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Effectiveness of breeding guidelines for reducing the prevalence of syringomyelia

S. P. Knowler BSc [1]
A. K. McFadyen PhD MSc BSc Dip.SAD CMath MIMA FSS [2]
C. Rusbridge BVMS PhD DipECVN MRCVS [1]

[1] Stone Lion Veterinary Hospital, 41 High Street, Wimbledon, SW19 5AU, UK.
[2] Reader in Health Statistics, School of Engineering & Computing, Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA

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Summary
Several toy breed dogs are predisposed to syringomyelia (SM), a spinal cord disorder, characterized by fluid filled cavitation. SM is a complex trait with a moderately high heritability. Selective breeding against SM is confounded by its complex inheritance, its late onset nature and high prevalence in some breeds. This study investigated the early outcome of existing SM breeding guidelines. Six hundred and forty three dogs, 550 Cavalier King Charles spaniels (CKCS) and 93 Griffon Bruxellois (GB), were identified having either one (454 dogs) or both parents (189 dogs) with MRI determined SM status. Offspring without SM were more common when the parents were both clear of SM (SM free; CKCS 70%, GB 73%). Conversely offspring with SM were more likely when both parents had SM (SM affected; CKCS 92%, GB 100%). A mating of one SM-free parent with an SM-affected parent was risky for SM affectedness with 77% of CKCS and 46% of GB offspring being SM affected. It is recommended that all breeding dogs from breeds susceptible to SM be MRI screened; that the SM status at 5 years old is established; and all results submitted to a central database that can be used by dog breeders to better enable mate selection based on estimated breeding values.

Introduction

SYRINGOMYELIA (SM) is characterised by fluid-filled cavities within the spinal cord and occurs secondary to obstruction of cerebrospinal fluid especially if that obstruction is at the foramen magnum. The most common predisposing cause in the dog is Chiari-like malformation (CM) (Rusbridge and others 2006), a condition characterised by disparity in size between the brain (too big) and the skull (too small) such that the cerebellum and brainstem are herniated into or via the foramen magnum (Cross and others 2009). Several toy breed dogs are predisposed to CM and SM. Studies into the inheritance of SM associated with CM in Cavalier King Charles spaniels (CKCS) have shown it to be a complex trait with a moderately high heritability ($h^2=0.37\pm0.15$ se) (Lewis and others 2010). It has a varying age of onset, there is 46 per cent prevalence in asymptomatic breeding CKCS but prevalence may be as high as 70 per cent in dogs over six years of age (Parker and others 2011). MRI, which is financially prohibitive, is currently the only means of confirming SM and its potentially late onset nature means that the optimum age to MRI screen for breeding purposes is unclear. In addition, the high prevalence means that it can be difficult for breeders to find suitable SM-free dogs. There is also a concern that breeding restrictions may result in further genetic bottle necking particularly as the CKCS is predisposed to many other inherited disorders (for review, see Gough and Thomas 2010). At the request of the CKCS breeding fraternity, interim breeding guidelines for SM were formalised at a international Cavalier club round table in 2006 (Cappello and Rusbridge 2007). Between September 2004 and 2006, similar guidelines had been used by a small number of CKCS breeders particularly in the Netherlands. The 2006 breeding guidelines had the aim of reducing early onset and/or clinical SM while attempting to maintain genetic diversity; they were implemented as a 'common sense' approach but without there being any evidence of the appropriateness or effectiveness. Dogs were graded according to MRI status and age as follows: A, an asymptomatic dog aged 2.5 years or older where SM is absent or with a central canal dilatation (CCD) with a transverse diameter less than 2 mm; C, an asymptomatic dog aged younger than 2.5 years without SM or CCD; D, an asymptomatic dog aged 2.5 years or older with SM which has a transverse diameter equal to or

greater than 2 mm; E, an asymptomatic dog aged younger than 2.5 years with SM or CCD; and F, a symptomatic dog of any age with SM. For historical reasons, there is no B grade. The Round Table Working Group suggested that dogs be bred according to the guidelines in Table 1. These breeding guidelines have also been used by many breeders of Griffon Bruxellois (GB) although it is yet to be determined if the pathogenesis of SM in the GB is the same as in the CKCS.

