Canine breeds at high risk of developing inflammatory bowel disease in the south-eastern UK

A. Kathrani, D. Werling, K. Allenspach

Genetics are an important factor in the development of human inflammatory bowel disease (IBD); however, there is very little information available regarding the role of genetics in canine IBD. The purpose of this study was to gather information about which canine breeds in the south-eastern UK are at a high risk for developing IBD. Determination of such breeds may help further genetic research in this complex disease. The computer medical records at the Queen Mother Hospital for Animals, Royal Veterinary College dating from August 1, 2003 to December 31, 2009 were retrospectively searched for cases diagnosed with IBD. Five hundred and forty-six dogs with IBD were identified, representing 86 different breeds. The comparison group consisted of all dogs from these same 86 breeds without IBD admitted to the hospital during the same period that amounted to 27,463 dogs. The breeds at significantly higher risk of developing IBD compared with mixed-breed dogs consisted of German shepherd dog (GSD) (OR=2.4101, 95 per cent CI=1.5826 to 3.36705, P<0.0001), border collie (OR=1.9936, 95 per cent CI=1.1655 to 3.4101, P=0.0118) and boxer (OR=1.6961, 95 per cent CI=1.0441 to 2.755, P=0.0328). This study demonstrates for the first time canine breeds in the south-eastern UK that are highly susceptible to developing IBD. Identification of such breeds may allow for a more focused investigation of genetic mutations associated with canine IBD.
with the mixed-breed dog. The OR was calculated by first calculating the proportionate changes in the risk of IBD by breed compared to the mixed-breed group. Significance was set at P<0.05.

Student’s t-test and chi-squared test were used to determine whether there were any significant differences between age at diagnosis of IBD and sex in the susceptible breeds, respectively. Student’s t-test and chi-squared test were carried out using Statistical Package for the Social Sciences version 15.0 software. Significance was set at P<0.05.

Results

Five hundred and seventy-two dogs with IBD were initially identified by searching the computer records during the period from August 1, 2003 till December 31, 2009, representing 86 different breeds including a mixed-breed group.

Breeds that were over-represented (frequency more than 15 cases) included the GSD (58), labrador retriever (56), boxer (51), mixed-breed dogs (56), rottweiler (24), border collie (22), staffordshire bull terrier (20), cocker spaniel (20), golden retriever (19), west highland white terrier (18), weimaraner (16) and jack russell terrier (16). The comparison group consisted of all dogs from these same 86 breeds without IBD admitted to the hospital during the same period and amounted to 27,463 dogs. Proportionate changes in the risk of developing IBD by breed compared with the mixed-breed group were calculated and presented using OR, 95 per cent CI and P-values (Table 1). The mean number of IBD cases across the breeds that were highly susceptible to IBD was 30.2 and the number of IBD cases in the mixed-breed dog group was 36.

The breeds at significantly higher risk of developing IBD compared with mixed-breed dogs consisted of weimaraner (OR=3.6797, 95 per cent CI=2.0167 to 6.7411, P<0.0001), rottweiler (OR=2.9697, 95 per cent CI=1.5826 to 5.6705, P=0.0328), boxer (OR=1.9367, 95 per cent CI=1.1655 to 3.4101, P=0.0118) and cocker spaniel (OR=1.9691, 95 per cent CI=1.0441 to 2.755, P=0.0328). The remaining breeds (labrador retriever, staffordshire bull terrier, cocker spaniel, golden retriever, west highland white terrier and jack russell terrier) that were initially over-represented in the data-set did not have significant OR when compared with the mixed-breed dogs (P>0.05).

