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LETTER TO THE EDITOR

Association of *MC1R* variants with melanoma risk and interaction with sun exposure: An M-SKIP project

Dear Editor,

Natural variation at the melanocortin-1-receptor (*MC1R*) locus is associated with increased risk of melanoma. *MC1R* also is one of the major genes controlling skin pigmentation. Red hair (R) alleles result in pheomelanin production and are associated with fair skin, red hair, freckling, inability to tan and risk of melanoma. However, not all *MC1R* variants are associated with both melanoma risk and cutaneous phenotypes, suggesting that *MC1R* could act both via pigmentary and non-pigmentary pathways.[1] Ultraviolet radiation (UVR) is a well-established environmental risk factor for melanoma. However, the few reports assessing whether sun exposure influences the association between *MC1R* variants and melanoma risk are inconsistent.[2–4]

The aim of this study was to evaluate whether sun exposure modifies the effect of *MC1R* variants on melanoma risk by analysing the *MC1R* gene–sun exposure interaction. We used data from nine melanoma case–control studies (4780 melanoma cases and 3541 controls) that were previously assembled and harmonized for the MC1R, skin cancer and phenotypic characteristics (M-SKIP) project, described elsewhere.[5] In each study, we assessed the effects of *MC1R* variants, chronic or intermittent sun exposure and sunburn (a surrogate of intermittent sun exposure less affected by recall bias) and interactions on melanoma risk. Intermittent sun exposure and sunburn were dichotomized according to their median. Age, sex, family history of melanoma and nevi (total number of nevi and presence of clinically atypical nevi) were included as covariates. A two-stage approach with random-effects models was adopted to calculate summary odds ratios (SORs) and 95% confidence intervals (CI). Stratified analysis by age at melanoma diagnosis, phenotype and melanoma body location was performed. Additive and multiplicative interactions were assessed by calculating the relative excess risk due to interaction (RERI) and by adding an interaction term in a logistic regression model, respectively. Heterogeneity among studies was assessed using the I^2 statistic.

The main effect of sunburn, but not intermittent or chronic sun exposure, on risk of melanoma was significant. Risk estimates for both chronic sun exposure and sunburns were higher among older (>40 vs. ≤40 years) adults and for chronically (vs. intermittently) exposed body sites (data not shown). Carriage of any *MC1R* variant and only *MC1R* R variants was associated with increased risk of melanoma. A significant additive interaction was observed for *MC1R* R variants and high number of sunburns in eight studies with this information available (RERI 0.61, 95%CI 0.03; 1.18), while a multiplicative interaction was not evident (Figure 1). On the contrary, additive or multiplicative interactions between *MC1R* variants and any sun-related measure was not observed in eight studies with this information available (Table 1).

Our findings are in line with those of other studies.[6] There are reports of greater melanoma risk with cumulative time outdoors in those who usually develop a deep tan[7] and with severe sunburn in those with a sun-resistant phenotype.[7,8] One study found the association between increased melanoma risk and greater sun exposure was more evident in participants with a less sun-sensitive phenotype, especially on continuously sun-exposed sites.[4] The authors propose that melanoma risk may saturate as sun exposure increases in sun-sensitive individuals but continue to increase on sun-exposed body sites of individuals with lower sun sensitivity or that sun-sensitive individuals adapt their behaviour by increasing sun protection.[4] Significance of additive interaction in our study could help determine at risk subgroups to target for melanoma prevention and early diagnosis interventions.

