



THE EFFECT OF A COAT COLOUR-ASSOCIATED GENES POLYMORPHISM ON ANIMAL HEALTH – A REVIEW

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Abstract

In recent years, the knowledge regarding molecular mechanisms of skin, hair and eye colouration in vertebrates has significantly broadened. It was found that some of the identified coat colour genes show negative pleiotropic effect. They are associated with hereditary diseases, often of a lethal character. Most of these diseases have their counterparts in humans. There is no effective treatment for these diseases, therefore animal models can help to identify the genetic background of diseases and to develop appropriate treatment. Much less is known on the association of coat colour with animal performance. However, there are reports on the effect of coat colour on body measurements and milk production in subtropical environments. The knowledge on pleiotropic effects of coat colour genes is important for breeders who should be aware of the consequences of their decision on mating animals with given genotype.

Key words: coat colour, diseases, productivity, pleiotropic effects

Coat colour in animals does not only play an aesthetic role, but also has substantial impact on many factors indispensable for survival. In wild animals it facilitates camouflage against predators, and it may affect herd position and natural selection. Some of the identified coat colour controlling genes show pleiotropic effect while also affecting behaviour and disorders, often of lethal character. Most of these diseases have their counterparts in humans (Reissmann and Ludwig, 2013). Advanced knowledge on domestic animal genome organisation and its modification (e.g. gene knockout and gene therapy) has brought new opportunities to consider some of species as useful models for human hereditary diseases. Among them pig (Flisikowska et al., 2014) and dog (Switonski, 2014) are the most important species.

In domestic animals coat colour genes are mainly studied for their association with various disorders. These disorders should be a particular concern of breeders

because they cause not only suffering or even death of affected animals but also are an important cause of economic losses. There are also evidences that coat colour genes influence production and reproduction traits (Becerril et al., 1993; Johansson et al., 2005), having an impact on economic effects of animal breeding.

The aim of this review is to show the pleiotropic effects of coat colour genes on animal health.

Coat colour genes associated with the health state of animals

Coat colour is determined during embryonic growth. Melanins (eumelanin and pheomelanin) are synthesized and stored in melanosomes, which are large organelles of melanocyte. Melanocytes are present not only in skin, but also in ears, eyes, brain, heart, lungs and adipose tissue (Bellone, 2010). Melanocyte precursor cells (melanoblasts), coming from the neural crest, migrate into the skin, follicles, eye, inner ear and other organs. If such migration is disrupted, some skin areas do not have melanocytes and their hair cover is white (Ferreira dos Santos Videra and Magina, 2013). Variation of pigmentation results from differences in size, shape and transport of melanocytes to the particular skin area, as well as differences in the amount and type of melanins which are synthesized (Hirobe, 2011). All of these factors as well as melanogenesis process are determined by a number of genes, most of them having pleiotropic effects. There are also other genes (e.g. *AP3B1* and *LYST*), which are responsible for biological processes and their impaired functioning results in an aberration of a coat colour (Jung et al., 2006; Kaplan et al., 2008).

***KIT* gene**

The *KIT* gene encodes tyrosine kinase receptor, which is the stem cell growth factor receptor. This protein plays a very important function in controlling differentiation, proliferation and survival of melanocytes and mast cells, and also participates in gametogenesis, hematopoiesis and T cell differentiation (Johansson et al., 2005; Fontanesi et al., 2010; Haase et al., 2009). The dominant allele of the *KIT* gene encodes defective transmembrane protein, unable to transmit signal, which disrupts melanocyte migration. The absence of melanocytes in the skin may lead to partial (piebaldism) or totally white coat colour. Individuals of this phenotype typically have coloured eyes. *KIT* gene has been extensively studied for its role in the health state of domestic animals while its mutations may have lethal effects.

