Review

Genetic Factors of Equine Osteochondrosis and Fetlock Osteochondral Fragments: A Scoping Review - Part 2

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Abstract

Equine osteochondrosis and osteochondral fragments in the fetlock joint are linked to various environmental and genetic risk factors. To assess the scope of the literature linking these risk factors to the development of these osteochondral disorders, while identifying knowledge gaps and challenges to guide future research, a scoping review was performed. This article constitutes the second part of this scoping review and focuses on genetic factors, with the first part addressing environmental factors. To identify potentially relevant papers, online bibliographical databases PubMed and Web of Science were utilised, supplemented with articles listed on the OMIA website (OMIA:000750-9796). After collecting entries, removing duplicates, screening titles, abstracts, and full-text documents for eligibility, and manually searching reference lists of the remaining articles, a total of 212 studies were identified for this scoping review. First, a brief overview of the etiopathogenesis of equine osteochondrosis and osteochondral fragments in the fetlock joint is provided. Subsequently, this article delves into the genetic aspects by presenting an overview of significantly associated quantitative trait loci and potential candidate genes. Next, the challenges in both phenotypic and genomic selection against these osteochondral disorders are discussed, with a focus on the difficulties in phenotyping, the establishment of large and representative reference populations, publication bias, lesion-specific heritabilities, and studbook policies. In conclusion, while there is considerable potential to implement preventive measures that can alleviate the economic burden and enhance animal welfare, further research is necessary. This research should utilize precise and standardized phenotype definitions applied across studies with preferably larger populations.

Keywords: Genetic factors; Horses; Osteochondrosis; Review

Introduction

This is the second part of a two-part scoping review examining the environmental and genetic factors of osteochondrosis (OC), palmar- and plantarproximal osteochondral fragments of the proximal phalanx (POF) and dorsoproximal osteochondral fragments of the proximal phalanx (DOF). In the first part, focusing on environmental factors (Van Mol et al., 2024), the aetiology and presentation of OC, DOF and POF were extensively introduced. Briefly summarised, OC involves a failure of endochondral ossification, where an area of growth cartilage fails to become mature bone (Rejnö and Strömberg, 1978), due to disrupted blood supply (Carlson et al., 1995; Jeffcott, 2004; Ytrehus et al., 2007; Olstad et al., 2013; Olstad et al., 2015a). This leads to abnormal and/or separated necrotic subchondral bone (Stromberg, 1979; Ytrehus et al., 2007; Olstad et al., 2015a) or, alternatively, after healing, results in normal subchondral bone (GrØndahl, 1991; Carlsten et al., 1993; Carlson et al., 1995; Dik et al., 1999; Baccarin et al., 2012; Jacquet et al., 2013; Santschi et al., 2020). OC develops at specific predilection sites and is often bilaterally symmetrical (Mcllwraith et al., 1991; McIlwraith, 1993; Pool, 1993; Barneveld and van Weeren, 1999).

POF occurs when pathological or physiological tensional forces at the distal attachment of the short and oblique sesamoid ligaments lead to traumatic overload of the fragile, growing skeleton, resulting in an avulsion fracture (Dalin et al., 1993; Pool, 1993; Nixon and Pool, 1995; Barneveld and van Weeren, 1999; Denoix et al., 2013b). For DOF, there is still some ambiguity about the aetiology being OC or (recent) traumatic fracture due to differences in the histological and clinical presentation between breeds and possibly within breeds (Adams, 1966; Pool, 1993; Kawcak and Mcllwraith, 1994; Henson et al., 1997; Declercq et al., 2009; Theiss et al., 2010).

A shared aspect in the etiopathogenesis of OC, DOF and POF, is the failure of the growing skeleton. Predisposing factors are multifactorial involving genetic and environmental factors. The objective of this part of the scoping review is to summarise the existing evidence regarding the involvement of genetic factors and discuss the challenges in both phenotypic and genomic selection.