Several groups of breeders and pet owners of CKCS and GB from the UK, Netherlands, Finland, Canada, USA, South Africa and Australia have participated in the research into the genetic basis of SM. Phenotypic and pedigree information for both breeds have been collated as part of a DNA collection programme used for genome-wide linkage studies carried out in collaboration with the University of Montreal. Lewis and others (2010) used a mixed linear REML model to investigate the mode of inheritance for SM associated with CM and identified two families for which the parents and offspring had SM status confirmed between three and four years of age. The criterion by which a dog was designated an SM-affected dog was the presence of SM or CCD that had a transverse diameter of 2 mm or more. This 2 mm 'cut-off' is not age dependent, that is, a dog deemed SM-free at three years of age will not necessarily be SM-free at five or six years of age. CM is defined as overcrowding of the caudal cranial fossa so that the cerebellum does not have a rounded shape, that is, there is indentation by the supraoccipital bone and/or the cerebellar vermis is impacted into or herniated through the foramen magnum.

This study seeks to investigate if the 2006 breeding guidelines are appropriate i.e. achieving a goal of reducing early onset SM and also aims to identify factors associated with increased or decreased risk of SM which might be useful for future breeding guidelines to be issued in conjunction with a proposed British Veterinary Association/Kennel Club CM and SM MRI screening scheme. Although a computerised Mate Selection Programme (Lewis and others 2010) is shortly anticipated for CKCS this is not yet available to other breeds with a tendency for SM and associated CM. Until such programs are developed and their accuracy verified some sort of breeding guidance is useful.

Materials and Methods

The CKCS CM and SM Microsoft Access ™ database constructed for use in the genome studies currently holds over 12,200 dogs linked by their pedigree. Of these, 1,282 dogs have full MRI and clinical phenotypical data with stored DNA extracted from blood, saliva or toenail clippings. The GB CM and SM Microsoft Access ™ database currently holds 1,394 dogs linked by their pedigree with 244 dogs with full MRI and clinical phenotypical data and mostly with stored DNA. All the MR images have been reviewed by one of the authors (CR) or in consultation with her to ensure consistency and all dogs were assigned an SM grade according to the current breeding guidelines (Table 1). In addition, to estimate the influence of late onset SM, an *A grade was assigned to dogs that had an MRI scan aged 5 years of age or more and were without SM or with a CCD with a transverse diameter less than 2mm. Within the CKCS group, 92 dogs had a second MRI scan in order to ascertain any change in SM status or progression of the condition. For the analysis results of the most recent MRI scan was used. Presence or absence of CM was noted but not analysed in the study because CM is not included in the 2006 breeding guidelines as this trait is almost ubiquitous in the CKCS breed. The offspring (outcome) of a mated pair was considered as an independent event and no account was taken of familial relationships within the cohort.

All dogs included in the study were reported as asymptomatic for SM and had been presented for MRI screening to ascertain their or their descendants' suitability for breeding purposes. According to the 2006 breeding guidelines, clinically affected (F grade dogs) should not be used for breeding and therefore are excluded from this study by default. Owners of dogs submitted for MRI screening were required to submit limited clinical information by answering questions regarding the common clinical signs of SM which might be observed in their dog (for the specific questions see http://www.veterinary-neurologist.co.uk/mriform/form.html). All dogs were permanently identified with a microchip or ear tattoo and the appropriate KC registration certificates were obtained giving details of dam and sire.

Using the above database, CKCS and GB dogs with MRI determined SM status that also had one or more parents with MRI determined SM status were identified. Dogs with inadequate records or with MRI that was of insufficient diagnostic quality were excluded. The decision of which dogs to use in the breeding program was entirely the individual choice of the breeders. Thus, although the 2006 breeding guidelines were available they were not necessarily followed. (http://www.veterinaryneurologist.co.uk/syringomyelia/docs/breedguide.pdf)

The following variables were recorded

- SM affectedness in offspring in all possible parental crosses i.e. *Ax*A,*AxA, *AxC, *AxD, *AxE, AxA, AxC, AxD, AxE, CxC, CxD, CxE, DxD, DxE, ExE and crosses that had one parent with unknown (U) SM status i.e. *AxU, AxU, CxU, DxU and ExU.
- age at which the dog was MRI scanned.

Results

A total cohort of 643 dogs comprising 550 CKCS (358 females and 192 males) and 93 GB (54 females and 39 males) were identified within the databases having one (392 CKCS and 62 GB) or both parents (158 CKCS and 31GB) with MRI confirmed status. The breakdown of the 643 SM grades, gender and parental status is demonstrated in Table 1 below.

