DEVELOPMENT OF HORSE MOLECULAR GENETICS AND THE DIAGNOSTICS OF MOST IMPORTANT MONOGENIC HEREDITARY DISEASES

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SUMMARY

Horses (*Equus caballus*) are an early-domesticated species, and they have been selected for many traits during hundreds of years. Nowadays, novel gene-based approaches have started to replace initial phenotypic features in selecting strategies. Developing molecular biological techniques have made possible a better understanding of horse diseases at the genome-wide level. Identification of specific gene mutations, or polymorphisms, by modern molecular methods would be an effective, cheap, and rapid tool to detect new genetic features of traits and diseases. The main aim of the review is to introduce the most common monogenic diseases in horses. The general genetic basis and effects of novel methods in horse genetics have been introduced. Furthermore, the notable stages of horse genomic research have been summarized. Besides the genetic alterations, the important clinical symptoms, current therapies, and the possible opportunities for prevention have been underlined.

Szíszkosz N. - Jávor A. - Kusza Sz.: A LOVAK MOLEKULÁRIS GENETIKAI VIZSGÁLATAINAK FEJLŐDÉSE ÉS A JELENTŐSEBB MONOGÉNES BETEGSÉGEK DIAGNOSZTIKÁJA

ÖSSZEFOGLALÁS

A háziló (*Equus caballus*) a legelső háziasított fajok közé tartozik, különböző tulajdonságokra végzett szelekciója több száz éven keresztül történt. Napjainkban a genetikai alapokon történő szelekció kezdi átvenni a szerepet a fenotípusos tulajdonságok alapján történő kiválasztással szemben. A folyamatosan fejlődő molekuláris biológiai technikák lehetővé teszik a lovak betegségeinek genomiális szintű diagnózisát is. A legújabb módszereknek köszönhetően mára elérhetővé vált az egy-egy tulajdonságért vagy betegségért felelős a specifikus génmutációk vagy polimorfizmusok hatékony, olcsó és gyors azonosítása. A közlemény célja a leggyakoribb monogénes betegségek összefoglalása, mely során az általános genetikai alapok mellet bemutatják modern molekuláris genetikai eszköztár alkalmazási területeit. A genetikai változások mellett leírják a főbb klinikai tünetek, az aktuális terápiákat és a megelőzés lehetőségeit. Továbbá, az olvasó megismerkedhet a lovak genomikai kutatásainak nevezetes mérföldköveivel is.

INTRODUCTION

Advancement of molecular biology is still unbroken after double-helix structure of DNA was discovered in 1953. DNA research could bring novel possibilities for scientists, particularly in the field of human investigations. However, animal researches are always slightly behind human studies, molecular era has changed it in basis as well; molecular biology has also an effect on animal husbandry. Initially, phenotypic features were almost the only starting point of vetenarinarian diagnosis or the basis of selection in animal breeding. In the beginning of the 20th century, several investigations have started to focus on blood groups and biochemical polymorphisms (*Andersson et al.,* 1987); nowadays, novel molecular experiments could allow the evaluation of horse genome in many different aspects (*McCue et al.,* 2012).

Horses have been selected for many traits during hundreds of years and they have a significant economic benefit (*Hintz,* 1980, *Gu et al.,* 2009). Horse sports like show-jumping or horse polo are popular all over the world, and they had been an essential part of military by the last century. Moreover, horses still act a prominent role in agriculture. This unique variegation indicates the importance of disease prevention of horses, and molecular genetics could be one of the several tools, that could facilitate this issue. The implementation of the Horse Genome Project was the greatest breakthrough in horse molecular genetics (*Finno et al.,* 2009); since then, knowledge of the structure and organization of the equine genome has grown rapidly (*Table 1.*) (*Brenner,* 2001). Disease specific gene tests could make a rapid diagnosis, while specific genetic markers of valuable traits could help to choose the direction of selection in the future (*Hayes et al.,* 2010; *McCue et al.,* 2012). *Table 2.* presents the frequent monogenic horse diseases, additional information on less frequent genetic diseases are summarized in a review paper (*Zöldág*, 2011). Recently, equine researchers have focused mainly on coat colour, genetic diseases and the genetic background of several important measures of valuable characters (*Rieder,* 2009; *Barrey,* 2010; *Georgescu et al.*, 2011).

