Supplementary Tables

Supplementary Table 1. Number of families with each *CDKN2A* mutation by continent and in all three continents*

Location of mutation in *CDKN2A* gene	*CDKN2A* sequence variation	Effect of sequence variation on p16INK4a protein	Effect of sequence variation on p14ARF protein	Europe	North America	Australia	All continents
5′UTR	c.-34G>T	p.?†	NONE	3	3		6
Exon							
1α	c.9_32del24	p.Ala4_Pro11del	NONE			1	1
1α	c.9_32dup24	p.Met1_Ser8dup	NONE	3	5	2	10
1α	c.44G>A	p.Trp15X	NONE		1		1
1α	c.46delC	p.Leu16TrpfsX10	NONE			1	1
1α	c.47T>C	p.Leu16Pro	NONE	1		1	2
1α	c.47T>G	p.Leu16Arg	NONE		1		1
1α	c.52_57dup	p.Thr18_Ala19dup	NONE	1			1
1α	c.68G>A	p.Gly23Asp	NONE	1	1		2
1α	c.71G>C	p.Arg24Pro	NONE	6		3	9
1α	c.88delG	p.Ala30fs	NONE	1			1
1α	c.95T>C	p.Leu32Prro	NONE	3		1	4
1α	c.104G>C	p.Gly35Ala	NONE	1		1	2
1α	c.123C>G	p.Pro38Arg	NONE	2			2
1α	c.132C>A	p.Tyr44X	NONE	1			1
1α	c.143C>T	p.Pro48Leu	NONE	1			1
1α	c.149A>C	p.Gln50Pro	NONE		1		1
1α	c.149A>G	p.Gln50Arg	NONE			1	1
1β	-5057Ex1β_-2740Ex1αdel	NONE	-5057Ex1β_-2740Ex1αdel	2			2
1β	c.60ins16	NONE	p.?	1			1
2	c.151G>T	p.Val51Phe	p.Gly65Val			1	1
2	c.157A>G	p.Met53Val	p.Asp67Gly		1		1
2	c.158T>C	p.Met53Thr	p.= ‡	1			1
2	c.159G>C	p.Met53Ile	p.Asp68His	10	4	4	18
2	c.167_197del	p.Ser56fs	chimeric p14ARF-p16 protein		1		1
2	c.167G>T	p.Ser56Ile	p.Gln70His	2			2
2	c.172C>T	p.Arg58X	p.Pro72Leu		1		1
2	c.176T>G	p.Val59Gly	p.Ser73Arg	2			2
2	c.185T>C	p.Leu62Pro	p.=	1			1
2	c.194T>C	p.Leu65Pro	p.=	2			2
2	c.199G>A	p.Gly67Ser	p.Arg81Gln	1			1
2	c.199G>C	p.Gly67Arg	p.Arg81Pro	2			2
2	c.199_213del15	p.Gly67_Asn71del	p.Pro17_Val22delinsLeu	1			1
2	c.202_203GC>TT	p.Ala68Leu	p.Arg82Leu	2			2
2	c.206A>G	p.Glu69Gly	p.=	1			1
2	c.212A>G	p.Asn71Ser	p.=		1		1
2	c.213C>A	p.Asn71Lys	p.Leu86Met	2			2
2	c.225_243del	p.Ala76fs	fusion p14ARF	8	3		11

