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Clinical Cancer Research

The Prostate Cancer Susceptibility Variant rs2735839 Near *KLK3* Gene Is Associated with Aggressive Prostate Cancer and Can Stratify Gleason Score 7 Patients

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Abstract

Purpose: Gleason score (GS) 7 prostate cancer is a heterogeneous disease with different clinical behavior. We sought to identify genetic biomarkers that may predict the aggressiveness of GS 7 diseases.

Experimental Design: We genotyped 72 prostate cancer susceptibility SNPs identified in genome-wide association studies in 1,827 white men with histologically confirmed prostate adenocarcinoma. SNPs associated with disease aggressiveness were identified by comparing high-aggressive (GS $\geq$8) and low-aggressive (GS $\leq$6) cases. The significant SNPs were then tested to see whether they could further stratify GS 7 prostate cancer.

Results: Three SNPs—rs2735839, rs10486567, and rs103294—were associated with biopsy-proven high-aggressive (GS $\geq$8) prostate cancer ($P < 0.05$). Furthermore, the frequency of the variant allele (A) at rs2735839 was significantly higher in patients with biopsy-proven GS 4+3 disease than in those with GS 3 + 4 disease ($P = 0.003$). In multivariate logistic regression analysis, patients carrying the A allele at rs2735839 exhibited a 1.85-fold (95% confidence interval, 1.31–2.61) increased risk of being GS 4 + 3 compared with those with GS 3 + 4. The rs2735839 is located 600 base pair downstream of the *KLK3* gene (encoding PSA) on 19q13.33 and has been shown to modulate PSA level, providing strong biologic plausibility for its association with prostate cancer aggressiveness.

Conclusions: We confirmed the association of the rs2735839 with high-aggressive prostate cancer (GS $\geq$8). Moreover, we reported for the first time that rs2735839 can stratify GS 7 patients, which would be clinically important for more accurately assessing the clinical behavior of the intermediate-grade prostate cancer and for tailoring personalized treatment and posttreatment management. *Clin Cancer Res; 20(19); 5133–9. ©2014 AACR.*

Introduction

The majority of prostate cancers diagnosed in the widespread use of PSA screening era are not life-threatening (1, 2). However, the fear of dying of cancer prompted most patients to proceed with treatment of nonaggressive prostate cancer, even for Gleason score (GS) 6 disease (3). Given the well-recognized overdiagnosis and overtreatment, physicians have gradually taken into account alleviation of the physiologic and psychologic burden for men diagnosed with nonaggressive prostate cancer that otherwise would not kill them (1, 4). On the other hand, intensive surveillance and intervention are required to reduce recurrence and disease-related deaths in men with more aggressive prostate cancer.

Although the definition of aggressive prostate cancer has differed across studies (5–8), the Gleason grading system remains the most powerful prognostic predictors for this cancer more than 40 years after its inception and nearly 10 years after its last update because it delineates the architectural patterns of tumors (9). GS is the core value in risk-scoring systems, including the D'Amico classification system (10), which incorporates the GS, clinical stage, and PSA level to stratify the risk of recurrence of localized prostate cancer before treatment and is used to guide treatment selection. GS 7, consisting of GS 3 + 4 and GS 4 + 3, is the intermediate grade in the Gleason grading system, accounting for 30% to 40% of all prostate cancer cases diagnosed with needle biopsy (11). GS 4 + 3 subtype has had less favorable clinical outcomes than the GS 3 + 4 subtype (12, 13). Patients with GS 7 prostate cancer are a heterogeneous group with dramatically different prognosis, and currently there are no reliable biomarkers to further

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Translational Relevance

Gleason score (GS) 7 prostate cancer is a heterogeneous group with different prognosis. Biomarkers are urgently needed to improve risk stratification of GS 7 patients. In this study, we identified a biologically plausible variant near the KLK3 gene (encoding PSA) that is associated with aggressive prostate cancer and especially can risk stratify GS 7 patients. This finding provides valuable information for assessment of the aggressiveness of GS 7 prostate cancer and may help clinicians tailor personalized treatment and posttreatment management for patients with this disease.

stratify this group. Likewise, the D'Amico intermediate-risk group is clinically heterogeneous because it includes many of GS 7 disease. Treatment options for GS 7 disease are controversial because the burden of combined treatment modalities may outweigh the potential benefit in some patients. Therefore, personalized treatments based on additional biomarkers to stratify GS 7 prostate cancer are urgently needed.

