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Associations Between iCOGS Single Nucleotide Polymorphisms and Upgrading in Both Surgical and Active Surveillance Cohorts of Men with Prostate Cancer

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Abstract

Background—Associations have been documented recently between some of the 23 single nucleotide polymorphisms newly discovered with the Collaborative Oncological Gene-environment Study iCOGS array that indicate prostate cancer (PCa) risk and aspects of disease aggressiveness. The utility of these iCOGS SNPs remains to be determined in active surveillance (AS).

Objective—To determine associations between iCOGS SNPs and upgrading among men who underwent surgical treatment and AS for low-risk PCa.

Design, setting, and participants—The genotypes of the 23 iCOGS SNPs were determined for all white subjects with biopsy Gleason score (GS) 6 including 950 men who underwent

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definitive treatment with surgery and 209 men who elected AS. The clinical and pathologic characteristics were documented for all subjects.

Outcome measures and statistical analysis—Men who underwent surgery were grouped according to their pathologic GS (upgraded was defined as GS ≥ 7; nonupgraded remained GS 6). Men who were enrolled in AS were also grouped according to their GS on subsequent surveillance biopsies. Statistical analyses were performed comparing the genotypes between the upgraded and nonupgraded groups.

Results and limitations—Overall, 31% and 34% of men were upgraded in the surgery and AS cohorts, respectively. Three iCOGS SNPs were significantly associated with the risk of upgrading in the surgical cohort. After correction for multiple testing, only rs11568818 on chromosome 11q22 remained significantly associated with upgrading. Assessment of this allele in the AS cohort reveals that it was present at noteworthy higher frequencies in men with high-grade disease on surveillance biopsies compared with nonupgraded men ($p = 0.003$). This study was primarily limited by the homogeneous patient population.

Conclusions—This is the first report of a SNP on chromosome 11q22 associated with higher grade disease in a surgical cohort that is also validated for eventual upgrading in a prospective AS cohort.

Patient summary—We examined the relationship between a group of genetic markers and prostate cancer (PCa) aggressiveness in a group of patients who underwent surgery for PCa and a group of patients who were enrolled in active surveillance. We found that these genetic markers helped predict which patients had more aggressive disease in both groups.

Keywords

Active surveillance; Genetics; Prostate cancer; Single nucleotide polymorphisms

1. Introduction

A major shift has occurred in our understanding of the hereditary basis of prostate cancer (PCa) in recent years due to advances in sequencing technologies at decreased costs. For example, recent studies using the Collaborative Oncological Gene-environment Study iCOGS array have provided more in-depth coverage that permitted the identification of 23 novel genetic variants, called *single nucleotide polymorphisms* (SNPs), that are associated with increased PCa risk. These contribute to a seemingly growing panel of approximately 100 panels of unique SNPs that have been associated with PCa susceptibility [1–11]. Although their association with PCa risk is well established, their association with adverse pathologic features (eg, high-grade disease) and clinical outcomes remains underinvestigated.

There has been a movement toward greater use of active surveillance (AS) for the management of low-risk PCa concurrent with our increased understanding of PCa genetics. The goal of AS is to intentionally delay definitive treatment of prostate tumors to decrease the possible morbidities associated with these therapies without compromising PCa survival. However, it has been shown that 33% of men (range: 14–41%) will progress to definitive

treatment at 5 yr on an AS protocol [12]. Given the high number of men who ultimately progress on AS, it would be desirable to better characterize the aggressiveness of low-risk PCa at AS enrollment.

We hypothesized that some of the iCOGS SNPs are associated with adverse pathologic features and can be used to predict higher grade disease. We sought to initially evaluate the association between the iCOGS PCa risk alleles [5] and the frequency of upgrading at radical prostatectomy (RP). We then attempted to validate these possible associations in an independent cohort of men enrolled in a formal AS program.

