

## A review of scientific literature on inherited disorders in domestic horse breeds

CD Bettley<sup>†</sup>, JM Cardwell<sup>‡</sup>, LM Collins<sup>§</sup> and L Asher<sup>\*#</sup>

<sup>†</sup> Preston Vets4Pets, 90 Moor Lane, Preston, Lancashire PR1 1JQ, UK

<sup>‡</sup> Veterinary Epidemiology and Public Health, The Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Herts AL9 7TA, UK

<sup>§</sup> Queen's University Belfast, School of Biological Sciences, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, UK

<sup>#</sup> School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington Campus, Loughborough, Leicestershire LE12 5RD, UK

\* Contact for correspondence and requests for reprints: lucy.asher@nottingham.ac.uk

### Abstract

The full extent to which inherited disorders occur in different breeds of domestic horse (*Equus caballus*) has not been previously investigated. A systematic search was carried out to review scientific literature on inherited disorders in domestic horse breeds and examine patterns in potentially inherited disorders. A two-part search was conducted: (i) electronic bibliographic databases for published studies; and (ii) existing online databases of inherited disorders in animals. A total of 230 papers were identified, discussing 102 inherited disorders in the horse. Few cases (17) were found in which disorders were reported to have a direct link to a conformational or phenotypic trait. Forty-nine breeds of domestic horse were described as being predisposed to one or more inherited disorders, but such predispositions did not distinguish between genetic or environmental causes. There were few patterns in the number of disorders to which breeds were reportedly predisposed or in the extent to which disorders were researched. The structure and grouping of disorders presented here could assist with standardisation in the terminology used for describing inherited disorders.

**Keywords:** animal welfare, breed, disease, horse, inherited defect, quality of life

### Introduction

It has been claimed that the horse has a low incidence of inherited disorders compared to some other domestic species such as the dog (Graves 2005). However, the full extent to which such disorders occur in domestic horse breeds (*Equus caballus*) has not been investigated. Breeding practices associated with the occurrence of inherited disorders in dogs, such as inbreeding, using small numbers of founding individuals and closed-stud systems (Bateson 2010), are also found in horse breeding (Cunningham *et al* 2001; Swinburne 2009). It appears that selection for aesthetic qualities is becoming more valued in the breeding of some domestic horse breeds. For example, categories at horse shows judged on aesthetic characteristics ('halter' or 'in-hand' showing) have increased in recent years with the Royal Windsor Horse Show introducing six new 'in-hand' classes for 2010. The selection of many horse breeds is still primarily on the basis of function, although selection can be based on the qualities of young animals (for example in thoroughbred and futurity racing).

### The impact of inherited disorders

Inherited disorders can compromise the quality of life and well-being of the horse. We define an inherited disorder as a condition resulting in, or predisposing to, a disturbance of normal functioning for which (at least in part) there is a genetic basis. The extent of disturbance is variable. Some conditions have relatively mild or transient consequences, for example most foals with narcolepsy or cataplexy may suffer just a few episodes early in life (MacKay 2005). Animals with an XX or XY sex reversal may suffer no impact aside from an inability to reproduce. Other disorders can cause long-term impairment of health or even death, either as a direct result of the condition or because the animal is euthanased. For example, Severe Combined Immunodeficiency (SCID) is a fatal disease in foals that causes a complete failure of antibody production and defective cell-mediated immunity (Finno *et al* 2009). Affected foals are likely to suffer the effects of several infectious diseases, often involving the respiratory tract and accompanied by secondary bacterial infections (Finno *et al* 2009), before the condition is diagnosed and they are euthanased.

## Breeding and inherited disorders

Several practices that have been used by horse breeders, such as closed-stud books, inbreeding, selective breeding and the repeated use of popular sires, are associated with increases in inherited disorders. For instance, inbreeding results in increased homozygosity and increased likelihood of inheriting an autosomal recessive disorder (Gough & Thomas 2010). A 'founder effect' can be seen in several horse breeds in which large proportions of individuals have a common ancestor which carried a mutant allele. For example, quarter horses can be traced back to Impressive, a stallion who carried the hyperkalaemic periodic paralysis (HYPP) mutation (Naylor *et al* 1992). Extensive breeding from this foundation sire's offspring has propagated the mutation.

