Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association of Prostate Cancer Risk Variants with *TMPRSS2:ERG* Status: Evidence for Distinct Molecular Subtypes

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Abstract

Background: Numerous genetic variants have been confirmed as prostate cancer risk factors. These variants may confer susceptibility to the development of specific molecular alterations during tumor initiation and progression. The *TMPRSS2:ERG* gene fusion occurs in roughly 50% of prostate cancers. Genetic risk variants may influence the development of this fusion. We sought to determine whether prostate cancer risk variants are differentially associated with *TMPRSS2:ERG* fusion–positive and negative cancer.

Methods: In the Health Professionals Follow-up Study and Physicians' Health Study Tumor Cohort, we evaluated the associations of 39 prostate cancer risk SNPs with *TMPRSS2:ERG* fusion status, measured by ERG protein expression. Logistic regression was performed to generate OR and 95% confidence intervals. The primary outcome was ERG^+ ($n = 227$) versus ERG^- ($n = 260$) prostate cancer. A secondary outcome was ERG^+ or ERG^- cancer versus controls without cancer.

Results: Six of 39 SNPs were significantly associated ($P < 0.05$) with ERG^+ versus ERG^- disease. Three SNPs were exclusively associated with the risk of ERG^+, one with risk of ERG^-, and two with associations trending in opposite directions for ERG^+ and ERG^-. Only two significant SNPs would be expected by chance.

Conclusions: Prostate cancer genetic risk variants are differentially associated with the development of ERG^+ and ERG^- prostate cancer.

Impact: Our findings suggest the molecular process of prostate carcinogenesis may be distinct for men with different underlying genetic predisposition. When examining risk factors for prostate cancer, the integration of molecular subtypes may enhance understanding of the etiology of this disease. *Cancer Epidemiol Biomarkers Prev; 25(5); 745–9. ©2016 AACR.*

Introduction

The *TMPRSS2:ERG* fusion is one of the most common molecular alterations in prostate cancer (1). Forty to 50% of prostate tumors are fusion positive (2), translating to more than 100,000 *TMPRSS2:ERG*–positive prostate cancers diagnosed in the United States annually (3). The fusion involves the androgen-regulated promoter *TMPRSS2* and the ETS transcription factor family member *ERG*. The discovery of *TMPRSS2:ERG* in 2005 was significant because it was the first common gene fusion identified in solid tumors, and it represents a model of hormonal regulation (by *TMPRSS2*) of an oncogene (*ERG*). *TMPRSS2:ERG* may thus define a distinct molecular subgroup of prostate cancers (4). However, few studies have investigated whether tumors with and without the fusion have different etiologies, evidence that is key to prevention efforts.

Numerous genetic risk variants identified by genome-wide association studies (GWAS) have been confirmed as prostate cancer risk factors (5–17). A recent report brings the total number of risk SNPs to 100 (18), a major step toward uncovering the genetic etiology of prostate cancer. It is known from family and twin studies that prostate cancer is highly heritable (19, 20), and as risk SNPs are identified, they explain an ever-increasing portion (currently ~33%) of this underlying heritability in European Americans (18).

Germline risk variants may confer susceptibility to the development of specific molecular alterations during tumor initiation and progression. Particularly as the development of *TMPRSS2:ERG* fusion is thought to be an early event in prostate carcinogenesis (21), inherited risk variants may influence its occurrence. No study to date has investigated the association between known prostate cancer risk SNPs and the risk of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-15-1078

molecular subtypes defined by presence or absence of the *TMPRSS2:ERG* fusion. We therefore tested this hypothesis within two prospective cohorts.

Materials and Methods

Study participants

Physicians' Health Study and Health Professionals Follow-up Study. The men in this study are participants in two long-term, ongoing prospective: the Physicians' Health Study (PHS) and Health Professionals Follow-up Study (HPFS). The PHS began in 1982 as a randomized, double-blind trial of aspirin and β-carotene in the prevention of cardiovascular disease and cancer among 22,071 healthy U.S. physicians ages 40 to 84 (22). The HPFS, a prospective cohort study on the causes of cancer and heart disease in men, consists of 51,529 U.S. health professionals who were ages 40 to 75 years in 1986 (23). In both studies, men were excluded if they had any serious medical conditions at baseline including all cancers (except nonmelanoma skin cancer). Participants are followed through regular questionnaires to collect self-reported data on diet, lifestyle behaviors, medical history, and health outcomes, including prostate cancer.

