Estimates of heritability of atrial fibrillation in the Standardbred racehorse

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Summary

Background: The number of Standardbred racehorses admitted to the Ontario Veterinary College Teaching Hospital (Guelph, Canada) for treatment of atrial fibrillation (AF) has been on the rise since the early 1990s. A small number of sires have been contributing to a large proportion of cases, indicating there may be a genetic predisposition to the arrhythmia in this breed.

Objectives: The objectives of this study were to determine the heritability of AF in Standardbred horses and whether heritability of the arrhythmia differs across gait[s] and/or sexes.

Study design: Heritability study based on retrospective review of clinical records and publicly available pedigree and racing records.

Methods: Standardbred horses admitted to hospital for treatment of AF that were born between 1978 and 2007 comprised the affected case population (n = 204). Five randomly selected racing contemporaries for each case, assumed to not suffer from the arrhythmia, comprised the control population (n = 1017). Racing contemporaries were identified by examining the race records of affected horses within the 6 months prior to their admission, and randomly selecting sex- and gait-matched horses from these races. Heritability was estimated from the sampled horses as a whole (n = 1221), as well as for both sexes and gait[s], using a generalised linear mixed model.

Results: Heritability of AF on the underlying liability scale was estimated to be (±s.e.) 0.30±0.04 in the entire data set; 0.30±0.06 in males; 0.24±0.08 in females; and 0.32±0.05 in pacers. After conversion to the observed scale, heritability estimates were 0.14, 0.15, 0.09 and 0.15, respectively.

Main limitations: There were insufficient data to estimate heritability of AF for trotters.

Conclusions: Modest heritability estimates were found for AF in the Standardbred horse, particularly in males and pacers, which support the hypothesis that there is a genetic contribution to the arrhythmia in this breed.

The Summary is available in Chinese – See Supporting Information.

Keywords: horse; cardiac arrhythmia; equine diseases; genetic parameters

Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in the horse [1], and also affects man [2], cattle [3], dogs [4] and cats [5]. It is particularly prevalent in the young Standardbred racehorse [6]. The incidence of AF in horses has been estimated from as low as 0.09% in Thoroughbred racehorses [7], up to 2.27% in a hospital referral population [8], although the amount of available research is small. There are no available data on the true incidence of this arrhythmia in the horse in general.

Much of the current research into human AF addresses its genetic background, as the arrhythmia has a tendency to appear in a familial setting [9,10]. Young male athletes also seem to be more highly susceptible to the arrhythmia [11,12]. A study in Danish twins has estimated the heritability of AF in humans at 0.62 [13]. However, there is limited information about genetic parameters of AF in horses. It has been observed that AF appears to have a familial component in the Standardbred horse [6], and an observed heritability of 0.096 has recently been reported with a preponderance of pacing sires being incriminated [14]. Some equine studies also report more affected males than females [14,15], while trotting and pacing lines are quite genetically distinct despite being from the same breed [16]. Assessment of the effects of sex and gait on heritability is required to form a more complete picture of genetic liability to AF in the Standardbred horse. The objectives of this study were: 1) to reassess the heritability of AF in the Standardbred racehorse using a different control cohort; and 2) to determine if estimates of heritability of AF in Standardbred differ across gait[s] and/or sexes.

Material and methods

Selection of case and control populations

The population of case animals has been described previously [14]; however, the contemporary control group was different, consisting of 5 horses for each case. The affected case population consisted of 204 Standardbred horses admitted to and treated at the Ontario Veterinary College Teaching Hospital diagnosed with AF and born between 1978 and 2007. The control group was generated by examining race records for all cases for races performed within the 6 months prior to their admission, and then randomly selecting 5 sex- and gait-matched racing contemporaries from these races using a random number generator. If a selected contemporary was already present in the case population, a different randomly selected contemporary was used instead, leading to a control population of 1019 horses. Thus, the sum of affected and control groups was 1223 horses. Since Standardbred horses compete at 2 different gaits, the pace and the trot, and at younger ages usually compete against horses of the same sex, producing the contemporary groups in this manner took into account differences in the population as a whole due to gait, age and sex. Also, with the possibility of some bloodlines being more local to one racing district than another, and the popularity of lines varying with time, racing contemporaries should be similar to affected horses in their breeding. Racing contemporaries were assumed to not have suffered from an instance of AF.