Methods

To conduct a scoping review that is rigorous, transparent and replicable, the recommendations of the PRISMA Extension for Scoping Reviews (PRISMA-ScR) protocol (Tricco et al., 2018) is followed and a detailed checklist is provided as Supplementary Checklist S1. To identify potentially relevant peer-reviewed literature, a search was performed in May 2023 by one author (BVM) with feedback on the process by all authors. The search was carried out on the bibliographic databases PubMed and Web of Science from 2003 to May 2023. The following search terms were used: (‘osteochondrosis’ OR ‘osteochondral fragment’ OR ‘developmental orthopaedic disease’ OR ‘juvenile osteochondral conditions’ OR ‘osteochondral lesion’) AND (‘equine’ OR ‘horse’ OR ‘pony’ OR ‘foal’ OR ‘yearling’ OR ‘warmblood’ OR ‘standardbred’ OR ‘trotter’ OR ‘thoroughbred’ OR ‘purebred’ OR ‘coldblood’). The bibliographic database search was supplemented with all (no publication date restrains) articles listed on the ‘online mendelian inheritance in animals’ website on osteochondrosis in Equus caballus (OMIA:000750-9796).

All the search results were exported in the reference manager EndNote for duplicate removal and study screening. For both parts of this scoping review, all unique titles and abstracts were screened for the eligibility criteria provided in Table 1. For the purpose of this review, papers on subchondral bone cysts, identified by some as possible manifestations of OC (Stromberg, 1979; Olstad et al., 2015b), as well as those referring to less common locations of OC, and types of fetlock fragments other than DOF and POF were excluded. Additionally, gene expression studies were excluded due to the recurrent uncertainty about whether changes in gene expression are related to the primary condition (OC, DOF, POF) or secondary responses. This uncertainty arises because the exact timing of natural lesion occurrence is unclear, and in experimental OC models, the aetiological background may differ.

Table 1
The eligibility criteria used in this two-part scoping review.

Criteria	Inclusion	Exclusion
Language	English	Other language
Publication type	Peer-reviewed primary literature	Non-peer-reviewed literature
Population	Horse (Equus ferus caballus)	Other animal species
Phenotype	Articular osteochondrosis of the fetlock, hock or stifle Palmar/plantar or dorsal osteochondral fragment of the fetlock	Osteochondrosis at other, less prevalent, locations Scientific papers discussing subchondral bone cyst Scientific papers about other types of fetlock fragments
Methods	Genome-wide association study based on single nucleotide polymorphisms Microsatellite-based genome-wide scan Pro- or retrospective study of environmental factors	Gene expression study
Concept	Description of genes potentially associated with the risk of developing the phenotype Description of environmental factors associated with an increased risk for developing the phenotype	Scientific papers that do not investigate genetic or environmental risk factors

Results

The literature search identified 565 articles on the Web of Science, 394 articles in PubMed and 168 articles in the OMIA database. After duplicate removal, 629 articles remained. Through analysis of article titles, abstracts, and full-text documents, 503 articles were excluded due to ineligibility. Through a manual search of reference lists, an additional 86 unique articles that met the eligibility criteria were identified and included for review. Ultimately, a comprehensive review was conducted on a total of 212 articles. This review is presented in two parts. The first part (Van Mol et al., 2024) addressed environmental factors, while this article constitutes the second part, focussing on the genetic factors of OC, DOF and POF. A general limitation of this review is its scope, which covers findings up to May 2023. Furthermore, the review focused exclusively on Equus ferus caballus (horse).

In the following sections, we first provided an overview of associated quantitative trait loci associated with OC, DOF, or POF. Subsequently, we summarized the potential candidate genes that received further description regarding their function and relationship with the disorder in the reviewed papers. Finally, we discussed the challenges in both phenotypic and genomic selection against these osteochondral disorders.

Genetic factors

Studies that examined the prevalence rates of OC, DOF and POF in different breeds within the Equus Ferus Caballus subspecies revealed significant variations among modern horse breeds (Sandgren et al., 1993a; Wittwer et al., 2006; Oliver et al., 2008; Lepeule et al., 2009; Verwilghen et al., 2009; Preston et al., 2010; Beckmann et al., 2012; Denoix et al., 2013a; Boado and Lopez-Sanroman, 2016; Naccache et al., 2018; Van Cauter et al., 2023), between horses and ponies (Voute et al., 2011; Hendrickson et al., 2015), and between untamed (feral) and domesticated horses (Valentino et al., 1999). These differences in prevalence rates are often used as arguments for a strong role of genetics.