	Cavalier King Charles Spaniel offspring					Griffon Bruxellois offspring					
Grade	Total CKCS	both parents grade known	one grade parent known	males	females	Total GB	both parents grade known	one parent grade known	males	females	Total both breeds
A*	25	0	25	13	12	11	5	6	5	6	36
A	120	31	89	79	41	30	10	20	11	19	150
C	154	53	101	103	51	10	6	4	3	7	164
D	147	32	115	93	54	33	9	24	16	17	180
E	104	42	62	70	34	9	1	8	4	5	113
Total	550	158	392	358	192	93	31	62	39	54	643

Table 1. *SM grades and gender for the 643 offspring, (550 CKCS and 93 GB) from one or both parents with a known SM status*.

In the rescanned CKCS group (92 dogs), 12 of 26 (43%) previously grade A dogs were now SM-affected. The mean age at repeat MRI was 3.4 years (range 2.5yrs – 4.3yrs) and the mean interval between MRI scans was 2.2 years (range 0.9-4.1years). In addition 20 of 66 (30%) previously grade C dogs were deemed SM-affected on repeat MRI. These findings suggest that the SM status of both young adult C grade dogs and even young A grade dogs can be ambiguous i.e. the SM status can change as the dog ages.

The parents of the offspring were not all novel as the cohort included a variety of relationships: siblings, half siblings, parent /grandparent/great grandparents, etc. There was no data for CxD breeding combinations in CKCS: and in the GB there was no data for: *AxE, AxA, AxC, AxE, CxC, CxD, CxE, CxU, DxE, ExE and UxC breeding combinations. The MRI status of the offspring are tabulated in in Tables 2 and 3 below

The most common breeding combination in both breeds was UxD i.e. a SM-affected dog with a dog of unknown status (34% CKCS and 38% GB parental combinations). The second most common breeding combination was *A orA xU (30% CKCS and 28% GB parental combinations). The proportion of breeding combinations that included at least one *A or A parent was 50% for CKCS and 55% for GB.

	Offspring grades					
parental cross	*A	A	C	D	E	total
*A*A		4	2			6
*AA		7	5	1	1	14
*AC		1	3	2		6
*AD		6	5	8	2	21
*AE					2	2
AA		3	8	2	2	15
AC		1	6	1	4	12
AD		3	4	5	14	26
AE		2	4	2	3	11
CC		1	1		1	3
CE			1		2	3
DD		1	7	11	7	26
DE		2	6		4	12
EE			1			1
U*A	13	23	18	22	6	82
UA	1	25	37	8	10	81
UC		8	9	1	1	19
UD	10	28	36	76	40	190
UE	1	5	1	8	5	20
total	25	120	154	147	104	550

Table 2
*Numbers of CKCS offspring and their SM grades from all possible parental combinations including Grade *A (dogs 5 years or more) and U (unknown MRI status).*

Unfortunately the proportion of SM-affected versus SM-free offspring cannot be tested statistically because it is not possible to estimate the significance of breeders' bias with respect to their pedigree knowledge in their breeding choices – for example, selecting breeding dogs that are closely related to an A grade dog, or avoiding dogs that are clinically affected but not MRI confirmed. However, taking into account this lack of statistical robustness, a number of observations could be made. Grade A or *A offspring (145 CKCS and 41 GB) generally only occurred when there was at least one A grade parent.

	offspring grades					
parental cross	*A	A	C	D	E	total
*A*A	2	2	1	2	1	8
*AA		4	4			8
*AC		1				1
*AD	3	3		4		10
AD			1	1		2
DD				2		2
U*A	5	6		11	1	23
UA		2		1		3
UD	1	12	4	11	7	35
UE				1		1
total	11	30	10	33	9	93

Table 3
*Numbers of GB offspring and their SM grades from all possible parental combinations including Grade *A (dogs 5 years or more) and U (unknown MRI status).*

