Review Article

Pigmentation Genome Influence in Animals and Human Interventions in its Course of Action

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Abstract |Colors' beauty creates a fascinating effect on the mind, presence of multi-colored birds, fishes, pure colored animals in our community and the wild always remained attractable to humans. The color pigmentation is essential in animals regarding beauty, tick resistance, photo-protection, camouflage appearance in wild, and identification. Pigmentation is a complex and multi-factorial regulated process to produce the melanin from melanocytes. Melanin amount, size, shape, and distribution control the color pigmentation of fiber, coat, and hairs in animals. Melanin production in an intricate course is under the control of Melanocortin 1 Receptor, alpha Melanocyte stimulating hormone and Agouti signaling gene. In most animals, three different alleles encoding melanocyte-stimulating hormone receptor MC1R of extension (E) locus and E^D allele determining the blackish coat color, a recessive e allele represented red coat color and the E^+ wild-type allele give a variety of colors. Variation in pigment production can be predicted with mutations on genetic asset and production factors. The human desire of keeping variated colored animals advanced the genetic field as in many species (sheep, cattle, horses, camels, dogs, cats, pigs) new variants of coat pigmentation are achieved by generating mutation in MC1R and ASIP allele. A row of scientists is working on genome sequences and mutations for getting a better and healthier pigmentation besides animal welfare. This review article contains a complete elaboration about the worth of pigmentation in animals, natural pigmentation process and new mutation and deviation in animal genome related to their pigmentation for human and animal welfare respectively.

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1. Introduction

Naturally, the survival of animals in the wild conditions completely following Darwin's theory "survival of the fittest" whereas the subjective for the domestication of animals depends upon human preferences. With the progression in the human population, the partialities for animal domestication included both quantitative and qualitative traits. The quantitative traits refer to the factors involved in animals production like milk and meat yield, fertility ratio, growth index and resistance against drugs, however, the beauty traits refer to qualitative like animals coat color, body-color, body conditioning score and also the presence, absence, and shape of horns. One of the animal's unique phenotypic trait is its coat color (Schmutz *et al*., 2002). The variation among coat pigmentation is a primeval theme for researchers as well as for farmers because it covers some unique features like selective mating, safety from the predator, photo-protection, parasites resistance, and people attractions (Safran and McGraw, 2004). So color pigmentation in animals has many benefits and their mutations and monitoring genes can be easily identified. In mice, 378 genes identified related to color pigmentation and act as a role model for basic pigmentation genetic analysis in animals (Silvers, 2012). In the 19th century, a successful attempt was made to develop the uniform coat color and pattern in English sheep breeds. Berryere *et al.* (2003) stated that topographic conditions and exposure to solar radiation also affect the animals' health as the individuals having a lighter color coat with dark pigmentation are well adopted in tropical regions.

The coat color is a substantial phenotypic trait considered by farmers for the identification of breed and reproduction. Another major advantage of coat color is the preparation of a fine type of fiber from different animals especially the sheep and goat. Two different types of melanin are responsible for the determination of coat color in mammals. The eumelanin involves the black and brown color pigments while the pheomelanin contains red and yellowish color pigments. Agouti and Extension loci are accountable for pigment production within the body (Fontanesi *et al*., 2010). Variation in this phenotypic trait depends upon the existence, dissemination and biological reactions of melanocytes containing two different forms of melanin i.e. eumelanin and pheomelanin. These biological reactions of melanocytes are crucial for defining the coat color and presence of a comparable amount of both eumelanin and pheomelanin in skin and hairs (Fontanesi *et al*., 2010). Rouzaud and Hearing (2005) stated that the mutations in the MC1R gene are responsible for maintaining or upgrading in terms of full dominance or partly dominance accountable to either black or dark color coat, while entirely recessive or partly recessive pale colored (red-yellow) coat phenotypes in animals. Due to the importance of coat color in animal domestication and its health purpose, coat color genetics is very obligatory for incipient scientists. Many researchers are working on new intervention and beneficial implementation in coat color pigmentation which supports the animal for good health, optimum growth, and animal beauty. This article embraces a precise literature review about functional description about coat color controlling genetics, natural process of pigmentation genes development and some new intervention of researchers in pigmentation genes' mutation for the profit of farmers and the survival of animals. This topic is also gain more worth due to favorite color pigmentation in pet animals through the process of mutation and for ticks' resistance in farm animals.

