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Invited Review

Melanocortin 1 Receptor Variants: Functional Role and Pigmentary Associations

Clio Dessinioti*, Christina Antoniou, Andreas Katsambas and Alexander J. Stratigos

Oncology Unit, 1st Department of Dermatology, University of Athens, Andreas Sygros Hospital, Athens, Greece

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ABSTRACT

The significance of human cutaneous pigmentation lies in its protective role against sun-induced DNA damage and photocarcinogenesis. Fair skin and red hair are characterized by a low eumelanin to pheomelanin ratio, and have been associated with increased risk of skin cancer. Cutaneous pigmentation is a complex genetic trait, with more than 120 genes involved in its regulation, among which the melanocortin 1 receptor gene (*MC1R*) plays a key role. Although a large number of single nucleotide polymorphisms (SNPs) have been identified in pigmentation genes, very few SNPs have been examined in relation to human pigmentary phenotypes and skin cancer risk. Recent GWAS have identified new candidate determinants of pigmentation traits, but *MC1R* remains the best characterized genetic determinant of human skin and hair pigmentation as well as the more firmly validated low-penetrance skin cancer susceptibility gene. In this review, we will address how the melanocortin system regulates pigmentation, the effect of *MC1R* variants on the physiologic function of the MC1 receptor, and how specific *MC1R* variants are associated with distinct human pigmentation phenotypes.

INTRODUCTION

Human pigmentary characteristics, such as skin, hair and eye color, together with the exposure to ultraviolet radiation, are the main modulators of an individual's risk for developing skin cancer (1). Human cutaneous pigmentation results from the synthesis of melanin pigments in epidermal melanocytes followed by their transfer to keratinocytes and their distribution throughout the skin. Pigmentation, and consequently sun sensitivity, is a polygenic trait and several candidate regulatory genes such as *ASIP* agouti signaling protein, MIM 6062010, *DCT* (MIM 191275), *MC1R* (melanocortin 1 receptor, MIM 1555555), *OCA2* (oculocutaneous albinism type 2, previously called *P* gene, MIM 611409), *SCL24A5* (solute carrier family 24, member 5, MIM 609802), *SCL45A2* (solute carrier family 45 member two, previously called membrane-associated transporter protein [*MATP*], MIM 606202), *TYR* (tyrosinase, MIM 606933) and *TYRP1* (tyrosinase-related protein 1, MIM 115501) have been identified (2–12). Recent genome wide association studies (GWAS) confirmed the association of various loci with pigmentary characteristics and cutaneous sun sensitivity, including single nucleotide polymorphisms (SNPs) in *MC1R* and *ASIP,* associated with hair color, sun sensitivity and freckling, SNPs in *TYR,* associated with eye color, skin color, sun sensitivity and freckling, and SNPs in *TYRP1* and *OCA2*, that were associated with eye color. Also, GWAS have reported novel potential "pigmentation genes," namely solute carrier family 24, member four (*SLC24A4*), associated with light hair color and blue eye color, two-pore segment channel 2 (*TPCN2*), associated with hair color, and interferon regulatory factor 4/exocyst complex component 2 (*IRF4/EXOC2*), associated with dark hair color, light eye and skin color and sun sensitivity (12). Such genetic approaches have provided insight into the regulation of human pigmentation; however, understanding of the molecular action of pigmentary genes, gene interactions and functional protein assays, is necessary to elucidate how allelic variation results in such a diversity of phenotypes in human populations (13).

To date, *MC1R* remains the best characterized genetic determinant of human skin and hair pigmentation as well as the more firmly validated low-penetrance skin cancer (malignant melanoma, basal cell carcinoma [BCC], squamous cell carcinoma [SCC]) susceptibility gene (11,14–17). In this review, we will address how the melanocortin system regulates pigmentation, the effect of *MC1R* variants on the physiologic function of MC1 receptor, and how specific *MC1R* variants are associated with distinct human pigmentation phenotypes.

THE MELANOCORTIN SYSTEM AND REGULATION OF PIGMENTATION

The melanocortin (MC) system is ambient and arose very early in vertebrate evolution. It consists of melanocortin peptides (α-, β-, γ- melanocyte-stimulating hormone [MSH]) derived from the proopiomelanocortin (*POMC*) gene, five melanocortin receptors, two endogenous antagonists (agouti and agouti-related protein), and two ancillary proteins (mahogany and syndecan-3) (18). MC receptors are G protein-coupled receptors (GPCR) with five subtypes in mammals and chicken. Despite high structural and genetic conservation of the MC receptors, the physiologic role of each subtype is very diverse.