When dogs with one unknown parent and ambiguous C grade dogs were excluded, there were only three grade A CKCS that had both parents SM-affected. These three dogs were under 2.7 years of age when MRI scanned i.e. their lifetime SM-free status was not assured. The study suggests that using at least one *A grade parent increases the likelihood of SM-free offspring. In the CKCS group (table 3) there are 131 (49 + 82) offspring where at least one parent was *A grade and, if we exclude the ambiguous C grade offspring (33) we have 98 offspring. Of these 54 (18 + 13 + 23) were either *A or A hence 54/98 (55%) were SM-free. For the same group of dogs, when at least one parent is A grade there were 145 (64 + 81) offspring (not double counting the *AA) and of these 59 were C grade leaving 86 offspring. Thirty-five of the 86 (41%) were either *A or A. Hence the majority of offspring (55%) were SM free from at least one *A parent as opposed to only 41% when only at least one A grade parent. If the GB data (table 4) is considered in a similar way, excluding the C grade offspring, 26 of the 45 (58%) offspring from at least one *A parent were *A or A, compared to 2 of the 4 (50%) offspring from at least one A grade parent albeit from a very small sample. Once again the offspring from a parental cross where at least one parent is *A increases the likelihood of them being SM-free.

However using only *A parents was not a guarantee of the offspring being SM-free. In the GB cohort, 3 of 8 dogs (37.5%) were SM affected from *A x*A parental crosses. Of these, two dogs were uncle and nephew from a GB family which did not have CM. The third had SM and CM and resulted from a mating of a *A dam with CM and CCD and *A sire that had neither CM nor SM.

In Table 4 below the ambiguous grade C dogs (154 CKCS and 10 GB) have been removed together with all offspring involving a C grade parent (24 CKCS and 1 GB) and there is a more straightforward comparison between the breeding of SM-free (*A or A with *A or A) and SM-affected dogs (D or E with D or E) with all possible combinations including a parent of unknown status (U). This is represented as a percentage of offspring in Fig 1.

It can be seen in both the CKCS and GB groups that offspring without SM were common when the parents were both clear of SM (SM-free; CKCS 70%, GB 73%). Conversely offspring with SM were likely when both parents had SM (SM-affected; CKCS 92%, GB 100%). In the CKCS group the 8% SM-free offspring were young dogs (less than 3.1 years old) and therefore are still at risk for developing SM. One of these young SM-free dogs had three affected siblings. There were only two dogs in the GB group i.e. the figure of 100% SM affected is unreliable. A mating of one SM-free parent with an SM-affected parent was risky for SM affectedness with 77% of CKCS offspring being SM-affected and 46% of GB offspring SM-affected.

		parental crosses						
		*A or A x *A or A	*A or A x U	*A or A x D or E	D or E x D or E	D or E x U	total	
offspring numbers	CKCS							
	no SM	14	62	11	2	44	133	36%
	SM	6	46	36	22	129	239	64%
	total	20	108	47	24	173	372	
	GB							
	no SM	8	13	6	0	13	40	49%
	SM	3	13	5	2	19	42	51%
	total	11	26	11	2	32	82	
	N=454							

Table 4
Comparison of numbers of CKCS and GB offspring from various parental combinations between SM-affected and SM-free dogs (U= unknown MRI status) N=454.

Discussion

SM associated with CM in the CKCS was first reported in 1997 (Rusbridge 1997). The timing coincided with the availability of spinal MRI for animals and it is unlikely that the emergence of SM was because it was a "new" disease but more a reflection of the ability to diagnose it (Rusbridge and Knowler 2004). It became apparent that SM was prevalent in the CKCS and was a disease that affected some other toy breed dogs (Rusbridge and Knowler 2004, Rusbridge and others 2009, Lewis and others 2010, Parker and others 2010). The spectrum of disease varies from asymptomatic to dogs with severe neuropathic pain and /or neurological deficits relating to spinal cord damage (Rusbridge and others 2007) The significance of asymptomatic dogs is that breeders may be unaware and the dogs' offspring may be symptomatic (Rusbridge and others 2005). With the increasing availability of MRI and with the provision of veterinary services offering SM screening at comparatively low cost, many breeders now ascertain the SM status of their dogs. However guidance was sought on how to select suitable breeding combinations (Cappello and Rusbridge 2007). A recommendation to breed only unaffected dogs is too simplistic and may even have a negative impact as it fails to take account of the problem that the majority of dogs are bred as young adults and SM can occur as a late onset disease. Also in the CKCS, the prevalence of SM may be as high as 70% in older dogs (Parker and others 2011) and there is a danger of further genetic bottlenecking. Therefore a group of veterinary neurologists offered a system that took account of age and also made provision for breeding asymptomatic SM-affected dogs that were free of other known inherited diseases (Cappello and Rusbridge 2007). However since the mode of inheritance of SM was unknown, this guidance may have been inappropriate for the CKCS or other breeds with a tendency for SM. The 2006 breeding guidelines have been adopted by several GB breeders. However, unlike the CKCS where CM appears to be ubiquitous, the GB can have SM independently from CM (Rusbridge and others 2009).

