Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2015 June ; 24(6): 992–997. doi:10.1158/1055-9965.EPI-14-1426.

Inherited genetic variants associated with occurrence of multiple primary melanoma

David C. Gibbs[1], **Irene Orlow**[2], **Peter A. Kanetsky**[3], **Li Luo**[4], **Anne Kricker**[5], **Bruce K. Armstrong**[5], **Hoda Anton-Culver**[6], **Stephen B. Gruber**[7], **Loraine D. Marrett**[8], **Richard P. Gallagher**[9], **Roberto Zanetti**[10], **Stefano Rosso**[10], **Terence Dwyer**[11], **Ajay Sharma**[2], **Emily La Pilla**[2], **Lynn From**[12], **Klaus J. Busam**[2], **Anne E. Cust**[5], **David W. Ollila**[1], **Colin B. Begg**[2], **Marianne Berwick**[4], and **Nancy E. Thomas**[1] **on behalf of the GEM Study Group**

[1]Departments of Dermatology and Surgery, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

[2]Departments of Epidemiology and Biostatistics and Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

[3]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

[4]Department of Internal Medicine, University of New Mexico Cancer Center, University of New Mexico, Albuquerque, NM, USA

[5]Sydney School of Public Health, University of Sydney, Sydney, New South Wales, Australia

[6]Department of Epidemiology, University of California, Irvine, California, USA

[7]USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, USA

[8]Cancer Care Ontario, Toronto, Ontario, Canada

[9]British Columbia Cancer Agency, Vancouver, British Columbia, Canada

[10]Piedmont Cancer Registry, Centre for Epidemiology and Prevention in Oncology in Piedmont, Turin, Italy

[11]The George Institute for Global Health, Oxford Martin School, & Nuffield Department of Population Health, Oxford University, United Kingdom

[12]Women's College Hospital, Toronto, Ontario, Canada

Abstract

Recent studies including genome-wide association studies have identified several putative low-penetrance susceptibility loci for melanoma. We sought to determine their generalizability to genetic predisposition for multiple primary melanoma in the international population-based Genes, Environment, and Melanoma (GEM) Study. GEM is a case-control study of 1,206 incident cases

---

Corresponding author: Nancy E. Thomas, MD PhD, Department of Dermatology, University of North Carolina, 405 Mary Ellen Jones Building, CB#7287, Chapel Hill, NC 27599. Phone: (919) 966-0785; Fax: (919) 966-6460; nthomas@med.unc.edu.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of multiple primary melanoma and 2,469 incident first primary melanoma participants as the control group. We investigated the odds of developing multiple primary melanoma for 47 single nucleotide polymorphisms (SNP) from 21 distinct genetic regions previously reported to be associated with melanoma. ORs and 95% CIs were determined using logistic regression models adjusted for baseline features (age, sex, age by sex interaction, and study center). We investigated univariable models and built multivariable models to assess independent effects of SNPs. Eleven SNPs in 6 gene neighborhoods (*TERT/CLPTM1L, TYRP1*, *MTAP*, *TYR, NCOA6*, and *MX2*) and a *PARP1* haplotype were associated with multiple primary melanoma. In a multivariable model that included only the most statistically significant findings from univariable modeling and adjusted for pigmentary phenotype, back nevi, and baseline features, we found *TERT/CLPTM1L* rs401681 ($P = 0.004$), *TYRP1* rs2733832 ($P = 0.006$), *MTAP* rs1335510 ($P = 0.0005$), *TYR* rs10830253 ($P = 0.003$), and *MX*2 rs45430 ($P = 0.008$) to be significantly associated with multiple primary melanoma while *NCOA6* rs4911442 approached significance ($P = 0.06$). The GEM study provides additional evidence for the relevance of these genetic regions to melanoma risk and estimates the magnitude of the observed genetic effect on development of subsequent primary melanoma.

