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GENETIC BACKGROUNDS OF OSTEOCHONDROSIS.

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1. Introduction

Osteochondrosis is one of major problem in present economical market of horses. Even if relation between illness and performances is not well known ([12], [15], [17], Brehm and Staecker, 2000), x-rays were greatly developed in the last years and is now an obligatory way to sell a horse. Is this large emphasis on this trait supported by a genetic background that would justify the importance of such selection intensity ?

Only papers with a true analysis of genetic factors will be presented here, no references will be done about studies which only suspect differences among several sires because it is an evidence that statistics must be done to prove that theses differences are not due to chance and in a genetic way these statistics must be built from a sufficient amount of data.

2. Definition of osteochondrosis /measures

Osteochondrosis (OC) in the horse is a disease characterised by the disturbance of the normal differentiation of condrocytes in growing cartilage, leading to impairment of endochondral ossification. It has been described in large number of different joints. It can be observed by mascroscopic inspection of lesions and verified by histological examination. Histological examination reveals loss of normal columnar arrangement of condrocytes, clustering of cells or chondrome formation, presence of retained vessels, condronecrosis and or fissures. Even if there is a relatively clear definition from this histological examination, studies are most often based of x-rays information because histological techniques need the euthanasia of the horse. Especially for genetic purpose, only radiological information was used because the number of horses needed must be high and a reasonable random sample of the population. So measure of osteochondrosis is based on the examination of the x-rays and so is a particular vision of macroscopic disturbance. This leads usually to a score that depends on the severity of lesions visible in x-rays findings: from irregularity on bony contour to large fragments, or in some cases on the supposed influence on the locomotion of the horse. So measure of severity of pathology belongs from different scales in each study. Finally it seems that there is not a strict borderline between horses with and without osteochondrosis, and so notation is subject to fluctuation in each study. This is the first factor of heterogeneity between studies. The second factor is the locations studied. There is not a total agreement about the origin of different articular lesions in different locations: is it always the same initial problem than OC or not? There are often different

names for theses lesions according to their locations. This yields to the second factor of heterogeneity according to the locations used to assess the appearance of OC. The presence of OC has not the same significance if you search it in a large number or a few numbers of joints. It is the problem of cumulative measure (all over the body) of OC. In order to get a general view of the problem, all research on osteo-articular lesions will be included in this review, even if it's not called OC because some authors think that it may be the same initial susceptibility that induces different external defects on articulation and bones according to the location of the joint.

3. Samples used / Number of horses needed / Breeds

There are two conditions in order to have a satisfactory estimation of heritability: the sample must be large, especially the number of horses by sires, and the sample must be at random.

In most studies the number of horses used and the number of offspring per stallion are rather small, even if the amount of labour to take x-rays from this number of horses remains very important. In comparison with the other species, it is the number of progenies per stallions or *a contrario* the number of different sires for a sample of horses that is the most restrictive problem. This problem remains even if the statistical model uses an animal model, and then if all ancestors are included in the analysis that increases the total number of horses used. The number of horses involved in the references is too often less than 500 ([15], [2], [4], [9], [1]) sometimes between 500 and 1000 ([2], [8], [6], [14], [13], [10], [11], [12]) and larger than 1000 at present in an only study: the study of Winter et al ([17], [18]) on horses sold in auction with 2182 and 3566 horses. I can also report here the results of our recent study on 1940 French Trotters, which I'll report on [*] future publication. The number of progeny per stallion range from about 7 ([15], [17], [9], [10], [11]), or between 10 and 20 ([4], [6], [14], [*]) and from 25 to 33 that is the maximum in the study of Philipsson (1993) ([2], [8], [1]). In a balanced design, standard error of estimates of heritability obtained from a sire model with 500 progeny and a number of 7 progeny by sire ranges from 0.12 for h^2=0.10 to 0.16 for h^2=0.50, which leads to a confidence interval at 5% of ±0.23 to ±0.31, so an interval of 0 to 0.33 in the first case and 0.19 to 0.81 in the second case for an estimation that must be between 0 and 1! So we can't expect from these studies more than an indication about the possibility of a genetic effect rather than the true magnitude of this effect.

