Short Communications

Foal immunodeficiency syndrome: carrier testing has markedly reduced disease incidence

S. D. Carter, L. Y. Fox-Clipsham, R. Christley, J. Swinburne

FOAL immunodeficiency syndrome (FIS), a fatal autosomal recessive disease found in three breeds of horses, was first reported (in the Fell pony) in 1996, and it soon became apparent that significant numbers of syndrome foals were being born each year. In each FIS case, the foals are clinically normal at birth, but start to weaken at 2–8 weeks (Scholes and others 1998) as they develop profound anaemia (Dixon and others 2000) and do not have the ability to produce their own antibodies (Thomas and others 2005), due to the almost total lack of B lymphocytes in the circulation or tissues (Thomas and others 2003), but with apparently normal levels of functional T lymphocytes (Bell and others 2001). The outcome is persistent opportunistic infections with no effective treatment; euthanasia is the preferred option. FIS has also been reported in Fell ponies in The Netherlands (Butler and others 2006), Germany (May and others 2011) and USA (Gardner and others 2006). In 2009, we confirmed a case of FIS in a Dales pony foal (Fox-Clipsham and others 2009).

The search for the genetic lesion thus became paramount, as the carrier parents were clinically normal, and it was feared that there could be high carrier rates in breeding Fell and Dales ponies. In 2009, we identified a single nucleotide polymorphism (SNP) in a sodium transporter (SLC5A3) which was completely associated with FIS and was homozygous in FIS foals and heterozygous in FIS carriers (Fox-Clipsham and others 2011a). The SNP is a functional alteration in an exon within the SLC5A3 gene, and within three months, we developed and launched a diagnostic test (available at http://www.animaldnadiagnostics.co.uk) based on PCR and sequencing to identify FIS carriers and early syndrome foals. This was made available to all equine owners and can be performed simply on pulled hair samples, removing the need for blood sampling.

The acquisition of the FIS test meant that we could identify carriers and make recommendations concerning the possible outcomes of specific breeding combinations, for instance, a carrier breeding with a normal pony, or two carriers breeding together. We regularly met with Fell and Dales pony owners to explain how they should use the FIS test to avoid producing a syndrome foal, and stressed the need to use the FIS test to avoid carrier-carrier matings. Concerns about depletion of the gene pool in pony breeds were soon quelled once it was explained that they could still safely use carrier ponies to breed with normal ponies. Indeed, it was pointed out that owners and breeders actually needed to widen their use of stallions to reduce the numbers of FIS foals and to preserve the gene pool.

In the first year of testing, our fears were confirmed when the FIS carrier rates were shown to be 39 per cent in breeding Fell ponies and 18 per cent in breeding Dales ponies. Broadening the testing to other at-risk breeds (known to crossbreed with Fell and Dales ponies), showed that 1 per cent of a coloured pony population were carriers (Fox-Clipsham and others 2011b). There may be other breeds containing FIS carriers; only further population testing will confirm or deny this possibility.

The next key question was how effective the carrier test would be in reducing the numbers of FIS foals being born in subsequent years. There have now been two breeding seasons (2011 and 2012) prior to which the owners could avail themselves of the test and avoid carrier-carrier matings. The test findings (Table 1) provide considerable hope for the future.

The FIS carrier rate in breeding adult Fell and Dales ponies varies over the three years of testing, but this variation was statistically significant (X^2(2df) p=0.3, and Fisher's Exact Test p=0.6, respectively). Importantly, there was a lower number of FIS-positive (diseased) Fell pony foals in 2011 and 2012 (although this only approached statistical significance (X^2(2df) p=0.1, X^2 for trend (1df) p=0.08) and no FIS cases in Dales ponies in 2011 or 2012. Obviously, the datasets may be skewed because of the animals selected for testing, which may introduce some bias. However, as many carriers will have been identified previously from breeding records, there is no reason to suppose that FIS-positive breeding stock would be preferentially submitted.

It is clear that the owners and breeders have taken the advice we provided about avoiding carrier-carrier matings, and that this has led to a major reduction in the number of syndrome foals born in the last two years. Although the definitive figures are not available, the total number of breeding Fell ponies that have been FIS tested in the last three years (n=1171) comprise a large proportion of the breeding population, and the testing has been done to guide breeding strategies. By the same measure, the 284 Dales ponies tested represent a large part of the breeding population of that breed.

Predictably, our breeding recommendations to use carrier-clear matings have not had a rapid impact on the large numbers of FIS carriers in the breeding populations of both breeds. Reducing car-

TABLE 1: Foal immunodeficiency syndrome (FIS)-positive test results in Fell and Dales ponies (adults and foals) (N/A=not applicable)

	Year	Number tested	Normal (%)	FIS carriers (%)	FIS diseased (%)
(A) Fell ponies					
Adults	2010	565	290 (51)	275 (49)	N/A
	2011	179	103 (58)	76 (42)	N/A
	2012	106	60 (57)	46 (43)	N/A
Foals	2010	142	72 (51)	58 (41)	12 (8)
	2011	108	60 (56)	39 (36)	9 (8)
	2012	71	32 (45)	38 (54)	1 (1)
(B) Dales ponies					
Adults	2010	180	158 (88)	22 (12)	N/A
	2011	53	44 (83)	9 (17)	N/A
	2012	36	32 (89)	4 (11)	N/A
Foals	2010	10	9 (90)	0 (0)	1 (10)
	2011	4	3 (75)	1 (25)	0 (0)
	2012	1	1 (100)	0 (0)	0 (0)

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rier numbers will either take much longer using the current breeding approach, or a change in breeding strategy to avoid breeding from carriers at all. With the carrier rate so high in the Fell ponies, such a restrictive recommendation would probably be unacceptable to many breeders, and would risk depleting the gene pool. On the other hand, the breeders who choose carrier-clear matings will need to test their offspring to see if their foal is a carrier.

The results are consistent with uptake of the FIS carrier test by the owners of at-risk ponies, and suggest that they have also taken our advice about breeding strategies to reduce the numbers of FIS-positive foals. This is a significant and swift impact of modern genomic technologies in clinical veterinary medicine, and is a healthy indicator of veterinary scientists and animal breeders working well together to improve animal welfare.

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