2. Materials and methods

2.1. Populations

All included subjects provided written informed consent for genetic studies prior to enrollment. Data were prospectively collected for all men at enrollment including age, family history of PCa, race, and serum prostate-specific antigen (PSA). Two populations of men of European ancestry were included in this study including a cohort of men who underwent RP and a cohort of men enrolled in a formal AS cohort approved by an institutional review board. All included men in the surgical cohort who underwent RP by a single surgeon (W.J.C.) at Northwestern University after 2005. The clinical and pathologic features of all subjects were recorded. All pathology specimens were reviewed at their respective medical centers (Northwestern or NorthShore University) by a genitourinary pathologist. Men were included if they had Gleason score (GS) 3 + 3 disease on diagnostic biopsy. The surgical cohort was then categorized into those who continued to have GS 6 disease (*nonupgraded*) and those who had higher grade disease (GS ≥ 7; *upgraded*) on surgical pathology.

The AS cohort included men who enrolled in a prospective protocol at NorthShore University Health System. Inclusion criteria for our AS program is limited to men with National Comprehensive Cancer Network very low-risk and low-risk PCa defined as an initial diagnosis on biopsy of GS 6, PSA <10, and three or fewer cores involved with cancer on a standard template 12-core prostate biopsy performed under ultrasound guidance. Confirmatory biopsies were performed within 6–12 mo using a magnetic resonance imaging (MRI) fusion biopsy with the BioJet real-time MR-transrectal ultrasound fusion biopsy platform (Analogic, Boston, MA, USA). Biopsies were then repeated every 12–18 mo or for cause. Men in this cohort were categorized into two groups based on the results of their surveillance biopsies: men who continued to have either no cancer or GS 6 disease (nonupgraded) and those who were diagnosed with higher grade disease (upgraded).

2.2. Genotyping

DNA samples were performed on whole blood samples that were sent out for genetic analysis. Genotyping was performed using the Centaurus platform (Nanogen Inc., San Diego, CA, USA). We genotyped 23 iCOGS SNPs that had previously been identified as potentially associated with increased PCa aggressiveness [5].

2.3. Statistical analysis

Clinicopathologic characteristics were compared by upgrading of PCa at surgery in the RP cohort. Categorical variables were compared using the chi-square test or Fisher exact test (for small cell size), and continuous variables were compared using the *t* test or Mann-Whitney *U* test. Cox proportional hazards models were used to determine predictors of time to upgrade within the AS cohort. The relationship between the allele counts of the iCOGS SNPs and upgrading in the two cohorts was investigated using the chi-square test. Bonferroni correction was used to account for multiple sampling. We then performed univariate and multivariate logistic regression models, adjusting for age and PSA, to evaluate the strength of the relationship between the SNPs and the likelihood of disease upgrading in the RP cohort. The association between the allele counts of the iCOGS SNPs and upgrading was validated within the AS cohort using univariate Cox proportional hazards models. All statistical analyses were performed with SAS v.9.2 (Cary, NC, USA) or Stata (College Station, TX, USA).

3. Results

Table 1 shows the clinical characteristics of 950 white men with biopsy GS 6 disease who underwent surgery after 2005. A total of 30.7% of these men had higher grade disease on surgical pathology. The average age of the overall group was 58.3 yr, and the upgraded group was significantly older than the nonupgraded group at 59.5 versus 57.8 yr, respectively ($p < 0.001$). The upgraded group had a significantly higher median PSA density of 0.11 versus 0.09 ng/ml per cubic centimeter of prostate ($p < 0.001$). In addition, the upgraded group had a significantly higher median PSA compared with the nonupgraded group (5.0 vs 4.5 ng/ml; $p < 0.001$). Pathologic tumor stage was significantly higher in the upgraded group compared with the nonupgraded group (Table 1).

