

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 ($P = 2 \times 10^{-5}$) 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. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1644–50)

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

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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 of 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 ($\geq 5\%$) by the criteria R^2 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 ($r^2 < 0.8$), 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 taqman 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 tagSNPs 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.

P values were attained by two tailed likelihood-ratio tests and we considered a *P* value of <0.05 statistically significant.

Results

The genotype distributions for three SNPs rs10513817 (*SST*), rs3746726 (*SSTR4*), and rs213654 (*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

Gene marker order-common/rare allele	Haplotype	Frequency (controls)	Prostate cancer risk		IGFI		IGFBP3	
			OR (95% CI)*	P*	β-estimate (95% CI) [†]	P [†]	β-estimate (95% CI) [†]	P [†]
<i>SST</i>	<i>GTTT</i> (2 copies)	25.4%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs10513817-G/T	<i>GTTT</i> (1 copy)	50.5%	1.1 (0.9 -1.2)	0.49	10 (-1 to 21)	0.09	96 (-35 to 226)	0.15
rs9824174-T/C	<i>GTCT</i> (1 copy)	24.7%	1.1 (0.9 -1.2)	0.45	3 (-10 to 16)	0.63	59 (-96 to 213)	0.46
rs16862418-T/C	<i>GTCT</i> (2 copies)	2.4%	1.1 (0.7 -1.7)	0.69	13 (-20 to 46)	0.45	361 (-25 to 746)	0.07
rs2378339-T/C	<i>GTTC</i> (1 copy)	22.3%	1.0 (0.8 -1.1)	0.52	-4 (-17 to 9)	0.51	-26 (-178 to 127)	0.74
	<i>GTTC</i> (2 copies)	1.7%	0.9 (0.6 -1.5)	0.77	1 (-36 to 38)	0.94	50 (-383 to 483)	0.82
	<i>GCTC</i> (1 copy)	19.3%	1.1 (0.9 -1.3)	0.47	17 (37709)	0.02	86 (-76 to 247)	0.30
	<i>GCTC</i> (2 copies)	0.8%	0.7 (0.4 -1.3)	0.22	-5 (-47 to 36)	0.81	34 (-452 to 519)	0.89
	<i>TTTC</i> (1 copy)	19.5%	1.3 (1.1 -1.5)	0.01	-3 (-17 to 12)	0.70	2 (-166 to 169)	0.98
	<i>TTTC</i> (2 copies)	1.1%	0.7 (0.4 -1.2)	0.21	81 (23-138)	0.006	174 (-497 to 846)	0.61
<i>SSTR1</i>	<i>CCC</i> (2 copies)	32.5%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs2228497-C/T	<i>CCC</i> (1 copy)	50.1%	1.0 (0.9 -1.2)	0.95	-6 (-18 to 6)	0.33	64 (-79 to 206)	0.38
