FGF4 Retrogene on Chromosome 12 (CFA12) Is Responsible for Canine Chondrodystrophy (CDDY) and Intervertebral Disc Disease (IVDD)

Plain Language Summary

What Question Were the Researchers Trying to Answer?

For many years, veterinarians observed a consistent pattern among certain dog breeds. Breeds with shortened limbs—such as the Dachshund, Beagle, French Bulldog, and American Cocker Spaniel—were also far more likely to develop severe intervertebral disc disease (IVDD). However, not all short-legged breeds experienced the same high risk.

Researchers sought to answer an important question:

Is there a specific genetic mutation responsible for both shortened limbs and premature spinal disc degeneration?

Their research demonstrated that the answer is **yes**.

What Is Chondrodystrophy?

Chondrodystrophy is a form of disproportionate dwarfism caused by altered cartilage and bone development during growth.

Dogs affected by chondrodystrophy typically have:

- Shortened limbs
- Altered bone growth
- Premature degeneration of the intervertebral discs
- A substantially increased risk of Hansen Type I IVDD

Importantly, shortened legs are only one aspect of the condition. The same developmental changes also affect the spinal discs, increasing the likelihood of painful spinal disease later in life.

What Are Intervertebral Discs?

The spine can be thought of as a stack of bones separated by soft, flexible cushions called **intervertebral discs**.

Healthy discs serve several essential functions:

- Absorb shock
- Allow the spine to bend and flex
- Protect the spinal cord

In healthy dogs, these discs remain soft and resilient for many years.

What Happens in Dogs with the Mutation?

In dogs carrying the chromosome 12 FGF4 retrogene, the intervertebral discs begin to age much earlier than normal.

Rather than remaining soft and gelatinous, the discs gradually:

- Lose moisture
- Become firmer
- Calcify
- Develop cracks and structural weakness

Eventually, a disc may rupture or herniate.

This condition is known as **Hansen Type I Intervertebral Disc Disease (IVDD).**

When disc material presses against the spinal cord, affected dogs may develop:

- Severe spinal pain
- Weakness
- Difficulty walking
- Paralysis
- Loss of bladder or bowel control

Many affected dogs require emergency surgery to relieve pressure on the spinal cord.

How Did the Researchers Identify the Cause?

The researchers compared DNA from:

- Dogs with shortened limbs
- Dogs with normal limb length
- Dogs diagnosed with IVDD
- Dogs without IVDD

They examined thousands of genetic markers across the canine genome and included multiple breeds rather than focusing on a single breed.

Remarkably, every analysis identified the same region on **canine chromosome 12 (CFA12).**

What Did They Discover?

The researchers identified an additional copy of an important developmental gene known as **FGF4**.

Normally, every dog possesses one functional FGF4 gene.

Affected dogs carried an extra copy inserted into chromosome 12. This duplicated copy is known as a **retrogene**.

What Is a Retrogene?

A simple analogy is to imagine a book.

Normally, the book contains one copy of each chapter. If one chapter is accidentally photocopied and inserted elsewhere in the book, that chapter is effectively read twice.

A similar process occurred in these dogs.

The FGF4 gene was accidentally copied and inserted into another location within the genome. As a result, the body receives additional growth signals from this duplicated gene.

Why Is FGF4 Important?

FGF4 is a developmental growth factor that plays a critical role during embryonic development by regulating the growth of:

- Bones
- Cartilage
- Limbs
- The spine

The additional copy of the gene causes developing tissues to receive excessive FGF4 signalling.

The researchers found that dogs carrying the chromosome 12 retrogene produced **approximately 20 times more FGF4** in developing spinal tissues than unaffected dogs.

This represents a substantial increase in gene activity.

How Does Excess FGF4 Affect Development?

The increased FGF4 signal alters skeletal development before birth.

Its effects include:

Long bones

- Reduced limb length

Growth plates

- Altered conversion of cartilage into bone

Intervertebral discs

- Premature maturation and early degeneration

Rather than remaining healthy for many years, the discs begin degenerative changes during puppyhood.

The Study's Most Important Discovery

The researchers demonstrated that a single genetic mutation produces two major effects simultaneously:

✓ Shortened limbs (chondrodystrophy)

✓ Premature degeneration of the intervertebral discs

These are not independent conditions but two consequences of the same genetic mutation.

How Strong Was the Association?

This study reported one of the strongest genetic associations identified in canine medicine.

Dogs carrying the chromosome 12 FGF4 retrogene were approximately **51 times more likely** to develop Hansen Type I IVDD than dogs without the mutation.

Genetic associations of this magnitude are uncommon and indicate that the mutation has a major influence on disease risk.