Table 2 demonstrates the clinical characteristics of the AS cohort. Overall, 209 men of European ancestry met the inclusion criteria including 71 who were upgraded on surveillance biopsies. The mean age of the cohort was 66.9 yr, and 38.4% of the patients reported a first-degree family history of PCa. There were no significant differences in clinical characteristics between the two groups of men on AS in time-to-event analysis. However, nonupgraded men had a significantly lower median serum PSA at enrollment compared with those men who were upgraded on surveillance biopsy (4.2 vs 5.2 ng/ml; $p < 0.001$). In addition, higher PSA density was associated with upgrading (hazard ratio [HR]: 1.1 by nanograms per milliliter per cubic centimeter of prostate; $p = 0.004$). The number of biopsy cores involved with cancer at enrollment as well as at last biopsy were significantly higher in the upgraded men ($p = 0.27$ and $p < 0.001$, respectively). Both cohorts were genotyped for the iCOGS SNPs (Table 3 and 4). SNPs rs11568818 on chromosome 11 ($p = 0.003$), rs2427345 on chromosome 20 ($p = 0.020$), and rs7141529 on chromosome 14 ($p = 0.009$) were significantly associated with upgrading in the surgical cohort. In a univariate logistic regression model, rs11568818 and rs2427345 remained significant predictors of upgrading in the surgical cohort. Multivariate regression analysis was performed to assess the association between the iCOGS SNPS and upgrading at the time of RP after controlling

for age, serum PSA level, and the other iCOGS SNPs (Table 5). Age, serum PSA concentration, rs11568818, and rs2427345 were associated with upgrading.

Finally, the associations between the three iCOGS SNPs and higher grade disease were then explored in an independent cohort of PCa patients undergoing AS. There was not a sufficient sample size to evaluate all 23 SNPs after correcting for multiple testing. Therefore, the analysis was limited to only the three SNPs with at least nominal associations with upgrading in the surgical cohort. When analyzed in a time-to-event nature, the HR for upgrading was statistically significant for rs11568818, rs2427345, and rs7141529.

4. Discussion

The rate of identification of PCa risk variants is rapidly increasing because of recent advancements in our understanding of the genetics of PCa. It is pertinent to determine whether any of these SNPs are associated with aggressive pathologic features. Although relationships between specific SNPs and adverse pathologic features (including grade and tumor volume) have been reported in some studies, only a few have evaluated associations with upgrading and/or their potential relevance in an AS cohort [13,14].

There is a great amount of interest around improving the ability of clinicians to predict progression of patients undergoing AS for PCa given the high number of progressors defined by having higher grade disease [12]. Previous publications have attempted to use clinical characteristics such as PSA, prostate volume, percentage of involved tissue, GS, and number of cores positive for PCa to develop nomograms to predict disease progression [15–18]. Our cohort suggests older men are more likely to have higher grade disease, which is consistent with previous findings by Ko et al [19]. Given that the study was comparing two different groups based on disease progression, rather than being a case-control design, this likely represents a true difference between the two groups. However, the predictive value of these patient characteristics is modest.

To our knowledge this is the first study to evaluate these iCOGS PCa risk SNPs within detailed cohorts of men with PCa undergoing surgery and AS. This set of SNPs was chosen for evaluation because of previous genome-wide association studies indicating that they may be associated with both PCa risk and aggressive PCa. In the initial report of the iCOGS SNPs, rs11568818, rs2427345, and rs7141529 had a nonsignificant trend toward association with aggressive PCa, defined as a GS ≥ 8, PSA >100 ng/ml, extrapelvic disease, or death from PCa [5]. Two of these SNPs were shown to be significantly associated with increased odds of upgrading at RP. The odds ratios of 1.44 for rs11568818 and 1.31 for rs2427345 are both statistically and clinically significant. Further study with more patients undergoing AS is required to further investigate these potential relationships. The ability to counsel patients of such increased risk of progression will empower patients to make more informed decisions regarding their care. There may be biologic plausibility to the two SNPs found to predict for upgrading at surgery. The rs11568818 is found on chromosome 11 and is a part of the exon sequence of matrix metalloprotease 7, which some have suggested plays a role in the invasiveness of PCa [20]. The rs2427346 is an intron on chromosome 20 associated with GATA binding protein 5 (*GATA5*) and Cdk5 and Abl enzyme substrate 2 (*CABLES2*), both

of which are associated with cell cycle progression. The rs7141529 is an intron on chromosome 14 upstream of RAD51 Paralog B (*RAD51B*), which is part of the DNA mismatch repair mechanism.

