Original Article
The rs20541 G>A polymorphism in the interleukin 13 gene is associated with a decreased risk of renal cell carcinoma in a Chinese population

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Abstract: Renal cell carcinoma (RCC) has multifactorial etiology and is the most common form (≥85%) of renal cancer. We conducted a hospital-based case-control study of 132 RCC cases and 145 matched controls to assess the functional genetic influences of single nucleotide polymorphisms (SNPs) on RCC development. Genotyping of 10 SNPs identified an association between the rs20541 G>A polymorphism in the interleukin 13 gene (IL13) and decreased risk of RCC. No association has been found for the other nine SNPs. Logistic regressions analysis further revealed rs20541 A Allele had a significant decreased RCC risk under the codominant model (AA vs. GA vs. GG, P = 0.021). Especially, under the dominant model [(GA + AA) vs. GG, OR = 0.52, 95% CI: 0.32-0.85, P = 0.0082], which indicating that it might 2-fold decrease RCC susceptibility. Future studies with larger sample size are needed to confirm our current findings.

Keywords: RCC, hospital-based, case-control, association analysis, IL13

Introduction
Renal cancer is the 10th leading cause of male cancer-associated death and the eighth most common cancer in the United States [1, 2]. Its most frequent pathological subtype is renal cell carcinoma (RCC) (≥85%), and RCC rates among males are approximately double than that among females [3]. RCC is regarded as a heterogeneous disease, although its underlying mechanisms are still not identified, including its presentation, pathology, and clinical course. It has multifactorial etiology, with environmental risk factors including cigarette smoking, diabetes, hypertension, and a family history of cancer [4-8]. However, the underlying molecular and genetic mechanisms for RCC initiation and development remain unknown. Recent evidence has nevertheless suggested that genetic factors might play an important role in RCC carcinogenesis, including single nucleotide polymorphisms (SNPs).

A potential role for the immune response in RCC risk has previously been demonstrated [9, 10]. Stimulated T lymphocytes produce interleukin (IL)-4 and IL-13 cytokines, of which IL-4 is a pleiotropic cytokine that plays a critical role with the IL-4 receptor (IL-4R) in the differentiation of antigen-stimulated T cells [10, 11]. IL-13 shows high affinity for IL13-Rα1, leading to heterodimerization with IL-4R and formation of a complex identical to the type II receptor [10]. IL-13 binds with IL-13Rα2; however, it fails to induce a signal [12]. IL-13 also shows antiproliferative effección numerous types of cancer cells, including RCC, and demonstrates immunoregulatory and anti-inflammatory functions through decreasing the production of proinflammatory cytokines [13]. Additionally, it has been shown to regulate the proliferation and differentiation of several immune cells, and may be involved in the pathogenesis of various types of cancers [14-16]. IL-13 and IL-4 share immunoregulatory functions and the common IL-4R chain on their receptor, inhibiting inflammatory cytokines and inducing immunoglobulin E (IgE) production [17, 18]. However, the interaction between IL-4, IL-13, and IL-4R in RCC is not clear.
The investigation of aberrations in genes encoding IL-4, IL-4R, and IL-13 widely implicates their roles in RCC progress and treatment response. For instance, the IL4 C-590T polymorphism may contribute to the IL-4-secreting ability, reduce the risk of RCC in a Chinese population, and play a major role in the mechanism of diabetic nephropathy [19-21].

VHL (Von Hippel-Lindau Tumor Suppressor, E3 Ubiquitin Protein Ligase) is a tumor suppressor gene [22]. Alteration of the VHL gene by mutation, loss of heterozygosity, and promoter methylation has been found to be important to RCC pathogenesis [23]. ITPR2 (Inositol 1,4,5-Trisphosphate Receptor, Type 2) is a protein coding gene belongs to the inositol 1,4,5-triphosphate receptor family. ITPR2 gene on 12p11.23 was firstly reported as a novel susceptibility loci for RCC in an European population GWAS study [2]. It is reported that germ line genetic variations in ITPR2 genes are associated with clear cell RCC in Chinese population [24]. KRT19P2 (Keratin 19 Pseudo gene 2) is a pseudo gene, which may be functional similar to other kinds of non-coding DNA [25, 26]. KRT19P2 showed a statistically expression between metastatic and non-metastatic HNSCC (head and neck squamous cell carcinoma) cells [27]. LINC00599 (Long Intergenic Non-Protein Coding RNA 599) is an RNA gene, and affiliated with the non-coding RNA class. LncRNA have shown an important regulatory role in RCC [28]. MIR146A (MicroRNA 146a) is an RNA gene, and is affiliated with the miRNA class. MIR146A gene has been implicated in the development of multiple cancers and the regulation of inflammation induced via the innate immune response [29].

