

## GENETIC CAUSALITY OF DOGS CARDIOVASCULAR DISEASES

*Koshtura OS, Master's Degree 2 years of study Faculty of Veterinary Medicine  
of the National University of Life and Environmental Sciences of Ukraine*

*Kostenko SA, PhD, assistant professor of genetics, breeding and animal  
reproductive biotechnology im.M.A.Kravchenka*

*Endocardiosis mitral valve is the most common cardiac disorders in dogs, especially small breeds. The possible genetic mechanisms of hereditary predisposition to diseases of the cardiovascular system in dogs. Diseases of the small breeds can be caused by a mutation of the gene IGF1, which is one of the main reasons for the decline in body size in dogs. Distribution endocardiosis mitral valve may be due to the fact that mutations that cause arising portions that are closely linked to the gene candidate small dogs STC2, which has a value selectively. Since this gene is closely linked site NKX2 -5, mutations in which are linked with numerous congenital heart disease.*

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Diseases of the circulatory system account for about 10% of the pathologies of small animals [1]. According to some scholars, one in ten of the disease is caused by heredity [1, 2]. Endocardiosis antrioventrikulyarnih valves - one of the most common cardiac abnormalities in dogs older age group. This is especially true of the mitral valve. The frequency of the disease depends on the ratio of the representatives of various species in the specific region and an average of 70% of dogs heart disease, with age the disease can lead to congestive heart failure and death. Combining morphologic and genetic components associated with dogs gives endocardiosis tool elements for detecting the disease.

The purpose of the work was to study the mechanisms of genetic conditions diseases of the cardiovascular system in dogs.

Endokardiosis of mitral valve, a condition also known as atrioventricular heart valves myxomatous degeneration noninflammatory nature, mucoid, valves myxomatous degeneration, or as chronic valvular fibrosis. The disease is characterized by the accumulation and fibrosis hlyukozaminhlikaniv valves and tendon strings.

The highest disease susceptibility was observed in dogs breed Cavalier King Charles Spaniel. Polygenic inheritance is supposed influence of gender and age. Also at risk include representatives of such species as the one and miniature poodles, miniature schnauzers, Chihuahua, Pomeranian spitz, Fox Terrier, Cocker Spaniel, Pekingese, Boston Terrier, Miniature Pinscher. With larger breeds endokardioz can occur in Dalmatian, German Shepherd, Ridgeback.

According to research Byukenon (Buchanan, 1979), pathology valve has the following distribution: 62% - endokardioz only of mitral valve; 1% - just tricuspid; 33% - both [3]. In cases of of mitral valve endokardioz most breeds that ill show average weight adults less than 9 kg [4].

In 2002, Chase and others have published analysis groups considering vaccination Portuguese water dog morphology [5]. This breed can vary in size from 16 to 27 pounds and 43-58 inches at the withers, allowing the isolation of a number of genes that influence the overall body size. The authors received five different breed dogs radiographs and measured > 70 aspects of skeletal shapes and sizes. From these results, they calculated the nine main components, the first of which covers the total size of the body and has about 45% of the variation in the breed. This basic component is linked to two loci in the genome, one on chromosome 15 dogs (CFA15) and second in CFA3. Localization CFA15 is in the vicinity of the IGF1 gene and studies have shown they affect the amount of people as well as mice. For further specifications loci Sutter and colleagues compared the single nucleotide polymorphism (SNP) allele frequencies in terms of small and large dog breeds and found that it is associated with IGF1 gene in all small dogs.

IGF1 - insulin-like growth factor-1, or somatomedin C - protein structure and function similar to insulin and is one of the most important members of the family of insulin-like growth factors engaged in endocrine, paracrine and autokrynnu regulation of growth, development and differentiation of cells and tissues. Also, this protein plays an active role in the aging process [6].

This study revealed two important facts about dogs: first - genes that affect the main morphological features are shared by multiple species, and the second - all small breed dogs have at least one common ancestor, which contributed to the spread of mutations in the gene IGF1.

While reducing IGF1 is associated with reduction in body size, IGF1 excess leads to an increase in heart size by increasing the size of cardiomyocytes. IGF1 gene affects both skeletal growth and the size of the heart, though the effect is not proportional according to studies conducted in mice [7]. Mutations in the gene IGF1 is a major cause of decline in body size in dogs, if the heart is not reduced to the same scale as small dogs, this one mutation may be responsible for the excessive compression that leads to vice valve [8]. In addition, IGF1 has a direct impact on the growth of the heart, which could cause a defect in the selection of small breeds.