A small number of individuals compete at both the pace and trot [17], and a small portion of the affected and control racehorses in this study were identified in this manner by Standardbred Canada. It has been...
observed that pacers and trotters tend to come from distinct ancestral lines [16], so an attempt was made to determine which gait these horses would be expected to compete at based on the gait of their 6 closest ancestors, and thus include them in that category for each analysis. The ancestry for 2 racehorses in the control population was mixed across both gaits to such a point that no tendency towards one gait or the other could be deduced. These individuals were excluded from all analyses, resulting in 1017 control horses and 1221 horses overall. A detailed account of the number of Standardbred racehorses admitted for treatment per year, and their racing contemporaries, which make up the control population used, is given in Supplementary Item 1.

Heritability analyses

In order to determine the amount of phenotypic variability in a population that is due to the underlying genetic variability, one can measure the heritability of a trait through population genetics [18,19]. It had been observed with the case population that a small number of sires contributed to a large proportion of the disease cases (Fig 1). Therefore, in order to evaluate the possibility of a genetic basis for AF in the Standardbred, the estimated heritability of the arrhythmia is a relevant parameter.

The pedigree for all 1221 horses was available and was composed of 12,071 individuals in total. Most diseases are considered to be threshold, or “all-or-none” traits, with an individual expressing the disease phenotype only when environmental and genetic effects combine to cross a threshold on an underlying normal curve of disease liability [20–22]. Consequently, information on disease status was added to the data provided by Standardbred Canada for the affected and control racehorses. The information was then analysed with the ASReml software package [23], using a generalised linear mixed model with a probit link function to estimate the underlying heritability of AF in the Standardbred. The complete generalised linear mixed model used included the effects of sex (male or female), gait (pace or trot), and the random additive effect of the horse. The additive genetic relationships among horses, derived from the known relevant pedigree, were fit into the model. The generalised linear mixed model fit using a probit link function allowed the calculation of heritability on an underlying normal liability scale. The advantage of working on the liability scale is that population parameters, such as variance components and corresponding heritability, are independent of the disease incidence [24]. The estimated expected heritability on the observed binomial scale was then obtained for different possible incidence rates of the disease in the population, using a simple transformation [20,21].

Heritability was obtained for the whole dataset, as well as when stratifying based on sex and/or gait. When estimating heritability of AF in pacers or trotters only, gait was removed from the model described above. While estimating heritability of AF in males or females only, sex was removed from the model. In the full model, sex had a highly significant effect ($P<0.001$) on AF, while gait did not reach the significance threshold ($P = 0.2$). Year of birth was also included in the full model in a preliminary analysis, but was dropped from subsequent analyses, because it explained very little variation in AF ($P>0.9$). Fixed effects in the models (i.e. sex, gait and year of birth) were tested using Wald F statistics for general linear mixed models [24].

Results

Numbers of affected and control racehorses for each stratification are detailed in Table 1. For the complete model, AF was estimated to have a heritability of 0.30±0.04 on the underlying scale, and 0.14 on the observed scale. When investigating only male horses, heritability was 0.30±0.06 on the underlying scale and 0.15 on the observed scale. There were only 8 affected female trotters in the case population, therefore gait was removed from the model in order to evaluate heritability of AF in females. This was estimated at 0.24±0.09 on the underlying scale, and 0.09 on the observed scale. The heritability of AF in pacers was estimated to be 0.32±0.05 on the underlying scale and 0.15 on the observed scale. Due to the low number of trotters, it was not possible to estimate heritability within this gait alone. This resulted in an estimate of 0.24±0.09 on the underlying scale, and 0.10 on the observed scale for female pacers. A higher estimate of heritability was found in male pacers at 0.31±0.06 on the underlying scale and 0.17 on the observed scale. It is noteworthy that the 95% confidence interval for all the heritability estimates overlapped, reflecting the associated relatively large standard errors of the heritability estimates. Complete heritability results can be seen in Table 2.

Fig 1: Total number of cases per year of Standardbred racehorses admitted to the Ontario Veterinary College Teaching Hospital for treatment of atrial fibrillation since 1991, and number of cases sired by 5 frequently occurring stallions.

