Is MC1R-RISK score a useful tool to evaluate the impact of MC1R SNPs on melanoma risk?

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Background

The melanocortin 1 receptor (MC1R) is a medium penetrance melanoma susceptibility gene affecting skin phenotype according to common SNPs. MC1R variants associated with red-hair phenotype (R alleles) confer a 2-fold risk of melanoma in the general population and a 3-fold risk in familial clusters. There are other common variants, not associated with red hair (r alleles), that can affect melanoma risk, even if with a lesser extent than R alleles. However, the association between MC1R and melanoma risk was often evaluated without taking into account the specific weight of each SNP. Here, we determined an individual MC1R risk score (MC1R-rs) by combining the MC1R risk alleles weighted by the effect size estimate of the most powerful GWAS studies on melanoma.

Methods

MC1R-SNPs were analyzed in 335 single and 263 multiple melanoma cases and 83 controls. MC1R-rs was calculated using the β value for each R/r SNP selected from previous independent GWAS analyses (β is the per-allele melanoma log OR for each SNP alternative allele). The cases with a β-unknown variant were excluded.

Results

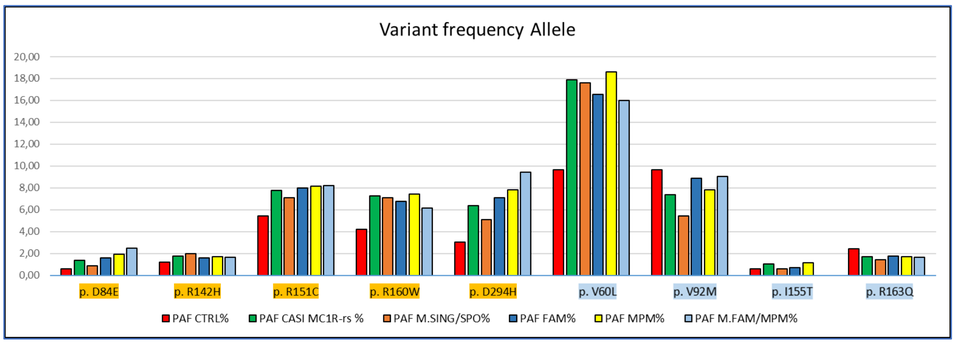
Table 1 - Frequency of common MC1R variants.

	R alleles					r alleles			
	c.252C>A p.D84E	**c.425G>A p.R142H**	**c.451C>T p.R151C**	**c.478C>T p.R160W**	**c. 880G>C p.D294H**	**c.178G>T p.V60L**	**c.274G>A p.V92M**	**c.464T>C p.I155T**	**c.488G>A p.R163Q**
Controls	1.2% (1)	2.4% (2)	10.8% (9)	8.4% (7)	6% (5)	15.7% (13)	**19.27% (16)**	1.2% (1)	4.8% (4)
Cases tot	4.6% (28)	4.3% (26)	21.4% (128)	19.2% (115)	19.9% (119)	**45.15%(270)**	21.07%(126)	2% (12)	4.5% (27)
M.Sing/Spo	1.7% (3)	4% (7)	14% (25)	14% (25)	10.3% (18)	33.5% (59)	10.3% (18)	1.1% (2)	3% (5)
MPM	3.8% (10)	3% (8)	15.6% (41)	14.5% (38)	15.2% (40)	33.8% (89)	15.2% (40)	2.3% (6)	3.4% (9)
M.Fam	3.2% (9)	3% (8)	15.3% (43)	13.16% (37)	13.8% (39)	30.9% (87)	16.7% (47)	1.4% (4)	3.2% (9)
M.Fam/MPM	5% (6)	2.5% (3)	15.6% (19)	12.3% (15)	18% (22)	28.7% (35)	17.2% (21)	0% (0)	3.3% (4)
β-value	0,40407	0,32712	0,47209	0,32296	0,37411	-0,00548	0,10358	0,16111	0,06454

At least one MC1R variant was found in the 80% of cases and in the 43% of controls. V60L is the most commonly presented variant in cases and V92M in controls.