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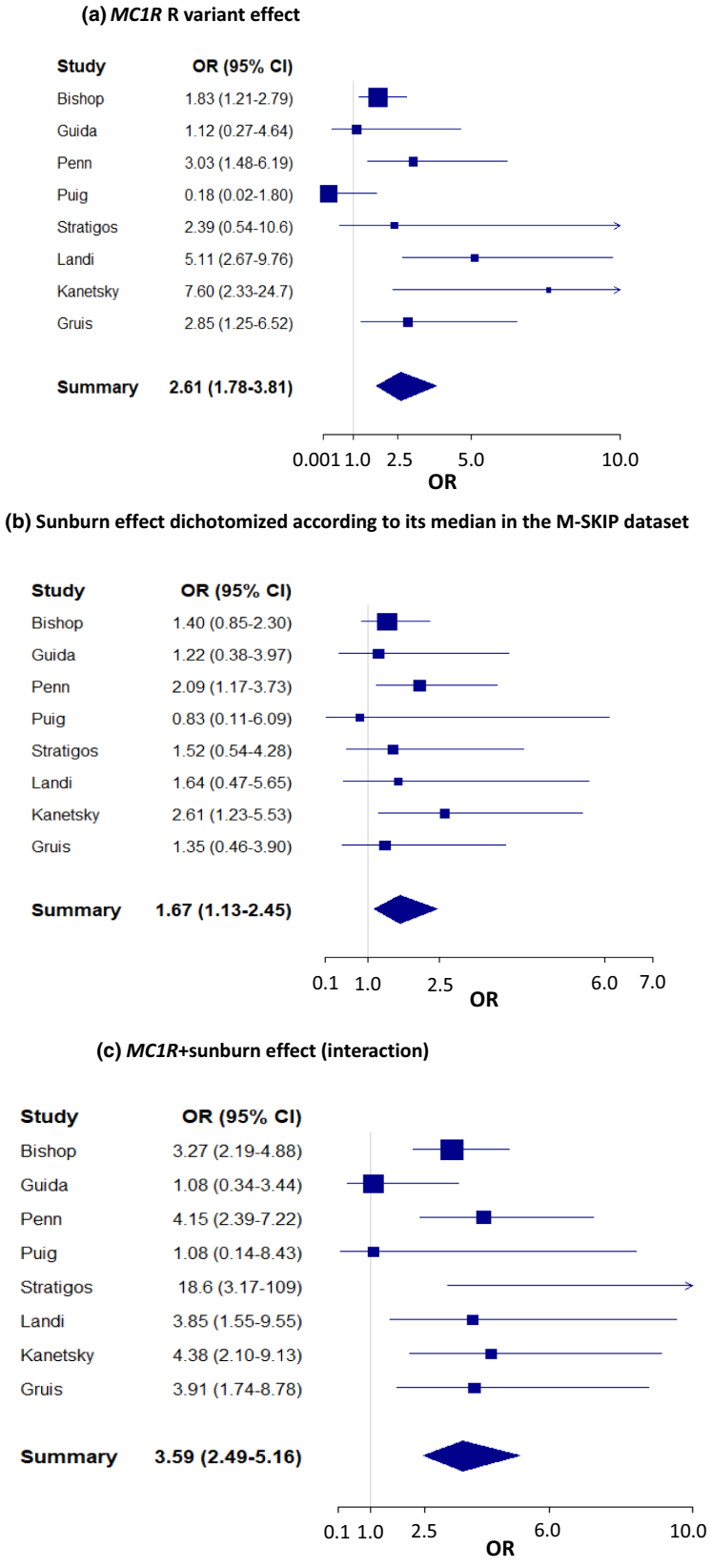

FIGURE 1 Forest plots for the visualization of between-study estimates for the effect of (a) any R MC1R variant, (b) sunburn and (c) MC1R variant+sunburn on melanoma risk. 'Summary' indicates the summary odds ratio with 95% confidence intervals (CI) for each effect estimates. In the absence of multiplicative interaction, the ORs in panel (c) are expected to be the product between ORs in panels (a) and (b).

TABLE 1 Pooled melanoma risk estimates for (1) main *MC1R* effect, (2) main intermittent and chronic sun exposure effects[a] and (3) interaction effects (interaction). *P*-value for the interaction is reported.

		SOR_{MC1R} (95% CI)[b]	$SOR_{sun\ expo}$ (95% CI)[b]	SOR_{int} (95% CI)[b]	Expected OR_{int}	*p*-Value	RERI (95%CI)[c]
Intermittent sun exposure effect[a]	Any variant	**1.72 (1.28; 2.31)**	1.05 (0.75; 1.49)	**1.66 (1.22; 2.25)**	1.81	0.93	0.22 (−0.30; 0.73)
	Any R variant	**2.24 (1.61; 3.12)**	1.06 (0.74; 1.53)	**2.37 (1.67; 3.38)**	2.37	0.60	0.37 (−0.19; 0.94)
	Any r variant	1.23 (0.94; 1.62)	1.05 (0.77; 1.43)	1.08 (0.81; 1.45)	1.29	0.48	0.08 (−0.45; 0.62)
Chronic sun exposure effect	Any variant	**1.62 (1.32; 1.97)**	0.89 (0.67; 1.20)	**1.59 (1.27; 2.00)**	1.44	0.73	0.00 (−0.33, 0.33)
	Any R variant	**2.08 (1.66; 2.61)**	0.92 (0.68; 1.26)	**2.20 (1.68; 2.88)**	1.91	0.61	0.08 (−0.36; 0.51)
	Any r variant	1.17 (0.92; 1.50)	0.86 (0.63; 1.17)	1.02 (0.76; 1.37)	1.01	0.91	−0.07 (−0.40; 0.26)