Keywords

Melanoma; risk; population-based; genotype; haplotype; single nucleotide polymorphism

Introduction

Clinically, melanoma is one of a small group of cancers where patients are at increased risk of potentially life-threatening subsequent primaries (1, 2) but the underlying genetic predispositions to multiple primaries are relatively unexplored. Recent genome wide association studies (GWAS) and candidate pathways studies have identified several low-penetrant genetic variants associated with cutaneous melanoma (3, 4). The majority of these variants are in gene regions associated with fair pigmentation, such as *TYRP1, TYR, HERC2/OCA2, SLC45A2,* and *ASIP*; nevi, such as *PLA2G6, MTAP,* and *NID1*; or both, such as *IRF4* (4–12). More recent GWAS have identified melanoma risk-associated variants in genes, including *ATM, MX2, PARP1, ARNT,* and *CASP8*, which may not be associated with phenotypic risk (8, 13). However, the risk associated with these low-penetrant genetic variants in relation to multiple primary melanomas has rarely been evaluated.

We studied these variants in the Genes, Environment and Melanoma (GEM) Study, a large, international population-based case-control study in which the ‘cases’ are patients with multiple primary melanoma (MPM) and the ‘controls’ are patients with single primary melanoma (SPM) (14, 15). Participants’ germline DNAs were genotyped for 47 polymorphisms from 21 distinct genomic regions. We compared the odds of carrying the genotypes and haplotypes in MPM relative to SPM patients in univariable and multivariable analyses and assessed effect modification.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Materials and Methods

Study Population

The GEM Study is a population-based case-control study that enrolled 1,206 cases diagnosed with MPM (a second or higher order invasive or *in situ* primary melanoma) between 1998 and 2003 and 2,469 controls diagnosed with invasive SPM in 2000. *In situ* melanomas were eligible as MPM in order to take into account surveillance when the patient had a previous invasive melanoma. Patients were recruited from eight population-based cancer registries in the United States (New Jersey, North Carolina, California), Australia (New South Wales, Tasmania), Canada (Ontario, British Columbia), and Italy (Turin), and one hospital center in Michigan. GEM recruitment procedures and data collection have been described (14, 15). The Institutional Review Boards of all participating institutions approved the protocol; informed consent was obtained from each participant.

Demographic and melanoma risk factors, including hair and eye color, ability to tan, and number of back nevi, were collected from telephone interview and self-administered questionnaire. Using a glossy-colored guide to aid in differentiating between nevi and other skin lesions, subjects had the nevi on their backs counted by a family member or friend; and back nevi counts were categorized as 0–10 or >10 for this article. Back nevus counts were significantly correlated with whole-body nevus diagrams in GEM (data not shown). A phenotypic index variable was derived from additively combining: hair color (black or dark brown=0; light brown or blond=1; red=2), eye color (black or brown=0; green, grey, or hazel=1; blue=2), and ability to tan in response to sun exposure (deeply or moderately=0; occasionally or none=1). Those with index scores of 0 or 1 were defined as very low/low, 2 as medium low, 3 as medium high, and 4 or 5 as high/very high risk.

Genotyping

DNA was collected from buccal swab kits. Single nucleotide polymorphisms (SNPs) were genotyped using the MassArray iPLEX platform (Sequenom Inc, San Diego, CA) with quality control measures as previously reported (16). Two SNPs of interest were not compatible with the Sequenom design, and proxy SNPs ($r^2 > 0.95$) were chosen (1000 Genomes, CEU population; Proxy SNP; Broad Institute).

Statistical Analyses

Logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for each SNP assuming an additive model of inheritance of the variant allele. All models were adjusted for baseline features: age, sex, an age by sex interaction, and study center. For each locus with multiple associated SNPs, we applied stepwise logistic regression to determine the SNP with the strongest association from among the significantly associated SNPs, keeping baseline variables fixed.

For the genes with at least two SNPs genotyped, we determined their haplotype blocks using the Haploview software algorithm (17) based on the pair-wise linkage disequilibrium information of the GEM population in combination with the HapMap CEU population (18). Within each haplotype block, we inferred the haplotypes in terms of probabilities for each

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

individual from the SNP genotype input data using the PHASE algorithm, a Bayesian method in which the prior was chosen to approximate the coalescent process (19). For each haplotype block, the haplotype associations with MPM were assessed through haplotype trend regressions (HTR) (20). The HTR method effectively took into account the haplotype phase uncertainty and reduced bias by incorporating the inferred individual haplotype probabilities as the predictor variables in the regression models. Haplotypes with low estimated frequencies (< 0.01) were grouped together, reducing the number of haplotype categories and increasing the efficiency and power of haplotype analysis. Each haplotype or grouped rare haplotypes were then compared to the most common haplotypes in our study population.

