Basic Genetic Concepts

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Introduction

Most of you are undoubtedly aware that color and certain diseases such as progressive retinal atrophy (PRA) are inherited – that is, passed down from one or both the parents. However, you may wonder how a trait that does not appear in the dam's pedigree can suddenly turn up in a litter out of Ch. Jake Hugelsberg. Is it inherited or just an accident? Surely, Jake has been used so often that someone would have noticed if the problem came from him.

Just how much of a role does genetics play in health, general conformation and temperament? Probably you would like to know exactly what traits are inherited; but, once someone starts talking about "partial dominance" or "expressivity," you get glassy-eyed. The objective of this guide is to explain some of the basics of inheritance and how to use these concepts to breed healthier dogs – hopefully without losing you in complex technical jargon.

What Traits (or Characteristics) Are Inherited?

The answer is "almost all," from temperament to size and coloring, as well as genetic diseases like progressive retinal atrophy (PRA). Infectious diseases are not inherited, though the susceptibility to them may be, to a greater or lesser extent.

The occurrence of any particular characteristic depends on two factors:
genetics and the environment. "Genetics" refers to the encoded information (instructions) controlling all biological processes that are carried within the cells of all living organisms. These encoded instructions are responsible not only for maintaining the continuity of a species (or breed), but also for many of the differences between individuals within a species or breed.

The environment also contributes to the differences between individuals.

The relative contribution of genetics and environment is not the same for every trait. Some traits, such as color, are influenced very little by the environment. For others, such as temperament, the effect of the environment is much greater. Geneticists use the term heritability to indicate the proportion of the total possible variability in a trait that is genetic. However, when genetic differences are not the main source of variability, the heritability of a trait may be difficult to establish and may not be the same for different breeds. Therefore, I cannot tell you that the heritability of size, for example, is 70% (or whatever it may be).

Before moving on to a more detailed discussion of genetics, I would like to take a brief look at what is meant by "environment," in the present context. For a puppy, the first environment it encounters is that of the mother's womb. Is the mother well nourished, healthy, and free from stress? How old is she? Is this her first litter? How big is the litter?

Once the puppy is born, it experiences a new environment, where it has to compete for food and attention. Litter size is still a factor. How much food does the puppy get? How much attention does it get from the mother, the breeder, and the eventual owner? Does it have a safe and healthy environment? Does it have other dogs to associate with? The answers to these questions define, in part, the puppy's environment.

Genes...

The gene is often called the basic unit of inheritance. A gene carries the information for a single step in a biological process; but most biological processes – even the ones that may appear to be simple – are made up of more than one step. Thus, one should not get the idea that a trait is determined by a single gene, but rather that the general rule is that many genes control a single trait. A good example is color. In some breeds, such as the Poodle and the Borzoi, there are a great variety of colors, so it should come as no surprise that this is the result of the action of a variety of genes. There are not only genes for making the different colored pigments, but also genes which control the distribution of the pigments, both within the individual hairs and over the entire body. (Other breeds may come in only one color. They have the same genes, but only a single allele of each.)

All animals have thousands of genes, but they do not float around loose in the cells. To make cell division and reproduction more manageable, genes are physically connected to other genes to form chromosomes. Most "higher" animals have two sets of chromosomes: one set from the mother and the other set from the father. So that the number of sets does not keep increasing from one generation to the next, sperm and eggs get only one set each. However, the mechanisms that assure this are not able to tell which chromosomes came from the mother and which from the father. Therefore, the set that is passed on in a particular egg or sperm is a mixed set. The number of possibilities depends on the number of chromosomes. Since dogs have 39 chromosomes in a set, the number of possible combinations is well over one billion! Therefore, the possibility of getting two litter-mates that have exactly the same combination of chromosomes is extremely remote. (Incidentally, wolves also have 39 chromosomes in a set and can breed with domestic dogs. Foxes, however, have only 19 chromosomes and cannot.)

One of the 39 chromosomes carries genes that determine sex. In mammals, the chromosomes carrying the "female" genes is designated X and the one carrying the "male" genes is designated Y. An animal with two X chromosomes will be a female, while one with an X and a Y will be a male. (One with two Ys will be in serious trouble!) Genes other than those determining sex are also located on these chromosomes and are said to be sex-linked.

