Influence of MC1R genotype on melanoma risk in relation to sun exposure

P102

I. Stefanaki[1], F. Botta[2], K. Antonopoulou[1], V. Evangelou[3], S. Gandini[2], F. Sera[4], E. Nagore[5], F. Corso[2], S. Caini[6], J. Newton-Bishop[7], D. Polsky[8], D. Lazovich[9], P.A. Kanetsky[10], P. Ghiorzo[11], N. Gruis[12], M.T. Landi[13], M.C. Fargnoli[14], J.C. García-Borrón[15], H. Nan[16], J. Little[17], S. Raimondi[2], A. Stratigos[1]

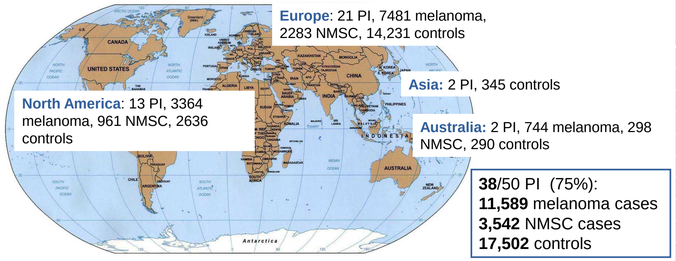
[1]Andreas Sygros Hospital, Athens, Greece; [2]IEO, Milan, Italy; [3]University of Ioannina, Greece; [4]UCL Institute of Child Health, London, UK; [5]Instituto Valenciano de Oncologia, Valencia, Spain; [6]ISPRO, Florence, Italy; [7]University of Leeds, UK; [8]New York University Grossman School of Medicine, New York, USA; [9]University of Minnesota, USA; [10]H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA; [11]University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy; [12]Leiden University Medical Center, The Netherlands; [13]NIH, Bethesda, USA; [14]University of L'Aquila, Italy; [15]University of Murcia and IMIB-Arrixaca, Murcia, Spain; [16]Indiana University, Indianapolis, USA; [17]University of Ottawa, Canada

Objective

Melanocortin-1-receptor (MC1R) is one of the major genes that control skin pigmentation and melanomagenesis. MC1R variants play a role in melanoma development both via pigmentary and non-pigmentary pathways (1, 2, **Fig.1**).
UVR is a well-established risk factor for melanoma. Data assessing sun exposure measures and the degree to which this variable influences the association between MC1R variants and melanoma risk, apart from phenotypic characteristics, are scarce.
The aim of this study was to evaluate whether sun exposure modifies the effect of MC1R variants on melanoma by analyzing MC1R gene – sun exposure interaction.

Fig. 1 – Pigmentary And non-pigmentary pathways from MC1R variants to melanoma risk

Fig. 2 – The M-SKIP Project



Methods and Materials

Cutaneous melanoma (CM) cases with information on chronic and/or intermittent sun exposure (N=3,365) and the corresponding controls (N=2,793) from 9 studies in which the MC1R gene was sequenced were obtained from the Melanocortin 1 receptor, SKin cancer and Phenotypic characteristics (M-SKIP) dataset, described in detail elsewhere (1, **Fig. 2**).
Sun exposure category was defined as a binary variable according to; (1) median and (2) highest versus lowest quartile. In each study, we calculated estimates for main effects of any MC1R variant, occupational or intermittent sun exposure and for a multiplicative interaction term using a logistic regression model, and considered age, sex, family history of melanoma, sunburn, common and atypical naevi, hair and eye color, freckles, and skin type as potential confounders. A two-stage approach with random effects models was adopted to calculate Summary Odds Ratios (SORs) and 95% Confidence Intervals (CI).

Tab. 1 – Estimates for occupational sun exposure-MC1R main effects and interaction

	OR_{MC1R} (95% CI)*	$OR_{sun\ expo}$ (95% CI)*	OR_{int} (95% CI)*	Expected OR (no interaction assumption)	p-value
Any variants	**1.55 (1.28; 1.89)**	0.94 (0.71; 1.24)	1.60 (1.29; 2.00)	1.46	0.60
Any R variants	**1.98 (1.63; 2.40)**	0.97 (0.75; 1.26)	2.22 (1.76; 2.81)	1.92	0.43
Any r variants	1.16 (0.93; 1.46)	0.92 (0.69; 1.22)	1.05 (0.80; 1.37)	1.07	0.80
V60L (r)	**1.41 (1.10; 1.79)**	0.88 (0.66; 1.17)	1.11 (0.83; 1.48)	1.24	0.34
D84E (R)	1.65 (0.94; 2.91)	1.00 (0.71; 1.41)	1.71 (0.78; 3.76)	1.65	0.86
V92M (r)	**1.35 (1.05; 1.75)**	0.92 (0.70; 1.20)	1.47 (1.06; 2.04)	1.24	0.37
R142H (R)	1.84 (0.99; 3.42)	0.92 (0.69; 1.21)	1.70 (0.68; 4.26)	1.69	0.95
R151C (R)	**2.09 (1.58; 2.75)**	0.92 (0.69; 1.23)	2.77 (1.75; 4.37)	1.92	0.20
I155T (R)	1.35 (0.69; 2.61)	0.98 (0.70; 1.36)	3.29 (1.04; 10.35)	1.32	0.31
R160W (R)	**1.80 (1.37; 2.36)**	0.92 (0.71; 1.22)	1.71 (1.16; 2.52)	1.66	0.83
R163Q (r)	1.37 (0.99; 1.88)	0.96 (0.73; 1.27)	1.22 (0.82; 1.80)	1.32	0.69
D294H (R)	**2.80 (1.78; 4.40)**	0.96 (0.73; 1.26)	**2.58 (1.49; 4.45)**	2.69	0.79