Recent genome-wide association studies (GWAS) have identified over 70 SNPs as genetic susceptibility loci for prostate cancer. Some of these prostate cancer susceptibility variants have been associated with disease aggressiveness (e.g., differentiate GS ≤ 6 from GS ≥ 8) and prognosis (e.g., associated with prostate cancer–specific survival). However, none of these SNPs have been shown to be able to further stratify GS 7 patients. Identifying genetic biomarkers capable of risk stratification in GS 7 patients has important clinical implications because it can improve prognosis prediction based on histopathologic features and also remedy diagnostic inaccuracy of downgrading tumors which occurred more commonly in needle biopsy (14).

In the present study, we genotyped 72 GWAS-identified prostate cancer susceptibility loci in 1,827 white patients with prostate cancer and analyzed associations of these variants with prostate cancer aggressiveness, particularly whether they can differentiate patients with localized GS 7 prostate cancer.

Materials and Methods

Study population

Men with previously untreated prostate cancer registered at The University of Texas MD Anderson Cancer Center were enrolled in this study. Blood samples were collected from 2,467 men before treatment. Their clinical data, including diagnosis date, PSA level at diagnosis, biopsy-proven GS, clinical stage, treatment, and pathologic and follow-up information were collected from medical records and at patient registration. Age at diagnosis was considered the age at the date of first prostate cancer–positive biopsy. PSA level at diagnosis was defined as the PSA level as determined at the time of diagnostic biopsy. All biopsy slides from outside institutions were reviewed by pathologists at MD Anderson. When the pathologic diagnosis was different, the GS assessment at MD Anderson was used.

Only white patients with localized disease at the time of diagnosis were included in our study. Two criteria were used to define aggressiveness: one based on the GS regardless of PSA level and clinical T stage and the other based on the D'Amico risk criteria. GS ≥ 8 or high D'Amico risk was defined as high-aggressive cancer. This study was approved by the MD Anderson Institutional Review Board. Each subject consented to having their clinical data obtained and providing blood samples for DNA extraction for research.

SNP selection and genotyping

About 80 SNPs reached genome-wide significance in association with the risk of prostate cancer in GWAS published (http://www.genome.gov/gwastudies/; refs. 15–28). These SNPs were selected for the design of a GoldenGate VeraCode assay (Illumina). After score-based selection, 72 SNPs were retained for genotyping. All DNA samples were extracted from peripheral whole blood by using the QIAamp DNA extraction Kit (QIAGEN). Genotyping assay was then run on the Illumina BeadXpress Reader. Genotyping data were analyzed and exported using the BeadStudio software. The genotyping call rate for the SNPs in this study was 99.86%.

Statistical analysis

This study included a two-step data analysis. In the first step, the allele frequencies of 72 SNPs were compared between the low-aggressive phenotypes and high-aggressive phenotypes for two criteria of disease aggressiveness, i.e., men with a GS ≤ 6 disease versus men with a GS ≥ 8 disease, and the D'Amico low-risk versus high-risk groups. In the second step, SNPs nominally associated with aggressiveness derived from the first analysis were further tested for their ability to stratify the GS 7 group (using GS $3 + 4$ and GS $4 + 3$ as proxy for aggressiveness).

Patients' clinical and disease characteristics were summarized as median values for continuous variables and as numbers and percentages for categorical variables. Statistical analyses were performed using the Stata software program (version 10.0; StataCorp). The association of the genotype of each SNP with risk of high-grade prostate cancer between GS ≤ 6 and GS ≥ 8 and between GS $3 + 4$ and GS $4 + 3$ was estimated as the OR and 95% confidence interval (CI) using unconditional multivariate logistic regression analysis with adjustments for age, PSA level at diagnosis, and clinical T stage. All *P* values were two-sided, with values less than 0.05 considered statistically significant. The *P* values were not corrected for multiple testing.