rs1135473-C/T	<i>TCT</i> (1 copy)	37.1%	1.1 (0.9 -1.3)	0.28	1 (-11 to 13)	0.88	-32 (-173 to 109)	0.66
rs12885336-C/T	<i>TCT</i> (2 copies)	5.1%	1.4 (1.1 -1.9)	0.02	-24 (-47 to 0)	0.05	-238 (-507 to 31)	0.08
	<i>CTC</i> (1 copy)	25.0%	1.0 (0.9 -1.2)	0.88	6 (-7 to 19)	0.34	-4 (-154 to 146)	0.96
	<i>CTC</i> (2 copies)	2.2%	0.9 (0.6 -1.5)	0.79	-5 (-42 to 31)	0.77	86 (-336 to 508)	0.69
<i>SSTR1</i> singleton	Major homozygote	88.7%	1.0 (Reference)	0.74	0 (Reference)	0.93	0 (Reference)	0.37
rs2250885-A/G	Heterozygote	11.1%	0.9 (0.8 -1.1)		2 (-14 to 17)		-78 (-262 to 106)	
	Minor homozygote	0.2%	1.9 (0.5 -7.0)		-19 (-120 to 83)		-203 (-1379 to 972)	
<i>SSTR2</i> block 1	<i>GGC</i> (2 copies)	44.5%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs7213907-G/A	<i>GGC</i> (1 copy)	43.7%	1.0 (0.8 -1.2)	0.91	0 (-13 to 13)	0.99	68 (-86 to 223)	0.39
rs16977537-G/T	<i>ATT</i> (1 copy)	29.9%	0.9 (0.8 -1.1)	0.39	-15 (-28 to -1)	0.03	-125 (-281 to 31)	0.12
rs1037257-C/T	<i>ATT</i> (2 copies)	3.4%	0.9 (0.6 -1.3)	0.50	5 (-24 to 34)	0.74	-4 (-342 to 334)	0.98
	<i>GVT</i> (2 copies)	1.1%	1.2 (0.7 -2.2)	0.52	15 (-25 to 54)	0.47	285 (-179 to 749)	0.23
<i>SSTR2</i> singleton	Major homozygote	93.5%	1.0 (Reference)	0.80	0 (Reference)	0.67	0 (Reference)	0.79
rs1037260-T/G	Heterozygote	6.5%	0.9 (0.7 -1.2)		4 (-16 to 25)		33 (-208 to 274)	
	Minor homozygote	0.0%	- (-)		- (-)		- (-)	
<i>SSTR2</i> block 2	<i>AGG</i> (2 copies)	12.8%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs2236750-A/G	<i>AGG</i> (1 copy)	44.7%	1.0 (0.8 -1.1)	0.66	-14 (-26 to -2)	0.02	-37 (-172 to 98)	0.59
rs728291-G/T	<i>ATC</i> (1 copy)	44.0%	1.0 (0.8 -1.1)	0.50	-2 (-14 to 9)	0.71	60 (-72 to 193)	0.37
rs1466113-G/C	<i>ATC</i> (2 copies)	13.2%	0.9 (0.7 -1.1)	0.32	-6 (-26 to 14)	0.53	-44 (-277 to 190)	0.71
	<i>GGG</i> (1 copy)	35.8%	0.9 (0.8 -1.0)	0.16	-4 (-15 to 8)	0.55	-53 (-190 to 84)	0.45
	<i>GGG</i> (2 copies)	5.8%	0.8 (0.6 -1.1)	0.21	-25 (-51 to 1)	0.06	-155 (-459 to 150)	0.32
	<i>AGC</i> (1 copy)	11.0%	0.8 (0.6 -1.0)	0.02	-9 (-26 to 8)	0.31	-35 (-238 to 168)	0.74
	<i>AGC</i> (2 copies)	0.1%	0.7 (0.1 -4.6)	0.74	-103 (-244 to 38)	0.15	-1174 (-2820 to 472)	0.16