To investigate the role of genetics in OC, DOF and POF development, differences in genetic variants covering the whole genome such as single nucleotide polymorphisms (SNPs) and microsatellites (MS) between cases and controls are analysed. By identifying genetic variants that are statistically associated with an increased risk for OC, DOF, and POF, genome-wide significant quantitative trait loci (QTLs) can be mapped. QTLs are DNA regions significantly associated with variation in OC, DOF, and POF occurrence among horses. These genetic variants and QTLs can be used for genomic selection and provide a starting point for further analyses to discover the specific genes causing the increased risk of OC, DOF, and POF.

Genomic selection is a breeding method in which selection decisions are guided by genomic breeding values (GBVs). Initially, GBVs for specific traits, such as osteoarticular health, were estimated using a large reference population that was both phenotyped and genotyped. In this reference group, the effects of genetic variants and QTLs on the phenotype(s) were estimated. These estimates were then applied to newly genotyped, yet unphenotyped, animals following a two-step system. Genomic selection captures the additive genetic effects of all loci contributing to genetic variation for a given trait while also accounting for residual effects, including environmental and non-additive factors (Meuwissen et al., 2001; Goddard and Hayes, 2007; Hayes et al., 2009). More recently, a more comprehensive method called single-step genomic best linear unbiased prediction (GBLUP) was introduced. This method integrates all available information, including pedigree, genomic, and phenotypic data, into a unified approach. Unlike traditional genomic selection, which relies heavily on large reference populations, single-step GBLUP can improve prediction accuracy by combining data sources, thereby reducing the required size of the reference population (Aguilar et al., 2010). This method has been tested in horses, showing potential as a valuable option for equine health data (Vosgerau et al., 2022).

In addition to estimating GBVs, it is valuable to evaluate the additive genetic and residual correlations between OC, DOF, and POF (Stock et al., 2005). Additive genetic correlations reflect the extent to which the same genetic factors influence these osteoarticular conditions, while residual correlations represent the shared non-genetic variation among them. Moreover, the genetic and residual correlations between OC, DOF, and POF and other traits, such as conformation, growth rate, or athletic performance, can be assessed (Stock and Distl, 2005a; Stock and Distl, 2005b; Stock and Distl, 2006a; Stock and Distl, 2006b; Stock and Distl, 2007; Stock and Distl, 2008). Understanding these correlations is important for breeders and policymakers, as it helps predict how selection for one trait might impact other important traits. This knowledge supports informed decision-making, guiding selection strategies to optimize the balance of desirable characteristics in the population (Sgrò and Hoffmann, 2004; van Rheenen et al., 2019).

Supplementary Table S2 provides a summary of significant QTLs associated with OC, DOF or POF. The "phenotype" column represents the definition of a case as used in each study. Based on the literature referred to in Table S2, osteochondrosis was defined as a change of the normal bone contour at a specific predilection site. This bone contour change included flattening, irregularity or indentation, with or without an irregular surrounding bone opacity, and with or without the presence of an adjacent radiopaque fragment. No differentiation was made in phenotype definition between OC and OCD based on the presence of a radiopaque fragment, despite some studies reporting distinct QTLs between these phenotypes. Our rationale behind this is the uncertainty whether horses that should have been classified as OCD cases may have undergone surgery to remove a radiopaque fragment, subsequently being wrongly classified as OC cases. Additionally, OC and OCD are regarded by most as a different presentation of the same disease, challenging the distinction between these groups and potentially leading to confounding and false positive signals due to smaller sample sizes. DOF was defined as the presence of a radiopaque fragment at the dorsoproximal border of the proximal phalanx. POF was defined as the presence of a radiopaque fragment at the palmar- and/or plantarproximal of the proximal phalanx.

The definition of a control encompassed all animals that do not meet the criteria for being a case. In certain studies on OC, the control definition was more stringent, disqualifying animals as controls if OC is present in any of the radiographed joints. No distinction was made in Supplementary Table S2 regarding these differing control definitions, due to our rationale that excluding cases in other joints can only be justified if OC is considered a generalised disease. In that scenario, control animals should be those without OC in any diarthrodial joint. However, none of the studies conducted radiographic screening of every diarthrodial joint due to practical constraints, thus questioning the efficacy of adopting a more stringent control definition. The following studies were excluded: 1) Lewczuk et al. (2017) and Lewczuk et al. (2018) due to incompatibility between their phenotype definition and our phenotype rationale; 2) Boneker et al. (2006) and Zabek et al. (2013) due to lack of a significant association between genetic variants and OC.

