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A polygenic two-hit hypothesis for prostate cancer

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Abstract

Prostate cancer is one of the most heritable cancers. Hundreds of germline polymorphisms have been linked to prostate cancer diagnosis and prognosis. Polygenic risk scores can predict genetic risk of a prostate cancer diagnosis. Although these scores inform the probability of developing a tumor, it remains unknown how germline risk influences the tumor molecular evolution. We cultivated a cohort of 1250 localized European-descent patients with germline and somatic DNA profiling. Men of European descent with higher genetic risk were diagnosed earlier and had less genomic instability and fewer driver genes mutated. Higher genetic risk was associated with better outcome. These data imply a polygenic “two-hit” model where germline risk reduces the number of somatic alterations required for tumorigenesis. These findings support further clinical studies of polygenic risk scores as inexpensive and minimally invasive adjuncts to standard risk stratification. Further studies are required to interrogate generalizability to more ancestrally and clinically diverse populations.

Prostate cancer is the second-most common malignancy in men and one of the most heritable (1). An estimated 57% of the variability in prostate cancer diagnosis is explained by genetic factors

(1). Elevated risk of prostate cancer diagnosis can be attributed to rare germline variants in DNA damage repair genes (2) or transcription factors (3) as well as aggregated weak effects from

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common variants (4,5). Polygenic risk scores (PRS) leverage common variants and predict risk of diagnosis (4,5).

There is mounting evidence that germline variation influences the somatic evolution of prostate cancer. Localized tumors in BRCA2 carriers molecularly resemble metastatic castrate-resistant disease (6). Specific germline single nucleotide polymorphisms are associated with *PTEN* deletion (7) and point mutations in *SPOP* (8), and the prostate cancer epigenome is influenced by the germline genome (9,10). It remains unknown how inherited genetic risk influences somatic evolution of a tumor.

We assembled a cohort of 427 localized prostate cancer patients with whole-genome sequencing (11–14). All patients had localized disease at diagnosis, were genetically confirmed to be of European descent, and were treated by image-guided radiotherapy or surgery. All samples were treatment naïve and macro-dissected by a genitourinary pathologist to obtain 70% tumor cellularity (Supplementary Table 1, available online). For replication we compiled a 552-patient cohort of treatment-naïve tumors arising in men of European descent from The Cancer Genome Atlas (15) supplemented by 140 primary prostate cancers (Supplementary Table 2, available online).

To identify if inherited genetic risk is associated with somatic evolution, we considered a 147-variant prostate cancer PRS (4) (Figure 1, A). This PRS was inversely associated with genomic instability, that is, proportion of the genome with a copy number aberration (PGA). This relationship held in both discovery and replication cohorts ($\beta_{\text{discovery}} = .16$, $P_{\text{discovery}} = .01$; $\beta_{\text{replication}} = -.27$, $P_{\text{replication}} < .001$; Figure 1, B and C) and was not driven by extremely unstable tumors (PGA > 80%; Supplementary Figure 1, A, available online). The PRS–PGA association was stronger for subclonal ($\beta = -.15$, $P = .005$; Supplementary Figure 1, B, available online) than clonal copy number aberrations (CNAs) ($\beta = .003$; $P = .95$; Supplementary Figure 1, C, available online) and was independent of tumor ploidy (Supplementary Figure 1, D, available online) and subclone number (Supplementary Figure 1, E, available online) (16). This relationship replicated for a 269-variant transancestry prostate cancer PRS ($\beta_{\text{discovery}} = -.011$; $P_{\text{discovery}} = .02$; $\beta_{\text{replication}} = .019$; $P_{\text{replication}} = .002$; Figure 1, A; Supplementary Figure 1, F and G, available online) (5). The negative association between PGA and genetic risk was significantly stronger than a null distribution created by randomly permuting 10 000 PRS ($P = .005$; Supplementary Figure 1, H, available online). The mutation density of single nucleotide variants (SNVs), indels, and genomic rearrangements was not associated with PRS (17) (Supplementary Figure 1, I–K, available online).

Tumors arising in individuals with higher PRS harbored fewer driver mutations ($\beta_{\text{discovery}} = -.18$, $P_{\text{discovery}} = .02$; $\beta_{\text{replication}} = -.20$, $P_{\text{replication}} = .009$; Figure 1, D and E). Driver mutations were defined as significantly recurrently mutated genes observed in more than 5% of the discovery cohort ($n = 17$; Supplementary Table 3, available online; see Methods). A similar trend was observed with a transancestry PRS ($\beta_{\text{discovery}} = -.009$, $P_{\text{discovery}} = .10$; $\beta_{\text{replication}} = -.008$, $P_{\text{replication}} = .16$; Supplementary Figure 1, L and M, available online) (5), and the effect was greater for subclonal vs clonal drivers ($\beta_{\text{subclonal}} = -.019$ vs $\beta_{\text{clonal}} = -.017$). No individual driver was associated with PRS (false discovery rate [FDR] > 0.1; Figure 1, F; Supplementary Table 4, available online). Thus, elevated genetic risk was associated with less genomic instability and fewer driver mutations at diagnosis.

