# Cardiac genetics: testing and interpreting in clinical practice

Niek Beijerink DVM, PhD, Dipl. ECVIM (Cardiology)

University of Sydney, Australia; Veterinaire Specialisten Vught; Anicura Specialistisch Verwijscentrum De Haaglanden
The Netherlands
niek.beijerink@sydney.edu.au

**Introduction**
Many forms of congenital and acquired disease have a strong breed predisposition suggesting a familial/genetic etiology. The small animal practitioner may be asked to provide consultation on genetic issues in order to provide information to owners of breeding animals to aid them in breeding decisions and to provide pet owners information about etiologies of disease.

Breed-specific lists of known (also non-cardiac) and presumed inherited diseases in the dog and cat can be found at several websites. Some good examples:

- Cats: https://icatcare.org/advice/cat-breeds/inherited-disorders-cats
- Dogs: www.vet.cam.ac.uk/idid
- Cardiac health testing in dogs and cats: https://cvm.ncsu.edu/genetics/submit-dna-testing

Key points during this lecture:

- My focus will be on what we know about genetics and the utility of understanding the genetic/mutation status of animals presented for (screening of) heart disease.
- The result of a genetic test, whether positive, or negative, do not provide information about the presence or absence of cardiac disease or about cardiac function at the time of testing. Echocardiography and other diagnostics always remain required to determine cardiac function. A genetic test with a positive result increases the likelihood of disease development in the future, but because there are likely many other unknown mutations that are associated with disease, a genetic test with a negative result does not preclude the change of the disease.

**Technique**
DNA testing can be performed on a variety of sample types including whole blood and a buccal mucosal (cheek) swab. The samples can be sent to several commercial labs for DNA analysis.

**Hypertrophic cardiomyopathy (HCM) in cats**
Hypertrophic cardiomyopathy (HCM) is the most common heart disease in cats and is characterized by concentric left ventricular muscle hypertrophy, impaired muscle relaxation and eventually may lead to congestive left-sided heart failure, aortic thromboembolism and sudden death in a subset of cats. This disease is also observed frequently in humans and is familial with over 1000 known mutations in many different human genes. Maine Coon and Ragdoll cats are observed to also possess a familial form of HCM that is inherited in an autosomal dominant pattern. Through genetic research in a colony of cats in the USA, a mutation in the myosin binding protein C 3 gene in Maine Coon cats was found. In Ragdoll cats, another mutation in myosin binding protein C 3 gene has been found. It is important to know that many Maine Coon cats and Ragdoll cats develop HCM while they screen negative on these mutations, suggesting (similar to humans) more (unknown) genetic defects are likely at play.

**Dilated Cardiomyopathy (DCM) in dogs**
Dilated cardiomyopathy represents the most common form of heart disease in large-breed dogs. DCM is like HCM an adult onset disease and as such it represents a problem for the breeding population as many dogs that develop DCM will have already produced offspring. Dobermann Pinschers are significantly overrepresented in prevalence of this disease. Human beings with DCM have many genes that are involved and multiple mutations in the same genes that lead to development of DCM. Doberman Pinschers appear to be the same. A mutation in a pyruvate dehydrogenase kinase 4 (PDK4; also called DCM1), a gene involved in myocyte metabolism, is described in Dobermans with DCM. This genetic mutation is not the only cause of DCM in Dobermans. Recently another mutation has been published (missense variant in the titin gene; named DCM2). Although there are Dobermans with DCM that are mutation negative, there is increased relative risk conferred by possessing the mutations in either a heterozygous or homozygous fashion.

**Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) in Boxer dogs**
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heart muscle abnormality that leads to fatty infiltration and fibrous tissue accumulation within the right ventricular myocardium, resulting in the hallmark of the disease: ventricular arrhythmias.
The best test to diagnose this condition currently is the presence of right-sided VPCs on Holter monitor that exceed 100 in a 24-hour period. This disease is classically described in the Boxer. In 2010 a mutation was discovered in a protein called striatin, which was demonstrated to co-localize with the cardiac desmosome.

**Subvalvular Aortic Stenosis in Newfoundland Dogs**
Subvalvular aortic stenosis (SAS) is a congenital heart defect that leads to restriction to left ventricular outflow and pressure overload on the left ventricle. Dogs severely affected with this condition on average live between 4 and 5 years of age with no interventional cardiology technique showing any survival benefit beyond the use of oral beta-blockers alone. The primary lesion is an abnormal fibrous tissue ridge below the aortic valve. Newfoundland dogs are overrepresented with a familial form of this disease. The pattern of inheritance is autosomal dominant with incomplete penetrance, much like the previously discussed conditions. Recently a mutation in phosphatidylinositol-binding clathrin assembly protein (PICALM) was identified that is associated with development of SAS in Newfoundlands.

