Pitfalls and Progress in the Diagnosis and Management of Canine Inflammatory Bowel Disease

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KEYWORDS

• Inflammatory bowel disease • Enteropathy • Bacteria • Diet

Inflammatory bowel disease (IBD) is the collective term for a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal (GI) signs and inflammation of the GI tract. It is widely accepted that IBD involves a complex interplay among host genetics, the intestinal microenvironment (principally bacteria and dietary constituents), the immune system, and the environmental triggers of intestinal inflammation.[1] However, the specific steps that lead to IBD and the basis for phenotypic variation and unpredictable responses to treatment are not known.

This article examines IBD in dogs, focusing on the interaction between genetic susceptibility and the enteric microenvironment (bacteria, diet), the utility of recently developed histologic criteria, the prognostic indicators, and the standardized approaches to treatment.

GENETIC SUSCEPTIBILITY

The predisposition of certain breeds to IBD strongly supports a role for host genetics (**Table 1**). However, causal genetic defects have not been identified to date.

The genetic basis of human IBD, principally Crohn disease (typified by granulomatous inflammation of the ileum and/or colon), ulcerative colitis (diffuse colonic

Disclosure: K.W.S. is a member of the Nestlé-Purina advisory council and has conducted research sponsored in part by Nestlé-Purina. A.E.J. has no conflicts of interest to disclose.
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Vet Clin Small Anim 41 (2011) 381–398
doi:10.1016/j.cvsm.2011.02.003 **vetsmall.theclinics.com**
0195-5616/11/$ – see front matter. Published by Elsevier Inc.

Table 1
Breed predisposition and canine IBD

Breed	Phenotype	Possible Genetic Basis
Irish setter[13]	Gluten-sensitive enteropathy	Autosomal recessive
German shepherd dog[3,10,11]	Antibiotic-responsive enteropathy	? IgA deficiency SNPs: TLR5, NOD2
Basenji[21]	Immunoproliferative small intestinal disease	—
Lundehund[23]	Protein-losing enteropathy, lymphangiectasia, atrophic gastritis, gastric carcinoma	—
Yorkshire terrier[22,37]	—	—
Rottweilers (Europe)[56,57]	Protein-losing enteropathy, lymphangiectasia, crypt lesions	—
Soft-coated wheaten terrier[14,15]	Protein-losing enteropathy, nephropathy	Common male ancestor
Shar-pei[20]	Cobalamin deficiency	Autosomal recessive, chromosome 13
Boxer dog[5,9,25]/French bulldog[58]	Granulomatous colitis (HUC)	SNPs: NCF2

Abbreviations: HUC, histiocytic ulcerative colitis; SNP, single nucleotide polymorphism.

inflammation), and celiac disease (inflammation and villous atrophy of the small intestine), is much better established. In Crohn disease, genetic susceptibility is increasingly linked to defects in innate immunity exemplified by mutations in the innate immune receptor NOD2/CARD15, which in the presence of enteric microflora may lead to upregulated mucosal cytokine production and delayed bacterial clearance or killing, thereby promoting and perpetuating intestinal inflammation.[1,2] The predisposition of certain dog breeds (see **Table 1**), along with clinical response to antibiotics, for example, in boxers and German shepherds, points to a similar interaction of host susceptibility and microflora in dogs.[3–6] In boxers with granulomatous colitis (GC), lasting remission correlates with the eradication of mucosally invasive *Escherichia coli* that have a novel adherent and invasive pathotype associated with Crohn disease,[5,7,8] and genome-wide analysis has identified disease-associated single nucleotide polymorphisms (SNPs) in a gene (*NCF2*) that is involved with killing intracellular bacteria.[9] Studies in German shepherds have identified polymorphisms in innate immunity factor TLR5, which segregates with disease, and have shown that German shepherds have increased *TLR2* and decreased *TLR5* expressions relative to healthy greyhounds.[10] In addition, 4 nonsynonymous SNPs were identified in exon 4 of the canine NOD2 gene. The heterozygote genotype for all 4 NOD2 SNPs was significantly more frequently found in the IBD population ($P = .04$; odds ratio [OR], 2.34; confidence interval [CI], 1.03–5.28) than in controls. These results were also mirrored in non–German shepherd breeds: the heterozygote genotype for all 4 SNPs was significantly more frequently found in a population of 96 dogs of different breeds with IBD than the non–German shepherd control population ($P = .0009$; OR, 3.06; CI, 1.55–6.05).[11] These results suggest that genetic abnormalities in innate immune sensing or killing enteric bacteria underlie the antibiotic responsiveness of German shepherds and boxer dogs.

In human beings, celiac disease is an inflammatory disorder of the small intestine with an autoimmune component and strong heritability. Genetic studies indicate