Short Communication

PTPRJ Haplotypes and Colorectal Cancer Risk

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Abstract

Recent studies from mouse mapping studies for cancer susceptibility have successfully led to the identification of a handful of susceptibility genes. Ptprj was identified as a strong candidate gene for mouse locus susceptibility to colorectal cancer 1, and one variant, rs1566734, showed evidence of preferential allelic imbalance in human colorectal tumors. Haplotypes in human PTPRJ have also been associated with protective effects for breast cancer risk. To determine if variants or haplotype in PTPRJ confer protective or risk effects for colorectal cancer (CRC), we genotyped rs1566734 and six additional PTPRJ haplotype tagging single nucleotide polymorphisms (SNP) in CRC cases and controls from the Molecular Epidemiology of Colorectal Cancer study. There was no evidence for cancer risk with rs1566734 in 1,897 cases and 1,954 controls with a homozygote odds ratio of 1.09 and 95% confidence interval of 0.85 to 1.39. The 6 tagging SNPs resulted in 6 main haplotypes (frequencies, >1%). None of the six tagSNPs individually showed significant evidence for risk; however, rs1503185 showed a nonsignificant protective effect. One haplotype was overrepresented in cases compared with controls, corresponding to a 34% increase in risk CRC, but there was no significant difference overall in haplotype frequencies between cases and controls (global test P statistic = 0.19). From this study, we observe no significant increase in risk for human CRC with variants or haplotypes in PTPRJ. Additional studies are warranted to study possible PTPRJ-interacting loci, which are observed with Scc1 in the mouse models for CRC susceptibility. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2782–5)

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States, not including skin cancer. Whereas mutations in genes such as APC, MLH1, MSH2, and MYH confer a high risk of colon cancer and track through families, they only account for ~5% of all CRC cases (1). For individuals in the general population, the risk of developing CRC is due to a combination of environmental factors, such as diet, and low penetrance cancer susceptibility and resistance genes that act in the context of other genetic variants and environmental factors (2). Mouse models of cancer susceptibility are proving useful for the identification of low penetrance cancer susceptibility genes (3, 4). Using mice susceptible to and mice resistant to CRC, Ptprj was identified as a strong candidate gene for Scc1, a colon cancer susceptibility locus (4). Ptprj is a good candidate for a cancer susceptibility gene. It has several functional roles consistent with tumor suppression including inhibition of cell growth, migration, and angiogenesis (5–8). It also has been shown to dephosphorylate a number of tyrosine kinase receptors important in carcinogenesis including PDGFβR, RET, and VEGFR2 (7, 9, 10). PTPRJ also seems to play a role in human CRC. In loss of heterozygosity studies in humans, PTPRJ was deleted in 19 of 39 informative colorectal carcinomas (4). Allele-specific loss of PTPRJ was assessed, and 13 of 16 colon tumors heterozygous for an A1176C (Q276P; rs1566734) polymorphism showed loss of the A allele, suggesting that this variant may be a cancer resistance allele in humans. Other studies have reported PTPRJ loss as an early event in colorectal tumorigenesis. Forty-seven percent of adenomas and 10% of aberrant crypt foci show PTPRJ loss, providing evidence for a role in tumor initiation or promotion (11, 12). PTPRJ is a candidate tumor suppressor gene for other cancer types. Loss of 11p11, the locus harboring PTPRJ, is observed in 50% of lung tumors, 78% of breast tumors, and 38% of thyroid anaplastic carcinomas (4, 13). Based on PTPRJ loss of heterozygosity in breast tumors, PTPRJ haplotype tagging single nucleotide polymorphisms (SNP) were assessed for breast cancer risk in individuals from the United Kingdom. One haplotype showed a protective effect for breast cancer (14). In this study, there was no association for cancer risk with a R326Q variant (rs1503185) that was in 100% linkage disequilibrium with the A1176C allele. The A1176C variant was not directly tested.
Table 1. *PTPRJ A1176C* genotypes and genotype specific risks

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Adjusted/matching</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>None</td>
<td>1,047 (55.2%)</td>
<td>1,094 (56.0%)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>AC</td>
<td>None</td>
<td>701 (36.9%)</td>
<td>717 (36.7%)</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td>CC</td>
<td>None</td>
<td>149 (7.9%)</td>
<td>143 (7.3%)</td>
<td>1.09 (0.85-1.39)</td>
</tr>
<tr>
<td>AC vs AA</td>
<td>Ethnicity, age, first-degree family history</td>
<td>1.02 (0.88-1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs AA</td>
<td>Ethnicity, age, First degree family history</td>
<td>1.03 (0.90-1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>Matched pairs</td>
<td>1.03 (0.90-1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>Matched pairs</td>
<td>1.11 (0.86-1.44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Because *PTPRJ* shows frequent early loss in colon adenomas and aberrant crypt foci and the *PTPRJ A1176C* allele showed preferential allelic loss in colon tumors, we hypothesized that the *A1176C* might function as a low penetrance CRC susceptibility allele. To determine if the *PTPRJ A1176C* contributes to increased CRC risk, we tested this variant in 1,897 incidence cases of CRC and 1,954 controls from the Molecular Epidemiology of Colorectal Cancer study. To further clarify the risk between *PTPRJ* and CRC, we also did haplotype analysis of *PTPRJ* using six tagSNPs.