Although the present study benefits from its relatively large sample size, prospective data collection, and moderate term follow-up, it is potentially limited by its homogeneous patient population (all were of European descent). Biopsy data did not include location of the tumors, and if one group had more anterior biopsies, there may have been a bias toward more upgrading. In addition, prostate and tumor sizes were not available for all patients included in the study, so we cannot comment on whether these SNPs are possibly related to tumor or prostate size, which may have introduced sampling error into the grading of prostate biopsy specimens (ie, biopsies of larger prostates may have been more likely to miss high-grade disease). There is also the possibility that some men who were upgraded harbored higher grade disease at diagnosis but were not identified at the time due to sampling error. In an era of prostate biopsies guided by MRI, undersampling may reduce the incidence of undergrading at initial diagnosis. Further studies of these SNPs in a larger, more diverse population would be warranted. In addition, longer term follow-up evaluating for biochemical recurrence may provide more information about the ultimate clinical significance of these findings.

As more SNPs from various studies are found to be associated with disease upgrading, study of these significant SNPs in a single cohort may provide an even more robust tool for risk stratification for aggressive PCa. An additional approximately 80 SNPs have been reported to be associated with PCa, and analysis of these SNPs may provide for a better predictive tool by presenting a summative effect. Only the 23 SNPs we reported on in this paper were studied in this patient population. In the future, it may be possible to create a panel of SNPs that can help with disease prognostication and help identify which subsets of men require treatment. However, this can only be accomplished after all SNPs associated with PCa risk have been identified, independently evaluated, and validated for their associations with disease aggressiveness.

5. Conclusions

Our results validate that only some of the iCOGS SNPs are associated with PCa susceptibility and aggressive disease in our cohort of men of European ancestry. In an AS cohort, they are significantly associated with increased odds of eventual upgrading. Further validation of their associations in independent study cohorts, including those of different ancestries, should be pursued.

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Take-home message

We examined the relationship between the 23 single nucleotide polymorphisms (SNPs) identified with the Collaborative Oncological Gene-environment Study iCOGS chip and prostate cancer upgrading in a surgical and active surveillance cohort. We found that these SNPs are associated with more aggressive disease in both surgical and active surveillance protocols.

Table 1

Clinicopathologic characteristics of surgical cohort by upgrading status

	Overall	Upgraded	Nonupgraded	*p* value
n (%)	950 (100.0)	292 (30.7)	658 (69.3)	
Age, yr, mean	58.3	59.5	57.8	<0.001
1st quartile ≤53, *n* (%)	239 (25.2)	57 (19.6)	182 (27.7)	<0.001
2nd quartile 53–58, *n* (%)	237 (25.0)	62 (21.3)	175 (26.6)	
3rd quartile 58–64, *n* (%)	272 (28.7)	102 (35.1)	170 (25.9)	
4th quartile ≥64, *n* (%)	200 (21.1)	70 (24.1)	130 (19.8)	
Median serum PSA, ng/ml	4.7	5	4.5	<0.001
0–2.5, *n* (%)	101 (10.7)	15 (5.1)	86 (13.1)	<0.001
2.5–4, *n* (%)	189 (20.0)	49 (16.8)	140 (21.4)	
4–10, *n* (%)	600 (63.3)	200 (68.5)	400 (61.1)	
>10, *n* (%)	57 (6.0)	28 (9.6)	29 (4.4)	
Median prostate volume, ml	46	45.1	46.5	0.22
Median PSA density, ng/ml/cm^3 prostate	0.10	0.11	0.09	<0.001
Pathologic Gleason score, *n* (%)				
6	658 (69.3)	0	658 (100.0)	<0.001
7	277 (29.2)	277 (94.9)	0	
8–10	15 (1.6)	15 (5.1)	0	
Pathologic stage, ≤pT2, *n* (%)	834 (88.0)	224 (77.0)	610 (92.8)	<0.001
>pT2, *n* (%)	114 (12.0)	67 (23.0)	47 (7.2)	
Extracapsular extension, *n* (%)	99 (10.4)	61 (20.9)	38 (5.8)	<0.001
Seminal vesicle invasion, *n* (%)	14 (1.5)	12 (4.1)	2 (0.3)	<0.001
Positive surgical margins, *n* (%)	114 (12.0)	51 (17.5)	63 (9.6)	<0.001
Lymph node metastases, *n* (%)	0 (0.0)	0	0	–
Median follow-up, mo	49	51	49	0.50