When the boxer genome sequence was completed in 2005, it was estimated that > 60% of the genome was represented homozygous areas that have an average length of 6 Mb [4]. SNP genotyping data analysis at least 10 dogs from each of the 60 species found that some individuals of all species were 10-50 homozygosity regions covering more than 10 Mb [9]. In most species, all individuals were homozygous regions overlap, at least 1 million bases. These areas homozygosity likely the result of selection for traits within species. When the sign is fixed within species, region of homozygosity or heterozygosity reduced created around the selected mutation and is known as a selective advantage. This area can be up to 1 MB within species depending on the age of selective mutation [4]. This means that any mutation within a gene or control element for within mln. Bases surrounding the selected mutation may be secured within a population with desirable traits and

the least likely to increase in frequency in response to selective pressure. Assuming that all small breeds are under selection for mutations in seven regions identified as loci regulating the size of several GWAS, there is a potential that seven Mb DNA is in all breeds simply because they are constitutionally small. These seven million base pairs of nucleotides containing an average of 70 genes, all of which can be related to the risk of heart defects in any breed that has them.

An interesting case can be found in the gene *STC2*, which has been identified as a candidate for the small size [9]. *STC2* was not involved with the development of the heart, but it is less than 80 kb of the gene *NKX2-5* (*NKX2-5*). Given their proximity, these genes share high LD with each other and within average selective advantage. *NKX2-5* is below *TGF $\beta$*  and *SMAD2* a signaling pathway that controls the formation of a heart valve. Mutations in *Nkx2-5* were associated with multiple congenital heart diseases including mitral valve abnormalities in humans. A mutation that affects *NKX2-5*, can easily spread with *STC2* gene when it was under selective pressure at any point in the process of breeding small dogs. Of course, the genes responsible for the development of abnormal valve does not have any influence on the degeneration of the valve cusps formed and many other genes [4].

We considered various mechanisms to explain the excess of small and dwarf breeds in the list of those who have the greatest risk. One possible cause of heart disease can be that small dogs have more heart in relation to body size than large dogs. This can be checked by measuring the size of the heart and overall body size, including the volume of the chest dogs of different sizes to determine whether there is a significant difference in relation to small breeds.

Another option may be finding small breed dogs that are not at risk. For example, the Brussels griffon is not mentioned in any of the published lists of species increased risk to endocardiosis mitral valve, despite an average adult weight of just nine pounds. Another possibility is to study the disease in species where animals have weight and above and below 9 kg, such as Boston Terrier.

Correlation between physical size and development of the disease within the same species will determine whether body size is a major cause of illness.

Many genes that influence growth and skeletal development also affect heart development. In addition, genes can be found nearby loci growth necessary for normal heart valve formation. Because all small breeds have many of the same mutations that cause small size, they are also related genes that could increase susceptibility to endokardiozu. Selective pressure on these genes make difficult process of binding to the smallest breeds because they are likely to be near fixation. However, as the size - a quantitative trait, the dog should be medium to large size, having at least one mutation in a small size. If these mutations alter the size and cause endokardiosis of mitral valve disease it has come to some small number and average size breeds that carry them. These species can be invaluable in the search for causal variant.

Many breeds at risk, which originate from the first small dog that gave genes predisposition to their offspring. As a source of risk endokardiozu, this program can be identified through genetic mapping of species at risk with a dense set of markers and a large database breed. It is formally possible that each species has developed a unique mutation that has become widespread due to the restrictive practices of breeding species. However, given the high incidence coupled with the similarity between species more likely that the common loci contributed to the development of the disease. None of the mechanisms listed above are not mutually exclusive and it is likely that further research will show that the combination of these characteristics proves endokardiosis reason for the emergence of of mitral valve.

In favor of the heritability of heart disease in dogs is demonstrated by the fact that 25-35% of patients with cardiomyopathy people found familial forms of the disease [7]. This is due to the vast majority of mutations in the genes encoding proteins of the cytoskeleton [7], as well as take part in muscle contraction [10]. Since there is a polygenic mode of inheritance, the disease is genetically heterogeneous. However, the most common form is considered an autosomal

dominant pattern of inheritance [7]. Described as an autosomal recessive (the syndrome Ahlström [7]), linked to the X chromosome (Duchenne muscular dystrophy) and mitochondrial [11]. Some relatives of patients with dilated cardiomyopathy have a preclinical, asymptomatic changes in the heart muscle [12]. Other cytoskeletal proteins involved in the development of heart valve disorders is the  $\alpha$ -cardiac actin, fodrin, Gas-2, desmin and nuclear lamins A and C [7]. Mitochondrial deletions and mutations probably cause endokardiosis by altering myocardial ATP. [7].