Genotype and haplotype associations with phenotypic index were estimated using multinomial models and with back nevi using logistic regression models. In subsequent analyses, we limited the participants to those with no missing data for phenotypic index, back nevus counts, genotypes, and haplotypes of interest. Baseline models for genotypes and haplotypes were adjusted for baseline features; we then also adjusted the models for phenotypic index and back nevi; and finally also included all genotypes and haplotypes of interest in a multivariable model. Further, in exploratory stratified analyses, we assessed effect measure modification by phenotypic index and back nevus counts. The likelihood ratio test was used to test interactions, comparing models with main effects to models with main effects and interaction terms. All statistical tests were two-sided with $P < 0.05$ considered statistically significant. All data were analyzed using R (http://www.r-project.org/) or SAS 9.3 (Cary, NC) programs.

Results

The SPM and MPM patients' age, sex, race, number of back nevi, phenotypic index, and tumors' Breslow thicknesses are in Table S1. Twelve non-Caucasian patients were excluded from analyses. Forty-seven SNPs within 21 genetic loci previously reported to be association with melanoma were genotyped. SNP locations, minor allele frequencies, numbers of cases and controls genotyped, and literature references are in Table S2. Proxy SNPs rs6735656 and rs12278954 were used, respectively, for *CASP8* rs10931936 and *ATM* rs1801516 identified by Barrett et al. (8).

Eleven SNPs in 6 gene neighborhoods (*TERT/CLPTM1L*, *TYRP1*, *MTAP*, *TYR*, *NCOA6*, and *MX2*) were significantly ($P < 0.05$) associated with MPM compared to SPM using additive models adjusted for baseline features (Table 1). The *MTAP* and *TYR* loci each had more than one significantly associated SNP. *MTAP* rs1335510 and *TYR* rs10830253 were brought forward for subsequent analyses because they each were the only SNP that remained in the stepwise logistic regression model for their locus.

Of the haplotypes examined (Tables 2 and S3), a *PARP1* haplotype (rs3219090, rs2695238) was significantly ($P = 0.03$) associated with MPM, as were haplotypes in *MTAP* and *TYR*, when adjusting for baseline features. However the statistical significance of the *MTAP* and *TYR* haplotype associations with MPM were weaker than the respective single *MTAP*

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

rs1335510 and *TYR* rs10830253 SNP associations (Table S3). Thus, only the *PARP1* haplotype was selected for further analysis.

Several of the MPM-associated genotypes were associated with phenotypic index or back nevus counts (Table S4), indicating that these SNPs are correlated with these phenotypes and may increase risk of MPM via these phenotypes, which are known melanoma risk factors.

When limiting the dataset to patients with no missing data for genotypes, haplotype, or traits of interest (Table 3), the *TERT/CLPTM1L, TYRP1*, *MTAP*, *TYR, NCOA6,* and *MX2* genotypes, but not the *PARP1* haplotype (*P* = 0.14), remained significantly associated with MPM after adjusting for baseline features. After additionally adjusting for phenotypic index and back nevi, the ORs did not appreciably change; although, the association with *NCOA6* rs4911442 became insignificant (*P* = 0.07). In a multivariable model further adjusting for genotypes and the *PARP1* haplotype, the *TERT/CLPTM1L, TYRP1*, *MTAP*, *TYR,* and *MX2* genotypes remained significant, but the *NCOA6* genotype (*P* = 0.06) and *PARP1* haplotype (*P* = 0.22) did not; none of the ORs appreciably changed.

In an exploratory stratified analysis adjusted for baseline features, no evidence was found of effect modification by phenotypic index or back nevus counts on the association of genotypes with MPM (Table S5). However, there was evidence of effect modification by back nevi, but not phenotypic index, on the association between the *PARP1* haplotype and MPM (*P* for interaction = 0.01). The *PARP1* haplotype AG was negatively associated (*P* = 0.02) with MPM when 0–10 back nevi were present, while both the AG (*P* = 0.03) and AC (*P* = 0.01) haplotypes were negatively associated with MPM when >10 back nevi were present.

