THE DLA DIVERSITY OF KROMFOHRLÄNDERS

Dogs spontaneously exhibit several different heritable diseases just as humans do. However, the incidence of many diseases in a breed can be as much as ten times higher than in humans. This phenomenon is due to the history of dog breeds. Breeds have often been developed from a few individuals and are always founded on severe inbreeding. Often the dogs used for breeding are closely related or certain individuals are overrepresented. Using close relatives increases the incidence of carriers for breed specific ailments and consequently increases the number of affected individuals.

Inbreeding narrows the dog's genetic diversity and thus threatens the health of the breed. One vital genomic region of the dog is the MHC complex. The term “MHC” or “Major Histocompatibility Complex” refers to one of the functions of the genes located there. The MHC genes are in charge of, among other things, identifying the dog's own tissue as well as the identification and elimination of foreign pathogens. Variability is crucial to these immune genes, enabling them to react to different viruses, bacteria and other foreign intruders. The dog's MHC genes go by the name DLA, an abbreviation of the words "dog leucocyte antigen".

Some dog breeds have very limited DLA gene diversity and this makes them susceptible to different autoimmune diseases. Dozens of such diseases are known, among them diabetes, lupus, rheumatism, polyarthritis, hypothyroidism, immune-mediated hemolytic anemia, Addison's disease and perianal fistelia. Several autoimmune diseases have been proven to be linked to these DLA-genes. Testing them may be important in combating these illnesses and to uphold diversity both in specific breeding programs and in the breed in general.

DLA diversity can now be charted from the DNA of dogs. The idea behind DLA diversity study is to test alleles (= different forms of the same gene, which differ slightly in their base sequence) of the dog's immune genes (3 different genes), and the haplotypes formed by three combined alleles. The information thus gleaned can be utilized in breeding by, for example, choosing a mate that genetically differs from the other as much as possible. This would ensure that the resulting puppies would be likely to inherit from their parents as many different gene combinations as possible, and this in turn would increase the diversity of the line and, in time, the entire breed.

Figure 1 displays the MHC genomic region, which is located in the canine chromosome 12. The MHC region's genes can be divided into three classes based on the activity of the proteins they produce. This research focused on analyzing the Kromfohrländers' class II genes DRB1, DQA1 and DQB1. The class II genes encode proteins that take part in the initial phase of the immune defense. They identify parts chopped of different foreign substances and introduce them to other cells involved in the immune defense. As there is a large amount of foreign matter to be identified, it is important that both individuals and populations retain different alleles. A small amount of alleles can increase the population's sensitivity to a variety of pathogens. A MHC homozygote may be more susceptible to communicable and autoimmune diseases.

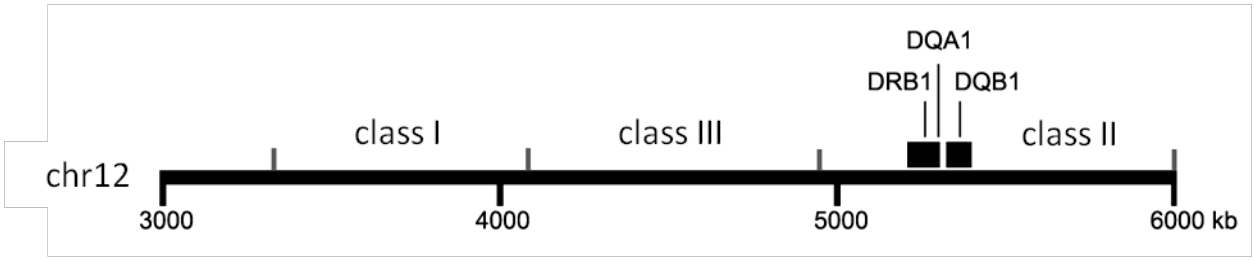

Figure 1. The canine MHC genomic region is located in chromosome 12. MHC classes I, III and II are in the chromosome sequentially. The Kromfohrländer study covered genes DRB1, DQA1 and DQB1. Each gene contains forms that differ from each other slightly in terms of their base sequence, in other words, alleles. The genes in question are located next to each other and belong to the MHC II class. (kb = kilobase, the DNA measurement)