			1_90, p16 82_156				
2	c.240_253del	p.Pro81fs	p.Thr95fs		2		2
2	c.242C>T	p.Pro81Leu	p.=	1			1
2	c.247C>A	p.His83Gln	p.Ala97Glu	1			1
2	c.251A>C	p.Asp84Ala	p.=	1			1
2	c.259C>T	p.Arg87Trp	p.Pro101Leu	1			1
2	c.260G>C	p.Arg87Pro	p.=		1		1
2	c.281T>C	p.Leu94Pro	p.=	1			1
2	c.296G>C	p.Arg99Pro	p.=	2			2
2	c.301G>T	p.Gly101Trp	p.Arg115Leu	29	3		32
2	c.307_308del	p.Arg103fs	p.Ala117fs	1	1		2
2	c.322G>A	p.Asp108Asn	p.Arg122Gln	1		1	2
2	c.334C>G	p.Arg112Gly	p.Pro126Arg	2			2
2	c.332_334dup	p.Arg112dup	p.127_128ins Ser	11			11
2	c.340C>T	p.Pro114Ser	p.Ala128Val	1			1
2	c.344T>G	p.Val115Gly	p.=	1			1
2	c.352G>A	p.Ala118Thr	p.Gly132Asp	1			1
2	c.358del	p.Glu120fs	p.Glu120fs	1			1
2	c.377T>A	p.Val126Asp	NONE	1	5		6
2	c.430C>T	p.Arg144Cys	NONE	1			1
2	c.457G>T	p.Asp153Tyr	NONE		2		2
Exons 1α, 2 and 3		Deletion	Deletion	1			1
Intron							
1β	c.193+3A>G	NONE	p.?	1			1
2	c.457+1G>T	p.?	p.?	1	1		2
2	c.458-105A>G	p.?	NONE	7	1	1	9
Total no. of families				**129**	**39**	**18**	**186**

*A total of 186 families from the Melanoma Genetics Consortium (GenoMEL) with at least two melanoma cases and presence of a *CDKN2A* mutation contributed to the study. The protocol for detecting *CDKN2A* mutations has been described elsewhere (7, 30, 31). Sequence variations (c.), including nucleotide changes, duplications, insertions, deletions, are described as recommended by the Ad-Hoc Committee of the Human Genome Variation Society (HGVS; http://www.hgvs.org/). Nucleotides are numbered from the first A of the ATG-translation initiation codon. The effect of sequence variations on the protein (p.) follows the HGVS recommendations. *CDKN2A* = cyclin-dependent kinase inhibitor 2A; UTR = untranslated region; del = deletion; dup = duplication; ins = insertion.

† Indicates a yet unknown change at the protein level and was used for insertion, deletion, intronic or 5'-UTR sequence variations.

‡ Indicates a silent change at the protein level (synonymous variation).

Supplementary Table 2. Frequency of *MC1R* variants in affected and unaffected *CDKN2A* mutations carriers analyzed by continent and in all three continents*

	Affected *CDKN2A* mutations carriers								**Unaffected *CDKN2A* mutations carriers**							
	Europe		**North America**		**Australia**		**All continents**		**Europe**		**North America**		**Australia**		**All continents**	
	No. of chromosomes† (n= 540)		No. of chromosomes† (n= 232)		No. of chromosomes† (n=174)		No. of chromosomes† (n= 946)		No. of chromosomes† (n= 454)		No. of chromosomes† (n= 154)		No. of chromosomes† (n= 76)		No. of chromosomes† (n= 684)	
MC1R amino acid change	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. w and without *MC1R* variant‡†	% of chrom. with and without *MC1R* variant§	No. of chrom. w and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§	No. of chrom. with and without *MC1R* variant‡	% of chrom. with and without *MC1R* variant§
Consensus sequence‡	168	31.1	64	27.6	59	33.9	291	30.8	218	48.0	81	52.6	37	48.7	336	49.1
Non-synonymous frequent variants‖																
V60L	73	13.5	47	20.3	22	12.6	142	15	50	11.0	16	10.4	4	5.3	70	10.2
V92M	53	9.8	19	8.2	13	7.5	85	9.0	52	11.5	10	6.5	8	10.5	70	10.2
R151C	80	14.8	29	12.5	51	29.3	160	16.9	36	7.9	11	7.1	10	13.2	57	8.3
R160W	58	10.7	27	11.6	13	7.5	98	10.4	36	7.9	6	3.9	4	5.3	46	6.7
Non-synonymous rare variants¶																
N15S	-	-	0	0	0	0	0	0	0	0	0	0	1	1.3	1	.1
H69P	0	0	0	0	0	0	0	0	1	.2	0	0	0	0	1	.1
S83P	0	0	3	1.3	0	0	3	.3	0	0	1	.6	0	0	1	.2
S83L	1	.2	0	0	0	0	1	.1	1	.2	0	0	0	0	1	.1
D84E	7	1.3	3	1.3	2	1.1	12	1.3	2	.4	3	1.9	0	0	5	.7
T95M	2	.4	0	0	0	0	2	.2	1	.2	0	0	0	0	1	.1
V122M	2	.4	0	0	0	0	2	.2	0	0	0	0	0	0	0	0
M128K	0	0	0	0	0	0	0	0	1	.2	0	0	0	0	1	.1
R142H	4	.7	1	.4	0	0	5	.5	1	.2	0	0	0	0	1	.1
Y152X	2	.4	0	0	0	0	2	.2	0	0	0	0	1	1.3	1	.2
I155T	10	1.9	5	2.2	1	.6	16	1.7	2	.4	5	3.2	0	0	7	1.0
R163Q	32	5.9	9	3.9	6	3.4	47	5.0	19	4.2	3	1.9	5	6.6	27	3.9
A171G	1	.2	0	0	0	0	1	.1	1	.2	0	0	0	0	1	.1
F196L	0	0	0	0	0	0	0	0	1	.2	0	0	0	0	1	.1
A218T	1	.2	0	0	0	0	1	.1	0	0	0	0	0	0	0	0
A218G	1	.2	0	0	0	0	1	.1	0	0	0	0	0	0	0	0
I221T	2	.4	0	0	0	0	2	.2	0	0	0	0	0	0	0	0
N279D	2	.4	0	0	0	0	2	.2	3	.7	0	0	0	0	3	.4
D294H	18	3.3	12	5.3	5	2.9	35	3.7	3	.7	4	2.6	3	3.9	10	1.5