Men diagnosed with prostate cancer and men never diagnosed with prostate cancer who were participants in these studies were included in the analyses. Cases were men diagnosed with incident, histologically confirmed prostate cancer between 1982 and 2004, and controls were cancer-free at the time of last follow-up (death or current end of study follow-up in 2012). All prostate cancer cases in this study were verified through medical record and pathology review. Through this systematic medical record review, we also abstract data on clinical information, including clinical stage and PSA at diagnosis. All participants included in this analysis are self-reported Caucasian.

The Human Subjects Committee at Partners Healthcare and the Harvard T.H. Chan School of Public Health approved these studies.

Risk SNP genotypes

Sixty-eight percent of PHS participants and 35% of HPFS participants provided a blood sample collected prior to cancer diagnosis. DNA was extracted from whole blood. In total, 39 of the known prostate cancer risk SNPs were genotyped previously as part of the NCI-funded Breast and Prostate Cancer Cohort Consortium (BPC3) using the TaqMan assay (Applied Biosystems) at the Harvard T.H. Chan School of Public Health (Boston, MA). Details on the SNP selection and genotyping are provided in ref.24. To reduce missing data, we combined information for SNPs in very high linkage disequilibrium. If missing rs12418451, we used genotypes from rs10896438 ($r^2 = 0.96$ in HapMap CEU population); if missing rs2928679, we used genotypes from rs13264338 ($r^2 = 0.97$); if missing rs1983891, we used genotypes from rs9381080 ($r^2 = 1.00$); and if missing rs11672691, we used genotypes from rs11673591 ($r^2 = 1.00$).

ERG status measurement

In both cohorts, we sought to retrieve archival formalin-fixed paraffin-embedded specimens. The PHS and HPFS Tumor Cohort includes men with prostate cancer from whom we have collected archival radical prostatectomy (RP; 95%) and transurethral resection of the prostate (TURP; 5%) specimens.

We characterized the presence or absence of the *TMPRSS2:ERG* fusion by immunohistochemical measurement of the ERG protein on tumor tissue microarrays (TMA), as described previously (25). ERG protein expression has been shown to have high concordance with fusion status measured by FISH (26). A single pathologist (blinded to outcome and genotype status), reviewed the TMA cores and considered cases with ERG staining on at least one core to be fusion positive. For 85% of cases where ERG was called positive, it was positive on all cores evaluated.

Statistical analysis

There were genotype data available for 487 men with prostate cancer and with ERG status (227 ERG^+ and 260 ERG^- cases), as well as 2,600 controls. To examine the association of SNPs with ERG status, we performed unconditional logistic regression estimating OR and 95% confidence intervals (CI) for each of the risk SNPs with the following outcomes: ERG^+ versus ERG^- cases, ERG^+ cases versus controls, and ERG^- cases versus controls. Risk SNPs were modeled as additive, with the homozygous genotype with the lowest risk (from original GWAS) as the referent. *P* values from analyses comparing ERG^+ with ERG^- cases can be viewed as a *P* value comparing the association of the SNP with the risk of ERG^+ cancer to the association of the SNP with the risk of ERG^- cancer. Analyses were performed with SAS version 9.3. All *P* values reported are two-sided and unadjusted for multiple comparisons ($P < 0.05$ considered significant).

Results

A description of the participants of this study is provided in Table 1. PSA at diagnosis is similar across the ERG^+ and ERG^- subtypes. ERG^+ cases are more likely to be later stage, as reported previously (25). Although more of the TURP specimens were ERG^+ ($N = 26$) than ERG^- ($N = 6$), restricting to RP specimens did not alter the results (data not shown).