### Pulmonic Stenosis (PS)

Pulmonic stenosis is characterized by congenital malformation of the pulmonic valves and sometimes hypoplasia of the the pulmonic annulus region, resulting in obstruction to right ventricular outflow, pressure overload and concentric hypertrophy of the right ventricle. Left uncorrected, syncope, right-sided congestive heart failure (ascites, pleural effusion) and arrhythmias with risk of sudden cardiac death can occur. Especially in Bulldogs pulmonic stenosis may be accompanied by coronary artery anomalies. Pulmonic stenosis produces a systolic left base murmur that must be differentiated from aortic/subaortic stenosis. Femoral pulses are often normal in PS whereas they are often weak with severe AS/SAS. Thoracic radiography may reveal right-sided cardiomegaly and a distinct main pulmonary artery bulge on the DV view. Echocardiography is necessary to make the diagnosis, rule out other concurrent cardiac defects, and assess severity and suitability for intervention.

### Aortic/Subaortic Stenosis (AS/SAS)

The majority of dogs with AS have a ridge of fibrous tissue below the aortic valve in the LV outflow tract, therefore subaortic in nature (SAS). This causes obstruction to left ventricular outflow, pressure overload and concentric hypertrophy of the left ventricle. Exercise intolerance, syncope, left-sided congestive heart failure (pulmonary edema) and arrhythmias with risk of sudden cardiac death are potential consequences, with sudden death being the most common outcome, and may occur at a young age in severe cases. Importantly, the lesions may not be present at birth but develop during the first 4–8 weeks of life. Therefore, it is not uncommon to not be able to hear a murmur at the first puppy check. SAS produces a systolic left base murmur that must be differentiated from PS. Femoral pulses are often weak. Severity of SAS increases with growth and maturity therefore murmur intensity increases during puppyhood. Thoracic radiography may reveal a prominent ascending aorta/aortic arch bulge and left ventricular enlargement, though concentric hypertrophy often does not produce gross cardiomegaly radiographically to the same extent that cardiac dilation does. Echocardiography is necessary to make the diagnosis, assess severity and candidacy for any therapy, and rule out other concurrent cardiac defects. Even with echocardiography, diagnosis of mild SAS can be very challenging.

### Atrial and Ventricular Septal Defects

Defects in the development of the embryonic ventricular septum, atrial septa, or endocardial cushions may result in atrial septal defects (ASD) and/or ventricular septal defects (VSD). When the degree of left-to-right shunting is substantive, ASD results in volume overload of the right atrium, the right ventricle, and pulmonary tree, whereas VSD results in volume overload of the left side of the heart and pulmonary tree (the right ventricle just acts as a passive conduit). Atrial septal defects can be challenging to detect on physical exam since they may produce no murmur due to low flow velocity, or a soft murmur similar to that of mild PS or an innocent murmur. A split second heart sound can sometimes be detected. Small VSDs produce very intense murmurs, typically loudest on the right, whereas larger VSDs may be associated with much softer murmurs.

### Atrioventricular valvular dysplasia

Dysplasia of either of the atrioventricular valves (mitral valve, tricuspid valve) can occur in both the dog and cat. It occurs when malformation of either valve leads to stenosis, and/or regurgitation. Mitral valve dysplasia can also cause a dynamic obstruction of the left ventricular outflow tract, especially in kittens. This leads to dilatation of the atria, which in turn, can lead to heart failure and arrhythmias. Clinical signs with mitral valve (MV) dysplasia include a left sided heart murmur, syncope (often associated with tachyarrhythmias), and left sided congestive heart failure. Thoracic radiography may show evidence of left atrial and left ventricular enlargement, and if present, pulmonary congestion and edema. Echocardiography is useful to assess the severity of valvular malformation, dynamic obstruction, regurgitation, stenosis (if present) and chamber enlargement. Treatment is usually limited to managing heart failure and arrhythmias. Once these occur, prognosis becomes guarded. Clinical signs with tricuspid valve (TV) dysplasia are similar except that a right sided heart murmur and right sided heart failure can occur.