*Corresponding author email: cliodes@hotmail.com (Clio Dessinioti)

The melanocortin 1 receptor (MC1R) has a defined role in pigmentation and may also play a role in mediating some of the anti-inflammatory actions of MSH. The MC2R mediates the function of adrenocorticotropic hormone (ACTH). The MC3R is involved in the regulation of the energy balance, whereas the MC4R has a fundamental role in control of feeding and body weight. The MC5R has a role in exocrine gland function (19).

Cutaneous pigmentation is determined by the amounts of melanin synthesized by epidermal melanocytes, and is known to protect against sun-induced DNA damage. Melanin is synthesized within melanosomes of melanocytes that, when mature, are passed to the surrounding keratinocytes (20). There are two forms of epidermal melanin, eumelanin (which has black–brown color) and pheomelanin (red–yellow color). Eumelanin synthesis in melanocytes is stimulated by activation of the MC1R expressed on melanocytes, by the binding of α-MSH, a tridecapeptide cleavage product of POMC (20–22). α-MSH is secreted in response to UVR, and binding of a-MSH to MC1R activates adenylate cyclase and increases cAMP formation (23). The *MC1R* signal transduction is mediated *via* coupling to the heterotrimeric G-protein, which activates adenyl cyclase and increases levels of cellular cAMP (24). Elevation in cAMP leads to activation of protein kinase A, which in turn leads to increased transcription of *MITF* (microphthalmia transcription factor). *MITF* plays a key role in the control of melanogenesis, and leads to increased transcription of a range of genes including *TYR* and *TYRP1*, involved in the control of the relative and absolute amounts of eumelanin and pheomelanin (Fig. 1) (20).

MC1R gene is located on chromosome 16q24.3 and encodes for a seven pass transmembrane receptor of 317 amino acids, which is expressed in several cell types, including epidermal and follicular melanocytes and keratinocytes (21,22).

The human *MC1R* is highly polymorphic in the Caucasian population and certain allelic variants of the gene are associated with red hair color (RHC) phenotype and increased risk of melanoma or nonmelanoma skin cancer (BCC, SCC) (14,23).

Recently, it was demonstrated that α-MSH as well as β-MSH can regulate tyrosinase activity directly in the melanosome in a receptor independent manner. Also, cAMP synthesis does not depend only on the MC1R signal. After the discovery of autocrine catecholamine, acetylcholine as well as estrogen and corticosteroid synthesis in melanocytes, several other receptors for cAMP synthesis have been identified, including the b2-adrenoceptor, muscarinic receptors (M1,M3,M5), α- and β-estrogen receptors and CRF/CRF-R1 signaling pathway. Interestingly, CRF can stimulate POMC and ACTH production (25). As almost all cutaneous cell types not only synthesize MCs but also express MC receptors, the cutaneous MC system is a complex endocrine, paracrine, and autocrine network (reviewed in Böhm *et al.*) (26).

MC1R VARIANTS AND THEIR EFFECT ON THE PHYSIOLOGIC MC1R FUNCTION

More than 100 human alleles of the *MC1R* gene with nonsynonymous changes have been identified to date (16,27–31). However, the consequences of these variants on the

