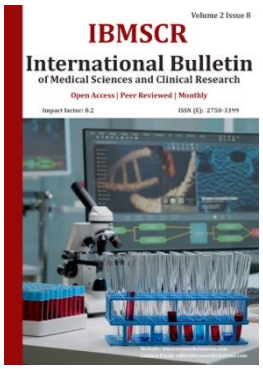

THE EFFECTS OF MUTATIONS ON ANIMAL GENETICS

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Annotation: This article examines the effects of mutations on animal genetics, highlighting their role in genetic diversity, adaptation, and evolutionary processes. It explores the types of mutations, their impact on genetic health, and their significance for conservation genetics and animal breeding. The article underscores the importance of understanding mutations in shaping the genetic landscape of animal populations.

Key Words: Mutations, Animal Genetics, Genetic Diversity, Evolutionary Processes, Genetic Disorders, Natural Selection, Conservation Genetics, Selective Breeding, Genetic Health, Evolutionary Biology.

Introduction: Mutations are fundamental drivers of genetic diversity, playing a pivotal role in shaping the genetic landscape of animal populations. This article delves into the effects of mutations on animal genetics, exploring their significance, mechanisms, and consequences for evolutionary processes. Pigmentation phenotypes have been under strong selection in domestic animals throughout their evolutionary history, and references to variation in pigmentation are indicated already in ancient literature and illustrations. For instance, the Greek historian Herodotus described that the Persian emperor Xerxes (in reign 485 to 465 BC) kept sacred white horses, most likely white horses caused by the Graying with age mutation (Rosengren Pielberg et al., 2008). Coat color variation is also described in old Roman literature (Forster and Heffner, 1968). Pigmentation must have been one of the first traits that were altered after domestication was initiated and extensive color diversity is a hallmark for domestic animals. The molecular characterization of mutations underlying these changes has given insight about mechanisms underlying pigmentation patterns. The evolution of pigmentation patterns in domestic animals constitutes a model for evolutionary change in natural populations. This review provides examples of mutations that disrupt pigmentation patterns and others that create pigmentation patterns. In addition to the patterns described here, it is worth noticing the Himalayan pattern that occurs in several species like cat, rabbit, mouse, and gerbil (Lyons et al., 2005), and is caused by temperature-sensitive mutations of tyrosinase producing white color but with dark pigmentation in cooler areas of the body, like the tips of the ears.

White Spotting Patterns in Domestic Animals.

White spotting patterns occur frequently in domestic animals. The most common causes are mutations in KIT encoding the KIT tyrosine kinase receptor, microphthalmia transcription factor (MITF), or endothelin receptor B (EDNRB), all with a crucial role for melanoblast migration and survival. Thus, a common reason for white spotting is lack of pigment cells in skin and/or in the hair/feather follicles.

The majority of KIT mutations causing pigment patterns in domestic animals are structural rearrangements. There are two reasons why these are common in domestic animals. One is

that structural rearrangements that do not touch the coding sequence may give a spectacular pigmentation pattern without causing negative pleiotropic effects, because KIT function is also essential for development of hematopoietic cells and for germ cells. The second reason is because some regulatory elements affecting KIT expression are located hundreds of kb both upstream and downstream of the coding sequence, disruption of these often gives spectacular spotting patterns. This is well illustrated by the domestic pig where a 450 kb duplication encompassing the entire coding sequence and more than 100 kb upstream and downstream of the coding sequence is causing the Patch phenotype characterized by large areas of the coat lacking pigmentation (Johansson Moller et al., 1996; Giuffra et al., 2002). Further, the Belt phenotype, characterized by a white belt across the foreleg, is associated with several duplications in non-coding regions of KIT (Rubin et al., 2012). The top dominant KIT allele, present in billions of pigs used for meat production world-wide, is Dominant white causing complete or near complete absence of skin and hair pigmentation. The Dominant white allele carries multiple causal mutations, including the different duplications associated with the Patch and Belt phenotypes, and in addition a splice mutation in one of the copies that leads to skipping of exon 17 encoding the tyrosine kinase domain. Thus, this results in a dominant negative receptor with normal ligand binding but inactivated tyrosine kinase signaling (Marklund et al., 1998; Rubin et al., 2012). The Dominant white allele is affecting pigmentation based on the combined effect of regulatory mutations (the duplications) and a coding change (splice mutation) in one of the copies. Due to this combination, it is the most dominant KIT allele as regards its effect on pigmentation in any mammal and with no or only very mild pleiotropic effects on hematopoiesis and fertility. Other examples of KIT structural rearrangements causing striking pigmentation patterns in domestic animals are Tobiano white spotting in horses caused by a 40 Mb inversion where one of the inversion breakpoints is located about 100 kb downstream of KIT (Brooks et al., 2008), and color sidedness in cattle caused by two serial translocations affecting KIT expression (Durkin et al., 2012).