Note: Statistically significant estimates and *p*-values are in bold.

Abbreviations: CI, confidence intervals; RERI, relative excess risk due to interaction; SOR, summary odds ratio.

[a]Dichotomized according to its median in the M-SKIP dataset (3 h/day).

[b]Study-specific ORs are adjusted for the following covariates, where available: age, sex, family history of melanoma, common and atypical naevi.

[c]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.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

All original studies were approved by an Ethics Committee.

ETHICS STATEMENT

All study participants provided a written consent to participate in the original study.

Irene Stefanaki[1]
Oriana D'Ecclesiis[2]
Silvano Vignati[2]
Aurora Gaeta[2]
Katerina Kypreou[1]
Saverio Caini[3]
Sara Gandini[2]
Eduardo Nagore[4]
Francesco Sera[5]
Francesca Botta[2]
Julia Newton-Bishop[6]
David Polsky[7]
DeAnn Lazovich[8]
Peter A. Kanetsky[9]
Susana Puig[10,11]
Nelleke A. Gruis[12]
Maria Teresa Landi[13]
Maria Concetta Fargnoli[14]
Alexander Stratigos[1]
Gabriella Guida[15]
Paola Ghiorzo[16,17]
Chiara Menin[18]
José C. García-Borrón[19]
Julian Little[20]
Hongmei Nan[21]
Sara Raimondi[2]
for the M-SKIP study group

[1]*1st Clinic of Dermatological and Venereal Diseases, Medical School National and Kapodistrian University of Athens, Andreas Sygros Hospital, Athina, Greece*
[2]*Department of Experimental Oncology, IEO European Institute of Oncology IRCCS, Milano, Italy*
[3]*Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research Prevention and Clinical Network (ISPRO), Florence, Italy*
[4]*Department of Dermatology, Instituto Valenciano de Oncologia, Valencia, Spain*
[5]*Department of Statistics, Computer Science and Applications G. Parenti, University of Florence, Florence, Italy*
[6]*Institute of Medical Research at St James's, University of Leeds, Leeds, UK*
[7]*New York University School of Medicine, NYU Langone Medical Center, New York, New York, USA*
[8]*Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA*
[9]*Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA*
[10]*Melanoma Unit, Dermatology Department, Hospital Clinic Barcelona, Universitat de Barcelona, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain*
[11]*CIBER de Enfermedades Raras, Barcelona, Spain*
[12]*Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands*

[13]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, USA*
[14]*Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*
[15]*Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari "A. Moro", Bari, Italy*
[16]*Department of Internal Medicine and Medical Specialties, University of Genoa, Genoa, Italy*
[17]*IRCCS Ospedale Policlinico San Martino, Cancer Genetics, Genoa, Italy*
[18]*Diagnostic Immunology and Molecular Oncology Unit, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy*
[19]*Department of Biochemistry, Molecular Biology and Immunology, University of Murcia and IMIB-Arrixaca, Murcia, Spain*
[20]*School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada*
[21]*Department of Epidemiology, Richard M. Fairbanks School of Public Health, Melvin & Bren Simon Cancer Center, Indiana University, Indianapolis, Indiana, USA*

Correspondence
Sara Raimondi, Molecular and Pharmaco-Epidemiology Unit, Department of Experimental Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy.
Email: sara_raimondi@hotmail.com

ORCID

Irene Stefanaki https://orcid.org/0000-0002-2964-370X
Susana Puig https://orcid.org/0000-0003-1337-9745
Maria Concetta Fargnoli https://orcid.org/0000-0002-7249-2556

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