The sampling of horses from the breed studied is often at random but even in this case, the number of progeny per stallions must often be higher than 3 or 5, which is necessary for the variance component estimation, but induces automatically a small selection. The less suitable situation is the use of horses from public auction ([17], [18], [*]), of performance tests ([9], [15], [10])

The breeds involved in these studies are really different. There are breeds for trotter races: standardbred ([3], [6], [8]), French trotter ([11], [*]), Norwegian trotter ([4]), breeds for sport horses: German breeds ([15], [16], [17], [18], Dutch breeds ([14]), French breeds [10], Italian breed [9] and specific breeds: Icelandic horses ([2], [1]), cold blood Finnhorses [13]. There is no reason that prevalence and heritability of OC must be the same in these different breeds.

4. Environmental factors: age

The collective publication of Barneveld and Weeren (1999) published in the supplement 31 of Equine Veterinary Journal suggest from several studies that there is a fluctuation of OC according to the age. It seems that there is a window of susceptibility during ossification process and number of lesions may be present at an early age and then regresses. So age at measure of OC is an important factor to be taken into account in the estimation of heritability. Studies are often performed on 2 and 3 years old horses, except for the Icelandic horse ([2], [1]), where the

horses are older (from 6 to 12 years old) and German sport horses sold in auction [17] and for some works about trotters where some horses are younger: (from 11 month to 2 years old for [8], from 6 months to 21 month for [6] and from 6 month for [*], so perhaps already in the "window". In any cases, horses where taken before any uses in competition or races, except for horses sold in auction [17] which is very important to avoid a lot of environmental factors due to the use of the horse.

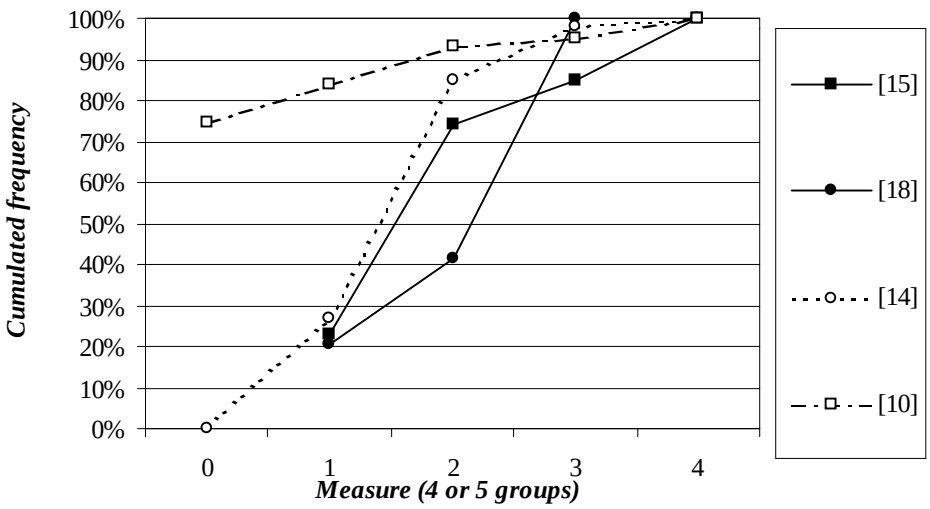
5. Results on frequency

The first comparison possible is the prevalence of the disease in each study.

Three points may be highlighted.

The first point is that there is a large variability in frequency by classes when there is a progressive measure of intensity of defects. To illustrate this case, let compare the frequency of navicular diseases on sport horses

Figure 1. Cumulative frequency of x-rays score for
Navicular disease in Genetic studies on Sport horses (references in brackets)



A progressive measure is really suitable in order to add information to calculate heritability but it leads to difficulties to compare prevalence but not automatically to compare heritability because it's only a problem of scale and definition of thresholds. This is the case for the comparison of the studies on sport horses.

The second point is that there is a better homogeneity on the studies on trotters with a simpler scale (0/1) for OC in hock: 10.5% of injured horses in the study of Philipsson et al ([8]), 14,3% in the study of Grondhal et al ([6]) and 14.5% in the our study ([*]). But this homogeneity is lower in fetlock: respectively 21,5%, 11,8% and 26,1%, so varies form simple to double.

The third point is that global measures depend largely on the number of locations examined. Global measures may be suitable in order to add a more sensitive measure, with different degrees of illness and may be used to test the assumption of a same genetic origin of joints problems but most authors found very low correlations between locations ([15], [8], [6], [12]) and then a global measure multiply prevalence on single measure and is hardly dependant on the number of locations used to construct it. For example if you consider OC on hock and fetlock, only 35% of sport horses are diagnosed ([10]) but if you add foot, hoof, carpus, stifle and pastern, 63% of

horses are injured! This may explains the 69.3% of lameness in standardbred in the study of Dolvick et al, even with the low level of abnormality on radiography in the other trotter populations. So care must be done when announcing the number of horses with abnormality because it depends largely on the number of investigations done.