Based on genome-wide association studies, whole genome scans, genomic refinement studies, and candidate gene analyses across 10 different equine breeds (Belgian Warmblood, Dutch Warmblood, French Trotter, German Coldblood South, Hanoverian Warmblood, Norwegian Standardbred, Polish Sport Horse, Spanish Purebred, Thoroughbred and U.S. Standardbreds), QTLs associated with OC and POF were identified on 27 autosomes and 1 sex chromosome, as presented in Supplementary Table S2. In these studies, no QTLs for OC could be detected on equine chromosomes 6-9, 11, 20, 24, 26, 30, X and Y, and no QTLs for POF could be detected on equine chromosomes 3, 5, 6, 10, 13-25, 28-30 and Y. For DOF, no QTLs have been reported, as none of the reviewed studies used the presence of DOF as a phenotype definition.

Across the different equine breeds the following major QTLs could be identified for OC and POF,without further subdivision into more specific phenotype definitions. For OC: ECA 1 (118.29 Mb - 194.2 cM), ECA 2 (8.68 Mb - 100.00 Mb), ECA 3 (20.70 Mb - 115.92 Mb), ECA 4 (0.00 cM - 72.2 cM), ECA 5 (40 cM – 100.10 cM), ECA 10 (48.25 Mb - 80.39 Mb), ECA 12 (27.65 Mb), ECA 13 (0.0 cM - 12.88 Mb), ECA 14 (16.35 Mb – 77.90 Mb), ECA 15 (24.0 cM - 88.68 Mb), ECA 16 (0.00 cM – 89.00 cM), ECA 17 (46.6 cM), ECA 18 (13.80 Mb - 78.2 cM), ECA 19 (0.00 cM - 2.00 cM), ECA 21 (0.00 cM - 54.50 Mb), ECA 22 (0.0 cM - 79.7 cM), ECA 23 (44.4 cM), ECA 25 (0.0 cM - 30.1 cM), ECA 27 (0.0 cM - 39.20 Mb), ECA 28 (7.0 cM - 42.62 Mb), ECA 29 (16.07 Mb - 16.94 Mb) and ECA 31 (21.70 Mb - 41.1 cM).

For POF: ECA 1 (110 cM – 160.5 Mb), ECA 2 (51.2 Mb), ECA 4 (7.8 cM - 73.3 cM), ECA 7 (69.6 Mb - 80.5 Mb), ECA 8 (79.3cM - 108.8 cM), ECA 9 (22.5 Mb - 26.9 Mb), ECA 11 (10.9 Mb), ECA 12 (0.0 cM), ECA 26 (7.0 cM), ECA 27 (22.6 Mb - 23.7 Mb), ECA 31 (17.0 Mb) and X (23.4 Mb). The positions of these QTLs were derived from published linkage maps, the EquCab2.0 reference genome assembly or the most recent EquCab3.0 reference genome assembly, depending on the source publication.

A total of 4 different phenotype definitions for POF and 20 different phenotype definitions for OC were used, with 2 studies excluded due to incompatible phenotype definitions with our phenotype rationale. In studies concerning POF, discrepancies arose as some researchers differentiated between cases and controls based on the presence or absence of POF at the animal level. However, others distinguished between POF occurring at the attachment sites of the lateral short sesamoidean ligament and the attachment site of the medial short sesamoidean ligament, or even categorized POF based on the affected joint (metacarpophalangeal vs. metatarsophalangeal joints). Similarly, for OC, differentiation between cases and controls stemmed from screening lesions in one specific joint or a combination of joints, sometimes including joints in which OC is less prevalent like the shoulder joint. At the joint level, OC-case definitions varied between studies from horses with abnormal bone contours (irregularities or indentations) with or without adjacent radiopaque fragments at common anatomical sites, to including these abnormalities at less common sites, or even different radiographic abnormalities that may not definitively indicate OC. Additionally, some studies did not specify the anatomical locations screened within the joint.