## Reviews of inherited disorders

Despite the number of inherited disorders affecting horses and research on specific inherited disorders, there has been a paucity of work in this department. Where reviews have been conducted, they have not attempted to exhaustively cover all potentially inherited disorders in the horse, or to systematically categorise these. Reviews of inherited disorders in the horse have been based on whether the genetic mechanisms are well understood (eg Bannasch 2008; Finno *et al* 2009), or on whether a particular body system is involved (Aleman 2008).

Aleman (2008) recently reviewed equine muscle disorders, including those that are hereditary such as hyperkalaemic periodic paralysis (HYPP), malignant hyperthermia and glycogen-branching enzyme deficiency (GBED). Finno *et al* (2009) conducted a review of equine diseases caused by known genetic mutations and summarised the clinicopathological and genetic features of each disease. Emphasis was placed on the prevalence, clinical signs, aetiology, diagnosis, treatment and prognosis of: equine polysaccharide storage myopathy (EPSSM); GBED; hereditary equine regional dermal asthaenia (HERDA); HYPP, junctional epidermolysis bullosa (JEB); lethal white foal syndrome (LWFS); malignant hyperthermia; and SCID. Bannasch (2008) similarly covered disorders due to known genetic mutations, and with a focus upon genetic testing.

Here, a systematic search strategy was used to objectively review the scientific literature on inherited disorders in domestic horse breeds. We conducted a two-part search of: (i) electronic bibliographic databases for published studies; and (ii) existing online databases of inherited traits in animals. The aims were: to produce a comprehensive list of disorders that may be inherited in horses; to look for clusters or patterns in the disorders identified; and to assess the extent to which these disorders have been studied and the causes of variation in this.

## Materials and methods

### Literature search

Online bibliographic databases (PubMed and Web of Science) were searched for papers indexed between January 1997 and April 2009. An online database of inherited

disorders in animals (Online Mendelian Inheritance in Animals 2009) was also searched for relevant references. Citations of each paper or reference found were screened, and those meeting the inclusion criteria retained. The criteria for inclusion of references were that they should be of peer-reviewed scientific publications, conference papers, or non-peer-reviewed expert opinion articles (eg from *In Practice*) that made reference to at least one inherited disorder in the horse. The search strategy was designed to include less common disorders, and those into which primary research had been undertaken prior to January 1997. A breed was considered to be predisposed to a disorder if the literature: (i) contained evidence of an increased incidence or prevalence in the breed; or (ii) explicitly stated there was a breed predisposition or increased susceptibility and included a supporting citation. Literature concerning 'congenital' disorders for which a genetic or inherited component was not specifically referred to was excluded. Disorders induced as models of human disease were excluded, as were single-case reports and papers not available in English. The review covered all breeds of domestic horse listed by the Oklahoma State University 'Breeds of Livestock' project (Desilva & Fitch 1995) with additional breeds identified by initial literature searches were incorporated for completeness.

As outlined above, a systematic search of the scientific and veterinary literature was conducted, using the online bibliographic databases and using the following combinations of search criteria:

[INHERITED] AND...

...[HORSE], [Breed name], [Type name],

[CONGENITAL] AND...

...[HORSE], [Breed name], [Type name]

[GENETIC] AND...

...[HORSE], [Breed name], [Type name], [Disease name]

[Disease name] AND...

.... [Breed name], [Type name]

[HEREDITARY] AND...

...[HORSE], [Breed name], [Type name], [Disease name]

[FAMILIAL] AND....

...[HORSE], [Breed name], [Type name], [Disease name]

[Breed name]

[Type name]

[Disease name]

Where available, information was extracted from each paper on: the country in which the study was conducted; the type of disorder; the breed(s)/type(s) of horse affected/predisposed; the body system primarily affected; mode(s) of inheritance; age of onset; the prevalence in each breed or the horse population as a whole; details relevant to prognosis; and on any related disorders. No judgement was made on the quality of the information extracted or on the strength of the evidence provided for disorders being inherited.

### Categorising disorders

Disorders were classified according to available evidence into the following groups: Conformation or phenotype related disorders (C) — those reported to result directly from selection for a conformational or phenotypic trait, including coat colour; Not conformation related disorders (D) — those for which there was no evidence of a direct link with conformation.

Disorders were each also classified into one of the following ten ‘body system’ categories: behavioural, cardiovascular, gastrointestinal, immune, integument, musculoskeletal, nervous or sensory, respiratory, urogenital, and multi-system. The body system was selected based on the primary area affected by the disorder.