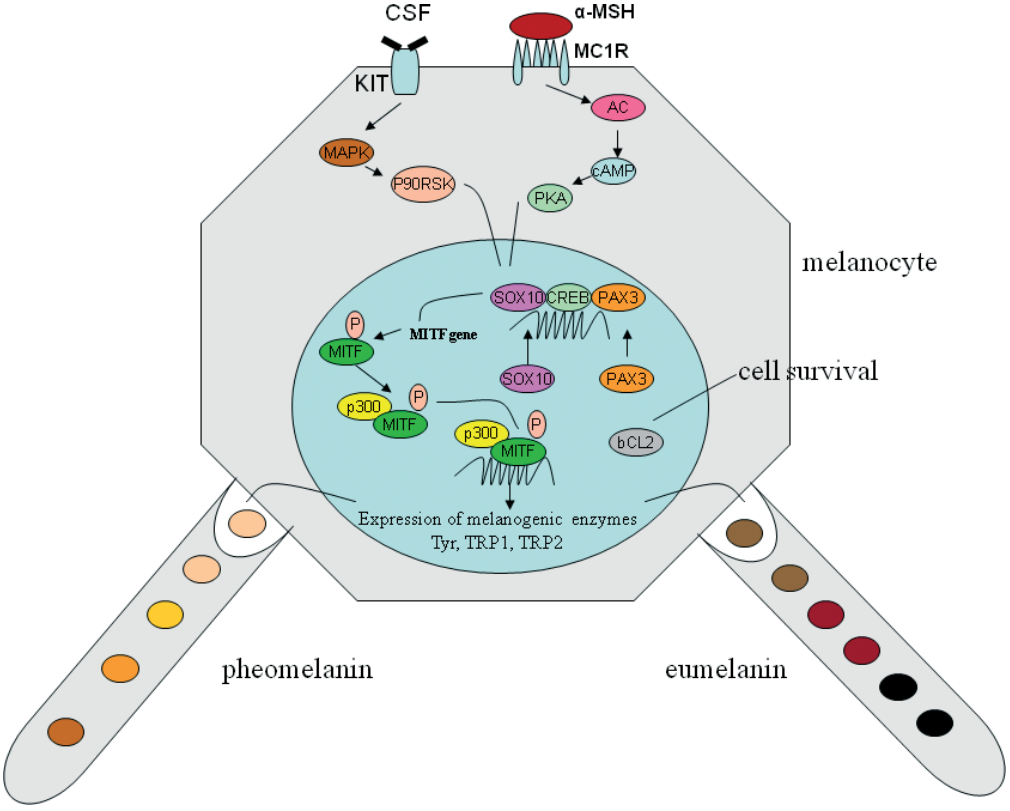


Figure 1. The role of MC1R signaling on melanogenesis. A-MSH binds to the MC1R receptor, which activates the PKA/cAMP pathway, leading to the expression of melanogenic enzymes that control eumelanin synthesis.

Table 1. *MC1R* variants: Outline of known functional role and phenotypic correlations.

MC1R variant	SNP rs number	Functional role	Phenotypic correlations	Specific population allele frequencies (%)*	European population specific allele frequencies (allele 1/allele 2)*
Any variant	–	–	Lighter skin color[29,39]	–	–
Two R variants	–	–	Increased susceptibility of melanocytes to UVR[51] Red hair, fair skin[36,39]	–	–
V38M	NR	Located in TM1 Moderate decrease in coupling to the c AMP pathway[16] LOF is due to reduced cell surface expression as consequence of retention in the ER[16]	–	0.5, Italy[46]	–
S41F	NR	Located in TM1 Nearly complete absence of functional coupling to the c AMP pathway[16] LOF is due to reduced cell surface expression as consequence of retention in the ER[16]	–	–	–
V51A	NR	Located in TM1 Moderate decrease in coupling to the c AMP pathway[16] LOF is due to reduced cell surface expression as consequence of retention in the ER[16]	–	–	–
V60L	rs1805005G > T	Reduced capacity to stimulat c AMP[52]	Blonde/light brown hair[29]	25.5, Italy[46] 12.4, Australia[71] 15.0, N. Europe[44] 11.3, Greece[14,43] 12.3†	0.122
D84E	rs1805006C > A	Lower response to a-MSH in cAMP, Slightly impaired ability to bind a—MSH[35]	Red hair	0.5, Italy[46] 1.5, N. Europe[44] 1.3†	0.012
V92M	rs2228479G > A	*ca* two-fold lower affinity for a-MSH than wild type MC1R[35,36,52] No alteration in the functional coupling of MC1R to adenylate cyclase[30]	Increased synthesis of phaeomelanin[36] Reduced defense mechanisms of melanocytes against UVR genotoxicity[34] Not associated with red hair phenotype[29]	3.0, Italy[46] 8.7, N. Europe[44] 4.2, Greece[14,43] 8.8†	0.097
M128T	NR	Located in TM3 Nearly complete absence of functional coupling to the c AMP pathway[16] #Unable to bind agonists efficiently, despite being trafficked to the cell surface[16]	–	–	–
R142H	rs11547464G > A	Red hair	–	3.0, Italy[46] 0.6, N. Europe[44] 0.6, Greece[14,43] 1.2†	0.004
R151C	rs1805007C > T	Diminished functional coupling of MC1R, poor stimulation of intracellular c AMP production in response to α-MSH[34]	Red hair, fair skin[39,49]	2.5, Italy[46] 9.9, N. Europe[44] 1.9, Greece[14,43] 9.1†	0.11
I155T	rs1110400C > T	–	Red hair	0.9,N. Europe[44] 0.9†	0.009

Table 1. Continued.