In contrast to pigs where there is an allelic series at the KIT locus, white spotting in dogs is largely determined by an allelic series at the MITF locus (Karlsson et al., 2007). This Spotting (S) locus was first described by Little (1957) and is composed of four alleles Solid (S, wild-type), Irish spotting (Si), Piebald (Sp), and Extreme white (Sw). Irish spotting occurs in breeds like Bernese mountain dogs, Collie and Basenji, and is characterized by limited white spotting on the chest and often with a white ring around the neck. The Piebald phenotype occurs in for instance Beagles and Fox terriers and is characterized by more extensive white spotting across the body. Finally, Extreme white occurs in Dalmatians, white Boxers, and white Bull terriers and presents as a near total absence of pigmentation but remaining spots of pigmentation show normal pigmentation implying no defect in pigment production per se. In contrast to the situation in mice where the majority of described alleles affect the coding sequence and is associated with severe negative pleiotropic effects in other tissues where MITF function is essential, none of the MITF alleles in dogs affect the coding sequence and they have no or only mild negative effects (Karlsson et al., 2007); a fraction of the Extreme white dogs show deafness. Furthermore, an interesting aspect of the dog MITF alleles is that the three mutant alleles do not represent three independent mutations but show haplotype sharing strongly suggesting that the three alleles have evolved by consecutive accumulation of several causal mutations in the non-coding part of MITF. Functional characterization indicated that a simple repeat polymorphism in

the MITF promoter is likely one of the causal variants affecting white spotting patterns (Baranowska Körberg et al., 2014). A non-coding variant in the 5' region of MITF is also associated with a white spotting pattern in cattle (Hofstetter et al., 2019). In horses, mutations in both MITF and PAX3 are associated with the Splashed white pigmentation pattern (Hauswirth et al., 2012).

A missense mutation in EDNRB Ile118Lys is causing the Overo white spotting pattern in horses and in the homozygous condition the Overo lethal white syndrome, where lethality is caused by intestinal aganglionosis (Metallinos et al., 1998; Santschi et al., 1998; Yang et al., 1998). This horse syndrome corresponds to the form of Hirschsprung disease in humans caused by mutations in the same gene. A missense mutation in EDNRB2 is also associated with a feather pigmentation pattern in chicken (see below).

MC1R Mutations in Pigs Both Disrupt and Create Pigmentation Patterning.

Melanocortin 1 receptor (MC1R) is one of the major coat color loci in the domestic pig. The wild boar piglets show a striking camouflage color composed of longitudinal dark- and light-colored stripes (Figure 1). In the great majority of pig breeds of the world, this camouflage color is disrupted by MC1R mutations, either dominant black or recessive red mutations (Kijas et al., 1998, 2001). Fang et al. (2009) tested pigs from 68 different breeds from Europe and China and found that pigs from only one, the Hungarian Mangalica, were homozygous for the wild-type allele. Domestication of pigs occurred in parallel in Europe and Asia from two different subspecies of the wild boar, the European wild boar and the Asian wild boar that separated from each other about one million years ago (Giuffra et al., 2000; Kijas and Andersson, 2001; Groenen et al., 2012). Two different missense mutations in MC1R causing dominant black color were selected in European and Asian domestic pigs, D124N and L102P, respectively. A comprehensive screen of the MC1R coding sequences in wild boars and domestic pigs from both Europe and Asia led to the conclusion that there is purifying selection to maintain camouflage in wild boars and selection to disrupt camouflage in domestic pigs (Fang et al., 2009). A conclusion based on the observation that seven out of seven nucleotide substitutions among European and Asian wild boars were all synonymous, whereas nine out of 10 nucleotide substitutions among domestic pigs were non-synonymous changes.

The disruption of camouflage pattern in pigs carrying dominant black or recessive red alleles at MC1R suggests strongly that a wild-type MC1R receptor, whose signaling activity is controlled by the relative abundance of melanocyte-stimulating hormone (MSH) and agouti (ASIP), is required for the development of this pattern. The most likely explanation is that differential expression of agouti is causing patterning as recently reported for periodic feather patterning in juvenile galliform birds (Haupaix et al., 2018). Furthermore, differential expression of the transcription factor ALX3 is associated with the development of periodic dorsal stripes in the African striped mouse, which resemble the camouflage pattern in piglets (Mallarino et al., 2016).