Conditions were treated as one disorder if the reported names were considered to be synonyms by the authors. There was wide variation in the description of disorders between papers. In some cases, description of a general disorder would overlap with specific disorders also covered by this review. To deal with this and avoid disorders being counted more than once, disorders were further classified according to whether they were: (i) specific (S), referring to a defined disorder with a unifying aetiology and/or pathogenesis; or (ii) broad (B), potentially referring to multiple specific disorders. Where appropriate, specific disorders were grouped under a broader disorder but only the specific disorders were counted in determining the number of inherited disorders and in statistical analysis. Where information was available, disorders were also categorised according to the mode of inheritance and age of onset (see Table 1).

Horse breeds were categorised according to mean height as follows:

- Pony and miniature — less than 14 hands 2 inches, or described as miniature;
- Short — more than 14 hands 2 inches to 15 hands 2 inches;
- Medium — more than 15 hands 2 inches to 16 hands 2 inches; and
- Tall: more than 16 hands 2 inches.

Breed popularity was assessed separately using two sources: first, the current UK population size of each breed from the National Equine Database (2009); and second, according to their ranking on an online guide to world horse breeds (Horse Tradition 2007).

### Prognosis score

A prognosis score similar to that developed for scoring disorders in dogs (Asher *et al* 2009) was used (Figure 1). The score ranged from 0 (representing a short isolated bout and complete return to normal) to 4 (imminent death as a direct result of the condition, or condition-related euthanasia) and it was assigned based on information available in the published literature. When scoring disorders for prognosis it was assumed that appropriate treatment and the highest quality care had been provided. Each disorder was scored in its mildest and most extreme forms to allow for ranges of severity.

**Table 1** Categorisation for information on mode of inheritance and age of onset.

Area of interest	Category
<b>Mode of inheritance</b>	Autosomal recessive
	Autosomal dominant
	X-linked
	Co-dominant
	Polygenic
	Mixed
<b>Age of onset</b>	<i>In utero</i> or at birth
	< 1 year
	1 to 5 years
	5 to 10 years
	> 10 years

### Statistical analysis

The data were used to derive information on: (i) the number of disorders reported per breed, using each breed as a unit for analysis; and (ii) on the number of publications identified on each disorder, using each disorder as a unit for analysis.

Spearman’s correlations were used to test for associations between the number of disorders per breed and the breed popularity (according to UK and worldwide figures). Kruskal-Wallis tests were used to explore relationships in each breed between height and number of disorders. A binary logistic regression model was used to explore the presence or absence of C disorders for each breed and in relation to the mean height of the breed.

Kruskal-Wallis tests were used to explore differences between breeds in the ‘body system’ affected, mode of inheritance, age of onset and prognosis. Categories were combined when there were few cases available for analysis. Associations between disorder category (C or D) and the number of publications were investigated using Mann-Whitney *U*-tests. Spearman’s correlations were used to examine the relationship between the number of publications found on each disorder and the number of breeds affected by that disorder and on the prevalence of the disorder in the breed (based on the maximum prevalence reported for that disorder).

Where appropriate, the Bonferroni correction for multiple testing was applied and the level of statistical significance was set at  $P < 0.05$ . Non-significant results are not reported.

### Results

Forty-seven of 221 (21.2%) breeds worldwide were described in the scientific literature as being predisposed to one or more inherited disorder. A comprehensive table of disorders related to these breeds, genetic information, prevalence, age of onset and prognosis is presented at the supplementary material to papers published in *Animal*

Figure 1

0	1	2	3	4
Short isolated bout and complete return to normal	Medium length isolated bout or successive short bouts, and return to normal	Extended bout and return to normal or successive short bouts and minor long-term impairments	Unremitting or chronic illness or bout(s) with major long-term impairment	Imminent death as a direct result of condition or condition-related euthanasia

Prognosis score (part of the Generic Illness Severity index for dogs; Asher et al 2009).

**Table 2 Spearman's correlations between the total number of disorders affecting each breed, and the worldwide popularity (Horse Tradition 2007; n = 36) and UK numbers of those breeds (National Equine Database 2009; n = 47).**

	Worldwide popularity rank		UK numbers	
	$\rho$	P	$\rho$	P
Total S disorders per breed	-0.644	< 0.001	0.420	0.04

Table shows correlation parameter rho ( $\rho$ ) and P-value.

