

# SYRINGOMYELIA NEWS

**Winter 2007**

## **A research update**

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It has been a busy few months in the canine syringomyelia world and some of the most recent developments are described below. Many clinicians across Europe and America are now conducting research into aspects of this disease and some had the opportunity to share ideas at Syringomyelia 2007. We hope that 2008 will bring further information on the pathogenesis and genetics of this devastating disorder. Happy holidays!!!!

**Pilot Study: Chiari-like malformation/syringomyelia (CM/SM) in an extended Griffon Bruxellois family.** Investigators: Penny Knowler, Lee Pieterse and Clare Rusbridge. Contributory funding: 'For the Love of Ollie' and 'Syringomyelia DNA Research'

The prohibitive cost of MRI screening has prompted breeders and veterinarians to investigate cheaper alternatives for selection of breeding dogs that confer a low risk of CM/SM. It has been proposed that skull miniaturization may have contributed to mismatch between brain size and caudal fossa volume - predisposing towards SM. As a consequence some breeders have suggested that the tendency for SM might be predicted by head shape or by a skull radiograph. Syringomyelia has recently been recognised as occurring in Griffon Bruxellois and our ongoing project has been looking into the incidence and characteristics. The investigation is still ongoing but has already revealed some interesting findings.

Lee Pieterse proposed that Griffon Bruxellois with skull characteristics of doming of the top combined with flattening at the back may have increased risk of SM in a similar manner that human conditions of craniosynostosis predispose Chiari type I malformation. We were unable to predict SM on the basis of head appearance (Syringomyelia Research Newsletter in May) but analysis of skull dimensions and radiographs continues. This includes correlating 3 month puppy skull radiographs to adult radiographs and MRI, to determine if early characteristics can be identified.

Most significantly, the family study of 31 Griffon Bruxellois showed segregation of dogs affected and unaffected by SM with and without CM. We hope that DNA from these dogs will provide the possibility to identify gene/s involved in CM and SM.

The project provided the groundwork for a larger proposed study collaborating with Georgia University:

**Syringomyelia in the Brussels Griffon (Griffon Bruxellois): Magnetic Resonance Imaging Findings, Clinicopathology, and Prevalence.** Principal Investigators: Dr

Marc Kent and Dr Simon Platt, Georgia University, USA Co-investigators: Dr Scott Schatzberg, (GU) Dr Clare Rusbridge and Penny Knowler (SLVC, UK) Funding AKC CHFGrant #1004.

### ***Search for the gene/s for CM/SM***

Considerable progress has been made in attempting to unravel the complexities of CM/SM and this continues with a successful grant application:

### **Identification of genes causing Chiari- like Malformation with Syringomyelia in the Cavalier King Charles Spaniel.**

Principal Investigator Dr. Zoha Kibar, University of Montreal (MU) Canada. Co-investigators: Dr Guy Rouleau, and Dr Marie-Pierre Dube (MU), Dr Clare Rusbridge and Penny Knowler, SLVC, UK, and Dr Sarah Blott from the Animal Health Trust, UK. Funding: AKC CHF Grant # 954:

The proposed study of identifying the gene(s) responsible for CM/SM will allow the development of a genetic test to identify carriers and devise breeding strategies to reduce or eliminate this devastating condition in affected breeds. This will be possible to a lesser extent with the identification of candidate loci by linkage analysis, and with much broader applicability once the precise gene is identified. These studies will also help better understand the underlying molecular and cellular pathogenic mechanisms for better diagnosis, prognosis and clinical management of CM and associated SM.

### ***Update report from the principal investigator Zoha Kibar:***

This team brings together significant expertise in the clinical and biological aspects of CM and associated SM, as well as in genetics and statistical analysis of complex traits. For the CKCS breed, CM is present in almost 100% of CKCS dogs in various degrees of severity, while SM is present in 50-70%. We have constructed a genealogy of more than 10600 related dogs spanning 24 generations from over 600 MRI confirmed dogs and established a wide DNA collection of over 1500 samples. We completed a whole-genome scan in 173 CKCS dogs selected based on SM-affected status and familial relationship. Genetic analysis identified six genomic regions that could harbour the SM gene(s). We are currently investigating these regions by additional genetic studies in a larger sample size. Since CM is present in almost all CKCS dogs, this genome scan will not identify the genes causing CM. Consequently, we will use the Griffon Bruxellois breed for this purpose. We will conduct a whole genome scan using these 31 dogs and the Illumina canine SNP chip (30K SNPs or single nucleotide polymorphisms). The candidate genetic interval(s) identified in both genome scans will be narrowed down using genetic studies the CKCS and BG breeds and other related breeds affected with CM. Once the candidate genomic region(s) have been delineated to the maximum resolution, we will use the positional candidate gene approach to identify the defective gene(s) in CM and/or SM.