TABLE 1: Stratifications for which heritability of atrial fibrillation in Standardbred racehorses could be estimated, and the number of affected, control and total horses used for each

<table>
<thead>
<tr>
<th>Stratification</th>
<th>Affected</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All horses</td>
<td>204</td>
<td>1017</td>
<td>1221</td>
</tr>
<tr>
<td>Males</td>
<td>140</td>
<td>527</td>
<td>667</td>
</tr>
<tr>
<td>Females</td>
<td>64</td>
<td>490</td>
<td>554</td>
</tr>
<tr>
<td>Trotters</td>
<td>24</td>
<td>293</td>
<td>317</td>
</tr>
<tr>
<td>Pacers</td>
<td>180</td>
<td>724</td>
<td>904</td>
</tr>
<tr>
<td>Male pacers</td>
<td>124</td>
<td>372</td>
<td>496</td>
</tr>
<tr>
<td>Female pacers</td>
<td>56</td>
<td>351</td>
<td>407</td>
</tr>
</tbody>
</table>

Estimates of heritability on the observed scale when considering different possible incidence rates of the disease in the population are also presented in Table 2, as the true incidence of this disorder in Standardbred horses is not known and would influence the observed scale heritability. When considering different proportions of affected individuals (1, 5, 10, 15 and 20%), the heritability estimates in the observed scale ranged from 0.02 to 0.15, 0.02 to 0.14, 0.02 to 0.12 and 0.02 to 0.15 for all the animals, males, females and pacers, respectively (Table 2).

A small number of stallions have contributed frequently to the number of disease cases over time. As seen in Table 3, of the 94 stallions with offspring in the affected population, 5 had 6 or more offspring in the affected population. Figure 1 details the distribution of the affected offspring of these 5 stallions in comparison to the total number of affected Standardbred horses admitted to Ontario Veterinary College Teaching Hospital born from 1991 to 2007.

Discussion

Estimating the heritability of liability to diseases assumes that the general population has an underlying normal distribution of liability, with the liabilities of all diseased individuals being greater than the liability threshold. Relatives of diseased individuals also have an underlying liability distribution with a variance equal to that of the general population [25]. The underlying, normally distributed liability results from a combination of effects caused by a variety of genes and random environmental components [26]. According to Meuwissen et al. [27], many traits, including diseases, are recorded in discrete categories (affected, unaffected), and a probit function links the underlying linear predictor to the expected value of the data. The probit link method is commonly used to estimate heritability of health or fitness traits on an underlying scale before conversion to the observed scale.

Most estimates of heritability in the Standardbred available in the literature focus on performance parameters such as earnings or number of wins as opposed to fitness traits. Philipsson et al. [28] investigated osteochondrosis in the hock and osteochondral fragments in the fetlocks of Standardbred trotters, and reported heritability estimates of 0.08 to 0.09 on the observed scale. Heritability of lameness in 3-year-old Standardbred trotters was estimated to be 0.33 using linear approximation of a binomial analysis [29].

Despite extensive human research, the only estimate of heritability of AF that could be found in the literature was reported by Christophersen et al. [13], who estimated the observed heritability of AF at 0.62, with little difference between men and women. While male pacers appeared to have higher heritability than female pacers, this does not necessarily indicate sex linkage of AF, since sex may influence the manner in which environmental effects influence the liability threshold for the arrhythmia. Due to the low number of trotters, it was not possible to estimate heritability within this gait alone. As the heritability estimate of AF in pacers was higher than the overall heritability estimate, this might suggest that the heritability of AF in trotters would be lower than in pacers.

No prior estimates of heritability in the Standardbred or the horse in general were found, except the observed heritability estimate of 0.096 in Physick-Sheard et al. [14], which used the same set of affected horses, but different control horses and estimation model, and did not account for possible gait and sex differences. It is noteworthy that Physick-Sheard et al. [14] did not find any evidence that inbreeding would play a role in liability for AF in Standardbred horses.

Estimates of heritability of AF on the observed scale were reasonably high for a disease trait, with all estimates ranging from 0.09 to 0.17. The majority of diseases in the horse are likely to involve many genes and environmental interactions [19]. According to Visscher et al. [22], a low heritability is typical of fitness-related traits, not necessarily indicating a small additive genetic variance, but rather being indicative of a proportionally larger environmental variance. This is encouraging for the possibility of future attempts to decrease the incidence of the arrhythmia in the population. Our findings highlight the genetic background of this disease, which could enable horse owners to make a more informed decision whether or not to use a horse for breeding when the horse’s disease status is known, with an aim to decrease the incidence of AF in the Standardbred population. In the future, if a continuous and consistent recording of AF cases is established, breeding values could be estimated to aid the selection of breeding horses against AF.

TABLE 2: Estimates of heritability of AF in the Standardbred racehorse on the underlying scale (h²_u), with corresponding standard error (s.e.) and 95% confidence interval (95% CI), and proportion of affected horses (p) used to determine heritability on the observed scale (h²_o).