**Materials and Methods**

The Molecular Epidemiology of Colorectal Cancer study is a population-based, matched case-control study of 1,897 incident CRC cases and 1,954 controls described previously (15, 16). Eligible cases included any person newly diagnosed with CRC between January 1, 1999, and March 31, 2004, from northern Israel. Potential controls were identified from the same region by generating a list of individuals from the Clalit Health Services database, matched with respect to year of birth, sex, clinical code, and Jewish versus non-Jewish ethnicity. Written informed consent was obtained from all study participants. This study was approved by the Institutional Review Boards at the University of Michigan, the Ohio State University, and Carmel Medical Center in Haifa.

The *PTPRJ A1176C* variant and six SNPs described in Lesueur et al. (rs7122335, rs2904315, rs4752894, rs1503185, rs905476, and rs1566729; ref. 14) were genotyped using the ABI PRISM 7900 sequence detection system. χ² tests were used to test Hardy-Weinberg equilibrium in the controls. The genotypic specific colon cancer risks were estimated as odds ratios (OR) with associated 95% confidence intervals (CI) by unconditional logistic regression as implemented in SAS v.9.0. Haplotypes were estimated using the estimation-maximization likelihood method and score statistics calculated for significance as implemented in R using the haplo.stats library (17). Power calculations were completed using a log-additive model (18).

**Results**

We genotyped 1,897 cases and 1,954 controls for the *PTPRJ A1176C* variant. There were no appreciable differences in gender (male cases, 50.8%; male controls, 50.0%), mean age of diagnosis [cases, 70.1 years (±11.8 years); controls, 70.6 years (±11.8 years)] or in Ashkenazi Jewish heritage (cases, 68.9%; controls, 63.3%). There was no deviation of genotype frequencies in controls from those expected under Hardy-Weinberg equilibrium. After adjustment for ethnicity, age, and first-degree family history of CRC, there was no meaningful increased risk of CRC associated with the presence of the *PTPRJ A1176C* variant (homozygote OR, 1.03; 95% CI, 0.90-1.18; homozygotes OR, 1.13; 95% CI, 0.88-1.44; Table 1).

Discussion

This is the first study, to our knowledge, that has tested the *PTPRJ A1176C* variant or tagSNPs in *PTPRJ* for CRC risk. *Ptprj* was identified as a low penetrance CRC cancer resistance allele in mice but had not previously been tested for risk in human CRC populations. In this large case/control population, we saw no evidence for increased CRC risk of the *A1176C* allele or combination of haplotype tagSNPs. These results also do not rule out the possibility that an untagged variant or haplotype

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confers risk, that variants in this gene are involved in epistatic interactions, which confer risk, or that population-specific difference or exposures in this study cohort, which consists of mostly Whites, individuals of Ashkenazi Jewish ancestry, may modify the effects of the PTPRJ A1176C Variant. It is also possible that in a larger study population, the effects of increased risk associated with haplotype geno glm.9 and the protective effect of rs1503185 could be established. Our study has exactly 80% power to detect a relative risk of similar magnitude for CRC to that previously reported for breast cancer, assuming a disease frequency of 6% and allele frequency of 17% for a log-additive model (18). As rs1503185 results in an amino acid substitution (QR326), this variant may have functional significance and therefore warrants further study.

The effects of PTPRJ on CRC risk may be modest or may be dependent on interacting genetic factors because other studies suggest these possibilities. In the crosses that led to the identification of Ptprj as a low penetrance CRC resistance gene, Ptprj interacts with two additional loci to further increase CRC risk (19). Given the mild protective effect seen for PTPRJ in over 4,000 breast cancer cases and controls (OR, 0.81; 95% CI, 0.72-0.92; ref 14) and the results presented here, a more comprehensive understanding of the genetic variability in PTPRJ in light of potential modifying factors, including genetic variation at potential interaction loci, is needed to better understand the cancer risk associated with PTPRJ.

In conclusion, this study showed no significant effect of PTPRJ on CRC risk. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Allan Balmain for thoughtful discussions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Table 3. CRC risks associated with PTPRJ haplotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR (95% CI) frequency cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7122335</td>
<td>0.99 (0.82-1.20) 0.99 (0.62-1.57) 0.98 (0.63-1.54)</td>
</tr>
<tr>
<td>rs2904315</td>
<td>0.87 (0.79-1.04) 1.19 (0.98-1.44) 0.99 (0.72-1.36)</td>
</tr>
<tr>
<td>rs4752894</td>
<td>1.15 (0.93-1.43) 0.90 (0.72-1.13) 0.80 (0.62-1.04)</td>
</tr>
<tr>
<td>rs1503185</td>
<td>0.86 (0.71-1.03) 0.70 (0.41-1.04) 0.63 (0.43-0.93)</td>
</tr>
<tr>
<td>rs905476</td>
<td>0.88 (0.73-1.06) 1.09 (0.91-1.32) 1.46 (0.98-2.16)</td>
</tr>
<tr>
<td>rs1566729</td>
<td>1.06 (0.87-1.30) 0.90 (0.73-1.10) 1.80 (0.92-3.51)</td>
</tr>
</tbody>
</table>

*MAF, minor allele frequency.

Acknowledgments

References


17. Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA. Score tests for association between traits and haplotypes when linkage phase is ambiguous. Am J Hum Genet 2002;70:425–34.


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