Results

Characteristics of patients

We included a total of 1,827 individuals with clinically localized prostate cancer in this contemporary series. Their

clinicopathologic features are listed in Table 1. On the basis of the pretreatment biopsy, 675 men had GS $\leq$6 prostate cancer, 921 had GS 7 disease, and 231 had GS $\geq$8 disease. When grouped according to D'Amico risk classification, 608 men were in the low-risk group, 861 were in the intermediate-risk group, and 346 were in the high-risk group. The majority of the subjects (95.7%) received their prostate cancer diagnoses from January 2005 to March 2012. About two thirds (62.8%) of the subjects presented with PSA levels ranging from 4 to 10 ng/mL, reflecting a widely PSA-screened population. Among the patients, 947 patients underwent definitive radical prostatectomy as primary treatment with or without combined treatments, 390 patients underwent definitive radiotherapy with or without androgen deprivation therapy, and 49 patients received other local or systemic treatment, including cryoablation, high-intensity focused ultrasound, transurethral resection of prostate, and androgen deprivation therapy.

Table 1. Clinical characteristics of the study patients with localized prostate cancer

Characteristics	*n* (%)
Total	1,827
Age at diagnosis, years	
Median (range)	62 (31–87)
Clinical stage, *n* (%)	
T1	1,504 (82.3)
T2a–T2b	142 (7.8)
T2c–T4	168 (9.2)
Tx	13 (0.7)
PSA level at diagnosis, ng/mL	
<4	453 (24.8)
4–10	1,147 (62.8)
10–20	154 (8.4)
$\geq$20	70 (3.8)
Unknown	3 (0.2)
Biopsy-proven GS	
$\leq$6	675 (36.9)
7	921 (50.4)
$\geq$8	231 (12.6)
D'Amico risk group	
Low	608 (33.3)
Intermediate	861 (47.1)
High	346 (18.9)
Not grouped	12 (0.7)
Primary treatment	
Radical prostatectomy	947 (51.8)
Radiotherapy	390 (21.3)
Other treatment[a]	49 (2.7)
Surveillance or unknown[b]	441 (24.1)

[a]Cryoablation, high-intensity focused ultrasound, transurethral resection of prostate, or androgen deprivation therapy.
[b]Patients undergoing active surveillance/watchful waiting or whose initial treatment information was unavailable.

Association of SNPs with prostate cancer aggressiveness

In the first step of our analysis, we compared the allele frequencies of 72 SNPs in patients with biopsy-proved GS $\leq$6 disease ($n = 675$) and those with GS $\geq$8 disease ($n = 231$) and between patients in the D'Amico low-risk group ($n = 608$) and high-risk group ($n = 346$). The allele frequencies of each SNP are presented in Supplementary Table S1. We found nominally significant associations ($P < 0.05$) of three SNPs—rs2735839 at 19q13, rs10486567 at 7p15, and rs103294 at 19q13—with GS in multivariate logistic regression analysis under an additive model when adjusting for age (Table 2). The rs2735839 and rs10486567 were the only 2 among all 72 susceptibility SNPs that were consistently associated with prostate cancer aggressiveness when comparing the D'Amico low-risk and high-risk groups ($P < 0.05$).

rs2735839 can stratify GS 7 patients

In the second step of our analysis, we analyzed the above three significant SNPs to determine their frequency in patients with GS 7 prostate cancer. In 921 men with biopsy-proven GS 7 disease, the frequency of the variant allele (A) at rs2735839 was significantly higher for the GS 4 + 3 subtype (0.17) than for the GS 3 + 4 subtype (0.11; $P < 0.001$; Figure 1), consistently with the higher frequency of allele (A) in GS $\geq$8 patients compared with GS $\leq$6 patients in step one analysis. By using unconditional multivariate logistic regression model, we observed a significantly increased risk of GS 4 + 3 disease in the presence of (A) allele for those with biopsy-proven GS 7 disease (OR, 1.85; 95% CI, 1.31–2.61; $P = 0.0005$) under a dominant model after adjustment for age, PSA level at diagnosis, and clinical T stage (Table 3). We observed no differences in rs103294 and rs10486567 allele frequencies between GS 3 + 4 and GS 4 + 3 cases.