6. Results on heritability

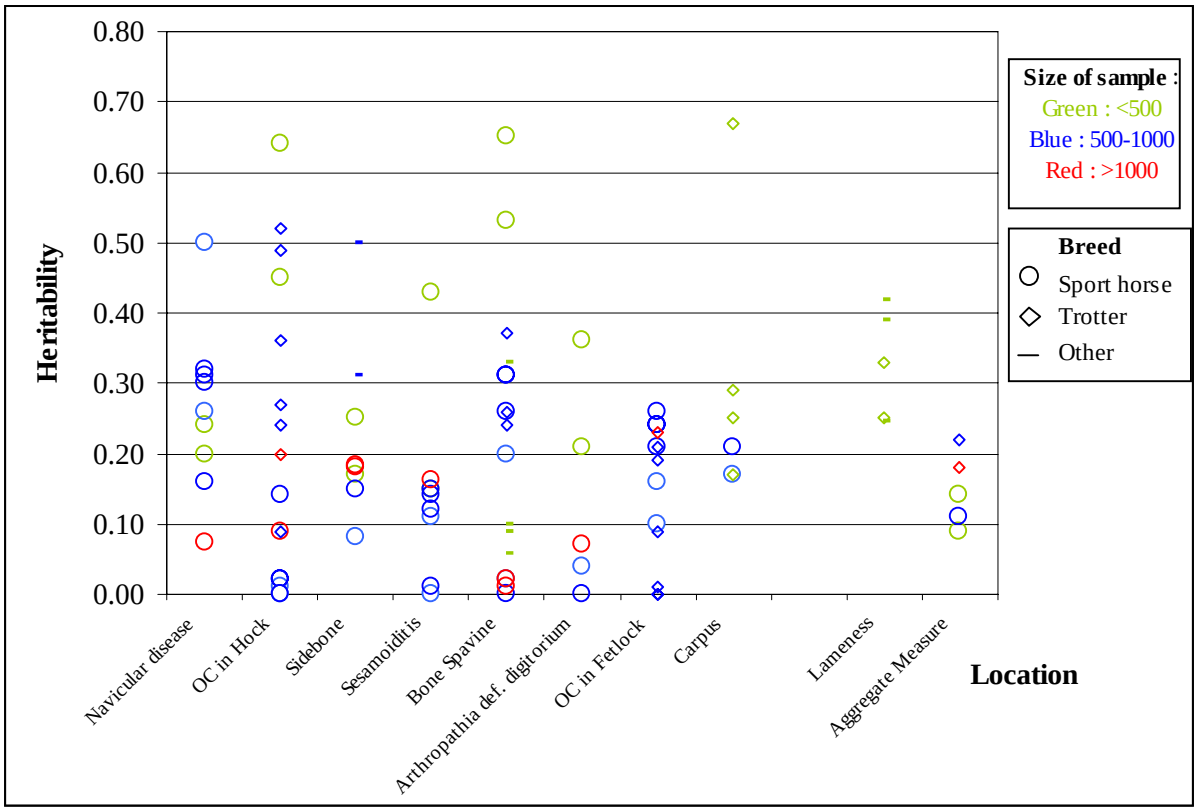
There are 17 to 5 estimations of heritability by location from the overall references. The range of variation of heritability by location is between 0.13 to 0.65 (difference between the maximum and the minimum estimates). The mean of this criterion is 0.40. This illustrates that the reliability on these heritabilities is rather low according to the number of horses involved in each study. A range of 0.40 to estimate heritability is to high to give satisfactory conclusions for the better way we will have to use to select against this problem. However, these variations may be explained by several factors, as we tried to outcome here.

The first factor of variation may be the model used. The measure is most often a discrete measure and in some cases a binary measure. The statistical model must deals with this particularity. We have rather the same number of results with continuous variable and discrete variable. Very often, continuous estimations are corrected for discrete measurement and the corresponding heritability is given (with a correction according to the frequency of the binary measure). The continuous model is supposed to under estimate heritability and it's the case in the majority of works which uses the two models ([14], [2], [4], [3]), except with the work of Winter et al ([15]) where some estimates with the continuous measure are higher than with the binary measure (0.25 against 0.17 for sidebone, 0.43 against 0.15 for sesamoïditis and 0.36 against 0.21 for Arthropathia deformans digitorum). So the behaviour of estimates in practical conditions especially in our case where the percentage of one category of horses is low (affected horses) and the number of progeny per sires low also is not obvious and corrected estimates is perhaps not the better choice.

