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# Current developments in canine molecular genetics. A review

Aktualne osiągnięcia genetyki molekularnej psów. Praca przeglądowa

**Summary**. In recent years, great progress in canine molecular genetics has been observed. DNA sequencing of a female Boxer was started in 2003. The next version of the dog genome sequence is now available online. Recently a microchip SNP array, covering over 170 thousand SNPs, has also become available. Simultaneously with the development of genetic maps and increasing accuracy of sequencing, a large number of causal mutations for various traits were identified. Most mutations were responsible for monogenic inherited diseases in dogs, but also for other traits. To date, candidate genes as markers for the size, colour and structure of hair, skeletal metric traits, behaviour and physiological traits were identified. At present, research of quantitative trait loci (QTL), analysis of candidate genes, and genome-wide association studies (GWAS) are carried out in dogs. In addition, the dog has become an animal model for many human hereditary diseases, as well as for farm animals. Recent studies primarily consist in determination of causal mutations that can lead to the development of genetic diseases, occurring in both dogs and humans. In the future, the results can be used to develop new treatments for inherited diseases in both species.

**Key words**: dog, SNP, QTL, molecular determination of traits, hereditary diseases, gene therapy, human

## INTRODUCTION

The domestic dog (*Canis lupus familiaris*) is one of 41 species within the *Canidae* family. It is the most intensively studied representative of the whole family, because of the widespread breeding (diagnostics of inherited diseases) and the occurrence of many breeds (the study of genetic variation). This species is also useful in studies on the ef-

fects of gene therapy and the etiology and symptoms of hereditary diseases (animal model for human and other livestock species).

Discoveries in recent years and intensive progress in molecular biology contributed to the knowledge of dog genome at the structural and functional level. They are closely related to the possibility of using knowledge of genomics in breeding of different breeds. Currently, it is expected that progress in breeding will be mainly based on the knowledge of the molecular basis of trait variability.

## GENOMICS OF THE DOG

The techniques of molecular biology and progress in bioinformatics have facilitated global analysis of the organization of genetic information in individual species (genomes). The rapid development of genomics was connected with the publication of the initial sequence of the human genome in February 2001. In 2003, a preliminary genome sequence (an accuracy of sequencing 1.5X) [Kirkness *et al.* 2003], and in 2005 – a full (7.5X) sequence of the dog genome was published [Lindblad-Toh *et al.* 2005]. The dog genome consists of 39 chromosomes, containing 2.4 Gb base pairs. It is estimated that the number of genes in the dog genome is the lowest of the known genomes of mammals and it is 19 300.

The contemporary dog species consists of hundreds of genetically isolated breeds which are diverse in terms of occurrence of genetic diseases and morphological and behavioural traits [Parker *et al.* 2004, Sutter *et al.* 2004, Ostrander and Wayne 2005]. The use of full information about the dog genome for genetic analyses requires dense SNP maps and understanding of genetic variation within and between breeds. Studies of the genome sequence provided information on DNA polymorphism. One of the results was the discovery of nearly 2.6 million SNP polymorphism (single nucleotide polymorphism) in the dog genome. Identification of millions of polymorphic sites was used for large-scale genome analysis with the use of microarrays, which enabled evaluation of the variability in tens of thousands sites of the dog genome [Sutter *et al*. 2004, Ostrander and Wayne 2005, Karlsson *et al.* 2007, Cadieu *et al.* 2009, Akey *et al.* 2010, Shearin and Ostrander 2010]. Genome-wide selection (GWS) uses high-density SNP maps. Currently, microarrays for the analysis of the SNP polymorphism of the dog genome are available (172 115 SNPs) [www.illumina.com]. Hence, genome-wide association studies (GWAS) became possible.

The marker map of the dog genome may be cytogenetic (physical), indicating the chromosomal localization of loci, and linkage (genetic), providing information about the order of the position of loci and distances between them. In 1993, an international consortium whose aim was to build the highly saturated marker map of the dog genome was formed (DogMap) [DogMap Consortium 1999].

In 1997, Mellersh *et al.* published the first linkage map of the dog genome. Construction of this map was based on 150 microsatellite markers, 139 of which were in 30 linkage groups. The total length of the map was 2073 cM and the average distance between the mapped markers was 14.03 cM. In subsequent years, studies aiming at increasing the density of markers located in the dog genome were conducted [Neff *et al*. 1999, Werner *et al.* 1999, Breen *et al.* 2001]. The latest linkage map of the dog genome was

presented by Wong *et al.* [2010]. The map comprising 3212 markers reached the average size of 2085 cM for both sexes with the average distance between the markers of 0.7 ± 0.9 cM. Over the past several years, a highly saturated genetic map of the dog genome was constructed. The number of the polymorphic genetic markers with known localization can be used for further studies connected with behaviour, genetic defects, and phenotypic variation of dogs' traits.