Discussion

In this study, we found that three GWAS-identified prostate cancer susceptibility SNPs may define high-aggressive prostate cancer owing to their significant associations with biopsy-proven GS in patients with localized disease. More interestingly, the variant allele of rs2735839 appears to be able to risk stratify patients with GS 7 disease. To the best of our knowledge, this is the first study to demonstrate that GWAS-identified susceptibility SNPs can be used to stratify GS 7 prostate cancer.

Although very few SNPs identified in GWASs have been consistently associated with cancer aggressiveness, our finding that rs2735839 is associated with prostate cancer aggressiveness is consistent with results of some previous studies. It was reported that this SNP, located at 19q13, was associated with GS (6, 7) and disease aggressiveness (6, 7, 29). We also observed that the variant allele (A) at rs2735839 was associated with more aggressive disease in patients with clinically localized prostate cancer. Xu and colleagues (29) found that the frequency of the allele (A) at rs2735839 was

Table 2. SNPs associated with prostate cancer aggressiveness in biopsy under an additive model

SNP	Chromosomal region	Gene	Genotype	Low-aggressive cancer	High-aggressive cancer	Adjusted OR (95% CI)[a]	*P*
SNPs associated with GS				GS ≤6 ($n = 675$)	GS ≥8 ($n = 231$)		
rs2735839	19q13.33	(Intergenic) *KLK3–KLK2*	GG\AG\AA	531\135\9	168\52\11	1.81 (1.23–2.65)	**0.002**
rs10486567	7p15.2	*JAZF1*	GG\AG\AA	429\227\18	126\90\15	1.54 (1.10–2.16)	**0.012**
rs103294	19q13.42	(Intergenic) *LILRB2–LILRA3*	CC\CT\TT	433\219\23	159\66\6	0.65 (0.45–0.95)	**0.024**
SNPs associated with the D'Amico risk group[b]				Low-risk ($n = 608$)	High-risk ($n = 346$)		
rs2735839	19q13	(Intergenic) *KLK3–KLK2*	GG\AG\AA	476\123\9	257\75\14	1.96 (1.28–3.00)	**0.002**
rs10486567	7p15.2	*JAZF1*	GG\AG\AA	386\206\16	191\136\19	1.70 (1.15–2.54)	**0.009**
rs103294	19q13	(Intergenic) *LILRB2–LILRA3*	CC\CT\TT	396\193\19	230\104\12	0.66 (0.41–1.06)	0.083

NOTE: Bold-faced values indicate significant differences.
[a]Adjusted for age, PSA level, and clinical T stage in the GS comparison and adjusted only for age in D'Amico risk group comparison.
[b]Twelve patients lacking complete information for risk assessment were not grouped.

0.11 in 528 men with less aggressive prostate cancer, compared with 0.14 in 1,017 men with more aggressive disease (defined as pathologic GS ≥7, pathologic T3 disease or higher, or lymph node or distant metastasis in that study) in a series of patients treated with radical prostatectomy. In addition, Pomerantz and colleagues (7) reported that the allele (A) at rs2735839 was associated with increased biopsy-proven GS and high risk of recurrence according to the D'Amico system in a study of 3,945 patients with prostate cancer. Furthermore, Kader and colleagues (6) reported that there was a significant increasing trend of A allele frequency among pathology-proved GS ≤6, GS 3 + 4, GS 4 + 3, and GS ≥8 diseases in 5,749 cases undergoing prostatectomy. Nevertheless, our study was the first to show a significant association of rs2735839 with GS 4 + 3 and GS 3 + 4. Clinically, it has been established that patients with GS 4 + 3 cancer have a greater disease extent and worse prognosis than those with GS 3 + 4 cancer (13), (30–33). Chan and colleagues (13) estimated that the 5-year actuarial risk of progression was 15% for GS 3 + 4 disease and 40% for GS 4 + 3 disease. In a multicenter study of 11,500 patients with prostate cancer treated with radical prostatectomy, Eggener and colleagues (33) observed a 3.5-fold higher 15-year prostate cancer–specific mortality for GS 4 + 3 disease than for GS 3 + 4 disease (4.2% vs. 1.2%), indicating more aggressive biologic behavior of GS 4 + 3 disease. Because we do not have sufficient numbers of progression and mortality events in our patient cohort, we used GS 3 + 4 and GS 4 + 3 as indicators of aggressiveness in GS 7 patients. The fact that rs2735839 can distinguish GS 3 + 4 and GS 4 + 3 patients suggests that this SNP can help risk stratify GS 7 patients.