...and Alleles

Most genes carry out their functions correctly, but some are altered by exposure to radiation (natural or man-made), certain chemicals, or even by accident when a cell divides. A gene may be thought of as a small program. There are many possible places in the program where an error (mutation) might be introduced. Many of these will have the same effect:
the program will not function. Others may modify the action of the program. Some may appear not to affect the program at all. (Since these produce no observable effect, we generally don't worry about them.) All, however, regardless of their effect, change the information carried in the program.

In genetics we call each version an allele. Some genes may have several different alleles in a population, but an individual can carry only two; one from the sire and one from the dam. When the two alleles are the same, the individual is said to be homozygous for that gene. When the alleles are different, it is heterozygous.

Naming Genes

There are rules for naming genes; unfortunately, not all geneticists use the same system. The one I will use here is common, but not universal.

A gene is named for the first mutant allele discovered. For example, in the fruit fly (Drosophila), which

normally has dark reddish-brown eyes, a mutant with white eyes was discovered many years ago. Consequently, the particular gene in which this mutation occurred is called "white" and given the symbol w. The mutant allele is designated w (notice that it is italicized), and the wild-type allele is designated w+. Another mutation, discovered later, has light yellowish-brown eyes and is called "eosin." However, it is also an allele of the same gene and is, therefore, not given a different letter designation. Instead, it is designated we. (This system reserves capital letter designations for dominant mutant alleles.)

The alternative system that you will more likely encounter is very similar, except we don't use a + sign to designate the wild-type allele.

This can introduce an element of confusion. For example, gray coat color is not considered the normal (wild-type) color in Poodles. However, as it is dominant, it is given the symbol G, while the wild-type allele is g.

The naming of genes can also be eccentric. The dilute gene results in a lightening of the basic color and, appropriately, is designated D. A second gene has a similar effect, and is called C (for color). However, the best known mutant allele of this gene is the one that results in albinos, so the gene really should be called A; but this designation had already been used for agouti.

Dominance

If, for a particular gene, the two alleles carried by an individual are not the same, will one predominate? Because mutant alleles often result in a loss of function (null alleles), an individual carrying only one such allele will generally also have a normal (wild-type) allele for the same gene, and that single normal copy will often be sufficient to maintain normal function. As an analogy, let us imagine that we are building a brick wall, but that one of our two usual suppliers is on strike. As long as the remaining supplier can supply us with enough bricks, we can still build our wall. Geneticists call this phenomenon, where one gene can still provide the normal function usually met by two, dominance. The normal allele is said to be dominant over the abnormal allele. (The other way of saying this is that the abnormal allele is recessive to the normal one.)

When someone speaks of a genetic abnormality being "carried" by an individual or line, they mean that a mutant gene is there, but it is recessive. Unless we have some sophisticated test for the gene itself, we cannot tell just by looking at the carrier that it is any different from an individual with two normal copies of the gene. Unfortunately, lacking such a test, the carrier will go undetected and inevitably pass the mutant allele to some of its progeny. Every individual, be it man, mouse or dog, carries a few such dark secrets in its genetic closet. However, we all have thousands of different genes for many different functions, and as long as these abnormalities are rare, the probability that two unrelated individuals carrying the same abnormality will meet (and mate) is low.

Sometimes individuals with only a single normal allele will have an "intermediate" phenotype. (For example, in Basenjis carrying one allele for pyruvate kinase deficiency, the average life-span of a red blood cell is 12 days, intermediate between the normal average of 16 days and the average 6.5 days in a dog with two abnormal alleles. Though often termed partial dominance, in this case it would be preferable to say there is no dominance.

To carry our brick wall analogy a bit further, what if the single supply of bricks is not sufficient? We will end up with a wall that is lower (or shorter). Will this matter? It depends on what we're trying to do with the "wall" and, possibly, on non-genetic factors. The result may not be the same even for two individuals that have built the same wall. (A low wall may keep out a small flood, but not a deluge!) If there is the possibility that an individual carrying only one copy of an abnormal allele will show an abnormal

phenotype, that allele should be regarded as dominant. Its failure to always do so is covered by the term "penetrance".

A third possibility is that one of the suppliers sends us substandard bricks. Not realizing this, we go ahead and build the wall anyway, but it falls down. We might say that the defective bricks are dominant. Advances in the understanding of several dominant genetic diseases in man suggest that this is a reasonable analogy. Many dominant mutations affect proteins that are components of larger macromolecular complexes. These mutations lead to altered proteins that do not interact properly with other components, leading to malfunction of the entire complex. Others are in regulatory sequences adjacent to genes and cause the gene to be transcribed at inappropriate times or places.

