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LETTER TO THE EDITOR

Using a genome-wide association (GWA) study of familial melanoma pedigrees (excluding CDKN2A+ pedigrees) and genetically matched controls, Teerlink et al. identified three single nucleotide polymorphisms (SNPs) in close proximity and high linkage disequilibrium (LD) in the 10q25.1 region (rs17119434, rs17119461, and rs17119490) associated with melanoma (Teerlink et al., 2012). These SNPs had low minor allele frequencies (MAFs) of 0.005 among controls utilized by Teerlink et al. (Teerlink et al., 2012), making detection of associations via traditional case-control methods challenging. We sought to confirm the relationship between these SNPs and melanoma utilizing the population-based Genes, Environment, and Melanoma (GEM) Study, designed to detect associations of rare genetic variants with melanoma (Begg et al., 2006).

The GEM Study is an international population-based case-control study of melanoma in which controls are those diagnosed with an invasive single primary melanoma (SPM) and cases are those diagnosed with multiple primary melanoma (MPM) ascertained between 1998 and 2003 in Australia, Canada, Italy, and the United States (Begg et al., 2006, Millikan et al., 2006). Per GEM protocol, in situ melanomas were considered to be incident melanomas if patients had prior invasive melanomas, in view of the careful surveillance that such patients would have received. The institutional review board at each participating recruitment site approved the study. Participants provided written informed consent. Patient characteristics were collected from phone interviews and self-completed questionnaires. DNA was collected from buccal brushes (Begg et al., 2005). SNPs were genotyped using the MassArray iPLEX platform (Agena Bioscience) with quality control measures described previously (Orlow et al., 2016). The tumor characteristics were obtained from the diagnostic pathology reports or centralized pathology review as previously described (Kricker et al., 2013, Taylor et al., 2015).

Logistic regression models estimated the odds ratios (ORs) and 95% confidence intervals (95% CIs) for each SNP adjusted for study features (age, sex, and study center) and an age by sex interaction. Participants with SPM who developed MPM during the ascertainment period (n=96) were included as both cases and controls. All tests were two-sided with P < 0.05 considered significant. All data were analyzed using Stata 15.

The demographics and tumor characteristics of the 2458 controls and 1205 cases in GEM are in Supplementary Table S1 online, excluding twelve participants not of European descent. The SNPs were in high LD with each other: D’= 0.92 for rs17119434 and rs17119461, 0.95 for rs17119434 and rs17119490, and 1.00 for rs17119461 and rs17119490. MAFs were between 0.012–0.013 for cases and 0.008–0.009 for controls, and the genotype frequency of homozygous minor allele carriage was zero for all three SNPs. The associations of these SNPs with MPM compared to SPM are in Table 1, and reported ORs reflect the comparison of heterozygous versus homozygous major allele genotypes.
SNPs rs17119461 and rs17119490 were significantly associated with MPM ($P < 0.05$), and rs17119434 approached significance ($P < 0.08$). rs17119461 had the strongest independent association with MPM ($OR = 1.77, 95\% CI = 1.06–2.97$).

To our knowledge, we provide the first confirmation of associations between SNPs in the 10q25.1 region and melanoma occurrence. The ORs (1.6–1.8) for MPM versus SPM were lower in GEM than the ORs (6.8–8.4) for familial melanoma cases versus genetically matched controls in Teerlink et al. As previously found for CDKN2A mutations, melanoma-risk variants in the general population can have a lower relative risk of melanoma than in a high-risk population (Begg et al., 2005). Teerlink et al. proposed a common ancestor to explain the high risk related to the 10q25.1 SNPs among their familial melanoma cases. A more plausible explanation, perhaps, is that the Teerlink et al. estimate is simply an overestimate, a common feature of many initial epidemiologic discoveries (Xiao and Boehnke, 2009). An advantage of the GEM study is that low frequency genetic variants are more likely to be observable in SPMs than normal controls (Begg et al., 2005). Further, the ORs found in the GEM study are more likely to represent the impact of these SNPs in the general population than the ORs found for multiple case families.

The 10q25.1 gene region lacks genes known to be associated with malignancy. A pseudogene, $YWHAZP5$, is the closest at 65kb away. $SORCS3$ and $SORCS1$ genes, both involved with vacuolar protein production, fall within 1Mb in either direction of the SNPs. Thus, the mechanism for these SNP associations with melanoma risk remains unknown. Notably, rs17119461 and rs17119490 were found to be nominally associated with pancreatic cancer, which shares genetic risk with familial melanoma (Wu et al., 2014).

Some melanoma genetic testing panels for patients meeting specific criteria include intermediate risk variants such as $MITF$ c.952 G>A that have a low MAF (~0.0015) (Delaunay et al., 2017). Thus, if validated in additional studies, rs17119461 may be a potential candidate for genetic testing in populations at high-risk of melanoma. Further, additional studies investigating the mechanism for the 10q25.1 SNP associations with melanoma risk are warranted.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

a      minor allele
A      major allele
Chrom  chromosome
CI      confidence interval
GEM    Genes, Environment, and Melanoma
MAF    minor allele frequency
IQR    interquartile range
LD     linkage disequilibrium

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OR  
odds ratio  
SNP  
single nucleotide polymorphism

References


Table 1.

Associations of genotypes from the 10q25.1 chromosomal region with multiple primary melanoma (n = 1205) compared with single primary melanoma (n = 2458) patients in the GEM Study.\(^1\)

<table>
<thead>
<tr>
<th>SNP (hg19)</th>
<th>MAF</th>
<th>Controls</th>
<th>Cases</th>
<th>Single primary melanoma n = 2458</th>
<th>Multiple primary melanoma n = 1205</th>
<th>Aa versus AA OR (95% CI)(^2)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs17119434 (107,505,161)</td>
<td>A/G</td>
<td>0.009</td>
<td>0.013</td>
<td>73 (3.0)</td>
<td>2344 (95.4)</td>
<td>41 (1.7)</td>
<td>1.59 (0.94–2.67)</td>
</tr>
<tr>
<td>rs17119461 (107,516,352)</td>
<td>T/C</td>
<td>0.009</td>
<td>0.013</td>
<td>64 (2.0)</td>
<td>2353 (95.7)</td>
<td>41 (1.7)</td>
<td>1.77 (1.06–2.97)</td>
</tr>
<tr>
<td>rs17119490 (107,522,927)</td>
<td>G/A</td>
<td>0.008</td>
<td>0.012</td>
<td>84 (3.4)</td>
<td>2334 (95.0)</td>
<td>40 (1.6)</td>
<td>1.70 (1.00–2.88)</td>
</tr>
</tbody>
</table>

Abbreviations: A, major allele; a, minor allele; CI, confidence interval; GEM, Genes Environment and Melanoma; hg19, human genome reference version 19; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism. Bold type font indicates the SNP with the strongest association.

\(^1\)Limited to participants of European origin.

\(^2\)We used logistic regression models to estimate the ORs and 95% CIs adjusted for study features (age at diagnosis (continuous), sex, and study center) and an age by sex interaction. The genotype frequency of homozygous minor allele carriage was zero for all three SNPs, and the ORs reflect the comparison of heterozygous versus homozygous major allele genotypes.