Insertions																
g_86_87insA	1	.2	2	.9	0	0	3	.3	0	0	3	1.9	0	0	3	.5
g_537_538insC	1	.2	0	0	0	0	1	.1	0	0	0	0	0	0	0	0
Synonymous frequent variants‖																
T314T	54	10.0	25	11.0	4	2.4	83	8.8	48	10.6	16	10.4	5	6.6	69	10.1
Synonymous rare variants¶																
R34R	0	0	1	.4	0	0	1	.1	0	0	0	0	0	0	0	0
C133C	1	.2	0	0	0	0	1	.1	0	0	0	0	0	0	0	0
R213R	0	0	0	0	0	0	0	0	1	.2	0	0	0	0	1	.1
Q233Q	0	0	0	0	0	0	0	0	2	.5	0	0	0	0	2	.3
A240A	0	0	0	0	0	0	0	0	0	0	1	.6	0	0	1	.1
I264I	0	0	3	1.3	0	0	3	.3	0	0	0	0	0	0	0	0
S316S	1	.2	0	0	0	0	1	.1	0	0	0	0	1	1.3	1	.2

*The frequency of *MC1R* variants was estimated in affected (melanoma patients) and unaffected *CDKN2A* mutation carriers genotyped for *MC1R* (473 affected mutation carriers: 270 from Europe, 116 from North America, 87 from Australia; 342 unaffected mutation carriers: 227 from Europe, 77 from North America, 38 from Australia). *CDKN2A* = cyclin-dependent kinase inhibitor 2A. *MC1R* = melanocortin-1 receptor. chrom. = chromosome.

†The number of chromosomes was twice the number of *CDKN2A* mutation carriers genotyped for *MC1R*..

‡The number of chromosomes carrying no *MC1R* variant (consensus sequence) and those carrying a given variant are shown for affected and unaffected *CDKN2A* mutation carriers per continent and in all three continents.

§The proportions shown in this table are the number of chromosomes carrying no *MC1R* variant (consensus sequence) or a given variant divided by the total number of chromosomes in affected and unaffected *CDKN2A* mutation carriers per continent and in all three continents.

‖The frequent variants shown in this table are those with an estimated frequency greater than or equal to 5% in *CDKN2A* mutation carriers from at least one continent and all three continents.

¶ The rare variants shown in this table are those with an estimated frequency less than 5% in *CDKN2A* mutation carriers from all three continents.

