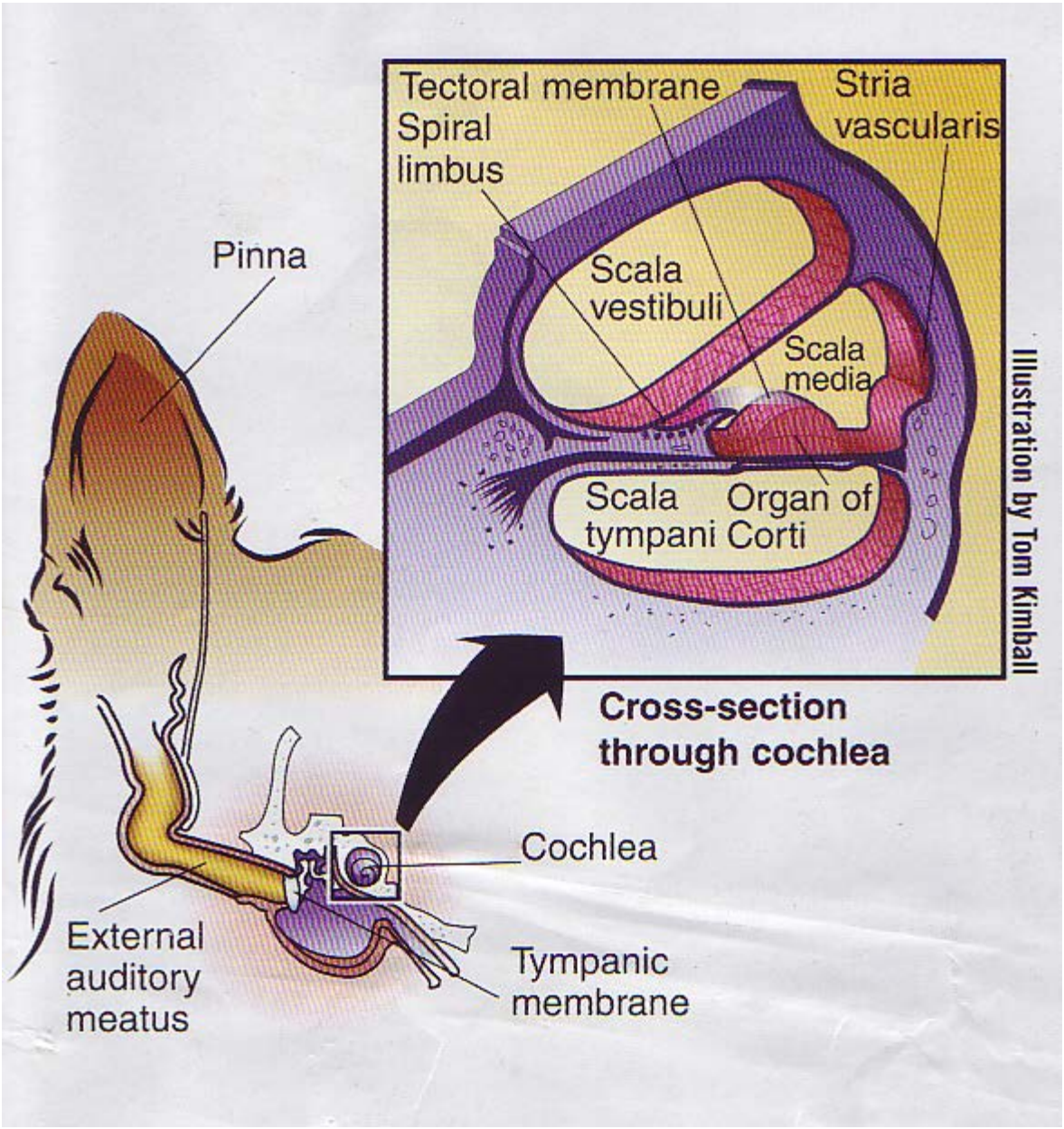
Among the domesticated species the dog has by far the greatest variety in phenotype - in size (from Chihuahua to Great Dane), color, color pattern (from spotted to brindled), and so on. Color and coloration patterns alone results from nine or more classical genes, each which has dominant and recessive alleles that separately and in combination are expressed in diverse patterns. Of those, two genes are important because they can impact auditory function in dogs, and to a lesser extent visual function. Those are piebald (the recessive alleles of the gene S), and the dominant allele of the merle gene (m). Nearly 90 dog breeds have been identified with congenital deafness. In most of these the deafness is heredity, and for nearly all it is associated with piebald or merle.



