New candidate genes for immunodeficiency identified by using dogs as genetic models

30 July 2015

IgA deficiency is one of the most common genetic immunodeficiency disorders in humans and is associated with an insufficiency or complete absence of the antibody IgA. Researchers led from Uppsala University and Karolinska Institutet in Sweden have now performed the first comparative genetic study of IgA deficiency by using the dog as genetic disease model. Novel candidate genes have been identified and the results are published in *PLOS ONE*.

People with low IgA are at higher risk for developing recurrent infections, allergies and autoimmunity. The underlying genetic factors of IgA deficiency are still largely unknown.

Previously the same research group identified several dog breeds prone to low IgA levels and also found that IgA levels vary widely between breeds [DOI: 10.1016/j.vetimm.2014.05.010.160.]. In this current investigation, the researchers performed genome-wide association studies (GWAS) in four of these breeds prone to low IgA levels. Mia Olsson, postdoc at the Department of Medicine at Karolinska Institutet and shared first author of the study comment on the value of dogs when studying this disorder:

"Since certain dog breeds are prone to exhibit extremely low IgA levels and do present with similar symptoms as human IgA deficient patients, they represent excellent models to map genes involved in this highly complex disease".

The researchers particularly identified three novel candidate genes; KIRREL3 and SLIT1, with documented roles in immune cell development, and SERPINA9 expressed exclusively at the site (germinal center) where a B-cell starts producing IgA.

The researchers also present a newly developed method to analyze a complex continuous trait in GWAS. Katarina Tengvall, PhD candidate at the Department of Medical Biochemistry and Microbiology at Uppsala University and shared first author of the study, points out that a novel strategy was required in order to analyze this trait in dogs:

"Due to the great differences in IgA between dog breeds, no cut-off to distinguish normal from abnormal IgA levels in dogs has yet been established".

This hampers the classical way of performing GWAS in which groups of affected and unaffected usually are compared. Moreover, the use of a continuous GWAS was impeded by natural fluctuations of IgA concentrations.

"To facilitate robust GWASs, we divided dogs into series of percentile groups to reflect the breed-specific IgA distributions and performed multiple GWASs. In the end we combined them into one final GWAS in each breed, thereby removing spurious false signals and successfully defined the associated genomic regions", says Katarina Tengvall.

The researchers thus shed light to a complex disease by suggesting novel candidate genes as well as presenting a new method for analyzing a trait based on a continuous variable (in GWAS).

"We will continue to study these genes and their potential involvement in IgA deficiency in dogs and we anticipate that it will be of importance also for the human equivalent", says Mia Olsson.

More information: "Genome-Wide Analyses Suggest Mechanisms Involving Early B-Cell Development in Canine IgA Deficiency" dx.plos.org/10.1371/journal.pone.0133844

Provided by Uppsala University