MC1R variant	SNP rs number	Functional role	Phenotypic correlations	Specific population allele frequencies (%)*	European population specific allele frequencies (allele 1/ allele 2)*
R160W	rs1805008C > T	Diminished functional coupling of MC1R, poor stimulation of intracellular c AMP production in response to α-MSH[34]	Red hair, fair skin[36,39]	3.0, Italy[46] 8.7, N. Europe[44] 1.0, Greece[14,43] 8.0†	0.07
R163Q	rs1805008G > A	–	Red hair	2.0, Italy[46] 4.8, N. Europe[44] 4.1†	0.047
N281S	NR	Located in TM7 Functionally silent[16]	–	–	–
C289R	NR	Located in TM7 Nearly complete absence of functional coupling to the c AMP pathway[16] Unable to bind agonists efficiently despite being trafficked to the cell surface[16]	–	–	–
D294H	rs1805009G > C	Lower response to a-MSH in cAMP, Slightly impaired ability to bind a—MSH[35]	Red hair	3.6, N. Europe[44] 2.8, Australia[71] 2.6†	0.027

*Allele frequency from (13,71). †Meta-analysis in Caucasian populations. R variants: D84E, R151C, R160W and D294H. TM = transmembrane domain; NR = not reported; N. Europe = Northern Europe.

physiologic function of MC1R have been only partially defined (Table 1) (16). Intracellular loops of GPCR, including MC1R, are necessary for protein interactions with GTP-binding proteins, suggesting that these may be key functional regions of the *MC1R*. Mutations detected in the second intracellular loop, have an effect on pigmentation phenotype (24).

Variations or polymorphisms of *MC1R* may result in decreased receptor function, either at the level of α-MSH binding or at the level of cAMP signaling, resulting in a quantitative shift of melanin synthesis from eumelanin to the red–yellow and potentially mutagenic pheomelanin (27,29,31). Aberrant traffic and intracellular retention is a common cause of MC1R dysfunction associated with RHC phenotypes (32,33).

Red hair color variants have been classified into strong (''R'') and weak (''r'') RHC alleles. R151C, R160W and D294H, have been defined as strong RHC (''R'') variants based not only on their diminished receptor function, reduced response to a-melanotropin and reduced functional coupling of the MC1R to adenylate cyclase *in vitro* (32–38), but also on their significant association with specific phenotypic features, such as red hair, fair skin and freckling (27,29,39–42). Classifications vary and some studies of the *MC1R* variants have also classified the D84E variant as R variant (43). Other two less frequent variants, R142H, I155T, have also been classified as R alleles based on results from strong familial association with RHC phenotype (44,45). The V60L, V92M and R163Q variants have a weak association with RHC phenotype and are designated as ''r'' alleles (42). *MC1R* polymorphisms have also been associated with sun sensitivity in individuals without red hair and with an elevated risk of melanoma and nonmelanoma skin cancer (14,42). Allelic frequencies of MC1R variants in specific populations are presented in Table 1. It was shown that the allele frequency of the combined ''R'' variant varies across European populations, with decreasing frequency from North to South, with a frequency of 21.5% in Britain/Iceland, 16% in Holland, 9.6% in France, 8.5% in Italy and 2.9% in Greece (43,46).

Residues R151 and R160 are located in the second intracellular loop, and the R151C and R160W variants are poorly expressed on the cell surface. D294 lies in the cytoplasmic side of the seventh transmembrane helix and D294H variant is expressed at cell membrane density higher than wt MC1R. Therefore, R variants display an altered cell surface expression that might underlie their functional impairment (37,38). In transfected cells *in vitro*, those allelic variants did not significantly reduce the binding affinity of a-MSH for MC1R as R151C and R160W, lie within the second intracellular loop of the MC1R, a region unlikely to be involved in receptor binding (28). Variants are intracellularly retained, namely V60L, D84E, R151C, Ll55T, R160W and R163Q show a decrease in functional ability to activate the cAMP pathway proportional to the degree of cell surface expression. Forward trafficking of MC1R is regulated by quality control (QC) mechanisms and misfolded or incorrectly assembled proteins are retained in the endoplasmic reticulum (ER) (47). It has been suggested that mutations within the TM1 domain of MC1R might interfere with normal trafficking and lead to a retention phenotype (16). On the other hand, variants in the TM7 are not recognized as aberrant by the ER, although they have a major effect on agonist binding and functional coupling (16). R variants encode for partial LOF receptors, with reduced ability to stimulate cAMP levels (32,33,35,37,38,48). The R142H has impaired function, but no decrease in cell surface expression indicating that they may have a defect in G-protein coupling and/or ligand affinity (49,50). The D294H