Piebald, which is present in the Dalmatian, Bull Terrier, Boston Terrier, Cocker Spaniel, Jack Russell Terrier, Chihuahua, and others, is a recessive gene.

There are three recessive alleles for piebald: Irish spotting (s_i), piebald (s_p), and extreme white piebald (s_w); dogs that have uniform color with little or no white carry the dominant allele (S). The piebald gene produces areas of white by suppressing pigmentation cells (melanocytes). Merle, which is present in the Shetland Sheepdog, Australian Shepherd, Dachshund, Great Dane and others, is a dominant gene. Merle produces a color pattern where patches of color are diluted or absent (white), again by acting on melanocytes; animals homozygous with the recessive allele (mm) have solid color. Dogs with piebald must be homozygous to have areas of white, while erls can be either heterozygous (mM) or homozygous (MM).

Dogs carrying piebald or merle can be deaf in one or both ears, but in a given ear the deafness is nearly always complete. Deafness results when the pigment gene is strongly expressed, not only suppressing melanocytes in skin and hair follicles, but also in a specialized vascular bed in the cochlea known as the stria vascularis. (Illustration below.) Suppression of strial melanocytes causes degeneration of this tissue, in turn causing death of hair cells in the cochlea, the nerve cells that detect sound. Death of hair cells results in deafness. Deafness is often, but not always, accompanied by blue eyes - strong gene expression also suppresses melanocytes in the iris, eliminated the brown pigment. The iris then looks blue for the same reason the sky look blue. However, not all blue-eyed dogs are deaf. There is no evidence to suggest that dogs carrying both the piebald and merle genes have an increased likelihood of deafness, but this has not been tested.



Although piebald is inherited as a simple recessive gene, and merle as a simple dominant gene, the deafness associated with these genes does not show simple inheritance. It is common for two hearing dogs to produce deaf offspring, but I've also bred two deaf dogs and gotten bilaterally hearing offspring. One possible explanation is that a second gene regulates how strongly the pigment gene is expressed, but other mechanism are possible. Studies have looked at this in several breeds, but the mechanism of inheritance for deafness is yet to be determined.

To understand piebald, it is useful to discuss the genes behind the pigment pattern in the Dalmatian. The underlying coat color is black (B, dominant) or liver (b, recessive). This is covered with white by the extreme white piebald gene, which is homozygous in all Dalmatians. Spots are then, in effect, punched through the white to show black or liver by the dominant allele of the ticking gene (t). Weak expression of piebald in the Dalmatian results in a patch, a black or liver area of skin present in newborn puppies that otherwise ware solid white. Patched Dalmatians are statistically less likely to be deaf than on-patched dogs. Unfortunately, patched Dalmatians are not permitted in the breed standard. Strong expression of piebald results in one or two blue eyes - statistically these dogs are more likely to be deaf than brown-eyed dogs - and deafness. Gender, spot size, and heaviness of spotting are unrelated to deafness. The association between blue eyes and increased likelihood of deafness has proven to be true in every breed in which I've studied it.

Every dog carries two alleles for every trait (i.e., eye color, variations in coat color, and in this hypothetical case, for a squiggly or straight tail). One allele is randomly inherited from each of the parents. In this hypothetical case, "Q" is the allele for the *dominant trait* of a squiggly tail, while "q" is the allele for the *recessive trait* of a straight tail.

Q = dominant for squiggly tail **q** = recessive for straight tail

Let's look at the litter of puppies below:

Sire:

Heterozygous for squiggly tail, his
Phenotype = Squiggly tail
Genotype = Qq

Dam:

Also *heterozygous* for squiggly tail, her
Phenotype = Squiggly tail
Genotype = Qq

Puppy 1

Genotype = Straight tail

randomly inherited the "q" allele from her sire and the "q" allele from her dam; she is *homozygous* for the recessive trait of a straight tail.

Puppy 2

Genotype = Squiggly tail

randomly inherited the "Q" allele from his sire and the "q" allele from his dam; he is *heterozygous* for the dominant trait of a squiggly tail.

Puppy 3

Genotype = Squiggly tail

randomly inherited the "q" allele from her sire and the "Q" allele from her dam; she is *heterozygous* for the dominant trait of a squiggly tail.

Puppy 4

Genotype = Squiggly tail

randomly inherited the "Q" allele from his sire and the "Q" allele from his dam; he is *homozygous* for the dominant trait of a squiggly tail.