Marker genome maps are the basic tool used in the search for loci, whose polymorphism may have a significant impact, for example, on the variability of quantitative traits. Prediction of candidate genes may be carried out with the use of different procedures, such as genome scanning with the use of the knowledge about marker map. Initially, microsatellite loci (SSR, STR) were markers used for genetic mapping. Microsatellites occur in varying degrees in the coding and non-coding regions of the genome. Results of studies indicate their potential functional significance. Microsatellite markers occur in genomes of all organisms; hence, they have become a versatile molecular tool, used mainly for individual identification, determination of species history, evaluation the level of intra-and intergroup genetic variability, construction of marker maps of genomes, gene mapping, linkage analysis and medical diagnostics, forensic medicine and forensics [Parker *et al*. 2004, Ostrander and Wayne 2005, Ślaska *et al.* 2007, Ślaska *et al.* 2008, Shearin and Ostrander 2010, Ślaska 2010].

## CONTROL OF PARENTAGE AND THE INDIVIDUAL IDENTIFICATION

Microsatellite markers were used for parentage control in many species of animals, including dogs. Fredholm and Wintero [1996] conducted parentage control investigations of 12 breeds of dogs, using 12 microsatellite loci. The probability of exclusion was 99.99%. Zajc and Sampson [1999] found the possibility of using 19 microsatellite sequences in parentage control of three breeds of dogs. The scientists found that the use of 5 (Labrador Retriever and German Shepherd) or 6 microsatellite loci (Whippet) characterized by the highest degree of polymorphism and access to data on the genotypes of both parents could give a 99% probability of exclusion. Kang *et al.* [2009] studied five breeds of dogs, including two Korean breeds (Jindo and Poongsan) and three other breeds (German Shepherd, Beagle, and Whippet). Each breed was genotyped with the use of 9 to 12 microsatellite sequences. The total probability of exclusion for individual breeds ranged from 0.9995 for the German Shepherd, through 0.9997 for the Whippet, to 0.999 for the other breeds studied. Currently, there are several widely used standard microsatellite multiplexes for individual identification and analysis of the genealogical relationships, selected according to their degree of informativeness. In 2005, the International Society for Animal Genetics [www.isag.org.uk] proposed using panels composed of 10 and 12 microsatellite markers. The American Kennel Club authorized tests for paternity exclusion and identification of parentage with the use of genotypes of 17 microsatellite markers amplified in two PCR multiplexes. The study included 108 breeds. With the use of the first multiplex containing 10 markers, the probability of exclusion exceeded 99% in 61% of the breeds. In conjunction with the second multiplex containing 7 markers, the probability of exclusion within the 100% of the breeds studied exceeded 99%. The authors suggested that a universal panel should consist of 10–15 genetic mark-

ers on average [Denise *et al.* 2004]. Examples of parentage identifications of dogs are described in many studies [reviewed in: Kang *et al.* 2009], which is understandable, given the high variability reaching 27.5% of the total genetic variation between dog breeds [Parker *et al.* 2004].

## DNA REGIONS RESPONSIBLE FOR THE PHENOTYPIC VARIABILITY, CANDIDATE GENES, AND MAJOR GENES OF QUANTITATIVE TRAITS

The basis for inter-individual and interbreed variability are molecular differences in the genetic information of individuals. Changes in DNA sequences in the coding or regulatory regions of genes may modify the protein structure, thus affecting many cellular mechanisms. The development of molecular genetics allowed identification of chromosomal regions containing loci of genes whose mutated alleles are responsible for the variability of traits important from the breeding point of view. The trait can be determined by a single gene (monogenic hereditary diseases) or be polygenic and identified with the use of genome regions affecting quantitative traits (quantitative trait loci, QTL) [Andersson and Georges 2004, Ślaska *et al.* 2007, Ślaska 2010].