Discussion

In the international GEM study, we found that SNPs in *TERT/CLPTM1L, TYRP1*, *MTAP*, *TYR, NCOA6*, and *MX2* and a *PARP1* haplotype were associated with the occurrence of MPM. *TERT/CLPTM1L* rs401681, *TYRP1* rs1408799, *MTAP* rs1335510, *TYR* rs10830253, and *MX*2 rs45430 were associated with MPM independently of each other and of phenotypic index and back nevi. *NCOA6* rs4911442 and the *PARP1* haplotype were not significant in the multivariable model, possibly as a result of diminished statistical power as there was little change in the odds ratios. There was no evidence for effect modification of SNP associations with MPM by patient phenotype; however, back nevi did modify the association of the *PARP1* haplotype with MPM.

The single SNP associations reported in GEM are in the same direction as those reported in the literature (Table S2). In a recent large meta-analysis, Chatzinasiou et al. found variants in 8 of the 21 low-penetrant loci examined in our study to have strong epidemiological credibility (Venice criteria overall grade, A) as associated with melanoma, although this study did not specify whether the associations were specific to MPM, SPM or both (21). Variants in each of these loci reached significance in our study except for *PIGU* rs910873 (*P* = 0.07), *MYH7B* rs1885120 (*P* = 0.11) and *SLC45A2* rs16891982 (*P* = 0.14), the ORs of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

which were in the same direction as previously reported. We are not aware of another group examining the *PARP1* rs3219090, rs2695238 haplotype. Pena-Chilet et al. (22) found a similar trend towards protection from melanoma with a *PARP1* haplotype containing the minor alleles of rs1136410 and rs3219090.

We know of only one other study addressing associations with MPM of common genetic variants in the loci discussed here. Helsing et al. (23) found no association of *ASIP* rs1015362 and rs4911414, *TYR* rs1126809, and *TYRP1* rs1408799 with MPM in patients identified through the Norwegian Cancer Registry compared to melanoma-free blood donors. Although this design differs from GEM, we also found no association of *ASIP* rs4911414 and *TYRP1* rs1408799 with MPM. We did not genotype *ASIP* rs1015362 and *TYR* rs1126809.

Strengths of our study include its large size, population-based case ascertainment, homogeneous questionnaire administration with respect to cases and controls, phenotypic trait adjustments, multivariable model, and examination of risk stratified by phenotypic traits. There may be a tendency for effect estimates of individual risk factors to be attenuated in our high baseline risk population (15). As evidence, several genotypes previously reported as associated with melanoma risk (*PARP1* rs3219090, *CASP8* rs13016963, *TYRP1* rs2733832, and *PIGU* rs910873) had borderline associations ($0.10 < P$ 0.05) in the same direction as the literature in GEM. However, the GEM study estimates are more relevant for survivors and their risk of subsequent melanoma than studies investigating lower risk populations. A limitation is that GEM may not have had sufficient power to detect associations of SNPs with lower minor allele frequencies (e.g. *SLC45A2* rs16891982, MAF=0.017).

Subsequent melanomas are a major problem for melanoma patients but few studies have explored their genetic predisposition. Our results provide evidence that several putative low-penetrance susceptibility loci for melanoma are generalizable to risk of subsequent melanoma. Also, validation of genetic associations in the large international population-based GEM study adds further credibility that these loci are melanoma risk-associated. Knowledge of genetic risk factors for subsequent melanoma could inform screening algorithms, future risk estimation modeling, and future prevention studies for melanoma survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: National Cancer Institute (NCI) grants R01CA112243 (N.E. Thomas), R01CA112524 (M. Berwick), R01CA112243-05S1 (N.E. Thomas), R01CA112524-05S2 (M. Berwick), CA098438 (C.B. Begg), U01CA83180 (M. Berwick), R33CA10704339 (N.E. Thomas), and P30CA016086 (S.H. Earp), P30CA014089 (S.B. Gruber), P30CA008748 (C. Thompson); National Institute of Environmental Health Sciences (P30ES010126 (J. Swenberg)); University of Sydney Medical Foundation Program grant (B.K. Armstrong); Michael Smith Foundation for Health Research Infrastructure Award (R,P. Gallagher).