In horses a single nucleotide polymorphism (SNP) in intron 3 of *KIT* gene, located on chromosome 3(ECA3q22), is associated with white phenotype (Mau et al., 2004; Holl et al., 2010; Thiruvankadan et al., 2008). The dominant allele in a homozygous status is lethal in the early embryonic period (Haase et al., 2007, 2009; Holl et al., 2010). White horses are heterozygotes (W/+), have pink skin, white coat, white mane and tail and pale hooves, but eyes show pigmentation. In horses of different breeds (Arabian, Thoroughbred, Camarillo White Horse, Holstein Horse, Franches-Montagnes, Miniature Horse, Shetland Pony, Freiburger, Quarter, Icelandic Horse, South German Draft Horse) over a dozen *KIT* gene mutations that cause spotted coat colour of varying intensity, from white spots to white coat colour have been identified so far (Haase et al., 2007, 2009; Lightner, 2010).

In horses the *KIT* gene is also the candidate gene for roan coat colour (Marklund et al., 1999). Horses of roan phenotype are characterized by grey coat colour that results from blending the basic colour with white bristles in the thorax, neck, and partially limb areas. Roan coat colour in horses is a semi-dominant trait (*RnRn*). The dominant homozygote (*RnRn*) is lethal in utero (Thiruvenkadan et al., 2008). Linkage analysis between *KIT* and the *RN*, performed by Marklund et al. (1999), showed strong linkage (no recombination was observed). Additionally a 79 base pairs insertion between exons 1 and 2 of the *KIT* gene (frameshift mutation) was partly associated with the roan phenotype. However, further research is necessary in order to identify the mutation responsible for roan coat colour.

In cattle a large number of mutations in *KIT* gene, located on chromosome 6, were identified in all of 21 exons, resulting in different pigmentation patterns (Fontanesi et al., 2010). *KIT* gene has been suspected to be associated with hereditary gonadal hypoplasia (predominantly left-sided in both sexes) in Finncattle and Swedish Mountain cattle, while this disorder occurs only in animals that are 60–100% white coloured (Venhoranta et al., 2013). The latest research carried out with the use of a genome-wide association study (GWAS) and a copy number variation (CNV) analysis showed a translocation of 492 kb segment (containing *KIT* gene) from BTA6 to BTA29. This study strongly suggests that the *KIT* gene dosage is associated with hereditary gonadal hypoplasia in the cattle breeds mentioned above (Venhoranta et al., 2013). This translocation occurs also in Belgian Blue and Brown Swiss cattle (Durkin et al., 2012) without known pleiotropic effects.

As the *KIT* protein also participates in controlling survival, proliferation and differentiation of hematopoietic cells, it has a significant effect on hematological indicators of blood. In pigs the *KIT* gene (locus *I*) is localized on chromosome 8 (SSC 8p12) (Pielberg et al., 2002). Piglets which are homozygous in respect of the dominant mutation of the gene *KIT* (*II*) show mild macrocytic anemia, having larger erythrocytes with lower hemoglobin concentration, therefore iron supplementation is necessary in their first weeks of life (Johansson et al., 2005). Allele *I* is associated with a duplication of *KIT*, in addition it has a splice mutation (G to A substitution) in the first nucleotide of intron 17 in one *KIT* copy. This splice mutation leads to skipping of exon 17, which encodes a highly conserved region of tyrosine kinases (Pielberg et al., 2002). Another mutation (p.Val1870Ala) in exon 19 of the *KIT* gene may be associated with melanoma development, tumour ulceration and cutaneous invasion in pig (Fernandez-Rodrigues et al., 2014).

KIT gene is also a protooncogene; if activated at an inopportune moment, it may lead to uncontrollable cell proliferation and thus be the cause of neoplasm formation. In cats the *KIT* gene, located on chromosome B1 (Cooper et al., 2006), is important for the pathogenesis of mast cell tumours (mastocytomas) (Isotani et al., 2006). In addition, another pleiotropic effect of the *KIT* gene was recorded. The dominant allele *W^T* in homozygote leads to the ocular phenotype in blue-eyed, white cats, which is associated with reduced pigmentation in the iris, the choroid, and the tapetum lucidum (a cell layer behind the retina) but spares the retinal pigment epithelium itself and is generally not associated with defects in visual function (Kaelin and Barsh, 2013). It is also known that white cats with blue eyes (one or both) are more suscep-

tible to deafness than other cats. Melanocytes present in the stria vascularis of the cochlea are indispensable for its correct development (Tachibana, 1999). However, analysis of this phenomenon is difficult because deafness in cats may be partial or complete in a given ear (Strain, 2007).

