

Report of the Meeting to discuss proposed BVA KC Syringomyelia MRI screening scheme held on 24th October at British Veterinary Association, 7 Mansfield Street, London, W1G 9NQ

Attendees

Sandra Webber, BVA
Dr Clare Rusbridge, Stone Lion Veterinary Centre (Chairman)
Dr Ruth Dennis, Animal Health Trust
Dr Luisa De Risio, Animal Health Trust
Prof Nick Jeffery, Cambridge University
Prof Mike Herrtage, Cambridge University
Dr Geoff Skerritt, Chestergates Referral
Dr Jeff Sampson, Kennel Club

Background and aims of the meeting

Syringomyelia (SM) has been recognized as a serious problem in the Cavalier King Charles Spaniel (CKCS) and also occurs in other toy breeds. MRI screening for the condition has been established during the last two –three years in a number of centres within the UK but there is a recognized need for a standardized protocol. It is hoped that an official scheme would eventually be endorsed by the BVA and hopefully the Kennel Club. Endorsement by these official bodies would mean that the scheme could be a requirement of the Accredited Breeder Scheme for the CKCS. This meeting was proposed to lay the foundations for such a scheme

It is anticipated that the results from this scheme will be used in a computer modelling system pioneered for the CKCS at the Animal Health Trust. This system is designed to facilitate selection against disease while controlling inbreeding and loss of diversity and is dependent on accurate phenotypic measurements, including those derived from MRI scans. The basis of the original database was information collected by Penny Knowler and Clare Rusbridge on clinical observations for SM and Chiari-like malformation (CM) on around 1,400 dogs of which ~ 700 had MRI scan results. The researchers, Dr Sarah Blott and Dr Tom Lewis, also have full access to the UK Kennel Club pedigree records for CKCS. Early estimates of the heritability of SM suggest it is around 0.7-0.8 or that 70-80% of the variation between individuals is genetic in origin and about 20-30% is environmental. The heritability is sufficiently high that genetic selection against the disease should be very successful. Heritabilities for CM, cerebellar herniation and 'medullary kinking' are also very high. Genetic correlations between these traits and SM are positive and less than one. This suggests that different genes may be controlling the expression of SM and CM and that it will be possible to select against SM even if dogs have CM.

The computer model can also take account of other inherited disease, such as mitral valve dysplasia, and generates an Estimated Breeding Values (EBV) for each dog. An EBV is the best measure available for complex traits of the genetic potential of individuals. EBVs can be calculated for most CKCS 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.

There is also a large collaborative study to identify and characterize the gene(s) responsible for CM / SM in the CKCS and Griffon Bruxellois breeds. The lead investigator is Dr. Zoha Kibar from the CHU Sainte Justine Hospital at the University of Montreal with co-investigators Drs Guy Rouleau, and Marie-Pierre Dube, from the University of Montreal, Dr Clare Rusbridge, and Penny Knowler, from the Stone Lion Veterinary Centre in London, UK, and Dr. Sarah Blott from the Animal Health Trust, UK. 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.

A genealogy of more than 10600 related CKCS dogs spanning 24 generations from over 700 MRI confirmed dogs was constructed and DNA collection of over 1500 samples was established. A whole-genome scan in 173 CKCS dogs selected based on SM-affected status and familial relationship was completed. Genetic analysis identified six genomic regions that could harbor the CM/SM gene(s). Investigation of these regions by additional genetic studies in a larger sample size is ongoing. In addition a new whole genome scan using the innovative canine SNP (or single nucleotide polymorphisms) genotyping technology is being conducted. The candidate genetic interval(s) identified in both genome scans will be further narrowed down using genetic studies in the CKCS and other related breeds affected with CM. Once the candidate genomic region(s) has been well defined, the positional candidate gene approach will be used to identify the defective gene(s) in CM/SM. The expected outcome of the study is to identify the gene(s) responsible for CM/SM and allow the development of a genetic test to identify carriers. 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.