The association between PRS and somatic mutation burden may be mediated by age. Patients with higher genetic risk were diagnosed at a younger age in both the discovery and replication

cohort (median difference: discovery = 4.9 years; replication = 3.0 years; Figure 2, A and B). PRS–PGA and PRS–driver associations were no longer statistically significant after adjusting for age, although with clear trends ($\beta_{\text{PGA}} = -.08$, $P_{\text{PGA}} = .23$; $\beta_{\text{drivers}} = -.13$, $P_{\text{drivers}} = .09$; Figure 2, C). These data suggest younger age at diagnosis partially mediates the negative association between inherited risk and genomic instability.

Early-onset prostate tumors (EOPC; diagnosis < 55 years) provide a natural experiment to explore the interaction of inherited genetic risk, age of diagnosis, and genomic instability. PRS was negatively associated with PGA in 238 additional EOPC tumors (18) ($\beta_{\text{EOPC}} = -.35$, $P_{\text{EOPC}} = .04$; Supplementary Figure 1, N, available online), and was fully mediated by age ($P = .36$).

Finally, given the strong link between genomic instability and disease aggression, we evaluated if inherited risk was linked to relapse (19). Previous studies have shown prostate cancer PRS is not associated with tumor grade at diagnosis (20) or likelihood of metastasis or death (21), but to our knowledge there have been no studies linking PRS with relapse after primary treatment. Although we did not observe associations between PRS and T category or pretreatment PSA (Supplementary Figures 1, O–R, available online), we observed a weak negative association between PRS and International Society of Urological Pathology (ISUP) grade group in the discovery cohort ($\rho = -.06$, $P = .25$), which replicated in the replication cohort ($\rho = -.16$, $P < .001$) (Supplementary Figure 1, S and T, available online). Compared with the discovery cohort, which was enriched for intermediate-risk prostate cancer by design, the replication cohort had a more even distribution of risk categories and was better powered for these analyses. PRS was negatively associated with relapse in both the discovery and replication cohorts, controlling for age and primary treatment (hazard ratio [HR]_{discoveryBCR} = 0.77, 95% confidence interval [CI] = 0.57 to 1.05, $P_{\text{discoveryBCR}} = .10$; HR_{replicationPFI} = 0.75, 95% CI = 0.54 to 1.02, $P_{\text{replicationPFI}} = .07$) (Figure 2, D). PRS showed a trend toward negative association with metastasis-free survival in the discovery cohort (HR_{discoveryMFS} = 0.58, 95% CI = 0.31 to 1.10, $P_{\text{discoveryMFS}} = .10$) (Figure 2, D). These data suggest germline risk influences the number of somatic alterations required for tumorigenesis, leading to lower age at diagnosis and favorable prognosis (22).

Knudson (23) discovered that germline loss-of-function variants in *RB1* required one somatic alteration to trigger retinoblastoma compared with sporadic cases, which required 2 somatic loss-of-function alterations. Hereditary retinoblastoma cases were diagnosed at a younger age than sporadic cases. Our data are analogous to a polygenic version of Knudson's "two-hit" hypothesis. Though not focused on one gene, germline variants that increase prostate cancer risk require fewer somatic alterations to trigger tumorigenesis and lead to a younger age at diagnosis. The association is stronger for subclonal vs clonal PGA, suggesting risk variants may exert selection pressures facilitating clonal sweeps. Given deletions are preferentially clonal and gains are preferentially subclonal (16), it is also possible PRS may associate differently with varying types of DNA damage. These findings suggest European men with high inherited risk may have more favorable outcomes given their more stable somatic genomes. Presently, these findings are limited to individuals of European descent. Well-documented ancestry-related variability in clinical and molecular presentation (24) motivates further interrogation of the utility of prostate cancer PRS in prognosis in larger and more diverse populations.