The study was conducted by The GEM Study Group: Coordinating Center, Memorial Sloan-Kettering Cancer Center, New York, NY: Marianne Berwick, M.P.H., Ph.D. (Principal Investigator (PI), currently at the University of New Mexico), Colin B. Begg, Ph.D. (co-PI), Irene Orlow, Ph.D. (co-Investigator), Klaus J. Busam, M.D. (Dermatopathologist), Anne S. Reiner, M.P.H. (Biostatistician), Pampa Roy, Ph.D. (Laboratory Technician), Ajay Sharma, M.S. (Laboratory Technician), Emily La Pilla (Laboratory Technician). University of New Mexico, Albuquerque: Marianne Berwick, M.P.H., Ph.D. (PI), Li Luo, Ph.D. (Biostatistician), Kirsten White, MSc (Laboratory Manager), Susan Paine, M.P.H. (Data Manager). Study centers included the following: The University of Sydney and The Cancer Council New South Wales, Sydney, Australia: Bruce K. Armstrong M.B.B.S.; D.Phil., (PI), Anne Kricker, Ph.D. (co-PI), Anne E. Cust, Ph.D. (co-Investigator); Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia: Alison Venn, Ph.D. (current PI), Terence Dwyer, M.D. (PI, currently at University of Oxford, United Kingdom), Paul Tucker, M.D. (Dermatopathologist); British Columbia Cancer Research Centre, Vancouver, Canada: Richard P. Gallagher, M.A. (PI), Donna Kan (Coordinator); Cancer Care Ontario, Toronto, Canada: Loraine D. Marrett, Ph.D. (PI), Elizabeth Theis, M.Sc. (co-Investigator), Lynn From, M.D. (Dermatopathologist); CPO, Center for Cancer Prevention, Torino, Italy: Roberto Zanetti, M.D (PI), Stefano Rosso, M.D., M.Sc. (coPI); University of California, Irvine, CA: Hoda Anton-Culver, Ph.D. (PI), Argyrios Ziogas, Ph.D. (Statistician); University of Michigan, Ann Arbor, MI: University of Michigan, Ann Arbor: Stephen B. Gruber, M.D., M.P.H., Ph.D. (PI, currently at University of Southern California, Los Angeles, CA), Timothy Johnson, M.D. (Director of Melanoma Program), Duveen Sturgeon, M.S.N. (co-Investigator, joint at USC-University of Michigan); University of North Carolina, Chapel Hill, NC: Nancy E. Thomas, M.D., Ph.D. (PI), Robert C. Millikan, Ph.D. (previous PI, deceased), David W. Ollila, M.D. (co-Investigator), Kathleen Conway, Ph.D. (co-Investigator), Pamela A. Groben, M.D. (Dermatopathologist), Sharon N. Edmiston, B.A. (Research Analyst), Honglin Hao (Laboratory Specialist), Eloise Parrish, MSPH (Laboratory Specialist), David C. Gibbs, B.S. (Research Assistant), Jill S. Frank, M.S. (Research Assistant), Jennifer I. Bramson (Research Assistant); University of Pennsylvania, Philadelphia, PA: Timothy R. Rebbeck, Ph.D. (PI), Peter A. Kanetsky, M.P.H., Ph.D. (co-Investigator, currently at H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida); UV data consultants: Julia Lee Taylor, Ph.D. and Sasha Madronich, Ph.D., National Centre for Atmospheric Research, Boulder, CO.

References

1. Ferrone CR, Ben Porat L, Panageas KS, Berwick M, Halpern AC, Patel A, et al. Clinicopathological features of and risk factors for multiple primary melanomas. JAMA. 2005; 294:1647–54. [PubMed: 16204664]
2. Uliasz A, Lebwohl M. Patient education and regular surveillance results in earlier diagnosis of second primary melanoma. Int J Dermatol. 2007; 46:575–7. [PubMed: 17550554]
3. Law MH, MacGregor S, Hayward NK. Melanoma genetics: recent findings take us beyond well-traveled pathways. J Invest Dermatol. 2012; 132:1763–74. [PubMed: 22475760]
4. Gerstenblith MR, Shi J, Landi MT. Genome-wide association studies of pigmentation and skin cancer: a review and meta-analysis. Pigment cell & melanoma research. 2010; 23:587–606. [PubMed: 20546537]
5. Gudbjartsson DF, Sulem P, Stacey SN, Goldstein AM, Rafnar T, Sigurgeirsson B, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet. 2008; 40:886–91. [PubMed: 18488027]
6. Bishop DT, Demenais F, Iles MM, Harland M, Taylor JC, Corda E, et al. Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet. 2009; 41:920–5. [PubMed: 19578364]
7. Nan H, Xu M, Zhang J, Zhang M, Kraft P, Qureshi AA, et al. Genome-wide association study identifies nidogen 1 (NID1) as a susceptibility locus to cutaneous nevi and melanoma risk. Hum Mol Genet. 2011; 20:2673–9. [PubMed: 21478494]
8. Barrett JH, Iles MM, Harland M, Taylor JC, Aitken JF, Andresen PA, et al. Genome-wide association study identifies three new melanoma susceptibility loci. Nat Genet. 2011; 43:1108–13. [PubMed: 21983787]
9. Amos CI, Wang LE, Lee JE, Gershenwald JE, Chen WV, Fang S, et al. Genome-wide association study identifies novel loci predisposing to cutaneous melanoma. Hum Mol Genet. 2011; 20:5012–23. [PubMed: 21926416]
10. Jannot AS, Meziani R, Bertrand G, Gerard B, Descamps V, Archimbaud A, et al. Allele variations in the OCA2 gene (pink-eyed-dilution locus) are associated with genetic susceptibility to melanoma. European journal of human genetics: EJHG. 2005; 13:913–20. [PubMed: 15889046]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

