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REVIEW

Genomic regions under selection for important traits in domestic horse breeds

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Abstract Horses were domesticated 5500 years ago, thousands of years later than other domestic animals; however, in this relatively short period, domestic horses have had a great impact on human history by accelerating civilization, revolutionizing warfare and advancing agricultural production. Modern breeding using marker-assisted selection has greatly accelerated breeding progress. Therefore, identification of genetic markers underlying the traits of interest in domestic horses is the basis for the modern breeding system. In this review, we present an overview of genetic mapping studies and genome wide analyses to identify the genomic regions targeted by positive selection for four important aspects of horses, coat color, racing performance, gait and height at withers. The *MC1R* locus, for example, has been shown to be the main gene responsible for chestnut color, and the *MSTN* locus has been shown to control the muscle fiber growth in racing breeds. The missense mutation in *DMRT3* is the causal mutation for the alternate gaits in horses. Height at withers, a quantitative trait, was mapped to four major loci (3:105547002, 6:81481064, 9:75550059 and 11:232597 32) that can explain 83% of the height variations in domestic horses.

Keywords horse, coat color, racing performance, gait, height

1 Introduction

Horses were first domesticated approximately 5500 BP[1], thousands of years later than other domestic animals, such as cattle, dogs, goats, pigs and sheep. In China, domesticated horses have not been widely found at archeological sites before the Late Shang Dynasty (approximately 3300 BP). During this relatively short period, domestic horses have had a great impact on human history by accelerating civilization, revolutionizing warfare and advancing agricultural production. Conversely, human activities have also influenced the recent evolution of domestic horses, especially development of multiple breeds with specific traits through strong selective breeding. Among these phenotypic traits, coat color, locomotion (gaits), racing performance and height at withers are the most important and easily observed domesticated traits. The height at withers was measured from the support surface of the animal to the highest point on its back. Because of the rapid progress in sequencing and genotyping techniques, the horse reference genome assembly was generated from a thoroughbred mare, Twilight[2], and the horse 50K SNP array was developed by the Equine Genome Diversity Consortium[3]. In this review, we focus on the recent advances in horse genomics through the mapping of candidate genomic regions targeted by selection during horse domestication. Positive selection, a force that drives the increase in the prevalence of traits that are advantageous or useful for humans, has played a central role in the domestication of animals[4].

2 Genes and genomic variations under selection for economically important traits

2.1 Coat color variation

Coat color was one of the earliest selection targets during horse domestication. Currently, domestic horses exhibit a wide variation in coat colors ranging from a unified single color to a composite coat (Table 1). Previous genetic studies have shown that coat color variations appeared rapidly during domestication[3], and many genes involved in melanin production and distribution have had an important role in the development of coat color in domesticated animals. *MC1R* (melanocortin 1 receptor),

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Table 1 Causative mutations for coat coloration in domestic horses

Causative mutation	Breed	Color	Gene ID	Reference
83Ser-Phe	European breeds	Chestnut	*MC1R*	[5]
83Ser-Phe	Morgan and Belgian horses	Chestnut	*MC1R*	[3]
4.6-kb duplication in intron 6	Gray horse	Gray	*STX17*	[6]
1617-bp insertion	Dun horse	Dun	*TBX3*	[7]
C189T	Mongolian horse	Chestnut	*TYRP1*	[8]

ASIP (agouti signaling protein), *TYRP* (tyrosine transporter), and *PMEL17* (premelanosome protein) are the candidate genes for coat color, and many mutations in these genes associated with variations in coat colors of chickens[9], sheep[10] and pigs[11] have been identified.

In early 1996, a single nonsynonymous mutation (83Ser-Phe) in the *MC1R* gene, which created a *Taq*I restriction site in the chestnut allele, was found to be responsible for the chestnut color in horses[5]. In Morgan and Belgian horse breeds, it was found that the *MC1R* missense mutation has been fixed, leading to the chestnut-base coat color[12]. The horse 50K SNP array was also used to map the chestnut color in American, Asian and European horses, resulting in identification of a conserved 750 kb haplotype at the *MC1R* chestnut allele across all breeds[3]. Furthermore, the agouti (*ASIP*), extension (*MC1R*), and brown (*TYRP*) loci were detected in European[13] and Przewalski's horses[14].