One of the MC1R alleles in pigs is also creating a stochastic pigment pattern. That is the black-spotting EP allele that evolved from the European dominant black allele (ED1), carrying the D124N missense mutation, by the insertion of two C nucleotides at codon 22 creating a mononucleotide repeat of 8 C (Kijas et al., 2001). A frameshift mutation at codon 22 is expected to result in a complete loss-of-function and lack of black eumelanin in the coat. But that is not the case, the most common phenotype is red with a more or less random distribution of black spots across the body or white coat with larger black spots; whether the

black spots occur on a white or red background is determined by one or more other genetic factors that have not yet been identified. The black-spotting phenotype associated with this allele ranges from almost no spots at all, in particular on the red background as in Tamworth pigs, to an entire black coat with six white points (tail, nose, and four white feet) in Berkshire. So, how is this possible? The explanation is that the 8 C mononucleotide repeat is somatically unstable and may lose two nucleotides or gain one nucleotide and thereby restore the open reading frame. When that happens, constitutive MC1R signaling is reactivated due to the presence of the D124N missense mutation. This somatic instability of the mononucleotide repeat was confirmed by RT-PCR analysis (Kijas et al., 2001). The phenotypic range associated with the black-spotting allele is most likely explained by sequence variants affecting the probability for somatic reversion to occur as well as loci affecting the proliferation of melanocytes after reversion has occurred.

A similar stochastic pattern of pigmented spots occurs in white horses carrying the dominant graying with age mutation. These horses are born normally colored but start to gray already during the first year of life and they are usually completely white before they are 10 years of age. Graying with age is caused by a 4.6 kb tandem duplication in an intron of syntaxin 17 (Rosengren Pielberg et al., 2008). Many horses that are heterozygous for this mutation show large number of small pigmented spots and are called flea-bitten gray. It appears plausible that this phenotype is caused by somatic loss of one of the duplicated copies or that it is inactivated by an epigenetic mechanism. A third example of a stochastic generation of a pigmentation pattern in domestic animals is the merle patterning in dogs in which pigmentation is diluted by a retrotransposon insertion in PMEL (previously denoted SILV), somatic deletion of the retrotransposon restores normal pigmentation (Clark et al., 2006).

Regulatory Mutations in TBX3 Disrupt Camouflage Color in Horses.

The majority of domestic horses have a non-dun phenotype characterized by intense pigmentation and caused by homozygosity for a recessive allele at the Dun locus. The dominant Dun phenotype occurs in some horses like Icelandic horses and the Norwegian Fjord horse, but this is in fact a wild-type color present also in the Przewalski's horse, a close relative to the ancestor of domestic horses. Dun is causing a pattern of dilution on the flanks but leaves a dark dorsal stripe and may be associated with other dark patterns which may include facial mask, shoulder cross, and zebra-like stripes on the legs (Imsland et al., 2016). There are many mutations described in the pigmentation literature causing pigment dilution caused by various defects in the pigment machinery. It is worth noticing that Dun in horses is in fact a wild-type phenotype contributing to camouflage by reducing the intensity of pigmentation.

Histological studies revealed that the difference between hairs from Dun and non-dun horses is that the latter have a symmetric deposition of pigment whereas hair from Dun horses have an asymmetric deposition of pigments on the outward-facing side of the hair (Imsland et al., 2016). Thus, this is a pigmentation pattern affecting the individual hair. High-resolution genetic mapping combined with whole genome sequencing data from Dun and non-dun horses revealed that the non-dun phenotype is caused by cis-acting regulatory mutations affecting tissue-specific expression of the TBX3 transcription factor gene (Imsland et al., 2016). TBX3 had never before been associated with pigmentation, but it is important during development and loss-of-function mutations cause the ulnar-mammary syndrome in humans that involves defects in limb, apocrine gland, tooth, and genital development (Bamshad et al.,

1997). Imsland et al. (2016) first showed that the majority of non-dun horses, including the reference horse used for the horse genome assembly, were homozygous for an 1609 bp deletion located about 5 kb downstream of TBX3, in a region showing high sequence conservation among mammals. The fact that not all non-dun horses were homozygous required further analysis which revealed the presence of two different alleles non-dun1 (lacking the deletion) and non-dun2 (with the deletion). The causal mutation for non-dun1 is a single nucleotide substitution within the region deleted in non-dun2! Furthermore, genotyping more than 1000 horses for these two causal variants explained a phenotypic heterogeneity among non-dun horses where horses homozygous for non-dun2 have the most intense pigmentation and non-dun1 horses show an intermediate phenotype often with a weak dorsal stripe (Imsland et al., 2016). Interestingly, non-dun1 is in fact also a wild-type allele since it was found in two ancient horses (4400 and 42,700 years old). This implies that there existed two different color morphs of the ancestor of domestic horses, Dun and non-dun1, possibly adapted to different environmental conditions.