11. Zhang W, Chen Y, Yang X, Fan J, Mi X, Wang J, et al. Functional haplotypes of the hTERT gene, leukocyte telomere length shortening, and the risk of peripheral arterial disease. PLoS One. 2012; 7:e47029. [PubMed: 23082138]
12. Fernandez LP, Milne RL, Pita G, Aviles JA, Lazaro P, Benitez J, et al. SLC45A2: a novel malignant melanoma-associated gene. Hum Mutat. 2008; 29:1161–7. [PubMed: 18563784]
13. Macgregor S, Montgomery GW, Liu JZ, Zhao ZZ, Henders AK, Stark M, et al. Genome-wide association study identifies a new melanoma susceptibility locus at 1q21.3. Nat Genet. 2011; 43:1114–8. [PubMed: 21983785]
14. Millikan RC, Hummer A, Begg C, Player J, de Cotret AR, Winkel S, et al. Polymorphisms in nucleotide excision repair genes and risk of multiple primary melanoma: the Genes Environment and Melanoma Study. Carcinogenesis. 2006; 27:610–8. [PubMed: 16258177]
15. Begg CB, Hummer AJ, Mujumdar U, Armstrong BK, Kricker A, Marrett LD, et al. A design for cancer case-control studies using only incident cases: experience with the GEM study of melanoma. Int J Epidemiol. 2006; 35:756–64. [PubMed: 16556646]
16. Orlow I, Roy P, Reiner AS, Yoo S, Patel H, Paine S, et al. Vitamin D receptor polymorphisms in patients with cutaneous melanoma. Int J Cancer. 2012; 130:405–18. [PubMed: 21365644]
17. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005; 21:263–5. [PubMed: 15297300]
18. International HapMap C. The International HapMap Project. Nature. 2003; 426:789–96. [PubMed: 14685227]
19. Stephens M, Donnelly P. A comparison of bayesian methods for haplotype reconstruction from population genotype data. Am J Hum Genet. 2003; 73:1162–9. [PubMed: 14574645]
20. Zaykin DV, Westfall PH, Young SS, Karnoub MA, Wagner MJ, Ehm MG. Testing association of statistically inferred haplotypes with discrete and continuous traits in samples of unrelated individuals. Human heredity. 2002; 53:79–91. [PubMed: 12037407]
21. Chatzinasiou F, Lill CM, Kypreou K, Stefanaki I, Nicolaou V, Spyrou G, et al. Comprehensive field synopsis and systematic meta-analyses of genetic association studies in cutaneous melanoma. J Natl Cancer Inst. 2011; 103:1227–35. [PubMed: 21693730]
22. Pena-Chilet M, Blanquer-Maceiras M, Ibarrola-Villava M, Martinez-Cadenas C, Martin-Gonzalez M, Gomez-Fernandez C, et al. Genetic variants in PARP1 (rs3219090) and IRF4 (rs12203592) genes associated with melanoma susceptibility in a Spanish population. BMC Cancer. 2013; 13:160. [PubMed: 23537197]
23. Helsing P, Nymoen DA, Rootwelt H, Vardal M, Akslen LA, Molven A, et al. MC1R, ASIP, TYR, and TYRP1 gene variants in a population-based series of multiple primary melanomas. Genes Chromosomes Cancer. 2012; 51:654–61. [PubMed: 22447455]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Association of genotypes with MPM (N = 1,206) compared with SPM (N = 2,469) in the GEM Study