KITLG (MGF) gene

The *KITLG* (tyrosine-protein kinase ligand) gene, also called *MGF* (mast cell growth factor) gene, encodes a tyrosine kinase receptor ligand. Ligand binds to the tyrosine receptor kinase KIT, stimulating migration, proliferation and survival of melanocytes, hematopoietic cells and germ cells (Marklund et al., 1999). *KITLG* also plays an important role in nerve cells development and mast cells development, migration and function (Scherer and Kumar, 2010).

In cattle *KITLG* gene (localized in locus *Roan*) was mapped to the telomeric end of BTA5 (Aasland et al., 2000). Roan pattern is common in two cattle breeds, Shorthorn and Belgian Blue. In exon 7 (nucleotide 654) of the *KITLG* gene, missense mutation was identified (C>A) causing a substitution of alanine by asparagine (Ala193Asp), whereas the asparagine is present in the protein encoded by allele *R*, and alanine – by allele *r*. Allele *R* is responsible for white coat colour, and allele *r* for the black (in Belgian Blue cattle) or red (in Shorthorn) coat colour (Seitz et al., 1999). These alleles are inherited with incomplete dominance, however, genotype *Rr* shows incomplete penetration. In both cattle breeds allele *R* is linked to genital development disorder, characterized by a missing or underdeveloped vagina, cervix or uterus. This disorder syndrome has been named White Heifer Disease (Charlier et al., 1996). Over 90% of affected heifers have white coat colour, and among the remaining 10% blue coloured heifers (Belgian Blue) or roan coloured heifers (Shorthorn) predominate.

In Karakul sheep, the W^R allele, a variant of the *W* gene responsible for white coat colour, is responsible for gray coat colour corresponding to roan phenotype in cattle. Dominant gray in homozygotes is lethal ($W^R W^R$). Homozygous individuals in respect of this gene have dysfunctional innervation of the alimentary system and often die just after birth. Gray Karakul are heterozygous ($W W^R$) (Schoeman, 1998). Most probably, homozygous white Karakul ($W W$) show symptoms similar to those in gray, but lambs survive longer. Their abomasum grows to a smaller size, and rumen and abomasum walls are much thinner and very poor in muscles (Schoeman, 1998). Genetic conditions for coat colour in sheep are least well known, and so it is not clear whether the alleles *W* and W^R described above belong to locus *W* (KIT gene) or locus *Roan* (*KITLG* gene).

EDNRB gene

The *EDNRB* gene encodes endothelin receptor type B, protein responsible for white spotting in animals. *EDNRB* affects proliferation, migration and differentiation of embryonic neural crest cells that develop into melanocytes and enteric ganglia cells (Bellone, 2010; Finno et al., 2009).

In horses the *EDNRB* gene determines the frame overo coat colouring type, which occurs in some breeds (e.g. American Paint Horse, Quarter Horse, and rarely

Thoroughbred). This coat colour is characterized by occurrence of white spots in the central body areas, while the horse's extremities, hooves, back, abdomen, chest and rump remain colour coated, which leads to a framed phenotype effect. This phenotype may vary from white spots covering 90% of the body to a seemingly uniformly coloured coat. Some foals may be deaf and have blue eyes in addition to the pigment defects and aganglionosis (Finno et al., 2009). Responsible for the frame overo coat colour type is the dinucleotide mutation in the *EDNRB* gene (c.353_354delinsAG), which leads to amino acid substitution of isoleucine by lysine (*Ile118Lys*) (Bellone, 2010; Lightbody, 2002; Yang et al., 1998). Frame overo horses are heterozygous, but occasionally there are heterozygotes of uniform coat colour. In turn, homozygotes in respect of Lys118 allele suffer from lethal white foal syndrome (LWFS), known also as Overo White Lethal Syndrome (OLWS) (Bellone, 2010). Foals with LWFS are born totally or nearly all white. Even on their first day after birth they feel colic as a result of intestinal obstruction caused by missing intestinal nerves (aganglionosis) (Bellone, 2010; Finno et al., 2009). Such dysfunctions lead to a foal's death several days after its birth. Cosegregation of p.Ile118Lys mutation with frame phenotype is not 100%: non-frame horses had the mutation and horses with a phenotype of frame had a genotype of p.Ile118. This suggests that the frame overo phenotype may be also caused by mutation in other genes (Bellone, 2010).