variant displays decreased affinity for agonists, and impaired functional coupling (32,33,35,37). Also, in primary human melanocyte cultures, the expression of 2 *MC1R* R variants (homozygous or compound heterozygous), or a R allele and V60L variant, resulted to loss-of-function (LOF) of MC1R and it abolished functional coupling to α-MSH, showing that R alleles are not equivalent in their impact on receptor function (51). The degree of residual signaling is not uniform among different R alleles, and it has not been established whether the r forms retain a higher residual signaling potential than the stronger R variants (16).

The functional relevance of the weaker (low penetrant) RHC (r) alleles, such as V60L, V92M, R163Q, is debatable, with some reports pointing to a minor signaling impairment, whereas others showed a behavior similar to wild type (34). One report suggested that the V92M substitution reduces the binding affinity of MC1R for a-MSH (33), whereas another found no alteration in the functional coupling of the receptor to adenylate cyclase (30). This variant was identified in Chinese individuals, and therefore is not associated with a red hair phenotype (29). Transfection studies have suggested that the V60L variant differs significantly from the wild-type MC1R in its ability to stimulate intracellular cAMP and that the V92M variant has *ca* two-fold lower affinity for a- MSH than wild-type MC1R (37,52).

These data may suggest that the strength of variant *MC1R* alleles may reflect the degree of impairment in signaling through the cAMP pathway. However, this interpretation is complicated by the fact that functional analysis has only been performed for approximately one-fifth of the variants described to date (16). Also, the minor alleles R142H, L155T may act as recessive RHC alleles when they are combined with the three common strong RHC alleles (R151C, R160W and D294H) (17,31,44). V60L (44) as well as D84E (17,44), may act as partially penetrant recessive RHC alleles.

Other nonsynonymous *MC1R* changes may also affect the receptor function (35). Most of these changes are relatively rare, but their frequency varies among populations (31), and it appears that they are more commonly found in Southern European populations than in those of North European descent (43). The functional study of six *MC1R* alleles found in Spanish melanoma patients (p.Val38Met, p.Ser41Phe, p.Val51Ala, p.Met128Thr, p.Asn281Ser and p.Cys289Arg) showed that agonist-induced signaling was similar for wild type, p. Val51Ala, and p.Asn281Ser, significantly reduced for p.Val38Met, very low for p.Ser41Phe and p.Met128Thr, and undetectable for p.Cys289Arg. LOF of *MC1R* alleles were frequently associated with aberrant forward trafficking and accumulation within the ER or with inability to bind properly the activator ligand (16).

The comparison of the *in vitro* receptor characteristics with skin and hair color data of individuals harboring *MC1R* variant alleles showed for the first time a direct correlation between variant MC1R cell surface expression, functional ability, and their effects on pigmentation phenotype (49). However, still a lot is to be learned regarding the association of *MC1R* variants with pigmentary characteristics, as the mechanisms by which their actions are exerted have not been fully elucidated (51). Also, *in vitro* observations do not always translate to corresponding clinical correlations, making it difficult to establish meaningful correlations between the signaling properties of *MC1R* variants and their penetrance for distinct pigmentation and photosensitivity phenotypes (16).

Furthermore, *MC1R* protects against UVR by a combination of pigmentary and nonpigmentary mechanisms *in vivo* (53). Regardless of constitutive pigmentation, inability of melanocytes to respond to a-MSH (due to LOF MC1R) reduces their defense mechanisms against UVR genotoxicity. Partial "LOF" *MC1R* variants, which are responsible for fair skin, may also have "nonpigmentary" consequences (53,54). They result in reduced receptor numbers at the cell membrane and/or significantly compromised intracellular signaling, leading to an imbalance of melanin synthesis toward that of pheomelanin (33,49). This sensitizes human melanocytes to the DNA damaging (cytotoxic) effects of UVR, which may increase skin cancer risk (34). Furthermore, for melanocytes, LOF mutations of MC1R were associated with higher cyclobutane pyrimidine dimer levels, impaired nucleotide-excision repair (NER), and increased susceptibility to apoptosis after UV irradiation (55,56). In primary human melanocyte cultures, it was shown that functional MC1R is required for optimal photoprotection and maintenance of genomic stability. The expression of 2 *MC1R* R variants (homozygous or compound heterozygous), or a R allele and V60L variant, resulted in aberrant UV response, with inability to inhibit hydrogen peroxide generation, reduce CPD and reduce the apoptotic effect of UV (51). Recently, it was suggested that incomplete repair of UVR-induced DNA damage (p53 clones) in cells lacking fully functional MC1R, coupled to a lower level of apoptosis, leads to subsequent clonal expansion of these mutated cells *in vivo* (26,53).

