# Supplementary Materials: Sex-Specific Associations of *MDM2* and *MDM4* Variants with Risk of Multiple Primary Melanomas and Mela-Noma Survival in Non-hispanic Whites

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**Table S1.** Characteristics of MDM2 and MDM4 gene variants investigated in the Genes, Environment and Melanoma study.

| Gene variants | D'[a] | R²[a] | N[b] | Position (GRCh38.p13) | A/a[c] | Relative position | MAF in GEM | MAF reported[d] | RegDB rank[e] & score[e] | |
|---|---|---|---|---|---|---|---|---|---|---|
| *MDM2* | | | | | | | | | | |
| rs117039649 (SNP285) | 1 | 0 | 3616 | Chr12:68808776 | G/C | intronic | 0.04 | 0.0349 | 2a | 0.419 |
| rs2279744 (SNP309) | | | 3457 | Chr12:68808800 | T/G | intronic | 0.35 | 0.3065 | 4 | 0.705 |
| *MDM4* | | | | | | | | | | |
| rs1563828 | 1 | 0.7 | 3575 | Chr1:204547449 | G/A | intronic | 0.31 | 0.3286 | 6 | 0.194 |

Abbreviations: GEM, Genes, Environment and Melanoma Study; N, number of samples with genotype data; A/a, Major/minor alleles; MAF, minor allele frequency; RegDB, Regulome database. [a] D' and r2 retrieved from NCI's LD Link (https://ldlink.nci.nih.gov/) for White non-Hispanic population (CEU, TSI, FIN, GBR). [b] N samples passing QC. [c] Major and minor alleles noted for the forward or plus strand; the designed assay typed the reverse or minus strand of rs1563828 (i.e., C>T). [d] dbSNP, ALFA project or gnomAD in European population. [e] RegulomeDB (https://regulomedb.org/regulome-search/). All public databases accessed last in February 2023.

**Table S2.** Minimally adjusted hazard ratios for *MDM2* and *MDM4* gene variants on the risk for melanoma-specific death in GEM by sex.

| Gene and RefSeq | All (n =3521) | | | | Females (n =1552) | | | | Males (n =1969) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N total / N deaths[a] | HR[b] | 95% CI[b] | P$_{trend}$[b] | N total / N deaths[a] | HR[d] | 95% CI[d] | P$_{trend}$[d] | N total / N deaths[a] | HR[d] | 95% CI[d] | P$_{trend}$[d] |
| *MDM2* | | | | | | | | | | | | |
| rs117039649 (SNP285) | 3521/248 | 0.70 | 0.41 - 1.21 | 0.21 | 1552/70 | 0.91 | 0.38 - 2.18 | 0.83 | 1969/178 | 0.62 | 0.31 - 1.24 | 0.18 |
| rs2279744 (SNP309) | 3367/236 | 0.89 | 0.74 - 1.08 | 0.24 | 1484/67 | 0.73 | 0.51 - 1.06 | 0.10 | 1883/169 | 0.97 | 0.78 - 1.21 | 0.80 |
| P$_{interaction}$=0.47 (rs117039649) and 0.26 (rs2279744) [c] | | | | | | | | | | | | |
| *MDM4* | | | | | | | | | | | | |
| rs1563828 | 3484/245 | 0.90 | 0.74 - 1.10 | 0.30 | 1541/70 | 1.12 | 0.78 - 1.61 | 0.56 | 1943/175 | 0.82 | 0.65 - 1.05 | 0.11 |
| rs4245739/SNP34091 | 3480/250 | 0.88 | 0.72 - 1.08 | 0.22 | 1532/70 | 1.07 | 0.73 - 1.57 | 0.72 | 1948/180 | 0.81 | 0.64 - 1.04 | 0.10 |
| P$_{interaction}$=0.20 (rs1563828) and 0.26 (rs4245739) [c] | | | | | | | | | | | | |

Abbreviations: N, number; HR, Hazard Ratio; CI, Confidence Interval; P$_{trend}$, trend p-values; P$_{interaction}$, p-value for interaction term. [a] N total, all participants; N deaths, number of melanoma-specific deaths. [b] Per allele HR, 95% CI, and p-values obtained from a Cox proportional hazards model adjusted for age at diagnosis of the first primary melanoma, sex, study center, single or multiple primary melanoma status, time dependent crossover status (for patients who entered the study with single primary melanoma and developed a subsequent melanoma during follow up). [c] Likelihood ratio test p-value for sex*SNP interaction term. [d] Per allele HR, 95% CI, and p-values obtained in stratified analysis by female or male sex.

