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MC1R variants in relation to naevi in melanoma cases and controls: a pooled-analysis from the M-SKIP project

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Editor,

There have been a limited number of studies exploring the possible influence of *MC1R* variants in naevi formation and/or their interaction with naevi in melanoma development. Kinsler *et al* reported that individuals with congenital melanocytic naevi (CMN) carried two *MC1R* variant alleles more frequently than controls.[1] In the same study *MC1R* variants were also associated with more and larger CMN. Vallone *et al* studied the effect of *MC1R* variants on naevus phenotype in a control population showing that *MC1R* variant carriers had larger naevi both on the back and on the upper limbs.[2] They also identified a positive association between *MC1R* red hair (R) alleles and visible vessels, dots and globules, and eccentric hyperpigmentation in naevi. Environmental factors, such as sun exposure early in life, seem also to play a role in determining naevus number and have been reported to interact with certain *MC1R* variants.[3] AnAustralian studyfound that *MC1R* R variants and high naevus count increase synergistically melanoma risk.[4] In the study of Cust *et al* there was a stronger association of *MC1R* variants with melanoma in those with none or few naevi than in those with some or many naevi.[5]

The first endpoint of this study was the evaluation of a potential association of the *MC1R* on the number of common naevi or on the presence of clinically atypical naevi in the control population. The second endpoint explored the possible role of *MC1R* variants in modifying the association of naevi with melanoma risk. We calculated study-specific Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) with logistic regression models, including the covariates reported in Table 1, and then estimated the Summary OR (SOR) by multivariate random-effects models. Multiplicative and additive interaction was assessed, respectively, by adding an interaction term in a logistic regression model and by calculating the Relative Excess Risk due to Interaction (RERI). The latter indicates synergic interaction on an additive scale where >0.[6] Heterogeneity among studies was assessed using the I^2 statistic, and 95% Prediction Intervals (PI) were calculated.

Data from ten melanoma case-control studies with information on common naevi (2,923 cutaneous melanoma (CM) cases and 2,800 controls) and nine with information on atypical naevi (2,900 CM and 2,211 controls) were gathered from the Melanocortin 1 receptor, SKin cancer and Phenotypic characteristics (M-SKIP) dataset, described in detail elsewhere.[7] The main characteristics of these studies are summarized in Table 1

SOR (95% CI) for the association between the presence of any *MC1R* variant and presence of ≥30 common naevi in controls was 0.96 (0.77–1.21), thus showing no statistically significant association, with low between-study heterogeneity (I^2=15%). SOR (95% CI) for the association between the presence of any *MC1R* variants and the presence of at least one atypical naevus in controls was 1.39 (0.91–2.12) showing no statistically significant association, with moderate between-study heterogeneity (I^2=33%). However, for single *MC1R* variants a statistically significant association between the R160W variant and the presence of at least one atypical naevus was detected (SOR: 2.64; 95%CI: 1.28–5.47, p=0.009), with moderate between-studyheterogeneity (I^2=43%) and 95% PI=0.43–16.33. The p-value should be interpreted with caution since it was not significant after Bonferroni correction; however, we think it would be worthwhile to further investigate and possibly validate this association in subsequent studies.

Regarding melanoma risk, no significant interaction of *MC1R* and common naevi was observed, both on a multiplicative and an additive scale. Concerning the possible role of *MC1R* variants in modifying the association of atypical naevi with melanoma risk, a significant additive interaction was suggested for any *MC1R* variant and atypical naevi (Table 2).

Our results are in agreement with the notion that *MC1R* is not implicated in naevogenesis, but also imply that it may act as a modifier of melanoma risk in individuals with atypical naevi by enhancing their risk to develop melanoma. Since methods for assessing additive interaction can help determine which subgroups to target in order to maximize the effect of medical policies,[6] our results could, after validation, lead to enhanced educational and clinical interventions in subjects with both a *MC1R* variant and atypical naevi.

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Table 1.

