

Beyond the MHC: A canine model of dermatomyositis shows a complex pattern of genetic risk involving novel loci

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Abstract:

Juvenile dermatomyositis (JDM) is a chronic inflammatory myopathy and vasculopathy driven by genetic and environmental influences. Here, we investigated the genetic underpinnings of an analogous, spontaneous disease of dogs also termed dermatomyositis (DMS). As in JDM, we observed a significant association with a haplotype of the major histocompatibility complex (MHC) (*DLA-DRB1*002:01/-DQA1*009:01/-DQB1*001:01*), particularly in homozygosity (P -val = 0.0001). However, the high incidence of the haplotype among healthy dogs indicated that additional genetic risk factors are likely involved in disease progression. We conducted genome-wide association studies in two modern breeds having common ancestry and detected strong associations with novel loci on canine chromosomes 10 (P -val = 2.3×10^{-12}) and 31 (P -val = 3.95×10^{-8}). Through whole genome resequencing, we identified primary candidate polymorphisms in conserved regions of *PAN2* (encoding p.Arg492Cys) and *MAP3K7CL* (c.383_392ACTCCACAAA>GACT) on chromosomes 10 and 31, respectively. Analyses of these polymorphisms and the MHC haplotypes revealed that nine of 27 genotypic combinations confer high or moderate probability of disease and explain 93% of cases studied. The pattern of disease risk across *PAN2* and *MAP3K7CL* genotypes provided clear evidence for a significant epistatic foundation for this disease, a risk further impacted by MHC haplotypes. We also observed a genotype-phenotype correlation wherein an earlier age of onset is correlated with an increased number of risk alleles at *PAN2* and *MAP3K7CL*. High frequencies of multiple genetic risk factors are unique to affected breeds and likely arose coincident with artificial selection for desirable phenotypes. Described herein is the first three-locus association with a complex canine disease and two novel loci that provide targets for exploration in JDM and related immunological dysfunction.

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Additional explanation: (Also, see definition of some terms at the end of this document)

Geneticist Dr. Leigh Anne Clark and her research group studied dermatomyositis (DMS) in Collies and Shetland Sheepdogs. They found 3 genes in Collies and Shelties that are involved in DMS. This study resulted in a **3 gene-DNA test** that will give breeders a tool to gradually diminish the incidence of DMS (over a period of years) while maintaining genetic diversity and desirable phenotypic traits within the breeds. In both breeds, genetic variations in the dog leukocyte antigen (DLA) complex on chromosome 12, a second gene on chromosome 10, and an additional change in a third gene on chromosome 31

were involved. The chromosome 31 risk allele is more common in Shelties than in Collies. In places in the research publication, the risk allele at the DLA complex is referred to as “C”, the risk allele on chromosome 10 as “A”, and on chromosome 31 as “B”. The normal (aka “wild type”) alleles are represented by lower case letters, c, a, and b. By this nomenclature, the vast majority of dogs of other breeds have the genotype: aabbcc.

Dog leukocyte antigen:

The upper case letter “C” represents *DLA-DRB1*002:01* (most common – about 78% of Shelties tested had at least one allele of this type and the majority (61%) of Shelties tested were homozygous) and the lower case letter “c” represents any alternate allele for *DLA-DRB1* with the more frequent alternate allele being *DLA-DRB1*023:01* (21% of Shelties tested has this one). The authors concluded that *DLA-DRB1*002:01* is a risk factor for DMS and that homozygosity confers increased susceptibility. Because of the high frequency of this allele in the Sheltie population, additional loci were thought likely to influence disease progression which led to the discovery of the influence of chromosomes 10 and 31.

Chromosomes 10 and 31:

Associated risk alleles were found on chromosome 10 (henceforth referred to as locus A) and on chromosome 31 (henceforth referred to as locus B). Being homozygous for the risk alleles at either gene increases the risk of a dog developing DMS, and 100% of dogs homozygous for both risk alleles (AABB) developed DMS.

Interaction of the 3 genes:

Homozygosity for the C allele increases the risk of a dog developing DMS. Based on the genotype, the risk of an individual dog developing DMS was classified as low (0% - 5%), moderate (33% – 50%), or high (90% – 100%). The more commonly observed genotypes in healthy dogs were AabbCC and aabbCC. (Eight of the nine possible ----cc genotypes were too rare to assign risk; however, affected Shelties were found with genotypes AaBBcc and AABbcc, and one affected collie with AABbcc. It is possible that these dogs were misdiagnosed, or that additional alleles may also be impacting the phenotype). All affected dogs had at least two risk alleles, and all but one were homozygous for at least one risk allele. When evaluating dogs with 2, 3, or 4 risk alleles at locus A and B, there was an inverse correlation between the number of risk alleles and the age of onset of the disease. “Dogs having four risk alleles developed DMS at a significantly younger median age (5 months) than did dogs with only two risk alleles (18.5 months). The complete penetrance of AABB genotypes, combined with an early age of onset, suggests that these dogs may be hypersensitive to commonplace environmental stimuli (e.g., routine puppy vaccinations).” The most common genotypes of affected dogs were AaBBCC followed by AAbbCC, AABbCC, and AABbCC.

Definitions:

Gene = a piece of DNA that encodes a protein

Allele = an alternate form of a gene. Genes can have many different alleles. Two alleles for each gene are inherited, one from each parent. If the same allele is inherited from both parents, the gene is homozygous; if the alleles are different the gene is heterozygous.

Locus = position on a chromosome. This could refer to a region on a chromosome or a specific gene.

DLA = Dog leukocyte antigen loci are part of the major histocompatibility complex (MHC) in dogs. The MHC plays a critical role in the immune response system. In dogs, there are 3 genes of the DLA, each with many different alleles. One allele comes from the sire and one from the dam. It is desirable for the genes to be heterozygous for the immune system to function well. The alleles of the 3 genes are associated with several immune mediated diseases (even thyroiditis). In humans, the similar genes are called the HLA or human leukocyte antigen loci.

DMS = dermatomyositis. Previously, Sheltie owners used the acronym "DM"; however, that acronym is now used for degenerative myelopathy which is a spinal cord abnormality.

Haplotype = a combination of alleles from a group of adjacent genes inherited together from a single parent. The three DLA genes (*DLA-DRB1*, *DLA-DQA1*, and *DLA-DQB1*) are located closely together on chromosome 12. Because of their close proximity, certain alleles tend to be inherited together in a haplotype. For example, the *DLA-DRB1*002:01* allele in Shelties and collies is inherited with *DQA1*009:01* and *DQB1*001:01*. Together the haplotype is *DLA-DRB1*002:01/-DQA1*009:01/-DQB1*001:01* (See Table 1 in the research publication, link above).

MHC = Major Histocompatibility Complex is a collection of genes that code for cell surface proteins which control the adaptive immune response. For a more detailed explanation see: https://en.wikipedia.org/wiki/Dog_leukocyte_antigen .

Penetrance = the extent to which a mutant genotype results in disease. Complete penetrance means all individuals with that genotype were diseased. Incomplete penetrance is said to be present when some individuals have the deleterious alleles but do not possess the corresponding phenotype.

Polymorphisms = genetic variation.