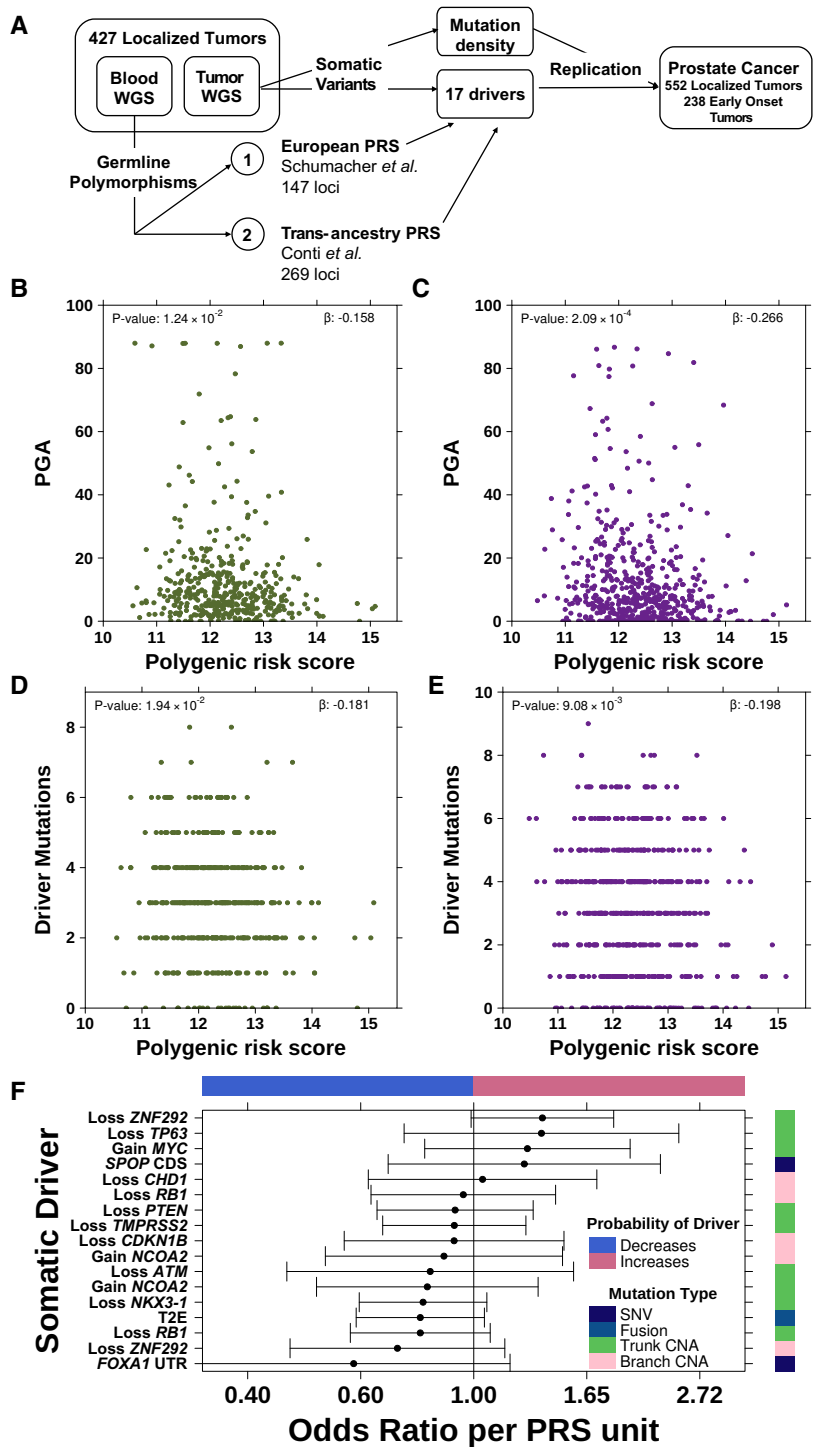


Figure 1. Genetic risk inversely associated with somatic mutation burden. **A**) Schematic of polygenic risk score (PRS) associations with the somatic mutational landscape of prostate cancer. The PRS was negatively associated with percent genome altered in both the discovery cohort (**B**) and the replication cohort (**C**). **Green dots** indicate discovery cohort and **purple dots** indicate replication cohort. The PRS was also negatively associated with the number of driver mutations in both the discovery (**D**) and replication (**E**) cohorts. **F**) PRS is not significantly associated with any individual somatic driver (false discovery rate [FDR] > 0.05). Forest plot shows odds ratio along with 95% confidence interval (x-axis) of PRS associated with each somatic driver (y-axis). Covariate on right indicates the mutation type of each somatic driver while the covariate along the top indicates the direction of effect (ie, whether high inherited risk prevents or promotes the acquisition of each driver mutation). WGS = whole genome sequencing; PGA = percent genome copy number altered; SNV = single nucleotide variant; CNA = copy number aberration.