MITF gene

MITF (microphthalmia-associated transcription factor) gene consists of 9 exons. MITF protein, encoded by exons 5–9 (Schmutz and Berryere, 2007), is known as the key transcription factor of melanocyte development, their survival, progression and proliferation (Pingault et al., 2010). MITF also activates expression of several melanogenic enzymes (Kaelin and Barsh, 2013).

MITF gene mutations in animals are linked to coat colour and condition white spotting, but in some species (dogs, cattle, horses) its pleiotropic effects can be seen.

In dogs, *MITF* gene is located in locus *S* on chromosome 20(CFA20q13). Dogs with extensive white spotting exhibit an increased risk of deafness compared to the coloured (Kaelin and Barsh, 2013). It is known that the melanocytes are required for normal development of cochlea and pigment-associated deafness is the result of absent melanocytes in the stria vascularis of the cochlea, which leads to early postnatal degeneration of the stria and secondary degeneration of the cochlear hair cells and neurons (Strain, 2004). Research by Stritzel et al. (2009) suggests that the *MITF* gene might play a role in canine congenital sensorineural deafness (CCSD) and blue eye colour in Dalmatian dogs. Moreover, Dalmatians with at least one blue eye have a higher prevalence of deafness (Cargill et al., 2004). A study on Dalmatian dogs (Stritzel et al., 2009) showed that a length polymorphism of the M promoter of *MITF* gene (LP-*MITF*-M) and *MITF*-flanking microsatellite (*RPC181-110P24*) are significantly associated with CCSD phenotype.

Also in horses, *MITF* gene mutations may have pleiotropic effects. Some horses with the so-called "splashed white" coat colour (characterized by a very distinctive large blaze, extended white markings on the legs, and blue eyes)

are deaf (Hauswirth et al., 2012, 2013). Two mutations were identified that condition the splashed-white phenotype: *MITF*^{prom1} (g.20,117,302Tdelins11) and *MITF*^{C280Sfs*20} (g.20,105,348_52del5; c.837_842delGTGTC). The third mutation *MITF*^{N310S} (g.20,103,081T>C; c.209G>A) determines macchiato phenotype in a Franches-Montagne horse. This mutation as well as *MITF*^{C280Sfs*20} are extremely rare (Hauswirth et al., 2012).

In cattle, the *MITF* gene is localized on chromosome 22. Mutation c.629G>T in this gene, resulting in substitution of arginine by isoleucine (Arg210Ile), is responsible for the German White Fleckvieh syndrome. This syndrome occurs in German Fleckvieh cattle and is described as Dominant White Phenotype and Bilateral Deafness, a dominantly inherited syndrome associated with hypopigmentation, heterochromia irides, colobomatous eyes and bilateral hearing loss (Philipp et al., 2011). This phenotype corresponds to the phenotype described in dogs and the Waardenburg type 2 and Tietz syndrome in human (Philipp et al., 2011).

***TRPM1* gene**

The *TRPM1* gene (also known as melastin – *MLSN1*) encodes transient receptor potential cation channel, subfamily M, member 1, protein important in cellular calcium homeostasis (Audo et al., 2009). TRMP1 has an important role in cellular signaling within various cells including neurons and melanocytes (Webb and Cullen, 2010). There are also studies indicating the role of the *TRPM1* gene in regulating melanogenesis, and a link has been found between *TRMP1* and tyrosinase activity (Guo et al., 2012).