The aim of our review is to give an compherensive overview on the progression of horse (*Equus caballus*) genetics. We focused on the most common monogenic disorders in horses enphasizing the novel results of molecular studies regarding this diseases.

FREQUENT MONOGENIC HORSE DISEASES

Polysaccharide Storage Myopathy (PSSM)

Polysaccharide storage myopathy is a glycogen storage disorder, it can be characterized by a variant of episodic exertional myopathies found in several equine breeds. There are several symptoms of the disease, including muscle atrophy, exercise intolerance, skin twitching, back pain, stiffness, difficulty getting up, trembling after exercise, and cramping. Since the disease had been controlled by a specific diet (eliminating carbohydrates such as grains and sweet feed) and changes the exercises, the importance of specific genetic markers has been rapidly increased targeting the earlier diagnosis. PSSM can be divided into two forms (type 1 and 2 PSSM). Type 1 PSSM are frequent among the following breeds: quarter horse-related bloodlines, Belgians, Mustangs, Percherons, Morgans, and

Table 1.

Main milestones in horse molecular genetics

Year	Main steps of *Equus* genetic researches	References
1992 - 1997	*Lear et al.* analysed synteny panels between horse and human. The first equine microsatellites markers were localized.	(*Lear et al.,* 1992), (*Breen et al.,* 1997)
1999	The International Equine Gene Mapping Workshop published a second-generation horse linkage map based on testing 503 half-sibling offspring from 13 sire families. Their map includes more than 300 markers in 34 linkage groups representing all the 31 autosomes excepting the sex chromosomes. Furthermore, a comprehensive comparative map between these two species was reported by *Caetano et al.* Their study contained 68 equine type I loci. *Oakenfull et al.* first examined the horse genome by fluorescence *in situ* hybridization (FISH) techniques to analyse the localisation of the alpha-globin gene complex.	(*Guérin et al.,* 1999), (*Caetano et al.,* 1999), (*Oakenfull et al.,* 1993)
2001	*Lindgren et al.* published 13 more genes using FISH and somatic cell hybrids.	(*Lindgren et al.,* 2001)
2002	*Milenkovic et al.* reported one of the first large-scale FISH-map that included 136 genes.	(*Milenkovic et al.,* 2002)
2005	In 2005 *Musilova et al.* reported additional 19 immunity-related loci.	(*Musilova et al.,* 2005)
2006	A medium density horse gene map was developed, contains 87 genes those were detected by FISH and 186 genes by the equine 5000-rad RH panel. Moreover, a previously unknown homology was detected between ECA27 and HSA8, as well as between ECA12p and HSA11p.	(*Perrocheau et al.,* 2006)
2006	*Swinburne et al.* generated another linkage map contains 742 markers in 32 linkage groups involving all autosomes and the X-chromosome.	(*Swinburne et al.,* 2006)
2006 2007	The horse genome sequence was completed with sequence available online for researchers. A year later, the equine gene map contained 713 genes, and a Thoroughbred mare named Twilight was chosen for whole genome sequence due to her inbred nature.	(*Bannasch,* 2008), (*Stübs et al.,* 2007)
2009	Up to 2008 the *Equus* gene map contained approximately 5000 markers. The EquCab2.0 and the EquineSNP50, which is an SNP-based microarray, was also available.	(*Goddard et al.,* 2009), (*Andersson et al.,* 2008)
2011	According to the first epigenetic study in horse, the spermatogenesis can be a model system for examining of the regulatory networks leading to the epigenetic control of gene expression during XY body formation.	(*Baumann et al.,* 2011)
2012	Copy number variations (CNVs) were also analysed in horses. The results suggest that CNVs are common in the horse genome. CNVs may modulate some biological processes underlying different characters observed between horses and horse breeds.	(*Doan et al.,* 2012)
2012	The first sequencing-based horse transcriptome data were described in 2012. In this study, six thoroughbred horses were analysed before and after exercise using RNA-Seq. Deferentially expressed genes and candidate genes were found that are related to the exercise.	(*Park et al.,* 2012)