In this case-control investigation, we evaluated the association between functional polymorphisms IL13 rs20541 G>A, IL4R rs1801275 A>G, VHL rs1642742 G>A, ITPR2 rs1049380 G>T, KRT19P2 rs2289030 G>C, LINCO0599 rs531564 G>C, and MIR146A rs2910164 C>G and RCC susceptibility. For this purpose, we performed genotyping analysis of the 10 SNPs using a sample of 132 RCC cases and 145 controls in a Chinese population.

### Materials and methods

#### Study subjects

This study was an ongoing hospital-based case-control study involved 132 histopathologically confirmed RCC patients and 145 cancer-free controls. Consecutive RCC patients were recruited between September 2014 and June 2015 at Renji Hospital, School of Medicine,
IL13 rs20541 G>A polymorphism and reduced RCC risk

School of Medicine. Written informed consent was obtained from all study participants. After informed consent was issued by all individuals, 5-ml samples of venous blood were collected for genomic DNA extraction.

Single nucleotide polymorphism selection and genotyping

Genomic DNA was extracted from peripheral blood leukocytes using standard procedures. The selected 10 SNPs in IL13, IL4R, VHL, ITPR2, KRT19P2, LINCO0599, and MIR146A genes, which are closely associated with RCC, were genotyped using PCR-ligase detection reaction (LDR) method on an ABI Prism 377
IL13 rs20541 G>A polymorphism and reduced RCC risk

Table 3. Distribution of selected demographic variables in RCC cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n, %)</th>
<th>Controls (n, %)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>57.9 ± 12.0</td>
<td>57.7 ± 11.9</td>
<td>0.956&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;60</td>
<td>75 (56.8%)</td>
<td>82 (56.6%)</td>
<td>0.964&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥60</td>
<td>57 (43.2%)</td>
<td>63 (43.4%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87 (65.9%)</td>
<td>96 (66.2%)</td>
<td>0.958&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>45 (34.1%)</td>
<td>49 (33.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>P-value obtained with t-test; <sup>b</sup>P-value obtained with χ² test.

Sequence Detection System (Applied Biosystems, Foster City, CA, USA) [2, 17, 19, 30-32], with technical support from Shanghai Genesky Biotechnology Company (Shanghai, China). For each SNP, alleles were distinguished by different fluorescent labels of allele specific oligonucleotide probe pairs. Different SNPs were further distinguished by different extended lengths at the 3' end. The primer sequences used for PCR reaction are shown in Table 1. Two allele-specific probes and one fluorescently labeled probe were used to amplify a fragment containing each variant (probe sequences are available from the corresponding author on request) were presented in Table 2.

The PCR reaction mixture (10 µL) contained 1× GC-I buffer (Takara, Shiga, Japan), 3.0 mM Mg<sup>2+</sup>, 0.3 mM dNTP, 1 U Hot Star Taq polymerase (Qiagen, Hilden, Germany), 10 ng of sample DNA, and 10 pmoles of each primer. PCR amplification was performed under the following conditions: 95°C for 2 min, followed by 11 cycles of 94°C for 20 s, 65°C for 40 s, 72°C for 90 s, then 24 cycles of 94°C for 20 s, 59°C for 30 s, and 72°C for 90 s, and a final extension at 72°C for 2 min. PCR products were purified with 1 U of Shrimp Alkaline Phosphatase and 1 U of Exonuclease I to degrade excess dNTPs and primers. LDR was carried out using 1 µL of 10× binding buffer, 0.25 µL of thermostable Taq DNA ligase, 0.75 µL of 1 mM 30 ligation primers mixture, 2 µL of multiplex PCR product, and 6 µL of double-distilled H<sub>2</sub>O. The reaction mixtures were subjected to 38 cycles of 94°C for 1 min and 58°C for 4 min, then stored at 4°C. Reaction mixtures (0.5 µL) were denatured at 95°C for 5 min in 9 mL Hi-Di formamide with 0.5 µL of the LIZ-500 size standard, and run on the ABI3130XL genetic analyzer. Data analysis was conducted using Gene Mapper Software v4.0 (Applied Biosystems). DNA sequencing was used to validate the LDR genotyping results, and was shown to correspond for randomly selected DNA samples of each genotype.