Dominant mutations may persist in populations if the problems they cause are subtle, not always expressed (see below), or occur later in life, after an affected individual has reproduced.

Expressivity and Penetrance

For a breeder, understanding the inheritance of a trait that is controlled by several genes and influenced by the environment can be a nightmare. Suppose, for example, that you are trying to breed apricot Poodles, but instead of getting only a single shade, your litters always have a variety of shades from pale to dark apricot. You might blame it on variable expressivity, which is just a convenient way of saying that you don't know what other genes or environmental factors are also playing a role in determining the color.

One of the classic examples of this in dogs is the variable expression of piebald spotting in beagles shown in Little (1957). The dogs all have the same Sp allele, but the colors range from black-and-tan with white feet to predominantly white with a few black spots.

Penetrance is a similar term-of-convenience (euphemism). If you are 99+ % certain that Fido carries the allele for six toes (because both his parents and all his sibs have six toes), but Fido has the normal five toes, you blame it on incomplete penetrance, try to look authoritative, and hope that no one asks additional questions. [Actually, it would probably be safer just to say that the trait is not always expressed and avoid possible embarrassment.] The difference between expressivity and penetrance is that with the former, the trait is expressed to a variable extent, while with the latter it may or may not be expressed even though the genetic makeup (genotype) of the animal suggests that it should be.

Sex Linkage

In dogs, as in most animals, sex is determined genetically, but not by a single gene. One of the 39 chromosome pairs is used especially for sex determination. The unusual feature of this system is that the female-determining chromosome, called the X chromosome, doesn't even look like the male-determining Y chromosome, though they are still considered a "pair" and are referred to as the sex chromosomes. (The other 38 are called autosomes.) As everyone likely already knows, females have two X chromosomes and males one X and one Y. The male normally produces an equal number of sperm carrying either the X or the Y chromosome. As his mate will be producing eggs carrying only X chromosomes, an equal number of female (XX) and male (XY) puppies should be produced. Of course, chance plays a major role and litters often don't have a perfect 1:1 ratio.

Mutations undoubtedly occur in genes that control the development and function of the ovaries, testes, and other reproductive organs, but few have been described, probably because disruption of the normal reproductive process results in infertility. However, there are also genes found on the sex chromosomes that have nothing to do with sex determination. Those found on the X chromosome have no equivalents on the Y chromosome. As a result, males have only one copy of these genes. (Since the terms "homozygous"

and "heterozygous" apply only when there are two copies, this situation is given a special name: hemizygous.)

When mutations occur in these X-linked genes, the pattern of transmission of the mutant phenotype differs from that seen for an autosomal gene. If a female carries such a trait, she will not express it (as long as it is recessive), but she will pass the trait to half her sons, and as they receive no X chromosome from their father, it doesn't matter what his genotype is – half will be affected. Half the daughters will be carriers, but as these are recessive traits, these carrier daughters will not be affected. If the problem does not affect survival and reproduction, an affected male may pass the gene on to his progeny; but only to his daughters, as his sons will get his Y chromosome, which doesn't have a copy of the gene.

A good examples of sex linkage is hemophilia A. I was recently consulted on a litter of 6 boys and 1 girl, in which 3 of the males started bleeding internally at 6 or 7 weeks and died within a week or two. Both parents and all the puppies tested clear for vWD, but testing for clotting factor VIII revealed that the affected puppies had less than 2% normal levels. The factor test does not distinguish between carriers and normal individuals well enough to give us an unambiguous diagnosis. However, because a male gets his one X-chromosome from his mother, we can safely conclude that the other 3 males are clear. However, their sister could be a carrier, and was spayed.

There are also traits that are sex-influenced, which means that their expression is influenced by the individual's sex. This does not imply that the gene is sex-linked. A human example is pattern baldness. The gene's expression is influenced by hormonal levels and only one copy of the baldness allele is sufficient to cause baldness in a man, whereas two copies are needed in a woman. In effect, it behaves as a dominant in males and as a recessive in females. Though half the sons of a female carrier will be affected, a heterozygous male will also pass the trait to half his sons.