1.1 The natural process of color pigmentation in animals

The color in mammals is controlled by the type of melanin and its proportion as it produces variation in terms of black, brown, red and yellow-pigmented fibers and hairs. This melanin is produced typically by melanocytes while in some other animals via different types of cells known as chromatophores. According to Hoekstra *et al.* (2006) the locality of melanin pigment in mammals and birds is under feathers, skin, and hairs. Logan *et al.* (2006) detailed that fish, amphibians and some reptiles have different types of pigment cells which show a variety of colors and function under hormonal and neural stimuli by accumulation and desertion. Lamoreux *et al.* (2010) specified that fish, amphibians, and reptiles possess leucophores, melanophore/melanocyte, xanthophore, cyanophores and iridophores which produce white, black/brown, red/yellow, blue and silver tinge respectively. The development of these pigments cells starts from in the early embryonic stage where melanoblasts (precursor cells of melanocytes) initiate the process in neural crest Thomas and Erickson (2008). Melanocytes (pigments producing cells) contains special organelle known as melanosome which accounts for the melanin production value (Slominski *et al*., 2004).

Lodish *et al.* (2008) described that maturation of melanosome occurs through a specific process from the neural crest and its transportation to keratinocytes caused pigmentation of skin and hairs. Pheomelanin and eumelanin pigments ratio and variation control the changes in animals' colors and these pigments develop from a long and precise process of nature (Lin and Fisher, 2007). The pigment production is a vital and comprehensive mechanism that starts from neural crest cells and known as Melanogenesis (Schallreuter, 2007). In this process, a group of pluripotent cells (neural cells) differentiates into two kinds of migratory cells known as early migratory cells and late migratory cells. Vance and Goding (2004) itemized that in embryogenesis the late migratory cells are the mothers of melanoblast which is known as the precursor pigment cells. At the start, these melanoblasts are not mature enough to produce pigments and they move to the specified location in different parts of the body while in the skin they got maturation into melanocytes by stimulation of keratinocytes under the epidermal basement membrane location (Krause and Foitzik, 2006). Melanocytes migrate into hair bulbs and underline skin tissues after accumulation and maturation pigmentation of skin and hair takes place at this site (Feeley, 2015). Dendritic structures and melanosomes in melanocytes help in pigment production and secretion into keratinocytes within their location in dermis or hair bulb (Yamaguchi and Hearing, 2009).

In humans, single melanocyte is attached to almost more than 40 keratinocytes for the transportation of mature melanosomes. Lodish *et al.* (2008) stated that melanosome maturation is a detailed 4 step procedure in which melanocytes and catalytic enzymes are mandatory its maturation and transportation to the exact location for pigment production. Wu *et al.* (2006) itemized that Rab27a, melanophilin, and myosinVa are proteins that facilitate the trafficking of melanosome between the actin cytoskeleton. During melanin production through melanogenesis, some dangerous by-products like H_2O_2 and hydroxyl radicals produced that cause DNA breakdown and this is the main reason for the confined production of melanin within melanosomes (Feeley, 2015). Prota (2012) described that the color of skin, hair, and fibers depends on melanin ratio, variation, shape, type, and distribution within the body. Melanin has two varieties known as eumelanin and pheomelanin, the former one is spherical with 1µm size whereas later one is an oval-shaped with 0.7 µm and their ratio determines the final color of an animal (Feeley, 2015). Le-Pape *et al.* (2008) reported that within melanosomes, the type and rate of melanin production in an intricate course under the control of Melanocortin 1 Receptor (MC1R). MC1R is a member of the G-protein-coupled receptors (GPCR) family and performs a variety of functions within the animal's body (Yang, 2011). MC1R is the focal switch of pigmentation production that pedals its quantity, quality, on and off by interaction with (α-MSH) alpha Melanocyte stimulating hormone and (ASIP) Agouti signaling protein (Barsh *et al.*, 2004). α-MSH binds with receptors and stimulates the activation of the receptor for the eumelanogenesis while ASIP is inverse in action as it binds to receptors and stops the α-MSH activation of receptors leading to pheomelanogenesis (McNulty *et al.*, 2005; Sánchez *et al.*, 2010).