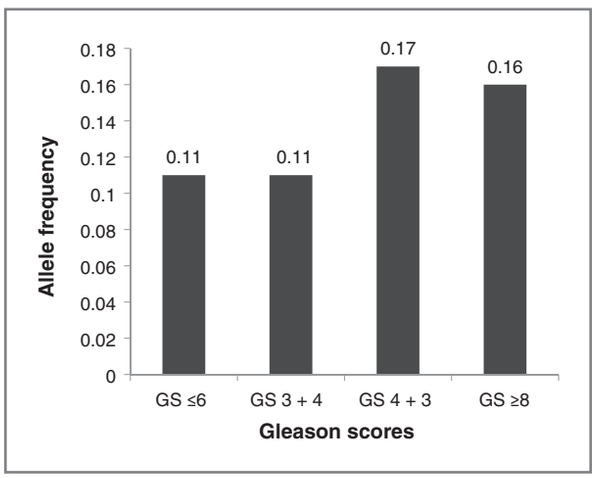

Figure 1. Frequency of the variant allele A at rs2735839 in biopsy-proven GS ≤6, 3 + 4, 4 + 3, and ≥8 cancer.

The rs2735839 is located 600 base pairs downstream of *KLK3* on chromosome 19. *KLK3* belongs to a family of genes encoding kallikreins, which are serine proteases clustered on 19q13. *KLK3* encodes for PSA (also called kallikrein-related peptidase). Genetic variants spanning the *KLK3* locus have been associated with PSA level in some association studies (27), (34–36). A prior study investigating the association of 23 SNPs in the *KLK3* gene with PSA level and prostate cancer risk showed that four alleles significantly associated with lower PSA levels were also associated with lower prostate cancer risk (37). Interestingly, in overall prostate cancer risk analysis, the major allele (G) of rs2735839 is associated with an increased risk, and the G allele was also associated with elevated PSA level. However, in the analysis of aggressiveness, the variant allele (A) is more frequent in more aggressive disease and less frequent in less aggressive disease. Because the majority of patients were diagnosed based on PSA screening, any alleles which contribute to elevated PSA levels are likely to be of higher frequency in patients with prostate cancer, particularly in low-grade, less aggressive screen-detected patients. However, a recent study showed that the association of *KLK3* variants with PSA level cannot completely explain their association with prostate cancer risk and suggests other independent effect of KLK3 variants on prostate cancer aggressiveness and prognosis (37). Notably, it has been

Table 3. Aggressiveness-related SNPs in biopsy-proven GS 3 + 4 ($n = 674$) and GS 4 + 3 prostate cancer ($n = 247$)

SNP	Genotype	GS 3 + 4, *n* (%)	GS 4 + 3, *n* (%)	Adjusted OR (95%CI)[a]	*P*
rs2735839	GG	542 (80.4)	171 (69.2)	Reference	
	AG	119 (17.7)	72 (29.1)	1.95 (1.37–2.78)	**0.0002**
	AA	13 (1.9)	4 (1.6)	0.90 (0.27–2.99)	0.861
	AG+AA	132 (19.6)	76 (30.8)	1.85 (1.31–2.61)	**0.0005**
rs10486567	GG	396 (58.8)	139 (56.3)	Reference	
	AG	232 (34.5)	99 (40.1)	1.22 (0.89–1.67)	0.221
	AA	45 (6.7)	9 (3.6)	0.57 (0.26–1.22)	0.145
	AG+AA	277 (41.2)	108 (43.7)	1.11 (0.82–1.51)	0.5
rs103294	CC	430 (63.8)	157 (63.8)	Reference	
	CT	214 (31.8)	75 (30.5)	0.96 (0.69–1.34)	0.815
	TT	30 (4.5)	14 (5.7)	1.27 (0.64–2.52)	0.494
	CT+TT	244 (36.2)	89 (36.2)	1.00 (0.73–1.37)	0.996

NOTE: Bold-faced values indicate significant differences.
[a]Adjusted for age, PSA, and clinical T stage.

reported that the variant allele (A) at rs2735839 is associated with increased prostate cancer–specific mortality in two independent studies (7, 38). Further analysis of the relationships among rs2735839, PSA level, and prostate cancer risk is warranted in the context of inclusion of multiple factors related to PSA level.

