Clinical sheet - Cardiology

Genetic testing for specific cardiac diseases in dogs and cats

Dilated cardiomyopathy in Dobermans

In the Doberman, a deletion of the gene encoding for the mitochondrial protein PDK4 (pyruvate dehydrogenase lipoamide kinase isozyme 4), involved in the regulation of transformation of pyruvate into energy, has been shown to be associated with the development of dilated cardiomyopathy (DCM) in this breed.[1]

This genetic anomaly can be detected on a blood or swab sample. The test evaluates the 2 copies (alleles) of the gene involved. The results can be:

- Negative homozygous (the 2 alleles are normal)
- Positive heterozygous (1 allele normal, 1 abnormal)
- Positive homozygous (the 2 alleles are abnormal)

In a study, 8/10 Dobermans without PDK4 mutation did not develop DCM but 2/10 did (probably because of other genetic anomalies not detected by this test), 6/10 with the PDK4 mutation did develop DCM but 4/10 did not, due to environmental factors and genetic modifiers. Therefore, this test stratifies the risk of development of DCM but does not predict with certitude what is going to happen.

The fact that other genes can be involved has been illustrated by another study on a European cohort of Dobermans (Germany and UK), which did not confirm the PDK4 deletion, but rather an anomaly on chromosome 5 (CF5).[2] There is no genetic test currently available for this particular genetic anomaly.

Studies are still ongoing to try to identify other genetic anomalies in Dobermans with DCM. In humans, there are than 20 gene mutations involved.

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Arrhythmogenic right ventricular cardiomyopathy in boxers

One of the genetic anomaly that has been associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) in Boxers is a deletion of the gene encoding for striatin, one of the proteins of the desmosome (structure linking 2 cardiac muscle cells). There are many different proteins of this structure involved in human familial ARVC.

A blood test is commercially available to look for that genetic anomaly. The results are, as for the DCM in Dobermans:

- Homozygous negative (the 2 alleles are normal)
- Heterozygous positive (one allele normal, one allele abnormal)
- Homozygous positive (the 2 alleles are abnormal)

In a cohort of 1690 boxers: 53% negative, 41% positive heterozygotes, 6% positive homozygotes. In 13 Boxers having expressed the disease (Holter positive), 10/13 were positive for the mutation.

Dogs homozygous positive tend to develop a more severe form (more arrhythmias). No breeding or breeding to negative dogs for several generations is recommended.
Dogs positive heterozygous should be screened with Holter and echocardiography. Genetic testing of the puppies is recommended for several generations.

Dilated cardiomyopathy in other breeds

Studies to identify genetic anomalies associated with DCM in Irish Woldhounds,[3] Great Danes are currently ongoing. Also, a search for other genes than the one encoding for PDK4 that may be associated with DCM in Dobermans is underway at North Carolina State University College of Veterinary Medicine (NCSU CVM).

Subaortic stenosis in newfoundlands

A study is currently under way at NCSU CVM to try to identify the genetic substrate of subaortic stenosis in this breed.

Hypertrophic cardiomyopathy in cats

In the Maine Coon and the Ragdoll, a mutation of the cardiac myosin binding protein C (MYCBP3) gene has been identified.[4] Genetic testing for this anomaly is available and can identify non-carriers from carriers (heterozygotes or homozygotes). The homozygous wild type (no mutant allele) will not

develop this form of HCM. The heterozygous cats may develop it, whereas the homozygous mutants, carrying the 2 mutant alleles, are more likely to develop a moderate to severe disease early in life, when compared to the heterozygous.

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References

1) Meurs KM, Lahmers S, Keene BW et al. A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman Pinscher. *Hum Genet*, 2012; 8: 1319-1325.
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Ragdoll photo www.paradis-des-chats.com