<table>
<thead>
<tr>
<th>Stratification</th>
<th>h²_u</th>
<th>s.e.</th>
<th>95% CI</th>
<th>p</th>
<th>h²_o</th>
<th>h²_o=0.01</th>
<th>h²_o=0.05</th>
<th>h²_o=0.10</th>
<th>h²_o=0.15</th>
<th>h²_o=0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.30</td>
<td>0.04</td>
<td>0.22-0.38</td>
<td>0.17</td>
<td>0.14</td>
<td>0.02</td>
<td>0.07</td>
<td>0.10</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>Males</td>
<td>0.30</td>
<td>0.06</td>
<td>0.18-0.42</td>
<td>0.21</td>
<td>0.15</td>
<td>0.02</td>
<td>0.07</td>
<td>0.10</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>Females</td>
<td>0.24</td>
<td>0.08</td>
<td>0.08-0.40</td>
<td>0.12</td>
<td>0.09</td>
<td>0.02</td>
<td>0.05</td>
<td>0.08</td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>Trotters</td>
<td>0.32</td>
<td>0.05</td>
<td>0.22-0.42</td>
<td>0.20</td>
<td>0.15</td>
<td>0.02</td>
<td>0.07</td>
<td>0.11</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>Pacers</td>
<td>0.31</td>
<td>0.06</td>
<td>0.19-0.43</td>
<td>0.25</td>
<td>0.17</td>
<td>0.02</td>
<td>0.07</td>
<td>0.11</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>Male Pacers</td>
<td>0.24</td>
<td>0.09</td>
<td>0.06-0.42</td>
<td>0.14</td>
<td>0.10</td>
<td>0.02</td>
<td>0.05</td>
<td>0.08</td>
<td>0.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Analysis did not converge for Trotters, probably due to the small sample size.
In the current study an observed heritability of 0.134 was estimated across gait and sexes for a 16.7% incidence of AF in the dataset. Table 2 provides the expected heritability for different possible levels of true incidence of AF in the horse population. If the true incidence was, for instance, 1% then the observed heritability would be expected to be 2% for the same underlying estimated heritability.

Looking at the pedigree of the 5 stallions with most affected offspring in the control group revealed that stallion ID1 is, in particular, highly represented, having sired close to half of the affected horses born in 2003, and 24 case horses overall, despite only having entered stud in 2001. It should be noted that among these 5 sires, not only is stallion ID4 the sire of ID1, his maternal grandsire is also the sire of the dam of stallion ID3, while stallions ID4 and ID2 share a great-grand sire. An increased incidence among relatives does not, however, provide a clear measure of heritability, since differences in incidence (phenotypic expression) have no simple genetic interpretation [30]. This is in contrast to the underlying liability, which provides a better assessment of the relative importance of genetic inheritance and environment [30]. Therefore, the existing pedigree relationships among affected individuals are an additional indication of a genetic background for AF in Standardbred horses.

Conclusions

Atrial fibrillation seems to be a moderately heritable arrhythmia in Standardbred horses, with possibly larger heritability estimates in males and pacers. A small group of sires showing a disproportionate number of affected offspring in the case group also had close genetic relationships. These results are indicative of a genetic component to AF in Standardbred horses, which enables owners to make a more informed decision about whether or not to use a horse for breeding when the horse’s disease status is known, with an aim to decreasing the number of Standardbred horses at risk of developing the arrhythmia.

Authors’ declaration of interests

The authors declare that there are no competing interests.

Ethical animal research

The authors have confirmed that no Animal Care Committee approval was necessary for this particular study, as all information required was obtained from an existing database. Owner informed consent has been obtained to use the dataset, via the breeders’ association.

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Authorship

M. Kraus participated in the design of the study, carried out the analyses and interpretation results, was involved in the discussions, and prepared and drafted the manuscript. P. Physick-Sheard and F. Schenklen participated in the design of the study, were involved in the discussions, helped to draft the manuscript and in the data acquisition. F. Schenklen also helped in the data analyses. L. Brito helped with the interpretation of results and manuscript preparation. All authors have read and approved the final manuscript.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Summary in Chinese.

Supplementary Item 1: Year of admission to Ontario Veterinary College Teaching Hospital for Standardbred racehorses affected with AF. Admissions data are broken down into affected Standardbreds (A) or randomly selected racing contemporaries used in the control population (C); male (M) or female (F); pacer (P) or trotter (T).