Overdiagnosis and overtreatment are the major problems in the clinical management of patients with prostate cancer. Because the wild-type allele (G) of rs2735839 is associated with elevated PSA and increased risk of patients with low-grade prostate cancer, for those patients with low-grade prostate cancer who have the wild-type allele, they are more likely to be overdiagnosed and cautions should be made when considering these patients for aggressive therapy to avoid overtreatment. Conversely, the variant allele (A) is associated with high-grade prostate cancer at diagnosis and may predict worse prognosis in GS 7 patients; therefore, for those patients who possess the variant allele, they are more likely to have high-risk, aggressive diseases and should be considered for more aggressive therapy. Although the effect size of this single SNP is not sufficient to make such a clinical decision about whether or not treat patients with aggressive therapy, the incorporation of the SNP, together with additional genetic information and other prognostic factors, into a comprehensive nomogram, may affect clinical practice in patients, particularly in patients with clinically defined intermediate risks (e.g., GS 7 diseases), a group for which current clinical decision making is particularly challenging and suboptimal. Patients with intermediate risks have more heterogeneous clinical courses and stand to benefit most from improved prognostication compared with patients with clinically defined low-risk or high-risk profiles to whom a much more substantial improvement of prognostication would be needed to affect clinical decision making.

We also found the variant allele (A) at rs10486567 associated with high-grade prostate cancer, although it could not differentiate between biopsy-proven GS 3 + 4 and GS 4 + 3 diseases. Rs10486567 resides at intron 2 of the *JAZF1* gene on chromosome 7p15.2 (18). Gallagher and colleagues (38) reported that the allele (A) was associated with biochemical recurrence and metastasis in patients with localized prostate cancer, indicating that this locus may have prognostic significance. The third SNP (rs103294) that was associated with GS $\geq$ 8 is located within the leukocyte immunoglobulin-like receptor gene cluster at 19q13.4 (15). Although the function of this SNP is unknown, our finding is interesting and worthy of further investigation.

Our study had a distinct advantage over previous studies: the vast majority of cases in our series were diagnosed after January 2005, the year when the Gleason grading system was modified in a consensus conference of the International Society of Urological Pathology (9). One of the major impacts of this modification was that it significantly decreased in the number of GS 6 tumors and increased in the number of GS 7 tumors detected via biopsy (39, 40). It was reported that after this modification, the percentage of needle biopsies indicating GS 6 tumors decreased from 68% to 49%, whereas the percentage of needle biopsies indicating GS 7 tumors increased from 26% to 39% (40). The GS in our contemporary series seemed less biased in the change of Gleason grading. This may partially explain why the significant difference in allele frequency at rs2735839 between GS 3 + 4 and GS 4 + 3 seen in our study was not observed in previous studies.

We could not analyze the associations of SNPs with prognosis (biochemical recurrence and mortality) due to the relatively short follow-up time and low number of events. Nevertheless, in Pomerantz and colleagues' study including the largest number (580) of prostate cancer–

specific deaths (7), the variant allele (A) at rs2735839 was significantly associated with prostate cancer–specific mortality, consistent with our observation that the variant allele was associated with aggressive diseases, supporting the prognostic value of this SNP.

In summary, we showed that the variant allele of the GWAS-identified prostate cancer susceptibility SNP rs2735839 near the KLK3 gene is associated with aggressive prostate cancer, and can be used to risk stratify GS 7 patients. Future work is warranted to identify additional genetic loci that can stratify GS 7 patients and test whether these genetic loci can predict prognosis of patients and help personalized clinical management of patients with intermediate-risk profiles.

Disclosure of Potential Conflicts of Interest

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