In horses the *TRPM1* gene is associated with the appaloosa spotting, which is characterized by basic coat colour patches expanded on the white area, symmetrical and centred over the hips, present in some horse breeds. The extent of spotting varies widely among individuals, the pattern is called “the leopard complex” (Bellone et al., 2008) and the locus responsible for that pattern is called “leopard” (*LP*). Search for the gene using a whole-genome scanning has shown that this locus contains two candidate genes *TRMP1* and *OCA2* (Oculocutaneous Albinism Type II). Dominant homozygotes for the *LP* gene have fewer coloured spots than heterozygotes and suffer from congenital stationary night blindness (CSNB). Horses affected with an acute CSNB form initially have a limited vision in dimmed light, with a vision disorder even under normal lighting conditions later on (Audo et al., 2009). The probable cause of both leopard (appaloosa) pattern and CSNB in horses is differentiated *TRMP1* gene expression (Bellone et al., 2008).

***PAX3* gene**

PAX3 gene encodes the paired box 3 transcription factor. *PAX3* shows affiliation with development of various cell types (e.g. central nervous system, skeletal muscle, somites, cardiac tissue, melanocyte, enteric glia). It also activates or represses the expression of markers of melanocyte development (*MITF*, *TYRP1*, *TYRP2*) (Pin-gault et al., 2010).

In horses, *PAX3* gene (localized on chromosome 6) mutation – C70Y (c.209G>A, resulting in amino acid substitution of cysteine by tyrosine), like the *MITF* gene

mutation, is linked to the splashed white phenotype (Hauswirth et al., 2012). On the other hand *PAX3* is required for several steps in neural development. Homozygosity for *PAX3*^{C70Y} allele will most likely result in embryo or fetal lethality. The mating of two heterozygous (*PAX3*^{+/PAX3}^{C70Y}) horses leads to production of an embryo homozygous for this allele, therefore horses with *PAX3*^{C70Y} allele should not be mated to each other (Hauswirth et al., 2012).

***PMEL17* gene**

The *PMEL17* gene (also called Silver, *SILV*) encodes premelanosomal protein 17, which plays an important part in melanosome development and affects eumelanin synthesis. Strong expression of *PMEL* is limited to pigmented tissues, including skin melanocytes, uveal melanocytes, and retinal and iris pigment epithelium (Theos et al., 2005).

In horses and ponies the *PMEL17* gene (locus *Z*) is associated with silver phenotype. Responsible for this phenotype is the missense mutation (g.1457C>T; p.Arg618Cys) in exon 11 with a dominant mode of inheritance (Brunberg et al., 2006; Reissmann et al., 2007). This mutation shows a link with multiple congenital ocular anomalies (MCOA). The study carried out by Brunberg et al. (2006) describes complete linkage between the *Silver* locus and the *PMEL17* gene, and a missense mutation is completely associated with the silver coat colour. Horses that are homozygous for the disease-causing allele have multiple defects, including fluid-filled cysts of the iris, ciliary body or retina, retinal dysplasia, megaloglobus, miotic pupils, iris stromal hypoplasia and cataract (MCOA-phenotype), whilst the heterozygous horses predominantly have cysts of the iris, ciliary body or retina (Cyst-phenotype). Also, individuals affected with MCOA bear a high risk of blindness incidence and difficulty in accommodation to changing light conditions, which may be reflected in their behaviour (Andersson et al., 2011). Multiple congenital ocular anomalies (MCOA) syndrome was first described in the Rocky Mountain Horse breed. Andersson et al. (2011) observed that MCOA syndrome is segregating with the *PMEL17* mutation in the Icelandic Horse population. They conclude that this should be taken into consideration for breeding decisions and highlights the fact that the MCOA syndrome is present in a breed that is more ancient and not closely related to the Rocky Mountain breed of horses.