Out of the 71 candidate genes identified from the 18 studies referred to in Supplementary Table S2, 32 received no further description regarding their function and relationship with OC and POF in the reviewed papers (*ADAMTS1, ATP8B4, ATXN7L1, CALN1, CLCA2, CNTN6, CTNND2, DLGAP2, FCHSD1, FGF1, GABRA1, GABRA6, GABRB2, HDAC3, MCTP1, NR3C1, NUDCD2, PDSS2, PPCDC, PREP, PROM1, QRSL1, RCP9, SEMA5A, SLC27A2, SLC35A4, SNUPN, SPATA24, TAS2R1, TRPM7, UBE2D2,* and *WDR63*).

The remaining 39 genes, their function and, if described in the source paper, the potential link with OC pathology were summarized in Supplementary Table S3. These candidate genes can be categorized based on the functions and associations reported in the source papers: 1) Genes involved in cartilage and bone development, metabolism and function (*ARHGAP26, CCNG1, COL1A2, COL24A1, COL9A2, EVC, EVC2, FAF1, HMMR, HYAL1, HYAL2, HYAL3, Il6, JAKMIP1, LAMB1, MAT2B, NCDN, UGDH* and *VEGFB*), some of which specifically influence the Wnt/β-catenin signaling pathway (*FAF1* and *JAKMIP1*), angiogenesis (*VEGFB*), or cause dwarfism (*CCNG1*, *EVC* and *EVC2*); 2) Genes associated with human joint disorders, such as osteochondrodysplasias (*COL5A1, COL27A1, MATN1* and *PTHR1),* Ehlers–Danlos syndrome (*COL3A1* and *COL5A2*) and osteoarthritis (*FRZB* and *LGALS3*); 3) Genes encoding proteins present in cardiac cells (*CLCA4* and *XIRP2*); 4) Genes involved in growth (*LCORL, IGF1*); 5) Genes involved in the immune response (*AOAH, CPVL* and *FCN3*); 6) Genes involved in cellular differentiation, migration, proliferation, signaling, and transport (*FBXO25, LAMB1* and *TBC1D22A*); 7) Genes involved in endoplasmatic reticulum stress (*RTN3* and *SLC35D*).

Challenges and opportunities in the selection against OC, DOF and POF

Despite the implementation of stringent phenotype-based selection criteria by different studbooks, reducing the prevalence of OC, DOF, and POF remains challenging. The reasons for this lack of success are suspected to be multifaceted. Consequently, efforts are now being directed towards enhancing the effectiveness of breeding programs by incorporating genomic selection through a GBVs estimation approach, acting on the significant genetic variants and QTLs, outlined in Supplementary Table S2. Genomic selection has the potential to address some of the limitations of phenotypic selection based on radiographic screenings, although some of these limitations also negatively impact genomic selection itself. The following sections discuss the challenges of both phenotypic and genomic selection, as well as the benefits of their complementary use.

Challenges in phenotyping

A primary reason that can contribute to a lack of success in both phenotypic and genomic selection could stem from the method of differentiation between affected and unaffected horses. Currently, most studbooks determine breeding eligibility based on radiographic screening protocols conducted after 18 months of age. This phenotype-based selection approach considers the dynamic nature of OC in warmbloods and thoroughbreds where the majority of OC lesions can only develop and fully regress until 18 months old (GrØndahl, 1991; Carlsten et al., 1993; Dik et al., 1999; Baccarin et al., 2012; Jacquet et al., 2013; Santschi et al., 2020). For Coldblood breeds, an exact point of no return where OC becomes permanent has not yet been defined (Wittwer et al., 2006). The period during which POF and DOF can develop, and potentially heal, remains uncertain. For POF, Carlsten et al. (1993) observed a dynamic nature in which the radiolucent zone that develops prior to fragment formation could revert to normal bone without leading to fragmentation. Both DOF and POF likely develop predominantly during the first months of life, and once an intra-articular fragment is formed, it appears to be permanent (Carlsten et al., 1993; Pool, 1993).

An additional complexity arises for POF and DOF, as these fragments can be arthroscopically removed without leaving an obvious radiological trace, resulting in false-negative diagnoses. This is less problematic for OC since subchondral bone defects remain visible on radiographs after fragment removal. However, in mild cases of OC, where only an irregular or flattened bone contour without adjacent fragmentation is present, uncertainty could arise leading to wrong classification. Moreover, the lack of standardized radiographic protocols across studbooks further contributes to a variable sensitivity in lesion detection.