Information on SNP location and genotype frequencies in ERG^+ cases, ERG^- cases, and controls is included in Supplementary Table S1. Results for the association of SNPs with

Table 1. Clinical characteristics for participants with ERG^+ prostate cancer and ERG^- prostate cancer

	ERG^+ ($n = 227$)	ERG^- ($n = 260$)
Lethal, *n* (%)	18 (7.9)	23 (8.8)
Age at diagnosis, mean (SD)	66.9 (6.5)	64.8 (6.3)
Gleason score, *n* (%)[a]		
5–6	51 (22.5)	61 (23.5)
7	139 (61.2)	149 (57.3)
8–10	37 (16.3)	49 (18.8)
Missing	0 (0.0)	1 (0.3)
Clinical stage, *n* (%)		
T1/T2	211 (93.0)	244 (93.8)
T3	9 (4.0)	4 (1.5)
T4/N1/M1	4 (1.8)	5 (1.9)
Missing	3 (1.2)	7 (2.7)
PSA at diagnosis, *n* (%)		
0–4	31 (13.7)	29 (11.2)
4–10	131 (57.7)	145 (55.8)
10–20	35 (15.4)	38 (14.6)
>20	9 (4.0)	23 (8.9)
Pre-PSA era (before 1992)	21 (9.3)	25 (9.6)

[a]From RP or TURP.

Table 2. Association of prostate cancer risk variants with ERG$^+$ versus ERG$^-$ tumor status with a case-only design, and risk of developing ERG$^+$ cancers (ERG$^+$ vs. controls) or ERG$^-$ cancers (ERG$^-$ vs. controls) with a case–control design