Statistical analysis

For each SNP, Hardy-Weinberg equilibrium test, allele frequencies, and genotype frequencies were calculated using the SNP Stats program and Plink software v1.9 (http://pngu.mgh.harvard.edu/~purcell/plink/) [33]. Differences in the distributions of demographic characteristics, allele frequencies between cases and controls were estimated using the χ² test or T-test. The Hardy-Weinberg equilibrium (HWE) was tested by a goodness-of-fit χ² test to compare the observed genotype frequencies to the expected ones among the control group. Logistic regression analysis was used to investigate the association of SNPs with RCC risk after adjustment for age and sex under three statistical models (codominant, dominant, and recessive inheritance). Estimation of the statistical power was performed using Stplan 4.3 software. Statistical analysis was performed using SPSS 11.5 software (Statistical Product and Service Solutions) and Microsoft Excel. For all results, P-values <0.05 was considered to represent statistically significant.

Results

Characteristics of the study population

The demographic and clinical characteristics of RCC and control subjects were summarized in Table 3. The 132 RCC cases were well matched with the 145 control subjects in terms of age (P = 0.956) and sex (P = 0.958). The mean age of the RCC patients was 57.9 years (SD 12.0; range 28-81 years), and 65.9% of subjects were males. The mean age of the control subjects was 57.7 years (SD 11.9; range 25-84 years), and 66.2% of healthy subjects were males.

Allelic and genotypic association with RCC risk

Preliminary analysis indicated that genotype frequencies for these ten polymorphisms among controls were all in Hardy-Weinberg equilibrium (all P>0.05), providing no evidence of pop-
IL13 rs20541 G>A polymorphism and reduced RCC risk

Table 4. Allele frequencies among the cases and controls

<table>
<thead>
<tr>
<th>rsNO.</th>
<th>Minor/Major Alleles</th>
<th>MAF</th>
<th>Hapmap CHB</th>
<th>HWEb</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1800925</td>
<td>T/C</td>
<td>0.15 (0.18)</td>
<td>0.156 (T)</td>
<td>0.5</td>
<td>0.380</td>
</tr>
<tr>
<td>rs20541</td>
<td>A/G</td>
<td>0.28 (0.4)</td>
<td>0.320 (A)</td>
<td>0.53</td>
<td>0.0054**</td>
</tr>
<tr>
<td>rs1801275</td>
<td>G/A</td>
<td>0.16 (0.184)</td>
<td>0.78 (G)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>rs1805010</td>
<td>G/A</td>
<td>0.48 (0.52)</td>
<td>0.461 (G)</td>
<td>0.12</td>
<td>0.446</td>
</tr>
<tr>
<td>rs1642742</td>
<td>G/A</td>
<td>0.26 (0.21)</td>
<td>0.194 (G)</td>
<td>1</td>
<td>0.224</td>
</tr>
<tr>
<td>rs779805</td>
<td>G/A</td>
<td>0.25 (0.22)</td>
<td>0.189 (G)</td>
<td>0.82</td>
<td>0.362</td>
</tr>
<tr>
<td>rs1049380</td>
<td>T/G</td>
<td>0.42 (0.503)</td>
<td>0.413 (T)</td>
<td>0.21</td>
<td>0.0504</td>
</tr>
<tr>
<td>rs2289030</td>
<td>C/G</td>
<td>0.2 (0.22)</td>
<td>0.199 (C)</td>
<td>1</td>
<td>0.566</td>
</tr>
<tr>
<td>rs531564</td>
<td>C/G</td>
<td>0.16 (0.19)</td>
<td>0.199 (C)</td>
<td>0.52</td>
<td>0.335</td>
</tr>
<tr>
<td>rs2910164</td>
<td>G/C</td>
<td>0.35 (0.37)</td>
<td>0.354 (G)</td>
<td>0.85</td>
<td>0.676</td>
</tr>
</tbody>
</table>

aMAF, minor allele frequency, data from 1000 Genomes Project for Han Chinese in Beijing, China (CHB); bP values of the Hardy-Weinberg test for each single nucleotide polymorphism (SNP) in control samples; **P value for allele frequency differences between cases and controls; **P<0.01.

The IL13 rs20541 AA genotype was not associated with RCC risk (Rec: OR 0.53, 95% CI: 0.25-1.11, P = 0.088) (Table 5). Considering the rs20541 A allele is lower in cases group in comparison to the controls, we could indicate that the rs20541 G>A polymorphism in IL13 have 2x decreased risk of RCC.

None of the other SNPs demonstrated a significant difference in genotype distributions between cases and controls (Table 5). Logistic regression analysis revealed that these nine SNPs were not associated with the RCC risk (Table 5).

Discussion

RCC is a multifactorial disease that is thought to result from a complex interaction between environmental, immunological, and genetic factors. The observed high clustering and heritability in RCC families shed light on the importance of genetic components in disease pathogenesis.

