Understanding the FGF4 Mutation: What These Landmark Studies Really Tell Us

In recent years, researchers have made major discoveries about one of the genes responsible for short legs and spinal disc disease in dogs. Two important scientific studies—one published in the *Proceedings of the National Academy of Sciences (PNAS)* and another in the journal *Genes*—have greatly improved our understanding of how mutations in the **FGF4 gene** affect canine health. While these studies contain complex genetic terminology, their findings can be explained in straightforward language.

The first thing to understand is that every dog has a normal **FGF4 gene**. This gene, whose name stands for *Fibroblast Growth Factor 4*, plays an important role during fetal development. It helps regulate the growth of bones and cartilage, ensuring that the skeleton develops normally before birth.

At some point during the evolution of domestic dogs, an unusual event occurred. An extra copy of the FGF4 gene was accidentally inserted into a different location in the dog's DNA. Scientists call this extra copy a **retrogene**. An easy way to picture this is to imagine a cookbook. Normally there is one recipe for chocolate cake. If someone accidentally photocopies that recipe and inserts it elsewhere in the book, the cake may end up being made twice. In much the same way, the extra copy of the FGF4 gene changes how much of the FGF4 protein is produced during development, altering the way bones and cartilage form.

One of the most important discoveries made by these researchers was that there are actually **two different FGF4 retrogenes**, and they do not have identical effects. One is located on chromosome 18 and the other on chromosome 12.

The **FGF4 retrogene on chromosome 18** mainly affects leg length. Dogs carrying this mutation tend to have shorter limbs, but the mutation has very little influence on spinal disc disease. This disorder is referred to as Chondrodyspiasia (CDP).

The **FGF4 retrogene on chromosome 12**, however, has much broader effects. Like the chromosome 18 mutation, it contributes to shorter legs, but it also changes how cartilage develops throughout the body. Most importantly, it affects the intervertebral discs—the cushions located between the bones of the spine. This discovery was a turning point because scientists realized that the chromosome 12 mutation, not the chromosome 18 mutation, is primarily responsible for the condition known as **chondrodystrophy**. (CDDY or CDY are both abbreviations for chondrodystrophy found on CFA12-FGF4. Different labs may use the two abbreviations.)

The word *chondrodystrophy* sounds intimidating, but its meaning is fairly simple. "Chondro" refers to cartilage, and "dystrophy" refers to abnormal development. In other words, chondrodystrophy means that cartilage develops differently than it normally would. While many

people think only of short legs, the condition affects much more than limb length. The same abnormal cartilage development also occurs inside the spinal discs.

To understand why this matters, it helps to know how a healthy spinal disc works. Each disc acts like a shock absorber between the vertebrae. It has a soft, jelly-like center surrounded by a tough outer ring. The disc is flexible and allows the spine to bend while protecting the spinal cord.

Dogs carrying the chromosome 12 FGF4 mutation experience changes in these discs very early in life. Instead of remaining soft and flexible, the jelly-like center gradually turns into cartilage and eventually becomes hardened by calcium deposits. Veterinarians refer to this process as **disc calcification**. Once the discs lose their flexibility, they become much more likely to crack or rupture under normal activity. When a damaged disc presses against the spinal cord, the result is **intervertebral disc disease (IVDD)**, which can cause severe pain, weakness, loss of coordination, or even paralysis.

The second study expanded on these discoveries by examining **569 dogs that required surgery for IVDD**. The researchers wanted to know whether the chromosome 12 and chromosome 18 mutations affected the age at which dogs developed spinal disease, the severity of disc calcification, and the overall risk of disc herniation.

Their findings were remarkably clear. Dogs carrying the chromosome 12 FGF4 retrogene developed spinal disease at a much younger age than dogs without the mutation. They also had significantly more calcified discs visible on radiographs. Most importantly, the presence of the chromosome 12 mutation dramatically increased the likelihood of developing IVDD.

The researchers calculated what is called an **odds ratio**, which is a way of comparing the likelihood of disease between two groups. An odds ratio of 1 means there is no difference between groups. In this study, the chromosome 12 mutation had an odds ratio of approximately **18**, meaning that dogs carrying the mutation were about eighteen times more likely to develop disc herniation than dogs without it. In genetics, this is considered an extremely strong association.

The study also found that the chromosome 18 mutation contributed very little to IVDD risk. While it may influence leg length, it does not appear to be a major cause of spinal disc disease.

One point that often causes confusion is the researchers' use of the word **dominant**. In genetics, dominant simply means that a single copy of a mutation is enough to produce an effect. A dog does not need two copies of the chromosome 12 mutation for the risk of IVDD to increase. Even one copy significantly raises the likelihood of developing disc disease.

The researchers also described some effects as **additive**. This means that having two copies of the mutation can increase certain changes even further. For example, dogs with two copies of the chromosome 12 mutation tended to have more extensive disc calcification than dogs with only one copy.

Despite these strong findings, the studies also emphasize an equally important point: **the mutation increases risk—it does not guarantee disease**. Not every dog carrying the chromosome 12 FGF4 mutation develops IVDD. Some remain healthy throughout their lives, while others experience spinal disease at a young age. This tells researchers that additional factors influence whether disease develops. Other genes, body weight, physical activity, body structure, and perhaps even chance all appear to play roles. Scientists continue to search for these additional genetic modifiers.

These findings are especially relevant when discussing breeds in which the chromosome 12 mutation has been identified, including the Bedlington Terrier. The presence of the mutation should not automatically be interpreted as evidence that a dog has "dwarfism" or that it will inevitably develop spinal disease. The studies themselves did not conclude that Bedlington Terriers have a breed-wide problem with dwarfism or IVDD. Instead, they established what the mutation does biologically whenever it is present: it alters cartilage development, increases the likelihood of disc degeneration, and raises the risk of intervertebral disc disease.

Equally important, the studies did not determine how common the mutation is within the Bedlington Terrier population, whether it affects breed type or structure, or whether it significantly changes the breed's overall risk for IVDD. Those questions require carefully designed, breed-specific research before any firm conclusions can be drawn.

Taken together, these two landmark studies transformed our understanding of canine skeletal genetics. They demonstrated that there are two separate FGF4 retrogenes with different biological effects, that the chromosome 12 mutation is the major genetic factor associated with chondrodystrophy and IVDD, and that even a single copy substantially increases risk. At the same time, they remind us that genetics rarely determines destiny. The FGF4 mutation should be viewed as an important **risk factor**, not as a diagnosis. Like many genetic discoveries, it provides valuable information for breeders and veterinarians, but it must always be interpreted alongside the individual dog, the breed as a whole, and the growing body of scientific evidence.