	ERG$^+$ vs. ERG$^-$		ERG$^+$ vs. controls		ERG$^-$ vs. controls	
SNP	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
rs13385191	0.93 (0.70–1.23)	0.61	1.18 (0.95–1.47)	0.13	1.27 (1.04–1.56)	0.02
rs1465618	1.00 (0.73–1.37)	0.98	0.98 (0.78–1.24)	0.88	0.99 (0.79–1.23)	0.89
rs721048	0.96 (0.68–1.35)	0.81	0.99 (0.77–1.29)	0.96	1.04 (0.82–1.31)	0.78
rs12621278	1.16 (0.68–2.00)	0.58	1.08 (0.70–1.68)	0.73	0.92 (0.62–1.35)	0.66
rs2292884	0.98 (0.74–1.29)	0.87	1.12 (0.90–1.39)	0.31	1.15 (0.93–1.41)	0.19
rs2660753	0.70 (0.49–1.02)	0.06	0.96 (0.71–1.30)	0.80	1.37 (1.07–1.76)	0.01
rs7629490	0.78 (0.59–1.02)	0.07	1.00 (0.81–1.24)	0.99	1.30 (1.07–1.57)	0.01
rs17021918	0.97 (0.73–1.29)	0.85	1.04 (0.84–1.28)	0.74	1.06 (0.87–1.30)	0.54
rs7679673[a]	1.34 (1.03–1.75)	0.03	1.49 (1.21–1.82)	0.0001	1.11 (0.93–1.34)	0.26
rs12653946[a]	0.69 (0.54–0.89)	0.004	0.85 (0.70–1.03)	0.10	1.26 (1.04–1.51)	0.02
rs1983891	0.91 (0.70–1.19)	0.49	1.19 (0.97–1.46)	0.09	1.32 (1.09–1.59)	0.01
rs339331	0.91 (0.69–1.21)	0.51	0.90 (0.73–1.10)	0.30	0.98 (0.80–1.20)	0.86
rs9364554	1.11 (0.83–1.48)	0.49	1.03 (0.83–1.29)	0.76	0.94 (0.76–1.15)	0.53
rs12155172	1.22 (0.89–1.66)	0.22	1.08 (0.86–1.36)	0.50	0.89 (0.71–1.12)	0.32
rs10486567	1.21 (0.89–1.66)	0.23	1.22 (0.96–1.55)	0.10	1.01 (0.82–1.25)	0.92
rs6465657	0.98 (0.75–1.27)	0.86	1.12 (0.92–1.36)	0.26	1.14 (0.95–1.37)	0.15
rs2928679	1.10 (0.86–1.42)	0.45	1.06 (0.87–1.28)	0.59	0.96 (0.80–1.15)	0.63
rs1512268[a]	0.68 (0.52–0.88)	0.003	0.81 (0.66–0.98)	0.03	1.19 (0.99–1.42)	0.07
rs1016343	0.75 (0.56–1.02)	0.06	1.14 (0.91–1.44)	0.25	1.50 (1.22–1.84)	<0.0001
rs16901979	0.78 (0.39–1.55)	0.48	1.10 (0.64–1.88)	0.73	1.39 (0.88–2.20)	0.15
rs16902094	1.01 (0.72–1.43)	0.94	1.12 (0.87–1.44)	0.38	1.11 (0.87–1.41)	0.41
rs620861	0.99 (0.76–1.29)	0.93	1.12 (0.91–1.37)	0.28	1.13 (0.94–1.37)	0.20
rs6983267	0.84 (0.64–1.10)	0.19	1.12 (0.92–1.37)	0.26	1.33 (1.10–1.61)	0.003
rs4242382	0.91 (0.62–1.32)	0.61	1.47 (1.09–1.98)	0.01	1.61 (1.23–2.11)	0.001
rs1571801	1.02 (0.75–1.40)	0.89	1.06 (0.84–1.33)	0.63	1.04 (0.84–1.28)	0.74
rs10993994	1.02 (0.78–1.32)	0.91	1.35 (1.11–1.64)	0.003	1.33 (1.11–1.60)	0.003
rs7127900	0.82 (0.60–1.10)	0.20	1.15 (0.91–1.45)	0.24	1.40 (1.13–1.73)	0.002
rs12418451	1.00 (0.76–1.31)	0.98	1.11 (0.90–1.38)	0.33	1.12 (0.91–1.37)	0.28
rs10896449	0.95 (0.74–1.23)	0.72	1.10 (0.91–1.34)	0.34	1.15 (0.96–1.39)	0.13
rs902774	1.42 (1.00–2.02)	0.05	1.47 (1.15–1.89)	0.003	1.06 (0.82–1.37)	0.66
rs11649743	0.94 (0.67–1.32)	0.71	1.08 (0.83–1.39)	0.58	1.14 (0.90–1.46)	0.28
rs4430796	0.92 (0.71–1.20)	0.55	1.27 (1.04–1.55)	0.02	1.38 (1.14–1.66)	0.001
rs1859962[a]	1.32 (1.01–1.72)	0.04	1.41 (1.16–1.72)	0.001	1.08 (0.90–1.30)	0.40
rs8102476	1.02 (0.79–1.32)	0.87	1.06 (0.87–1.29)	0.59	1.03 (0.86–1.24)	0.72
rs11672691[a]	1.40 (1.03–1.91)	0.03	1.42 (1.12–1.81)	0.005	1.01 (0.82–1.25)	0.93
rs2735839	1.10 (0.74–1.65)	0.64	1.49 (1.10–2.03)	0.01	1.36 (1.03–1.79)	0.03
rs5759167	1.15 (0.89–1.50)	0.29	1.19 (0.98–1.45)	0.08	1.04 (0.87–1.25)	0.66
rs11704416[a]	1.49 (1.07–2.08)	0.02	1.20 (0.95–1.52)	0.13	0.81 (0.63–1.04)	0.10
rs5945619	1.15 (0.95–1.38)	0.15	1.23 (1.07–1.42)	0.003	1.08 (0.94–1.23)	0.28

[a]Significantly associated with ERG status.

ERG$^+$ versus ERG$^-$, as well as the association with the risk of ERG$^+$ and the risk of ERG$^-$ compared with controls, are presented in Table 2. When comparing the ERG$^+$ to the ERG$^-$ cancers, an OR greater than 1 suggests that men with ERG$^+$ disease are more likely to carry the risk allele than men with ERG$^-$ disease, whereas an OR less than 1 suggests that men with ERG$^-$ disease more commonly carry the risk allele than men with ERG$^+$ disease. Six SNPs were statistically significant comparing ERG$^+$ to ERG$^-$ cancers ($P < 0.05$), and another four SNPs were borderline statistically significant ($P = 0.06$–0.07). By chance, in the ERG$^+$ versus ERG$^-$ analysis, we would only expect two associations to be statistically significant at $P < 0.05$ (i.e., $0.05 \times 39 = 1.95$). When we examined the patterns of the association for the 10 SNPs differentially associated with ERG$^+$ or ERG$^-$, we found four were significantly associated with ERG$^+$ compared with controls but not ERG$^-$ (rs7679673, rs902774, rs11672691, rs1859962), three were significantly associated with ERG$^-$ compared with controls but not ERG$^+$ (rs2660753, rs7629490, rs1016343), and the associations trending in opposite directions for ERG$^+$ and ERG$^-$ for three (rs12653946, rs1512268, rs11704416).

