Evaluation of the MHC class II as a candidate for sudden acquired retinal degeneration syndrome (SARDS) in Dachshunds

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Background

Sudden acquired retinal degeneration syndrome (SARDS) is a common cause of incurable blindness in dogs. This disease is diagnosed in dogs with a rapid and complete loss of vision combined with a normal appearing ocular fundus and a flatline electroretinogram (ERG; Figure 1). In some cases, affected dogs also exhibit systemic signs like polyuria, polydipsia, polyphagia, lethargy, or weight gain. The cause of this disease is unknown, although an association with endocrinopathies or an autoimmune pathogenesis has been suggested.1

Certain dog breeds are at an increased risk of SARDS, suggesting a heritable component of the disease.2 Discovery of genetic factors predisposing to development of SARDS in Dachshunds (one of the most commonly affected breeds) could contribute to a deeper understanding of the disease’s etiology, would assist in identification of at-risk animals, and could potentially lead to the development of treatments.

Genome-Wide Association Study

The authors hypothesized that regions of the canine genome associated with the presence of SARDS could be identified in a genome-wide association study (GWAS) using a portion of the Affymetrix® custom canine SNP array. Genomic DNA for whole genome analysis was isolated from EDTA-preserved whole blood using the Puregene kit. Fifteen cases and seventeen control Dachshunds were compared across 404,619 SNPs. Cases and controls were analyzed for population stratification by using a custom canine SNP array. In some cases, affected dogs also exhibit systemic signs like polyuria, polydipsia, polyphagia, lethargy, or weight gain. The cause of this disease is unknown, although an association with endocrinopathies or an autoimmune pathogenesis has been suggested.1

A preliminary region of association was found on Chromosome 12 at the approximate location of the DLA class II genes (although the association did not have genome-wide significance). The genes in this region encode for MHC II, an extremely important molecule of the immune system. If the association between MHC II and SARDS is found to be true, it could be a step toward understanding the etiology of the disease.

Figure 1. Electroretinograms (ERG) tracings from a normal control dog (blue) and a dog affected with SARDS (red). In the tracing from the normal dog, note the characteristic biphasic waveform consisting of an initial negative deflection (a), which is generated by the photoreceptors, followed by a positive deflection (b) which reflects inner retinal function. In comparison, the ERG tracing of a SARDS-affected dog is described as a “flat-line”, due to the absence of detectable a or b waves.

Figure 2. Manhattan plot comparing 404,619 SNPs of 15 affected and 17 control Dachshunds. Genomic inflation factor = 1. Red line: Bonferroni corrected p value for multiple testing (p < 6.9 × 10^-8). Arrow: A preliminary region of association was found on Chromosome 12 at around 2 - 3 Mb, although the association did not have genome-wide significance.

Figure 3. Expanded view of the region of association on Chromosome 12, overlapping the MHC class II genes: DLA-DRB1 (bp 2151409 - 2164564), DLA-DQA1 (bp 2221181 - 2227600) and DLA-DQB1 (bp 2244820 - 2250733). A preliminary region of association was found on Chromosome 12 at around 2 - 3 Mb, although the association did not have genome-wide significance.

Table 1. Alleles of DLA-DRB1, DLA-DQA1 and DLA-DQB1 found to be significantly associated with the diagnosis of SARDS (preliminary data).

<table>
<thead>
<tr>
<th>Allele</th>
<th>Case Freq</th>
<th>Controls Freq</th>
<th>p-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*09401</td>
<td>0.22</td>
<td>0.06</td>
<td>0.0026</td>
<td>4.39</td>
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<tr>
<td>DQA1*00901</td>
<td>0.10</td>
<td>0.28</td>
<td>0.0060</td>
<td>0.30</td>
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<tr>
<td>DQB1*00101</td>
<td>0.30</td>
<td>0.30</td>
<td>0.0041</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Three alleles were found to be significantly associated with the diagnosis of SARDS with preliminary data (Table 1). Among cases, DRB1*09401 was the second-most common allele of DLA-DRB1. Among controls, DQA1*00901 was the second-most common allele of DLA-DQA1, and DQB1*00101 was the most common allele of DLA-DQB1.

Discussion

The DLA is a highly polymorphic region of the canine genome in which associations are rarely found on GWAS, so the presence of even a weak association between the DLA and SARDS is worth consideration. The presence of both protective and risk alleles in preliminary DLA typing data supports this association, and could be used as evidence in support of an autoimmune etiology of SARDS.

Selected References


Acknowledgements

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