The nature of genetic disease

By Dr John Armstrong

MANY people label any problem that appears to be inherited a "genetic disease". However, though there are legitimate genetic diseases, there are also a variety of problems that have an inherited component but are of a fundamentally different nature. Dealing effectively with any genetic problem requires an understanding of the relationship between the genes (genotype) and the phenotype. In many cases this is lacking. In this article, I would like to describe some of the differences, in order to give breeders and owners a better understanding of what they are dealing with.

Inborn Errors of Metabolism: The true "genetic diseases"

The first clearly-described relationship between genotype and metabolic deficiencies is credited to Sir Archibald Garrod, an English physician. In 1901, he showed that the inherited disease alkaptonuria results from an inability to metabolise certain amino acids, leading to the accumulation of homogentisic acid. Some of this compound accumulates in skin and cartilage (the latter leading to arthritis). The rest is excreted in the urine, turning it black. Garrod suggested that the metabolic block was caused by an enzyme deficiency, though this was not confirmed until the enzyme (homogentisic acid oxidase) was characterized in 1958.

Since Garrod's time, many other inherited metabolic diseases have been discovered. Some can be managed by careful attention to diet; others cannot. A particularly nasty example is Tay-Sachs disease, which involves an enzyme important in lipid metabolism. Individuals homozygous for a deficiency in this enzyme accumulate a compound called a ganglioside in the nervous system. They appear normal at birth, but progressively lose motor function and die around three years of age. There is no treatment. Most of these conditions involve mutations that lead to the production of a nonfunctional enzyme, or one that is totally absent. In heterozygotes, the single good copy of the gene is generally able to produce sufficient enzyme to handle the normal workload. However, in a few cases, carriers as well as affected individuals have to be careful about their diet or may exhibit less severe phenotypic effects.

Examples of inherited metabolic diseases in dogs include phosphofructokinase deficiency in Cocker and Springer Spaniels, and pyruvate kinase deficiency in Basenjis.

Not all mutations involve metabolic pathways. Some involve proteins that have structural roles in cells and tissues. Others involve regulatory genes that control the correct sequence of events during development. These may lead to such problems as septal defects in the heart or the failure of the embryonic kidney to develop into the adult form.

Nevertheless, all can legitimately be considered genetic diseases, as there is a direct one-to-one relationship between a single mutated gene and a particular problem.

Conformational Diseases: The result of unnatural selection. Problems such as bloat (gastric dilatation-volvulus, or GDV) and hip dysplasia clearly have a genetic component, but also an environmental component and, perhaps, a behavioural one, as well (which also may be determined partially by the genes). Bloat is not a "genetic disease" in the same sense as the metabolic and other disorders described above, and it seems unlikely that a single gene is responsible for bloat. One might better compare a bloat attack to a bad case of indigestion in a human. Some people are more prone to such attacks than others, and there may well be an inherited component, but other factors also come into play. Research into bloat suggests that diet, behaviour and conformation may all play a role.

Leaving aside the question of the role of genetics in behaviour, the results suggest that the incidence of bloat increases with the size of the dog and the depth-to-width ratio of the chest cavity. This is a conformational problem, not a genetic disease. Certainly, the overall conformation is, ultimately, determined by the genes, but not by a single gene. There are probably dozens or hundreds of genes that go into determining the shape and size of the head, trunk, and limbs. Wherever there is genetic variability, one can select for larger, smaller, narrower, wider, etc. If the fancy as a whole decides that a taller, narrower dog looks more "refined," more of that description will be kept for breeding purposes, and the population will be shifted toward a more bloat-prone conformation.

When it comes to the question of correcting this problem, the solution, in theory, is simple. We stop breeding for a bloat-prone conformation and select for a slightly smaller dog with a chest cavity that is not so deep or narrow. Some may regard this as a retrogressive step, but we have to decide which we want to sacrifice.

I do not rule out the possibility that two dogs of identical conformation may have one or more genes that lead to one being more bloat-prone than the other. If we could identify these genes, we might be able to reduce the incidence of GDV somewhat while retaining some of the desired "refinement".

While it may be argued that there is nothing wrong with a tall, narrow

dog aside from the greater risk for bloat, selecting for a conformation that is not functionally sound is a recipe for disaster. Wild canids do not move awkwardly. Any that did would be eliminated by natural selection. After thousands of years of evolution, the musculoskeletal system of the average wolf has found a combination that works efficiently. Because there is diversity in the gene pool, there is always the possibility of a chance combination of genes that produces an individual that can move more quickly and efficiently. There is also the possibility that a less efficient combination may arise, but it is not likely to be favoured.

In the artificial world of the show dog, one can insulate an individual from natural selection and favour a conformational extreme, because the breeder or the public thinks it looks more attractive or just different. Two such extreme dogs, bred together, may lead to something even more extreme and more popular. However, the changes in one component must be accompanied by changes in others, or the result, from a structural standpoint, may impose stresses that the components are not designed for.

The result will be components easily damaged or deformed while the puppy is still growing. In such a case, one may not be dealing with genes that are "bad" and make a non-functional or defective product, but just with a bad combination of genes. But if, during this "unnatural selection," the genes necessary to make a good combination have been discarded, where does this leave the breed?

All in the Family (Part 4)

We continue to follow a family of Irish Setters in which several dogs have already bloated. This family study is another attempt to better understand genetic influences on bloat, which can cluster within certain families (familial bloat) or occur in unrelated animals (sporadic bloat). Geneticist Dr Robert Schaible and Irish Setter breeder Jan Ziech collaborated with the Purdue Bloat Research Team in this study.

Measurement data and bloat histories were collected for all but one of 15 surviving pups in two litters, whelped in 1988 and 1991, respectively, that had the same dam but different sires. The parents' measurements and bloat histories were obtained.

The pedigree was plotted on a scale of chest depth/width ratios. The ratios in this family were spread across a wide range of values for Irish Setters enrolled in the ongoing prospective study.

The pattern suggested that incomplete dominance of a major gene is the mode of inheritance of chest depth/width ratio. The data support the hypothesis that dogs with a deeper chest relative to width are at greater risk of developing bloat than dogs of the same breed with smaller chest depth/width ratios. The pattern for this family will not be complete, however, until all dogs have been followed throughout their lifetime.

Breeders who want to do a similar family study can call Dr Schaible at 812-876-9884.

This is the final article in a series on genetics written by Dr J Armstrong who was researching with the Canine Diversity Project. Dr Armstrong's untimely death last year was a huge loss to canine genetic research - it is up to breeders to put his principles into practice.

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