Proposed BVA KC Syringomyelia MRI screening scheme

SUMMARY

Members of Panel

Members of the panel must be board certified in neurology or radiology and have the capacity to read DICOM images i.e. have E Film™ or similar

Certification

Breeders will receive a YES / NO answer on whether the dog has central canal dilatation or syringomyelia

If the dog has a syringomyelia then certificate will also detail the maximum transverse width of the syrinx on a T1W image cranial to the C4-5 disc space

Imaging

The minimum required images are

1) Sagittal T1W from intra thalamic adhesion to as far caudal as possible – **The images must include a mid sagittal section of spinal cord visible in one section from the cisterna magna to the C4/C5 intervertebral disc space.**

If this cannot be achieved because the dog has scoliosis secondary to syringomyelia then a dorsal image of the spinal cord must be included.

2) Sagittal T2W as above

3) T1W Transverse images though the maximum width of the syrinx if there is SM or as a block centred on C2/C3 and extending from at least mid point of the vertebral body of C2 and reaching the mid point of the vertebral body of C3

Identification of dogs and labeling of images

Dogs presented for scanning must have permanent identification in the form of microchip / tattoo and Kennel Club Registration number

The microchip / tattoo and the Kennel Club Registration number together with the name, sex, breed and date of birth should be incorporated onto the DICOM images.

Age of dogs

The wording of the certificate will clearly state that this is the MRI status of the dog at the current time and that the situation may change

The minimum screening age is 12 months

It is also recommended that breeders determine the MRI status of their breeding stock at 2-3 years and again when 6 years of age. This will provide further information about that individual dog's estimated breeding value EBV (and therefore the EBV of that individual dog's offspring)

Proposed Procedure

DICOM files on a CD are submitted together with the appropriate documentation to the BVA

BVA will check documentation and DICOM images before sending on to 2 members of the panel.

Those 2 panel members will reach a consensus decision – if they disagree then the images will be referred to the arbitrator.

Results are submitted to the BVA

Certificate is issued to the owner

Results are submitted to the Kennel Club and can be accessed by appropriate individuals e.g. Canine Genetics Unit at the Animal Health Trust

Appeals will be submitted to the arbitrator of the panel

Procedure for non-diagnostic images

An image is designated non-diagnostic by a consensus opinion from the 2 panel members.

In the case of conflict (i.e. one panel member considers acceptable and the other not) then the arbitrator will make the final decision

If images are non-diagnostic then the veterinarian concerned will be informed in writing as to why the images are unacceptable, together with constructive advice for improving them.

Inclusion of breeds other than CKCS

This scheme is not breed specific i.e. any breeder may participate providing the dog has permanent identification in the form of tattoo or microchip.

Inclusion of dogs from other countries

This scheme is also not limited to the UK i.e. images and appropriate documentation may also be submitted from other countries

Dogs scanned before the scheme comes into effect

Breeders are encouraged to submit result certificates for SM and mitral valve dysplasia, together with the Kennel Club registered name and number of the dog or a 5-generation pedigree to Dr Sarah Blott, CKCS Health Breeding Programme, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU. PDF copies of the certificates can also be sent to sarah.blott@aht.org.uk

It is likely that it will be many months before an official scheme can be started. This is because of the lengthy consultation and preparation process that is involved.

Prior to the scheme coming into effect it is recommend that from **January 2009**

- 1) The approved protocols for imaging are followed – this will include permanent identification of dogs with microchip or tattoo
- 2) That the images are reviewed by a board certified radiologist or neurologist.

Proposed BVA KC Syringomyelia MRI screening scheme

DETAILED CHAIRMAN'S REPORT

Members of Panel

Members of the panel must

- be board certified in neurology or radiology
- have the capacity to read DICOM images i.e. have E Film™ or similar

Proposed founding members of the panel are to be Dr Clare Rusbridge, Dr Ruth Dennis, Dr Luisa De Rasio, Prof Nick Jeffery, Prof Mike Herrtage and Dr Geoff Skerritt. It is proposed that the initial arbitrator for panel disagreements be Prof Mike Herrtage as he is familiar with the low field MR images.

