Short Communication

Genetic Variation in the SST Gene and its Receptors in Relation to Circulating Levels of Insulin-Like Growth Factor-I, IGFBP3, and Prostate Cancer Risk

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Abstract

Background: Somatostatin (SST) and its receptors (SSTR1-5) may have a role in prostate cancer by influencing the IGFI hormone axis or through direct effects on prostate epithelia. We have investigated if genetic variation in the SST and SSTR1-5 genes influences prostate cancer risk and/or circulating IGFI and IGFBP3 hormone levels.

Materials and Methods: We analyzed 28 haplotype tagging single nucleotide polymorphisms in the SST and SSTR1-5 genes in a case-control/genetic association study to investigate the association between genetic variation and prostate cancer risk. The study included 2863 cases and 1737 controls from the Cancer Prostate in Sweden (CAPS) study. To investigate the genetic influence on circulating hormone levels, plasma concentrations of IGFI and IGFBP3 were analyzed in 874 controls of the CAPS study and 550 male subjects from the Northern Sweden Health and Disease Cohort (NSHDC).

Results: No clear association between prostate cancer risk and genetic variation of the SST and SSTR1-5 genes was identified. The SSTR5 missense single nucleotide polymorphism rs4988483 was associated with circulating IGFI (P = 0.002) and IGFBP3 (P = 0.0003) hormone levels in CAPS controls, with a per allele decrease of ~11%. This decrease was replicated in NSHDC for circulating IGFBP3 (P = 0.01) but not for IGFI (P = 0.09). Combining CAPS and NSHDC subjects indicated evidence of association between rs4988483 and both IGFBP3 (P = 2 × 10^-5) and IGFI (P = 0.0004) hormone levels.

Conclusions: Our results suggest that genetic variation in the SSTR5 gene and, particularly, the rs4988483 single nucleotide polymorphism influence circulating IGFI and IGFBP3 hormone levels with no measurable effect on prostate cancer risk.

Introduction

Somatostatin (SST), a polypeptide hormone, can inhibit cell proliferation of normal and neoplastic cells. SST could thus play a role in carcinogenesis (1, 2), and SST analogues have been investigated as therapeutic agents for several tumor sites, including prostate cancer, displaying some antineoplastic effect in hormone-refractory prostate cancer patients (1).

Acting through its receptors (SSTR1-5), SST also has a clear role in the regulation of pituitary synthesis and release of growth hormone, which in turn provides the principal physiologic stimulus for the synthesis of insulin-like growth factor-I (IGFI) in liver and other tissues (3). IGFI stimulates cell proliferation and decreases apoptosis, and has been implicated in cancer development by results from a vast range of in vitro and in vivo studies (4-6). In prospective epidemiologic studies, elevated levels of IGFI in the circulation have consistently been associated with several types of cancer, including prostate cancer (7-10). Recently, the Endogenous Hormones and Prostate Cancer Collaborative Group have again investigated this relation in a pooled analysis of 12 cohorts, including in total 3,300 prospective cases and 4,450 controls (11). In the latter study, increasing circulating levels of IGFI conferred a clear trend toward increased risk of prostate cancer. In addition, we recently identified several variants in the 3’ region of the IGFI gene associated with both increased prostate risk as well as elevated circulating IGFI levels, a finding supporting the role of IGFI in prostate cancer etiology along the lines of Mendelian randomization (12). SST seems to result in suppressed levels of both...
IGFI and GH1 (13). SST and its receptors may therefore play a role in prostate cancer development by inhibiting cell proliferation directly, or by affecting growth hormone and IGFI circulating hormone levels.

In the present study, we have investigated if genetic variation in the SST and SSTR1-5 genes influences circulating hormone plasma levels of IGFI, IGFBP3, and also prostate cancer risk.