An argument supporting the differentiation between cases and controls after 18 months old is the high incidence of OC and POF during the first months post-partum (Stromberg, 1979; Carlsten et al., 1993; Dik et al., 1999). This suggests that early lesions should not necessarily be considered pathological, but rather as anatomical variations (Firth and Poulos, 1984). Consequently, it is proposed that, similarily to the development, the regenerative capacity is influenced by genetics (Barneveld and van Weeren, 1999). Horses with a false-negative diagnosis due to successful healing might possess the genetics that predispose them to effective recovery, supporting their inclusion in the breeding population (Drabbe et al., 2022). The decision regarding horses with DOF and POF is challenging. Rejecting these horses for breeding purposes may seem unfair to owners who are unaware that surgical fragment removal could have prevented rejection. Conversely, accepting these horses into the breeding pool raises concerns for the population, as it contradicts the principles of selective breeding aimed at reducing the prevalence of these diseases.

As a result, in a phenotype-based selection approach, horses genetically predisposed to OC, DOF or POF may be accepted as breeding animals if the lesions they developed are undetectable during radiographic screening due to regeneration or surgical intervention or the lesions are mild, thereby hindering genetic progress. Complementary genetic/genomic selection offers a potential solution by directly assessing the genetic predisposition of horses to develop OC, DOF and POF. With (genomic) estimated breeding values, horses with a normal phenotype due to the aforementioned factors but with a genetic predisposition to develop the osteoarticular abnormality can be identified and excluded from the breeding population, thereby increasing the efficacy of selection.

A key challenge lies in precisely identifying the genetic variants, QTLs and specific genes linked to increased genetic susceptibility for OC, DOF, and POF. Most genetic analyses are case-control association studies that rely on the radiographic case-control definitions, which are susceptible to the same challenges of healing, surgery, or mild lesions mentioned above. This introduces noise into the genetic analyses and can lead to incorrect results. To adress this issue, it is important to establish a large and representative reference population that can be expanded over time. Such a reference population can help to account for variability, thereby improving the reliability of genetic analyses. However, building a sufficiently large reference population in horses remains challenging due to management practices. Horses are often spread over large geographic areas, with no centralized breeding herds, making it difficult to efficiently collect sufficient data. Additionally, while the cost of genotyping has decreased steadily over the years, the cost of phenotyping remains high, as radiological screenings are required to assess the osteoarticular status. This continues to be an important financial barrier for large-scale studies.

An additional challenge in genetic case-control association studies lies in the variability of phenotype definitions and differences in study populations, as illustrated in Supplementary Table S2. Moreover, there appears to be publication bias, as we identified only two published studies reporting no significant associations between genetic variants and OC, while all other studies reported at least one significant association. Furthermore, none of the reviewed studies used the presence of DOF as a phenotype definition. This raises questions regarding whether the absence of published genomic research on this phenotype is because no significant QTLs could be detected, or if indeed no analyses have been conducted on this disorder yet. These factors, either individually or in combination, could explain the lack of consensus among the current genetic analyses, complicating the consolidation and comparison of research outcomes and application of this information for genomic selection.

Challenges due to potential lesion-specific low heritabilities

A second factor for limited genetic progress is the potential overestimation of the assumed genetic background. Heritability estimates vary widely between breeds and even within breeds at the joint level and specific lesions within the joint. Some estimates are as high as 0.52, while others approach zero (Naccache et al., 2018; McCoy et al., 2019). Although this variability in estimates can be attributed to differences in radiographic scoring methods, level of phenotype differentiation, type of heritability estimation (pedigree- or SNP-based), statistical modelling, sample type (age, context and year of examination), sample size, population history familial structure in groups of relatives and gene frequency (Bruns, 2005; van Grevenhof et al., 2009; Jonsson et al., 2011; Distl, 2013; Hilla and Distl, 2014; McCoy et al., 2019; Zimmermann and Distl, 2023), it also suggests that in some populations, for certain types of osteochondral lesions with low heritability, the phenotype is predominantly influenced by environmental factors. This implies that differences in prevalence of some specific types of osteochondral

disorders within a population of horses may be mainly driven by differences of environmental factors rather than genetic factors.