Imsland et al. (2016) also established a plausible molecular mechanism underlying camouflage color in Dun horses, which is disrupted in non-dun horses. In Dun horses, TBX3 has an asymmetric expression in the hair follicle that matches the asymmetric deposition of pigment. KIT ligand (KITL) shows downregulation in the area where TBX3 is expressed, which in turn means that pigment cells are not attracted to this part of the hair follicle explaining the lack of pigment deposition. In contrast, TBX3 is not expressed in the hair follicle in non-dun horses explaining the symmetric deposition of pigment. Thus, the results suggest that the deleted region contains an enhancer required for TBX3 expression in the hair follicle.

The work on the Dun horse coat color revealed a previously unknown function for TBX3 and a previously unknown mechanism for generation of camouflage color in mammals. This mechanism is present at least in all equids including zebras. For instance, the Somali wild ass, the wild ancestor of the donkey, shows a very clear Dun phenotype with diluted pigmentation on the flanks, a dorsal black stripe and zebra-like leg stripes. It is possible that this mechanism for camouflage pattern is also active in other mammals including different species of deer and antelopes.

Mutations in the CDKN2A Tumor Suppressor Gene Create Pigmentation Pattern in Chicken.

Sex-linked barring is an iconic plumage phenotype present in breeds like Barred Plymouth Rock and Coucou de Rennes (Figure 2A). This phenotype shows sex-linked dominant inheritance and is characterized by feathers with periodic black and white bars. In the initial identification of the causal gene for this phenotype, Hellström et al. (2010) mapped this locus to a 12 kb region containing only the CDKN2A tumor suppressor gene encoding two transcripts INK4b and ARF. CDKN2A had never before been associated with a pigmentation phenotype but has a well-established link to pigment cell biology because heterozygosity for loss-of-function mutations in this gene is a major risk factor for familiar forms of malignant melanoma in humans (Hussussian et al., 1994). Sequence analysis of the 12 kb region across many breeds of chicken revealed three CDKN2A alleles: wild-type (N), Sex-linked barring (B1), and Sex-linked dilution (B2); the latter is a variant of Sex-linked barring but causing a more diluted pigmentation and not as sharp contrast between the black and white bars as in Sex-linked barring. Four sequence variants, all in or near the ARF transcript, were

unique to the B1 and B2 alleles and not found in any of the sequenced wild-type chromosomes (Figure 2B). B1 carried a V9D missense mutation while B2 was associated with an R10C missense mutation, and both carried two SNPs in non-coding sequences. The two missense mutations were very strong candidates for being causal because they were both non-conservative and affected the MDM2-binding domain of the ARF protein. However, it was a mystery why both mutations occurred on the same very rare haplotype characterized by two non-coding changes not found among wild-type chromosomes.

Since all cells in our body contain DNA, there are lots of places for mutations to occur; however, not all mutations matter for evolution. Somatic mutations occur in non-reproductive cells and so won't be passed on to offspring.

For example, the yellow color on half of a petal on this red tulip was caused by a somatic mutation. The seeds of the tulip do not carry the mutation. Cancer is also caused by somatic mutations that cause a particular cell lineage (e.g., in the breast or brain) to multiply out of control. Such mutations affect the individual carrying them but are not passed directly on to offspring.

The only mutations that matter to large-scale evolution are those that can be passed on to offspring. These occur in reproductive cells like eggs and sperm and are called germ line mutations.

Effects of germ line mutations.

A single germ line mutation can have a range of effects:

Detrimental effect.

Some mutations harm an organism's ability to survive and reproduce. For example, in humans, Marfan syndrome is caused by a mutation affecting a protein that forms part of connective tissue, leading to heart problems and other health challenges. Detrimental mutations known as lethals disrupt DNA critical to survival and cause the death of the organism.

Beneficial effect. Other mutations are helpful to the organisms that carry them. For example, DDT resistance in insects is sometimes caused by a single mutation. While resistant insects might be downer for us, they are undoubtedly helpful for bugs trying to survive on pesticide-laden crops.