The second factor is the model involved. With discrete variable, only a sire model may be applied as no valuable animal model estimates had been developed. This is not a problem where there is no selection or assortative mating, but in most breeds, selection against OC is already performed on stallions and so conditions of this selection is not always taken into account. That's why Van Heelsum [14] used information on stallions also with an animal model but with a continuous variable. The corresponding heritabilities corrected for the frequency of affected horses lead to the same estimates than the binary sire model in this case except for OC in hock where heritability varies from 0.02 to 0.14.

Estimates of heritability are summarized in the following figure. They are sorted by breed and by confidence we can have due to the number of horses involved in the study. According to the locations, variability of estimates is different. There is great variability between estimates for OC in hock and Bone Spavine, also in hock. There is a better homogeneity for the other locations, especially when the weighed is lower for studies with small number of horses. The higher estimates seem to belong mostly from studies with low number of horses. The best homogeneity is for global measure all over the body or lameness that include a lot of factors but remain reasonably heritable (0.20-0.30). Perhaps these criteria that are not the best ones to study the illness are a not so bad for selection purpose because they are expected more directly related to performances and nevertheless heritable.

Figure 2. Estimates of heritability of all references
depending on the breed and the sample size analysed.



The heritabilities estimates for OC in hock varies from 0 to 0.64 and for trotters from 0.20 to 0.52 if we except the estimation of Philipsson ([8]) on the continuous scale and keep only its transformation on the binary scale (0.24). So heritability of OC may be supposed relatively moderate to high in Trotters but problem remains in riding horses where the range of heritability is not well determine and is lower than 0.20 for works with more than 500 horses. For bone spavin, heritability range from 0 to 0.64 or 0.32 if we except works with less than 500 horses. Level of heritability is really not clear.

There is no evidence of precise differences in heritability between breeds. There so much variability between studies that there is no clear differences between breeds except perhaps for OC in hock between trotters and riding horses if you suppress high heritabilities obtained by Willms et al ([15], [16]) on only 400 horses, the heritability of OC seem higher for trotters than for riding horses. But it's not the case for the two other locations studied in trotters: Bone Spavine and OC in Fetlock. The heritabillity found for ossification of cartilage of the front feet on Finnhorse by Ruohoniemi et al ([13]) seems also larger than those found for riding horses for sidebone.

7. Conclusion

In conclusion, heritability of osteo-articular lesions is not yet well determined. The overall weakness of horses subject to lameness has a moderate heritability (0.20-0.30) but precise estimates of exact pathology in the different locations may reveals different figures. There is a certain homogeneity in the following locations: heritability of navicular desease (abnormality on sesamoide bone), OC in fetlock and abnormality on carpus are middle sized (0.20-0.30), heritability of sidebone (abnormality on distal phalanx) and sesamoiditis (abnormality on plantar

aspect of the metacarpo or metatarso-phalangeal joint) are lower (0.10-0.20) and heritability of Arthopathia deformans digitorum (abnormality on distal interphalangeal joint of the fore foot) is very low (<0.10). For OC in hock there is not really homogeneity in results, it seems that heritability of OC in hock for trotter is relatively high (>0.25) but perhaps very low in riding horses and there is no unanimity for Bone Spavine (abnormality on distal tarsal row).

How can we manage to have a better idea of these parameters in order to build an effective selection process? The main improve will be to have a better (in term of scale of progeny) and larger design. The second improve may be found in the definition of the affected horse. Two opposite ways are possible and must be definitively cut. The first one is to have a better continuous scale of measurement in order to overcome problems with discrete variables especially when a low percentage of horses is affected and when the low number of progeny leads to problem in statistical estimation. The opposite way which will not improve statistical problems but perhaps improve the definition of the trait is to consider as abnormal only very affected horses for example with the two legs (right and left) with abnormality because it may bring up the true predisposition to illness which may be confused when adding all low affected horses due to other circumstances. This is the way proposed by Dolvik and Klemetsdal (1994) [4] and followed by Ricard et al ([11], [*]).

Note that there are not yet publications on molecular results. The only molecular result on OC in livestock was found in pig with no significance evidence of QTL for OC, but some markers were detected for scores of leg weakness (Lee et al, 2003). Another way to clarify the way from OC in radiographic findings to DNA may be to use metabolic parameters (Billinghurst et al, 2004) related to OC in order to decrease the noise between phenotypic measure and genetic background.

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