**Optimisation of breeding strategies to reduce inherited disease in pedigree dog populations** Principal Investigator: Dr Sarah Blott (Animal Health Trust) Co-Investigators: Professor John Woolliams (Roslin Institute) Collaborators: Dr Clare

Rusbridge and Penny Knowler (SLVC), Dr Luisa De Risio (Animal Health Trust)  
Professor Nick Jeffery (University of Cambridge) Funding: UK Kennel Club  
Charitable Trust

This project is unanimously supported by the CKCS Regional Clubs and aims to help breeders' decision making using state-of-the-art genetic methods in a user-friendly format – 'a computerised mate selection program'. Using the 'DNA for Healthy Cavaliers' database constructed for the genome scan, the first phase of the project will determine genetic parameters (heritabilities and genetic correlations for syringomyelia and mitral valve disease). Full KC pedigree records will then be used to review the population structure of the UK CKCS so that appropriate breeding strategies can be determined, and computer modelling will show how different approaches affect the incidence of disease/s. Methods of genetic evaluation will be developed that include the use of estimated breeding values (EBVs) and DNA diagnostic markers identified by the genome scans (hopefully) from Montreal University. These two powerful methods of genetic evaluation will be integrated so that the long-term health of the breed is maintained. Initially this will be for CKCS and but could be extended to other breeds such as the Griffon Bruxellois.

### **Syringomyelia 2007 International Symposium -23rd-26th October Rugby, UK**

This event was organised by the Ann Conroy Trust, endorsed by Society of British Neurological surgeons, the Spinal Society of Europe and the University of Birmingham. As part of the Scientific Faculty, Clare helped to ensure an eclectic mix of delegates: -neurosurgeons, neurologists, geneticists, scientists, pain management specialists, veterinary surgeons, mathematicians, physiotherapists, nurses, dog owners and breeders all brought together by a common interest - to better understand the enigma of syringomyelia. All had much to learn from each other. International speakers included Dr U Batzdorf, Dr T Milhorat and Dr E Oldfield from the USA, Dr T Nagashima from Japan, Dr J Klekamp from Germany, Dr M Stoodley from Australia and Dr M Czosnyka from Cambridge. There were 69 original papers and 24 posters.

### **Veterinary Aspects and Genetics. (Friday 26th October)**

3 invited speakers were:

- Dr Clare Rusbridge (UK): Canine syringomyelia: a painful problem in man's best friend.
- Dr Dominic Marino (USA): Foramen magnum decompression with cranioplasty for the treatment of Chiari-like malformation in dogs.
- Dr Guy Rouleau (Canada): The search for the gene(s) predisposing to Chiari I malformation with syringomyelia.

There were also 4 original papers:

1. Morphometric study of the caudal fossa in Cavalier King Charles Spaniel dogs by MRI. Carrera I, Dennis R, Sullivan M. Small Animal Clinical Science, Veterinary School, University of Glasgow, UK.
2. Radiographic morphology of the cranial vertebral column in Cavalier King Charles Spaniels and its relationship to syringomyelia. Talbot CE, Rusbridge

- C, Granger N, Jeffery ND. Department of Veterinary Medicine, University of Cambridge UK & Stone Lion Veterinary Centre, London, UK.
3. Screening of Cavalier King Charles Spaniels for Chiari-like malformation. CA Loughin, DJ Marino. Long Island Veterinary Specialists, New York, USA.
  4. Studies of PRNP gene in patients with syringomyelia from the Bashkortostan region of Russia. Mirsaev TR, Borisova NA, Pervushina EV. Bashkir State Medical University, Ufa, Russian Federation.

Evening Veterinary Satellite Meeting was primarily dedicated to breeders and pet owners with shorter presentations. The invited speakers were joined with our collaborator Dr Sarah Blott who presented her exciting proposals for the development of breeding schemes for companion animals outlined above. Dr Sophia Cerda Gonzalez from the USA joined the 'Ask the Experts' – chaired by Dr Bruce Fogle consisted of questions from dog owners collected and collated by breeders, V. Hull and S. Robinson and pet owners S. Smith and C. Fowler to address their concerns.

We are extremely indebted to Karlin Lillington who recorded and edited this session. She has produced two CDs, and each comes in a paper slipcover:

CD1:

Dr Clare Rusbridge, Stone Lion Veterinary Centre: "Canine syringomyelia: an introduction"

Mr Graham Flint, Queen Elizabeth Hospital, Birmingham: "Human Chiari malformation and syringomyelia"

Dr Sarah Blott, Animal Health Trust: "Breeding for health in pedigree dogs: optimization of breeding strategies to reduce inherited disease"

Dr Dominic Marino: Long Island Veterinary Specialists "Experiences in surgery for canine syringomyelia."

CD 2:

Dr Guy Rouleau, University of Montreal: "The search for gene(s) predisposing to Chiari 1 malformation with syringomyelia"

Q&A: questions posed by breeders and pet owners to the full panel (60 minutes)

The two CDs with the full content of the Rugby event -- talks and Q&A -- are available from Cafepress: <http://www.cafepress.com/cavaliertalk/4311456>. They are priced at \$10.99 each and the entire transaction will be managed by Cafepress, and people can use their credit card to buy online. They will be posted directly to them from Cafepress. All proceeds -- about half the cost of the CD -- go directly to CM/SM genome research.

If you would like to support our research please send donations clearly identified with 'Syringomyelia DNA Research' so that the money is 'ring-fenced' either to Clare Rusbridge (address at top of Newsletter) or Dr Guy Rouleau, MD PhD FRCP(C) Director, Ste-Justine Hospital Research Center and The Center for the Study of Brain Diseases, FAO Dr Zoha Kibar, 3175 Cote-Ste-Catherine, Room A711, Montreal, QC H3T 1C5 Canada.

Thanks to David Harwood who has already donated \$500 matched by Carol Fowler

and Sandy Smith towards the 'search for the gene/s' knowing this is an important piece of the jigsaw and money is essential for rapid progress.