**Table S3.** Hazard ratios for *MDM2* and *MDM4* gene variants on the risk for melanoma-specific death in GEM by sex, adjusted for Stage (subanalyses).

| SNP and cohort | | N total / N deaths[a] | HR[b] | 95% CI[b] | P$_{value}$[b] | HR[c] | 95% CI[c] | P$_{value}$[c] |
|---|---|---|---|---|---|---|---|---|
| | All | 2614/ 193 | 0.71 | 0.40, 1.23 | 0.22 | 0.77 | 0.44, 1.37 | 0.38 |
| rs117039649 | Females | 1160/ 56 | 0.62 | 0.22, 1.72 | 0.35 | 0.89 | 0.32, 2.47 | 0.83 |
| | Males | 1454/ 137 | 0.72 | 0.37, 1.41 | 0.34 | 0.72 | 0.36, 1.45 | 0.36 |
| | All | 2494/ 185 | 0.8 | 0.64, 1.00 | 0.05 | 0.8 | 0.64, 0.99 | 0.04 |
| rs2279744 | Females | 1108/ 53 | **0.57** | **0.36, 0.92** | **0.02** | **0.55** | **0.34, 0.88** | **0.01** |
| | Males | 1386/ 132 | 0.89 | 0.70, 1.15 | 0.38 | 0.89 | 0.69, 1.15 | 0.36 |
| | All | 2596/ 193 | 0.92 | 0.74, 1.15 | 0.47 | 0.9 | 0.72, 1.12 | 0.35 |
| rs1563828 | Females | 1154/ 56 | 1.08 | 0.72, 1.62 | 0.71 | 1.12 | 0.73, 1.71 | 0.61 |
| | Males | 1442/ 137 | 0.86 | 0.67, 1.12 | 0.27 | 0.83 | 0.64, 1.08 | 0.16 |
| | All | 2581/ 196 | 0.88 | 0.70, 1.11 | 0.30 | 0.86 | 0.68, 1.08 | 0.20 |
| rs4245739 | Females | 1141/ 56 | 0.99 | 0.64, 1.54 | 0.97 | 1.03 | 0.65, 1.62 | 0.91 |
| | Males | 1440/ 140 | 0.84 | 0.64, 1.10 | 0.20 | 0.8 | 0.61, 1.05 | 0.11 |

Abbreviations: N, number; HR, Hazard Ratio; CI, Confidence Interval. [a] N total, all participants with available Stage; N deaths, number of melanoma-specific deaths. [b] Per allele HR, 95% CI, and p-values obtained from a Cox proportional hazards model adjusted for age at diagnosis of the first primary melanoma, sex, study center, single or multiple primary melanoma status, time-dependent crossover status (for patients who entered the study with single primary melanoma and developed a subsequent melanoma during follow up), anatomic site and logged Breslow thickness of the deepest primary melanoma. [c] Per allele HR, 95% CI, and p-values obtained from a Cox proportional hazards model adjusted for age at diagnosis of the first primary melanoma, sex, study center, single or multiple primary melanoma status, time-dependent crossover status, anatomic site and stage, considering the deepest primary melanoma.

