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Melanoma in Arabian horses

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Abstract: Background: Melanoma consider the most common tumor that affect about 80% of Arabian horses. Gray color of Arabian horses is the most susceptible to melanoma than other colors that make many researches confirm that there are link between graying color mutation and melanoma. Melanoma is a hereditary disease that affect horse life, performance and appearance so study this disease is very important to recognize causes of this disease and determine best treatment. In this review we will discuss severity of melanoma on horses, distribution, histopathology, differential diagnosis of melanoma, link between gray color and melanoma occurrence and genetic background of melanoma

Keywords: Horse, melanoma, hereditary disease, histopathology

Introduction: The Arabian horse, one of the oldest domesticated animal breeds in history, is distinguished by its inherent beauty, graceful gait, athletic endurance, and capacity to flourish in hot, dry climates due to its evolution in the Middle East's arid conditions **(Cosgrove *et al*., 2020).** Horses have been intrinsically tied to human society since they were originally domesticated about 5000 years ago **(Librado et al., 2021).** Wide-set eyes, an arched neck, a dish-shaped facial profile, and a high tail carriage characterize the distinctive conformational phenotype of the modern Arabian horse **(Nagel, 2013).** Implying that these characteristics might be strongly selected for contemporary Arabian breeders, especially for horse lines whose main purpose is to compete in non-ridden shows **(Ricard et al., 2017).**

Many years after genome sequencing programs for cattle, pigs, sheep, and chickens were started, horse genomics was acknowledged as crucial to veterinary care and horse breeding **(Pielberg, 2008).** Genetic disease of the horse is a mutation of structure of one or more

genes. Neonatal, breed-limited, recurrent malformations are prime candidates for diseases with genetic rather than environmental causes, while some genetic problems may not show symptoms at birth and may not be exclusive to a particular breed **(Bowling, 1980).** Melanoma is one of hereditary diseases that primarily affects Arabian horses. Sarcoidos and squamous-cell carcinoma are the two most common types of skin cancer in horses, respectively, with melanomas being the third most common **(Valentine, 2006).**

Melanoma is a dermatologic disease that common in Arabian horses and One of the most frequent medical conditions that lead owners to seek veterinary care **(Scott et al., 2001).** Equine melanomas affect roughly 80% of gray horses over the age of 15 years. Melanomas in horses are tumors that typically form beneath the tail and, in more severe cases, need to be surgically removed. Dermal melanomas, which appear as small, individual tumors, and dermal melanomatosis, which appears as separate tumors that combine to form a huge mass, are the two most prevalent forms of melanomas **(Reed et al., 2017)**.

Severity of melanoma in Arabian horses

During stages of the disease in which there is slow growth, lesions may exist for many years and cause no clinical problems for either horse or owner. Sometimes the bulk of the tumor in the throat latch region is so great that the affected horses cannot comfortably turn their heads, flex at the poll, or feed and drink. Similarly, perianal tumors often grow to a size that impairs defecation and causes fecal impaction. Large lesions may develop necrotic cores capable of ulceration, leading to secondary bacterial infection. Surgically reducing the size of advanced lesions is challenging and frequently not beneficial **(Tamzali, 2015).**

Fissures that penetrate deeply into soft tissue and occasionally into bone emerge as a result of expandable tumor growth's deep infiltration of the muscle and potential impairment of the blood supply. Intestinal blockage or metastases are typically the cause of a horse's melanoma death **(Moore et al., 2013).**

Distribution of melanoma:

Initially, many melanomas appear as a solitary, tiny, elevated nodule on the perineum. Small melanomas may be noticed by horse owners while their horses are being groomed, or veterinarians may notice them by accident while doing routine medical exams **(Fleury et al., 2000).** Some horses may have more than one nodule visible at once. Common locations for nodules are the parotid/jugular furrow, the sheath, the perineum, the tail base, the commissures of the lips, and the subauricular lymph nodes **(Seltenhammer et al., 2003).**

Prevalence and Grades of melanoma

Melanoma consider the most common skin diseases in gray horses and they can reach a prevalence between 10% and 80%. This prevalence differs according to the horse's age and breed **(Sánchez, 2019).** Inspection and palpation were used to identify melanoma grades, which included areas such as perianal, anal region, and udder where melanoma is commonly found. Patients were categorized using a modified classification approach based on their clinical picture. (allowing for the intermediate marks, 0.0, 0.5 ... 4.5, 5.0) by **Desser et al. (1980).**

Grade	Description
0	Free of melanoma
1	Early stages of plaque-type or one solitary nodule of 0.5 cm diameter situated on typical locations.
2	Several nodules of 0.5 cm diameter or one solitary nodus of 2 cm diameter on typical locations
3	One or several nodular melanoma of 5 cm diameter intra- and/or subcutaneous on typical locations (or lips).
4	Extensive confluent melanoma, covered with skin, signs of destruction (necrosis, ulceration) and metastasis.
5	Exophytic growth of tumours, which show wet surface and ulceration, metastasis into different organs accompanied by paraneoplastic syndromes (cachexia, fever, metabolic disorders).