More studies with large numbers of both genotypic and phenotypic records investigating the heritability of specific types of osteochondral disorders, such as the study by Russell et al. (2017), are necessary to accurately determine the heritability of each individual osteochondral disorder (sub)type. Once obtained, the heritability estimate of a specific osteochondral disorder, along with data on the prevalence, economic impact, and welfare implications, can help studbooks make informed decisions about whether to select against that specific disorder. If studbooks decide to select against a trait with low heritability due to substantial economic and/or welfare impact, it is advisable to first address negative environmental factors and establish a large reference population to facilitate effective selection against these traits. Additionally, genomic selection offers opportunities to distinguish whether a horse with a specific osteochondral disorder has a genetic predisposition for the disorder or if it developed the condition due to negative environmental factors. By making this differentiation, studbooks could potentially avoid excluding animals from the breeding population if they possess other desirable traits for this population. This approach can also help to maintain a larger and more diverse genetic pool.

Challenges in (inter)national studbook policies

A final factor contributing to limited genetic progress in osteoarticular health is national and international studbook politics. Most studbooks typically impose stricter regulations on stallions, while the selection process of mares is less stringent. Moreover, studbooks have the freedom to choose whether or not to test and select on health traits such as OC, DOF, and POF (WBFSH, 2024). This freedom in policy may lead to the use of affected animals for breeding within their own studbooks or their introduction into other studbooks with a liberal policy.

Conversely, certain desired traits targeted for selection may be positively correlated with the occurrence of these osteoarticular disorders, undermining health improvement. Historically, many horse breeds have undergone selective breeding to achieve increased withers height (Viklund et al., 2011; Ablondi et al., 2019; Salek Ardestani et al., 2019; Almeida et al., 2021), a practice that continues today with studbooks often requiring a minimum withers size for breeding eligibility. Moreover, breeders often focus on improving the physical appearance of foals and yearlings, particularly for auction purposes (Kronfeld et al., 1990; Harris et al., 2004), thereby promoting increased growth rates. However, these accelerated growth rates may, unintentionally, contribute to a higher occurrence of OC, DOF and POF (Sandgren et al., 1993b; Firth et al., 1999; Gee et al., 2005; Donabedian et al., 2006; Fradinho et al., 2019), raising equine welfare concerns.

Opportunities in the selection against OC, DOF and POF

In our view there are a number of actions that would contribute to a more accurate selection against OC, DOF and POF. A valuable step would be to determine the heritability of both the developmental and regenerative capacities of the subtypes of OC, DOF, and POF. Additionally, calculating the genetic and residual correlations among OC, DOF, POF, and with other traits is important. This information will help establishing the most appropriate age(s) for screening foals for selection purposes and to identify which specific conditions are worth selecting for, considering both heritability and their influence on other traits. Until these factors are scientifically established, and given the impracticality and financial burden of longitudinal screenings of foals during their first year, the optimal timing for radiographic screening remains at a minimum age of 18 months. At this age, none of the disorders can heal naturally, allowing

for a definitive radiographic status (GrØndahl, 1991; Carlsten et al., 1993; Pool, 1993; Dik et al., 1999; Baccarin et al., 2012; Jacquet et al., 2013; Santschi et al., 2020). For DOF and POF, however, distinguishing between horses that had these fragments surgically removed and those that never developed them remains challenging. A potential approach could involve written declarations or passport documentation of surgical procedures by veterinarians. However, this system would be difficult to enforce and could place veterinarians in a conflict of interest between studbooks and their clients.

Although much research has been conducted on environmental factors, many aspects still require further clarification (Van Mol et al., 2024). Consensus statements should be developed to outline optimal equine management practices for the various desired traits, and these statements must be regularly updated as new research and knowledge emerge. We believe that, alongside genomic breeding, substantial progress can be made through improved equine management, particularly in addressing osteoarticular lesions with low heritability.