It is envisaged that the panel will be expanded and/ or members rotate as the scheme expands.

Other appropriately qualified neurologists and radiologists will be invited to express an interest in joining the panel.

Certification

Breeders will receive a YES / NO answer on whether the dog has

- 1) Central canal dilatation – defined as visible dilatation of the central canal that is less than 2mm wide on a transverse MRI image
- 2) Syringomyelia – defined as a fluid filled cavity that includes or is distinct from the central canal that has a maximal width of 2mm or greater on a transverse MRI image

A fluid filled cavity less than 2mm that is distinct from the central canal is also defined as syringomyelia

If the dog has a syringomyelia then certificate will also detail the maximum transverse width of the syrinx on a T1W image cranial to the C4-5 disc space

Other information e.g. ventricular size (measured as width of lateral ventricles relative to brain width at the level of the pituitary gland) and, cerebellar herniation (CM), material within the tympanic bullae may be recorded as part of prospective studies but this information would not constitute part of the certification because a direct relation / relevance to syringomyelia has not been proved.

MRI

Imaging

Protocol for imaging – Appendix 1

Protocol settings for Esaote machines - Appendix 2

The minimum required images are

- 1) Sagittal T1W from interthalamic adhesion to as far caudal as possible – **images will be deemed non-diagnostic if the CNS from the cisterna magna to C4/C5**

intervertebral disc space is not continuously visible in a single sagittal image.

The exception to this is if the dog has scoliosis in which instance a dorsal plane image of the spinal cord containing the entire cisterna magna – C4/C5 spinal cord must be included. Dogs with scoliosis as a consequence of SM typically have a wide syrinx. If this is not the case the presence of scoliosis may be questioned and the images rejected.

2) Sagittal T2W as above

3) T1W Transverse images though the maximum width of the syrinx if there is SM or as a block centred on C2/C3 and extending from at least mid point of the vertebral body of C2 and reaching at least as far caudally as the mid point of the vertebral body of C3

(NB it is realised that for MRI machines > 1 Tesla that T2W are preferred for best appreciating fluid –filled cavities however the majority of centres in the UK imaging for SM screening purposes are currently using low field machines. In the low field machines the T1W images are more accurate for measuring purposes and therefore for the purposes of standardisation it was agreed that measurements would be made from T1W transverse images

Additional images, e.g. transverse images to assess ventricular size and tympanic bullae, may be performed by some centres however they will not be a requirement for certification

If the imaging is not of the whole spinal column (e.g. upper cervical region only) then wording on the certificate will reflect this and state that this does not exclude more severe change elsewhere in the spine.

Identification of dogs and labeling of images

To be incorporated on the scheme then the dog must have permanent identification in the form of a microchip or tattoo

As microchips interfere with MRI scanning they must not be placed in the cranial cervical area – correct placement is between the scapulae

The veterinary surgeon that is MRI scanning the dog will sign a form to confirm that they have verified the microchip or tattoo number and that it corresponds to the given pedigree name

The microchip / tattoo and the Kennel Club Registration number together with the name, sex, breed and date of birth should be incorporated onto the DICOM images. **Failure to include this information will result in rejection of the images.** As this information cannot be entered retrospectively it is essential that it be done correctly at the time of scanning.

If the dog is not Kennel Club registered then the Veterinary Surgeon obtaining the MRI scan should declare that the dog is 'unregistered'. The dog must still be identified with a microchip and tattoo

Instruction of how to enter information in the fields so that they appear on the subsequent DICOM images may be required especially for the early ESOATE machines.

