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Preliminary genetic analyses of important musculoskeletal conditions of Thoroughbred racehorses in Hong Kong

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ABSTRACT

A retrospective cohort study of important musculoskeletal conditions of Thoroughbred racehorses was conducted using health records generated over a 15 year period ($n = 5062$, 1296 sires). The prevalence of each condition in the study population was: fracture, 13%; osteoarthritis, 10%; suspensory ligament injury, 10%; and tendon injury, 19%. Linear and logistic sire and animal regression models were built to describe the binary occurrence of these musculoskeletal conditions, and to evaluate the significance of possible environmental risk factors. The heritability of each condition was estimated using residual maximum likelihood (REML). Bivariate mixed models were used to generate estimates of genetic correlations between each pair of conditions.

Heritability estimates of fracture, osteoarthritis, suspensory ligament and tendon injury were small to moderate (range: 0.01–0.20). Fracture was found to be positively genetically correlated with both osteoarthritis and suspensory ligament injury. These results suggest that there is a significant genetic component involved in the risk of the studied conditions. Due to positive genetic correlations, a reduction in prevalence of one of the correlated conditions may effect a reduction in risk of the other condition.

Introduction

Musculoskeletal conditions and injuries (MSC) are commonly encountered in Thoroughbred racehorses worldwide. Their prevalence tends to exceed that of cardiac problems and epistaxis, which contribute significantly to the burden of health problems for Thoroughbred racehorses (Williams et al., 2001). The frequency and severity of MSC create a substantial financial burden for the racing industry, compromise equine welfare and create negative publicity for the sport. Many previous studies have attempted to identify risk factors for MSC in racehorses (see, for example, Stephen et al., 2003; Ely et al., 2004; Parkin et al., 2004a; Pinchbeck et al., 2004; Jacklin and Wright, 2012). These studies varied in many ways, including case definition, identity of the target population, and whether diagnoses were made in racing and/or training.

Due to differences in the spectra of risk factor associations, and in the populations to which those findings can be extrapolated, robust advice for stakeholders on the avoidance of risk of MSC has not been forthcoming. Few previous studies have attempted to identify a significant role for genetic risk in the development of these conditions, and have focused Warmblood breeds rather than Thoroughbreds (Pieramati et al., 2003; Oki et al., 2008; Jonsson et al., 2011). The identification of a significant genetic component to disease aetiology could be exploited as a basis for controlling risk in conjunction with the modification of environmental factors. The ultimate goal in this pursuit is to minimise individual and population risks through the prudent use of both environmental and genetic disease information. In this study, we estimated the heritability of a number of important MSC in racing Thoroughbreds in Hong Kong, to provide a benchmark for subsequent genetic analyses.

Materials and methods

Data

The data used in this study were provided by the Hong Kong Jockey Club (HKJC). All Thoroughbred racehorses in Hong Kong are owned by HKJC, and are housed together at Sha Tin Racecourse in the New Territories, and managed as a unit. As there are no racehorse breeding facilities in Hong Kong, all HKJC Thoroughbreds are imported. All racing is on two flat courses, Happy Valley in Hong Kong city and at Sha Tin. Racing surfaces are composed of all-weather 'dirt' or sand based turf.

The HKJC employs a team of full-time veterinarians who are responsible for the clinical care of all horses. Compulsory retirement is enforced for horses that reach 10 years old, have two or more officially recorded episodes of exercise-induced

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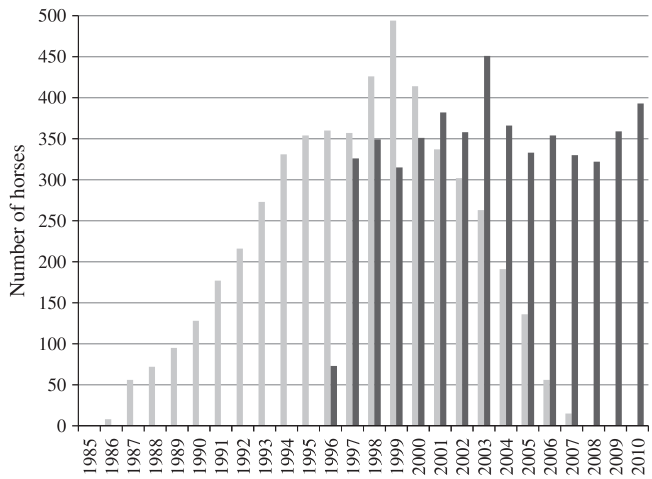

Fig. 1. Number of horses in the current dataset that were born or retired between 1985 and 2010. Light grey bars, year of birth; dark grey bars, year of retirement.

pulmonary haemorrhage or have two occurrences of cardiac arrhythmia. Retirement for other medical conditions, or for management reasons, is at the discretion of the veterinarian, trainer and owner, and can occur at any time. Horses are continually imported and retired throughout the racing year, with the racing season taking place between September and June. Fig. 1 contains information on the years of birth and retirement of these horses. The health and pedigree records used in this study were collected by the HKJC and stored in a purpose-built Microsoft Access database.

