Null Results in Brief

MIC1 and IL1RN Genetic Variation and Advanced Prostate Cancer Risk

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Introduction

Recently, polymorphisms in macrophage inhibitory cytokine-1 (MIC1) and interleukin 1 receptor antagonist (IL1RN) were identified to be associated with prostate cancer risk (1-3). MIC-1 is a divergent member of the transforming growth factor-β superfamily of cytokines. In the Cancer Prostate in Sweden study, the nonsynonymous MIC1 H6D polymorphism was associated with a lowered risk of prostate cancer (CG versus CC; odds ratio (OR), 0.85; 95% CI, 0.70-1.04) yet an increased risk of prostate cancer death (CG/GG versus CC; OR, 1.72; 95% CI, 1.06-2.78; ref. 1).

IL1RN inhibits the proinflammatory response of interleukin 1-α and interleukin 1-β cytokines. The IL1RN haplotype (ATGC) was significantly associated with prostate cancer risk in the Cancer Prostate in Sweden study (homozygous carriers versus noncarriers; OR, 1.6; 95% CI, 1.2-2.2), with larger effects observed among advanced disease (homozygous carriers versus noncarriers; OR, 1.8; 95% CI, 1.3-2.5; ref. 3). To further investigate these previous reports, we comprehensively surveyed the common genetic variation of MIC1 and IL1RN and tested whether inherited differences at these loci predispose men to advanced prostate cancer.

Materials and Methods

Study Subjects. This study includes 506 advanced incident prostate cancer cases and 506 controls from the major medical institutions in Cleveland, Ohio. Advanced prostate cancer cases were defined as having either a Gleason score ≥7, tumor-node-metastasis stage ≥T2c, or prostate-specific antigen at diagnosis >10 ng/mL. Controls were frequency matched to prostate cancer cases by age (within 5 years), racial/ethnic group, and medical institution. Detailed information about this study has been reported previously (4). Institutional Review Board approval was obtained from the participating medical institutions, and informed consent was obtained from all study participants.

Genetic Characterization and Tag Single Nucleotide Polymorphism Selection. We determined the genetic structure of MIC1 and IL1RN by using publicly available genotype data from the International HapMap project (5). For MIC1, we evaluated 12 single nucleotide polymorphisms (SNP; minor allele frequency, >5% among Caucasian pedigrees; average density, 1 SNP/477 bps) that spanned ~3 kbs upstream of the transcription start site and ~2 kb downstream of the 3' untranslated region. For IL1RN, we examined 41 SNPs (average density, 1 SNP/440 bps) that spanned ~1 kb upstream and ~700 bps downstream. We did not capture the genetic variation of African populations because our sample size did not have sufficient power for African American–specific analyses.

To capture the common genetic variation for MIC1 and IL1RN, we identified tag SNPs using the Tagger software (6). We selected 6 and 7 tag SNPs for MIC1 and IL1RN, respectively, which had a minimum r2 > 0.8 with the unmeasured SNPs for each gene (Supplementary Table A). For MIC1, we “forced in” the previously associated H6D polymorphism (rs1058587) to be selected as a tag SNP. The 6 tag SNPs for MIC1 and 7 tag SNPs for IL1RN captured all 12 and 41 SNPs, respectively, with an average r2 of 98.8% and 95.9%, respectively.

Genotyping. Genotyping was done by the Taqman allelic discrimination assay. One SNP (rs1058587) could not be assayed by Taqman and was genotyped using the Amplifluor SNPs HT Genotyping system. All assays were read on a 7900HT Sequence Detection System. All assays were undertaken by individuals blinded to case-control status. For MIC1 and IL1RN, the average genotyping success rate was 100% and 99.9%, respectively, and the concordance rate for 2% replicate samples was 100% for both genes. There were no deviations from Hardy-Weinberg equilibrium (P > 0.01).

Statistical Analysis. ORs and 95% CI were estimated by unconditional logistic regression to examine the association between MIC1 and IL1RN SNPs and multimarker haplotypes and prostate cancer risk. We estimated multimarker haplotype frequencies by the expectation-maximization algorithm using the tagSNP software (7). OR estimates were adjusted for the matching variables: age, racial/ethnic group, and medical institution. All reported P values are two sided.

Results

MIC1. For the previously associated H6D polymorphism, the allele frequency among Caucasians (controls/cases, 27.2%/
In this comprehensive evaluation of the \( Pc \) cancer cases and controls were similar (association between the 7 frequency differences > 0.13). There were no significant associations between the \( H6D \) polymorphism and prostate cancer risk (Table 2; Supplementary Table C). There were no significant associations between the five remaining \( MIC1 \) SNPs and prostate cancer risk (Table 1).

**IL1RN.** The allele frequencies for \( IL1RN \) between prostate cancer cases and controls were similar (Ps for allele frequency differences > 0.13). There were no significant association between the 7 \( IL1RN \) tag SNPs and 4 multimarker haplotypes and prostate cancer risk (Table 2; Supplementary Table C).

**Discussion**

In this comprehensive evaluation of the \( MIC1 \) and \( IL1RN \), we found no substantial influence of common genetic variation in these two genes on prostate cancer risk. We did observe a nonsignificant inverse association between the \( MIC1 \) \( H6D \) polymorphism and prostate cancer as seen in the Australian study (1). To further clarify this effect, we genotyped the \( H6D \) polymorphism in a sibling study of 439 prostate cancer cases and 479 unaffected brothers (-90% White, 9% African American, and 1% Asian or Latino; ref. 8). By using a sibling-based design, we exclude the potential of bias due to population stratification as controls and cases were ascertained from the same genetic source. In this sibling study, there was no association between the \( H6D \) polymorphism and prostate cancer risk (CG/CC versus GG; OR, 1.18; 95% CI, 0.82-1.7; \( P = 0.20 \)). A weaker nonsignificant association was seen among Caucasians (CG/CC versus GG; OR, 0.85; 95% CI, 0.66-1.22; \( P = 0.66-1.09 \); data not shown). In contrast to the Swedish study, which used a haplotype tagging approach to capture the genetic variation of the locus from 16 polymorphisms, our study used a tagging approach (6) that reconstructed 41 common polymorphisms across the \( IL1RN \) locus.

In summary, our study does not support the role of common genetic variation at \( MIC1 \) in prostate cancer susceptibility. We had 80% power to detect a minimum OR of 1.48 for a SNP with a 10% allele frequency (\( \alpha = 0.05 \); two-sided hypothesis test; log-linear model; ref. 9). Future studies should investigate whether other inflammatory genes or the combined effects of several genes in the inflammatory pathway are more likely to influence prostate cancer risk.

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References


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