The genomic source of the piebald gene has recently been shown to be the pigment gene MITF [7]. MITF plays a role in the development of melanocytes and some nerve cells, and defects in this gene have been shown to be responsible for deafness in the human deafness disorder Waardenburg Syndrome Type II [8]. However, it is not yet known what defect in MITF is responsible for deafness in dogs carrying piebald.

The association between blue eyes and deafness, appears to hold for merle also, but this has not been systematically studied. In fact, there have been very few studies of merle in comparison to piebald. It is unclear whether deafness in merle occurs only in homozygous merles, because until recently there was no test to identify the genotype of merle dogs. However, it is known that homozygous merle dogs often have additional healthy problems. Much of the scientific literature on merle in the past focused on problems seen in homozygous merles and in breeds where the merle gene can produce dramatic effects - in some cases including deafness, blindness and microphthalmia, and sterility. Even heterozygous dogs in these breeds can have less serious visual and auditory deficits. These effects do happen with some breeds, but unfortunately many have taken this truth and extrapolated it to apply to all breeds carrying the merle gene, which is not necessarily true. For example, dogs in the Catahoula breed can be homozygous merle without any of these health defects, and heterozygotes do not seem to be affected. Until recently is was not possible to even distinguish between mM and MM merles in some breeds.

In many breeds carrying merle, breeders know not to breed homozygous merles, and visual and auditory deficits do not seem to be a problem in the heterozygotes. Studies have examined auditory function and visual function in heterozygous and homozygous dappled (merle) Dachshunds. These studies, from geographically and numerically restricted populations, found hearing loss and deafness and visual abnormalities, but only examined small numbers of dogs - 38 in the first study and 18 in the second. Dappled Dachshunds, when carefully bred to avoid MM, do not appear to have deafness or blindness in the general population, so one must be careful to not raise alarms at the presence of merle in a breed until experience shows that a true problem exists.

A large leap in understanding merle occurred when Clark and Murphy of Texas A&M University identified and sequenced the canine gene for merle in 2006. The gene, named SILV (also known as Silver in mice), plays a role in pigmentation in skin, eye, and ear. Dogs with the merle phenotype have a short piece of DNA inserted into this gene - a DNA modification known as a short interspersed element (SINE). This work was performed with Shetland Sheepdogs, then confirmed in merles from 11 other breeds, including the Chihuahua. The sequence of the SINE was the same in all breeds, suggesting that all breeds in the study shared a common ancestor.

A DNA test for the merle gene is now available that can identify heterozygous (mM) or homozygous (MM) carriers of the dominant allele of the merle gene, using cheek swabs. See GenMARK's web site (http://www.genmarkag.com/home_companion.php) for details. As is the case with piebald, it is not yet known what change in SILV causes canine deafness.

Neither the piebald gene nor the merle gene is inherently bad - the Dalmatian would not be a Dalmatian without piebald, for example. For the foreseeable future dog breeds carrying either gene will see production of occasional deaf puppies. The prevalence of deafness - until a DNA test becomes available to determine which dog will produce deafness - can in the meantime be minimized by careful breeding practices. In breeds that have an acknowledged deafness problem, do not breed unilaterally deaf dogs, don't repeat a breeding that produced deaf dogs, breed away from families or lines that have produced deaf dogs, and avoid breeding blue-eyed dogs. Do not breed homozygous merle dogs. With the availability of a DNA test for merle, it has become obvious that the deleterious effects associated with merle vary in their impact from breed to breed and possibly even between different lines in the same breed. This has caused a change in my thinking about merle - I no longer automatically consider its presence in a breed to be a source of problems because of the recent evidence of breed variation. As a result, I caution against moves to eliminate merle from a breed's standard until it is shown that the presence of the gene in that breed produces a significant problem. Knowledge is a journey, not an end point, and we certainly have much to learn still about merle, piebald, and the mechanism by which they can produce deafness and other health disorders.

Dr. George M. Strain is professor neuroscience at the Louisiana Stat University School of Veterinary Medicine in Baton Rouge. His training is in electrical engineering, biomedical engineering, physiology, and neurology. He has been involved in research in dogs for more than 20 years, and is considered to be the leading authority on deafness in animals. Dr. Strain has published extensively on deafness - diagnosis, breed prevalence, association with pigmentation, and genetics, for both the layman and researchers - and has performed hearing tests (BAER) on 10,000 dogs. Dr. Strain's web site, Deafness in Dogs and Cats , has a wealth of information on deafness.