Thus, any trait that appears more frequently in males than females is suspect as either sex-linked or sex-influenced. If it is passed from the father or the mother to half the sons, it is likely sex-influenced. If it seems to skip a generation and the pattern is grandfather to grandson, it is likely sex-linked.

Determining the Mode of Inheritance

Suppose that you have a litter in which several of the puppies appear to be less healthy than their litter-mates. Suppose that after a few weeks it is readily apparent that they are growing more slowly and appear less energetic. What do you do? Obviously, the first step is take them to your vet for examination.

Without going into details (as this is a hypothetical example), let us suppose that, after appropriate tests, he concludes that they have a hole in the septum between the two sides of the heart that is resulting in a mixing of oxygenated and de-oxygenated blood. Quite aside from any considerations about euthanizing the affected pups, the question remains: what caused the problem? Was it simply a developmental accident, an environmentally-induced condition, or is it genetic? [I have deliberately picked a condition that may arise for any of these reasons.]

As a rule-of-thumb, if only a single pup is affected, the problem has not turned up before in related litters, and the problem does not occur frequently in the breed, it is likely a developmental accident. Nevertheless, given the usual under-reporting of health problems, especially those that may be genetic, a second litter between the same sire and dam might be warranted.

On the other hand, if all – or even the majority – of the pups were affected, one might be more inclined to look for something in the environment that could have perturbed the normal developmental process. The majority of genetic abnormalities are recessive and, under normal circumstances, the parents are unlikely to

be affected (i.e., homozygous). Therefore, if the problem is a genetic one, it is more likely that the parents will be phenotypically normal carriers (i.e., heterozygous), and the expectation is that one-quarter of the progeny will be affected.

While this is important to keep in mind, obtaining a proportion of affected pups in a litter that is substantially lower or higher than one-quarter is no guarantee that the problem is not genetic. Even the larger breeds produce litters of only eight or so, so you would expect only two to be affected. One or three affected would not be considered unusual, and even getting none affected is not considered sufficiently improbable to alarm a geneticist. You might well get no affected pups in one litter and four affected pups in the next!

Dominant mutations having a significant impact on health will, in most cases, result in death before reproductive age is reached. There are exceptions, such as Huntington's Disease in humans. Any late-onset genetic disease, whether dominant or recessive, represents a potential problem. At least with a dominant, you can wait for the progeny to reach an age where the problem would normally have developed, then breed unaffected animals with reasonable assurance that they are not undetected carriers. For example, if the inherited condition develops at six or seven years, you can wait until the dog is three or four years old before breeding it, then not breed any of the progeny until the parents reach seven or eight years of age.

For a dominant mutation that is rare, most crosses will be between a heterozygous affected individual (Aa) and a normal one (aa). The expectation is that one-half the progeny will be Aa. Should both parents be Aa, one-quarter of the progeny will be aa (normal) and three-quarters either Aa or AA. Sometimes, the AA progeny will be affected more severely, or even die before birth.

Doing the necessary crosses to establish the mode of inheritance can be an expensive and time-consuming task, to which is added the thankless prospect of putting down sick puppies and finding pet homes for the remainder. Consequently, test matings are seldom done on a scale sufficient to produce numbers that can be subjected to statistical analysis. [One notable exception is the monumental study by Bourns on day-blindness in Alaskan Malamutes.]

One alternative to test matings is retrospective analysis of the pedigrees of affected animals. As one generally needs a number of related animals occurring over several generations, the problem will likely already have become fairly common. The accuracy of such analyses is directly affected by the number of relatives for which data exists; a strong argument for the open exchange of information between owners, breeders, veterinarians, and researchers.

References

Little, C.C. "The Inheritance of Coat Color in Dogs", Howell, New York, 1957.

Willis, M.B. "Genetics of the Dog", Whitherby, London, 1989.

Notes

The term wild-type literally means the most common type found in the wild. In a Samoyed, it would be the color white. In a Poodle, it would be black. Though we usually equate "wild-type" with "normal" and a white Samoyed is certainly normal for the breed, Samoyeds nevertheless have a genetic deficiency in pigmentation.

Actually, we should not be saying that the allele functions abnormally. The allele carries the wrong information. The consequence of that information being used results in an abnormal functioning of some process.

Agouti is a sort of mottled brown color not seen in most dog breeds. Geneticists try to be consistent in their naming of genes and don't use different symbols for different species, providing the genes are known to have the same action.