Histological and Pathological nature of melanoma:

Melanoma result from abnormal proliferation of melanocytes **(MacKay, 2019)**. Melanocytes are dendritic cells that mostly located in the skin, in the outer root sheath of hair follicles and inside the basal layer of the epidermis, where they are generated from neuroectodermal melanoblasts **(Knottenbelt, 2015)**. melanocytes create the melanin found in the skin, eyes, and hair through a process called melanogenesis. Melanin's dark pigmentation allows it to absorb UV-B rays, shielding the skin from the harmful effects of sunlight **(Agar, 2004).**

According to **MacGillivray (2002),** 14% of cutaneous melanomas have the potential to develop into malignancy. However, the author noted that this percentage is probably inflated because benign melanomas are not often submitted. A later study investigating a group of 296 Lipizzaner reported a 50% incidence of melanomas and no clinical evidence of malignancy **(Seltenhammer, 2003)**.

Gross and microscopic pathology

Valentine (1995) was studied melanoma in horses, based on a review of 53 cases that were studied in the past. She presented that there are at least 4 manifestations of equine melanotic disease: melanocytic nevus, discrete dermal melanoma, dermal melanomatosis, and anaplastic malignant melanoma. Discrete dermal melanoma and dermal melanomatosis, collectively mentioned to as dermal melanoma, represent the large majority of melanoma diagnoses in gray horses **(Sullins, 2020).**

Gray horses are susceptible to discrete cutaneous melanomas, which typically appear as single masses in either typical or unusual sites. Gray horses that suffer from dermal melanomatosis often have numerous cutaneous tumors, at least one of which presents in a "typical" place. These typical sites include the undersurface of the tail, anal, perianal and genital regions, perineum, and lip commissures. Like discrete dermal melanoma, dermal

melanomatosis is most frequently present in mature horses. However, the typical age of those with cutaneous melanomatosis is slightly older, at 17 years old **(Seltenhammer et al., 2004)**.

Hematology and Biochemistry

The majority of skin tumor cases do not exhibit a notable alteration in the wide range of parameters assessed in standard laboratory profiles. A state of chronic disease and chronic blood loss can cause modifications at their limit; these changes typically manifest as normochromic or hypochromic, normocytic or microcytic anemia **(Knottenbelt, 2015)**. However, **Conrado et al. (2020)** identified a neutrophilia with multiple circulating melanin-containing neutrophils in a horse with disseminated melanoma during complete blood count analysis so it indicates that minimal bloodwork data may be useful in the detection of melanoma metastases in horses with cutaneous melanocytic tumors who also show with systemic illness symptoms.

Association between melanoma and gray color:

Melanomas are extremely uncommon in colored horses, which lends respect to the theory that the biochemistry responsible for the formation of gray coat color and melanoma development are closely related **(Swinburne *et al*., 2002).** Graying with age in horses is an autosomal dominant trait, characterized by gradual loss of hair pigmentation and associated with high incidence of melanoma and vitiligo-like depigmentation **(Sundström, 2012).** Gray horses ordinarily have a high incidence of melanomas. Horses with the mutation causing the Gray color are foaled any color (e.g., bay, black or chestnut) but gradually lose hair pigmentation and, by the age of 6–8 years, become white. Dark skin pigmentation is retained in gray horses but hair pigmentation gradually deceased **(Fleury et al., 2000).**

The manifestation of this mutation as a white horse had a strong impact on human culture and left numerous traces in art and literature from Asia and Europe (for example, Pegasus and the unicorn). The oldest written record of the presence of white horses, to our knowledge, is by the Greek historian Herodotus. The prestige of riding a white horse has thus led to selection of the Gray causing mutation by humans; this mutation is by far the most common cause of white color in horses **(Sponenberg, 2017).**

It is more likely that gray horses acquired melanomas after going white than previously and there could be a human equivalent for this occurrence. At 2 years of age the animals begin to gray and by 9 years they are white completely. The white patch on the nose remains unchanged. Loss of pigment around the eyes and anus begins after 2 years of age. Arabian horses typically live 12 to 15 years, while some can reach 20 years old. The cancers start around the anus and many horses have melanomas by the time they are 5 or 6 years old **(Zembowicz, 2004).**

