

Genetics of Syringomyelia and Breeding Strategies to Reduce Occurrence

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Syringomyelia is believed to be a complex disease, where the disease phenotype results from the effects of several genes plus environmental influences. The phenotype includes not only the affectation status of the individual but also clinical observations and measurements made from MRI scans. In order to determine the genetic basis of the disease two different approaches are being taken. The first uses a population-based approach, where phenotypic measurements and pedigree information are used to estimate the heritability of the disease. This requires that we have accurate phenotypic measurements, including MRI scans, on as much of the population as possible, together with pedigrees so that genetic relationships between individuals can be identified. Where information exists on other diseases, such as Mitral Valve Disease, this can also be included in the analysis allowing genetic correlations between diseases to be established. It is important to know about correlations, or relationships, between diseases so that any selection strategies take account of the possible influence that selection against one disease may have on other diseases. The second approach to understanding the genetic basis of a disease is to use molecular genetics and gene mapping techniques to try to identify the underlying causative mutations. This approach is also being used to try to identify genes causing both Syringomyelia (SM) and Chiari Malformation (CM) in the Cavalier King Charles Spaniel (CKCS) and other toy breeds such as the Brussels Griffon. It is hoped that this will identify regions of the genome harbouring the genes causing these conditions.

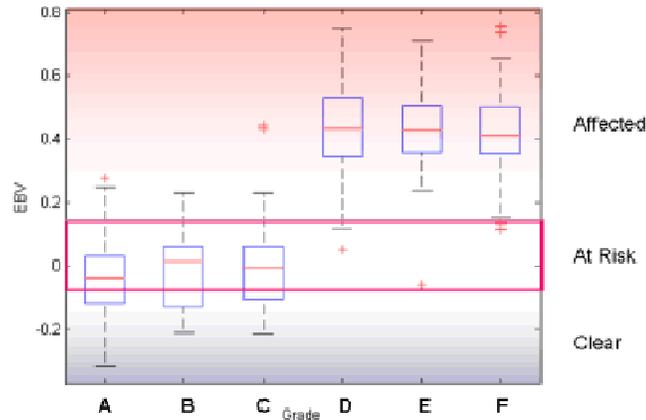
Data collected by Penny Knowler and Clare Rusbridge is currently being used as the basis for the population-based analysis of heritability. Their database contains clinical observations for SM and CM on around 1,000 dogs and MRI scan results for around 700 of these dogs. We have also been given access to the full UK Kennel Club pedigree records for CKCS. This enables us to estimate the heritability of SM and the genetic correlations between SM and measurements made from the MRI scans.

The information obtained from this analysis then allows us to derive estimated breeding values (EBVs) for all measured dogs as well as all dogs in the pedigree. Once the results of the gene mapping studies become available it is hoped to bring this information together with the population analysis to facilitate the calculation of genomic breeding values (geBVs). Early estimates of the heritability of SM suggest it is around 0.7-0.8 (Preliminary estimate which may be subject to later modification) or that 70-80% of the variation between individuals is genetic in origin and about 20-30% is environmental. In the case of SM not much is known about the environmental influences and these may include in-utero or developmental effects. The heritability is sufficiently high, however, that genetic selection against the disease should be very successful. Heritabilities for Chiari Malformation, Cerebellar Herniation and Medullary Kinking are also very high. Genetic correlations between these traits and SM are positive and, interestingly, less than one. This suggests that different genes may be controlling SM and CM and that it will be possible to select against SM even if dogs have the malformation (CM). One concern that we have at the present is that the estimates of heritability may be biased upwards.

This is because the data has been ascertained on the basis of clinical cases. Most dogs will be MRI scanned because of concern that the dog may have SM or because the family or line is known to be afflicted by the condition. It is probably fairly rare that unaffected dogs from clear lines would be MRI scanned. We are taking various approaches to trying to iron out the bias, most based on modifying the statistical analysis, but it would also be beneficial if some dogs identified as unaffected could be MRI scanned. The plan is to then consolidate the estimated breeding values (EBVs) and try to estimate them for the entire UK registered population of CKCS. To help towards this aim we would like to collate the results of MRI scans coming from all clinics that are currently offering scans. We intend to set up a webpage where people can submit information directly and which gives details of where information can be sent by post. We hope to have this in operation in the next few weeks. Estimated Breeding Values (EBVs) are the best measure available for complex traits of the genetic potential of individuals. The breeding value is the sum of the genetic effects and is the equivalent of an animal's genotype at all the genes contributing to the disease. The EBVs for SM allow us to go from a dichotomous outcome (affected or unaffected) to an underlying continuous scale of liability. This gives us a much finer grading on which to evaluate dogs, leading to much more accurate selection. As an example, the figure below shows how EBVs compare with the A-F grading based on the MRI scans (gradings proposed by Clare Rusbridge). Grades A-C have more favourable (lower or more negative) EBVs while grades D-