M.Sing/Spo = cases with 1 melanoma diagnosis without family history of melanoma
MPM = multiple primary melanoma cases
M.Fam = melanoma cases with positive family history

Fig.1 - Variant frequency allele in controls and melanoma subgroups



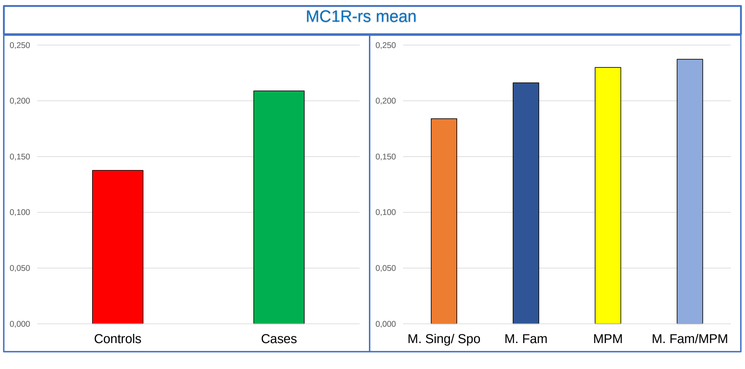
The allele frequency trend was heterogeneous among different groups. However, we found that all R variants had a higher allele frequency in cases vs controls.

Table 2 - Rare MC1R variants

c.207G>A p.L69L	c.911A>T p.E304V	c.265G>A p. G89R	c.364G>A p.V122M
c.243C>A p.A81A	c. 637C>T p. R213W	c.C56T p.T19I	c.638G>A p.R213Q
c.652G>A p.A218T	c.247T>C p.S83P	c.86 dup p.N29Kfs*14	c.873C>T p.A291A
c.699G>A p.Q233Q	c.284C>T p.T95M	c.104G>A p.C35Y	c.792C>T p. I264I
c.310G>A p.G104S	c.399C>T p.C133C	c.241G>C p. A81P	c.861C>G p.I287M
c.537dupC p.I180Hfs*58	c.G515T p.S172I	c.412A>G p.I138V	c.832A>G p.K278E
c.869A>G p.N290S	c. 456C> A p.Y152X	c.52C>G p.P18A	c.781C>G p.L261V
c.837C>A p.N279K	c.*581A>G	c.248C>T p.S83L	c. 520_522del p.Val174del

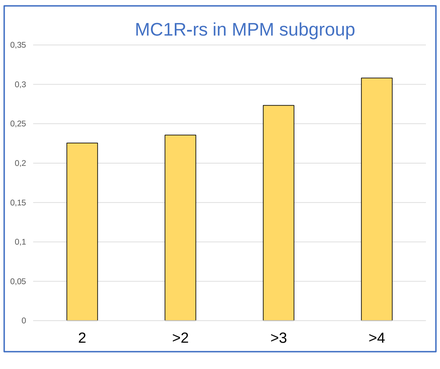
Other rare MC1R variants were found in a small percentage of cases.
Orange highlighted variants were each found also in one control.
β-value of these variants was not yet known, so MC1R-rs was calculated combining only β-value of R/r alleles.

Fig.2 - MC1R-rs mean in cases vs controls and vs different melanoma subgroups.



We observed a MC1R-rs mean higher in cases than controls (0.21 vs 0.14). The Familial/MPM subgroup showed the biggest MC1R-rs (0.24).

Fig.3 - MC1R-rs mean according to number of melanomas.



In the MPM subgroup, MC1R-rs mean increases as the number of melanomas increases.

Conclusions

This study suggests that MC1R-rs might be useful to evaluate the individual melanoma risk according to own MC1R profile. However, further analyses should be done by increasing control cohort and including rare MC1R variants. The goal is to establish a MC1R-rs cut off to identify individuals who are at high-risk of developing melanoma and multiple melanoma.