During the period in which the data for this study were collected there were a median of 1028 horses per annum in training. Horse health information was contained in two tables; one contained records of the results of all Official Veterinary Examinations (OVEs) carried out between 1995 and 2010 (8690 records), and the other contained free text entries detailing the reason(s) for retirement from racing of all horses retired between 1992 and 2010 (5520 records). An OVE may be requested by the trainer/owner/steward at any time, in response to detection of a possible veterinary problem. The horse must 'pass' an OVE before being permitted to continue racing. The results of these examinations are the content of the OVE records used here. The OVE and retirement tables were merged after indexing by alphanumeric horse identification codes and all records entered before September 1996 were removed due to a significant amount of incomplete information. Pedigree information included the name of the sire, dam, paternal and maternal grandsires for each horse. Missing or erroneous pedigree information was corrected using a Thoroughbred pedigree information site.[1] The resulting composite table of 5062 complete records, detailing all OVEs and subsequent reasons for retirement, was uploaded into content analysis software WordStat v6.1 (Provalis Research).

Free text records containing disease information were evaluated for the presence of words or phrases indicating diagnosis of certain user-defined categories of disease (Lam et al., 2007). The presence or absence of each disease category (coded 1 or 0) in each horse was exported as a Microsoft Excel spreadsheet (thus multiple records per horse were condensed into a single record per horse). All text or alphanumeric variables were numerically recoded before heritability analyses were performed. Conditions investigated were fracture, sesamoid bone fracture, distal limb fracture (inclusive of carpus/tarsus), suspensory ligament injury, tendon injury, superficial digital flexor tendon injury, degenerative joint disease and osteoarthritis.

Case definitions

A horse was defined as a case for a condition if it had ever been recorded as suffering from that condition, whether this was a cause of retirement or an OVE. Controls for each condition were horses that had never been diagnosed with that condition.

Non-genetic effects

Some data were available on potential environmental risk factors at the horse level. The gender of the horse was categorized as male or female, with neuter status at the time of retirement coded as '0' for not neutered and '1' for neutered. Year of birth, retirement and importation to Hong Kong were recorded as four digit numbers, e.g. 1999. Age at retirement was recorded in years (range 2.2–10.9, mean 6.0). The age at the time of import to Hong Kong ranged from 1.7 to 7.0 years (mean 2.8 years).

The provenance of each horse was captured in a number of variables: country of origin of the horse, its sire, dam and maternal grandsire were recorded as '1' for Australia or New Zealand, '2' for the UK, Ireland or the USA, and '3' for all other countries; the continent of origin was recorded as '1' for Europe, '2' for Australasia, '3' for North America and '4' for all others, and the hemisphere of origin was recorded as either Northern (1) or Southern (2).

The lifetime winnings of each horse were recorded in Hong Kong Dollars. The number of races run throughout the career of each horse was recorded as an integer, and the 'length of career' calculated as the difference in days between the first race date and the date of retirement. A variable called 'intensity' was created by the length of career in weeks, divided by the number of races run generating the mean number of weeks between adjacent races. A total of 15 variables were available for analysis.

Model building

Summary statistics for each continuous variable were produced and assessed, and categorical variables were examined for sufficient distribution across levels. Where numbers of cases or controls within a level fell below a pre-defined minimum of five, amalgamation of a number of levels was considered. Univariable analyses were conducted to identify relationships between all potential risk factors with all conditions. Variables with *P*-values of <0.2 were retained for multivariable modelling. All retained variables were ordered by log likelihood before sequential insertion into each multivariable model. Each multivariable model included sire or animal as a random effect (i.e. each outcome was modelled twice) prior to the inclusion of fixed effects. Fixed effect variables were retained within a multivariable model if the Wald test *P*-value was <0.05.

Within each model, correlation coefficients between every pair of retained variables were produced, and any >0.8 were investigated for the effects of removal of one of the correlated variables. All potential two-way interactions were investigated and retained if the Wald *P*-values of the interaction term and the likelihood ratio test were <0.05. All model building was performed in R v.2.15.1 (R Development Core Team, 2008), using packages 'lme4' (Bates et al., 2012) and 'MKmisc' (Kohl, 2013).

Heritability and genetic correlations

The final models were analysed using ASReml v.3 genetic analysis software (VSN International), and heritabilities were calculated from the variance components. Each condition was investigated using both sire and animal models, on linear and logistic scales. The general form of the linear model was:

$$Y = Xb + Za + e$$

where Y is the vector of observations, X and Z are known incidence matrices, b is the vector of fixed effects, a is the vector of random additive genetic effects with the distribution assumed to be multivariate normal with parameters $(0, \sigma_s^2 I)$ for sire models and $(0, \sigma_a^2 A)$ for animal models, e is the vector of residuals with multivariate normal distribution and parameters $(0, \sigma_e^2 I)$, and where I denotes an identity matrix, A is the numerator relationship matrix, and σ^2 denotes variance. The general logistic model form was:

$$\log\left(\frac{p}{1-p}\right) = Xb + Za + e$$

where p denotes the prevalence of the condition in the population, and all other components are as before. Residual variance in logistic models was set to $\frac{\pi^2}{3}$. Heritability in sire models was determined by:

$$h^2 = \frac{\sigma_s^2 \times 4}{\sigma_p^2}$$

where σ_s^2 is sire variance, and σ_p^2 is total phenotypic variance, composed of sire and residual variance. Animal model heritability was determined by:

$$h^2 = \frac{\sigma_a^2}{\sigma_p^2}$$

where σ_a^2 is the animal variance. To be defined as heritable, the inclusion of sire or animal in the final model had to be significant based on a likelihood ratio test *P*-value of <0.05, and the heritability estimate generated had to exceed the 95% confidence interval (1.96 × standard error). For this reason, results pertaining to sesamoid bone fracture, distal limb fracture, superficial digital flexor tendon injury and degenerative joint disease are not shown. Genetic correlations were determined by generation of appropriate bivariate sire linear models without fixed effects.

[1] See: http://pedigreeinfo.com.