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Review Article

Dog as a model in studies on human hereditary diseases and their gene therapy

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ABSTRACT

During the last 15 years spectacular progress has been achieved in knowledge on the dog genome organization and the molecular background of hereditary diseases in this species. A majority of canine genetic diseases have their counterparts in humans and thus dogs are considered as a very important large animal model in human biomedicine. Among canine monogenic diseases with known causative gene mutations there are two large groups classified as retinal dystrophies and lysosomal storage diseases. Specific types of these diseases are usually diagnosed in a single or several breeds. A well known disorder, restricted to a single breed, is congenital stationary night blindness described in Briards. This disease is a counterpart of Leber amaurosis in children. On the other hand, one of the most common monogenic human diseases (Duchenne muscular dystrophy), has its canine counterparts in several breeds (e.g., the Golden retriever, Beagle and German short-haired pointer). For some of the canine diseases gene therapy strategy was successfully applied, e.g., for congenital stationary night blindness, rod-cone dystrophy and muccopolysaccharydoses type I, IIIB and VII. Since phenotypic variability between the breeds is exceptionally high, the dog is an interesting model to study the molecular background of congenital malformations (e.g., dwarfism and osteoporosis imperfecta). Also disorders of sexual development (DSD), especially testicular or ovotesticular DSD (78,XX; SRY-negative), which is widely distributed across dozens of breeds, are of particular interest. Studies on the genetic background of canine cancers, a major health problem in this species, are also quite advanced. On the other hand, genetic studies on canine counterparts of major human complex diseases (e.g., obesity, the metabolic syndrome and diabetes mellitus) are still in their infancy.

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1. Introduction

The dog is an exceptional species in term of phenotypic variation observed among its approx. 400 breeds. A large number of breeds with unique traits, including size, morphology, coating and behavior, reflect breed-specific gene pools. Selection, crossing and genetic drift have facilitated fixation of favored alleles, but sometimes it was accompanied by increased frequency of undesired gene variants (mainly recessive) causing hereditary diseases. There are approx. 450 genetic diseases known in dog breeds and many of them

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Table 1 – Neuronal ceroid lipofuscinoses (NCL) and muccopolysaccharidoses (MPS) with known mutations segregate in specific dog breeds.

Breed	Genes which mutations cause the diseases
NCL [50–52]	
Miniature Dachshund	*CLN1* (PPT1 – palmitoyl-protein thioesterase 1)
Miniature Longhair Dachshund	*CLN2* (TPP1 – tripeptidyl peptidase 1)
American Staffordshire Terrier	*CLN4* (ARSG (arylosulfatase G)
Border Colie	*CLN5*
Australian Shepherd	*CLN6*
English Setter	*CLN8*
Bulldog	*CLN10* (*CTSD* – cathepsin D)
Tibetan Terrier	*ATP13A2* (ATPase type 13A2)
MPS [53–55]	
Plott Hound	α-L-Iduronidase (MPS I)
Wirehaired dachshund	Heparan N-sulphatase (MPS IIIA)
Schipperke	α-N-acetylglucosaminidase (MPS IIIB)
Miniature Pinscher, Miniature Schnauzer	N-acetylglucosamine 4-sulphatase (MPS VI)
German shepherd, Brazilian terrier	β-Glucuronidase (MPS VII)

are restricted to a single breed or several breeds. A majority of canine hereditary diseases (approx. 360) have clinical and molecular counterparts in humans [1]. In the OMIA database (Online Mendelian Inheritance in Animals, http://omia.angis.org.au/home/, accessed on November 22, 2013) it was indicated that 344 canine genetic diseases are potential models for human diseases. According to the OMIA database, the number of such diseases in other domestic animal species is significantly smaller: in the cat (182), cattle (160), horse (118), sheep (98) and the pig (86). Thus, it is not surprising that the dog is considered as a very valuable large animal model for human genetic diseases and their therapy, including gene therapy [2,3].

Searching for molecular background of monogenic diseases is easier than complex ones. To support this obvious opinion one can mention a research project LUPA, founded in 2008 by the European Commission, with the aim to use the dog as a model in studies on human complex disorders. In 2011 the identification of mutations for 4 monogenic diseases was reported, while in case of complex disorders it was possible to map chromosome regions harboring unknown causative mutations, only [4]. Nevertheless, during last 20 years, since establishing the DogMap consortium for the dog genome organization studies in 1993, an exceptional progress of molecular knowledge on canine hereditary disorders has been achieved. In this short review the present status of this knowledge and successful attempts of gene therapy applied for some of them are described.

2. Monogenic disorders with known mutations

Due to a large number of monogenic disorders observed in pure breeds, which molecular background is relatively easy to decipher, majority of studies were focused on them. The first gene mutation causing a canine hereditary disease, hemophilia B, was reported in 1989 [5]. Since that time mutations have been described for 130 diseases and a majority of them (107) are inherited according to the autosomal recessive pattern [6].

There are traits which depend on expression of numerous genes and thus mutations of different genes may similarly affect the phenotype – e.g., retinal dystrophies causing visual dysfunction. In humans hundreds of the causative mutations are known in almost 200 genes (http://www.sph.uth.tmc.edu/RetNet). Also in the dog a pretty large number of known mutations responsible for retinal dystrophies were identified. Altogether, 24 mutations in 18 canine genes have been reported [7]. An example of these mutations is a 4 bp deletion in the *RPE65* gene, causing a well-known congenital stationary night blindness – CSNB in the Briard breed, which is a counterpart of childhood blindness, called Leber congenital amaurosis – LCA [8].

Another large group of monogenic canine diseases comprises lysosomal storage diseases – LSD. Due to a deleterious mutation in one of the genes encoding lysosomal enzymes an accumulation of different substrates takes place and can cause the deterioration of cellular and tissue function. In humans over 50 such diseases have been described [9]. Depending on the accumulated substrates these diseases are classified into several categories, e.g. mucopolysaccharidoses (MPS) and neuronal ceroid lipofuscinoses (NCL). These two categories of LSD have been extensively studied in dogs. Until now 8 different mutations in 8 different genes, causing subtypes of NCL, have been described. Interestingly, these mutations were identified in 8 different dog breeds (Table 1). With regard to MPS diseases the causative mutations in 5 genes have been identified and again they are distributed in specific breeds (Table 1).

Among other canine gene mutations there are counterparts of common hereditary human diseases, e.g. Duchenne muscular dystrophy (DMD), which is a sex-linked disease. Its incidence in newborn boys is approx. 1:3500. Mutations of the dystrophin gene have been found in several dog breeds, including the Golden retriever, Beagle, German short-haired pointer and the Cavalier King Charles spaniel [10]. Golden retrievers with muscular dystrophy, due to the intronic transition A > G causing abnormal mRNA splicing (loss of exon 7), are commonly used in model studies focused on testing different therapeutic procedures for human DMD. The same mutation was found in the Beagle breed. Other

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