PHENOTYPIC EXPRESSION OF DISTINCT *MC1R* VARIANTS

The significance of human cutaneous pigmentation lies in its protective role against sun-induced DNA damage and photocarcinogenesis. Fair skin and red hair, characterized by low melanin content and a low eumelanin to pheomelanin ratio, are associated with increased risk of skin cancer. To date, although more than 100 candidate pigmentation genes containing common genetic variants have been identified in comparative genomics of pigmentary genes, genome wide and specific allele association studies (reviewed in Sturm, 2009 [13]), the variants in the *MC1R* gene have been consistently implicated in the variation of pigmentary phenotypes as well as skin cancer risk (12,57–61).

Roger Cone (in Robbins *et al.*) first cloned the *MC1R* gene underlying mouse mutants which had yellow rather than brown hair, because they produced more pheomelanin (red or yellow) than eumelanin (brown or black). These mutations were found to be LOF mutations (50). This gene was then sequenced by Rees and colleagues (in Valverde *et al.*) and they found LOF mutations in many humans redheads, resulting in the enhanced production of pheomelanin (27). The promoter region of human *MC1R* was sequenced and characterized (62). The fact that human *MC1R* is more polymorphic than other pigment genes, underlies its role in constitutive pigmentation (9). Variants of *MC1R* are associated with phenotypic features, such as red hair (17,27,29,59,60), light skin color (15,59), freckles (17,27,29,39,44,63), solar lentigines (63,64), facial

photoaging (65) and the skin type associated with burning rather than tanning after sun exposure (15,17,27,39,60).

The 3 R *MC1R* variants (R151C, R160W and D294H) have been significantly associated with red hair color, supporting the major contribution of the *MC1R* gene to the red hair color phenotype, an autosomal recessive trait (27,45,48,57,66). *MC1R* polymorphisms have also been associated with sun sensitivity in individuals without red hair and with an elevated risk of melanoma and nonmelanoma skin cancer (14). The penetrance of each variant allele was studied for red hair and fair skin among Australian twins. Red hair and fair skin were significantly associated with D84E (OR: 62, 95% CI: 18–224), R151C (OR: 118, 95% CI: 51–272), R160W (OR: 50, 95% CI: 22–116) and D294H (OR: 94, 95% CI: 34–263). Weak RHC (r) alleles were V60L, V92M, R163Q, with combined OR of 5 (95% CI: 3–11) (45,67). Also, *MC1R* variants (especially the D294H variant) were associated with red hair and fair skin in individuals from a British population (27) and in a study of Australian monozygotic and dizygotic twins (29). The R151C, R160W and D294H variants were significantly associated with red hair and light skin type in an Irish population. No individuals harboring two of these three variants did not have red hair. Despite these associations many subjects with dark hair/darker skin type harbored *MC1R* variants, but there was no evidence of any particular association of variants with the darker phenotype (39).

A meta-analysis on the association of *MC1R* variants with pigmentation traits showed that red hair and fair skin color were associated with the MC1R variants R160W (OR: 5.00, 95% CI: 3.43–7.28 for red hair, OR: 2.81, 95% CI: 1.43–5.50 for fair skin) and D294H (OR: 5.92, 95% CI: 4.07–8.61 for red hair, OR: 5.10, 95% CI: 1.23–21.23 for fair skin), whereas red hair color alone was associated with D84E (OR: 2.99, 95% CI: 1.51–5.91), R142H (OR: 4.96, 95% CI: 1.73–14.23) and R151C (OR: 8.10, 95% CI: 5.82–11.28). No association with phenotypic characteristics was found for V60L, V92M variants (42). A meta-analysis of GWAS of genetic loci associated with pigmentation traits (hair, eye and skin color) reported significant association of *MC1R* variants R151C and R160W with light and red hair color, sun sensitivity and freckling, but not with skin or eye color (12).