Long-range PCR analysis revealed that the mutation that responsible for graying is a duplication located in intron 6 of STX17. The intron was sequenced to determine the exact position of the duplication. The Gray haplotype showed 38 SNPs in intron 6 of STX17

compared to non-Gray haplotypes. Notably, the ancestral non-Gray haplotype mentioned above had a sequence identical to that of the Gray haplotype but did not include the duplication **(Pielberg et al., 2008).** Other study performed on 14 breed of horses and diagnostic test for duplication was utilized to screen both gray and non-gray horses. When compared to gray heterozygotes, horses homozygous for the STX17 mutation exhibited faster graying and more homogeneous whiteness at the end of the process. They also had significantly higher incidence of melanoma **(Nowacka et al., 2021).** So all this studies confirm there are genetic link between the gray coat color and the higher incidence of melanocytic tumors in gray horses **(Sánchez et al., 2019).**

Diagnosis of melanoma

The diagnosis is made by fine-needle aspiration or biopsy from the tumor (**Curik, 2013).** Melanocytic tumor is confused with many black nodular tumefaction so melanocytic tumors should be considered as a potential diagnosis. Examples are nodular sarcoid, cutaneous lymphoma, parasitic cysts, hemangioma, mast cell tumor, fibroma, parotid salivary gland disease and guttural pouch disease, Gasterophillus spp. granuloma **(Knottenbelt, 2015).** The absence of black pigment during FNA and the histopathology report of a biopsy sample are the most reliable methods to exclude each of these differentials. However, a melanotic melanomas may raise doubts. In these cases, the best approach in these situations is immunohistochemistry **(Pimenta et al., 2023).**

Genetic Background of melanoma:

It has been demonstrated that melanocytic tumor heredity in gray horses is moderate **(Curik, 2013)**. According to a study including 295 gray Lipizzaner horses, additive inheritance may have an effect on the development of disease, as evidenced by the heritability estimate of 0.36 with a standard error of 0.11 **(Seltenhammer, 2003).** It is unclear whether the genetic tendency of certain horse breeds, like Arabians, Lipizzaners, Thoroughbreds, and Andalusian horses, is breed-specific or impacted by the breeds' high incidence of gray coat color **(Sánchez, 2019).**

Role of STX17, NR4A3, ASIP, Dpf3 and MC1R genes in melanoma occurrence:

1-STX 17 Gene:

Syntaxin 17 (STX17) is a divergent member of the syntaxin family of proteins originally found by Scheller and colleagues in a yeast two-hybrid screen designed to identify novel mammalian SNAREs (soluble N-ethylmaleimide-sensitive factor-attachment protein receptors). STX17 has a role in mediating membrane fusion events critical in regulating vesicular transport among various intracellular membrane compartments. STX17 is partially associated with the endoplasmic reticulum and shows nuclear localization in some malignant cells (**Zhang et al., 2005).**

Sundström et al. (2012) found a link between the STX17 mutation's copy quantity and the development of melanoma, and determined that this duplication is a factor that causes melanoma. So graying and melanoma have been linked to a 4.6 kilobase duplication in intron 6 of the syntaxin-17 (STX17) gene **(Rosengren et al., 2008).** This duplication contains a

regulatory element containing binding sites for microphthalmia associated transcription factor (MITF) and NR4A3, key components in the regulation of melanocyte gene expression and cell function **(Jiang et al., 2012).** However, the mechanistic features of the duplication remain unknown. Moreover, *RACK1* (receptor for activated C kinase 1) protein stands as a candidate molecular marker for the veterinary diagnosis of malignant melanocytic tumors in horses (**Campagne, 2012).**

The overexpression of STX17 and NR4A3, a nearby gene, is observed in gray horse melanomas, indicating that the duplicated region functions as a cis-acting regulatory element that is particular to melanocytes. MITF and NR4A3 mediated up regulation of melanin production and proliferation of hair follicle and dermal/epidermal melanocytes is the link between the STX17 mutation, gray coat color and melanoma formation **(Rosengren et al., 2008)**.

The molecular processes underlying the well-established association between gray phenotypic mutation (4.6 kilobase duplication in intron 6 of the syntaxin-17) and the development of melanocytic tumors are still understood, and it is also unclear whether other somatic mutations contribute to melanomagenesis **(Smalley et al., 2003).**

2-NR4A3 Gene:

NR4A genes are a subfamily of nuclear receptors that includes NR4A1 (Nur77), NR4A2 (Nurr1), and NR4A3 (NOR-1) in mammals **(Smith et al., 2005).** NR4A genes have been involved in a wide range of biological processes including proliferation, differentiation, apoptosis, and tissue remodeling and in pathologies such as neurological disorders including Parkinson disease, schizophrenia and manic depression, inflammatory and cardiovascular disease, and cancer **(Maxwell et al., 2006).**