(Continued on the following page)

Table 1. Part B. Associations between genetic variation in SST and the SSTR genes and prostate cancer risk and circulating hormone levels (Cont'd)

Gene marker order-common/rare allele	Haplotype	Frequency (controls)	Prostate cancer risk		IGFI		IGFBP3	
			OR (95% CI)*	P*	β-estimate (95% CI) †	P †	β-estimate (95% CI) †	P †
SSTR3 block1	GGG (2 copies)	12.6%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs6572-C/G	GGG (1 copy)	44.7%	1.0 (0.9 -1.2)	0.96	-3 (-15 to 9)	0.63	-16 (-155 to 122)	0.82
rs4820273-G/A	CGA (1 copy)	40.8%	1.1 (1.0 -1.3)	0.13	-13 (-25 to -1)	0.04	-99 (-239 to 42)	0.17
rs5756562-A/G	CGA (2 copies)	9.8%	0.9 (0.7 -1.2)	0.53	-8 (-30 to 15)	0.50	10 (-251 to 272)	0.94
	GGA (1 copy)	30.0%	1.1 (0.9 -1.2)	0.52	-4 (-17 to 9)	0.54	3 (-149 to 156)	0.97
	GGA (2 copies)	4.0%	1.3 (0.9 -1.8)	0.20	-14 (-45 to 17)	0.38	49 (-316 to 414)	0.79
	CAA (1 copy)	23.1%	1.1 (1.0 -1.3)	0.18	4 (-10 to 17)	0.60	-5 (-161 to 152)	0.95
	CAA (2 copies)	2.4%	0.8 (0.5 -1.2)	0.25	-20 (-51 to 10)	0.19	-94 (-452 to 264)	0.61
SSTR3 block2	ACT (2 copies)	13.6%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs9610669-A/C	ACT (1 copy)	44.5%	1.1 (1.0 -1.3)	0.12	-3 (-15 to 10)	0.66	-64 (-210 to 81)	0.39
rs229569-C/T	CTT (1 copy)	32.4%	1.0 (0.9 -1.1)	0.81	-8 (-19 to 4)	0.21	-69 (-208 to 69)	0.33
rs229563-T/C	CTT (2 copies)	5.5%	0.7 (0.5 -1.0)	0.06	-17 (-43 to 8)	0.18	101 (-197 to 399)	0.51
	ACC (1 copy)	25.9%	1.0 (0.9 -1.2)	0.89	-4 (-18 to 11)	0.61	49 (-119 to 216)	0.57
	ACC (2 copies)	2.3%	1.3 (0.9 -2.1)	0.18	-18 (-58 to 23)	0.39	-29 (-499 to 440)	0.90
	CCT (1 copy)	25.4%	1.0 (0.9 -1.2)	0.71	-12 (-27 to 4)	0.14	-22 (-197 to 154)	0.81
	CCT (2 copies)	2.5%	1.0 (0.6 -1.5)	0.88	-10 (-49 to 29)	0.61	-45 (-499 to 409)	0.85
	CCC (1 copy)	20.8%	1.0 (0.8 -1.2)	0.87	-14 (-30 to 2)	0.08	-40 (-225 to 145)	0.67
	CCC (2 copies)	1.5%	1.1 (0.6 -1.9)	0.78	-20 (-66 to 27)	0.41	-105 (-649 to 438)	0.70
SSTR4	TAG (2 copies)	8.1%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs220979-T/A	TAG (1 copy)	42.8%	1.0 (0.9 -1.2)	0.76	-4 (-18 to 9)	0.54	17 (-140 to 174)	0.83
rs3746726-A/C	TCG (1 copy)	40.6%	0.9 (0.8 -1.1)	0.35	-8 (-22 to 5)	0.21	-67 (-222 to 88)	0.40
rs2007363-G/T	TCG (2 copies)	7.6%	1.0 (0.7 -1.3)	0.74	-28 (-54 to -1)	0.04	-109 (-417 to 200)	0.49
	AAT (1 copy)	33.2%	1.0 (0.8 -1.2)	0.81	0 (-13 to 14)	0.97	94 (-62 to 251)	0.24
	AAT (2 copies)	5.1%	0.8 (0.6 -1.1)	0.17	3 (-25 to 31)	0.86	305 (-21 to 631)	0.07
	AAG (1 copy)	27.7%	1.0 (0.8 -1.2)	0.74	-4 (-19 to 10)	0.55	38 (-131 to 207)	0.66
	AAG (2 copies)	3.1%	0.8 (0.5 -1.2)	0.24	12 (-20 to 44)	0.46	68 (-305 to 440)	0.72
SSTR5	GTG (2 copies)	9.5%	1.0 (Reference)		0 (Reference)		0 (Reference)	
rs213653-G/A	GTG (1 copy)	42.5%	1.0 (0.9 -1.2)	0.64	0 (-13 to 13)	0.99	-38 (-186 to 110)	0.61
rs213654-T/C	GCT (1 copy)	42.7%	0.9 (0.8 -1.1)	0.22	2 (-11 to 16)	0.71	64 (-88 to 216)	0.41
rs11644051-T/G	GCT (2 copies)	10.6%	0.9 (0.7 -1.1)	0.26	6 (-17 to 30)	0.60	92 (-183 to 367)	0.51
	ACT (1 copy)	38.7%	0.9 (0.8 -1.1)	0.31	6 (-8 to 19)	0.41	32 (-122 to 186)	0.68
	ACT (2 copies)	7.8%	0.8 (0.6 -1.1)	0.11	10 (-14 to 34)	0.42	39 (-244 to 322)	0.79
	GTT (1 copy)	9.7%	1.0 (0.8 -1.3)	1.00	3 (-19 to 24)	0.80	-7 (-254 to 240)	0.95
	GTT (2 copies)	0.7%	0.5 (0.2 -1.3)	0.14	98 (26 -170)	0.01	951 (113-1789)	0.03
	ATT (1 copy)	8.1%	1.0 (0.7 -1.3)	0.77	8 (-13 to 30)	0.45	4 (-245 to 253)	0.98
	ATT (2 copies)	0.2%	0.6 (0.1 -2.9)	0.55	16 (-124 to 156)	0.82	-45 (-1,667 to 1577)	0.96
SSTR5 -singleton	Major homozygote	90.9%	1.0 (Reference)	0.20	0 (Reference)	0.002	0 (Reference)	0.0003
rs4988483-C/A	Heterozygote	8.9%	1.2 (0.96-1.5)		-23 (-42 to -4)		-333 (-553 to -112)	
	Minor homozygote	0.3%	0.6 (0.2 -2.1)		-103 (-186 to -21)		-1111 (-2065 to -156)	