The mean age at diagnosis of IBD in border collie dogs was seven years and six months (range: one year and two months-12 years and eight months), in GSDs it was five years and three months (range: six months-11 years and five months), in rottweiler dogs it was five years and five months (range: one year and two months-10 years and 10 months), in weimaraner dogs it was five years and six months (range: two years-10 years and six months) and in boxer dogs it was three

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number of IBD cases</th>
<th>Number of non-IBD cases</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Mean age at diagnosis (range)</th>
<th>Sex (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD</td>
<td>58</td>
<td>1605</td>
<td>2.4101</td>
<td>1.5826-3.6705</td>
<td>&lt;0.0001</td>
<td>5y3m (6m-11y5m)</td>
<td>0.610.39</td>
</tr>
<tr>
<td>Rottweiler</td>
<td>31</td>
<td>1219</td>
<td>1.6961</td>
<td>1.0442-2.755</td>
<td>0.0328</td>
<td>4y (8m-9y7m)</td>
<td>0.50.50</td>
</tr>
<tr>
<td>Border collie</td>
<td>22</td>
<td>723</td>
<td>1.9396</td>
<td>1.1655-3.4101</td>
<td>0.0118</td>
<td>7y5m (1y2m-13y8m)</td>
<td>0.570.43</td>
</tr>
<tr>
<td>Weimaraner</td>
<td>16</td>
<td>290</td>
<td>3.6797</td>
<td>2.0167-6.7411</td>
<td>&lt;0.0001</td>
<td>5y6m (2y-10y6m)</td>
<td>0.530.47</td>
</tr>
</tbody>
</table>

Data are also presented on the OR of developing IBD compared with the mixed-breed dog, together with the 95% CI and P-value. The age at diagnosis of IBD and male to female ratio seen in the susceptible breeds are also presented.
years and nine months (range: eight months–nine years and seven months). There was a significant difference in the age at diagnosis of IBD between border collies and GSDs and between border collies and boxers (*P*<0.01).

The present study demonstrated that GSDs, boxers and rottweilers are closely related breeds as they belong to the same genetic cluster (Parker and others 2004). This may therefore explain their increased susceptibility to IBD, as they may share ancestral-associated susceptibility loci (Parker and others 2004). The same study demonstrated that the border collie breed belongs to a separate genetic cluster. The results of the study showed that border collies had a significantly greater age at diagnosis of IBD compared with GSDs and rottweilers. As the border collie belongs to a separate genetic cluster, this breed may have different IBD susceptibility loci compared with other dog breeds. In addition, early age of onset of IBD may implicate a genetic factor and therefore the pathogenesis of IBD in the border collie may be less genetically implicated than the other four susceptible breeds of dog as they had a higher age of onset (Fig 1).

However, a more recent publication has demonstrated that these five canine breeds belong to different clusters of dogs; the GSD breed belongs to the working dogs, the boxer breed belongs to the mastiff-like dogs and the rottweiler is close to the retriever breeds (Vonholdt and others 2010). There is also unproven belief that the weimaraner breed may have been developed from bloodhounds (which belongs to the scent hounds group). Therefore, given the wide distribution of origin of these breeds, this may suggest that although some breeds may share the same molecular defect before the breed selection, new mutations can still occur in a specific breed or line and cause similar clinical signs.

Mouse models of IBD have demonstrated that the genetic background (that is the strain of mouse) profoundly influences the severity of the experimental colitis seen. For example, C57Bl/6 mice have mild transient colitis to trinitrobenzene sulphonic acid whereas SJL/J mice have chronic aggressive disease with the same stimulant (Bouma and others 2002). Therefore, determining the clinical severity of IBD by using the Canine Chronic Enteropathy Clinical Activity Index (CCECAI) (Allenspach and others 2007) may help to ascertain if the genetic background of the different canine breeds influences the severity of IBD. Unfortunately, due to the retrospective nature of this study, the CCECAI could not be calculated for all the cases and therefore this comparison could not be made.