1. táblázat. Fontosabb mérföldkövek a lovak molekuláris genetikájában

some warm-blood breeds. On the other hand, Arabians and other light breeds, as well as the quarter horse-related breeds, can be affected with type 2 PSSM. Both forms of PSSM have an own inheritance pattern. Type 1 PSSM follows an autosomal dominant inheritance, thus mutated phenotype manifests in heterozygous and homozygous individuals as well (*Bannasch,* 2008). *McCue et al.* (2008) reported a gain-of-function mutation in the glycogen synthase enzyme-encoding (*GYS1*) gene and haplotype analysis and allele age estimation showed this mutation follows similar inheritance pattern among horses from different breeds. The characteristic mutation of *GYS1* is in exon 6 in the skeletal muscle, resulting in an amino acid substitution (arginine to histidine) (*Rosie et al.,* 2012). Genetic tests are already available for the verifications of type 1 PSSM from mane or tail hair roots, and unclotted blood samples. Detection of amylase-resistant crystalline polysaccharide from muscle biopsy samples is also available, but it is an invasive method. In contrast to PSSM1, causative gene alterations have not known in PSSM2. Since, therefore there are no genetic tests and muscle biopsy is the only way for diagnosis. A decision tree could facilitate the diagnosis of PSSM. According this algorithm, muscle biopsy is indicated only in that case when PSSM mutation analysis is negative (*Söderqvist et al.*, 2013). *McCue et al.* (2008) studied the ryanodine receptor 1 gene (*RYR1*) mutation that can also be associated with PSSM in American Quarter Horses and Paint horses. They established that horses with both the *GYS1* and *RYR1* mutations have a more severe clinical phenotype than horses with the *GYS1* mutation alone (*McCue et al.,* 2009).

Malignant Hyperthermia (MH)

Malignant hyperthermia is a hereditary muscle disorder without any symptoms until exposing the animal to anaesthesia, stress or extreme exercises. The disease follows autosomal dominant inheritance; quarter horses and related breeds are affected in the majority of cases (*Finno et al.,* 2009). *Aleman et al.* (2009) investigated anaesthetic-induced and non-anaesthetic manifestations of malignant hyperthermia. They confirmed that a single point mutation in the *RYR1* at nucleotide 7365 (C7360G) results in an amino acid substitution in MH (*Table 2.*) (*Aleman et al.,* 2009). *RYR1* mutation can also associate with *GYS1* mutation in PSSM (*McCue et al.,* 2009). The symptoms develop rapidly, without a quick treatment, it could be fatal if they are not treated quickly. The typical signs of the disease are high body temperature, acidosis, abnormal heart rhythm, increased heart rate, muscle rigidity, shallow breathing, high blood pressure and sweating (*Pirone et al.,* 2010).

Hereditary Equine Regional Dermal Asthenia or Hyper-elastosis Cutis (HERDA or HC)

This autosomal recessive disorder is caused by a fatal error during skin formation (*Finno et al.*, 2009). The conditions of HERDA are usually expressed by the age of two. The first sign typically occurs short after the horse is saddled first time when the skin becomes hyper-extensible and severe wounds will be at the back. *Tryon et al.* (2007) identified a mutation in the equine (peptidil prolylisomerase B, *PPIB*) gene on ECA1 (*Equus caballus* chromosome 1) (*Table 2.*), that is associated with HERDA in the American Quarter Horse by using the homozygosity mapping

Table 2.