				Additive Model	
Chromosome	**Gene neighborhood**	**SNP**	**a/A**	**Per allele OR (95% CI)[a]**	***P* value**
1	*ARNT*	rs7412746	C/T	0.97 (0.87–1.08)	0.56
1	*PARP1*	rs3219090	A/G	0.90 (0.80–1.01)	0.07
1	*PARP1*	rs2695238	C/G	0.96 (0.85–1.07)	0.43
1	*NID1*	rs3768080	G/A	0.94 (0.85–1.05)	0.25
1	*NID1*	rs10754833	C/T	0.93 (0.84–1.04)	0.20
2	*CASP8*	rs6735656[b]	G/T	1.08 (0.96–1.22)	0.21
2	*CASP8*	rs13016963	A/G	1.10 (0.99–1.22)	0.09
5	*TERT*	rs2242652	T/C	1.04 (0.91–1.18)	0.60
5	*TERT*	rs2853676	A/G	1.07 (0.95–1.19)	0.28
5	*TERT*	rs13356727	G/A	1.10 (0.98–1.22)	0.10
5	*TERT;CLPTM1L*	rs4975616	G/A	1.06 (0.94–1.18)	0.34
5	*TERT;CLPTM1L*	rs401681	T/C	**1.14 (1.02–1.26)**	**0.02**
5	*SLC45A2*	rs16891982	C/G	0.71 (0.45–1.12)	0.14
5	*SLC45A2*	rs35391	T/C	0.70 (0.39–1.28)	0.25
5	*SLC45A2*	rs26722	T/C	0.66 (0.36–1.23)	0.19
5	*SLC45A2*	rs13289	G/C	0.99 (0.88–1.10)	0.81
6	*IRF4*	rs12203592	T/C	1.10 (0.97–1.24)	0.14
6	*IRF4*	rs872071	A/G	0.96 (0.86–1.07)	0.43
9	*TYRP1*	rs1408799	T/C	0.90 (0.80–1.01)	0.07
9	*TYRP1*	rs2733832	C/T	**0.87 (0.78–0.97)**	**0.01**
9	*MTAP*	rs2218220	T/C	**0.88 (0.79–0.98)**	**0.02**
9	*MTAP*	rs1335510[d]	G/T	**0.82 (0.73–0.91)**	**0.0003**
9	*MTAP*	rs7023329	G/A	**0.87 (0.78–0.96)**	**0.008**
9	*MTAP*	rs10811629	G/A	**0.85 (0.76–0.94)**	**0.002**
11	*CCND1*	rs11604821	G/A	1.03 (0.92–1.15)	0.64
11	*CCND1*	rs1485993	T/C	1.03 (0.92–1.15)	0.57
11	*CCND1*	rs11263498	T/C	1.01 (0.91–1.13)	0.82

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Chromosome	Gene neighborhood	SNP	a/A	Additive Model	
				Per allele OR (95% CI)[a]	*P* value
11	*TYR*	rs1042602	A/C	0.91 (0.82–1.02)	0.11
11	*TYR*	rs10765198	C/T	**1.22 (1.10–1.36)**	**0.0003**
11	*TYR*	rs1847142	A/G	**1.21 (1.09–1.35)**	**0.0004**
11	*TYR*	rs10830253[d]	G/T	**1.23 (1.10–1.37)**	**0.0002**
11	*ATM*	rs12278954[c]	A/C	0.91 (0.78–1.05)	0.20
15	*OCA2*	rs1800407	A/G	1.10 (0.92–1.32)	0.29
15	*OCA2*	rs1800401	T/C	1.11 (0.86–1.42)	0.43
15	*HERC2*	rs1129038	G/A	0.99 (0.87–1.13)	0.88
15	*HERC2*	rs12913832	A/G	1.00 (0.88–1.13)	0.97
20	*ASIP*	rs17305657	C/T	1.12 (0.95–1.33)	0.18
20	*ASIP*	rs4911414	T/G	1.10 (0.99–1.23)	0.08
20	*PIGU*	rs910873	A/G	1.16 (0.99–1.36)	0.07
20	*PIGU*	rs17305573	C/T	1.15 (0.96–1.36)	0.12
20	*NCOA6*	rs4911442	G/A	**1.19 (1.03–1.38)**	**0.02**
20	*MYH7B*	rs1885120	C/G	1.15 (0.97–1.36)	0.11
20	*LOC647979*	rs1204552	A/T	1.10 (0.91–1.32)	0.32
21	*MX2*	rs45430	G/A	**0.87 (0.77–0.97)**	**0.01**
22	*PLA2G6*	rs6001027	G/A	1.03 (0.92–1.16)	0.61
22	*PLA2G6*	rs132985	T/C	0.96 (0.87–1.07)	0.51
22	*PLA2G6*	rs738322	G/A	0.95 (0.85–1.06)	0.35