In this hospital-based case-control study of RCC, we explored the associations of IL13 rs1800925, rs20541; IL4R rs1801275, rs1805010; VHL rs1642742, rs779805; ITPR2 rs1049380; KRT19P2 rs2289030; LINC00599 rs531564; and MIR146A rs2910164 in cases and controls are shown in Table 4. Initially, we carried out a standard allelic association analysis for all ten SNPs and found that only rs20541 was significantly associated with the risk of RCC (P = 0.0054) (Table 4). The frequency of the rs20541 minor allele A was lower in cases than in controls (0.28 vs. 0.4). Genotype frequencies of IL13 rs20541 were 9% (AA), 39% (GA), and 52% (GG) in cases, and 16%, 48%, 37% in control subjects, respectively. However, all other SNPs did not reach the significant level of association. To investigate how the alleles within these SNPs loci were interacting in conferring genetic risks to RCC, we further conducted multivariate logistic regression analysis under three common genetic models (codominant, dominant, and recessive inheritance). The results showed that the adjusted genetic risk estimates of rs20541 under the codominant model (AA vs. AG vs. GG) were significant (P = 0.021). The odds ratio (OR) for GA genotype was 0.57 (95% confidence interval (CI): 0.34-0.94), and OR for AA genotype was 0.40 (95% CI: 0.18-0.88). Where under the dominant model [(GA + AA) vs. GG], the OR for (GA + AA) genotype was 0.52 (95% CI: 0.32-0.85, P = 0.0082). In the case of the recessive (Rec) model [AA vs. (GA + GG)], IL13 is expressed in a variety of cells, including activated human T-helper type 2 cell, and is shown to potently reduce the expression of the inducible isof orm of nitric oxide synthase, and prostaglandin E2 and cyclooxygenase-2 production by mesangial cells, as well as to inhibit the release of vascular permeability factor by peripheral blood mononuclear cells from patients with lipoid nephrosis [34-36]. IL13 exhibits a pleiotropic effect both in immunoregulation and inflammation, suggesting a possi-
ble involvement for this cytokine in carcinogenesis. Recently, it was reported that IL13 induced the production of transforming growth factor-β by myeloid cells to mediate cancer immunosurveillance in mouse cancer models, while the increased production of IL13 was observed in bladder cancer patients as an apparent immune response against inflammation [37, 38]. Therefore, IL13 variants could be expected to have an effect on cancer immune responses, and hence carcinogenesis.

IL13 is 4.6 kb in size, located on Chromosome 5 (5q23-5q31), and consists four exons and three introns [39]. IL13 rs20541 variants have been reported to be associated with allergic rhinitis, eczema, and asthma [40-42]. Recent studies found that IL13 played a central role in IgE production or allergies, and the combined IL13 genotype polymorphism was observed to decrease the risk of brain glioma [16]. The contributions of IL13 polymorphisms to the predisposition to diverse cancer types such as glioblastoma multiforme, mastocytosis, and glioma have also been documented [15, 16, 40]. However, no definite association was discovered between IL13 rs20541 and RCC until now.

Several limitations should be addressed in the present study. First, the RCC patients and controls were recruited from one hospital, so may not provide a good representation of the general population. Second, the polymorphisms investigated in this study were chosen for their functional consideration, so future work should examine additional genes for markers interactions with IL13.

