

**Table S1. Individual Phenotypic Index Characteristics and Separated MC1R Genotypes in Relationship to Histopathologic Pigmentation in Incident Primary Melanomas from 2387 patients in the GEM Study**

Characteristics	Pigmented Melanoma (n = 2209) <sup>a</sup>	Amelanotic Melanoma (n = 178) <sup>a</sup>	Amelanotic vs. Pigmented Melanoma					
			Study Design Features <sup>b</sup>		Study Design Features + Phenotype <sup>c</sup>		Study Design Features + Phenotype + <i>MC1R</i> <sup>d</sup>	
			OR (95% CI)	P Value <sup>e</sup>	OR (95% CI)	P Value <sup>e</sup>	OR (95% CI)	P Value <sup>e</sup>
<u>Phenotype</u>								
<u>Hair Color</u>								
Black/Dark Brown	655 (29.7)	53 (29.8)	1 [Reference]		1 [Reference]		1 [Reference]	
Light Brown/Blonde	1348 (61.0)	99 (55.6)	0.99 (0.69-1.42)	0.96	0.83 (0.57-1.22)	0.35	0.82 (0.56-1.21)	0.32
Red	206 (9.3)	26 (14.6)	1.83 (1.09-3.07)	0.02	1.22 (0.69-2.16)	0.49	1.31 (0.63-2.70)	0.47
<u>Eye Color</u>								
Brown	426 (19.3)	26 (14.6)	1 [Reference]		1 [Reference]		1 [Reference]	
Grey/green/hazel	842 (38.1)	63 (35.4)	1.42 (0.87-2.32)		1.40 (0.85-2.30)		1.39 (0.84-2.29)	
Blue	941 (42.6)	89 (50.0)	1.74 (1.09-2.77)		1.73 (1.06-2.82)		1.73 (1.06-2.83)	
P value for trend				0.02		0.03		0.03
<u>Ability to Tan</u>								
Deeply/moderately	1263 (57.2)	85 (47.8)	1 [Reference]	0.006	1 [Reference]	0.05	1 [Reference]	0.07
Occasionally/none	946 (42.8)	93 (52.3)	1.58 (1.14-2.18)		1.40 (1.00-1.98)		1.37 (0.97-1.95)	
<u>Back nevi</u>								
Present	1904 (86.2)	139 (78.1)	1 [Reference]	0.006	1 [Reference]	0.02	1 [Reference]	0.02
Absent	305 (13.8)	39 (21.9)	1.76 (1.18-2.65)		1.65 (1.10-2.49)		1.64 (1.09-2.47)	
<u>Freckles</u>								
None to few	1912 (86.6)	143 (80.3)	1 [Reference]	0.007	1 [Reference]	0.15	1 [Reference]	0.21
Many	297 (13.4)	35 (19.7)	1.76 (1.17-2.65)		1.40 (0.89-2.19)		1.34 (0.85-2.12)	
<u>Genetics</u>								
<i>MC1R</i> <sup>f</sup>								
wt/wt	357 (16.2)	23 (12.9)	1 [Reference]		-	-	1 [Reference]	
wt/r	479 (21.7)	34 (19.1)	1.15 (0.66-2.02)		-	-	1.13 (0.64-1.98)	
wt/R	501 (22.7)	35 (19.7)	1.18 (0.67-2.06)		-	-	1.16 (0.66-2.04)	
r/r	223 (10.1)	20 (11.2)	1.48 (0.78-2.81)		-	-	1.43 (0.75-2.73)	
R/r	429 (19.4)	43 (24.2)	1.71 (0.99-2.95)		-	-	1.42 (0.81-2.51)	
R/R	220 (10.0)	23 (12.9)	1.90 (1.02-3.56)		-	-	1.08 (0.48-2.46)	
P value for trend				0.007				0.27

Abbreviations: CI, confidence interval; GEM, genes, environment, and melanoma; MC1R, melanocortin 1 receptor; MPM, multiple primary melanoma; OR, odds ratio; SPM, single primary melanoma.

<sup>a</sup>Data are given as number (percentage) of melanomas unless otherwise specified.

<sup>b</sup>Adjusted for study design features: sex, age, study center, and lesion status (SPM or index MPM)

<sup>c</sup>Adjusted for study design features, freckling, back moles, hair color, eye color, and ability to tan.

<sup>d</sup>Adjusted for study design features and all characteristics displayed in the table.

<sup>e</sup>P values were calculated according to logistic regression models and P values for trend were calculated including MC1R categories as ordinal variables.

<sup>f</sup>*MC1R* "R": D84E, R142H, R151C, R160W, and D294H, all nonsense and insertion/deletion; "r": all other variants; "wt": consensus.

**Table S2. *MITF* E318K in Relationship to Histopathologic Pigmentation in Incident Primary Melanomas from 2361 patients in the GEM Study<sup>a</sup>**

	Pigmented Melanoma	Amelanotic Melanoma	Amelanotic vs. Pigmented Melanoma	
<i>MITF</i> E318K Mutation Status	n (%) <sup>b</sup>	n (%) <sup>b</sup>	OR (95%CI)	<i>P</i> Value <sup>c</sup>
Absent	2127 (97.4)	173 (97.7)	1 [Reference]	0.82
Present	57 (2.6)	4 (2.3)	0.86 (0.22-2.37)	

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Patients with missing data for *MITF* E318K mutation status (n=26) were excluded.

<sup>b</sup>Data are given as number (percentage) of melanomas.

<sup>c</sup>*P* value was calculated using an exact logistic regression model.