A key role in the identification of chromosomal regions containing QTLs is played by saturated genome maps. Progress in the use of polymorphic markers in genetic mapping of the different animal species facilitates identification of genome regions containing loci which affect economically important traits (economic trait loci, ETL). Localization of probable regions containing ETL and their identification could lead to increased genetic progress of traits important for breeding. This technology could bring measurable benefits for the dog in terms of growth and development, genetic diseases, behaviour, and coat colour [Andersson and Georges 2004, Świtoński 2004, Andersson 2009, Ślaska 2010]. Within several years, many regions where quantitative trait loci may occur were identified in different animal species with sequenced genomes. To date, numerous point mutations (QTM, quantitative trait mutations, QTN, quantitative trait nucleotide) exerting a large phenotypic effect have been described [Andersson 2009].

Currently, identification of QTL regions is carried out with the use of commercial SNP microarrays, which allow conducting association studies covering the entire genome (WGA, whole genome associations). The number of SNP markers equally distributed across the genome increased the density of genome maps. Thus, the chance for a more precise localization of QTL (fine mapping), or finding new quantitative trait loci was increased. Akey *et al.* [2010] genotyped more than 21 thousand autosomal SNPs using a genome-wide scan for selection of 275 dogs belonging to 10 different breeds. The authors identified candidate genes for phenotypic traits, such as size (*HMGA2* and *IGF1R*), colour and structure of hair (*SILV* and *MITF*), behaviour (*CDH9*, *DRD5,* and *HTR2*), morphology of the skeleton (*SOX9*), and physiological traits (*FTO*, *SLC2A9,* and *SLC5A2*). Moreover, they evidenced the significant association between the polymorphism of the *HAS2* gene (hyaluronic acid synthase gene) on chromosome CFA13 and skin wrinkling in Shar-Pei. The degree of skin wrinkling in this breed is correlated with a high content of mucin (histologically) and high levels of hyaluronic acid (biochemically) [Zanna *et al.* 2008].

Genome-wide association studies over a thousand dogs belonging to 80 breeds were used to determine the genetic determinants of phenotypic traits of hair [Cadieu *et al.* 2009]. Based on the inter- and intra-breed variability, the authors identified mutations in the genes RSPO2, FGF5, and KRT71 (encoding R-spondin-2, fibroblast growth factor-5, and Keratin-71, respectively), which together determine most of the phenotypic features of hair of purebred dogs. Therefore, the features of hair coat may be determined by the combined effect of only a few genes. Also Akey *et al*. [2010] suggested several keratin genes on chromosomes CFA27 CFA9 as candidate genes for the curly coat phenotype, including the KRT71 gene, which was also indicated by Cadieu *et al.* [2009].

Studies of dog genomics focuses mainly on identification of markers of genetic defects and diseases. However, studies aimed to determine the genetic basis of the complexity of morphological diversity are conducted. Due to the large differences in body weight (from 2 kg – Chihuahua, to 80 kg – Bull mastiff) and the shape of the skeleton (from Bassets, through Boxers and Whippets to Great Danes), dogs have become an interesting object of studies aiming at determination of the polygenic nature of quantitative traits.

The genetic bases of the differences in the body size and proportions between the different breeds of dogs have not been fully elucidated yet. However, potential candidate genes were selected. These include *TCOF1*, *IGF1,* and *MSTN*. Expression of the *TCOF1* gene occurs during the skeletal development. Association between this gene and the short and broad skull has been proved [Haworth *et al.* 2001]. In turn, the level of *IGF1* in dogs was associated with the size, and haplotype blocks within the sequence of the *IGF1* gene were related to the body size [Chase *et al.* 2002, Sutter *et al.* 2007]. It was shown that the variability of the level of insulin-like growth factor (*IGF1*) is correlated with the difference in the body size of Poodles, suggesting that the *IGF1* gene may be a candidate gene for the differentiation of the body size in dogs. With the use of microsatellite markers, Chase *et al.* [2002] identified quantitative trait loci (QTLs) that were associated with various types of metric traits of the skeleton of the Portuguese Water Dog. The QTL in two chromosomes (CFA15 and CFA37) were determined for one group of measurements describing the overall size of the skeleton. One of those markers were localized near the *IGF1* gene. In addition, for the other groups of measurements, the quantitative trait loci were identified in five chromosomes [Chase *et al.* 2002].

