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Review

Pleiotropic effects of coat colour-associated mutations in humans, mice and other mammals

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ABSTRACT

The characterisation of the pleiotropic effects of coat colour-associated mutations in mammals illustrates that sensory organs and nerves are particularly affected by disorders because of the shared origin of melanocytes and neurocytes in the neural crest; e.g. the eye-colour is a valuable indicator of disorders in pigment production and eye dysfunctions. Disorders related to coat colour-associated alleles also occur in the skin (melanoma), reproductive tract and immune system. Additionally, the coat colour phenotype of an individual influences its general behaviour and fitness. Mutations in the same genes often produce similar coat colours and pleiotropic effects in different species (e.g., *KIT* [reproductive disorders, lethality], *EDNRB* [megacolon] and *LYST* [CHS]). Whereas similar disorders and similar-looking coat colour phenotypes sometimes have a different genetic background (e.g., deafness [*EDN3/EDNRB, MITF, PAX* and *SNAI2*] and visual diseases [*OCA2, RAB38, SLC24A5, SLC45A2, TRPM1* and *TYR*]). The human predilection for fancy phenotypes that ignore disorders and genetic defects is a major driving force for the increase of pleiotropic effects in domestic species and laboratory subjects since domestication has commenced approximately 18,000 years ago.

Contents

Abbreviations: αMSH, alpha-melanocyte-stimulating hormone; AS, Angelman syndrome; ATRN, Attractin (mahogany); ASIP, Agouti signalling protein; BLOC, Biogenesis of lysosomal organelles complex; CCSD, Canine congenital sensorineural deafness; CHS, Chediak-Higashi syndrome; CSD, Congenital sensorineural deafness; CSNB, Congenital stationary night blindness; EDN3, Endothelin 3; EDNRB, Endothelin receptor type B; GS, Griscelli syndrome (type 1 or 2); HPS, Hermansky-Pudlak syndrome with different types; HSCR, Hirschsprung disease; IPE, Iris pigment epithelium; KIT, V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, tyrosine kinase receptor (c-kit); KITLG, KIT ligand (steel factor); LFS, Lavender foal syndrome; LYST, Lysosomal trafficking regulator; MC1R, Melanocortin 1 receptor; MCOA, Multiple congenital ocular anomalies; MCOLN3, Mucolipin 3 (TRPML3); MGRN1, Mahogunin ring finger 1 (E3 ubiquitin protein ligase); MITF, Microphthalmia-associated transcription factor; MYO5A, Myosin VA (heavy chain 12, myoxin); OA, Ocular albinism; OCA, Oculocutaneous albinism type 1–4; OCA2, Oculocutaneous albinism II (pink-eye dilution homolog); OLWS, Overo lethal white syndrome; OSTM1, Osteopetrosis associated transmembrane protein 1 (Grey lethal osteopetrosis); PAX3, Paired box 3; PMEL, Premelanosome protein (Pmel17, SILV); PWS, Prader-Willi syndrome; RAB27A, RAB27A member RAS oncogene family; RAB38, RAB38 member RAS oncogene family; RPE, Retinal pigmented epithelium; SLC24A5, Solute carrier family 24, member 5; SLC2A9, Solute carrier family 2 (facilitated glucose transporter), member 9; SLC45A2, Solute carrier family 45, member 2, MATP; SNAI2, Snail homolog 2 (Drosophila), (SLUG), SOX10, SRY (sex determining region Y)-box 10; STX17, Syntaxin 17; TRPM1, Transient receptor potential cation channel, subfamily M, member 1 (melastatin-1); TYR, Tyrosinase, TYRP1, Tyrosinase-related protein 1; WS, Waardenburg syndrome (type 1, type 2 combined with Tietz syndrome type 3 Klein-Waardenburg syndrome, type 4 Waardenburg-Shah syndrome).

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1. Introduction

Humans have always been fascinated by the wide variation of fur and plumage colours in animals. Evolutionary biologists are particularly impressed by the enormous range in colour diversity and its prominent role in adaptation and selection [1–3]. The evolutionary importance of the phenotypic trait "colouration" is well documented for many functions, including camouflage, mate selection, communication, regulation of physiological processes, UV protection and defence against parasites. In addition to environmental adaptation, artificial selection has altered the coat colour design of species under human care since domestication began [2]. Recent genetic studies examining coat colours provided important insights into the inheritance of coat colour-associated alleles and on the underlying gene pathways. Steingrimsson et al. [4] concluded that we know more about the pathways and proteins that regulate the development and function of melanocytes (pigment-producing cells) than we know about every other cell type in any mammalian organism. Thus far, several thousand alleles have been described from approximately 150 identified coat colour-associated genes [2]. In the laboratory mouse (*Mus musculus*), nearly 1000 coat colour-associated alleles have been observed in approximately 130 genes [4]. Specific coat colours often greatly influence the phenotypic description of lineages. For example, the famous inbred mouse strain DBA is named according to its visible colourations (D = diluted; B = brown; A = agouti). Currently, the coat colour phenotype is commonly used as the definitive marker of mouse inbred stains [4], and domestic breeds are also named according to their coat or plumage colouration [2].

Nevertheless, the exact characterisation of a coat-colour phenotype and its underlying genotype is a difficult task because nearly identical phenotypes in a species or among species can be produced from the same gene or from different genes acting in the same pathway or in different pathways [2]. Thus, different coat and eye colour-associated genes or loci can influence pigmentation in various ways. Notably, coat colour-associated mutations are often associated with pleiotropic effects including disorders of the sensory organs, disturbed reproduction and skin diseases. Although many of these disorders have serious consequences for the fitness of the affected organism, the characterisation of these disorders is incomplete. Currently only a few reviews, often focused on humans, mice or a specific domestic species [5–9], address the pleiotropy of coat colour-associated mutations. In this study, we summarise the recent studies on the pleiotropic effects of coat colour-associated mutations in humans, mice and additional mammals.

2. Sensory organs and nerves

Pigment cells are essentially important for the functionality of organs of perception, especially the senses of the eyes and ears. In mammals, the quantity, packaging and quality of melanin in the diverse layers of the eye determine the colouration of the eye and significantly influence visual acuity. Specifically, reducing the amount of pigment affects both the general development and function of the eye [7,10–12] and dilutes the eye colour and influences the iris patterns, which are often associated with eye diseases. Consequently, the eye-colour is a valuable indicator of disorders in pigment production and eye dysfunctions.

2.1. Albinism

Biologically and medically relevant ocular phenotypes were described for a number of mouse strains with diluted phenotypes [13]. Oculocutaneous albinism (OCA) is the most famous syndrome of hypopigmentation in coat colouration and eye-colour and vision disorders; in OCA, the reduced production of pigments often results in serious dysfunction of the eye. In humans, a large number of different mutations in the *tyrosinase* (*TYR*) gene causes oculocutaneous albinism type 1 (OCA1) and generates nystagmus and hypoplasia in conjunction with reduced visual acuity [14].

Fig. 1. Examples of pleiotropic effects of coat colour-associated mutations: (A) skin lesions as consequence of actinodermatitis in a cremello horse (mutated gene *SLC45A2*), (B) white tiger with great susceptibility to infection diseases (a mutation in the *LYST* gene seems to be likely), (C) a nearly deaf extreme white splashed-white overo spotted horse (*MITF* and *EDNRB*), (D) an eye cysts in a silver-bay horse (*PMEL*), (E) a Merle coloured dog – homozygote individuals are deaf (*PMEL*); (F) melanoma in a grey horse (*STX17*).