Materials and Methods

Study Population. Cancer Prostate in Sweden (CAPS) is a population-based case-control study that has been extensively described previously (12, 14). In brief, after notification from regional oncological centers, 2,975 case patients donated a blood sample and filled out a questionnaire concerning demographic, medical, and life-style data. Altogether, 1,896 control subjects were randomly selected from the Swedish population register within groups of men matching the case distribution for age (groups of 5-y interval) and residency with a participation rate of ~60%. In the present study, 2,863 cases and 1,737 controls were available for genotyping. Information on clinical characteristics were obtained from the National prostate cancer register. Clinical characteristics available in National prostate cancer register included local tumor stage, lymph node stage, metastasis at bone scan, tumor differentiation assessed by Gleason score, and serum prostate-specific antigen level at time of diagnosis.

Plasma samples for analyses of circulating IGFI and IGFBP3 hormone levels were available for the first part of the CAPS study, CAPS1, including 874 control subjects (mean age at blood draw, 69.7 y). Written informed consent was obtained from all participants and the research ethical committee at the Karolinska Institutet and Umeå University Hospital approved the study.

The Northern Sweden Health and Disease Cohort (NSHDC) is a long-term population-based study also extensively described before (9). Subjects included in the present study were originally used in a nested case-control study of prostate cancer (9). In total, 550 subjects collected prospectively were available for genotyping in which plasma IGFI and IGFBP3 levels have been measured in the present study (mean age at blood draw, 57.8 y for cases and 58.6 y for controls). All participants signed an informed consent form and the study was approved by the Ethical committee of Umeå University Hospital.

Single Nucleotide Polymorphism Selection, Hormone Measurements, and Genotyping. Single nucleotide polymorphisms (SNP) were selected using a haplotype tagging approach as described previously (12, 15). Genotype data on SNPs genotyped by the HapMap consortium across the SST and SSTR1-5 loci were obtained. Additional SNPs previously studied by our group (16), were genotyped in HapMap (CEU-CEPH) DNA, and the LD-structure was analyzed together with the HapMap data. Haplotype blocks were defined using a slightly relaxed criteria compared with those described by Gabriel et al. (17). Genes SST, SSTR1, SSTR4, and SSTR5 were contained in single haplotype blocks, whereas SSTR2 and SSTR3 were covered by two blocks. Haplotype tagging SNPs were then selected aiming to capture common haplotypes (≥5%) by the criteria R² of >0.8 in each block using tagSNPs (18). SSTR1, SSTR2, and SSTR5 had “singleton” SNPs that positioned outside the haplotype blocks, and were not correlated (r² < 0.8), with any SNP inside the blocks and were therefore also genotyped. In total, 34 haplotype tagging SNPs were selected, but we were unable to design tagman assays for two SNPs in SSTR4 (rs11696609 and rs3991894) and one SNP in SSTR5 (rs619698) due to DNA sequence complexity.

Genotyping was carried out as described previously (16) with cases and controls distributed randomly on genotyping plates and technicians blinded to cases/control status. Genotyping call rates ranged between 92% and 99% and genotype concordance rates were higher than 99.7% in duplicate samples.

Measurements of plasma levels of IGFI and IGFBP3 in subjects from CAPS were done at the IARC by an ELISA by DSL (Diagnostic Systems Laboratories) as described previously (16). In CAPS, the mean intra-assay coefficients of variation (CV) were 4.1% for IGFI and 7.4% for IGFBP3, and the mean interassay coefficients of variations were 10.4% for IGFI and 7.8% for IGFBP3. Measurements of plasma levels of IGFI and IGFBP3 in subjects from NSHDC were done using double-antibody, immunoradiometric assays from Immunotech as described previously (9). In NSHDC, the mean intra-assay coefficients of variations were 4.2% for IGFI and 3.3% for IGFBP3, and the mean interassay coefficients of variations were 11.9% for IGFI and 3.1% for IGFBP3.

Statistical Analysis. We investigated the relationship between SNPs and hormone levels using linear regression models adjusting for age. In analyses of prostate cancer risk, odds ratios were assessed using conditional logistic regression models. For each SNP, a variable indicating the number of rare alleles carried by an individual was included as a covariate in the appropriate regression model, thus creating a codominant model. Haplotype dosages were calculated using tagSNPs (18) to indicate each subject’s probability of being heterozygote (having one copy) or homozygote (having two copies) for each haplotype. The tagSNP’s dosage variables were then implemented as covariates in the appropriate regression model keeping homozygotes of the most common haplotype as reference category. These statistical analyses were done in SAS 9.1 (SAS Institute).