The gray coat color in horses has been mapped to a 4.6-kb duplication in intron 6 of the *STX17* gene (syntaxin-17), which is a cis-acting regulatory mutation[6]. The gray horses also carry a loss-of-function mutation in the agouti *ASIP* locus. Meanwhile, in Arabian and Lippizaner horses, the gray allele is associated with the increased risk of melanoma; further analyses reported a copy number expansion of the *STX17* gene in melanoma tissues of gray horses[15,16]. Therefore, increase in the copy number of the *STX17* gene was used by researchers as a marker to assess the risk of melanoma in Quarter horses[17], which makes disease prevention at an early stage possible.

Another example of coat color selection in horses is the wild-type dun coloration caused by a 1617-bp insertion in the *TBX3* locus on chromosome 8[7]. The dun color is the ancestral coat color of equids. A dun individual is mostly pale in color, but carries intensely pigmented primitive markings, most notably, a dorsal stripe. The *dun* mutation causes radially asymmetric expression of the transcription factor TBX3 in hair follicles, leading to a circumferential distribution of melanocytes in the individual hairs. Polish Konik horses have been reported to carry two new variants in this locus[18].

There are very few mapping studies of the coat color in native Chinese horses. A missense mutation in exon 2 of the *TYRP1* gene was detected in the chestnut color Chinese Mongolian horses[8]. The *STX17* duplication has been observed in most Chinese indigenous horses, except Balikun and Guanzhong breeds; however, the frequency of gray coat color in Chinese horses has been found to be relatively low[19].

2.2 Racing performance

In the last few hundred years, humans have favored horses with greater strength, racing speed or endurance and have selected specialized horse breeds with excellent racing performance. Racing performance varies among different breeds and is of high economic importance to the modern equine industry. Quarter horses, for example, are famous for their performance in 400 m sprints, and thoroughbreds, which have been introduced around the world, race distances ranging from 1 to 3.2 km. The famous Akhal Teke horses can compete in endurance races over 160 km. A SINE insertion in the promoter region and a SNP (g.66493737C/T) in the first intron of the *MSTN* (myostatin) gene have been found to be significantly associated with the fiber type proportions and diameter as well as with the muscle fiber composition in quarter horses[12]. Additionally, this mutation was suggested to be more predictive of optimal racing distance in thoroughbreds than a SINE insertion[20]. A SNP (g.66493737C/T) in the *MSTN* gene showed significant association with racing performance; the C/C genotype horses are better suited to fast but short-distance races, the C/T genotype horses compete favorably in middle-distance races, and the T/T genotype horses have greater stamina for long-distance races[21]. A larger population of 1396 horses was used in another study to validate the gene in a genome-wide association study (GWAS) and an estimated breeding value (EBV) analysis[22]. Notably, the *MSTN* locus was also found in Chinese horse breeds[23]. All these studies indicate that the *MSTN* locus has a pivotal role in race horse performance.

In Chinese horse breeds, six SNPs (g.26T > C, g.156 T > C, g.587A > G, g.598C > T, g.1485C > T, g.2115 A > G) in the *MSTN* gene were detected by sequencing[23]. Unfortunately, no racing performance association studies have been conducted in these horses and it would, therefore, be meaningful to know whether the *MSTN* locus is associated with racing performance in Chinese horse breeds.

The *MSTN* locus is not the only determinant of racing performance in horses. A coevolving gene cluster on chromosome 22 has been subjected to strong artificial selection in Korean thoroughbred racing horses, representing a different mechanism from European thoroughbred breeds. This gene cluster contains the *RALGAPA2* gene (Ral GTPase-activating protein catalytic alpha subunit 2), which regulates a variety of cellular processes in signal trafficking. The neighboring genes, *INSM1* (insulinoma-associated 1), *PLDN* (pallid), and *RIN2* (ras and rab interactor 2), have similar roles in signal trafficking[24].

2.3 Gaits

Horse locomotion has also been recurrently selected, in particular, the ability to perform alternate gaits. The alternate gaits are typical characteristics of horse breeds and can be classified into four categories: pace, regular rhythm ambling, lateral ambling and diagonal ambling, according to the pattern of timing and sequence of footfalls. One of the milestones in the horse gait research was published in the journal *Nature* in 2012. The authors mapped the gait trait to the *DMRT3* gene (doublesex and mab-3 related transcription factor 3). The causal mutation results in a premature stop at codon 301 in *DMRT3*, which has a substantial effect on the ability to perform alternate gait in horses and locomotion in a knockout mouse model[25]. Further validation of this mutation was performed in the worldwide horse populations[26]. In Finn horses, individuals carrying the AA genotype had better race performance, whereas CC and AC individuals appeared to be better adapted for classical riding disciplines[27]. In Nordic and Standard bred horses, examples with the AA genotype obtained evaluation of breeding values (EBVs) higher than other genotypes in the same pedigree[28]. In Icelandic horses, which are a famous multigaited horse breed, the AA genotype reinforces the coordination of ipsilateral legs, whereas the CA genotype has a negative effect on synchronized movement of diagonal legs[29]. In China, Chakouyi, an ancient post horse with the ability to pace, was reported to have a high frequency (67.2%) of the *DMRT3* mutation[30]. In summary, the *DMRT3* mutation (the causal mutation for gaits in horses) has practical implications for the breeding and training of multi-gaited horses. Other studies have also reported trot[31], dressage[32] and jump[33] performances of horses.

