RESEARCH PROGRESS REPORT SUMMARY

Grant 02338: The Genetics of Bloat in German Shepherd Dogs: The Roles of Immune System Genes and the Gut Microbiome

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Research Institution: Fred Hutchinson Cancer Research Center

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Original Project Description:

While gastric dilatation volvulus (GDV or bloat) is a serious problem for many large canine breeds, little is known about the causes of this deadly disease. The most significant factors may be genetic, since certain breeds are more susceptible than others, and strong familial predispositions are seen within breeds. The investigators have recently shown a significant association of three immune genes with bloat in Great Danes. For each of the three genes, one allele (variant) is found at unusually high frequency in dogs that have been treated for bloat, and the presence of any one of these "risk" alleles triples the chance that the dog will experience bloat at some time in its life. The research team also showed that the bacterial population living in the gut (the gut microbiome) is altered in dogs with bloat, and in dogs that carry these "risk" alleles, which may predispose these dogs to bloat. It is not known if other breeds show this same association of genetics and microbiome with bloat. The team will investigate whether bloat in German Shepherd Dogs is associated with the same risk alleles and the same microbiome profiles as were seen in Great Danes. The results of this work could lead to genetic tests for at-risk dogs, as well as dietary or probiotic therapies to prevent bloat.

Publications: None at this time.

Presentations: None at this time.

Report to Grant Sponsor from Investigator:

We have proposed that genetic tendency to bloat may be caused largely by certain "risk" variants of genes of the immune system. These genes are responsible for distinguishing foreign cells from "self", and as such, regulate which bacterial species in the gut will survive and which will be targeted for destruction. So these genes regulate the so-called "gut microbiome". We hypothesized that dogs with a particular set of immune gene variants will maintain an unhealthy microbiome that predisposes them to bloat. Our recent research has supported this hypothesis in Great Danes.

The purpose of the proposed research is to expand the genetic and microbiome analysis of bloat to German Shepherds. We proposed to repeat the genetic and microbiome analysis, described for Great Danes, in this group of German Shepherds. We plan to sequence the 3 immune genes, DLA88, DRB1, and TLR5, and determine if any variants associate with bloat. We will then analyze the gut microbiome profiles of 50 affected dogs and 50 controls to look for changes in the bacterial population that correlate with bloat.

Early Result of Genetic Analysis

With about 95% of the genetic data now in, we have preliminary analysis of the association of genetic variants with bloat. These results already show strong genetic associations with bloat that may lead to genetic tests for risk of this condition in German Shepherds.

DLA88 Gene. This gene is the most difficult to resolve, but only about 15% remain to be called. For the gene, DLA88, so far no variants associate with bloat. The "Risk" variant of this gene, DLA88:05101, that associated with bloat in Great Danes, has not been seen in German Shepherds. Since the frequency of GDV in German Shepherds is 4-5 fold lower than in Great Danes, the 05101 allele may be correspondingly less frequent in the Shepherds. Even by that logic, we should have seen this allele 3-4 times so far in the German Shepherd data set. Alternatively, the DLA88:05101 may play a breed-specific roll in bloat in Great Danes.

DRB1 Gene. The DRB1 data is complete. Our data for the DRB1 gene shows an association of variant 1201 with bloat. This is the same variant that was identified in Great Danes as a "risk" variant. So DRB1:1201 may be a good genetic marker for bloat in a wide variety of breeds. However, the significance of this association is questionable in German Shepherds, due to the low frequency of the variant in the breed. Additionally, allele 1501 associates with the bloat group in German Shepherds. This allele was relatively rare in Danes (about 3% of all alleles) but is very frequent in Shepherds (30-50%). The risk effect of 1501 is dose-dependent: that is, dogs with two copies of this variant are at higher risk of bloat than dogs with just one copy. Allele 1101 show a significant protective effect, associating with the healthy control group.

TLR5 Gene. In our previous study, this gene had only two variants in Great Danes, designated as “A” and “B”. The “B” allele was found to be a risk allele, with a 4-fold higher frequency in the bloat group. The emerging data for TLR5 in German Shepherds also shows two variants. But, as with DLA88, the risk variant found in Danes is not found in German Shepherds. Instead, we have observed a new variant, designated as “C”, which has not been previously reported in any breed. The “C” variant associates strongly with the control group, defining it as a protective variant. Since only 2 variants exist in the German Shepherds, “A” is a risk variant in this breed. But this same “A” variant was defined as the protective allele in Danes, because the other allele (“B”) associated with the GDV group. So this sets up a possible hierarchy of TLR5 variants, with “C” as the most protective, “B” as the most risky and “A” as relatively neutral, with respect to bloat risk. The predominance of the risky “B” variant in Danes and the protective “C” in Shepherds correlates with the much higher risk of bloat in Great Danes.