One Copy Versus Two Copies

The researchers also showed that the mutation affects different traits in different ways.

Limb Length

- **N/N (no mutation):** tallest dogs
- **CDDY/N (one copy):** moderately shortened limbs

- **CDDY/CDDY (two copies):** shortest limbs

This demonstrates a **dose-dependent effect**, with increasing copies producing progressively shorter limbs.

Risk of IVDD

The pattern differed for spinal disease.

A single copy of the mutation was sufficient to substantially increase susceptibility to IVDD.

Although two copies may further increase disease severity, one copy alone is enough to create a markedly increased risk.

For this reason, researchers describe the mutation as:

- **Semidominant** for limb length
- **Dominant** for IVDD susceptibility

This distinction remains important in modern breeding recommendations.

Was This the First FGF4 Mutation Identified?

No.

Researchers had previously identified another FGF4 retrogene located on **chromosome 18 (CFA18).**

Although both mutations shorten limb length, they differ significantly in their effects on spinal disease.

Chromosome 18 FGF4	Chromosome 12 FGF4
Causes shortened limbs	Causes shortened limbs
Little evidence that it independently causes IVDD	Strongly associated with IVDD
Present in some breeds with relatively low IVDD rates	Present in most breeds with high IVDD prevalence

This finding clarified that the chromosome 12 mutation—not the chromosome 18 mutation—is the principal genetic driver of Hansen Type I IVDD.

Which Breeds Carry the Chromosome 12 Mutation?

The chromosome 12 FGF4 retrogene was identified in numerous breeds with a well-recognised predisposition to IVDD, including:

- Dachshund
- Beagle
- French Bulldog
- American Cocker Spaniel
- Pembroke Welsh Corgi
- Shih Tzu
- Lhasa Apso
- Pekingese

The presence of the mutation closely corresponded with the high incidence of IVDD observed in these breeds.

Why Is This Important for Breeders?

Before this study, shortened limbs were often regarded primarily as a cosmetic breed characteristic.

This research demonstrated that the same genetic mutation responsible for shortened limbs also alters the structure and long-term health of the intervertebral discs.

In other words, physical appearance and disease risk are genetically linked.

What Did the Researchers Recommend?

The authors concluded that DNA testing offers an effective tool for reducing the incidence of IVDD over time.

They recommended that breeders use genetic testing to:

- Identify dogs carrying the mutation
- Make informed breeding decisions
- Gradually reduce the frequency of the mutation
- Lower the incidence of IVDD within the breed

Importantly, the researchers did **not** recommend immediately excluding all carrier dogs from breeding. Instead, they emphasised balancing disease reduction with the preservation of genetic diversity through thoughtful breeding strategies.

Why Is This Study Relevant to Bedlington Terriers?

Although Bedlington Terriers were not included in this study, the findings established fundamental biological principles that apply to any breed carrying the chromosome 12 FGF4 retrogene (CDDY).

The study demonstrated that this mutation:

- Alters limb development during fetal growth
- Causes degeneration of the intervertebral discs long before clinical signs appear
- Significantly increases the risk of Hansen Type I IVDD with just one copy
- Produces greater limb shortening with two copies and may further increase disease risk
- Influences health as well as physical appearance

These findings provide the biological basis for evaluating CDDY in any breed, including the Bedlington Terrier, and explain why many breed organisations now incorporate CDDY testing into breeding recommendations.

Key Take-Home Messages

1. The researchers identified an additional copy of the **FGF4** gene on chromosome 12 as the principal genetic cause of canine chondrodystrophy (CDDY) and Hansen Type I IVDD.
2. The mutation causes both shortened limbs and premature degeneration of the intervertebral discs.
3. Dogs carrying the mutation produce substantially higher levels of FGF4 during embryonic development, altering the formation of bones and spinal discs before birth.
4. A single copy of the mutation markedly increases the risk of IVDD, while two copies generally produce even greater limb shortening and may further increase disease severity.
5. This discovery transformed veterinary genetics by providing a reliable DNA test that enables breeders and veterinarians to reduce the incidence of one of the most common and debilitating inherited neurological diseases in dogs through informed breeding decisions.

Study Citation

Brown EA, Dickinson PJ, Mansour T, Sturges BK, Aguilar M, Young AE, Korff C, Lind J, Ettinger CL, Varon S, Pollard R, Brown CT, Raudsepp T, Bannasch DL. *FGF4 retrogene on CFA12 is responsible for chondrodystrophy and intervertebral disc disease in dogs.* Proceedings of the National Academy of Sciences of the United States of America. 2017;114(43):11476–11481. doi:10.1073/pnas.1709082114.