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**ASSOCIATION OF MELANOCORTIN-1 RECEPTOR VARIANTS WITH  
PIGMENTARY TRAITS IN HUMANS: A POOLED-ANALYSIS FROM THE M-SKIP  
PROJECT**

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**Short title: MC1R and pigmentary traits: a pooled-analysis**

**Abbreviation used:** MC1R, melanocortin-1 receptor; RHC, red hair color; UVR, ultra violet radiation;  $\alpha$ -MSH,  $\alpha$ -melanocyte stimulating hormone; cAMP, cyclic adenosine monophosphate; NMSC, Non Melanoma Skin Cancer; WT, wild-type; HW, Hardy-Weinberg; SORs, Summary Odds Ratios; CI, Confidence Interval; MCA, multiple correspondence analysis

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## To the Editor

Skin pigmentation is due to the accumulation of eumelanin, which is brown-black pigment and photoprotective, and pheomelanin, which is yellow-red pigment and may promote carcinogenesis (Valverde et al., 1995). The melanocortin-1 receptor (MC1R) gene regulates the amount and type of pigment production and is a major determinant of skin phototype (Garcia-Borron et al., 2005; Valverde et al., 1995). Binding of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) to MC1R stimulates the enzymatic activity of adenylate cyclase enzyme, thereby elevating intracellular cyclic adenosine monophosphate (cAMP) levels. MC1R is a highly polymorphic, especially in Caucasian: more than 200 coding region variants have been described to date (Garcia-Borron et al., 2014; Gerstenblith et al., 2007; Perez Oliva et al., 2009). Six variants - D84E, R142H, R151C, I155T, R160W and D294H - have been designated as 'R' alleles due to their strong association with the 'red hair color' (RHC) phenotype characterized by red hair, fair skin, freckles and sun sensitivity. The V60L, V92M and R163Q variants are found to have a weaker association with the RHC phenotype and have been designated as 'r' alleles (Garcia-Borron et al., 2014; Raimondi et al., 2008).

Previous studies demonstrated that several alleles are associated with phenotypic characteristics and that MC1R variants are associated both with melanoma and non-melanoma skin cancer (NMSC) (Han et al., 2006; Pasquali et al., 2015; Scherer et al., 2008; Tagliabue et al., 2015) with a stronger role for darker-pigmented populations, suggesting that non-pigmentary pathways link MC1R with skin cancer development. Since the role and strength of each MC1R variant in determining specific phenotypic characteristics and the RHC phenotype remains unclear, we performed a pooled-analysis of individual-level data from the M-SKIP project, described in full elsewhere (Raimondi et al., 2012). We selected from the M-SKIP database all 5,366 cancer-free

controls with MC1R gene sequenced and information on at least one of the following phenotypic characteristics: hair color, eye color, skin type and freckles, thus including 16 independent studies from 18 publications (Table S1).

We found greater Summary Odds Ratios (SORs) for carriers of two MC1R variants compared with carriers of only one variant allele (Table 1). Furthermore carriage of any MC1R variant, one variant and two or more variants, compared with not having such variants (i.e. wild-type (WT) subjects), were significantly associated with fair hair color, skin type I/II and presence of freckles. Red hair color was significantly associated with carrying any MC1R variant (SOR; 95%CI: 3.54; 1.91-6.55) and with carrying two or more variants (SOR; 95%CI: 10.17; 5.28-19.58), but not with carrying one MC1R variant (SOR; 95%CI: 1.18; 0.57-2.44). No significant association was observed for light eye color and MC1R. Sensitivity analyses indicated that the observed between-study heterogeneity may be attributable to single studies: when we excluded the studies that were outliers, we obtained similar pooled-ORs as the original ones, but no longer with evidence of heterogeneity (results not shown). No evidence of publication bias was found by Egger's test. All the investigated MC1R variants compared with WT subjects were positively associated with skin type I/II and freckles (Table S2). The three variants that seemed to play the most important role in skin type determination and presence of freckles were D84E, R151C and D294H. Red hair color was significantly associated with all MC1R variants except for V92M and R163Q.

We visualized the associations between hair color, eye color, skin type, freckles and the three main studied geographical areas by Multiple Correspondence Analysis (MCA) (Figure S1a/b). A two-dimension MCA solution, with Dimension 1 (Dim1) on the horizontal axis and Dimension 2 (Dim2) on the vertical axis, was considered the most adequate because the first and second

dimension presented Benzecri-adjusted inertias of 85.31% and 11.31% respectively (Table S3), accounting for 96.62% of the total association. The extreme RHC phenotype (red-hair, skin type I and freckles) was associated either with carrying at least 2 MC1R variants (Figure S1a) or with the presence of major penetrant ('R') alleles (Figure S1b). We suggest that Dim1 can be interpreted as a "pigmentation score" because it differentiates well between dark and fair phenotypic characteristics. The median pigmentation score increased with increasing number of MC1R variants, and for single MC1R variants it was higher ( $p < 0.0001$ ) compared with WT subjects (Figure S2).

