Null Results in Brief

DNA Repair Gene XRCC3 241Met Variant Is Not Associated with Risk of Cutaneous Malignant Melanoma

Zhigang Duan, Hongbing Shen, Jeffrey E. Lee, Jeffrey E. Gershenwald, Merrick I. Ross, Paul F. Mansfield, Madeleine Duvic, Sara S. Strom, Margaret R. Spitz, and Qingyi Wei

Introduction

CMM is the most serious form of skin malignancy, causing 7400 deaths in the United States in 2002. Although CMM etiology remains unclear, sporadic CMM is known to be associated with ionizing radiation, such as UV light, that causes various types of DNA damage. The cellular response to DNA damage includes activation of various DNA repair pathways involving dozens of genes with unique repair functions. Many polymorphisms identified in these genes are thought to modulate individual susceptibility to cancers. One such polymorphism is a sequence variation in exon 7 (C18067T), resulting in an amino acid change at codon 241 (Thr241Met) in XRCC3, a DNA repair gene that codes for a protein involved in the homologous recombinational repair pathway. A recent case-control study from the United Kingdom found that this XRCC3 241Met variant allele was associated with a significantly increased risk of CMM, and therefore we conducted a larger study to replicate this finding.

Materials and Methods

Study Population. All CMM patients were newly diagnosed and histopathologically confirmed untreated incident cases at The University of Texas M.D. Anderson Cancer Center from August 1994 to February 2001. The cancer-free control subjects, who were genetically unrelated to the cases, were recruited from visitors to our institution and frequency-matched to the cases by age (±5 years), sex, and ethnicity. After informed consent was obtained, a blood specimen was collected from each subject.

Genotyping. We designed primers 5′-GCTGTCTCCGGGC-ATGGGCTC-3′ (forward) and 5′-ACGACGCTAGGGTGCA-ACC-3′ (reverse) to amplify a 208-bp fragment. The restriction enzyme NlaIII (New England Biolabs, Beverly, MA) was used to detect this Thr241Met polymorphism (Thr/Thr homozygotes, 208 bp; Thr/Met heterozygotes, 208, 120, and 88 bp; Met/Met homozygotes, 120 and 88 bp). More than 10% of the samples were repeated, and the results were 100% concordant.

Statistical Analysis. The association between XRCC3 genotype and CMM was estimated by computing ORs and 95% CIs from both univariate and multivariate logistic regression analyses using SAS software (Version 8; SAS Institute, Cary, NC).

Results

The 305 cases (52% males) and 319 controls (51% males) were non-Hispanic whites, with no difference in mean age (49.3 years for cases and 51.2 years for controls). The XRCC3 genotype and allele frequencies were not significantly different between cases and controls (P = 0.73 and 0.47, respectively; Table 1), and the genotypes in controls were in Hardy-Weinberg equilibrium (P = 0.88). The frequencies of the XRCC3 variant homozygous genotype (14.1%) and allele (0.389) in controls were consistent with those in a recent United States study of 453 Caucasian controls (15.0% and 0.381, respectively; Ref. 3) and lower than those in a study of 308 Italian controls (17.8% and 0.420, respectively; Ref. 4) but higher than those in a study of 96 Caucasian controls (the study only reported allele frequency, which was 0.33; Ref. 5) and a study by Winsey et al. of 211 Caucasian controls (11% and 0.30, respectively; Ref. 2). Logistic regression analysis indicated that neither the homozygous 241Met/Met (adjusted OR, 0.92; 95% CI, 0.54–1.57) nor 241Thr/Met (adjusted OR, 0.94; 95% CI, 0.65–1.37) genotype was associated with CMM risk.

Discussion

Our data did not provide evidence to support the findings of Winsey et al. (2) that XRCC3 241Met variant was significantly associated with an increased risk of CMM. This discrepancy is likely due to lower frequencies of the XRCC3 variant genotype and allele frequency in the controls of the study of Winsey et al. (2), which represent the lowest frequencies in published data to date. In addition, the study of Winsey et al. (2) investigated polymorphisms of several genes (XRCC1, XPD, ERCC1, and XRCC3) in 125 CMM cases and 211 hospital controls without matching on age and sex, and a positive association found only...
for XRCC3 may be due to chance. We concluded that this Thr241Met polymorphism does not appear to have a major impact, if any, on CMM risk in our study population.

Acknowledgments
We thank Margaret Lung for assistance in recruiting study subjects, Dr. Li-E Wang and Kristina Dahlstrom for technical support, and Joanne Sider for manuscript preparation.

References

Table 1  CMM risk associated with XRCC3 Thr241Met polymorphism

<table>
<thead>
<tr>
<th>XRCC3 genotypes (Thr241Met)</th>
<th>Cases (n = 305)</th>
<th>Controls (n = 319)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Thr/Thr (wild type)</td>
<td>119</td>
<td>39.0</td>
<td>116</td>
<td>36.4</td>
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<tr>
<td>Thr/Met (heterozygous)</td>
<td>148</td>
<td>48.5</td>
<td>158</td>
<td>49.5</td>
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<tr>
<td>Met/Met (variant)</td>
<td>38</td>
<td>12.5</td>
<td>45</td>
<td>14.1</td>
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<tr>
<td>Thr/Met + Met/Met</td>
<td>186</td>
<td>61.0</td>
<td>203</td>
<td>63.6</td>
</tr>
<tr>
<td>Met allele frequency</td>
<td>0.367</td>
<td>0.389</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR was adjusted for age, sex, sunlight exposure, skin type, and family history of skin cancer.*
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