After many years, the hypothesis concerning the effect of polymorphism in the *IGF-1* gene was confirmed. QTL conditioning traits associated with the size of the skeleton of the Portuguese Water Dog were identified in the 15th chromosome [Sutter *et al.* 2007]. Then the association between SNP and the skeletal size was determined, which allowed indication of the gene encoding insulin-like growth factor (*IGF1*, *insulin-like growth factor-1*) as the major gene. By designating haplotype blocks I and B, the authors found that homozygous dogs for haplotype I were larger and had a higher level of *IGF1* in the blood serum, in contrast to homozygous dogs for haplotype B. In addition, the researchers estimated that the variation of the *IGF1* was 15% of the overall variability of the skeleton size. Fondon and Garner [2004] suggested that the phenotypic plasticity of dogs might be associated with the microsatellite sequences within genes. The study used models of skeletons representing 92 breeds of dogs and 37 regions of DNA sequences located within 17 genes, indicating their relationship with the various features of the skeleton. Molecular studies of purebred Portuguese Water Dogs showed that the FH2295

microsatellite sequence is associated with the quantitative trait loci (QTL) controlling 43.6% of the variation of the body size in this breed [Chase *et al.* 2002, Sutter *et al.* 2008]. Bérubé *et al.* [2012] used two variants of tetranucleotide sequence of FH2295, with 5 and 24 repetitions of the CTTT motif. The smallest dogs were homozygous for the long allele (24 repeats), and the largest dogs – homozygotes with five repetitions of the motif. Therefore, the authors proposed using two variants of the FH2295 marker length as predictors of the body size of female Portuguese Water Dogs [Bérubé *et al*. 2012].

Using the information about the proven impact of *MSTN* gene polymorphism on the musculature in different animal species, Mosher *et al.* [2007] described dinucleotide deletion in the third exon of the *MSTN* gene (Cys → stop) of Whippet dogs. This mutation caused "double" muscling in Whippets (*bully whippets*). Heterozygous dogs for the mutation of the *MSTN* gene were more muscular and one of the fastest in racing competitions, compared with dogs without mutant alleles. Homozygous *bully whippets* were also characterized by the highest body weight [Mosher *et al*. 2007].

Together with the studies on the body weight and the shape of skeleton of dogs, research is conducted to determine the genetic determinants of hair colour. In recent years, the influence of the *MC1R* gene (*melanocortin 1 receptor*) on the agouti colour were determined. This gene controls the type of synthesized pigment in hair of mammals [Berryere *et al.* 2005]. In addition, studies were conducted on the determinants of black coat colour, inheritance of which appears to be independent of the *MC1R* gene [Kerns *et al.* 2003, Candille *et al.* 2007]. The effect of melanophilin gene polymorphism (*MLPH*) to "lighten" of the coat colour was studied by Philipp *et al*. [2005]. The genetic basis of two monogenic traits was also identified: the white colour of hair coat and the stripe on the back (*hair ridge*) [Karlsson *et al*. 2007, Salmon Hillbertz *et al.* 2007]. This is a special discovery, given the association between the aforementioned traits with defects. The occurrence of white coat colour is conditioned by the *MIFT* gene (*microphthalmia-associated transcription factor*), which also determines pigmentation and hearing disorders in man and mouse. Concurrently, it was found that the presence of white spots, spotted coat, or white coat was not conditioned by three different mutations in the *MIFT* gene, but is determined by the occurrence of three variants of the regulation of gene expression [Andersson 2009].

## PRACTICAL USE OF MARKER-ASSISTED SELECTION (MAS)

### Hereditary dogs' diseases

Currently, breeding programs of different animal species employ tests for detection of gene polymorphism and other markers conditioning traits important from the breeding point of view. Many tests are used in practice also in dogs. However, they mainly concern defects and genetic diseases. Catalogues of known inherited diseases of dogs are available online free of charge. They provide important information on the distribution of diseases and genetic predispositions. They are Canine Inherited Disorders Database (CIDD, www.upei.ca/cidd), Inherited Diseases in Dogs (IDID, www.vet.cam.ac.uk/idid) and

Online Mendelian Inheritance in Animals (OMIA, omia.angis.org.au) associated with the Listing of Inherited Disorders in Animals (LIDA, www.sydney.edu.au/vetscience /lida).

Nearly 370 genetic disorders, similar in dogs and human, have been described [IDID, http://www.vet.cam.ac.uk/idid], but only some of them have been identified at the molecular level. Previously, 577 genetic defects were described in dogs, 151 (26%) of which were diagnosed at the molecular level [http://omia.angis.org.au/; as at 06/13/2012].