Because the recruitment of subjects in the CAPS and NSHDC studies differed, we combined the results between genetic variants and hormone levels by pooling the trend estimates from each study group. The pooled trend estimates were assessed as a weighted mean with weights calculated as the inverse of the study specific variance. This analysis was done using the StatsDirect software.

Results

The genotype distributions for three SNPs rs10513817 (SST), rs3746726 (SSTR4), and rs213564 (SSTR5) deviated significantly (P = 0.008, 0.002, 0.0004, respectively) from
Table 1. Part A. Associations between genetic variation in SST and the SSTR genes and prostate cancer risk and circulating hormone levels

<table>
<thead>
<tr>
<th>Gene marker order-common/rare allele</th>
<th>Haplotype</th>
<th>Frequency (controls)</th>
<th>Prostate cancer risk</th>
<th>IGFI</th>
<th>IGFBP3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)*</td>
<td>P*</td>
<td>β-estimate (95% CI)</td>
<td>P*</td>
</tr>
<tr>
<td>SST</td>
<td>GTTT</td>
<td>(2 copies) 25.4%</td>
<td>1.0 (Reference)</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs10513817-G/T</td>
<td>GTTT</td>
<td>(1 copy) 50.5%</td>
<td>1.1 (0.9 - 1.2)</td>
<td>0.49</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs9824174-T/C</td>
<td>GTCT</td>
<td>(1 copy) 24.7%</td>
<td>1.1 (0.9 - 1.2)</td>
<td>0.45</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs16862418-T/C</td>
<td>GTTC</td>
<td>(2 copies) 2.4%</td>
<td>1.1 (0.7 - 1.7)</td>
<td>0.69</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs2378339-T/C</td>
<td>GTTC</td>
<td>(1 copy) 22.3%</td>
<td>1.0 (0.8 - 1.1)</td>
<td>0.52</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs1037257-</td>
<td>rs16977537-</td>
<td>(block 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7213907-</td>
<td>rs2250885-</td>
<td>(block 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs12885336-</td>
<td>RS16862418-</td>
<td>(block 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9824174-</td>
<td>GTCT</td>
<td>(1 copy) 19.3%</td>
<td>0.9 (0.6 - 1.5)</td>
<td>0.77</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs1037260-</td>
<td>TTTT</td>
<td>(1 copy) 19.5%</td>
<td>1.3 (1.1 - 1.5)</td>
<td>0.01</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs12885336-</td>
<td>TTTT</td>
<td>(2 copies) 1.1%</td>
<td>0.7 (0.4 - 1.2)</td>
<td>0.22</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs16977537-</td>
<td>TTTT</td>
<td>(2 copies) 1.1%</td>
<td>0.7 (0.4 - 1.2)</td>
<td>0.21</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>SSTR1</td>
<td>CCC</td>
<td>(2 copies) 32.5%</td>
<td>1.0 (Reference)</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs2228497-C/T</td>
<td>CCC</td>
<td>(1 copy) 50.1%</td>
<td>1.0 (0.9 - 1.2)</td>
<td>0.95</td>
<td>0 (Reference)</td>
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<tr>
<td>rs1135473-C/T</td>
<td>TCT</td>
<td>(1 copy) 37.1%</td>
<td>1.1 (0.9 - 1.3)</td>
<td>0.28</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs12885336-C/T</td>
<td>TCT</td>
<td>(2 copies) 5.1%</td>
<td>1.4 (1.1 - 1.9)</td>
<td>0.02</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>SSTR1 singleton</td>
<td>CTC</td>
<td>(1 copy) 25.0%</td>
<td>1.0 (0.9 - 1.2)</td>
<td>0.88</td>
<td>0 (Reference)</td>
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<tr>
<td>rs2250885-</td>
<td>CTC</td>
<td>(2 copies) 2.2%</td>
<td>0.9 (0.6 - 1.5)</td>
<td>0.79</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs1037260-</td>
<td>CTC</td>
<td>(2 copies) 2.2%</td>
<td>0.9 (0.6 - 1.5)</td>