Seven of the nine MC1R variants analyzed in this study, V60L, D84E, R142H, R151C, I155T, R160W and D294H, are clearly hypomorphic with significant reduction in cAMP signaling potential (Beaumont et al., 2007; Herraiz et al., 2012; Kadearo et al., 2010; Scott et al., 2002). Within this group of variants, the lowest SOR for red hair, skin type I/II or freckles corresponds to V60L. Interestingly, this variant was also the one with the smallest functional impairment in terms of coupling to the cAMP pathway, when the seven variants analyzed here were compared under identical experimental conditions (Herraiz et al., 2012).

Results also showed that V92M and R163Q behave as 'r' alleles, with a weak albeit significant association with cutaneous phenotypic traits. In heterologous systems, V92M has been reported to display either a slight functional impairment (Herraiz et al., 2012) or normal coupling to the cAMP pathway (Beaumont et al., 2007), whereas R163Q apparently signals as efficiently as WT. Therefore, it appears that the ability of V92M or R163Q to activate the cAMP pathway is similar, if not identical to WT. This suggests that other mechanisms account for their association with cutaneous phenotypic characteristics, for example, V92M or R163Q might impair functional coupling to signaling module(s) different from the cAMP cascade. MC1R

promiscuously binds to a variety of intracellular partners with signaling potential and this ability might depend on WT conformation. However, little is known as to the effects of other variants on MC1R binding to its various protein partners, and the phenotypic consequences of such molecular interactions also remain largely unknown. Further research is needed to understand the scaffolding properties of MC1R, the functional consequences of the formation of signaling complexes orchestrated by the receptor, and the effects on these processes of the myriad of natural variants in the MC1R gene.



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**Table 1. Summary Odds Ratios for the association between combined MC1R variants and phenotypic characteristics**

Phenotypic characteristic	MC1R	studies/controls	SOR (95% CI)	I <sup>2</sup> (%)	p-value <sup>3</sup>
Hair color - fair vs. dark <sup>1</sup>	Wild-type	13/1371	1.00 (reference)		
	Any variant	13/2758	<b>1.91 (1.38-2.65)</b>	<b>59</b>	<b>&lt;0.01</b>
	1 variant	13/1991	<b>1.55 (1.12-2.15)</b>	39	0.07
	2+ variants	13/767	<b>3.32 (2.34-4.72)</b>	<b>62</b>	<b>&lt;0.01</b>
Hair color - red vs. others	Wild-type	7/705	1.00 (reference)		
	Any variant	7/1474	<b>3.54 (1.91-6.55)</b>	0	0.80
	1 variant	7/1016	1.18 (0.57-2.44)	0	0.83
	2+ variants	7/458	<b>10.17(5.28-19.58)</b>	0	0.77
Eye color - fair vs. dark <sup>2</sup>	Wild-type	14/1530	1.00 (reference)		
	Any variant	14/2832	1.12 (0.96-1.30)	12	0.33
	1 variant	14/2079	1.11 (0.94-1.32)	10	0.35
	2+ variants	14/753	1.16 (0.93-1.45)	0	0.80
Skin type - I, II vs. III, IV	Wild-type	14/1540	1.00 (reference)		
	Any variant	14/3046	<b>2.26 (1.81-2.83)</b>	<b>49</b>	<b>0.02</b>
	1 variant	14/2211	<b>1.95 (1.51-2.53)</b>	41	0.06
	2+ variants	14/835	<b>3.58 (2.68-4.78)</b>	<b>42</b>	<b>0.05</b>
Freckles - yes vs. no	Wild-type	9/1067	1.00 (reference)		
	Any variant	9/2257	<b>2.52 (1.99-3.20)</b>	33	0.16
	1 variant	9/1528	<b>2.00 (1.52-2.64)</b>	36	0.13
	2+ variants	9/729	<b>4.47 (3.25-6.15)</b>	38	0.12

SOR=Summary Odds Ratio, CI=Confidence Intervals. Note: significant ORs and p-values are in bold

<sup>1</sup>Fair hair color were: red, blond, dark blonde, light brown. Dark hair color were: brown, black, dark brown. <sup>2</sup>Fair eye color were: blue, green, grey, hazel. Dark eye color were: brown, black. <sup>3</sup>Q test p-value