Description of the studies included in the analysis

Country	Type of controls*	N cases/ N controls∞	Other available confounder^	Available data on common/atypical naevi	First author, publication year
The Netherlands	Hospital	115/378	Sun exposure, skin phototype, freckles	Both	Kennedy 2001
Italy	Hospital	153/160	Sun exposure, skin phototype	Both	Fargnoli 2006
Greece	Hospital	82/144	Sun exposure, skin phototype	Both	Stratigos 2006
Spain	Healthy	105/155	-	Common naevi	Fernandez 2007
UK	Hospital	916/468	Sun exposure, skin phototype, freckles	Both	Bishop 2009
USA	Healthy	713/245	Sun exposure, skin phototype, freckles	Atypical naevi	Kanetsky 2010
Italy	Healthy	116/168	Skin phototype, freckles	Both	Menin 2011
Italy	Healthy	230/220	Skin phototype, freckles	Both	Ghiorzo 2012; Pastorino 2004
Spain	Hospital°	495/331	Skin phototype	Both	Puig-Butillé 2013
USA	Healthy	875/764	Sun exposure, skin phototype, freckles	Common naevi	Penn 2014
Italy	Hospital	82/100	Sun exposure, skin phototype	Both	Guida 2015

*Healthy controls are population controls, blood donors, friends or partners of cases.

∞Total number of cases and controls included in the analyses. In each study, some subjects had information on common naevi only, atypical naevi only or both.

^Beyond age, sex, family history of melanoma, sunburns, hair and eye color, which were available in all the studies. Sun exposure includes separate information on chronic and intermittent sun exposure.

°Include high risk melanoma subjects, defined as individuals belonging to melanoma-prone families or with a high naevus count.

Table 2.

Pooled melanoma risk estimates for 1) carriers of *MC1R* gene variants with no atypical naevi (*MC1R* effect), 2) non-carriers of *MC1R* variants with at least one atypical naevus (naevi effect), 3) carriers of *MC1R* gene variants with at least one atypical naevus (*MC1R*+naevi effect). P-value for the multiplicative interaction and RERI for additive interaction are reported. OR from each single study is adjusted by all the available covariates.

***MC1R* variants**	**N studies**	***MC1R* effect SOR (95%CI)**	**Naevi effect SOR (95%CI)**	***MC1R*+naevi effect SOR (95%CI)**	**Multiplicative interaction**		**Additive interaction**
					Expected *MC1R* +naevi effect* OR (95%CI)	**Interaction p-value**	**RERI x(95%CI)∞**
Any variant	8	1.69 (0.92–3.10)	**5.45 (2.73–10.89)**	**6.33 (3.36–11.91)**	9.21	0.61	**1.03 (0.13; 1.93)**
V60L	8	1.60 (0.77–3.30)	**5.97 (2.72–13.12)**	**6.10 (2.84–13.09)**	9.55	0.63	0.87 (−0.29; 2.03)
D84E	4	1.03 (0.36–2.92)	**3.02 (1.41–6.47)**	2.82 (0.88–8.98)	3.11	0.68	−0.08 (−1.69; 1.54)
V92M	7	1.52 (0.87–2.67)	**4.72 (2.54–8.77)**	**6.19 (3.24–11.84)**	7.17	0.26	1.24 (−0.23; 2.70)
R142H	4	1.49 (0.52–4.28)	**2.61 (1.62–4.23)**	1.73 (0.52–5.76)	3.89	0.18	−1.95 (−8.54; 4.64)
R151C	5	**1.58 (1.08–2.32)**	**2.66 (1.71–4.12)**	**5.20 (3.07–8.82)**	4.20	0.60	1.29 (−0.63; 3.21)
R160W	7	**2.01 (1.08–3.75)**	**4.31 (2.24–8.30)**	**4.88 (2.48–9.59)**	8.66	0.21	1.02 (−049; 2.54)
R163Q	4	1.29 (0.78–2.14)	**2.52 (1.57–4.04)**	**2.65 (1.39–5.03)**	3.25	0.82	0.02 (−1.31; 1.36)
D294H	3	3.67 (0.54–24.92)	4.73 (0.82–27.12)	**9.91 (1.30–75.59)**	17.36	0.70	2.24 (−1.17; 16.18)

CI=Confidence intervals; RERI=Relative Excess Risk due to Interaction; SOR= Summary Odds Ratio.

Note: significant results are in bold. Comparison group for the calculated ORs is represented by individuals without *MC1R* variants and with no atypical naevi.

* Under the hypothesis of independence on the multiplicative scale between *MC1R* and common naevi: OR is the product of ORs for *MC1R* effect and naevi effect.

∞ RERI>0 indicates the presence of additive interaction, thus a significant positive additive interaction is suggested when lower limit of 95% CI is above 0.