Managing the genetics of chondrodystrophy (CDDY)

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Description of the DNA mutation and phenotype:

Unlike other disease causing mutations found in dogs, the mutation that causes chondrodystrophy is not a change within a gene. The actual change in DNA that leads to chondrodystrophy is the insertion of an extra copy of a gene called *FGF4* (Fibroblast growth factor 4) to a new location on a different chromosome. FGF4 is a developmental signaling molecule. *FGF4* is normally expressed in the developing embryo at very defined locations and at precise time points. Specifically, it is expressed in the developing limb buds that are destined to become the legs and along the somites and notochord, which are embryonic tissues that will develop into the spine and intervertebral discs. The extra copy of the gene produces 10 times more FGF4 protein than normal in the intervertebral disc.

Chondrodystrophy changes the character of all of the intervertebral discs at a young age. The discs have abnormal degeneration of the nucleus pulposus, which is the center of the intervertebral disc that normally provides cushion and flexibility to the back. The end of the degeneration process is a mineralized or calcified disc. The change in the cellular structure of the disc is what predisposes it to herniate (move into the spinal canal impinging on the spinal cord). The chondrodystrophic degenerative phenotype is evident in all the intervertebral discs as early as 10 weeks of age in dogs homozygous for CDDY but is absent in breed matched dogs lacking the mutation (Murphy et al., 2019).

This mutation is dominantly inherited so that dogs with an extra copy of the *FGF4* gene and thus one copy of the chondrodystrophy mutation have degenerative intervertebral discs. Sometimes the abnormal nucleus pulposus ruptures impinging on the spinal cord causing pain and paralysis. Multiple factors are thought to influence whether a particular disc herniates (ruptures) in an individual dog.

Allele Frequency:

The allele frequency is a measure of how common the CDDY variant is compared to the normal version of the chromosome that does not have the extra inserted *FGF4* gene (denoted as N). The allele frequency represents the fraction of a given allele with in the population. For example, if a breed was found to have an allele frequency of 0.25 that would mean that 25% of the alleles in the population studied were CDDY and 75% of the alleles, at this chromosome position in that same population, were N. The estimated allele frequency based on a population of dogs tested shortly after the discovery of the mutation can reflect the breeding population and can be used to make population based breeding decisions.

Chondrodystrophy occurs in many breeds and its allele frequency varies in those breeds it has been reported to range from 0.02 to 1 (Batcher *et al.*, 2019). It also occurs quite commonly in mixed parentage dogs. A very comprehensive study to investigate allele frequencies across breeds was performed by Batcher and colleagues and is provided below. Additionally the Veterinary Genetics Laboratory has calculated allele frequencies by breed and will update these data as more breeds are tested (link to website data).

Breed	Total	CDDY Allele Frequency
Alaskan Malamute	21	0
Alpine Dachsbracke	174	0.59
Appenzeller Sennenhund	121	0
Australian Cattle Dog	11	0
Australian Shepherd	46	0.02
Basset Griffon Vendéen Petit	10	0
Basset Hound	32	0.63
Bavarian Mountain Hound	69	0.91
Beagle	12	1.00
Bernese Mountain Dog	11	0
Bichon Frise	71	0.18
Border Collie	5	0
Border Terrier	6	0
Boston Terrier	5	0
Brittany	17	0
Bull Terrier	5	0
Bulldog, English	13	0
Bulldog, French	106	0.97
Cairn Terrier	10	0
Cavalier King Charles Spaniel	21	1.00
Chesapeake Bay Retriever	40	0.08
Chihuahua	199	0.10
Chinese Crested	9	0.22
Clumber Spaniel	5	1.00
Cocker Spaniel, American	9	0.94
Cocker Spaniel, English	14	0.96
Coton de Tulear	12	0.58
Dachshund (Swiss)	136	0.94
Dachshund (US/UK)	257	0.98
Dandie Dinmont Terrier	27	0.89
Danish Swedish Farmdog	29	0.10
Doberman Pinscher	14	0
Entlebucher Mountain Dog	8	0.69
Fox Terrier	11	0
German Hound	16	0.66
German Shepherd Dog	15	0
Glen of Imaal Terrier	8	0
Golden Retriever	14	0
Great Dane	12	0
Irish Setter	8	0
Jack Russel Terrier	12	0.08
Labrador Retriever	21	0