The *PMEL17* gene in dogs (*SILV* gene), located in locus *M*, is linked to the merle coat colour. The merle pattern, characterized by patches of diluted pigment, is a standard colour for several breeds recognized by the American Kennel Club, including the Shetland Sheepdog, Australian Shepherd, Cardigan Welsh Corgi, and Dackshund. Studies on *SILV* gene in merle and nonmerle Shetland Sheepdogs showed a retrotransposon insertion in the border of intron 10 and exon 11 of *PMEL17* (Clark et al., 2006). Dogs that carry the merle mutation suffer from both auditory and ophthalmologic abnormalities. Dogs heterozygous or homozygous for the *merle* locus typically have blue eyes and often exhibit a wide range of auditory and ophthalmologic abnormalities, which are similar to those observed for the human auditory-pigmentation disorder Waardenburg syndrome (Clark et al., 2006). Homozygous (double merle) genotype is associated with multiple abnormalities of the skeletal,

cardiac, and reproductive systems and can have sublethal effect. Therefore, merle-to-merle matings are dissuaded (Clark et al., 2006).

In cattle, *PMEL17* gene mutations were identified that are responsible for coat-colour dilution. In some cattle breeds (Simmental, Hereford) those mutations segregate with hypotrichosis, a disorder in which there is a congenital deficiency of hair. Two mutations were identified – three base pair deletion (c.50_52delCTT) in exon 1, causing the deletion of a leucine from the signal peptide and a C>A transition in codon 612 in exon 11 resulting in substitution of alanine by glutamic acid (Jolly et al., 2008). There are no reports concerning the effect of hypotrichosis on animal productivity, but there are reports that affected calves indicated a predisposition to cold stress and poor growth rate, at least in the first year of life (Jolly et al., 2008).

***MLPH* gene**

The *MLPH* gene encodes melanophilin, protein involved in melanocyte transport. *MLPH* gene mutations may cause skin and hair pigmentation disorders.

In dogs *MLPH* gene mutations cause coat colour dilution as well as a disorder called colour dilution alopecia (CDA, also known as colour mutant alopecia). A dog's *MLPH* gene is located in locus *D* (dilution). Colour dilution alopecia, in many dog breeds, is associated with a dilute coat colour and hair loss is usually most severe on the dorsal trunk, especially colour-diluted area on the skin. The initial clinical signs are the gradual onset of a dry, dull and poor hair coat quality, hair follicles are characterized by atrophy and distortion. Heavily clumped melanin is present in the epidermis, dermis and hair follicles (Kim et al., 2005). First clinical signs of CDA are usually noticed between 3 and 12 months of age, rarely later in life, and lesions are usually slowly progressive with age. In some breeds, such as the pinscher breeds and the Rhodesian ridgebacks, the reported coat quality of dilute dogs ranges from normal to severely CDA affected (Welle et al., 2009). Studies of over 900 dogs from 20 different breeds showed perfect association of the noncoding c.-22G>A mutation in *MLPH* gene with dilute coat colour, supporting the hypothesis that this polymorphism is indeed the causative mutation of CDA (Welle et al., 2009).

***STX17* gene**

STX17 gene encodes syntaxin 17, protein which has a hairpin-type structure mediated by two transmembrane domains, each containing glycine zipper motifs. This unique transmembrane structure contributes to its specific localization to completed autophagosomes (Itakura and Mizushima, 2013). Syntaxin is probably involved in proliferation of melanocytes (Bellone, 2010).

In horses the *STX17* gene was mapped to chromosome 25(ECA25q). Mutation g.6575277_6579862dup (4.6 kb duplication) in intron 6 of *STX17* causes gray pattern (progressive graying) (Cieślak et al., 2013). Rosengren Pielberg et al. (2008) proposed that this duplication is a cis-acting regulatory element that upregulates syntaxin 17 and another gene in critical interval (NR4A3). Both *STX17* and the neighbouring *NR4A3* gene are overexpressed in melanomas from gray horses (Rosengren Pielberg et al., 2008). This mutation is associated with a high incidence of melanoma and vitiligo-like depigmentation. Homozygous horses have more skin depigmenta-

tion and have a higher incidence of melanoma compared to heterozygous (Rosen-gren Pielberg et al., 2008). Even though melanoma in gray horses is less malignant than in horses with a uniform coat colour, metastases to other organs (lymph nodes, liver, spleen, skeletal muscle, lungs) do happen (Bellone, 2010).