Abbreviation: OR, odds ratio.

*Odds ratios were assessed by conditional logistic regression.

†β-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 ($P = 0.0008$; $n_{\text{tests}} = 61$). The effect of rs4988483 seemed to be most consistent with a codominant mode of inheritance, with an approximate 11% per 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 adjust-

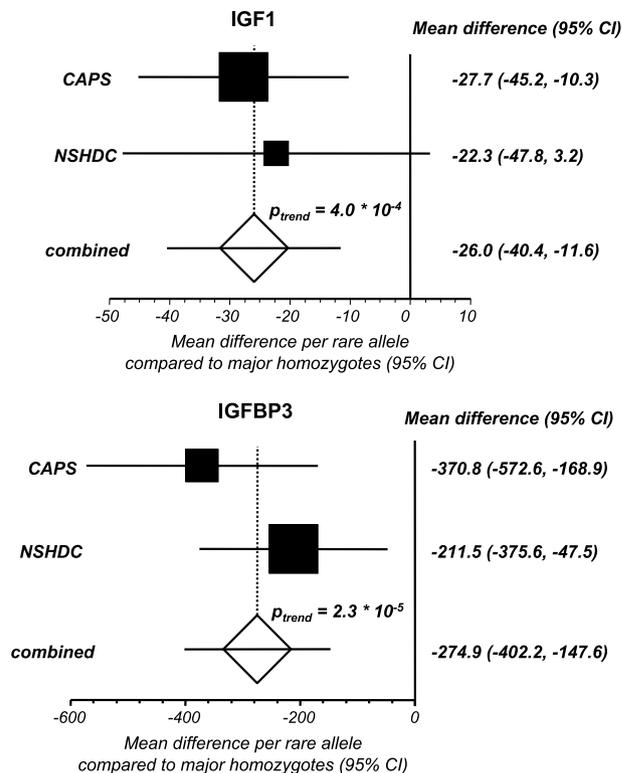


Figure 1. Combined analyses of the rs4988483 trend estimates in relation to plasma IGFI and IGFBP3 levels assessed by calculating the weighted mean of the study specific trend estimates. Horizontal line, 95% CIs. The size of the squares represents the weight that the corresponding study exerts in the weighted mean. The combined estimate is marked with an unfilled diamond that has an ascending dotted line from its upper point.

ing 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 IGFI and IGFBP3 hormone levels. In this a large-scale investigation of common genetic variation in the *SST* and the *SST 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 relatively modest change in hormone levels was limited. A few associations were observed between genetic variation in the *SSTR2* gene and prostate cancer risk, but the statistically modest nature of these associations suggests that they may have arisen by chance. Nevertheless, it is interesting that the associations of both haplotypes associated with risk seem independent from one another, and that they are pronounced in cases with earlier age of diagnosis, consistent with the notion of genetic susceptibility being more relevant to cancer of an earlier age at diagnosis.

A limitation of the study was the failure to design assays for three of the haplotype-tagging SNPs in the *SSTR4* and *SSTR5* genes. Therefore, if there is a true effect modifying allele—either in relation to hormone levels or prostate cancer risk—that is located on any of the poorly captured haplotypes within these genes, our statistical power to detect those associations are limited.

In conclusion, genetic variation in the *SSTR5* gene may explain some of the inherited variability of circulating IGFI and IGFBP3 hormone levels, but these associations does not seem to translate into prostate cancer risk.

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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⁷ <http://blocks.fhrc.org/sift/SIFT.html>

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