Actas Dermosifiliogr. 2009;100:Supl. 2:84-7

# DNA Polymorphisms: What They Are and Their Role in Human Pigmentation

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Abstract. The color of the skin, hair and eye is controlled by multiple genes and is among the most visible examples of human phenotypic variation. Genetics correlate phenotypic with genotypic variation. Recent scientific work reveals DNA polymorphisms at least partially responsible for some of the differences observed in human pigmentation. These are the focus of this review.

Key words: single nucleotide polymorphism, polymorphisms, pigmentation.

## POLIMORFISMOS DE ADN: QUÉ SON Y SU ROL EN LA PIGMENTACIÓN HUMANA

Resumen El color de la piel, el pelo y los ojos está controlado por múltiples genes y es uno de los ejemplos más visibles de la variabilidad fenotípica humana. La genética correlaciona la variabilidad fenotípica con la genotípica. Recientes publicaciones científicas revelan que los polimorfismos del ADN son responsables, al menos parcialmente, de algunas de las diferencias observadas en la pigmentación humana. Éstas serán el objetivo de la presente revisión.

Palabras clave: polimorfismos de nucleótido único, polimorfismos, pigmentación.

## Introduction

The information derived from annotation of human DNA sequence allows studies that correlate phenotypic variation with genotypic variation. The most common sources of genetic variability are single nucleotide polymorphisms (SNPs) and small microinsertions/ microdeletions (indels). SNP is a DNA sequence variation occurring when a single nucleotide differs between members of a species (or between paired chromosomes in an individual). Microindel describes a mutation resulting in a colocalized insertion and deletion and a net gain or loss in 1 to 50 nucleotides. When genetic variants occur in at least 1% of the population, they are termed polymorphisms. If the polymorphism results in a change of the amino acid sequence of a protein, it is called a nonsynonymous change; otherwise, it is termed a synonymous change. If the polymorphism appears outside of coding units (ie, genes), it is merely defined by the sequence alteration. Penetrance describes the proportion of individuals carrying a particular variation of a gene that also expresses an associated trait. Heritable alleles vary from low penetrance (usually common SNPs that will cause the associated trait in a minority of carriers) to high penetrance (mutations that will probably or certainly cause their associated trait).

The interest of the scientific community on genetic polymorphisms is enormous. DNA sequencing allows scientists to identify genotypes that render individuals susceptible to or cause various diseases. In this review we focus on polymorphisms involved in human pigmentation. However, analogous reviews could be written for any other condition/disease.

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## Human Skin Colour

### Outline of Pigmentation

Pigmentation of the skin, hair and eye is among the most visible examples of human phenotypic variation within and between ethnic groups. It is chiefly determined by the number, size and distribution of pigment-filled melanosomes, and the ratio of black/brown eumelanin to yellow/red phaeomelanin pigment[1]. Multiple genes harboring genetic variants are involved in this process[2].

Among them, the melanocortin-1 receptor (MC1R) is one of the key genes that regulates skin color. It encodes a transmembrane G-protein receptor (Mc1r) located on the

cell surface of melanocytes. MC1R functions as a receptor for the α-melanocyte stimulating hormone (α-MSH). When α-MSH binds to Mc1r, the intracellular level of cyclic adenosine monophosphate (cAMP) is increased by a G-protein-coupled adenylate cyclase system. As a result, melanocytes are stimulated to switch melanin production from the red/yellow pheomelanins to the brown/black eumelanins. Agouti signaling protein (ASIP) has also been shown to bind MC1R, blocking MC1R-stimulated elevation of cAMP, thus acting as an inverse agonist. The enzyme tyrosinase (TYR) catalyzes three distinct reactions in the pathway of melanin production: hydroxylation of monophenol (L-tyrosine), dehydrogenation of catechol (L-DOPA), and dehydrogenation of DHI. The optimal activity of tyrosinase in human melanocytes requires an appropriate ionic environment, which is partially controlled by P-protein functioning as an ion exchange membrane channel[3,4]. P-protein is encoded by the OCA2 gene (human type II oculocutaneous albinism-related gene)[5]. Membrane-associated transporter protein (MATP) is encoded by the SLC45A2 gene (solute carrier family 45, member 2), and has been considered a sodium-hydrogen exchanger of melanosomes, regulating tyrosinase activity in human melanocytes. SLC24A5, the human ortholog of the golden gene in zebrafish, codes for a potassium-dependent sodium/calcium exchanger spanning the melanosomal membrane. Thus, SLC24A5 protein, by controlling calcium concentration, may have an important role in pH regulation in the melanosome[6] and in controlling activation of the silver gene to produce Pmel17 (which is required to form mature eumelanosomes)[7].

## Polymorphisms in Known Pigmentation Genes

### *MC1R*

Large population studies have shown that MC1R is remarkable polymorphic in Europeans, and probably a key determinant of color variation in this population. Several polymorphisms in MC1R are associated with red hair and fair skin and poor tanning ability (known as the RCH phenotype), in particular Arg151Cys, Arg160Trp and Asp294His. These MC1R variants cause reduced receptor function and thus abrogate the signaling cascade that leads to elevation of intracellular cAMP; therefore, pheomelanogenesis rather than eumelanin synthesis is retained. Interestingly, there is little if any nonsynonymous variation in MC1R amino acid sequences in African populations, indicating that this gene is under strong selective pressure to preserve its function on that continent. MC1R does not appear to have a major role in pigmentation differences between ethnic groups[8]. MC1R variants have also been linked with auburn hair, freckles and "rust-coloured" skin in black Jamaicans[9].