Supplementary Table 3. Association of *MC1R* variants and number of *MC1R* variants with melanoma risk in *CDKN2A* mutation carriers analyzed by country within Europe*

Country	No. of participants affected / unaffected†	Any *MC1R* variant		Number of *MC1R* variants				
				1 variant		≥ 2 variants		Trend test
		OR (95% CI)‡	*P*§	OR (95% CI)‡	*P*§	OR (95% CI)‡	*P*§	P_{trend}‖
France	52/43	4.93 (1.73 to 14.02)	.02	1.68 (.58 to 4.84)	.25	8.00 (2.96 to 21.66)	.007	.002
Italy	32/14	1.10 (.35 to 3.53)	.87	1.12 (.35 to 3.53)	.85	.97 (.05 to 17.28)	.98	.94
The Netherlands	52/61	1.46 (.64 to 3.32)	.44	.93 (.42 to 2.06)	.87	3.07 (1.12 to 8.40)	.12	.16
Spain	30/36	9.45 (2.48 to 36.05)	.04	8.25 (2.0 to 34.07)	.04	11.40 (2.66 to 48.79	.02	.03
Sweden	22/26	12.01 (2.61 to 55.20)	.04	13.2 (2.0 to 87.6)	.03	11.09 (3.57 to 34.43)	.04	.09
United Kingdom	82/47	2.28 (.77 to 6.81)	.19	1.48 (.47 to 4.68)	.50	3.64 (1.14 to 11.60)	.07	.02

*The association of each *MC1R* variable (any *MC1R* variant, number of *MC1R* variants) with melanoma risk was estimated by using homozygosity for the *MC1R* consensus sequence as the reference category. *CDKN2A* = cyclin-dependent kinase inhibitor 2A. *MC1R* = melanocortin-1 receptor. OR = odds ratio. CI = confidence interval.

†The number of GenoMEL participants from each European country contributing to the analysis of a given *MC1R* variable (any *MC1R* variant, number of *MC1R* variants) that were affected with melanoma and their unaffected relatives.

‡ The odds ratios and 95% confidence intervals were estimated by the generalized estimating equations (GEE) method using a logit link function and an exchangeable correlation matrix to take into account the correlations among the family members' melanoma affection status (affected, unaffected). The odds ratios shown in this table are adjusted for age, sex.

§*P* values associated with the two-sided generalized score test used to test for association between melanoma risk and *MC1R* variants.

‖P_{trend} values associated with the two-sided trend test which tests for a change in melanoma risk with a linear increase in the number of *MC1R* variants (0, 1, ≥2 variants).

Supplementary Table 4. Associations of *MC1R* variants with melanoma risk stratified by hair color in *CDKN2A* mutation carriers from all continents*

***MC1R* Variants**	**Red or blond hair**			**Brown or black hair**		
	No. of participants affected / unaffected†	**OR (95% CI)‡**	***P*§**	**No. of participants affected / unaffected†**	**OR (95% CI)‡**	***P*§**
Individual *MC1R* variants						
V60L	40/ 20	.95 (.31 to 2.94)	.93	92/100	3.10 (1.60 to 6.01)	.004
V92M	30/20	.93 (.28 to 3.12)	.91	75/100	2.69 (1.43 to 5.04)	.005
R151C	67/21	4.01 (.90 to 17.81)	.08	75/83	4.07 (1.98 to 8.37)	.0004
R160W	53/21	1.73 (.55 to 5.48)	.35	57/80	3.41 (1.56 to 7.47)	.01
No of *MC1R* variants	128/56			213/185		
1		.79 (.25 to 2.55)	.70		2.51 (1.48 to 4.28)	.003
≥ 2		2.62 (.91 to 7.54)	.09		5.15 (2.65 to 10.00)	5.55×10^{-5}

*The associations of individual *MC1R* variants and number of *MC1R* variants were estimated by using individuals homozygotes for the *MC1R* consensus sequence as the reference category. *CDKN2A* = cyclin-dependent kinase inhibitor 2A. *MC1R* = melanocortin-1 receptor. OR = odds ratio. CI = confidence interval.

†The number of GenoMEL participants contributing to the analysis of a given *MC1R* variable (individual *MC1R* variants, number of *MC1R* variants) that were affected with melanoma and their unaffected relatives for each category of hair color (red or blond vs brown or black).

‡The odds ratios and 95% confidence intervals were estimated by the generalized estimating equations (GEE) method using a logit link function and an exchangeable correlation matrix to take into account the correlations among the family members' melanoma affection status (affected, unaffected). The odds ratios shown in this table are adjusted for age, sex and geographic locales.

§*P* values associated with the two-sided generalized score test used to test for association between melanoma and *MC1R* variants.