Zhou and Skolnick (2012) stated that MC1R is one of the key genes in the mammalian pigmentation course as it encodes a transmembrane protein. MC1R is also considered as an extension locus for ASIP because a functional MC1R is a requisite for the normal expression of ASIP alleles. Agouti gene produces a protein product (ASIP) that serves as an antagonist to MC1R and governs the pattern and distribution of eumelanin against pheomelanin within the skin and coat fibers (McNulty *et al.*, 2005). Agouti gene shows its expression under the influence of some unique regulatory elements which are very common in mice (Vrieling *et al.*, 1994), rabbits (Fontanesi *et al.*, 2010), dogs (Kerns *et al.*, 2004) pigs (Drögemüller *et al.*, 2006) and cattle (Girardot *et al.*, 2006). Bonetto *et al.* (2005) specified that α-MSH is a hormone which opposite to ASIP function and it acts as agnostic to MC1R for eumelanin synthesis. Olivares *et al.* (2001) denoted that a group of enzymes known as Tyrosinase is mandatory for catalytic activity for melanin production. So pigmentation of animal color and fibers is a complex procedure that involves a chain of factors, genes, and enzymes in its course of action.

1.2 An analytical review of animal pigmentation genes and mutational variations

The orthodox genomic findings of sheep at Extension locus recognized the presence of two allele sequences, the E^D representing the dominant black and (E^+) as a wild type. The findings also suggested that the (E^D) for the black color coat in a few breeds, however (E^+) is frequently reported in more breeds. Agouti alleles segregation at (E^+) is vibrant as 20 alleles are accountable for maximum color disparity (Fontanesi *et al.*, 2011). In contrast to other species, the presence of recessive alleles at Extension locus in sheep still has not been acknowledged evidently (Fontanesi *et al.*, 2010). Three different alleles encoding melanocyte-stimulating hormone receptor MC1R of bovine extension (E) locus were classified. An E^D allele determining the blackish coat color, a recessive e allele represented red coat color and the E^+ wild-type allele fabricating a vast range of different coat colors, reflecting the capability of MC1R being adjustable (Klungland *et al.*, 1995). Våge *et al.* (2003) studied the Dala breed of Norway and documented two mutations at (E^D) dominant black. The mutations were termed as non-sense mutations p.M73k and p.D121N.

The pharmacological classification of two amino acid changeovers revealed that the only p.M73K holds the ability to initiate receptor probability to enhance the high affinity triggered state. (Royo *et al*., 2008) also presented these mutations in Corriedale, Damara, Black Merino, Black Castellana, and Karakul sheep breeds. Other hypotheses presented that these mutations produce a weaker response for receptor activation thus the possibility of both mutated locations and homozygosis behavior would be responsible for whole black-coated animals (Våge *et al*., 2003) The substitute type of the MC1R gene documented by Våge *et al*. (2003) should relate to the (E^+) Extension allele. (Norris and Whan, 2008) studied the ASIP gene screening and found the replication of 190-kb tandem at gene. They also stated that the dominance of white color in contrast to a tan color in agouti sheep (A^{Wt}) is due to AHCY coding region CDS and ITCH promoter region (Yang *et al*., 2013). Moreover, an uncategorized mutation and removal of 5bp at exon 2 and non-sense alteration at exon 4 were considered as one of the major causes of black recessive non-agouti (A^a) allele (Gratten *et al*., 2010). The homozygosis ratio of individuals having allele A^a would not possess phenotypic difference from the individuals having E^D allele, however, a few black colored breeds have reported the contemporary existence of both alleles. There is still doubt regarding the presence of dominant A^{Wt} allele and ASIP duplication gene that determine the white color coat of individuals because some other genetic influences also tangled in determining the white color in some ovines (Renieri *et al*., 2008).

The coat color in some goat breeds especially the (*Capra hircus*), is significant in determining the level of wool production, heat tolerance index in harsh climatic conditions and also for breed identification (Sponenberg *et al*., 1998). The key impact of Agouti locus regarding the coat color and distribution pattern has been stated by several researchers who extensively studied the herd records and segregation data inside breeds and during the experimental trials (Adalsteinsson *et al*., 1994). All these studies resulted in the comprehension of about 20 alleles among which a few overlaps. Some preliminary studies stated the existence of three basic alleles; Agouti- wild type A allele, a^t black and tan color and a non-agouti black recessive an allele (Nazari-Ghadikolaei *et al*., 2018). Further studies presented a series of alleles including the nomenclature like A^{Wt} (white/tan) and many other different alleles have been suggested.