Lagotto Romagnolo	53	0
Maltese	87	0.03
Mixed Breed	572	0.10
Newfoundland	13	0
Norwich Terrier	19	0
Nova Scotia Duck Tolling Retriever	172	0.35
Pekingese	28	0.63
Pinscher, Miniature	9	0.06
Podengo Pequeno	7	0
Poodle, Miniature and Toy	114	0.57
Poodle, Standard	55	0
Portuguese Water Dog	12	0.13
Pug	7	0
Rottweiler	10	0
Russell Terrier	10	0
Russian Tsvetnaya Bolonka	6	0.17
Schnauzer, Miniature	8	0
Schweizer Laufhund	65	0.11
Schweizerischer Niederlaufhund	46	0.51
Scottish Terrier	12	0.04
Shetland Sheepdog	13	0
Shih Tzu	110	0.25
Siberian Husky	11	0
Skye Terrier	13	0.77
Springer Spaniel, English	22	0.41
St. Bernard	10	0
Weimaraner	13	0
Welsh Corgi, Cardigan	6	0.75
Welsh Corgi, Pembroke	51	0.81
West Highland White Terrier	10	0
Whippet	5	0
Yorkshire Terrier	12	0.04
TOTAL	3223	0.41

*Adapted from Batcher, K.; Dickinson, P.; Giuffrida, M.; Sturges, B.; Vernau, K.; Knipe, M.; Rasouliha, S.H.; Drögemüller, C.; Leeb, T.; Maciejczyk, K.; Jenkins, C.A.; Mellersh, C.; Bannasch, D. Phenotypic Effects of FGF4 Retrogenes on Intervertebral Disc Disease in Dogs. Genes 2019, 10, 435

Recommendation on Genetic Testing:

For purebred dogs, where sufficient number of dogs have been tested, and the allele is fixed (in other words the frequency is 1.00) it is reasonable to assume that all dogs in that breed will be homozygous for CDDY and therefore genetic testing is not necessary because the genotype and therefor risk of disease is known in these cases. However, in breeds where the allele is present but not fixed it is recommended to have your dogs tested and consider the breeding counseling advice presented below.

Counseling:

Since this mutation is dominant, dogs with a single copy of the mutation will have abnormal intervertebral discs.

In a recent study by Batcher and colleagues (Batcher et al 2019), investigating 569 dogs, no difference in the age of surgery in dogs with 1 or 2 copies of CDDY was identified. Disc herniation with just 1 copy of CDDY was common across breeds including mixed breeds. As expected based on the well-defined types of disc herniation (Hansen Types I, II and Type III), chondrodystrophy is not the sole cause of disc herniation in dogs. In this study, 75.2% of the dogs that had surgery had chondrodystrophy. Since some of the breeds identified in this study segregated the CDDY mutation, the relative risk for disc herniation was calculated. It varied from 5.5 (Chihuahua) to 15.1 (mixed breed). This means that a dog with 1 or 2 copies of CDDY is 5-15 times more likely to have a disc herniate then a dog without the mutation.

Based on the dominant nature of the mutation and the high allele frequency within some breeds selection against CDDY should be done cautiously. Breeds with a lower allele frequency (defined here as <0.25) can use the genetic test to select away from the CDDY allele in one generation. It is recommended that breeds with an allele frequency in the range of >0.25, <0.5) select away from this mutation over several generations and to mate dogs with CDDY to dogs with two copies of the normal allele to reduce the allele frequency without a dramatic effect on breed diversity. Breeds with a high allele frequency (>0.5) will benefit from a much slower approach over multiple generations. There are some breeds that only have CDDY and no normal chromosomes in the breed and are thus said to be fixed for this trait, in these breeds all dogs test as CDDY/CDDY. It is not possible to breed away from this trait within breeds where the mutation is fixed.

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