Progressive graying occurs in many breeds of horses, but in some breeds (such as Lipizzaner and Andalusian) it is a predominant colour. The rate and location of graying varies from horse to horse. The *STXI7* gene is epistatic towards all other coat colour genes except the *KIT* gene that conditions white colour coating (Bowling and Ruvinsky, 2000).

***MYO5A* gene**

The *MYO5A* gene encodes the myosin Va protein, which is important for melanosome transport in melanocytes (Pastural et al., 2000). Mutations of this gene are related to disruption in the transfer of mature melanosome to the tips of dendrites (Fernandez et al., 2009).

In horses the *MYO5A* gene is strictly associated with the Lavender Foal Syndrome (LFS), known also as Coat Colour Dilution Lethal (CCDL). This syndrome occurs in Arabian horses and is inherited as a recessive trait (Bellone, 2010; Brooks et al., 2010). Foals of this phenotype (recessive homozygote), described as lavender-like colour, show coat colour from iridescent silver to pale lavender shade, whence the syndrome name. The term CCDL is accepted as more appropriate, as not all foals have lavender coat. In some animals the coat colour is pewter (pale slate grey) or pink (pale chestnut) (Fanelli, 2005). LFS (CCDL) is characterized by neurological symptoms such as involuntary muscle contractions, neck and back muscle contractions leading to a backward bent of the head and body (opisthotonus), nystagmus and awkward movement of extremities. The foals cannot stand up, lie on their side moving their legs helplessly, probably as an attempt to change their position (Bellone, 2010). As they are not able to survive, they are subjected to euthanasia right after their birth.

LFS is probably linked to a single-base deletion in exon 30 (g.138235715del) of the *MYO5A* gene, which probably leads to a premature stop codon (Bellone, 2010). This mutation affects melanocyte function, disrupting melanosome transport to keranocytes. Similarly in nerve cells, glutamate receptors and secretory granules are not transported correctly, which may explain incidence of neurological disorders (Bellone, 2010). To prevent LFS incidence, horses carrying *MYO5A* mutations should not be allowed to breed.

***TYR* gene**

The *TYR* gene (located in locus *C*) encodes tyrosinase, the melanin synthesis pathway enzyme catalyzing the first two steps, and at least one subsequent step, in the conversion of tyrosine to melanin. In mammals, the *TYR* gene consists of five exons, and it encodes the protein consisting of about 530 amino acids (Hudjashov et al., 2013). Numerous *TYR* gene mutations are known in various animal species; they cause tyrosinase deficiency, which results in inhibition of melanin synthesis and lack of pigmentation (albinism) (Ferreira dos Santos Videra and Magina, 2013). Albinotic

animals are very sensitive to sunlight exposure (UV rays), responding rapidly with inflammatory conditions of the skin, with frequent blistering and callosity. This phenotype is a result of the pigment missing from the hair coat, skin, iris and retina under simultaneous presences of melanocytes (Scherer and Kumar, 2010).

***MC1R* gene**

The *MC1R* (melanocortin-1-receptor) gene is active in melanocytes and controls the amount of eumelanin production. It is located in locus *Extension*, over 950 base pairs long, has only one exon, but shows high polymorphism (Scherer and Kumar, 2010). *MC1R* gene polymorphism is related to melanistic coat colour in many animal species. Melanism, the opposite of albinism, is characterized by hyperpigmentation of skin, hair and eyes, resulting from increased melanin content. It may be a form of environmental adaptation or occur as a disorder. In many animal species melanistic males are more aggressive (Ducrest et al., 2008). Selecting for tameness and against aggression means selecting for physiological changes in the systems that govern the body's hormones and neurochemicals (Trut, 1999). Animals with pale coat colour are less aggressive than darker and this relation results from the common synthesis pathway of adrenalin and dopaquinone (a precursor of melanin) (Reissmann and Ludwig, 2013).