Age of dogs

SM is a late onset disease and initial analysis of the available SM data suggests that the risk of having the pathology peaks at age 6-7 years

The wording of the certificate will clearly state that this is the MRI status of the dog at the current time and that the situation may change

The minimum screening age is 12 months

It is recommended that the dog is screened again when 6 years of age. This would be to provide information primarily about the risk of SM and the estimated breeding value (EBV) in offspring and relatives

It is also recognized / recommended that breeders screen the dogs at an in-between age, e.g. 2-3 years, to gain further information about that individual dog's EBV because

- 1) A dog that is clear of SM at 12 months old will not necessarily remain so and the estimated breeding value will reflect this i.e. a dog that is clear of SM at 3 years of age is likely to have a better EBV than a dog that is clear at 12 months
- 2) 6 years old is above the normal breeding age of most bitches

Consideration is been given to having a certificate that will lapse after a period of time e.g. after 2 to 3 years

Phenotypic information

No phenotypical information (other than breed, sex and age) will be collected although individual centres may collect that information with owner consent for their own clinical records.

Proposed Procedure

DICOM files on a CD are submitted together with the appropriate documentation to the BVA

BVA will check documentation and DICOM images before sending on to 2 members of the panel. They will verify that the DICOM images can be opened and contain pertinent information and that the Kennel Club number corresponds to the pedigree name on the certificate

Those 2 panel members will reach a consensus decision – if they disagree then the images will be referred to the arbitrator.

Results are submitted to the BVA

Certificate is issued to the owner

Results are submitted to the Kennel Club and can be accessed by appropriate individuals e.g. Canine Genetics Unit at the Animal Health Trust

Appeals will be submitted to the arbitrator of the panel

Procedure for non-diagnostic images

An image is designated non-diagnostic by a consensus opinion from the 2 panel members.

In the case of conflict (i.e. one panel member considers acceptable and the other not) then the arbitrator will make the final decision

If images are non-diagnostic then the veterinarian concerned will be informed in writing as to why the images are unacceptable, together with constructive advice for improving them.

Veterinary surgeons who submit images will ideally have attended a training course. If an individual is regularly submitting non-diagnostic images, then they will be invited to attend a training session before they are allowed to continue submitting images to the scheme.

Inclusion of breeds other than CKCS

This scheme is not breed specific i.e. any breeder may participate providing the dog has a permanent identification in the form of tattoo or microchip.

Inclusion of dogs from other countries

This scheme is also not limited to the UK i.e. images and appropriate documentation may also be submitted from other countries

Dogs MRI scanned before the scheme comes into effect

Breeders are encouraged to submit result certificates for SM and mitral valve dysplasia, together with the Kennel Club registered name and number of the dog or a 5-generation pedigree to Dr Sarah Blott, CKCS Health Breeding Programme, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU. PDF copies of the certificates can also be sent to sarah.blott@aht.org.uk

However there is concern over the validity of the data. Re-evaluation of all previous certification and DICOM images is too big a task so all previously issued certificates will be accepted. However for the purposes of the EBV database only those certificates signed by a board certified radiologist or neurologist will be regarded as accurate. For all other certificates, if the information is pivotal, then it should be possible to make a courteous request that the DICOM information be forwarded to and reviewed by a board certified radiologist or neurologist.

It is likely that it will be many months before an official scheme can be started. This is because of the lengthy consultation and preparation process that is involved.

Prior to the scheme coming into effect it is recommended that from **January 2009**

- 1) The approved protocols for imaging are followed – this will include permanent identification of dogs with microchip or tattoo
- 2) That the images are reviewed by a board certified radiologist or neurologist.