The DLA diversity of Kromfohrländers

The DLA diversity of 100 Kromfohrländers was studied at the Canine Genetics Research Group led by prof. Lohi in the University of Helsinki and Folkhälsan Institute of Genetics, Finland. The results of the DLA study are shown in Table 1. The breed was found to have five DRB1 alleles, three DQA1 alleles and five DQB1 alleles. The DRB1, DQA1 and DQB1 genes form three-allele combinations, which are inherited together and called a haplotype. Kromfohrländers have five different haplotypes. These haplotypes are named Krom1, Krom2, etc. for simplicity.

Table 1. MHC haplotypes and their frequencies in Kromfohrländers in Finland and Glats in Germany.

				Frequency (%)	
Haplotype	**DRB1**	**DQA1**	**DQB1**	**Finland**	**Germany (glat)**
Krom1	01501	00601	02201	29,2	22,7
Krom2	10103	00101	00802	25,5	13,6
Krom3	01502	00601	02301	23	13,6
Krom4	07401	05011	00701	21,1	31,8
Krom5	00901	00101	08011	1,2	18,2

For comparison, examples of different haplotype frequencies from other previously studied breeds are listed in Table 2. However when making comparisons, one should remember that more important than the amount of haplotypes is the way they are distributed in the population. In Kromfohrländers too, most dogs carry one of the four most common haplotypes. The number of haplotypes depends on the history of the breed and breeding practices. One should also keep in mind that the MHC genes are not entirely neutral genomic regions, but may be subject to different levels of selective pressures in nature. The MHC genes play a pivotal role in the immune defence and all haplotype combinations are not necessarily beneficial to life. This may explain the rarity or absence of some combinations in a breed.

Table 2. The frequency of MHC haplotypes in other breeds studied in Finland.

Breed	**Number of dogs in the study**	**Number of identified haplotypes**
Whippet	100	13
Icelandic Sheepdog	58	10
Finnish Hound	50	8
Löwchen	72	8
Nova Scotia Duck-Tolling Retriever	176	5
Kromfohrländer	**180**	**5**

One of the aims of MHC mapping is to find out how big proportion of the dogs in the studied population is homozygous with respect to certain haplotypes. Homozygosity means that the dog has inherited same haplotype from both of its parents. A majority of Kromfohrländers are not homozygous in the MHC region: they have inherited different haplotypes from their parents. In this study, 33 dogs were homozygous for the MHC haplotypes, which is 18% of the total number of studied dogs. 5.5% of these dogs were homozygous with respect to Krom1, 4.5% to Krom2, 3.9 % to Krom3, and 4.5% to Krom4. Thus, homozygosity is seen for the four most common haplotypes in the population.

Each breed has a breed specific "DLA map". It mirrors the population history of the breed and breeding practices. Most studied breeds have 3-5 haplotypes and Kromfohrländers also fall into that category. Interestingly though, different haplotypes are evenly shared which is not the case in most breeds who often have two major haplotypes together with some rarer.

About testing for DLA diversity

Maintaining the diversity and in particular the heterozygosity of the MHC genomic region is important. Several recent studies indicate that homozygosity increases the risk for autoimmune diseases. The DLA profile of Kromfohrländers now provides an opportunity to preserve this diversity by taking it into an account in breeding programs. All breeding lines should be used. The following is an example of how one could monitor the breed's diversity through DLA gene testing:

1. Test the DLA genes of the bitch intended for breeding and 2-3 possible studs.
2. Compare the haplotypes of the bitch and the possible studs and choose the stud whose haplotype is the most different from the bitch's.
3. This should ensure different gene combinations for the future litter. If the bitch and stud both have the same haplotype, the pups inherit only those same gene forms and this narrows the genotype of the line and the breed and may pose a risk to the health of the breed in a longer run.

Enquiries about future DLA testing should be directed to Genoscoper Oy, www.genoscoper.com.

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