***ASIP* gene**

The *ASIP* gene, located in locus *Agouti*, encodes agouti-signaling-protein. *ASIP* of mammals has 4 exons, codons 2–4 encode agouti-signaling-protein consisting of 131 to 135 amino acids. Expression of this gene is regulated by several promoters. *ASIP* is responsible for switching eumelanin to pheomelanin and back synthesis, resulting in temporal and spatial distribution of pheomelanin and eumelanin granules within each hair shaft (Lightner, 2009; Manne et al., 1995). Coat colour conditioned by the activity of this gene is characterized by occurrence of black hairs with a yellow stripe in their subapical part (agouti phenotype), but they can also be entirely yellow.

Agouti-signaling-protein does not only play an important role in melanogenesis, but has also been shown to be potentially linked to obesity. The *ASIP* gene is expressed in a wide variety of tissues in mammals, including adipose tissue. Analysis of *ASIP* expression in tissues of Japanese Black, Holstein and Charolais steers indicates physiological functions of *ASIP* in cattle (Albrecht et al., 2012).

***AP3B1* gene**

The *AP3B1* gene encodes adaptor-related protein complex 3, beta 1 subunit. This protein may play a role in organelle biogenesis associated with melanosomes, platelet dense granules, and lysosomes (Jung et al., 2006).

In dog mutation in *AP3B1* gene (localized on chromosome 3) has a pleiotropic effect on coat colour, causes a pale colour with a grey tinge and a disorder called Grey Collie Syndrome (GCS, known as Cyclic Neutropenia) (Schmutz and Berryere, 2007), inherited as an autosomal recessive trait (Bauer et al., 2009). The mutation responsible for GCS has been identified as an insertion of an adenine in exon 21 of

AP3B1 gene, leading to a frame shift and premature protein termination signal (Benson et al., 2004). In affected individuals a drastic decrease in the count of neutrophils, a vital element of resistance against bacterial infections, occurs at 12–14 day intervals. These pups are weaker, and also have platelet defects with dense granules and defective aggregation. Because of fluctuations in the blood count these dogs are also susceptible to bleedings. With these serious disorders, even with good medical care, affected individuals live only 2–3 years, and most of them die in their first weeks of life (Bauer et al., 2009).

LYST gene

The *LYST* gene (also known as *CHS1*) encodes lysosomal trafficking regulator, which has impact on organelle size by controlling membrane fission events (Kaplan et al., 2008). Mutations of *LYST* gene in cattle, cats, Aleutian mink, killer whales, mice, rats and human are associated with the Chediak-Higashi syndrome (CHS), an autosomal-recessive disorder characterized by hypopigmentation, recurrent infections and a progressive primary neurological disease (Kaplan et al., 2008). CHS is caused by defect in a specific subset of vesicles which presumably results from mal-regulation of vesicle fusion or fission (Kunieda, 2005). Hypopigmentation is caused by defective structure or function of melanosomes in melanocytes, which are not processed normally. Melanin, synthesized in melanosomes, is trapped within the giant melanosomes and is unable to contribute to skin, hair, and eye pigmentation (Anistoroaei et al., 2013).

In cattle recessive mutation of the *LYST* gene, transition of adenine to guanine at 6065, resulting in substitution of histidine by arginine (His2015Arg), causes an acute CHS form in Japanese Black cattle. Affected animals have abnormal granules in leukocytes, partial cutaneous albinism, and an increased bleeding tendency (Kunieda, 2005). Chediak-Higashi syndrome in cattle corresponds to a human inheritable disorder (CHS1).

Conclusions

The effects of coat colour genes on animal health and performance are not appreciated or even remain unknown among animal breeders. The link between various coat types with disease incidence deserves more attention, as mating individuals of some genotypes leads to disease risks or lethal effects for the offspring. Consideration should also be given to the ethical aspect of mating practices that may result in birth of impaired individuals.

An important aspect of pleiotropic effect of coat colour genes is the fact that animals affected by diseases that are conditioned by variants of such genes can be human disease models that increase the capability for developing appropriate treatment and facilitate understanding of the genetic background of a disease.

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