<td>0.79</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs12885336-</td>
<td>CTC</td>
<td>(2 copies) 2.2%</td>
<td>0.9 (0.6 - 1.5)</td>
<td>0.79</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>SST block 2</td>
<td>AGG</td>
<td>(2 copies) 12.8%</td>
<td>1.0 (Reference)</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs236730-</td>
<td>AGG</td>
<td>(1 copy) 44.7%</td>
<td>1.0 (0.8 - 1.1)</td>
<td>0.66</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs1461133-</td>
<td>AGG</td>
<td>(1 copy) 11.0%</td>
<td>0.8 (0.6 - 1.0)</td>
<td>0.02</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs1461133-</td>
<td>AGC</td>
<td>(2 copies) 0.1%</td>
<td>0.7 (0.1 - 4.6)</td>
<td>0.74</td>
<td>0 (Reference)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
<table>
<thead>
<tr>
<th>Gene marker order-common/rare allele</th>
<th>Haplotype</th>
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<th>Prostate cancer risk</th>
<th>IGFI</th>
<th>IGFBP3</th>
<th>( \beta )-estimate (95% CI)</th>
<th>( \beta )-estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTR3 block1</td>
<td>GGG</td>
<td>(2 copies)</td>
<td>12.6%</td>
<td>1.0</td>
<td>(Reference)</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td>rs2572272-C/G</td>
<td>GGC</td>
<td>(1 copy)</td>
<td>44.7%</td>
<td>1.0</td>
<td>(0.9 -1.2)</td>
<td>-3 (15 to 9)</td>
<td>0.63</td>
</tr>
<tr>
<td>rs4820273-G/A</td>
<td>CGA</td>
<td>(1 copy)</td>
<td>40.8%</td>
<td>1.1</td>
<td>(1 -1.3)</td>
<td>0.13</td>
<td>13 (25 to 1)</td>
</tr>
<tr>
<td>rs5756562-A/G</td>
<td>GCG</td>
<td>(2 copies)</td>
<td>9.8%</td>
<td>0.9</td>
<td>(0.7 -1.2)</td>
<td>0.53</td>
<td>-8 (30 to 15)</td>
</tr>
<tr>
<td>SSTR4 block2</td>
<td>ACT</td>
<td>(2 copies)</td>
<td>16.6%</td>
<td>1.0</td>
<td>(0.9 -1.3)</td>
<td>-6 (19 to 4)</td>
<td>0.64</td>
</tr>
<tr>
<td>rs9610669-A/C</td>
<td>ACT</td>
<td>(1 copy)</td>
<td>44.5%</td>
<td>1.0</td>
<td>(0.9 -1.1)</td>
<td>-8 (15 to 1)</td>
<td>0.66</td>
</tr>
<tr>
<td>rs229569-C/T</td>
<td>CT</td>
<td>(1 copy)</td>
<td>32.4%</td>
<td>0.7</td>
<td>(0.5 -1.0)</td>
<td>-17 (43 to 8)</td>
<td>0.18</td>
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<tr>
<td>rs229563/T/C</td>
<td>CT</td>
<td>(2 copies)</td>
<td>5.5%</td>
<td>1.0</td>
<td>(0.9 -1.2)</td>
<td>-4 (18 to 11)</td>
<td>0.61</td>
</tr>
<tr>
<td>SSTR5</td>
<td>GTG</td>
<td>(2 copies)</td>
<td>9.5%</td>
<td>0.8</td>
<td>(0.5 -1.2)</td>
<td>-14 (30 to 2)</td>
<td>0.84</td>
</tr>
<tr>
<td>rs213563-C/G</td>
<td>GTG</td>
<td>(1 copy)</td>
<td>45.5%</td>
<td>1.0</td>
<td>(0.9 -1.2)</td>
<td>-20 (66 to 27)</td>
<td>0.41</td>
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<tr>
<td>rs213654-T/C</td>
<td>GCT</td>
<td>(1 copy)</td>
<td>42.7%</td>
<td>1.0</td>
<td>(0.8 -1.2)</td>
<td>-28 (54 to -1)</td>
<td>0.61</td>
</tr>
<tr>
<td>rs1164051-G/T</td>
<td>ACT</td>
<td>(2 copies)</td>
<td>38.7%</td>
<td>0.9</td>
<td>(0.8 -1.1)</td>
<td>-8 (22 to 5)</td>
<td>0.83</td>
</tr>
<tr>
<td>ATT</td>
<td>ACT</td>
<td>(2 copies)</td>
<td>7.8%</td>
<td>0.8</td>
<td>(0.6 -1.1)</td>
<td>-25 (31 to 3)</td>
<td>0.94</td>
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<tr>
<td>rs4984883-C/A</td>
<td>GGC</td>
<td>(2 copies)</td>
<td>8.9%</td>
<td>0.8</td>
<td>(0.5 -1.2)</td>
<td>-119 (170)</td>
<td>0.67</td>
</tr>
<tr>
<td>SSTR5 -singleton</td>
<td>ATT</td>
<td>(1 copy)</td>
<td>8.1%</td>
<td>1.0</td>
<td>(0.7 -1.3)</td>
<td>-15 to -9</td>
<td>0.61</td>
</tr>
<tr>
<td>rs4984883-C/A</td>
<td>ATT</td>
<td>(2 copies)</td>
<td>0.2%</td>
<td>0.6</td>
<td>(0.1 -2.9)</td>
<td>16 (124 to 15)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.