This paper serves to report the early outcome of using the 2006 breeding guidelines for dogs contributing to a genome project and whose pedigrees were known. The study suggested that that older SM-free offspring were more likely if both parents were SM-free and SM-affected offspring were more likely if both parents had SM. There was a trend that truly SM-free dogs (*A) only resulted when at least one parent was *A. This finding seems logical but since *A and A grade dogs are in a minority it is problematic for breeders to select SM-free dogs especially when the SM status of the dog can alter with age. Often the true SM status may not be known until after the dog is used for breeding. In 2010 there were 2136 CKCS litters registered with the UK Kennel Club (8095 puppies). Of these, 33% had a sire aged less than 2.5 years old on the day of mating and 36% had a dam less than 2.5 years old on the day of mating. This translates as 55% of the KC registered CKCS puppies having one parent under 2.5 years and 14% having both (Grahame Ford, personal communication). Thus a recommendation that only A or *A grade parents be used is unlikely to be practical for breeders. If a younger SM free dog (C grade) is mated to an older dog (A grade) then there is greater risk for SM than with two A grade parents. The data in the study (tables 2 and 3) suggested that 63% (12/19) of offspring were SM-free from A or*A x C parents. This is likely to be an over-estimation of the proportion of SM- free dogs since these figures include C grade offspring which may develop SM as they become older. However it could be argued that a recommendation to include at least one A grade dog in any proposed mating is a reasonable, practical alternative since it allows breeders to use their younger dogs. However a far better proposal for prevention of SM and maintaining genetic diversity is a proposed Mate Select program using estimated breeding values (EBV). EBVs are a statistical estimate of the genetic risk for a given disease in an individual dog and a measure of the likelihood of their passing on the disease to their offspring (Lewis and others 2010). An EBV is the best method of genetic evaluation available for complex traits and can be calculated for most

dogs even if they have not undergone an MRI scan, as long as they are related to dogs which have been MRI scanned. In other words, knowing the EBV may help breeders choose safer breeding combinations. However the validity of EBVs depends on the collection of accurate population-wide data. Moreover for the scheme to be successful, it is important that MR images from every MRI scanned dog be submitted for assessment, including clinical cases and whether or not the animal is required for breeding. Since dogs were shown to be SM-affected when MRI was repeated at 5 years or older and after they had been used for breeding, it is advantageous for breeders to ascertain the SM status of the dog when at least 5 years old. Even if the dog is no longer being used for breeding purposes, this information is likely to be valuable for breeding decisions for the dog's descendants and for determining accurate EBVs.

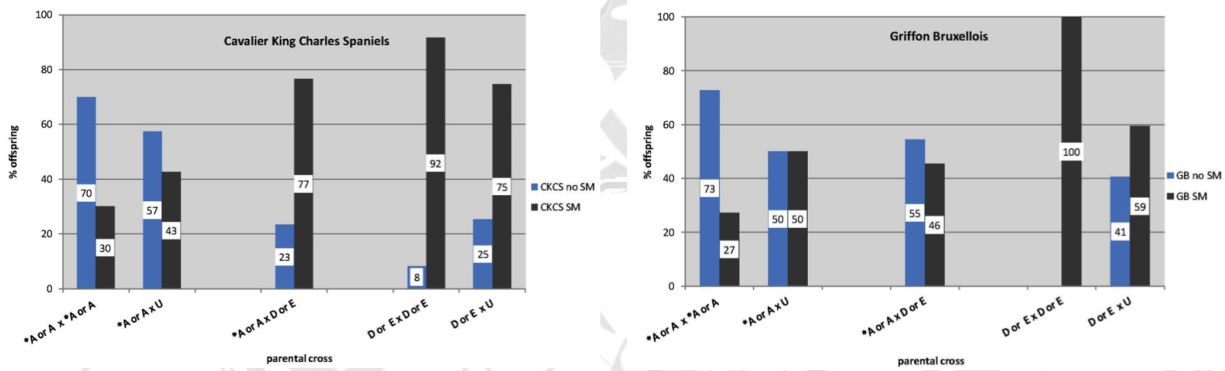

Figure 1.