**Table S4.** Minimally adjusted hazard ratios for *MDM2* and *MDM4* haplotypes and melanoma-specific death by sex.

| | **All (n=3663)** | | | | **Females (n=1595)** | | | | **Males (n=2068)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haplotype | Frequency | HR[a] | 95% CI[a] | P$_{global}$[a] | Frequency | HR[c] | 95% CI[c] | P$_{global}$[c] | Frequency | HR[c] | 95% CI[c] | P$_{global}$[c] |
| *MDM2* | | | | | | | | | | | | |
| **rs117039649 - rs2279744** (SNP285-SNP309) | | | | | | | | | | | | |
| G-T | 0.64 | 1.00 | (ref) | | 0.64 | 1.00 | (ref) | | 0.64 | 1.00 | (ref) | |
| G-G | 0.32 | 0.92 | 0.76 - 1.12 | | 0.33 | 0.71 | 0.49 - 1.05 | | 0.32 | 1.02 | 0.82 - 1.28 | |
| **C**-G | 0.03 | 0.60 | 0.31 - 1.14 | | 0.03 | 1.00 | 0.37 - 2.71 | | 0.03 | 0.47 | 0.20 - 1.11 | |
| C-T | 0.01 | 1.09 | 0.30 - 3.94 | 0.39 | 0.01 | 0.28 | 0.01 - 14.74 | 0.36 | 0.01 | 1.69 | 0.43 - 6.65 | 0.33 |
| P$_{interaction}$=0.24[b] | | | | | | | | | | | | |
| *MDM4* | | | | | | | | | | | | |
| **rs1563828 - rs4245739** | | | | | | | | | | | | |
| *All* | | | | | | | | | | | | |
| C-A | 0.68 | 1.00 | (ref) | | 0.68 | 1.00 | (ref) | | 0.68 | 1.00 | (ref) | |
| T-C | 0.26 | 0.92 | 0.74 - 1.13 | | 0.26 | 1.12 | 0.76 - 1.65 | | 0.26 | 0.84 | 0.66 - 1.08 | |
| T-A | 0.05 | 0.87 | 0.56 - 1.35 | | 0.05 | 1.15 | 0.56 - 2.38 | | 0.05 | 0.77 | 0.44 - 1.33 | |
| C-C | 0.01 | 0.03 | 0 - 18.27 | 0.52 | 0.01 | 0.01 | 0 - 3.25x10$^9$ | 0.92 | 0.01 | 0.026 | 0 - 29.0 | 0.30 |
| P$_{interaction}$=0.64[b] | | | | | | | | | | | | |

Abbreviations: N, number; HR, Hazard Ratio; CI, Confidence Interval; P$_{global}$, global p-value; P$_{interaction}$, p-value for interaction term; ref, reference group. [a] Per-haplotype subdistribution; HR, CI, and global p-values obtained from a Cox proportional hazards model adjusted for age at diagnosis, sex, study center, single or multiple primary melanoma status, plus a time-dependent variable for cases with single primary melanoma who developed a subsequent melanoma during follow-up. The referent group corresponds to the most common haplotype. [b] Likelihood ratio test p-value for sex*haplotype interaction term. [c] Per-haplotype HR, CI, and global p-values in models adjusted for age at diagnosis, center, single or multiple primary melanoma status, and time-dependent variable for cases with single primary melanoma who developed a subsequent melanoma during follow-up (as per footnote 'a', except sex), in analysis stratified by sex.

**Table S5.** A. Characteristics of other credible variants: SNPs co-inherited *with the MDM2/MDM4* SNPs tested in GEM that modulate gene transcription in unaffected skin, and distal organs/tissues.

| RefSeq_Test[a] | SNP in LD with Tests[b] | D'[b] | R2[b] | Gene : Consequence | RegDB Rank[c] | RegDB Score[c] |
|---|---|---|---|---|---|---|
| *MDM2* | | | | | | |
| | rs1201644 | 1 | 0.591 | MDM2 Splice donor | 1f | 0.55436 |
| rs2279744 | rs1625525 | 1 | 0.487 | MDM2: Intron | 1f | 0.55436 |
| | rs2120742 | 1 | 0.454 | LOC100130075: Non coding transcript exon | 1f | 0.55436 |
| *MDM4* | | | | | | |
| rs1563828 | rs12041243 | 1 | 0.129 | MDM4: Intron | 1b | 0.51695 |
| rs1563828 | rs12039365 | 1 | 0.129 | MDM4: Intron | 1f | 0.55324 |
| rs4245739 | rs4951407 | 0.979 | 0.682 | LOC105371692: Regulatory region | 1f | 0.55436 |
| rs4245739 | rs4951407 | 0.979 | 0.682 | LOC105371692: Regulatory region | 1f | 0.55436 |
| rs1563828 & rs4245739 | rs1380576 | 1 | 0.95 | MDM4: Intron | 1b | 0.99621 |
| | rs1380576 | 1 | 0.95 | MDM4: Intron | 1b | 0.99621 |
| | rs4951393 | 1 | 0.992 | MDM4: Intron | 1d | 0.64833 |
| | rs4951393 | 1 | 0.992 | MDM4: Intron | 1d | 0.64833 |
| | rs10494852 | 0.991 | 0.925 | PIK3C2B: Intron | 1f | 0.22271 |
| | rs10494852 | 0.991 | 0.925 | PIK3C2B: Intron | 1f | 0.22271 |
| | rs10900594 | 0.991 | 0.917 | Intergenic | 1f | 0.22271 |
| | rs10900594 | 0.991 | 0.917 | Intergenic | 1f | 0.22271 |
| | rs12039454 | 1 | 1 | TF binding site | 1f | 0.55436 |
| | rs12039454 | 1 | 1 | TF binding site | 1f | 0.55436 |
| rs1563828 & rs4245739 | rs16853958 | 1 | 0.926 | Intergenic | 1f | 0.55324 |
| | rs16853958 | 1 | 0.926 | Intergenic | 1f | 0.55324 |
| | rs2369244 | 1 | 0.992 | MDM4: Intron | 1f | 0.55436 |
| | rs2369244 | 1 | 0.992 | MDM4: Intron | 1f | 0.55436 |
| | rs4252725 | 1 | 0.926 | MDM4: Intron | 1f | 0.60183 |
| | rs4252725 | 1 | 0.926 | MDM4: Intron | 1f | 0.60183 |
| | rs4951382 | 0.99 | 0.792 | PIK3C2B: Intron | 1f | 0.55436 |
| | rs4951382 | 0.99 | 0.792 | PIK3C2B: Intron | 1f | 0.55436 |
| | rs7556371 | 0.99 | 0.815 | PIK3C2B: Intron | 1f | 0.22271 |
| | rs7556371 | 0.99 | 0.815 | PIK3C2B: Intron | 1f | 0.22271 |