Internationally accepted, uniform phenotyping protocols and phenotype definitions should be established. In our opinion, the following radiographic projections should be considered the minimum requirement for evaluating OC, DOF, and POF: lateromedial projection of all four fetlock joints; dorso(30°)lateral-plantaromedial oblique and plantaro(45°)lateral-dorsomedial oblique projections of both hocks; and caudo(60°)lateral-dorsomedial oblique projection of both stifles. If a POF is visible on the lateromedial projection of one of the fetlocks, additional dorso(45°)lateral-plantaromedial oblique and dorso(45°)medial-platarolateral oblique views of this fetlock are recomended. These views help to determine whether the fragment is at the attachment site of the lateral or medial short sesamoidean ligament at the proximal phalanx, as the laterality of POF development is thought to be influenced by different genes (Sandgren et al., 1993; Lykkjen et al., 2012; Lykkjen et al., 2013). Additional radiographs, such as those assessing navicular bone quality, osseous cyst-like lesions, vertebral malformation, and less common forms of OC, could also be valuable for research and selection purposes. However, the costs and benefits of more extensive screening protocols must be carefully weighed.

To define the OC phenotype, we suggest a semiquantitative scoring system based on the bone contour of specific anatomical predilection sites of OC: 0 - normal, 1 - flattened, 2 - irregular, 3 - notch, and 4 - notch with adjacent osteochondral fragment(s). This classification system is comparable to the one introduced by van Grevenhof et al. (2009) and provides a standardized method for characterizing OC lesions. Such a system allows for consistent phenotypic descriptions across studies and can be applied in both semiquantitative and binary (case/control) genetic analyses. For the binary genetic analyses, a “grey zone” can be established between horses exhibiting normal bone contours (score 0) and those with definitive OC lesions (scores 3 and 4). Horses classified within this grey zone can be excluded from the analysis, thereby increasing the sensitivity and specificity of the assessment by concentrating on clearly defined phenotypic extremes. However, it should be noted that this proposed system does not necessarily reflect the severity or extent of the injury; rather, it serves as a categorization tool for research and selection purposes. Additionally, since many studbooks already screen male animals, there should also be a framework that encourages the screening of female animals.

In terms of genotyping, significant efforts are being made to establish parentage control using SNP chip genotype profiles. This approach should be strongly encouraged, not only for conditions such as OC, DOF and POF, but also for other multifactorial disorders and the

selection of athletic traits in future equine performers. If all foals are genotyped for parentage control, these genotypes would be ‘on the shelf’ available for research and genomic selection. Several larger studbooks are already adopting this practice, which may pave the way for large-scale use of genomic information. To further promote this method of parentage control and address the challenges of building a large, representative dataset, a multidisciplinary approach involving international policymakers, equine veterinarians, and geneticists seems beneficial. Developing improved management practices, enhanced selection protocols, and a collaborative framework among studbooks is essential. This framework should include securing sustainable funding, creating a centralized platform for data storage and sharing, and establishing clear agreements on the ownership and legal access to phenotype data. These efforts would facilitate data access for studbooks and experts, fostering collaboration and enabling more informed selection practices. Ultimately, these advancements would benefit all stakeholders and, most importantly, contribute to enhanced equine welfare.

Conclusion

Various genes appear to play a role in the different types of osteochondral disorders, supporting the use of (genomic) estimated breeding values to enhance selection efficacy. Further analysis of pathways linked to detected QTLs and genetic variants could improve our understanding of the genetics of these disorders and advance the selection process. A recurring challenge in both genetic and environmental studies is that no two horses share the same genetic background, and large groups within one identical environment are seldom available. Additionally, the lack of uniform phenotyping protocols across studies further complicate research efforts. To address these issues, it is essential to establish precise and standardized phenotype definitions that can be consistently applied across studies. Study populations should always be as standardized as possible. However, given the nature of horse breeding, where often only a relatively small number of animals can be sampled with the same environmental background, it seems more feasible to establish large reference populations through international collaborations, thereby correcting for the noise in genomic studies caused by environmental differences. Additionally, it should be recognized that finding no association for certain phenotypes can be as important as finding a significant association, provided the study has sufficient power.

This approach would not only enhance comparability across studies but also increase the reliability of research findings, ultimately leading to improved accuracy in breeding value estimations and more effective selection strategies to reduce the prevalence of OC, DOF, and POF. Further research is encouraged, as there remains much to be clarified in the various research domains. Importantly, the multifactorial nature of OC, DOF and POF also presents an opportunity to implement a combination of environmental and genetic preventive measures that can alleviate the economic burden and, most importantly, enhance animal welfare.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi: …

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