Next steps

- 1) There is a meeting between the Kennel Club and the BVA to discuss the health schemes on 25th November 2008. Information from this meeting will be presented / discussed at that venue
- 2) The scheme must be self financing and a business plan detailing costs such as IT, distribution of results, generation of certificates etc must be produced.
- 3) Other appropriately qualified neurologists and radiologists will be forwarded a copy of this report and be invited to express an interest in joining the panel in the future.
- 4) A Seminar day for training vets who wish to provide an MRI service acquiring images for the scheme will be organized. Appendix 4 details the veterinary practices known to be interested in or currently MRI scanning CKCS for SM - All will also be sent a copy of this report so that they are kept apprised of the current situation.
- 5) Prof Nick Jeffery proposed that part of the long term aims of this scheme should be analysis of the results to ensure that the scheme is actually achieving its objectives i.e. reducing the incidence of SM. These results must be published in a peer reviewed journal - i.e. not exist merely as a Kennel Club report. The AHT Canine Genetics Unit will be contacted to discuss this objective. It is understood

that a long term plan of the computer program is to model different breeding strategies to identify the most appropriate approach and that ultimately when the underlying genes for SM and CM have been identified then genomic breeding values (geBVs) for SM can be developed.

Other related business

DNA

There is no diagnostic test for SM available based on DNA. DNA collected is mostly for research purposes and typically in the form of buccal swabs, toe nail clippings or blood remaining from that taken for diagnostic testing.

One of the difficulties in the study to characterize the gene(s) responsible for SM is the paucity of normal dogs. This is because most dogs over 5 years of age have an MRI as part of a neurological work up and have clinical signs. Therefore if such "SM - clear" dogs are identified as part of the screening process then the veterinarian / breeder is encouraged to submit an appropriate DNA sample (as above) to the CHU Sainte Justine Hospital at the University of Montreal

Breeders are being encouraged to donate a DNA sample from buccal swab samples. This is with the aim that once DNA markers have been identified then the donated samples can be screened for their disease genotypes. This will aid in the more precise estimation of breeding values.

It is proposed that buccal swab packs and instructions are supplied to practices performing MRI scans to enable sampling when appropriate and with owner consent

Appendix 1 - Protocol for imaging.

Dogs presented for scanning must have permanent identification in the form of microchip / tattoo

The minimum age of a dog for submission under the Scheme is one year. There is no upper age limit

The following documents must be made available at the time of MRI scanning

- (i) The Kennel Club (KC) Registration Certificate of the dog if it is registered with the KC,
- (ii) Any related transfer or change of name certificate
- (iii) Certificates relating to microchip / tattoo
- (iii) Prior to MRI, the owner must complete and sign the first section of the certificate (the Owner's Declaration) verifying that the details given in that section relate to the dog being submitted, that the details are correct and granting permission for the results to be used in the ways specified
- (iv) the veterinary surgeon must complete and sign the Veterinary Surgeon's declaration that they have verified the microchip or tattoo number

The microchip / tattoo and the Kennel Club Registration number together with the name, sex, breed and date of birth should be incorporated onto the DICOM images.

Positioning of the dogs may vary with the scanner / veterinarian but the head should be in extension.

It is important that the dog be positioned so that the neck is straight

The minimum required images are

- 1) Sagittal T1W from intra thalamic adhesion to as far caudal as possible – **The images must include a mid sagittal section of spinal cord visible in one section from the cisterna magna to the C4/C5 intervertebral disc space.**

If this cannot be achieved because the dog has scoliosis secondary to syringomyelia then a dorsal image of the spinal cord must be included. Dogs with scoliosis as a consequence of SM typically have a wide syrinx. If this is not the case the presence of scoliosis may be questioned and the images rejected.

- 2) Sagittal T2W as above

- 3) T1W Transverse images through the maximum width of the syrinx if there is SM or as a block centred on C2/C3 and extending from at least mid point of the vertebral body of C2 and reaching the mid point of the vertebral body of C3

Optional extras

Additional images e.g. transverse images to assess ventricular size and tympanic bullae may be performed by some centres however they will not be a requirement for certification.

