

Spring 2013

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## Recommended Citation

Noorai, Rooksana E. and Clark, Leigh Anne, "Genome-wide association study in collies identifies a novel locus for dermatomyositis" (2013). *Graduate Research and Discovery Symposium (GRADS)*. 26.  
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# Genome-wide association study in collies identifies a novel locus for dermatomyositis

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## Introduction

Dermatomyositis (DM) is an autoimmune disease of dogs characterized by an inflammatory response in the skin and muscle tissue, typically around the face, paws, and tail. Clinical findings consistent with DM include the development of skin lesions such as hair loss, redness, scaling and crusting (Figure 1). Dogs afflicted with DM often develop disfiguring scarring and secondary skin infections. Signs of muscle involvement in severe cases include muscle atrophy, megaesophagus, aspiration pneumonia, and difficulty eating or walking [1]. Naturally occurring DM in the dog is the only animal model available for study of a clinically similar human disease termed juvenile dermatomyositis.

Diagnosis of DM is made by a veterinary histopathologist using skin punch biopsies of actively afflicted tissue. Current treatment for DM includes the management of symptoms, such as severe pain and secondary skin infections. Unfortunately, there is no cure for DM and clinical signs may reoccur. Onset of DM ranges from two months to several years of age. A dog may have produced multiple litters before the onset of clinical signs, making it difficult for breeders to control disease transmission.

The two breeds with the highest prevalence of DM are collies and Shetland sheepdogs [1 - 3]. The inheritance of DM is suggested to be autosomal dominant [2]. Anecdotal reports suggest that triggers for developing DM may include vaccination, abrasion, estrus, or abandonment. In this study, we sought to use a genome-wide association study to identify the genetic factor(s) underlying DM in the collie breed.

## Materials & Methods

- Blood samples from DM-affected and healthy pedigree collies were recruited from the pet population.
- All DM-affected collies had a positive or differential diagnosis of DM.
- All healthy control collies were at least 7 years old, free from any dermatologic conditions, unrelated to a DM-affected collie, and unrelated to all other study collies within 3 generations.
- DNA was isolated from whole blood samples using the DNeasy blood and tissue kit (QIAGEN, Valencia, USA) and adjusted to a concentration of 100ng/  $\mu$ L.
- Illumina CanineHD Infinium BeadChips were used to profile 173,662 SNP genotypes per collie.
- GenomeStudio was used to analyze the raw data files and generate SNP calls.
- The PLINK input Report Plug-in v2.1.1 was used to format the data.
- By convention,  $P_{\text{raw}}$  values  $\leq 0.0001$  were considered significant.
- R was used to generate a Manhattan Plot from the  $-\log_{10}$  of the  $P_{\text{raw}}$  value for each SNP.



Figure 1. Collie and Shetland sheepdogs affected with dermatomyositis. Skin lesions are shown on the face and feet.

## Results

A total of 46 collies samples were obtained, primarily from the United States. The age of DM affected collies ranged from 3 months to 11 years (at the time of sampling), while control dogs were 7 to 12 years. Case/control analyses were carried out using 26 DM-affected and 20 healthy collies (Figure 2a). A total of 90 SNPs were significantly associated with DM ( $P_{\text{raw}} \leq 0.0001$ ), 68 of which were located at the centromeric end of chromosome 10 (Figure 2b). The most significant result obtained was for SNP BICF2P147652, located on chromosome 10 at position 5.15Mb ( $P_{\text{raw}} = 3.03 \times 10^{-9}$ ). Analysis of genotypes in the chromosome 10 region revealed a 10.5 Mb haplotype for which all DM-affected collies had at least one copy (12 homozygous, 14 heterozygous). The haplotype was also present in 60% of healthy collies (2 homozygous, 10 heterozygous).

## Discussion

In this study we utilized genome-wide SNP profiles to identify a genomic region associated with DM. The majority of associated SNPs, and those with the most significant p-values, were clustered on chromosome 10. A large haplotype spanning this region is present in all DM-affected collies.