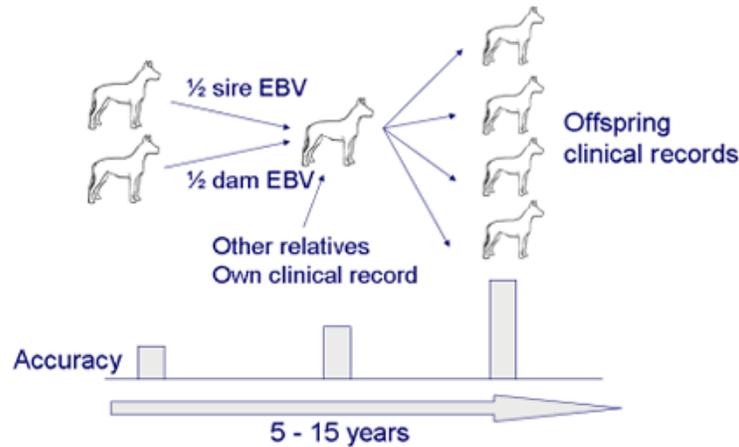
F are unfavourable. The gradings, however, do span a range of breeding values and some dogs graded A-C may have EBVs which suggest they can pass on a degree of disease risk to their offspring.

EBVs compared with A-F phenotypic grading



Using EBVs allows us to distinguish between higher and lower risk dogs in the grading categories A-C. EBVs can be calculated for most dogs even if they have not been MRI scanned, as long as they are related to dogs that have been scanned. The predicted EBV of an individual is half the EBV of its sire plus half the EBV of its dam. All dogs will have an EBV at birth but the EBV may be modified by the dog's subsequent clinical record or MRI scan and by information coming from other relatives. The EBV becomes more accurate as information on offspring becomes available, because we start to gain insight into which half of the sire and dam genes were actually inherited when we see transmission of the genes to offspring. The accuracy of the EBV increases with numbers of offspring and this may take some time to achieve. In contrast, genomic breeding values (geBVs) provide a high accuracy from birth. By looking directly at the DNA genotypes we can see which genes were inherited from the sire and from the dam, without having to wait for offspring. Genomic breeding values can be used for accurate evaluation at an early stage, before the disease phenotype may be apparent and before a dog is used for breeding.

Advantages of geEBVs compared with EBVs



In addition to selecting away from individual known diseases, such as syringomyelia, it is important to consider the long-term health of the breed. Population diversity and maintenance of diversity is important in order to minimize the risk of future new diseases arising. We want to apply state-of-the-art genetic selection techniques that use optimal contribution theory to help avoid unequal representation of individuals in future generations or 'genetic bottlenecks' occurring. This ensures that increases in inbreeding and loss of diversity are minimized. Our aim is to develop internet-based tools that allow breeders to have direct access to these state-of-the-art techniques to help them make optimal selection decisions.

The Cavalier King Charles Spaniel will be the first dog breed in the world for which these techniques will be available. We also plan to explore different breeding strategies, based on computer modelling. This will help us to establish the time-scale over which the disease incidence can be reduced, the range of breeding values that should be used for breeding and the acceptable rate of diversity loss to minimize future disease risk. The immediate next steps in the project are to:

- Widen our data collection effort to include information for as broad a section of the population as we can. We will be setting up a webpage which will give details on how information can be submitted to us.
- Look at ways in which we can get a more accurate or unbiased estimate of the disease incidence.

- Investigate whether SM could be caused by a single gene or whether the multiple gene (polygenic) model fits the data better.
- Include information on Mitral Valve Disease (MVD) with the aim of producing EBVs for MVD.
- We are also working towards the longer term aims of:
- Modelling different breeding strategies and identifying the most appropriate strategy.
- Carrying out molecular genetic analysis of SM and CM to identify the underlying genes, collaboration with the University of Montreal, Clare Rusbridge and Penny Knowler.
- Developing genomic breeding values (geBVs) for SM.

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