Abbreviations: RefSeq, reference sequence; SNP, single nucleotide polymorphism; LD, linkage disequilibrium; RegDB, RegulomeDB. [a] SNPs tested in the GEM study and in this study: rs2279744 in MDM2, rs1563828 and rs4245739 in MDM4. For the tested MDM2-rs117039649 no SNPs in LD matched our selection criteria in relation to functional relevance or effect on transcription in skin and target distal tissues. [b] SNPs in high LD with SNPs tested in GEM participants (D'>0.95). [c] RegulomeDB ranks 1a to 1f.

**Table S5.** B. Effect of other credible *MDM2/MDM4* variants on transcription in unaffected skin, and in distal organs/tissues often targeted during melanoma metastases.

| SNP in LD with Tests [a] | Gene Symbol [b] | Effect Allele Freq. [b] | Skin not sun exposed [b] Effect Size | Skin not sun exposed [b] P-value | sun exposed [b] Effect Size | sun exposed [b] P-value | Brain spinal cord [b] Effect Size | Brain spinal cord [b] P-value | hippocampus [b] Effect Size | hippocampus [b] P-value | substantia nigra [b] Effect Size | substantia nigra [b] P-value | cerebellum [b] Effect Size | cerebellum [b] P-value | Lung [b] Effect Size | Lung [b] P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MDM2** | | | | | | | | | | | | | | | | |
| rs1201644 | SLC35E3 | A=0.507 | | | | | -0.443 | $5 \times 10^{-12}$ | -0.33 | $3 \times 10^{-6}$ | -0.348 | $8 \times 10^{-6}$ | | | | |
| | NUP107 | A=0.507 | | | 0.119 | $2 \times 10^{-5}$ | | | | | | | | | | |
| rs1625525 | SLC35E3 | C=0.458 | | | | | -0.49 | $3 \times 10^{-16}$ | -0.33 | $4 \times 10^{-6}$ | -0.397 | $2 \times 10^{-7}$ | | | | |
| | MDM2 | C=0.458 | | | | | -0.366 | $2 \times 10^{-7}$ | | | | | | | | |
| | NUP107 | C=0.458 | | | 0.138 | $3 \times 10^{-7}$ | | | | | | | | | | |
| rs2120742 | SLC35E3 | T=0.441 | | | | | -0.504 | $4 \times 10^{-17}$ | -0.352 | $5 \times 10^{-7}$ | -0.379 | $3 \times 10^{-7}$ | | | | |
| | MDM2 | T=0.441 | | | | | -0.383 | $6 \times 10^{-8}$ | | | | | | | | |
| | NUP107 | T=0.441 | | | 0.176 | $5 \times 10^{-11}$ | | | | | | | | | 0.132 | $1 \times 10^{-6}$ |
| **MDM4** | | | | | | | | | | | | | | | | |
| rs12041243 | PIK3C2B | G=0.242 | -0.147 | $4 \times 10^{-6}$ | -0.176 | $9 \times 10^{-11}$ | | | | | | | | | | |
| rs12039365 | PIK3C2B | G=0.242 | -0.147 | $4 \times 10^{-6}$ | -0.176 | $9 \times 10^{-11}$ | | | | | | | | | | |
| rs4951407 | MDM4 | G=0.702 | | | | | | | | | | | -0.246 | $6 \times 10^{-5}$ | -0.115 | $5 \times 10^{-5}$ |
| | PIK3C2B | G=0.702 | -0.115 | $8 \times 10^{-6}$ | -0.125 | $2 \times 10^{-7}$ | | | | | | | | | | |
| rs1380576 | MDM4 | C=0.723 | | | | | | | | | | | -0.264 | $2 \times 10^{-5}$ | -0.12 | $2 \times 10^{-5}$ |