Variation in the degree and type of pigment can be achieved by a dosage effect of one or two alleles and a range of mutations with quantitatively different effects on binding and signaling through the *MC1R* gene (10). Expression of two R alleles results in LOF of MC1R (34). The dominant negative effects of MC1R variants on the wild-type allele has been analyzed, as allelic interaction has been recognized to confer a heterozygote carrier effect on skin pigmentation (32,49). Differences in *MC1R* variant gene dosage appear to cause a range of pleiotropic effects on hair as well as skin color, with heterozygotes tending to be intermediate between homozygotes and wild-type individuals for skin type, freckling and shade of hair (40). The effect of a single variant allele on fair skin type has been confirmed. Further evidence for a heterozygote effect comes form the association of a single variant allele with red beard hair color and freckling (44). Despite *in vitro* observations, the V92M allele has been observed frequently in dark-skinned Caucasians and Asian populations as well as in fair-skinned individuals (68,69). A study in the UK and Ireland showed that the identification of a dosage effect of *MC1R* variant alleles on sensitivity to UVR, and the large attributable risk for heterozygotes, suggests that the *MC1R* gene is closely associated with variation in the skin's response to UVR in most of the population who do not have red hair (40). Also, associations between MC1R polymorphisms and the risks of experiencing sunburn and of having freckles were found independently of skin color, suggesting that *MC1R* polymorphisms do not necessarily alter the skin color, but can sensitize the skin to UV-induced DNA damage (70).

MC1R R variants alleles (R151C, R160W, D294H) in the homozygous form were associated with lighter constitutive pigmentation. V60L also had a lightening effect on skin color relative to wild-type individuals, whereas V92M actually appeared to be associated with a slightly darker constitutive skin color. All *MC1R* alleles that were associated with lighter constitutive skin color were also associated with impaired tanning when in the homozygous state. Regarding mean skin reflectance, *MC1R* heterozygotes for the D84E, R151C, II55T, R160W and D294H R alleles, showed a lightening effect on constitutive and tanned skin color. V92M, in heterozygous state, had a lightening effect on constitutive and tanned skin color. V60L and R163Q alleles had a small lightening effect on skin color. The V92M, R151C and R160W alleles in the heterozygous form were significantly associated with red/blonde hair color (50).

Three *MC1R* alleles—R151C, R160Q and D294H—were statistically associated with red hair; one allele, Val60Leu, was associated with blonde/light brown hair, and any variation from the consensus allele was associated with lighter skin tones (29,39). The minor alleles R142H and I155T may act as recessive RHC alleles when in combination with the three common R alleles (31,71).

CONCLUSIONS

Categorization of skin- and hair-color phenotypes cannot be applied as an accurate predictor of the outcome of an individual's lifetime sun exposure and skin cancer risk. A more precise and individualized genotypic assessment of that risk is needed (59). It is clear that not all whites share identical risk for skin cancers such as BCC, and better understanding of the genetic basis of UV-sensitive skin types will greatly enhance targeting of skin cancer prevention campaigns and skin cancer therapies.

Recently, it has been postulated that phenotypic traits may be a circumstantial characteristic linked to skin cancer risk, and that the risk conferred by *MC1R* variants is exerted *via* nonpigmentary pathways (53). *MC1R* gene expression is regulated by paracrine factors, including its own ligands (α-MSH, endothelin-1, basic FGF and agouti signaling protein), by specific endocrine sex hormones (b-estradiol, testosterone) and by UVR. Differences in the responses of cultured normal human melanocytes to some of these factors suggest differential regulation of *MC1R* gene expression, which may contribute to the variation in constitutive and UV-induced cutaneous pigmentation in humans. Whatever proves to be the case, the study of the biochemical properties of variant MC1R may shed light to how specific *MC1R* variants exert their effects on pigmentary traits, sun sensitivity and skin cancer risk, and may provide a better understanding of the complex molecular pathogenesis of skin cancer.

