Germline Sequence Variants and Prostate-Specific Antigen Interpretation

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Prostate-specific antigen (PSA)\(^2\) is the primary biomarker used to screen for prostate cancer. PSA has limited specificity as a marker, however, and it can be increased in multiple noncancerous conditions [e.g., prostatitis, benign prostatic hyperplasia (BPH)] and after prostatic manipulation (e.g., catheterization) \((1, 2)\).

There is now emerging evidence that PSA concentrations may also be affected by genetic variables. Through genome-wide association studies, investigators have identified more than 30 single-nucleotide polymorphisms (SNPs) that are associated with prostate cancer susceptibility. Eeles et al. reported a strong association of SNPs on chromosomes 10 \((\text{rs10993994})\) and 19 \((\text{rs2735839})\) with PSA concentration and prostate cancer risk \((3)\). It is noteworthy that rs2735839 is located near the \(\text{KLK3}\) \(^3\) (kallikrein-related peptidase 3) gene on chromosome 19, which encodes PSA, potentially underlying the relationship.

In 2009, our group further explored the potential implications of these intriguing findings for prostate cancer screening \((4)\). With 505 men from the Baltimore Longitudinal Study of Aging, we used mixed-effects models to evaluate the relationships between genotype, PSA, and prostate cancer risk. In a model with age and date, there was a 1.18-fold (18%) increased risk ratio for prostate cancer per unit increase in PSA. In an expanded model that also considered the SNP genotypes on chromosomes 10 \((\text{rs10993994})\) and 19 \((\text{rs2659056 and rs2735839})\) and the interaction between genotype and PSA, we found significant differences in prostate cancer risk by PSA that depended on genotype. Specifically, the risk ratio for prostate cancer was 1.28 (95% CI, 1.20–1.38) per unit increase in PSA for carriers of a minor allele, whereas it was 1.10 (95% CI, 1.06–1.15) in men without a minor allele. We concluded that genetic variants significantly altered the risk of prostate cancer per unit increase in the PSA concentration and that additional study was warranted to evaluate a potential role for genetic markers in the interpretation of PSA for prostate cancer risk assessment.

More recently, Gudmundsson et al. performed a large genome-wide association study to further evaluate sequence variants affecting population variation in PSA concentration \((5)\). First, they performed a genome-wide association study of a large population of Icelandic men not diagnosed with prostate cancer, and after correction for multiple testing, they identified 12 SNPs at 6 different loci with significant associations with PSA concentration. They next followed up on these observed associations by genotyping the most significant SNP at each locus in 2 different populations from Iceland and the UK with no history of prostate cancer.

Overall, the 2 SNPs with the greatest overall association with PSA concentration in this study were rs17632542 and rs2735839 \(\text{[the same SNP associated with PSA concentration and prostate cancer risk in the aforementioned study (4)]}\), which are correlated with each other and are located near the PSA-coding gene, \(\text{KLK3}\). Other SNPs that reached genome-wide significance were rs401681 and rs2736098 near the \(\text{TERT}\) \(\text{[telomerase reverse transcriptase]}\) gene on chromosome 5, rs10788160 near the \(\text{FGFR2}\) \(\text{[fibroblast growth factor receptor 2]}\) gene, rs10993994 near the \(\text{MSMB}\) \(\text{[microseminoprotein, beta-]}\) gene (as in prior studies) on chromosome 10, rs11067228 near the \(\text{TBX3}\) \(\text{[T-box 3]}\) gene on chromosome 12, and rs4430796 at the \(\text{HNF1B}\) \(\text{[HNF1 homeobox B]}\) gene on chromosome 17.

In the next portion of the study, Gudmundsson et al. studied a combined population of 5325 prostate cancer cases and 41 417 controls from several European countries and the US. They replicated a statistically significant association between 4 of the PSA-associated alleles from the first portion of the study and prostate cancer risk; however, only 1 allele \((\text{rs17632542})\) was associated with age at diagnosis and a reduced odds of aggressive prostate cancer \((\text{odds ratio, 0.78; P = 0.0099}));\) none of the other alleles were associated with age at diagnosis or disease aggressiveness.

In an exploratory analysis, the authors sought to determine whether the increased risk of prostate cancer associated with several of these variants was due to a...
“PSA bias” related to their known association with PSA concentration. To test this possibility, they divided the population into those diagnosed before 1992 (“pre-PSA era”) and those diagnosed from 1992–2008 (“PSA era”). Interestingly, the KLK3 variant (rs2735839) was associated only with increased prostate cancer risk during the PSA era, but no era effect was observed for the other variants.

In a second exploratory analysis, Gudmundsson et al. asked whether the observed association between the SNPs and PSA could be explained by BPH. They compared 2312 Icelandic men who underwent medical or surgical management for BPH (including treatment with 5α-reductase inhibitors, which are known to lower the PSA concentration) vs 33 779 presumed-healthy Icelandic men. Other than KLK3 variant rs2735839, which had a modestly significant association with BPH, the BPH and control populations showed no differences in frequency for any of the other variants.

In the next portion of the study, Gudmundsson et al. evaluated a population of 2300 Icelandic men who had undergone prostate biopsy between 1998 and 2008. They found that the majority of alleles associated with increased PSA occurred at significantly higher frequency among men with a negative prostate biopsy than in population controls, a result suggesting that genetic variation in PSA may contribute to unnecessary biopsies.

Finally, the authors created a multiplicative model of 4 variants primarily associated with PSA concentration. They demonstrated that the top 5% of the genetic PSA distribution had 23%–47% and 40%–92% higher PSA concentrations than the Icelandic and UK population averages, respectively. On the basis of these relative PSA distributions, the authors proposed personalized cutoff values. For example, for men in the highest 5% PSA grouping (according to genotype), they suggested a threshold of 4.9–5.9 ng/mL instead of 4 ng/mL, whereas for the lowest 5% PSA grouping according to genotype, they suggested a reduction in the threshold to 1.7–2.8 ng/mL.

In summary, Gudmundsson et al. have presented a large and elegant study of the relationship of germline sequence variants with the serum PSA concentration. An important limitation of the study is that the study population comprised Caucasian men of European ancestry, potentially limiting its generalizability to other ethnic groups with different genetic profiles. In addition, although alternative PSA thresholds are suggested in this study, prospective studies are necessary to determine whether adjustment of PSA concentrations based on genotype would lead to an improvement in clinical outcomes. If validated prospectively, these combined findings suggest that genetic markers may be useful in the future to help improve screening protocols.

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