Studies of comparative genomics showing interspecies gene homologies play a significant role in understanding the genetic background of canine diseases. It is estimated that 93% of the genes in the human and dog genomes are orthologous [Goodstadt and Ponting 2006]. Most genetic defects in dogs were described based on the knowledge of analogous mutations in human genetic diseases. Thus, it was possible to detect causal mutations in selected candidate genes in dogs. Currently, the most commonly reported genetic diseases include: retinopathies, Duchenne muscular dystrophy, haemophilia A and B, leukocyte adhesion deficiency, hip dysplasia, epilepsy, diabetes, cardiovascular diseases, autoimmune diseases and cancers (breast cancer, melanoma, lymphoma) [Lequarré *et al.* 2011, Nowend *et al.* 2011, Derrien *et al.* 2012, Miyadera *et al.* 2012, Wilson and Wade 2012].

**The dog as a model species**

The dog has become a promising model for studies of human genetic diseases, including the application of gene therapy. This is the reason of increasing interest in detailed knowledge of the dog genome [Świtoński 2004, Breen 2008, Świtoński and Szczerbal 2008]. It is expected that about 500 thousand markers would be necessary to analyze SNPs covering the entire human genome, [Kruglyak 1999, The International HapMap Consortium 2003]. However, in comparable studies on the dog, hypothetically "only" 100 thousand SNP are necessary [Sutter *et al.* 2004]. Therefore, mapping of polygenic diseases, characterized by homologous etiology in the dog and human (epilepsy, cancers, autoimmune disease, deafness, heart disease) is certainly more effective in dogs than in man. To increase the possibility of using dog as a model to study the analogous human disease in 2008 LUPA project was founded by the European Commission. Canine geneticists and doctors from 12 European countries, collected DNA samples from large numbers of dogs which suffer the diseases those are analogous to human disorders. The aim of the project was to find the causative genes and mutations and to understand the molecular mechanisms leading to similar diseases in dogs and humans. This would help clarify the genetic basis of complex diseases in humans and the development of new treatments. The project concerned cancers, cardiovascular diseases, inflammatory diseases, neurological diseases and monogenic diseases [Lequarré et al, 2011].

Indication of mutations responsible for the development of canine diseases allowed attempts at the gene therapy. Some of them were successful, e.g. therapy of inherited retinal dystrophy (analogue to the childhood blindness called Leber), haemophilia (associated with a blood clotting factor VIII deficiency), and a lysosomal storage disease (mucopolysaccharidosis – MPSVII, MPSI) [Świtoński 2004, Świtoński and Szczerbal 2008, Nowend *et al.* 2011].

Two of the well-known livestock diseases – malignant hyperthermia (MH) of pigs and bovine leukocyte adhesion deficiency (BLAD), also apply to the dog. Analogous etiology of the diseases in these species and the dog was found [Kijas *et al.* 1999, Roberts *et al.* 2001]. Determination of the genetic basis of malignant hyperthermia (MH) and

canine leukocyte adhesion deficiency (CLAD) gave a reason to believe that the dog can also be a model species in studies of other farm animal species.

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**Streszczenie**. W ostatnich latach odnotowano ogromny postęp w genetyce molekularnej psów. W 2003 r. rozpoczęto sekwencjonowanie DNA samicy boksera. Obecnie dostępna jest online kolejna wersja sekwencji genomu psa, a ostatnio dostępne stały się mikromacierze SNP, obejmujące ponad 170 tys. SNP. Równolegle do rozwoju map genetycznych i zwiększania dokładności sekwencjonowania zidentyfikowano szereg mutacji przyczynowych dla różnych cech. W większości mutacje były odpowiedzialne za choroby dziedziczne monogenowe psów, ale również za inne cechy. Do tej pory wskazano geny kandydujące na markery cech związanych z wielkością, kolorem i strukturą sierści, cechami metrycznymi szkieletu oraz cechami behawioralnymi i fizjologicznymi. Obecnie mogą być prowadzone badania dotyczące poszukiwania *loci* cech ilościowych (QTL) oraz analiza genów kandydujących i badania asocjacyjne całego genomu (GWAS) psa. Ponadto pies stał się zwierzęciem modelowym w badaniach wielu chorób dziedzicznych człowieka, jak również zwierząt gospodarskich. Najnowsze badania dotyczą przede wszystkich określenia mutacji sprawczych prowadzących do powstania chorób genetycznych występujących zarówno u psów, jak i ludzi. W przyszłości wyniki tych badań mogą stać się podstawą do opracowania nowych metod leczenia chorób dziedzicznych u obu gatunków.

**Słowa kluczowe**: pies, SNP, QTL, molekularne uwarunkowanie cech, choroby dziedziczne, terapia genowa, człowiek