The frequent monogenic horse diseases

Diseases	Synonyms	OMIA ID	Affected gene(s)	Encoded protein
Glycogen Branching Enzyme Deficiency (GBED)	Glycogenosis type IV, Polyglucosan body disease, Amylopectinosis	000420-9796	*GBE1*	Glycogen branching enzyme
Hereditary Equine Regional Dermal Asthenia (HERDA**)**	Cutaneous asthenia	000327-9796	*PPIB*	Peptidil prolyl isomerase B
Herlitzjunctional epidermolysis bullosa (H-JEB**)**	Epidermolysis bullosa, junctional	001677-9796; 001678-9796	*LAMA3, LAMB3, LAMC2*	Laminin - alpha 3, Laminin– beta 3, Laminin - gamma 2
Hyper-kalemic Periodic Paralysis (HyPP**)**	Periodic paralysis II in *Equus caballus*	000785-9796	*SCN4A*	Sodium channel, voltage-gated, type IV, alpha subunit
Lethal White Foal Syndrome (LWFS/ OLWFS/ LWS**)**	Overo Lethal White Foal Syndrome, Lethal White Syndrome	000629-9796	*EDNRB, RAB27A, MYO5A*	Endothelin receptor type B, Ras-associated protein RAB27a, Myosin Va
Malignant Hyperthermia (MH)	N/A	000621-9796	*RYR1 GYS1*	Ryanodine receptor 1 (skeletal), Glycogen synthase 1 (muscle)
Osteochondrosis (OC)	N/A	000750-9796	*N/A*	Candidate genes on ECA 2, 4, 16, 18, 28 and 30
Polysaccharide Storage Myopathy (PSSM**)**	Exertional rhabdomyolysis in *Equus caballus*	001158-9796	*GYS1, RYR1*	Glycogen synthase 1 (muscle), Ryanodine receptor 1 (skeletal)
Severe Combined Immunodeficiency (SCID**)**	N/A	000220-9796	*DNA-PKcs*	DNA-dependent kinase

2. táblázat. Gyakori monogénes lóbetegségek

method. They found a missense mutation (c. 115G>A) in *PPIB* gene that alters a conserved glycine residue. According to a recent comprehensive molecular genetic study, the heterozygote form of g.901C>T SNP polymorphism in *PPIB* gene is associated with chestnut coat colour. On the other hand, a homozygote form of g.66493737C>T and g.22684390C>T SNPs are related to racing endurance in Thoroughbred horses (*Doan et al.,* 2012). The specific gene test could detect affected horses prior to development of clinical signs and carriers of HERDA. Improving specific gene tests is an urgent problem, because this incurable feature of this illness requires euthanizing the affected horses.

Lethal white foal syndrome (LWFS)

This disorder is also known as overo lethal white foal syndrome (OLWFS) or lethal white syndrome (LWS), as well as lethal white overo (LWO). Affected foals are almost completely white and characterized aganglionosis in the intestines; therefore, the foals die shortly after birth (*Webb et al.,* 2010). LWFS is caused by

a point mutation in the endothelin B receptor (*EDNRB*) gene on the ECA17, and it follows an autosomal recessive inheritance (*Table 2.*). The tipycal LWFS phenotype manifests when affected horses have both mutated alleles of *EDNRB* gene, while carriers do not display any clinical signs of disease (*Bannasch,* 2008). The gene abberation results in a Ile to Lys substitution at codon 118 of the protein (*Santschi et al.,* 1998). This congenital illness frequently express in American paint horses. A human disorder, Hirschsprung disease is very similar to LWFS, thus it could facilitate for the researchers to understand the genetic background of LWFS in horses. Ras-associated protein RAB27a (*RAB27A*) and myosin Va (*MYO5A*) are novel candidate genes of this disease. *Brooks et al.* (2010) reported candidate locus of LFS using SNP chip. The whole genome scan identified an associated region containing these two functional genes. Mutation analysis of *MYO5A* identified a single base deletion in exon 30, changing reading frame of sequence and resulting in an early stop codon. A PCR–RFLP (restriction fragment length polymorphism) method used to investigate the frequency of the mutant gene. Genetic tests are available for detecting this disease (*Brooks et al.,* 2010).

