Cat Welfare Trust Annual Report

Rosemary Fisher - Secretary

In 2016, the Trust was approached by Veterinary Cardiologist David Connolly, Senior Lecturer in Cardiology at the Royal Veterinary College. Their Cardiology group has a particular interest in hypertrophic cardiomyopathy (HCM) and has published widely on this subject. The Trust was asked for funding to help with an exciting project: To identify the genetic architecture promoting the development of hypertrophic cardiomyopathy in British Short Hair Cats to enable assessment of a novel therapeutic agent.

Background:

HCM has an exceedingly high prevalence in cats: it affects up to 1 in 7 cats and is the most commonly diagnosed feline myocardial disease. The prognosis for cats with HCM is very variable, with average survival reported as being between 596 and 1,297 days. Affected cats with severe HCM frequently present with congestive heart failure (CHF), thromboembolic disease or may experience sudden cardiac death (SCD). Therefore, in many cats HCM is a devastating and distressing disease which results in significant morbidity and mortality.

HCM is also diagnosed in about 1 in 500 people. It is the leading cause of sudden death in young adults and results in significant disability in survivors. In both cats and humans, HCM is inherited as an autosomal dominant trait with variable penetrance. In humans, alterations in two genes, β- myosin heavy chain and myosin-binding protein C (MYBPC) account for approximately 75% of cases where an underlying mutation has been identified. In Maine Coon and Ragdoll cats the HCM causing mutations were also found in the MYBPC gene reflecting the close similarity of the disease between the two species.

Update from David Connolly April 2023

As of April 2023 progress has been made towards the above objectives for both aim 1 – using genome wide approaches on DNA from case and control cats to map and evaluate genomic regions affecting HCM susceptibility and aim 2 – using RNA-sequencing of RNA extracted from myocardial samples from case and control cats to identify gene expression signatures of HCM.

Aim 1 Progress;

We have received genotyping data from 132 BSH DNA samples (93 HCM and 39 Controls) and have performed bioinformatic analyses including Genome-wide Association Studies and Principal Component Analysis to a) Identify potential markers of interest associated with HCM and b) determine any population substructure.

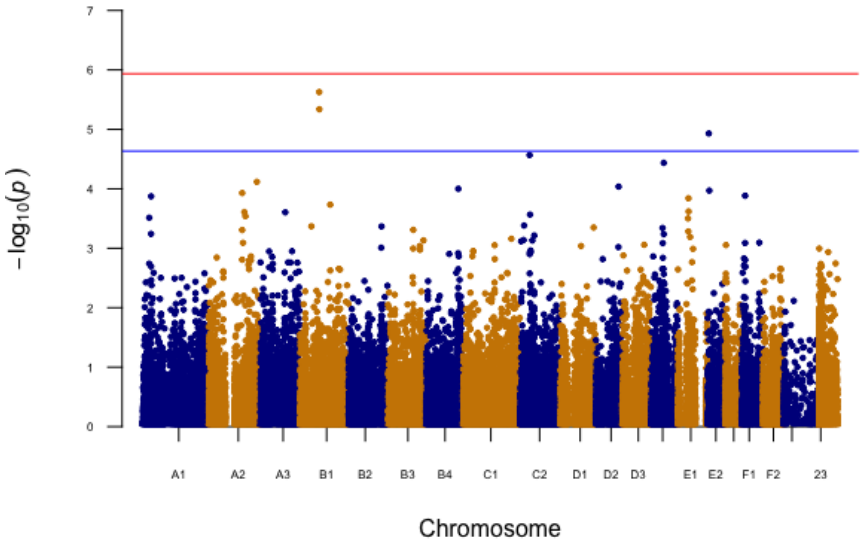


Figure 1. Manhattan Plot illustrating GWAS results for HCM susceptibility for British Shorthairs. Genomic position, sorted by chromosome, and $-\log_{10}$(P-value) on the X and Y axes. Threshold lines; Blue: Suggestive significance, Red: Genome-wide significance: P<0.05 after Bonferroni correction and one false discovery per genome scan.