NOTE: Limited to Caucasians. Bold type indicates P values < 0.05.

Abbreviations: a, minor allele; A, major allele.

[a] Adjusted for age at diagnosis, sex, age by sex, and study center.

[b] rs6735656 is a proxy for rs10931936 (r^2=0.965).

[c] rs12278954 is a proxy for rs1801516 (r^2=1.00).

[d] The *MTAP* and *TYR* loci each had more than one SNP with a significant association (P value<.05). SNPs with the strongest association in stepwise logistic regression models are noted.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Association of a *PARP1* haplotype with multiple primary melanoma in the GEM study

Gene Haplotype	SNP 1	SNP 2	Haplotype frequency	OR (95% CI)[a, b]	Global *P* value
PARP1: rs3219090 (SNP1), rs2695238 (SNP2)					
1	G	G	0.672	1.00 (reference)	**0.03**
2	A	C	0.300	0.93 (0.83–1.05)	
3	A	G	0.017	0.53 (0.34–0.81)	
4	G	C	0.011	0.93 (0.56–1.56)	

[a] The reference category is the haplotype with the highest frequency.

[b] Adjusted for age, sex, age by sex, and study center.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Genotype and haplotype associations with MPM (N = 1,074) compared with SPM (N = 2,137) for participants with no missing data in the GEM Study

Gene neighborhood	SNP(s)	Model	OR (95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value	OR (95% CI)[c]	*P* value
<u>*Genotypes*</u>								
TERT;CLPTM1L	rs401681	ADD	1.21 (1.08–1.35)	0.001	1.20 (1.07–1.35)	0.0006	1.19 (1.06–1.33)	0.004
TYRP1	rs2733832	ADD	0.83 (0.74–0.94)	0.0020	0.85 (0.75–0.95)	0.0009	0.85 (0.76–0.96)	0.006
MTAP	rs1335510	ADD	0.80 (0.71–0.89)	0.00010	0.80 (0.71–0.90)	0.0004	0.81 (0.72–0.91)	0.0005
TYR	rs10830253	ADD	1.23 (1.09–1.38)	0.0005	1.19 (1.06–1.33)	0.003	1.20 (1.06–1.34)	0.003
NCOA6	rs4911442	ADD	1.18 (1.01–1.38)	0.03	1.16 (0.99–1.35)	0.07	1.16 (0.99–1.35)	0.06
MX2	rs45430	ADD	0.87 (0.77–0.97)	0.02	0.87 (0.77–0.98)	0.02	0.85 (0.75–0.96)	0.008
<u>*Haplotype*</u>								
PARP1	rs3219090; rs2695238	AC[d]	0.97 (0.85–1.09)		0.99 (0.87–1.12)		0.99 (0.88–1.13)	
PARP1	rs3219090; rs2695238	AG[d]	0.52 (0.29–0.92)	0.14	0.55 (0.31–0.97)	0.22	0.55 (0.31–0.97)	0.22
PARP1	rs3219090; rs2695238	GC[d]	1.13 (0.64–1.97)		1.09 (0.62–1.91)		1.10 (0.62–1.95)	

NOTE: Participants were included who had no missing data for phenotypic index, back nevus counts, or genotypes or haplotyes included in the table.

Abbreviations: ADD; additive.

[a] Adjusted for age at diagnosis, sex, age by sex, study center.

[b] Adjusted for age at diagnosis, sex, age by sex, study center, phenotypic index, and back nevi (0–10, >10).

[c] Adjusted for age at diagnosis, sex, age by sex, study center, phenotypic index, back nevi (0–10, >10), and all genotypes/haplotypes in the table.

[d] Reference category determined by the haplotype with the highest frequency.