About goat genetics findings, it was observed that the key role of Extension locus in determining the coat color has an insignificant impact in contrast to Agouti locus. An incomplete caprine gene mapping of ASIP gene has been categorized following the goat CHI 13 chromosome, with the exception that a single mutation at 4 exons has been reported in Chinese goat breed that is also an insufficient proof for the confirmation of goat color (Tang *et al*., 2008). The color of the body coat is a polygenetic character along with occasional epistatic connections. The role of MC1R and ASIP is renowned for color patterns and some researches acknowledged the significance of MC1R in the coat color of goat, cattle and sheep (Fontanesi *et al*., 2009). Likewise, transmutations in the MC1R gene have been associated with many coat color outlines in the Girgentana, Maltese, Derivata di Siria, Murciano-Granadina, Camosciata Delle Alpi and Saanen goats as well (Fontanesi *et al*., 2009). By evacuating the cAMP production, the epistatic interaction among MC1R and ASIP resulted in diminishing MC1R action ultimately increasing the pheomelanin production. The pheomelanin is the product of dominant allele (A) located at ASIP locus, whereas the eumelanin is resultant from recessive allele (a) in the blackish-brown phenotypic trait (Adalsteinsson *et al*., 1994). The dominant A^{Wt} (white/tan) allele in Saanen goats, gives the impression of a whitish coat (Martin *et al*., 2016).

A systematic study regarding pigmentation color in human and mice has been conducted because the gene taking part in pigmentation pattern have pleiotropic properties (Mohanty *et al*., 2008) and it is recorded that 130 genes are responsible for coat color in mice. With exception from mice, a few loci are accountable for coat coloring in most animal species as (Barsh, 2001) find A (agouti), E (extension), C (albino), D (dilution) and R (roan) as major loci accountable for coat color in cattle. The comparable amount of Eumelanin and pheomelanin is responsible for skin and hair color as both are the key constituents for mammalian pigmentation. The principle genes that create an impact upon the amalgamation of two pigments, Eumelanin and pheomelanin are TYRP1 and DCT formerly (TYRP2), MC1R, ASIP (agouti) and TYR (Seo *et al*., 2007). Different cattle coat colors may be a result of dilution as whitish, creamy, dun, gold, yellowish, pale reddish, grey or brown.

Such colors join in optical reflection and occasionally names are pronounced according to different colors in diverse breeds. (Feeley, 2015) stated that a vast type of modification can produce brown-colored fiber as a result of brown eumelanin synthesis and it is very common with an association of Tyrp1 gene in dogs (Schmutz *et al.*, 2002), cats (Lyons *et al.*, 2005), cattle (Berryere *et al.*, 2003) mice (Zdarsky *et al.*, 1990) and sheep (Gratten *et al.*, 2007).

So essential element of pigmentation is melanocytes and its differentiation, proliferation, and migration can be controlled by the influence of many genes (Wilkie *et al.*, 2002). Vance and Goding (2004) narrated that any interruption in the proper development of melanocytes and migration can cause different defects like white spotting, age-related grey color, and any mal-pigmented phenotypes.