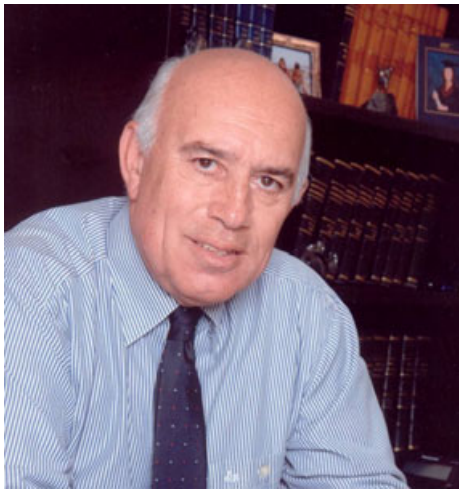
AUTHOR BIOGRAPHIES

Clio Dessinioti

Clio Dessinioti completed her 3-year residency at the Department of Dermatology of the University of Athens, in Andreas Sygros Hospital, Athens, Greece, where she worked as a clinical/research fellow since 2007. She completed her PhD thesis in 2011 with a focus on epidemiologic and genetic risk factors of patients with basal cell carcinoma. Dr. Dessinioti has participated as sub-investigator in 10 multicenter clinical trials and she has been invited as a speaker in national and international meetings. She is a member of various international dermatologic societies, including the European Academy of Dermatology and Venereology. Dr. Dessinioti's research interest include acne, psoriasis, skin cancer and photocarcinogenesis.

Christina Antoniou

Christina Antoniou qualified from University of Athens Medical School. Her dermatology and research training took place in the Department of Dermatology at Andreas Sygros Hospital, Athens, Greece. She is currently a professor in the Department of Dermatology at the University of Athens Medical School, Andreas Sygros Hospital. Dr. Antoniou's interests include clinical research into common dermatological conditions, an activity that led to the establishment of the photodermatoses clinic, psoriasis clinic and T-cell lymphoma clinic at Andreas Sygros Hospital. She is supervisor of the phototherapy department and head of the lymphoma clinic. Dr. Antoniou has been a principal investigator and worked extensively on Phase III studies with most of the biologic agents for psoriasis. She has written more than 90 articles in peer-reviewed journals, including British Journal of Dermatology, Archives of Dermatology, Journal of the American Academy of Dermatology (AAD) and Journal of Investigative Dermatology. She is a member of a variety of professional societies, including the European Academy of Dermatology and Venereology (EADV), AAD, International Society of Dermatology (ISD), Women's Dermatology Society and the Hellenic Dermatologic and Venereology. Dr. Antoniou has been a visiting professor and invited speaker at many national and international venues.



Andreas Katsambas

Andreas Katsambas is Professor and Chairman of the Department of Dermatology and Venereology at the Andreas Sygros Hospital, University of Athens, Greece. Professor Katsambas has had many appointments within scientific associations, including President of the Hellenic Society of Dermatology and Venereology, board member of the International League of Dermatological Societies (ILDS) and Chairman of the ILDS Awards Committee, as well as member of the American Academy of Dermatology Committee of International Affairs. He was also a President of the European Academy of Dermatology and Venereology (EADV) from 2008 to 2010, and served as Secretary General between 1992 and 2000. Professor Katsambas has published over 300 peer-reviewed manuscripts in international medical journals and has co-edited two books. Among others, he is a member of the editorial board of the Journal of the American Academy of Dermatology, Archives of Dermatology and the Journal of the European Academy of Dermatology and Venereology. Professor Katsambas's research interests are in psoriasis, acne, pigmentary disorders, dermatologic treatment and sexually transmitted infections.

Alexander J. Stratigos

Alexander J. Stratigos, MD is Associate Professor of Dermatology and Venereology in the Department of Dermatology, University of Athens Medical School, Andreas Sygros Hospital (Greece). He earned his medical degree from the University of Athens and completed an internship in internal medicine and residency in dermatology through Harvard Medical School (United States). His clinical interests include psoriasis, cutaneous photosensitivity, lasers and melanoma and skin cancer, specifically risk associations, the impact of genetic variations and the value of screening in melanoma patient populations. He serves as an editorial board member of the Journal of the American Academy of Dermatology, SkinMed Journal: Dermatology for the Clinician and the Journal of the Hellenic Society of Dermatology and Venerology. He is the author of more than 100 publications in Greek and peer-reviewed international medical journals, seven textbook chapters and one book. Dr. Stratigos is a member of numerous professional societies, including the European Academy of Dermatology and Venereology, European Association of Dermato and Oncology, International Dermoscopy Society, American Academy of Dermatology, British Association of Dermatologists, Hellenic Society of Dermatology and Venereology and Hellenic Society for Melanoma Research. He is also a member of the Ethics Committee. He was the Organizer of the 6th European Association of Dermato-Oncology Congress held in Athens, June 16–19, 2010.

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