NR4A3 has function in cell cycle regulation and an established link with carcinogenesis, as chimeric fusions of NR4A3 and EWSR1, TCF12 or TAF15 cause extraskeletal myxoid chondrosarcoma **(Maxwell et al., 2006).** Furthermore, CCND2, is consider target gene for NR4A3**,** showed pronounced expression in Gray melanomas **(Nomiyama et al., 2006)**. Cyclins are crucial regulators of the cell cycle, and over expression of cyclins is associated with tumor development **(Gray-Schopfer et al., 2007).**

The region of the Gray-causing mutation contains four genes: NR4A3 (nuclear receptor subfamily 4, group A, member 3), STX17, TXNDC4 (thioredoxin domain–containing-4¢) and INVS (inversin). A collection of 694 Gray Lipizzaner horses in which these four traits have been observed were genotyped for four genes. Northern blot and RT-PCR analysis showed that all four genes are expressed in melanomas but there was markedly high expression of NR4A3 in Gray melanomas **(RosengrenPielberg, 2008).**

3-ASIP and MC1R:

Agouti signaling protein (ASIP) and melanocortin-1 receptor (MC1R) are two genes thought to play an important role in melanocytic tumor development. MC1R responsible for production of the black hair pigment eumelanin by increasing MITF expression, whereas ASIP antagonist MC1R by inhibiting black hair pigment production. When mutation occur in

ASIP, this inhibition does not occur. When unrestricted MC1R production of eumelanin caused by ASIP mutation is added to enhanced melanocyte proliferation caused by STX17 mutation, so developing melanocytic tumors increases. Dermal and epidermal skin melanocytes under over proliferation result in neoplastic transformation, which leads to melanocytic tumor formation **(MacKay, 2019)**. It is believed that the enhanced proliferation of cutaneous melanocytes may be a link between the graying gene and phenotypic effects **(Seltenhammer et al., 2003).**

4- ERK pathway

The extracellular signal-regulated kinase (ERK) pathway has an essential role in cancer development by stimulating cell proliferation and migration. In human melanocytic tumors, ERK activation is caused mainly by somatic mutations in BRAF, RAS, GNAQ, GNA11, GTPases and KIT. A less common cause is a decreased expression of the negative regulators of the pathway **(Roskoski, 2018).** Although ERK1/2 was detected in all of the tumors examined, samples from gray horses had a significant greater expression. Furthermore, prior to tumor growth, large levels of ERK1/2 were discovered in the normal skin of gray horses, adding to the information about these horses' predispositions **(Wong et al., 2019). Jiang et al. (2014)** examined ERK involvement in horse melanocytic cancers based on these facts. Their findings showed that, in contrast to somatic alterations previously discovered in human melanocytic cancers, the ERK pathway is activated in equine melanocytic tumors.

Recent next-generation sequencing investigations of equine melanomas have shown mutant genes, including as NRAS, TP53, KIT, and BRAF, that are shared by canine and human melanoma and may behave as activating mutations in the ERK pathway **(Wong et al., 2019).**

5-DPF3 gene

DPF3 (d4, zinc and double PHD fingers, family 3), also known as CERD4, has role in maintaining cellular homeostasis with emphasis on the control of cell growth, proliferation and apoptosis **(Lin et al., 2019).** According **to Hoyal et al. (2005),** DPF3 is linked to a higher risk of breast cancer and lymph node metastasis in humans. They also proposed that DPF3 activity may be reduced by downregulating transcription levels or adversely affecting RNA splicing, which would reduce the induction of apoptosis in cells.

A Study performed a genome wide association analysis in 141 Lipizzaner horses and subsequently identified one candidate gene on chromosome 24 involved in melanoma pathogenesis in gray horses. The associated SNP was located in the intronic region of DPF3. Also replication study in 1210 horses from seven breeds reviewed that the G/G genotype of the DPF3 associated SNP shows putative melanoma suppression effects. As a conclusion DPF3 represents a potential candidate gene, which might play an important role in melanoma occurrence **(Druml, 2022).**

Conclusion:

Melanoma is an autosomal recessive hereditary disease that occur in many breeds of horses including Arabian horses and gray horses are the most susceptible to melanoma than other colors. Melanocytic tumors result from abnormal proliferation of melanocytes with

numerous genetic determinants. Many studies reviewed that there are many genes that may contribute in melanoma occurrence and metastasis. The predominant genes are STX17, ASIP, NR4A3, DPF3 and MC1R genes but STX17 is still the candidate gene of melanoma occurrence.

We think that there are specific mutations that lead to high frequency of melanoma. Determine this mutation is very important and consider the first step in creating efficient therapies. So many researches are required to study the genetic causes of melanoma.

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