Comparison of numbers of CKCS and GB offspring from various parental combinations between SM-affected and SM-free dogs. *Dogs were graded according to age and MRI status as follows:* ***CKCS/GB no SM*** *i.e. SM is absent or with a central canal dilatation (CCD) with a transverse diameter less than 2mm,* ****A*** *- aged 5 years or more;* ***A*** *- 2.5 – 4.9 years;* ***CKCS/GB SM*** *i.e. SM present or CCD with transverse diameter greater than 2mm,* ***D*** *aged 2.5 years or more;* ***E*** *aged less than 2.5 years;* ***U*** *unknown MRI status. Dogs (offspring or parents) with C grade (SM free; less than 2.5 years) have been excluded from this analysis to give a more straightforward comparison. This is because C grade dogs are ambiguous and their SM status changes to either A, E or D or F grade depending on the age and affectedness of the dog.*

This study also looked at the risk of using dogs of unknown status. Many breeders are reluctant to MRI scan their dogs for which they may cite a number of reasons including cost and risk of anaesthesia or sedation. Undoubtedly, fear of an unfavourable result also plays a part. Not all unscanned dogs are equal and experienced breeders may select a dog on the basis of it having relatives that are SM-free or select a stud dog that is known to have produced a high proportion of SM-free offspring: one unscanned champion stud dog was mated with 16 bitches resulting in 11 C-grades, 10 A-grades and only 3 SM affected offspring. Results from this study suggested that using a SM-affected dog (grade D) with a dog of unknown status resulted in higher numbers of SM-affected dogs in the older population (75% SM affected CKCS and 59% affected GB). Using a SM-free (*A or A) CKCS with an unknown dog still resulted in 43% of older offspring being SM-affected (50% GB) and therefore it is recommended that all breeding dogs from breeds susceptible to SM be MRI screened.

The most controversial part of 2006 breeding recommendations was that it permitted older clinically asymptomatic SM-affected dogs to be bred to older SM-free dogs. This was because there were only a few A grade dogs identified when the breeding guidelines were first proposed and overuse of these might limit genetic diversity, reducing the effective population size. This investigation showed that a proportion of the offspring from such a cross can be SM-free however in the CKCS the number of SM-affected dogs was far greater than SM-free dogs (77% SM-affected). Moreover, where these offspring had siblings, the ratio of SM-free to SM-affected was 1:1 compared to 3.5:1 for *A or A x *A or A parents or 1: 1.7 for D or E xU parents (unpublished data, Knowler and Rusbridge). It is debatable whether it is ethical to knowing breed a dog with an inherited disease especially when the majority of the offspring may be destined for the pet-owning public and this study suggested that it is not advisable to use SM-affected dogs at all for breeding. However, if the prevalence of SM is as high as 70% in the CKCS (Parker and others 2011), this will have dire consequences for the effective population size of the breed. Again it is hoped that using an EBV Mate Select Program may allow safer parental crosses, maintaining genetic diversity while decreasing the number of SM affected offspring.

One problem noted with the 2006 breeding guidelines was that if the dog was deemed asymptomatic but SM-affected when first scanned over 2.5 years old it was attributed a grade D status. However in some cases it was suspected, due to the size of the syrinx, that if the dog had been scanned when younger then the syrinx would have been apparent - in other words, the dog was actually an E grade. It was also possible that some dogs may have been clinically affected (i.e. an F grade) as the early behavioural signs of pain from SM and/or CM can be subtle and/or intermittent and may not be detected in a routine clinical examination. In addition some breeders fail to recognise or acknowledge clinical signs of SM and/or CM. Since the aim of the guidelines is to reduce the incidence of early onset and clinical SM, a future recommendation is that a D status (or equivalent) will only be appropriate if the dog was first proved by MRI to be SM-free before 2.5 years of age. One encouraging observation was that the proportion of grade E (SM-affected less than 2.5 years of age) dropped from an average of 15 dogs per year in years 2004-6 to 11 dogs per year in years 2007-9 i.e. the breeding guidelines may be achieving the goal of reducing the risk of early onset SM however this hypothesis would be needed to be tested in a more vigorous study.