Herlitz junctional epidermolysis bullosa (H-JEB)

Herlitz junction epidermolysis bullosa (H-JEB) has been described in Belgian draft horses, American Cream Draft, Breton drafts, Comtois, and American Saddlebreds. Interestingly, approximately 17% of Belgian horses in North America are carriers. In European breeds about 8–27% of horses are carriers and about 3% of Saddlebreds are heterozygous. Foals are born alive, but the symptoms occur soon after birth. The typical clinical signs are abnormal reddening, developing festering on the skin, in addition to cockling of the skin and mouth epithelia. The malfunction of the laminin 5 heterotrimetic basement membrane protein plays an advantage role in this lethal disease. The three genes mentioned encoded the three glycoprotein subunits of laminin 5, called α3, β3 and γ2 chains. Alterations in the *LAMA3, LAMB3* or *LAMC2* gene can be responsible for the development of this disease (*Table 2.*). *Graves et al.* (2009) identified a 6589bp deletion involving exons 24–27 in the LAMA3 gene on ECA8, and created a molecular gene test. This alteration was found in American Saddlebred foals that showing the typical symptoms of illness. (*Graves et al.,* 2009; *Doan et al.,* 2012). This disease also occurs in humans (*Pulkkinen et al.,* 1994), cats, sheep, and dogs (*Milenkovic et al.,* 2003). *Milenkovic et al.* (2003) demonstrated in two breeds (Breton and Comtois) that JEB are homologous to human H-JEB, and they proposed the use of genetic guidance based on a fast molecular test for the identification of healthy carriers. Furthermore, they detected a mutation in the exon 10 of the LAMC2 gene on ECA5 (*Milenkovic et al.,* 2003; *Doan et al.,* 2012).

Hyper-kalemic Periodic Paralysis (HyPP)

Hyper-kalemic Periodic Paralysis is a hereditary disorder resulting in abnormalities in skeletal muscles. The illness can occur in humans, and follows an autosomal semi-dominant inheritance. It means, heterozygous horses have an intermediate phenotype; whereas homozygous horses have a more severe phenotype (*Bannasch,* 2008). American Quarter horse-related breeds are affected and can suddenly die due to attacks of paralysis. Additional symptoms may present,

usually at 2 to 3 years of age, including muscle trembling, abnormal whinny and generalized weakness. Since heterozygous horses are also affected, it is the reason why it is important to test horse carriers. Hyper-kalemic periodic paralysis was the first horse genetic disease to be detected by a specific DNA test due to the base-pair sequence substitution in the *SCN4A* gene (*Bannasch,* 2008). Muscle fibre contractions are controlled by the sodium channels in the muscle cell membrane. A point mutation in the sodium channel gene is responsible for HyPP, resulting in defective sodium channels; therefore, muscles will be overly excitable. DNA sequence analysis detected a mutation in the aforementioned *SCN4A* sodium channel gene on ECA11 (*Table 2.*) (*Rudolph et al.*, 1992). The analysed samples are amplified using two primer pair for an internal control of the polymerase chain reaction. The method can separate the homozygous affected and heterozygous affected, as well as healthy horse genotypes (*Finno et al.*, 2009).

Severe combined immunodeficiency (SCID)