| | PIK3C2B | C=0.723 | -0.108 | $4 \times 10^{-5}$ | -0.11 | $5 \times 10^{-6}$ | | | | | | | | | | |
| rs4951393 | MDM4 | A=0.711 | | | | | | | | | | | -0.271 | $9 \times 10^{-6}$ | -0.135 | $2 \times 10^{-6}$ |
| | PIK3C2B | A=0.711 | -0.116 | $8 \times 10^{-6}$ | -0.112 | $3 \times 10^{-6}$ | | | | | | | | | | |
| rs10494852 | MDM4 | T=0.725 | | | | | | | | | | | -0.251 | $7 \times 10^{-5}$ | -0.111 | $1 \times 10^{-4}$ |
| | PIK3C2B | T=0.725 | -0.103 | $1 \times 10^{-4}$ | -0.117 | $1 \times 10^{-6}$ | | | | | | | | | | |
| rs10900594 | MDM4 | C=0.727 | | | | | | | | | | | | | -0.118 | $2 \times 10^{-5}$ |
| | PIK3C2B | C=0.727 | -0.108 | $4 \times 10^{-5}$ | -0.109 | $6 \times 10^{-6}$ | | | | | | | | | | |
| rs12039454 | MDM4 | C=0.713 | | | | | | | | | | | -0.271 | $9 \times 10^{-6}$ | -0.132 | $3 \times 10^{-6}$ |
| | PIK3C2B | C=0.713 | -0.111 | $2 \times 10^{-5}$ | -0.111 | $3 \times 10^{-6}$ | | | | | | | | | | |
| rs16853958 | MDM4 | C=0.728 | | | | | | | | | | | | | -0.118 | $2 \times 10^{-5}$ |
| | PIK3C2B | C=0.728 | -0.107 | $5 \times 10^{-5}$ | -0.115 | $2 \times 10^{-6}$ | | | | | | | | | | |
| rs2369244 | MDM4 | C=0.728 | | | | | | | | | | | -0.271 | $9 \times 10^{-6}$ | -0.132 | $3 \times 10^{-6}$ |
| | PIK3C2B | C=0.728 | -0.111 | $2 \times 10^{-5}$ | -0.113 | $3 \times 10^{-6}$ | | | | | | | | | | |
| rs4252725 | MDM4 | C=0.728 | | | | | | | | | | | -0.249 | $5 \times 10^{-5}$ | -0.116 | $3 \times 10^{-5}$ |
| | PIK3C2B | G=0.728 | -0.104 | $7 \times 10^{-5}$ | -0.111 | $5 \times 10^{-6}$ | | | | | | | | | | |
| rs4951382 | RP11-430C7.5 | C=0.754 | | | | | | | | | | | | | 0.158 | $2 \times 10^{-5}$ |
| | PIK3C2B | C=0.754 | -0.112 | $3 \times 10^{-5}$ | -0.131 | $8 \times 10^{-8}$ | | | | | | | | | | |
| rs7556371 | RP11-430C7.5 | A=0.749 | | | | | | | | | | | | | 0.152 | $4 \times 10^{-5}$ |
| | PIK3C2B | A=0.749 | -0.103 | $9 \times 10^{-5}$ | -0.123 | $4 \times 10^{-7}$ | | | | | | | | | | |

Abbreviations: SNP, single nucleotide polymorphism; LD, linkage disequilibrium. [a] SNPs in high LD (D'>0.95) with SNPs tested in GEM participants.  [b] Effector genes and related data retrieved from the GTEx (Genotype-Tissue Expression) project's portal (v8 data retrieved on 10/15/2021) for not sun exposed skin tissues (suprapubic area,   n=605), sun exposed skin (tissues from lower leg area,

n= 517), brain tissues from spinal cord (cervical c1, n=126); hippocampus (n=165); substantia nigra (n= 114), and lung (n= 515). No significant results were obtained for liver and small intestine. No data were available for bone.