If performed these transverse images should be centred so that one slice is perpendicular to the lateral ventricle and passes through the pituitary and another passes through the centre of the tympanic bullae. It is acceptable that these images be transverse localiser images (i.e. taking ~ 30second) on the ESAOTE machines (see Appendix 2)

Appendix 2 - Protocol settings for VET MR ESAOTE machines

Image from ~ level of the thalamus / corpus callosum to as far caudal as possible.

A transverse localiser is done after the initial scout. 29 seconds ET 18, rep time 340, slices 9, num ac 1, reading and encoding FOV 200, sample nr 192, phases 128, hamming none, slices 9, thickness 8.0, gap 1.8. This allows you to plan the sagittal shots centring on the dorsal spines of the vertebrae . Then the following sequences are done

1) T1 sagittal - these parameters are set up to give a short FOV and therefore greater contrast.

ET 26, Rep time 530 Slices 10, Num Aq 4 Reading FOV 170, encoding FOV 170, Sample # 320, phases 232, Hamming filter low, thickness 4.5, gap 0.4

2) Turbo spin echo (like T2W) sagittal

ET80 rep time 2800, slices 10, num acq 2, reading FIV 200 encoding FOV 200, sample # 256, phases 192, hamming filter non, thickness 4.5, gap 0.4.

3) T1W 3D transverse centring on the C2/C3 disc space or the widest part of the syrinx

ET 16, flip angle 65, rep time 38, n acq 1, reading and encoding FOV 180, 3D 80 sample # 256 3D phases 40, hamming none, aniso 3d (checked), 3d thick 9.1.

The first 2 sequences are ~ 10 minutes long, The 3rd sequence is ~ 4 minutes so the whole process should take ~ 30 minutes.

Optional extra

Additional (quick ~ 30second) transverse localiser images through lateral ventricles at level of the pituitary gland and also through and tympanic bullae - this is so an assessment can be made of ventricular size / symmetry and whether there is material in the middle ear.

This information is not currently important for grading but is being analysed prospectively

Appendix 3 Criteria scored by panel members

Presence or Absence of Syringomyelia – syringomyelia defined as a fluid filled cavity that includes or is distinct from the central canal that is 2mm wide or greater on a transverse MRI image

A fluid filled cavity less than 2mm that is distinct from the central canal is also defined as syringomyelia

If syringomyelia is present then the maximum width is measured from a transverse image

Presence or absence of central canal dilatation – central canal dilatation is defined as a dilatation of the central canal that is less than 2mm wide on a transverse MRI image

Other parameters may be recorded as part of ongoing research into the pathogenesis of syringomyelia. These are still to be decided upon but may include.

1. Length of visible syringomyelia (must also record length of spinal cord imaged).
2. Ventricular ratio – the maximum width of the lateral ventricles divided by the maximum width of the forebrain taken from a transverse section made at the level of the pituitary gland
3. Ventricular asymmetry
4. Chiari malformation - Consideration will have to be given as to whether to include information on CM for other breeds as this malformation is less common than in the CKCS and in the case of the Griffon Bruxellois has a significant association with syringomyelia
5. Material within right / left / both tympanic bullae
6. Measurements from cervical vertebral canal

Appendix 4 Centres currently offering or interested in (reduced cost) scanning (unlikely to be exhaustive list and does not include all Universities and AHT)

UK

The cost is generally around £200 – £300 inclusive of VAT per dog. For most centres this includes the cost of interpretation and providing the certificate. Some centres offer a discount for more than one dog. Some centres scan the head & cervical region under sedation, some others use anaesthesia.

Dr Geoff Skerritt
Chester Gates Referral Hospital
Telford Court
Chester Gate
Chester CH1 6LT.
Tel: 01244 853823
Email: SKERRVET@aol.com

Gerard te Lintelo
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Jonathan Underwood
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Tel 01252 511988

Alex Gough MA VetMB CertSAM CertVC
MRCVS
Bath Veterinary Referrals
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