Results

No significant interaction of MC1R and sun exposure was observed for either occupational or intermittent sun exposure. SOR and 95% CI for the risk of melanoma for occupationally-exposed subjects with any MC1R variant was 1.60 (1.29-2.00) compared to non-occupationally-exposed subjects without MC1R variants (p-value for interaction: 0.60, **Tab.1**).
SOR (95%CI) for the risk of melanoma for carriers of any MC1R variant with high intermittent sun exposure compared to non-carriers of MC1R with low intermittent exposure was 1.64 (1.22-2.20; p-value for interaction: 0.82, **Tab.2**).

➢A little positive interplay with sun exposure may be possible for MC1R R variants highly associated with RHC phenotype, especially D84E, R142H, R151C and R160W (**Fig. 3**).

➢A little negative interplay with sun exposure may be possible for MC1R r variants not associated with RHC phenotype, especially V60L and R163Q (**Fig. 3**).

Tab. 2 – Estimates for intermittent sun exposure-MC1R main effects and interaction

	OR_{MC1R} (95% CI)*	$OR_{sun\ expo}$ (95% CI)*	OR_{int} (95% CI)*	Expected OR (no interaction assumption)	p-value
Any variants	**1.63 (1.23; 2.16)**	1.06 (0.77; 1.47)	**1.64 (1.22; 2.20)**	1.73	0.82
Any R variants	**2.16 (1.57; 2.99)**	1.08 (0.76; 1.52)	2.35 (1.67; 2.30)	2.33	0.61
Any r variants	1.18 (0.90; 1.56)	1.07 (0.79; 1.46)	1.18 (0.84; 1.50)	1.26	0.76
V60L (r)	**1.39 (1.00; 1.90)**	1.05 (0.75; 1.46)	1.37 (0.98; 1.92)	1.46	0.51
D84E (R)	1.62 (0.78; 3.40)	1.08 (0.67; 1.74)	1.85 (0.80; 4.28)	1.75	0.69
V92M (r)	**1.51 (1.12; 2.04)**	1.03 (0.78; 1.37)	1.29 (0.93; 1.77)	1.56	0.53
R142H (R)	1.17 (0.52; 2.63)	1.03 (0.72; 1.48)	2.17 (0.86; 5.48)	1.21	0.95
R151C (R)	**2.37 (1.70; 3.31)**	1.05 (0.77; 1.44)	2.52 (1.74; 3.63)	2.49	0.41
I155T (R)	1.94 (0.74; 5.08)	0.98 (0.66; 1.46)	1.35 (0.50; 3.67)	1.90	0.58
R160W (R)	**1.83 (1.30; 2.58)**	1.06 (0.78; 1.45)	2.09 (1.43; 3.07)	1.94	0.68
R163Q (r)	1.43 (0.94; 2.16)	1.02 (0.73; 1.43)	1.22 (0.79; 1.89)	1.46	0.98
D294H (R)	**2.53 (1.55; 4.14)**	0.99 (0.72; 1.37)	3.16 (1.77; 5.65)	2.51	0.47

Conclusion

MC1R and sun exposure independently affect melanoma risk, with no synergic or antagonist effect.
A possible reason for the lack of interaction may be the compensative effect of synergistic and antagonistic effect

Fig. 3 – Summary of the direction of sun-exposure-MC1R interaction terms

Intermittent sun exposure	Chronic sun exposure: Positive interaction	Chronic sun exposure: Negative interaction
Positive interaction	R variants, D84E (R), R142H (R), R151C (R), R160W (R)	D294H (R)
Negative interaction	Any variant, V92M (r), I155T (R)	r variants, V60L (r), R163Q (r)

References

1. Raimondi S et al. Int J Cancer (2008) 122, 2753-60.
2. Tagliabue E et al. Cancer Manag and Res (2018) 10: 1143-1154.
3. Raimondi S et al. BMC Med Res Meth (2012) 12, 116.