PSA = prostate-specific antigen.

Table 2

Clinicopathologic characteristics of active surveillance cohort by upgrading status and univariate Cox proportional hazards models for time to upgrading

	Overall *n* (%)	Upgraded *n* (%)	Nonupgraded *n* (%)	Hazard ratio (95% CI)	*p* value
n	209 (100.0)	71 (34.0)	138 (66.0)		
Age at enrollment, yr, mean	66.9	67.2	66.8	0.99 (0.96–1.03)	0.85
≤53	4 (1.9)	2 (2.9)	2 (1.5)	Reference	
53–58	15 (7.3)	6 (8.7)	9 (6.5)	0.63 (0.13–3.15)	0.58
58–64	55 (26.6)	17 (24.6)	38 (27.5)	0.67 (0.15–2.89)	0.59
≥64	133 (64.3)	44 (63.8)	89 (64.5)	0.54 (0.13–2.26)	0.40
Family history of PCa	73 (38.4)	28 (42.4)	45 (36.3)	1.2 (0.75–1.99)	0.42
Serum PSA, ng/ml, at enrollment, median	4.4	5.2	4.2	1.1 (1.04–1.15)	<0.001
≤2.5	33 (15.9)	8 (11.4)	25 (18.1)	Reference	
2.5–4	50 (24.0)	13 (18.6)	37 (26.8)	1.2 (0.49–2.84)	0.72
4–10	105 (50.5)	37 (52.9)	68 (49.3)	1.9 (0.89–4.10)	0.10
>10	20 (9.6)	12 (17.1)	8 (5.8)	3.4 (1.40–8.43)	0.007
Prostate volume, ml, median	44.5	41.0	45.0	0.99 (0.97–1.01)	0.19
PSA density, ng/ml/cm^3, median	0.09	0.11	0.09	1.1 (1.02–1.10)	0.004
Between 1 and 3 positive cores for cancer at enrollment	7 (9.7)	4 (15.4)	3 (6.5)	3.3 (1.15–9.57)	0.027
No. of cores at last biopsy					
0	60 (43.2)	4 (11.4)	56 (53.9)	Reference	
1	22 (15.8)	5 (14.3)	17 (16.4)	4.4 (1.06–18.5)	0.042
2	14 (10.1)	5 (14.3)	9 (8.7)	12 (2.79–50.1)	<0.001
≥3	43 (30.9)	21 (60.0)	22 (21.2)	17 (5.09–57.8)	<0.001

CI = confidence interval; PCa = prostate cancer; PSA, prostate-specific antigen.