Discussion

Our findings suggest that tumors that develop the *TMPRSS2:ERG* fusion, one of the most common alterations in prostate cancer, have a different genetic etiology from those that do not. We observed several known prostate cancer risk SNPs are differentially associated with the risk of developing prostate tumors either with or without the fusion. Such specificity has been observed in breast cancer subtypes, where GWAS have identified unique loci associated with the risk of ER-positive or ER-negative disease (27).

TMPRSS2:ERG is thought to be an early event in carcinogenesis, and our data indicate that inherited genetic variation may influence its occurrence. We have previously shown that some of these SNPs function as *cis* acting expression Quantitative Trait Loci (eQTL), and were associated with the expression of *KRT6B*, *SP7*, *AXL*, *DMRTC2*, *CHMP2B*, and *IRX4* in tumor (28). These genes are now candidates for possible mechanisms for *TMPRSS2:ERG* fusion development. Our results are also in line with the study that suggested a familial susceptibility of developing fusion-positive prostate cancer

(29); this linkage analysis suggested several loci located on chromosomes 9, 18, and X were associated with fusion-positive prostate cancer. Moreover, we recently reported that shorter CAG repeat length in the androgen receptor (*AR*) was associated with an increased risk of ERG^+ but not ERG^- disease (30). In addition, rare variants in the DNA repair genes *POLI* and *ESCO1* were associated with an increased risk of ERG^+ cancer (31). Taken together, these data demonstrate the importance and usefulness of studying molecular subtypes individually. In attempting to discover new risk factors for prostate cancer, genetic or otherwise, this strategy should be considered.

Despite being underpowered given the known small effect sizes of these risk variants, we still observed several SNPs exclusively associated with the risk of fusion-positive or fusion-negative disease. However, we did not adjust for multiple comparisons, using only $P < 0.05$ as significant (Bonferroni-corrected significance would be $P < 0.0013$ in the main ERG^+ vs. ERG^- analysis), so these results could be due to chance. Validation of these results should be attempted in additional studies. These findings suggest that the molecular process of prostate carcinogenesis may be distinct for men with different underlying genetic predisposition. We hypothesize there may be additional genetic variants that uniquely contribute to the development of fusion-positive or fusion-negative prostate cancer. Specifically identifying SNPs associated with fusion-negative tumors may uncover genes and pathways that help define other molecular subtypes. When attempting to identify risk factors for prostate cancer, molecular subtypes of disease should be considered separately.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these results.

Authors' Contributions

Conception and design: K.L. Penney, A. Pettersson, H.D. Sesso, L.A. Mucci
Development of methodology: L.A. Mucci
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.T. Lis, H.D. Sesso, M. Loda, L.A. Mucci
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Acknowledgments

The authors thank Dr. Meir Stampfer for his comments and contribution to the study analysis and Sam Peisch for assistance with manuscript preparation. The authors are grateful to the participants and staff of the Physicians' Health Study and Health Professionals Follow-Up Study for their valuable contributions, as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

Grant Support

The Physicians' Health Study was supported by grants CA34944, CA40360, CA097193, HL26490, and HL34595. The Health Professionals Follow-up Study was supported by grants UM1CA167552, CA133891, CA141298, and P01CA055075. This study was supported by CA136578, U01CA098233, and P50CA090381. K.L. Penney and L.A. Mucci are supported by Prostate Cancer Foundation Young Investigator Awards. L.A. Mucci was supported by a grant from the NCI (R01 CA136578). K.L. Penney was supported by the A. David Mazzone Research Awards Program. R.E. Graff was supported by a training grant from the NIH and the NCI (R25 CA112355). A. Pettersson was supported by the Swedish Research Council (Reg. No. 2009–7309), and the Royal Physiographic Society in Lund, Sweden.

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Received October 20, 2015; revised January 26, 2016; accepted January 27, 2016; published OnlineFirst March 3, 2016.

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