**Table S6.** Interaction between MDM2 and *MDM4* SNPs on risk for developing multiple melanoma, and risk of melanoma-specific death.

| *MDM2*MDM4* SNPs | N | Exponentiated beta coeficient | 95% CI | $P_{Interaction}$ |
|---|---|---|---|---|
| *Interaction between MDM2 and MDM4 SNPs on risk [a]* | | | | |
| rs4245739 * rs117039649 | 3553 | 0.86 | 0.54, 1.36 | 0.50 |
| rs4245739 * rs2279744 | 3397 | 1.08 | 0.90, 1.29 | 0.40 |
| rs1563828 * rs117039649 | 3564 | 0.82 | 0.52, 1.29 | 0.40 |
| rs1563828 * rs2279744 | 3399 | 1 | 0.84, 1.18 | 0.97 |
| *Interaction between MDM2 and MDM4 SNPs on survival [b]* | | | | |
| rs4245739 * rs117039649 | 3519 | 1.86 | 0.81, 4.24 | 0.14 |
| rs4245739 * rs2279744 | 3363 | 0.92 | 0.67, 1.26 | 0.6 |
| rs1563828 * rs117039649 | 3530 | 1.53 | 0.67, 3.48 | 0.3 |
| rs1563828 * rs2279744 | 3365 | 0.92 | 0.68, 1.24 | 0.6 |

Abbreviations: N, number; CI, Confidence Interval; $P_{interaction}$, p-value for interaction term. [a] Adjusted for age, sex, age*sex interaction, and centre. [b] Adjusted for age, sex, centre, status_orig, and time-dependent covariate.

**Table S7.** Minimally adjusted hazard ratios for *MDM2* and *MDM4* diplotypes and melanoma-specific death by sex.

| | **All** (n=3519) | | | | **Females** (n=1547) | | | | **Males** (n=1972) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diplotypes | Frequency | HR[a] | 95% CI[a] | $P_{global}$[a] | Frequency | HR[c] | 95% CI[c] | $P_{global}$[c] | Frequency | HR[c] | 95% CI[c] | $P_{global}$[c] |
| *MDM2* **rs117039649** (SNP285) - *MDM4* **rs4245739** | | | | | | | | | | | | |
| GG-AA | 1713 | 1.00 | (ref) | 0.33 | 763 | 1.00 | (ref) | 0.85 | 950 | 1.00 | (ref) | 0.15 |
| GG-AC | 1,346 | 0.84 | 0.64, 1.10 | | 583 | 1.22 | 0.74, 2.02 | | 763 | 0.72 | 0.52, 1.00 | |
| GG-CC | 219 | 0.71 | 0.39, 1.28 | | 93 | 0.83 | 0.25, 2.73 | | 126 | 0.66 | 0.33, 1.31 | |
| GC/CC-AA | 130 | 0.45 | 0.18, 1.10 | | 55 | 0.82 | 0.20, 3.45 | | 75 | 0.34 | 0.11, 1.09 | |
| GC/CC-AC | 93 | 0.97 | 0.45, 2.08 | | 46 | 1.51 | 0.46, 4.95 | | 47 | 0.80 | 0.29, 2.19 | |
| GC/CC-CC | 18 | 0.77 | 0.11, 5.54 | | 7 | <0.01 | 0.00, >999 | | 11 | 0.97 | 0.13, 6.95 | |
| | $P_{interaction}$=0.14 | | | | $P_{interaction}$=0.95 | | | | $P_{interaction}$=0.09 | | | |

Abbreviations: N, number; HR, Hazard Ratio; CI, Confidence Interval; $P_{global}$, global p-value; $P_{interaction}$, p-value for interaction term; ref, reference group. HR, CI, and global p-values obtained from a Cox proportional hazards model adjusted for age at diagnosis, sex, study center, single or multiple primary melanoma status, plus a time-dependent variable for cases with single primary melanoma who developed a subsequent melanoma during follow-up. The referent group corresponds to the most common combined genotypes.