2.4 Height at withers

Height is an easily observed phenotype in the horse and varies markedly in domestic horses, ranging from 80 cm tall at withers in the Shetland pony to more than 2 m in Shire and Percheron horses (Table 2). This intraspecies range in heights is only exceeded by the height variations in domestic dogs[37]. A height of 148 cm at withers is the defined criterion for classifying ponies. Shetland and Debao, two of the most famous pony breeds, have heights less than 100 cm. The heritability of height was estimated to be medium to high in pony breeds. With the development of high-throughput sequencing technology, four loci that can explain 83% of horse size variations were identified, including 3:105547002, 6:81481064, 9:75550059 and 11:23259732, as well as four nearby genes also associated with height, *LCORL* (ligand dependent nuclear receptor corepressor-like), *NCAPG* (non-SMC condensing I complex subunit G), *HMGA2* (high mobility group AT-hook 2), and *ZFAT* (zinc finger and AT-hook domain containing)[34]. Of the four, loci 3:105547002 can account for 18% of body size variations[38]. This result was further validated in Franches-Montagnes horses[39]. In German Warmblood horses, the *LCORL*/*NCAPG* locus (3:105547002) has a strong association with height at withers[40]. Additionally, the relative expression levels of *LCORL* demonstrated a significant association with the size of the horses[41], indicating that this gene could become a potential marker for molecular breeding of height at withers. Two recent papers have reported that missense mutations in *HMGA2* (c.83G > A; p.G28E) and *ACAN* (g.94370258G > C) have a strong association with dwarfism in Miniature Shetland ponies[35,42].

In Chinese horse breeds, in addition to the *HMGA2* locus, *TBX3* (T-box 3) is most substantially associated with small stature of Debao ponies, a native breed in South-west China, which have potentially unique genetic components underlying their small stature[36]. Large deletions in the pseudoautosomal region of chromosome X/Y have been associated with dwarfism in Shetland ponies[43].

3 Adaption to extreme environments

Animals living on high plateaus have adapted to the high-altitude conditions, such as hypoxia, low temperature, high solar radiation and lack of biological production. The genetic mechanism for adaption to high altitude appears to be more complicated than any other phenotype. In feral Andean horses introduced to the high Andes by the Spanish in the 1500s, *EPAS1* (endothelial PAS domain protein 1) coding for a transcription factor involved in the

Table 2 Causative mutations for the height at withers in domestic horses

Causative mutation	Breed	Average height/cm	Gene ID	Reference
3:105547002, 6:81481064, 9:75550059 and 11:23259732	European	80–200	*LCORL*, *NCAPG*, *HMGA2*, *ZFAT*	[34]
c.83G > A; p.G28E	Shetland	80	*HMGA2*	[35]
ECA8.18101000 and ECA8.18120526	Debao pony	106	*TBX3*	[36]

hypoxia-induction-pathway was identified as a significant selection signal[44]. Yakutia is among the coldest regions in the Northern Hemisphere, with winter temperatures dropping below −70°C; Yakutia horses have lived in this region for six to eight centuries. Using comparative genomics analysis, two candidate genes *BARX2* (BARX homeobox 2) and *PHIP* (pleckstrin homology domain interacting protein) associated with hair development and insulin metabolism, respectively, were identified as contributing to the adaptation of Yakutia horses[45].

4 Conclusions and prospects

Recently high-throughput sequencing has contributed greatly to illustrate the genomic mechanisms underlying a variety of economic traits in horse breeds. Some of the newly discovered causative mutations in association to these economic traits have been applied to the progeny test and selective breeding in horse industry. In future, the application of genome selection in horse breeding and the progress of the accurate phenotypic testing for these economic traits as well as the adaptation traits will facilitate the identification of more reliable candidate genetic markers with the function validation and the improvement of the current horse breeds.

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Compliance with ethics guidelines Xuexue Liu, Yuehui Ma, and Lin Jiang declare that they have no conflicts of interest or financial conflicts to disclose.

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