This is an autosomal recessive disease frequently occurs in Arabian horse breeds. A 5-bp long deletion generates frame-shift mutations in the catalytic subunit of DNA-dependent kinase gene (*DNA-PKcs*) on ECA9 (*Table 2.*). This genetic alteration results in the lack of a full-length kinase (*Wiler et al.*, 1995). The deleterious effect of DNA-PKcs mutation can result in disturbed B and T lymphocyte maturation (*Brosnahan et al.*, 2010). Consequently, affected foals are defenceless against pathogens, because the lack of normal function of cellular or humoral immune responses. There is no any clinical sign of the disease at birth, but the foals will die as a result of infections (adenovirus or *Pneumocystis carinii*) as soon as the level of maternal antibodies will be decreased. The incidence of heterozygous carriers Arabians is 8.4% in the USA; furthermore, heterozygote horses are associated with an increased incidence of sarcoid tumours (*Brosnahan et al.*, 2010). *Piro et al.* (2011) determined the frequency of the disease in Morocco using a DNA-based test. Twenty-one horses were carriers: 14 Arabians, 6 Arab-Barbs and one Anglo-Arab horse. In addition, analysing these horses' genealogies showed that three imported stallions dispersed the mutant gene variant of *DNA-PKcs* in Morocco. Normal and carrier horses could be better distinguished using more molecular markers to identify the heterozygous individuals. A research group in Morocco used 17 microsatellite DNA loci routinely to verify horse parentage. They estimated genetic diversity among normal Arabian horses, SCID carrier Arabian horses, normal Arab-Barb horses, and SCID carrier Arab-Barb horses (*Piro et al.*, 2011).

Glycogen Branching Enzyme Deficiency (GBED)

Glycogen branching enzyme deficiency (GBED) is an autosomal recessive inherited disease. Affected horses are unable to store enough energy to fuel their muscles and the brain or other organs. A point mutation in exon 1 in the glycogen branching enzyme gene (*GBE1*) gene (ECA26q12-q13) is responsible for disease (*Table 2.*) (*Brosnahan et al.,* 2010). There is a C to A substitution at base 102 that results in a tyrosine (Y) to stop (X) substitution in codon 34 of exon 1 in the *GBE1*. GBED is always fatal; the symptoms include contracted muscles and low body temperature (*Brosnahan et al.*, 2010). In affected foals, there is no

measurable GBE-enzyme activity or immune-detectable GBE, and because of this, they cannot form normally branched glycogen in tissues.

Osteochondrosis (OC)

Osteochondrosis is considered to be one of the most important problems in European sport horse breeding, as the frequency of OC is 25% or more in certain populations (*Lewczuk et al.,* 2012). Osteochondrosis (OC) is a severe bone development abnormality, which can also occur in humans and other animals, however, it is most frequent in pigs, dogs and horses. Tiny cracks and breaks in the cartilage on the bone surface are the important features of OC. These malformations can also result in a reduced value and utility of the animal. The healthy development of bones is under genetic regulation, and it depends on feeding and the training. Some evidence of a genetic component to OC exists, but the complete background is still unclear (*Corbin et al*., 2012). Novel molecular techniques (e.g. whole genome scan, candidate gene analysis and SNP microarrays) become very promising tools to analyse the molecular background of osteochondrosis. Potential candidate genes were identified on ECA2/4/16/18/28 and ECA30 (*Table 2*.) (*Lewczuk et al.,* 2012). In a recent study, *Corbin et al.* (2012) identified quantitative trait loci (QTL) associated with osteochondritis dissecans (OCD) in Thoroughbreds by GWAS. They found that an SNP on ECA3 is associated with OCD at a genome-wide level and localised in the intergenic region of the genome. In addition, they also tested the effect of previously identified QTL in the current population; for this reason, the effects of 24 SNPs were directly tested. The significant SNP was aligned on ECA3, and two of 24 SNPs were found to be associated with OCD (*Corbin et al.,* 2012).

DISCUSSION

In the last century, agriculture hereby animal husbandry as well as horse breeding have fundamentally changed due to novel molecular investigations. Analysis of the different traits, diseases, and various infections have become possible at DNA or genome-wide levels. Realising the horse genome caused the greatest breakthrough in horse molecular genetics; novel molecular markers could slowly replace the classical phenotype-based selection methods in the future. Moreover, these findings could affect rapid genetic disease identification. DNA-based tests play a prominent role in the quick identification of hereditary diseases and they also allow the identification of major genes and genetic markers linked to QTL (*Stock et al.,* 2013). In addition, a genetic test for specific genes could define how horses will be managed and trained to reduce the risk of disease and injury. It also could facilitate the improvement of methods for prevention, diagnosis and treatment of many conditions (*Chowdhary et al.,* 2008).

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