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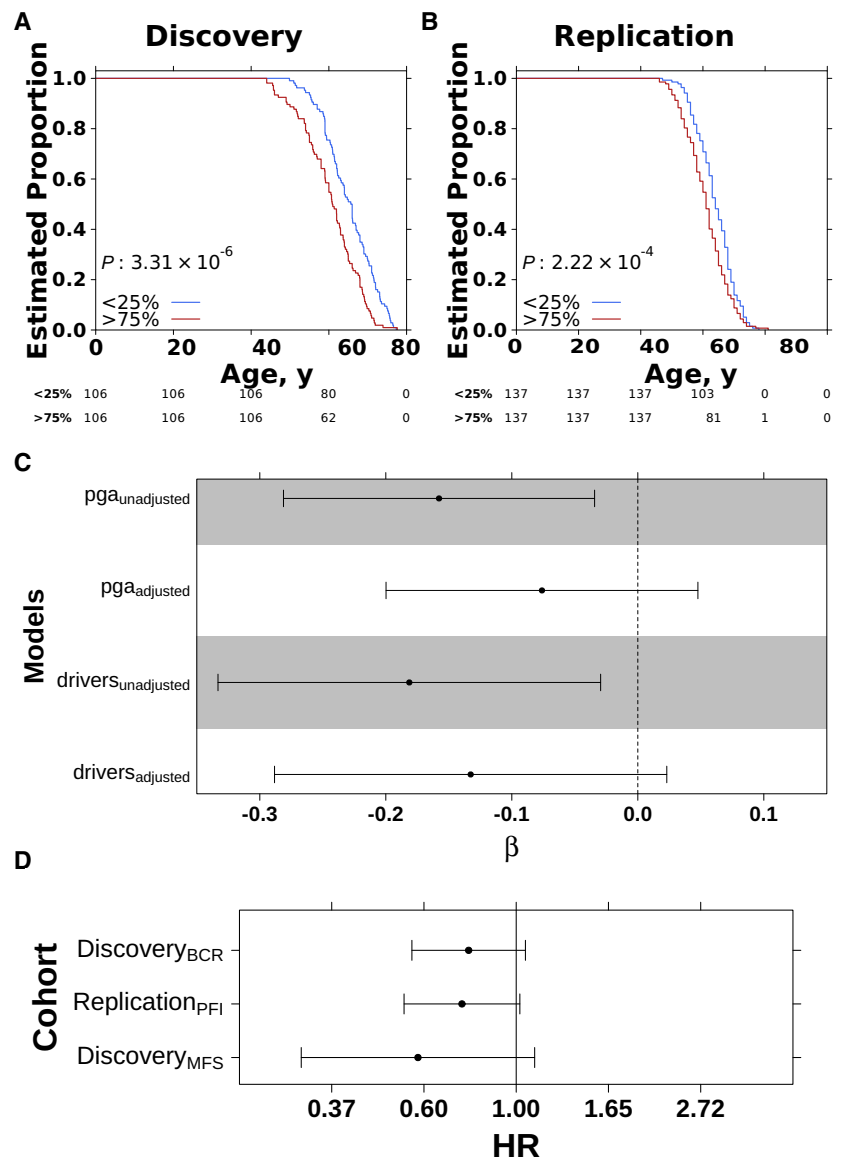


Figure 2. Genetic risk inversely associated with age at diagnosis. Kaplan-Meier curves of time to diagnosis (age) stratified by high (>75%) vs low (<25%) polygenic risk score (PRS) in discovery (A) vs replication (B). C) Coefficients from linear model quantifying association between PRS and proportion of the genome with a copy number aberration (PGA) (Box Cox-transformed) or number of driver mutations with or without adjustment of age of diagnosis. **Error bars** show 95% confidence interval and background shading reflects P value less than .05. D) PRS is negatively associated with relapse after primary treatment in both the discovery and replication cohort. Scatterplot shows the hazard ratio and 95% confidence intervals from a CoxPH model correcting for the first 5 genetic principal components and age. Biochemical recurrence (BCR), progression-free survival (PFI), and metastasis-free survival (MFS) were used as endpoints. HR = hazard ratio.

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Data availability

Raw sequencing data are available in the European Genome-phenome Archive under accession EGAS00001000900 (<https://www.ebi.ac.uk/ega/studies/EGAS00001000900>). Processed variant calls are available through the International Cancer Genome Consortium (ICGC) Data Portal under the project PRAD-CA (<https://dcc.icgc.org/projects/PRAD-CA>). TCGA whole genome and whole exome sequencing (WGS/WES) data are available at Genomic Data Commons Data Portal (<https://gdc-portal.nci.nih.gov/projects/TCGA-PRAD>).

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