In addition, canine IBD can also be classified retrospectively depending on the response to treatment. Those responding to an elimination diet or antibiotics are diagnosed as food-responsive diarrhoea or antibiotic-responsive diarrhoea, respectively. Canine IBD patients which do not fall into either of the two latter categories and require corticosteroids to treat their clinical signs are termed steroid-responsive diarrhoea (Allenspach and others 2007). Unfortunately, due to the lack of follow-up for the cases included in this study, the diagnosis of IBD could not be further subclassified and compared between groups. However, ascertaining if there is a significant difference in treatment subgroups between the breeds of dogs may help to further determine how similar the IBD is between the different susceptible breeds and whether they are therefore more likely to share genetic factors.

Canine IBD is also commonly classified according to the area of intestine affected and the type of inflammatory infiltrate seen in the intestinal biopsy (Jergens and others 1992). However, it has been previously demonstrated that there is significant inter-pathologist variation when assessing intestinal biopsies (Willard and others 2002) and therefore the World Small Animal Veterinary Association (WSAVA) intestinal histopathology guidelines were introduced (Washabau and others 2010). Unfortunately, as the current study was of a retrospective nature, intestinal biopsies from most of the cases included did not have WSAVA scoring and therefore a comparison could not be made between the different breeds of dogs.

In human beings, the most influential genes involved in Crohn’s disease (CD) belong to the group of genes involved in cellular autophagy pathways and the genes coding for receptors of the innate immune system recognising bacteria in the intestinal lumen (Hugot and others 2001, Hampe and others 2007, Parkes and others 2007), whereas, genes coding for proteins that are involved in enhancing mucosal barrier function are significantly associated with UC (Barrett and others 2009, Thompson and Lees 2011). All the CD and UC susceptibility alleles have been replicated in independent sample
populations. We have previously demonstrated the significance of polymorphisms in TLR4 and TLR5 in GSDs (Kathrani and others 2010). In order to confirm the significance of these loci for other dog breeds, the authors would need to replicate the findings in other canine breeds that are also susceptible to IBD. The results of this study highlight canine breeds susceptible to IBD and give the relatedness of breeds, breed complexes and other factors to the GSD. This information can be used to identify the similarity among different breeds, they would be chosen to confirm findings as they will more likely share susceptibility loci. In contrast, confirming TLR4 and TLR5 susceptibility loci in the border collie dog may help to ascertain whether these are true IBD susceptibility loci common to all breeds or whether breed-specific loci exist in canine IBD. Such information would help to determine if novel diagnostics and therapeutic approaches could be applied to all canine breeds or whether subtle unique forms of IBD exist in different breeds which are difficult to distinguish clinically and thus may be easier to discern at the molecular level. Such information may allow for a better subclassification of canine IBD and thus ultimately lead to better diagnostics and therapeutics.

One of the study’s limitations was that the breeds were ascertained using written medical records. Therefore, some breeds may have been inaccurately recorded as pedigree information is not routinely assessed. In addition, the study population was that of a tertiary care facility and may therefore not accurately reflect the population of the dog breeds at large. The population of dogs admitted to a tertiary care facility may be affected by cost, distance of travel, and perceptions of dog breeders or owners about the benefit of taking a dog to a tertiary care facility and other factors.

In summary, the purpose of the study was to identify dogs at high risk of developing IBD in the south-eastern UK. Using the information generated from this study, a more directed approach to genetic detection of IBD susceptibility loci could be carried out in susceptible breeds.

References

ALLENSPACH, K., HOUSE, A., SMITH, K., MCNEILL, F. M., HENDRICKS, A., CHATTERJEE, A., ALTUG16L1 T300A are strongly associated with Crohn’s disease in a study of New Zealand indigenous cases. Journal of Gastroenterology 45, 777-783


Canine breeds at high risk of developing inflammatory bowel disease in the south-eastern UK

A. Kathrani, D. Werling and K. Allenspach

Veterinary Record 2011 169: 635 originally published online September 6, 2011
doi: 10.1136/vr.d5380

Updated information and services can be found at:
http://veterinaryrecord.bmj.com/content/169/24/635.full.html

These include:

References
This article cites 38 articles, 4 of which can be accessed free at:
http://veterinaryrecord.bmj.com/content/169/24/635.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/