The final feature that is common in small breeds and may promote endokardiosis is extended lifespan. Often noted that small dogs live longer on average than large dogs. Endokardiosis - a disease of aging heart. This led to the assumption that small dogs are diagnosed more often simply because they live long enough for the disease progressed. While age is certainly a factor, but life is unlikely to be the only reason for the increase in the occurrence endokardiosis small dogs. For example, symptoms endokardiosis of mitral valve can not be detected until the dog is not until age 9, but evidence of valvular dysfunction can be detected up to 4 years. This works well within the lifetime dog of any breed, regardless of size.

The study of cellular aging suggests that large dogs age faster than smaller ones. If cellular senescence and aging Valvular comparable, the 10-year-old heart a little dog looks like a 6-year-old giant dog and heart disease are diagnosed at an earlier age in larger dogs. Finally, endokardiosis diagnosed in large dog breeds such as German shepherd and great dane, and these species are often among the sourcing of all breeds with the shortest life expectancy. Therefore, it would seem that life alone can not explain the presence of the disease. The data of this study are invaluable, as was also discussed issues regarding the age of onset and rate of progression in different species.

## ***Conclusions***

*1. Endokardiosis of mitral valve is the most common cardiac violations in dogs, especially small breeds.*

*2. Cardiovascular disease dogs of small breeds may be due to a mutation of the gene IGF1, which is one of the main reasons for the decline in body size in dogs. If the heart is not reduced to the same scale as small dogs, this one mutation may be responsible for excessive compression, which leads to vice valve.*

*3. Distribution endokardiosis of mitral valve may be due to the fact that mutations that cause it emerged in areas closely linked to the gene candidate small dogs STC2, which has a selective value. Since this gene closely linked site NKX2 -5, in which mutations associated with multiple congenital heart defects.*

## **REFERENCES**

- 1. Руденко А.А. Поширеність та етіологічна структура серцево-судинних хвороб у собак / А.А.Руденко, М.І.Цвіліховський // Ветеринарна медицина України.- 2009.-№ 10.- С.13-15.*
- 2. Мартин М., Коркорэн . Кардиореспираторные болезни собак и кошек. - М.: Аквариум, 2004.- С. 54-86.*
- 3. Клименко А.В. Диагностика и лечение эндокардиоза митрального клапана у собак / А.В Клименко // Мир ветеринарии. – 2014.- №1. – С. 30-33.*
- 4. Parker HG1, Kilroy-Glynn P. Myxomatous mitral valve disease in dogs: does size matter? / Parker HG1, Kilroy-Glynn P.// J Vet Cardiol. 2012 Mar;14(1).- P. 19-29.*

5. Genetic basis for systems of skeletal quantitative traits: principal component analysis of the canid skeleton / Chase K, Carrier DR, Adler FR, Jarvik T, Ostrander EA, Lorentzen TD, Lark KG. // Proc Natl Acad Sci U S A.- 2002.-1999.- P.9930-9935.
6. Exercise training enhanced SIRT1 longevity signaling replaces the IGF1 survival pathway to attenuate aging-induced rat heart apoptosis / Lai CH, Ho TJ, Kuo WW, Day CH, Pai PY, Chung LC, Liao PH, Lin FH, Wu ET, Huang CY // Age (Dordr).- 2014.- Oct.- 36(5).- P. 9706.
7. Mitchell, Richard Sheppard; Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson (2007). Robbins Basic Pathology (8th ed.). Philadelphia: Saunders. pp. 345
8. Is mitral valve prolapse due to cardiac entrapment in the chest cavity? ACT view / Raggi P, Callister TQ, Lippolis NJ, Russo DJ.// Chest. 2000 .-Mar.- 117(3).- P. 636-42.
9. Boyko AR, Quignon P, Li L, Schoenebeck JJ, Degenhardt JD, Lohmueller KE, Zhao K, Brisbin A, Parker HG, vonHoldt BM, Cargill M, Auton A, Reynolds A, Elkahoul AG, Castelhamo M, Mosher DS, Sutter NB, Johnson GS, Novembre J, Hubisz MJ, Siepel A, Wayne RK, Bustamante CD, Ostrander EA. A simple genetic architecture underlies morphological variation in dogs. PLoS Biol. 2010 Aug 10;8(8). <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2919785/pdf/pbio.1000451.pdf>
10. Ross J. Dilated cardiomyopathy: concepts derived from gene deficient and transgenic animal models / Ross J. // Circ J. - 2002 .-March. - 66 (3): P. 219–24.
11. Many roads lead to a broken heart: the genetics of dilated cardiomyopathy / Schönberger J, Seidman CE // American Journal of Human Genetics.-2001. August 69 (2).- P. 249–60.
12. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease / Mahon NG, Murphy



RT, MacRae CA, Caforio AL, Elliott PM, McKenna WJ // *Annals of Internal Medicine*.- 2005.- July.- 143 (2): P.108–15.