### *Agouti Signaling Protein Gene (ASIP)*

The role of Agouti signaling protein in the variation of human pigmentation remains unclear. The SNP in the 3'-untranslated region of ASIP 8818A > G was found to be associated with darker pigmentation in humans[10-12], however, this has not been confirmed in later studies[13,14]. Another SNP near ASIP gene (haplotype) was found to be associated with skin sensitivity to burn after sun exposure, red hair and freckles[15].

### *SLC45A2 Gene*

The SLC45A2 gene encodes the MATP protein. Two nonsynonymous SNPs have been identified in the SLC45A2 gene: Phe374Leu and Glu272Lys, which were associated with normal pigmentation variation within and between populations[16]. Specifically, the 374Leu substitution was present at a significantly higher frequency in Asians (f = 0.887), African Americans (0.586) and Australian Aborigines (f = 0.725) than in Caucasians (0.066). Caucasians with 374Leu tended to have darker pigmentation, the highest frequency of the substitution was seen in individuals with black hair (odds ratio [OR] 25.6), olive skin (OR 28.6) and dark eyes (OR 3.5)[14,16,17]. The allele 374Leu was also independently reported to significantly increase the possibility of having black hair (OR 7.05) and is considered a major determinant of hair color in Europeans[18]. The effect of SLC45A2 Glu272Lys on pigmentary phenotypes has been questioned[14,16]. The role of other polymorphisms in the promoter region of the SLC45A2 gene, reported to be involved in normal variation of human pigmentation[19], has not been verified in studies with larger samples[20]. The functional significance of these mutations on the MATP protein has not been fully elucidated, but the 374Leu allele may result in optimal intramelanosomal pH for eumelanin production[16].

### *SLC24A5 Gene*

The golden gene SLC24A5 causes significant lightening of the stripes in zebrafish[6]. The human ortholog SLC24A5 was also discovered and it was shown that the alanine-to-threonine substitution at amino acid 111 (A111T) had a lightening effect on human pigmentation. The 111A ancestral form of the protein has a high frequency within more darkly pigmented populations, such as Africans, Native Americans, and East Asians (f = 0.93-1.0), whereas the 111T variant allele is virtually fixed in Europeans (f = 0.987-1.0)[6,21]. Genotype-phenotype studies indicate that 25-38% of variation in skin color between Africans

and Europeans was due to this single SLC24A5 polymorphism.

### *Tyrosinase Related Protein-1 Gene (TYRP-1)*

To date, no polymorphisms of the TYRP-1 gene are associated with human pigmentation. However, the TYRP-1 protein was reported to be elevated 2,6 times in darkly pigmented African and Indian skin types compared with lightly pigmented Mexican, Chinese and European skin types[22]. A single SNP has a significant, genome-wide association with blue (vs. non blue) eyes[15].

## Oculocutaneous Albinism Type II Gene (OCA2)

The OCA2 gene encodes the trans-melanosomal membrane protein "P". Polymorphisms of OCA2 gene are clearly associated with eye color[23-26]. The HERC2 gene is thought to further influence eye color by inhibiting OCA2 gene expression[24]. The role of OCA2 gene polymorphisms in determining skin color is still uncertain although SNP Arg305Trp seems to be marginally associated with skin color[14,27].

### Two-Pore Segment Channel 2 Gene (TPCN2)

The TPCN2 gene was recently associated with blond (vs. brown) hair, revealing a previously unknown connection between TPCN2 and pigmentation[15]. Specifically, two variants within the gene, Met484Leu and Gly734Glu, were found to be related with the blond versus brown hair phenotype. The TPCN2 protein participates in calcium transport in the melanosome similar to the proteins encoded by known pigmentation genes SLC24A4 and SLC24A5.

### Interferon Regulatory Factor-4 Gene (IRF4)

IRF4 codes for a transcription factor affecting gene expression in response to interferon and other cytokines. Han et al[20] first demonstrated a convincing association between an IRF4 gene polymorphism (rs12203592) and hair, eye and skin color, and tanning response. This first report suggesting a link between a particular IRF4 locus and human pigmentation has recently been confirmed[28]. The mechanism underlying the involvement of this immune regulatory gene in determining pigmentation phenotypes remains unclear.

### Kit Ligand for the Kit Receptor Gene (KITLG)

KITLG has a role in controlling migration, survival and proliferation of melanocytes[29]. KITLG variation in humans was investigated by Miller et al[30] and an association between skin colour and an ancestral SNP (rs642742A > G) allele in West Africans was shown. The frequency of the ancestral A allele is at least 92% in West Africans, whereas the frequency of the derived G allele is at least 86% in Europeans and East Asians. Authors estimate that substitution of ancestral alleles with derived alleles contributes perhaps to a 20% decrease in skin melanization between West Africans and European/East Asians. The derived G-allele alters a noncoding sequence that is highly conserved in mammals and therefore represents a candidate mutation that could affect KITLG expression. Indeed, experimental studies[30] suggest that KITLG expression is higher in the skin of Africans compared with Europeans and that injecting KITLG into human skin increases melanocyte size and dendricity and should therefore result in darker skin.

In 2007 Sulem et al[31], based on samples from Iceland and Denmark, located an SNP (rs12821256) that was significantly associated with blond versus brown hair (OR = 2.32). Individuals with the rs12821256(C) allele were roughly two times more likely to have blond than brown hair.

### Solute Carrier Family 24, Member 4 Gene (SCL24A4)

Sulem et al[31] found a variant in the SLC24A4 gene that was associated with hair and eye color in Icelanders and Dutch. One of the tagged SNPs was rs12896399; the T allele showed a similarly strong association with blond versus brown hair (OR = 2.56) and blue versus green eyes (OR = 2.06). Han et al also found an association of the same SNP with hair/eye color in their genome association wide study[20]. The SLC24A4 gene belongs to the family of potassium-dependent sodium/calcium exchangers.

**Conflict of interest**
Authors have no conflict of interest to declare.

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