This report has a number of limitations but particularly that it is not an independent and controlled breeding programme. The source of information is from that submitted at the time of MRI screening and the breeders made the decisions with regard to which dogs to breed and which dogs to submit for MRI screening and at what age. Although participants were worldwide the study has been biased towards identifying as many SM-free dogs as possible as a control cohort for the genome project. Due to the lack of independence of the individual offspring from each other, the authors have confined themselves to making observations and have avoided testing for statistical significance given all appropriate testing procedures require independent observations thus resultant p-values would have been meaningless. It is possible these observations are misleading given this lack of independence, the short study timescale and the limited numbers in the GB cohort. Despite these limitations however, the authors believe that it is useful for breeders to have some feedback on the breeding programs they have been using, even if this is simply a starting point for a more formal study.

The study is also limited by the potentially late onset nature of SM. In the study, 46.9 % of the CKCS and 20% GB were scanned under the age of 2.5years (i.e. C/E grades). Given the natural history of SM, it is likely that a proportion of the A and C grade dogs will ultimately prove to be SM-affected. The cost of scanning older dogs, often retired in pet homes, means data collection is difficult. Continuing to monitor the outcome of parental crosses and proportion of SM-affected offspring should be an important future goal in any proposed MRI screening program. A further limitation of the study is that does not take account of the SM-affectedness of grandparents, whose status breeders may or may not know.

The study also suggests that, although the 2006 breeding guidelines might increase the proportion of SM-free dogs, a reservoir of affected dogs remain. An EBV Mate Select Program may help in this respect but in the near future this is only anticipated for the CKCS breed. For other breeds it is recommended that as much information about the ancestors is ascertained as possible and that EBV Mate Select Program be developed as rapidly as possible. The relationship between CM and SM is complex (Rusbridge and others 2009, Driver and others 2010). This study does not take account of CM since this is not included in the 2006 breeding guidelines. This is partly because CM is almost ubiquitous in the CKCS (Cerda-Gonzalez and others 2009). In the past 24 months, one of the authors (CR) reported 564 MRI scans from breeding CKCS and there were no dogs without CM and only six dogs (1.1 per cent) with mild CM. The tendency for CM may be a fixed genetic trait in the CKCS. The subsequent development of SM may be dependent on other modifying or protective genes that influence severity and age of onset. It is possible that both the 2006 breeding guidelines and an EBV mate select programme may merely select for protective traits, reducing the incidence of clinical and early disease but without reducing the prevalence of the main gene(s) for SM associated with CM. Epistasis (gene interaction that perturbs the normal Mendelian ratios) is a common feature of complex traits and different breeds with SM may have their own unique genomic characteristics (modifier genes) with any gene mutation. In the GB cohort, 67 of 93 dogs (72 per cent) had CM. Of the CM-free GB dogs, nine of 26 (35 per cent) had SM. This suggests in this breed the genetic aetiology of SM may be different from CKCS. It will only be possible to understand the mode of inheritance when genome studies are completed. It is expected that the use of genomic breeding values will further reduce the incidence of this disease.

In conclusion, the results from this study suggest that it is appropriate to continue using the breeding guidelines for both the CKCS and GB until a more robust system based on EBV or genetic testing is available. The following modifications are suggested but it should be realised that these are the recommendations that are based on limited data and consequently should be subjected to further prospective vigorous study:

1. To increase the number of SM-free offspring, at least one parent should be ascertained to be SM-free by MRI as a young adult. In ideal circumstances, both parents would be SM-free. According to the study by Parker and others (2011), the optimum age for this early MRI screening is 36 months.

2. If an SM-affected dog is used, for example, to preserve desirable traits or to increase genetic diversity then ideally the chosen mate would either be selected on the basis of its EBV and/or would be an older SM-free dog (five years or older). The offspring of the proposed mating should also be MRI scanned and ideally bred to older SM-free dogs.

3. The SM status of the dog when at least five years old should be established. SM has a complex inheritance and an EBV mate select programme should allow breeders to select safer breeding combinations. To ensure success, the programme requires a substantial collection of accurate populationwide data. Consequently, all breeding dogs from breeds susceptible to CM and SM should be MRI screened and these results should be submitted to a central source. Pedigree and clinical history from dogs presenting with clinical signs of CM and/or SM should also be submitted to this central system.

4. 'D' status (or equivalent) will only be appropriate if the dog was first proved to be SM-free before 36 months of age.

5. Future breeding recommendations should also take account of dogs with CCD less than 2 mm.

6. Guidance for other breeds like the GB will need to take account of any additional research findings with regard to the relationship between CM and SM.

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