*Odds ratios were assessed by conditional logistic regression.

\(^1\) \( \beta \)-estimates refers to regression coefficients from linear regression model.
that expected by Hardy-Weinberg equilibrium among the control population but not in cases. These deviations from Hardy-Weinberg equilibrium complicate the haplotype analyses and the results of these SNPs should be interpreted with caution. Because haplotype tagging SNPs were selected based on their ability to tag the common haplotypes rather than individual SNPs, we here focus on outlining the result from the haplotype-based analyses. However, we also analyzed the haplotype tagging SNPs separately, but no additional associations in relation to prostate cancer risk and/or hormone levels were observed. Mean hormone plasma levels in CAPS controls were 193 ng/mL [95% confidence interval (CI), 188-198] for IGFI and 3297 ng/mL (95% CI, 3239-3354) for IGFBP3. Mean hormone plasma levels in NSHDC subjects were 211 ng/mL (95% CI, 206-216) for IGFI and 2390 ng/mL (95% CI, 2,353-2,427) for IGFBP3.

Genetic Variation and Circulating of IGFI and IGFBP3 Hormone Levels. Associations between genetic variation in the SST gene and its receptors and hormone levels in CAPS controls are shown in Table 1. In the SSTR5 gene, the rs4988483 SNP was associated with a decrease in both circulating IGFI (\(P = 0.002\)) and IGFBP3 (\(P = 0.0003\)) hormone levels among CAPS controls. The association between the rs4988483 SNP and IGFBP3 hormone levels was the only significant association when using the Bonferroni-adjusted \(P\) value threshold (\(P = 0.0008; n_{	ext{final}} = 61\)). The effect of rs4988483 seemed to be most consistent with a codominant mode of inheritance, with an approximate 11% allele decrease in IGFBP3 levels relative the baseline levels of CAPS controls. We attempted to replicate this observation in the independent NSHDC study. In NSHDC, rs4988483 was also significantly associated with a decrease in circulating IGFBP3 hormone levels (\(P = 0.01\)) but not significantly associated with IGFI hormone levels (\(P = 0.09;\) Fig. 1). Combining the estimates from the CAPS (controls) and NSHDC studies indicated evidence for association between rs4988483 and circulating IGFBP3 levels (\(P = 2 \times 10^{-5}\)) and IGFI levels (\(P = 0.0004;\) Fig. 1). Because plasma IGFI and IGFBP3 were correlated (\(r^2 = 0.5\) in CAPS controls), we also did analyses of the relation between rs4988483 and IGFI adjusted for IGFBP3, and the relation between rs4988483 and IGFBP3 adjusted for IGFI. In these analyses, IGFBP3 accounted for the association between rs4988483 and IGFI (\(P_{\text{adjusted}} = 0.35\)), whereas the association between rs4988483 and IGFBP3 was attenuated but still significant (\(P_{\text{adjusted}} = 0.04\)) when adjusting for IGFI.