1.3 Role of humans in encouraging and sustaining of colors pigmentation

Preferred selection of rare genetic mutations by mankind has dynamically altered the animal's coat pigmentation in terms of whole variated color along with additional bands, stripes or spots on the skin. The genetic mutation, especially in the DNA, is an integral part of an evolutionary process that may affect the protein synthesis mechanism besides resulted in diversified coat colors (Fang *et al.*, 2009). Concerning the number of genes accountable for determining the body coat color and possess adversarial pleiotropic interactions, it is mordant to state that the majority of wild animal ancestors exhibit uniformity and restriction in coat coloring patterns. Various genetic actions would be applied for a rapid modification in color pigmentation even if the process of natural selection overcomes the alterations where they seem. The former and latest DNA studies for swine's and horses suggested that the variations occurred in coat color during the domestication process. Humans vigorously exhilarated the spread of advanced color pigmentation by approving new mutations. Without human intervention, it is obvious that wild animals cannot persist in the basic coat color more than a pedigree in a natural environment (Linderholm and Larson, 2013). The body coat color has its central impact on breed identification as well as in economic setup. Keeping in view the alterations of color pigmentation, the Chinese merino sheep genomic sequence was manipulated by CRISPR/Cas9 sheep agouti signaling protein. The deletion of 4bp resulted in the production of lambs with barge face and blackish coat while the 2bp deletion resulted in a blackish-white spotted coat. The existence of on spot mutation of D9 and D5 also involved in color patterns while the co-effect of both ASIP and D9/D5 aided the collection of diversified lambs (Zhang *et al.*, 2017).

Fontanesi *et al.* (2011) stated that the human desire of gaining the only grey colored masseuse sheep has been achieved. Mutated ASIP and MC1R gene besides duplication of alleles with exon 2 imparts pleasant greyish coat color. Prehistoric Eurasian dog breeds are still considered unique due to their direct link with old mighty wolf populations and magnificent lighter coat color. The gene Melanocortin 1 receptor (MC1R) and canine-B-defensin (CBD103) in combination with a new variant R301C of MC1R are responsible for coat color selection in canids. A DNA fragmentation study exposed the presence of all these genetic variants through ancient dogs-wolf morphotype samples. The presence of genetic assortment in old canids as earlier as 10,000 years ago, as the dominant K^B allele CBD103 and R301C (MC1R) responsible for melatonism and lighter hair coat color respectively (Ollivier *et al.*, 2013).

Exosomes exert a wide range of biological functions, primarily via cell-to-cell cross-talk and the delivery of effectors or signalling molecules that regulate diverse cellular processes. Because they also contribute to cancer development and metastasis, their detection in a variety of biological fluids represents a promising strategy to gain pathogenic information and to identify specific biomarkers of diagnostic and prognostic relevance. In the era of precision medicine, the great promise of Exo concerns their potential application to non-invasive strategy aimed at the early definition of biomarkers to identify the responders to immunotherapy or for discovering specific dysfunctions of the immune system (Tucci *et al.*, 2018).

Neuromelanin is produced after the first 2–3 yr of life (Zecca *et al.*, 2001) and accumulates with aging (Zecca *et al.*, 2008). NM differs from the peripheral melanins as it predominates in catecholaminergic neurons of the SN and the locus coeruleus and is formed by the oxidation of catecholamines, dopamine (DA), and noradrenaline. These areas in the human brain undergo severe degeneration during the progression of Parkinson's disease (PD) (Zarow *et al*., 2003).

To minimize the deleterious effects of UVR, public education on photoprotective measures should be continued. Although there are a wide variety of agents with photoprotective properties, which range from antioxidants to plant extracts to DNA repair enzymes, a better understanding of melanin, its photoprotective properties and contributions of melanocytes to cancer would be desirable. This should permit new approaches to safely modulate pigmentation in the absence of sun to increase pigmentation for cosmetic reasons as well as to prevent skin cancer (Brenner and Hearing, 2008)

Crioula sheep is commonly domesticated in Brazil due to its naturally colored medullated wool, its progeny is maintained by natural producers as well as via nucleus conservation banks to promote handicraft industry and sale activities. A research study conducted to recognize single nucleotide polymorphisms in data re-sequencing from three core genes ASIP, MC1R, and TRYP1. Results suggested that the epistatic interaction between MC1R and ASIP genotype clarifies the exact wool color pattern however very minute ratio of the TYRP1 variant also affects the genuine medullated coat color. This behavior of making germ-plasm banks of desired characteristics reflects human intervention in the natural selection process (Cavalcanti *et al*., 2017). It is generally accepted that coat color affects the behavior of animals but this ideology was scorched by Hunter (2018) that mutations in MC1R are accountable for coat color variation but has nothing to do with animals behavior like tameness because such alleles are commonly diminished in wild populations due to their more access to predation in contrast to domesticated ones.