<table>
<thead>
<tr>
<th>rsNo.</th>
<th>SNP Property</th>
<th>Variant</th>
<th>Frequency</th>
<th>Case</th>
<th>Control</th>
<th>Adjust OR (95% CI)</th>
<th>Adjust P-Value</th>
<th>Adjust OR (95% CI)</th>
<th>Adjust P-Value</th>
<th>Adjust OR (95% CI)</th>
<th>Adjust P-Value</th>
</tr>
</thead>
<tbody>
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<td>rs1800925</td>
<td>5'Flanking</td>
<td>CC</td>
<td>96 (73)</td>
<td>99 (68)</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.42</td>
<td>1</td>
<td>0.62</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>TC</td>
<td>32 (24)</td>
<td>40 (28)</td>
<td>0.82 (0.48-1.42)</td>
<td>0.81 (0.48-1.36)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>TT</td>
<td>4 (3)</td>
<td>6 (4)</td>
<td>0.69 (0.19-2.53)</td>
<td>0.72 (0.20-2.64)</td>
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<tr>
<td>rs20541</td>
<td>exon4</td>
<td>GG</td>
<td>69 (52)</td>
<td>53 (37)</td>
<td>1</td>
<td>0.021*</td>
<td>1</td>
<td>0.0082**</td>
<td>1</td>
<td>0.088</td>
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<tr>
<td></td>
<td></td>
<td>GA</td>
<td>51 (39)</td>
<td>69 (48)</td>
<td>0.57 (0.34-0.94)</td>
<td>0.52 (0.32-0.85)</td>
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<tr>
<td></td>
<td></td>
<td>AA</td>
<td>12 (9)</td>
<td>23 (16)</td>
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<td>0.53 (0.25-1.11)</td>
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<tr>
<td>rs1801275</td>
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<td>84 (64)</td>
<td>100 (69)</td>
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<tr>
<td></td>
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<td>AG</td>
<td>44 (33)</td>
<td>43 (30)</td>
<td>1.23 (0.73-2.06)</td>
<td>1.28 (0.77-2.13)</td>
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<tr>
<td></td>
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<td>GG</td>
<td>4 (3)</td>
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<td>2.45 (0.43-13.90)</td>
<td>2.27 (0.40-12.76)</td>
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<tr>
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<td>GG</td>
<td>26 (20)</td>
<td>36 (25)</td>
<td>1</td>
<td>0.59</td>
<td>1</td>
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<tr>
<td></td>
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<td>GA</td>
<td>76 (58)</td>
<td>78 (54)</td>
<td>1.35 (0.74-2.45)</td>
<td>1.35 (0.76-2.39)</td>
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<tr>
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<td>31 (21)</td>
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<td>1.08 (0.61-1.91)</td>
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<td>90 (62)</td>
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<tr>
<td></td>
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<td>1.32 (0.82-2.14)</td>
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<td>9 (7)</td>
<td>7 (5)</td>
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<td>1.44 (0.52-4.01)</td>
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<td>rs779805</td>
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<td>AA</td>
<td>75 (58)</td>
<td>89 (61)</td>
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<td>0.65</td>
<td>1</td>
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<td>AG</td>
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<td>57 (43)</td>
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<tr>
<td></td>
<td></td>
<td>CC</td>
<td>5 (4)</td>
<td>5 (3)</td>
<td>1.03 (0.29-3.71)</td>
<td>1.11 (0.31-3.94)</td>
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<tr>
<td>rs531564</td>
<td>UTR</td>
<td>GG</td>
<td>95 (72)</td>
<td>98 (68)</td>
<td>1</td>
<td>0.62</td>
<td>1</td>
<td>0.43</td>
<td>1</td>
<td>0.43</td>
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<tr>
<td></td>
<td></td>
<td>CG</td>
<td>33 (25)</td>
<td>40 (28)</td>
<td>0.85 (0.49-1.47)</td>
<td>0.81 (0.48-1.36)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CC</td>
<td>4 (4)</td>
<td>7 (5)</td>
<td>0.58 (0.16-2.08)</td>
<td>0.60 (0.17-2.15)</td>
<td></td>
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<tr>
<td>rs2910164</td>
<td>UTR</td>
<td>CC</td>
<td>55 (42)</td>
<td>59 (41)</td>
<td>1</td>
<td>0.83</td>
<td>1</td>
<td>0.87</td>
<td>1</td>
<td>0.54</td>
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<td></td>
<td></td>
<td>GC</td>
<td>62 (47)</td>
<td>66 (46)</td>
<td>1.01 (0.61-1.67)</td>
<td>0.96 (0.59-1.55)</td>
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<td></td>
<td></td>
<td>GG</td>
<td>15 (11)</td>
<td>20 (14)</td>
<td>0.80 (0.37-1.73)</td>
<td>0.80 (0.39-1.64)</td>
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*Number (%); **The P value and odds ratio (OR) (95% confidence interval [CI]) were obtained by logistic regression after adjusting for sex and age;Assuming M represents the major allele and m represents the minor allele, genetic models can be described as follows: codominant: M/m vs. M/M and m/m vs. M/M; dominant: (m/m + M/m) vs. M/M; recessive: m/m vs. (M/M + M/m); *P<0.05, **P<0.01.
that could be used to predict the susceptibility of RCC. Third, the moderate sample capacity limited the statistical power of this study. Finally, further studies are needed to confirm our findings and to clarify the RCC genetic mechanism, especially with regard to the gene-environment interaction.

Conclusion

In conclusion, this study provides evidence that the functional $IL13$ rs20541 polymorphism may contribute to decrease the risk of RCC. However, our sample size was limited and the statistical power of the analysis was low. Therefore, additional studies of larger populations and rigorous design of tissue-specific biological characterizations are necessary to confirm our current observations.

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Disclosure of conflict of interest

None.

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