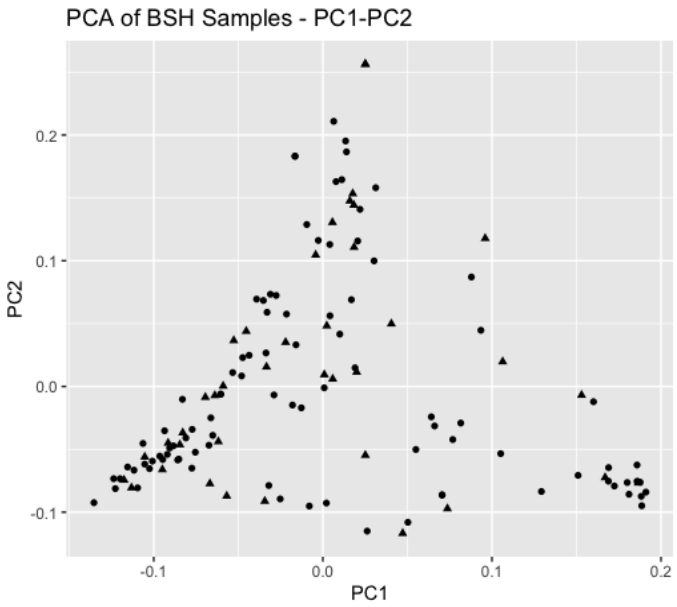
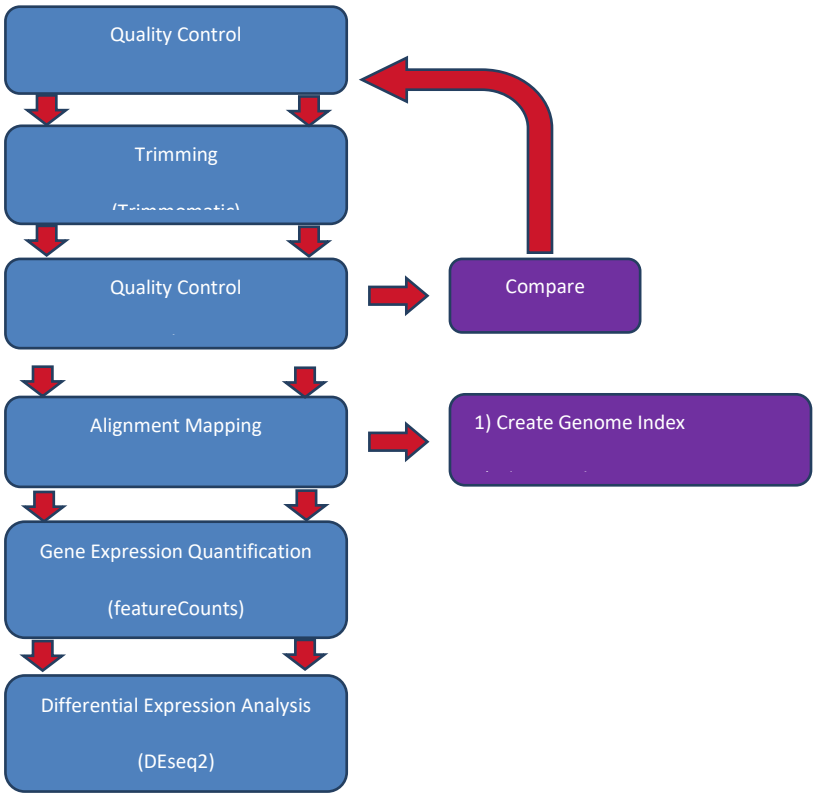


Figure 2. PCA Plot for British Shorthairs with PC1 and PC2 as axes. Case and Control are illustrated by data-point shape (Circle = HCM, Triangle = Normal). PC1 and PC2 are the two principal components that capture the most variation.

These results have identified multiple SNPs of suggestive significance located in ChrB1in an intergenic region, ChrC2 in an intergenic region and ChrE2 in an exonic region. This analysis in ongoing, for example we are working on Fst analysis, regional heritability mapping and heritability estimates.

Aim 2 Progress;

We have received RNA-sequencing data from 28x myocardial samples, of which 10 are BSH (7xHCM, 3xControl). This analysis is progressing through the following pipeline;



We are currently in the final stage of this pipeline, performing Differential Expression Analysis using DESeq2 – this will enable identification of the gene expression profile/transcriptomic signature of HCM. Combined with the DNA work, we will hopefully be able to identify potential target genes and pathways.

Future ongoing work:

We are preparing to extract RNA from RNA-stabilised blood to further our transcriptomic analyses. This aspect of the study is of particular interest as if there are circulating transcriptomic markers of HCM that can be detected, this could be a very interesting avenue with regard to a diagnostic test for BSHs.

Pilot study for the development of a genetic test for hereditary cochleosaccular degenerative deafness in cats

The GCCF Genetics Committee has received a proposal for the development of a genetic test for hereditary deafness in white cats.

Proposal

Feline buccal swabs from previously diagnosed deaf and hearing white cats will be sent for DNA sequencing. Owners will be recruited on a voluntary basis and the cats will have been previously designated as hearing or deaf using the brain auditory evoked response (BAER) testing technique. The data returned will be analysed in depth in order to generate a list of candidate genes for further investigation in a later study, with the aim of developing a test for genes associated with deafness.

Aims and Objectives

The aim of this pilot project is to assemble a list of potential genetic markers of deafness in white cats, thus facilitating the development of a test for deafness to assist in future breeding strategies.

Projected Cost: £12,000