Fang *et al*. (2009) documented that the DNA mutations in wild and domesticated pigs as the absence of protein mutation in wild type pigs confirmed their natural camouflaged appearance while the presence of protein mutations (up to three-layered) in domestic pigs evidenced the selection by farmers over the large course of time resulted in current pinkish and white-colored boars. The camouflage appearance of pelage skin coat is in wild caprines along with a change in skin color according to weather like *O. Orientalis* exhibit brownish fawn in summer to reddish-brown tinge in the autumn season. The prevention of caprines by carnivore predation acquired through human intervention is also of supreme importance in changing the anatomy, skin coat color and behavior besides maintaining the camouflage appearance of wild sheep and goat that we find in today's domesticated caprines (Zohary *et al*., 1998).

The insensible selection had played a major role in changing the outlook (physiological, anatomical and behavioral characters) of currently present domesticated sheep from their wild ancestors. It is documented that the involvement of humans in animals assembling and controlling leads to an automated drastic change procedure. Predation defense, culling process, and other environmental factors altered the selection procedure. A sensible selection procedure assures the conservation of pure breeds.

1.4 Coat color concerning heat tolerance index

Hair color pigmentation attributes a direct relation with the heat tolerance index. As documented in a study conducted in Brazil among different sheep groups. Coat thickness, hair follicle numbers, ratio of sweat glands in skin tissues all take part in the heat tolerance capacity of the individual. The skin type and the pigmentation level showed direct relation as the lighter coat color is more the heat tolerance adaptation as seen in white-coated sheep in contrast to brown colored sheep and other hair coat color. Castanheira *et al*. (2010) stated that coat pigmentation -a crucial factor in the heat tolerance index by determining the physiological characters in White Santa sheep as the individuals exhibited lower normal rectal temperatures, heartbeat and respiration rates in contrast to compared groups. Apart from coat color the thickness and coat length also have a direct relation with heat adaptation (McManus *et al*., 2011). The tropical native cattle breeds have a higher pigmentation ratio in contrast to temperate region cattle. This natural pigmentation along with whitish coat helps tropical cattle underlying skin cells from harmful short wave UV radiation. Individuals with lighter coats reflect more light than darker ones and absorb about 50% less solar radiation (Da Silva *et al*., 2003). Long, dense and light brown hair coat color ascertained to be best 97.10% heat tolerated in contrast to short, less dense and black-white hair coat least 80.90% heat tolerated dwarf sheep individuals in an experimental study. Zimova *et al*. (2018) described that to cope with harsh environmental stress, the animals of the polar region have specialized genetic characters that help to maintain their internal body temperature.

Biannual seasonal coat color molting from brown in summer to white in the winter season is one of the chief characters that help different species of birds and mammals to live in harsh Northern hemisphere climate. Current drastic climatic change has created a negative impact on the natural camouflaged appearance of snowshoe hare and Arctic fox as the photoperiod duration is the main precursor for the color molting process. This minimum flexibility in seasonal molting has caught the attention to control mismatching camouflage appearance in animal species under climatic change.

Conclusions and Recommendations

Coat color pigmentation is an indispensable trait delimited multifactorial under melanocyte's sway and liable for animal's appearance and identification. Melanin production is an intricate course switched by MC1R, α-Melanocyte stimulating hormone, as well as the Agouti signaling gene with three diverse alleles indoctrinating the extension locus (E) of MC1R in consort with E^D dominant, recessive e, and E^+ wild-type allele defining the blackish, reddish and variated animal coat colors respectively. In advanced genetics programs mutation in MC1R and ASIP allele has accomplished the human desire of keeping variated coat colored animals especially the companion ones. Moreover, coat thickness, hair follicle numbers, ratio of sweat glands in skin tissues attributes a direct relation with the heat tolerance index and helped scientists to apprehend animals' comportment towards challenging climatic conditions globally.

Novelty Statement

Article comprehensively introduces the value of animal pigmentation, the natural pigmentation process, and new mutations and variations in the animal genome related to human pigmentation, thereby bringing well-being to humans and animals.

Author's Contribution

Moazam Ali: Conceptualization, writing original draft preparation.
Wajid Ali: Data curation, writing reviewing and editing.
Ayhan Ceyhan: Supervision, writing reviewing and editing.
Zeeshan Ahmad Bhutta: Methodology, writing reviewing and editing.

Conflict of interest

The authors have declared no conflict of interest.

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