Table 3

Allele counts of iCOGS single nucleotide polymorphisms within the surgical cohort by upgrading status

				Nonupgraded, %			Upgraded, %			*p* value
	Location	**SNP**	**Allele**	**0**	**1**	**2**	**0**	**1**	**2**	
SNP 1	11	rs11568818	AG	29.1	50.4	20.5	39.7	46.1	14.2	0.003
SNP 2	17	rs11650494	GA	82.3	16.9	0.8	79.4	18.5	2.1	0.17
SNP 3	2	rs11902236	CT	51.2	39.2	9.6	48.8	37.6	13.6	0.20
SNP 4	7	rs12155172	GA	58.7	34.4	7.0	59.8	32.9	7.3	0.9
SNP 5	1	rs1218582	CT	20.9	50.2	28.9	19.4	51.8	28.9	0.86
SNP 6	12	rs1270884	CT	25.1	48.0	27.0	21.8	52.8	25.4	0.37
SNP 7	4	rs1894292	GA	29.6	49.7	20.7	26.7	47.3	26.0	0.20
SNP 8	6	rs1933488	AG	35.6	45.1	19.3	38.1	44.8	17.1	0.64
SNP 9	6	rs2273669	AG	73.0	25.0	2.0	68.3	28.5	3.2	0.26
SNP 10	20	rs2427345	CT	39.9	45.2	14.9	49.8	40.1	10.1	0.020
SNP 11	6	rs3096702	CT	46.7	40.6	12.7	41.0	41.3	17.7	0.09
SNP 12	X	rs35330386	CT	77.9	0.0	22.1	79.7	0.0	20.3	0.58
SNP 13	2	rs3771570	CT	70.9	25.6	3.6	68.2	29.0	2.8	0.50
SNP 14	10	rs3850699	TC	53.3	39.7	7.1	51.1	38.9	10.0	0.31
SNP 15	1	rs4245739	AC	55.9	38.4	5.7	56.2	37.5	6.4	0.91
SNP 16	20	rs6062509	TG	49.3	41.8	8.9	50.4	43.7	6.0	0.33
SNP 17	17	rs684232	AG	40.6	45.0	14.5	41.3	45.2	13.4	0.91
SNP 18	5	rs6869841	CT	56.8	37.2	6.0	59.8	36.3	3.9	0.39
SNP 19	8	rs6984769	CT	67.1	30.4	2.5	70.7	26.8	2.5	0.54
SNP20	14	rs7141529	CT	23.5	54.8	21.7	31.3	44.2	24.5	0.009
SNP 21	18	rs7241993	CT	50.2	41.5	8.3	52.6	38.6	8.8	0.71
SNP 22	3	rs7611694	AC	41.7	44.0	14.3	36.9	49.7	13.5	0.28
SNP 23	14	rs8008270	CT	66.5	30.3	3.2	71.1	24.6	4.3	0.18

SNP = single nucleotide polymorphism.

Table 4

Univariate model: association between iCOGS single nucleotide polymorphisms and upgrading in the surgical cohort

SNP	OR	95% CI	*p* value
rs11568818	1.4	1.2–1.7	0.0008
rs2427345	1.4	1.1–1.7	0.005
rs7141529	1.1	0.9–1.4	0.31

CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.

Table 5

Multivariate model: association between clinical characteristics, iCOGS single nucleotide polymorphisms, and upgrading in the surgical cohort

SNP	OR	95% CI	*p* value
Age	1.03	1.02–1.05	0.007
PSA	1.05	1.01–1.10	0.04
rs11568818	1.46	1.17–1.82	0.0009
rs2427345	1.32	1.05–1.65	0.02
rs7141529	1.14	0.92–1.42	0.25

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen; SNP = single nucleotide polymorphism.

Table 6

Univariate Cox proportional hazards models for time-to-upgrade by allele counts of iCOGS single nucleotide polymorphisms within active surveillance cohort

	Location	SNP	Hazard ratio	95% CI	*p* value
SNP 1	11	rs11568818			
		0	Reference		
		1	3.7	1.71–7.89	<0.001
		2	5.3	2.22–12.70	<0.001
SNP 10	20	rs2427345			
		0	Reference		
		1	3.1	1.72–5.50	<0.001
		2	3.7	1.41–9.89	0.008
SNP 20	14	rs7141529			
		0	Reference		
		1	3.1	1.36–7.11	0.007
		2	3.2	1.23–8.23	0.017

CI = confidence interval; SNP = single nucleotide polymorphism.