Welfare section at the UFAW website; <http://www.ufaw.org.uk/supplementarymaterial.php>. A total of 230 papers published between January 1997 and April 2009 were found that included information on 102 distinct breed-related inherited disorders in the domestic horse. The 102 disorders identified were categorised into 17 conformation or phenotypic related (C) and 85 non-conformational (D) disorders, and also into 89 specific (S) and 13 broad (B) disorders. There were 14 SC disorders, 75 SD disorders, 3 BC disorders and 10 BD disorders.

Of the 17 disorders which were reported to be related to a conformational or phenotypic trait, 10 were related to pigment (mostly coat colour), four were related to body shape and four were related to height. Disorders linked with selection for a particular body shape affected the musculoskeletal system whereas disorders linked with pigment mostly affected nervous/sensory systems, and mostly comprised ocular disorders.

The 'body system' most affected by inherited disorders was the musculoskeletal system: 38 disorders primarily affect this. There were 22 disorders that primarily affect the 'nervous/sensory' body system, eight that affect the integument and urogenital systems, seven of the respiratory system, six of the cardiovascular, five of the gastrointestinal and four each relating to behavioural problems and to the immune system.

Information on mode of inheritance was reported in the literature for 33 disorders. Autosomal recessive was the mostly commonly reported (14) mode of inheritance, followed by autosomal dominant (10); polygenic (4); X-linked (3); co-dominant (1); and mixed (1). Age-of-onset data were found for 50 disorders. Thirty-two of the conditions surveyed are present from birth, seven develop within the first year, seven develop between 1 and 5 years of age and only one was reported to develop after 10 years of age. Prevalence estimates were found for 42 disorders. In some breeds, EPSSM, melanoma, Anterior Segment Dysgenesis and retained placenta affect more than 50% of animals. Only for one disorder, cleft palate, was the prevalence estimated to be less than 1%.

It was possible to assign a prognosis score to 34 disorders. Ten disorders were scored at 4, signifying imminent death as a direct result of the condition, or related euthanasia. Prognosis scores for a further 12 disorders ranged up to a maximum of 4. Ten disorders had a prognosis score lower than 3.

#### Disorders per breed

The five most popular pure breeds in the UK were the thoroughbred (334,964), Shetland pony (57,769), Welsh pony and horse (15,426), Highland pony (8,171) and fell pony (7,912) (NED 2009). The five most popular breeds worldwide, starting with the most popular, were the Arab, quarter horse, paint, miniature and thoroughbred, respectively (Horse Tradition 2007).

According to the results of the literature surveyed, the thoroughbred was predisposed to the highest number of inherited disorders (28), followed by the quarter horse (18), Arab (17) and miniature horse (9). Miniature horses were linked with four C disorders which was the highest in any breed.

There was no association between height at the withers and the number of disorders or C disorders. More popular breeds in the UK and worldwide were found to be linked to more disorders in the literature (see Table 2).



### Papers per disorder

The disorders about which there were the largest number of publications were: EPSSM (31 papers), followed by GBED and SCID (14 each), and HYPP and LWFS (13 each).

There were no associations between 'body system', mode of inheritance, age of onset or maximum prevalence estimates. The more papers found on each disorder the more breeds tended to be reportedly affected by it (Spearman's rho:  $\rho = 0.560$ ,  $n = 75$ ,  $P < 0.001$ ).

### Discussion

A total of 230 papers discussing 102 disorders that are thought to be inherited in the horse were identified. Most disorders were not linked with conformation (17/102 were conformation-related, 85/102 were not conformation-related). Forty-seven breeds of domestic horse were reportedly predisposed to one or more inherited disorders. Almost half (22/49) of the breeds identified as being predisposed to an inherited disorder were reported in the literature as affected by just one inherited disorder. By comparison, every one of the top 50 breeds of dog in the UK was reportedly predisposed to an inherited disorder, a total of 396 inherited disorders were identified in dog breeds and 63 were linked with conformation (Asher *et al* 2009; Summers *et al* 2010).

There were few cases where breeding for a specific aesthetic trait was apparently linked to an inherited disorder. Exceptions related to size (eg the miniature horse), or breeding for specific coat colours (eg grey in the Lipizzaner and Camargue breeds, silver in Rocky Mountain horses).