According to popular culture, it seems that mutations mainly cause either cancer or superpowers. Of course, the cancer is true enough. But in the real world, beneficial mutations are rare. Most mutations have no effect or a detrimental effect. And major evolutionary change (e.g., the "superpower" of flight in bats!) generally involves the accumulation of many, many mutations over many, many generations, with a few notable exceptions…

Little mutations with big effects: Mutations to control genes.

Some regions of DNA control other genes, determining when and where other genes are turned "on". Mutations in these parts of the genome can substantially change the way the organism is built. The difference between a mutation to a control gene and a mutation to a less powerful gene is a bit like the difference between whispering an instruction to the trumpet player in an orchestra versus whispering it to the orchestra's conductor. The impact of changing the conductor's behavior is much bigger and more coordinated than changing the behavior of an individual orchestra member. Similarly, a mutation in a gene "conductor" can cause a cascade of effects in the behavior of genes under its control.

Many organisms have powerful control genes that determine how the body is laid out. For example, Hox genes are found in many animals (including flies and humans) and designate where the head goes and which regions of the body grow appendages. Such master control genes help direct the building of body "units," such as segments, limbs, and eyes. So evolving a major change in basic body layout may not be so unlikely; it may simply require a change in a Hox gene and the favor of natural selection.

1. Understanding Mutations: Mutations are alterations in the DNA sequence that can arise spontaneously or be induced by external factors such as radiation or chemicals. They encompass a wide range of changes, including substitutions, insertions, deletions, and chromosomal rearrangements.

2. Types of Mutations: a. Point Mutations: These involve changes in a single nucleotide base and can lead to amino acid substitutions, insertions, or deletions, potentially altering protein function. b. Chromosomal Mutations: Larger-scale alterations, such as deletions, duplications, inversions, or translocations, can affect gene dosage, gene expression, or chromosomal structure.

3. Impact on Genetic Diversity: Mutations serve as the raw material for evolution, driving genetic variation within and between populations. They contribute to adaptation by generating alleles with new functional properties that may confer advantages in changing environments.

4. Genetic Disorders and Diseases: While some mutations are benign or even beneficial, others can result in genetic disorders or diseases in animals. These may manifest as developmental abnormalities, metabolic disorders, or predispositions to certain conditions.

5. Evolutionary Processes: a. Natural Selection: Mutations provide the substrate for natural selection, allowing advantageous alleles to increase in frequency within populations over time. b. Genetic Drift: Random fluctuations in allele frequencies, influenced by mutation rates, population size, and other factors, can lead to genetic drift and affect genetic diversity within populations. c. Gene Flow: Mutations can contribute to genetic differentiation between populations, particularly when coupled with limited gene flow.

6. Conservation Genetics: Understanding the effects of mutations is crucial for conservation efforts, as genetic diversity is a key component of population resilience and adaptability. Monitoring mutation rates and genetic health informs management strategies for endangered species.

7. Applications in Animal Breeding: Selective breeding programs harness mutations to introduce desired traits or eliminate undesirable ones in domesticated animals. Molecular techniques enable targeted manipulation of genetic variation for agricultural or biomedical purposes.

Conclusion: Mutations are integral to animal genetics, driving genetic diversity, adaptation, and evolutionary change. While mutations can have deleterious effects, they also fuel innovation and provide the substrate for natural selection. Understanding the effects of mutations on animal genetics is essential for elucidating evolutionary processes, managing genetic health in conservation contexts, and harnessing genetic variation in breeding programs.

References:

1.Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). Molecular Biology of the Cell (4th ed.). Garland Science.
2.Charlesworth, B., & Charlesworth, D. (2010). Elements of Evolutionary Genetics. Roberts and Company Publishers.
3.Crow, J. F., & Kimura, M. (2009). An Introduction to Population Genetics Theory. Harper & Row.
4.Hartl, D. L., & Clark, A. G. (2006). Principles of Population Genetics (4th ed.). Sinauer Associates.
5.Kimura, M. (1983). The Neutral Theory of Molecular Evolution. Cambridge University Press.
6.Lynch, M., & Walsh, B. (2007). Genetics and Analysis of Quantitative Traits. Sinauer Associates.
7.Nei, M. (1987). Molecular Evolutionary Genetics. Columbia University Press.
8.Slatkin, M. (2001). Molecular Evolution. Oxford University Press.
9.Storz, J. F. (2016). Evolutionary Genetics: Concepts and Case Studies. Oxford University Press.
10.Weir, B. S., & Cockerham, C. C. (1996). Genetic Data Analysis II: Methods for Discrete Population Genetic Data. Sinauer Associates.