These data support an autosomal dominant mode of inheritance, as all affected dogs carried one or two copies of the associated haplotype. Because the haplotype was also present among controls, the allele shows reduced penetrance, perhaps due to an environmental trigger. While we were unable to grade the severity of the clinical signs in all participants, it is interesting that puppies younger at age of onset were more often homozygous. This finding suggests that while one copy is sufficient for disease onset, two copies may cause a younger age of onset and/or a more severe phenotype.

The associated haplotype harbors  $\sim 100$  genes, including several with an immune related function. To reduce the number of candidate genes, future studies will focus on DM in Shetland sheepdogs. These herding breeds share a recent common ancestor and likely share a founding mutation. An across-breed approach will allow us to use differences in homogeneity that exist between the breeds to narrow the haplotype. We have identified a locus on chromosome 10 that likely harbors a genetic factor underlying DM.

## References

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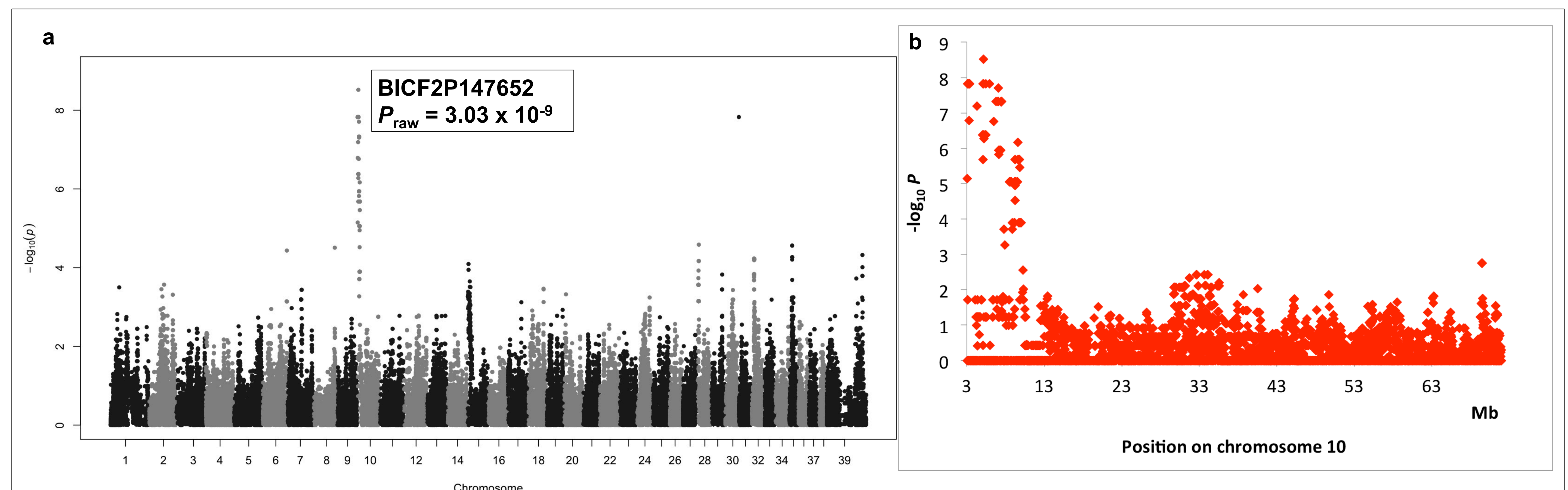


Figure 2. Genome-wide association for DM using 26 affected and 20 healthy control collies. (a) Raw  $P$  values ( $-\log_{10} P_{\text{raw}}$ ) for each SNP are plotted by chromosome and reveal a strong association on chromosome 10 (b) The raw  $P$  values are plotted against position on chromosome 10 and show that the significant SNPs are clustered near the centromeric end.