### Patterns in breed predispositions

The thoroughbred was the most popular purebred horse in the UK (NED 2009) and was ranked 5th in popularity worldwide (Horse Tradition 2007). The results indicate that the greater the popularity, in terms of worldwide ranking and the numbers in the UK, the greater the number of disorders a breed is reported to be predisposed to. It seems likely that this finding reflects a higher awareness of predispositions in popular breeds, through an increased frequency of presentation of these breeds to veterinary health professionals. Worldwide popularity results should be interpreted with caution since this was derived from the comparative ranking of all 6,831 sites hosted by horse breeders and horse-breed associations registered with the search engine Google in October 2007. We also noted that economically important breeds, such as the thoroughbred and the quarter horse appeared more often in the scientific literature with more reports of breed predisposition. No association was found between height and the number of disorders to which a breed was reportedly predisposed.

Breed predispositions in horses must be interpreted with caution. Breeds may be genetically predisposed to a condition (either directly or mediated by their conformation or phenotype), but they may also be predisposed due to environmental biases related to function. For example, breeds such as thoroughbreds may be more likely to have a disorder due to the stresses put upon certain muscles or

joints. Other environmental influences might be related to management practices, for example certain management practices, such as extended periods of stabling (McGreevy *et al* 1995), are risk factors for developing stereotypic behaviour (Luescher *et al* 1998). It is important in epidemiological studies investigating inherited disorders to attempt to separate genetic from environmental causes.

### Patterns in inherited disorder research

There were more inherited disorders identified that relate to the musculoskeletal system than to any other body system. These findings probably reflect the fact that horses are still primarily bred for physical performance; either because there has been more focus upon disorders which affect this system or because the expression of these disorders is greater due to demands on this system.

Disorders that were more frequently reported in the scientific literature, tended to affect larger numbers of breeds. The causal direction of this relationship is unclear. It may be that more breeds were identified as being affected because there had been more research into these disorders or, alternatively, that research has tended to be focused on disorders that affect more breeds.

The commonest mode of inheritance was autosomal recessive. Many of the conditions surveyed are evident at birth. If the mode of inheritance of these conditions has been correctly identified then this is an encouraging finding, as such conditions are potentially easier to reduce in a population than for instance polygenically inherited disorders.

In 2007, genome mapping was used to identify two new genetic mutations for HERDA and EPSSM. Following the development of tests for some genetic disorders, some breeders have begun to demand checks. In 1996, the American Quarter Horse Association (AQHA) officially recognized HYPP as a genetic disorder or undesirable trait. Mandatory testing for HYPP was instituted, and the AQHA later ruled that foals born in 2007 or later that tested homozygous for HYPP (H/H) would not be eligible for registration (AQHA 2009). However, whilst the number of inherited disorders for which diagnostic tests exist is increasing, the way in which these disorders are bred out of a population needs to be carefully considered. Some horse breeds with smaller populations may have a high prevalence of carriers, and excluding all carriers from the breeding population could have a deleterious effect on genetic diversity within the breed (Traas *et al* 2006; Bannasch 2008), unless there is out-crossing with other breeds.

Overall, we found that there was a lack of reliable, country-specific data on the prevalence of inherited diseases in horses. Prevalence data were available for just 40 of the disorders. There was also little information available for prognostication and the quality of information was variable. The potential benefits of research in this field will be maximised if standard terminology is used in describing disorders. Disparities in terminology and case definitions between papers represented one of considerable challenges for this study. We attempted to group disorders

according to shared aetiology and/or pathogenesis. It is hoped that this structure may prove useful in standardised reporting of disorders in future publications. In this context, the terms for each disorder listed first in the table of inherited disorders may prove helpful (see supplementary material), alternatively, confusion could be avoided by listing known or commonly used synonyms (also identified in the supplementary material).

### Animal welfare implications

Animal welfare is compromised in animals suffering from inherited disorders to a greater or lesser extent. Many of the inherited disorders reviewed here cause pain and distress, and in some cases this can be severe. To assess the extent of the welfare impacts in detail, a generic severity scoring system would need to be developed, similar to that developed for dogs (Asher *et al* 2009; Summers 2010), and used with prevalence estimates (Collins *et al* 2010) and data on the age of onset and the duration of the conditions (Collins *et al* 2011). Selective breeding provides an opportunity to minimise inherited disease in a population either through breeding animals with a phenotype which is less likely to result in disease, or through breeding practices which select against inherited disease. It is important that such breeding practices be employed to prevent inherited disorders being perpetuated through future generations of horses.

### Conclusion

A total of 230 papers discussing 102 potentially inherited disorders in the horse were identified. Few disorders were linked specifically with conformation or phenotype. Forty-seven breeds of domestic horse were reportedly predisposed to one or more inherited disorders, but such predispositions may have been genetic or environmental.

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