Genetic Variation and Prostate Cancer Risk. No clear associations between genetic variants of the SST and SSTR genes and prostate cancer risk were observed overall (see Table 1), or in subanalyses as stratified by clinical tumor characteristics. The rs4988483 SNP that was associated with hormone levels was not associated with prostate cancer risk. In SSTR2, two haplotypes were modestly associated with prostate cancer risk, with heterozygote carriers of the GGT haplotype in block 1 (located directly proximal to SSTR2) displaying an odds ratio of 1.3 (95% CI, 1.1-1.5), and for a second haplotype, AGC, located in block 2 (covering the coding region of SSTR2), heterozygotes had an odds ratio of 0.8 (95% CI, 0.6-1.0). These associations were unchanged when adjusting one for the other, implying independence. The associations between these SSTR2 haplotypes were both more prominent in individuals with younger age at diagnosis (age <65 years), with heterozygote carriers of the GGT and AGC haplotypes displaying odds ratios of 1.6 (95% CI, 1.2-2.1; \(P = 0.002\)) and 0.5 (95% CI, 0.4-0.8; \(P = 0.0003\)), respectively. Evidence for heterogeneity between the risk estimates for the cases diagnosed before and after age 65 years was present for the AGC haplotype (\(P = 0.004\)) but not for the GGT haplotype (\(P = 0.09\)). One SSTR1 haplotype was associated with increased risk, with homozygote carriers having an odds ratio of 1.41 (95% CI, 1.1-1.9; \(P = 0.02\)), but this association was not more prominent in any subanalysis as stratified by age at diagnosis or by clinical tumor characteristics.

Discussion

Heritability studies suggest that 40% to 60% of the variation in circulating levels of IGFI and IGFBP3 hormones is genetically determined (19, 20). Although the IGFI and IGFBP3 genes are the most obvious candidates to account for this variability (12, 21), other...
members of the growth hormone/IGFI axis are also candidates to influence circulating IGFI and IGFBP3 hormone levels. In the present study, we report a missense SNP in the SSTR5 gene associated with a decrease in plasma levels of IGFBP3 by 11% per rare allele as confirmed in an independent study population.

Increased SST expression seems to result in suppression of both GH1 and IGFI circulating levels (3), suggesting that genetic variation causing over transmission of the SST signal would also lower IGF1 and IGFBP3 hormone levels. In this a large-scale investigation of common genetic variation in the SST and the SSTR receptor genes in the Swedish population, 1 SNP in the SSTR5 gene resulted in a per allele decrease of ~11% in circulating IGFBP3 hormone levels. It is not clear if this particular SNP is causative or if it is in LD with a true causative allele. The rs4988483 SNP encodes a missense change in the SSTR5 protein (M48L); however, the consequence of this change is not predicted to be damaging to function based on evolutionary conservation (by SIFT7; ref. 22). The literature on the relation between SSTR5 and circulating IGFI and IGFBP3 hormone levels are limited. In a previous study on women, we found no significant association for the rs4988483 SNP in relation to levels of IGFBP3 (16), possibly indicating sexual dimorphism.

Overall, there were no clear association between genetic variation in the SST or SSTR1-5 genes and prostate cancer risk. Prospective epidemiologic studies suggest positive association between cancer risk (including prostate cancer) and circulating IGFI hormone levels, and possibly IGFBP3 hormone levels (9, 23). Along the lines of Mendelian randomization (24), an SNP associated with a decrease in circulating IGFI/IGFBP3 levels would translate into a decreased risk of developing prostate cancer. We found no significant association between rs4988483 and prostate cancer risk, although our statistical power to detect a risk effect mediated by a decrease in plasma levels of IGFBP3 by 11% per rare allele as confirmed in an independent study population.

Further independent studies of the rs4988483 SNP in relation to IGFI and IGFBP3 hormone levels are warranted to confirm this finding.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Genetic Variation in the SST Gene and its Receptors in Relation to Circulating Levels of Insulin-Like Growth Factor-I, IGFBP3, and Prostate Cancer Risk

Mattias Johansson, James D. McKay, Fredrik Wiklund, et al.


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