The Belgian Shepherd's tale

genome-wide study across 9 dog breeds reveals an association of fructosamine concentration to a locus in Belgian Shepherds

Forsberg, S.; Kierczak, M.; Merveille, A. C.; Gouni, Vassilki; Ljungvall, Ingrid; Wiberg, M.; Willesen, Jakob; Hanås, S; Lequarré, Anne-Sophie; Sørensen, L. M.; Tiret, L.; Momozawa, Y.; McEntee, K.; Seppälä, E.; Koch, Jørgen; Battaille, G.; Lohi, H.; Fredholm, Merete; Georges, M.; Chetboul, Valérie; Hägström, Jens; Carlborg, Ö.; Lindblad-Toh, K.; Höglund, K.

Published in:
Welcome 2013

Publication date:
2013

Document version
Early version, also known as pre-print

WELCOME

2013

The 7th International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Cambridge, Massachusetts, USA

MAIN SPONSOR:

Nestlé PURINA

CO-SPONSOR:

BROAD INSTITUTE

SESSION 12 : Cancer II

13:00 - 13:20

The Belgian Shepherd's tale: genome-wide study across 9 dog breeds reveals an association of fructosamine concentration to a locus in Belgian Shepherds

Forsberg S*[1], Kierczak M*[1], Merveille AC[2], Gouni V[3,4], Ljungvall I[5], Wiberg M[6], Willesen JL[7], Hanås S[8], Lequarré AS[2], Sørensen LM[7], Tiret L[9,10], Momozawa Y[2,11], McEntee K[12], Seppälä E[13-15], Koch J[7], Battaille G[2], Lohi H[13,14], Fredholm M[7], Georges M[2], Chetboul V[3,4], Häggström J[5], Carlborg Ö[1], Lindblad-Toh K[16,17], Höglund K[18] *Authors contributed equally

[1] *Computational Genetics Section, Department of Clinical Sciences, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, Uppsala, Sweden*
[2] *Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Liège, Liège Belgium*
[3] *Université Paris-Est, Ecole Nationale Vétérinaire d'Alfort, Unité de Cardiologie d'Alfort, Centre Hospitalier Universitaire Vétérinaire d'Alfort, Maisons-Alfort , France*
[4] *INSERM, Créteil, France*
[5] *Department of Clinical Sciences, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, Uppsala, Sweden*
[6] *Department of Equine and Small Animal Medicine Faculty of Veterinary Medicine University of Helsinki, Helsinki, Finland*
[7] *Department of Clinical Veterinary Medicine and Animal Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
[8] *Evidensia, Animal Clinic Västerås, Västerås, Sweden*
[9] *INRA, UMR955 de Génétique Fonctionnelle et Médicale, Maisons-Alfort, France*
[10] *Université Paris-Est Créteil, CNM project, Ecole nationale vétérinaire d'Alfort, Maisons-Alfort, France*
[11] *Japan Laboratory for Genotyping Development, Center for Integrative Medical Sciences, RIKEN Yokohama Institute, Yokohama, Japan*
[12] *Laboratory of Physiology, Faculty of Medicine, Université Libre de Bruxelles, Bruxelles, Belgium*
[13] *Department of Veterinary Biosciences, Research Program in Molecular Neurology Research Programs Unit, University of Helsinki, Helsinki, Finland*
[14] *Folkhälsan Institute of Genetics, Helsinki, Finland*
[15] *Department of Medical Genetics, University of Helsinki, Helsinki, Finland*
[16] *Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden*
[17] *Broad Institute of MIT and Harvard, Cambridge, MA, USA*
[18] *Department of Anatomy, Physiology and Biochemistry, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, Uppsala, Sweden*

Serum fructosamine concentration reflects glycemic status over a few weeks and is useful for diagnosis and monitoring of diabetes mellitus. Understanding the genetics of glucose metabolism is important from both a biological and medical point of view. In this study, we aimed at elucidating the genetic background underlying glucose metabolism in healthy dogs by studying genetic associations with fructosamine concentration.

We included healthy dogs (N=528) representing 9 breeds of different body sizes, utilities and genetic origin. Dogs were examined as part of the European LUPA project in five countries. Absence of disease was ensured by case history, thorough clinical work-up and hematologic and biochemical blood analyses. Concentration of fructosamine was measured in serum and dogs were genotyped using Illumina 170k Canine HD array.

GWAS identified no significant hit considering all breeds together, but a breed-specific significant association to fructosamine concentration was found for a locus (main-effect locus) in Belgian Shepherds (BS), (Nindividuals = 121, praw = 1.27 x 10-7, p10k_perm = 0.0016). By comparing allele frequencies between BS and pooled non-BS, we identified sweeps unique to the BS breed. Next, among the topmost sweeps, we identified a capacitator locus potentially interacting with the main effect locus. The capacitator locus is close to fixation in BS while segregating in the other breeds, which may explain the lack of the main-effect locus association in breeds other than BS. We identified promising candidate genes at both loci and our current work is directed towards fine-mapping the associated loci and validating the potential interaction between loci. The BS is a hard-working, herding type of dog. During breeding, dogs with efficient glucose metabolism might have been selected. We speculate that the detected associations with fructosamine concentration might be protective against diabetes mellitus.

45. Putative genetic links between early repolarisation syndrome and epilepsy

Schlamowitz S[1], Gulløv C[2], Mortensen PK[3], Berendt M[2], Koch J[1], Fredholm M[3]

[1] *Cardiology Group, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark*
[2] *Veterinary Clinical Neurology, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark*
[3] *Genetics and Bioinformatics, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark*

The Petit Basset Griffon Vendeen (PBGV) dog originates from France where it was developed from the Grand Basset Griffon Vendeen for rabbit hunting. Breeders of PBGV dogs have observed an increase in the number of epileptic dogs. A population study including animals born in a 10-year period estimated the prevalence of epilepsy in the Danish PBGV population at 8.9% in the PBGV's. Risk factor analysis revealed a significant effect of litter (Gulløv et al. 2011). This suggests a genetic basis of epilepsy in this breed. Based on this study, 53 animals unrelated at the parental level representing 30 epilepsy-negative and 23 epilepsy-positive animals were selected for a genome wide association study. A putative association was identified to the disease on a locus on chromosome 24.

A subset of the dogs included in the study described above was subjected to a thorough clinical investigation including cardiology examination. This revealed that a number of the dogs presented with a J wave, a positive deflection of at least 0.1 mV immediately after a positive QRS complex at the J point in the ECG. This characteristic is a hallmark of the ECG pattern of Early Repolarization Syndrome (ERS). Further investigations at this institute have revealed a significantly higher prevalence of J waves in PBGV's as compared to 10 other dog breeds (data not published).

Since mutations in ion channels have been implicated both in epilepsy and diseases of the heart we hypothesis that there might be a common genetic background for the J wave appearance and epilepsy in PBGV. The present study is focused on two candidate genes, i.e. the KCNJ8 and KCNG1 genes which both encode subunits of potassium ion channels. KCNJ8 has been linked to ERS in humans and has had one disease causing mutation identified, and KCNG1 is positioned within the locus identified on chromosome 24. Sequence data generated from affected and non-affected dogs will be presented.