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Finding a Needle in the Haystack: The Search for Germline Variants Associated with Prostate Cancer Clinical Outcomes

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Genome-wide association studies (GWAS) have resulted in the identification of numerous single-nucleotide polymorphisms (SNPs) that are associated with prostate cancer (PCa). Schumacher et al [1] recently identified 62 novel PCa susceptibility loci using over 140 000 PCa cases and controls of European ancestry. In combination with 85 previously identified PCa susceptibility SNPs, these variants capture 28% of the familial risk of PCa. The identification and characterization of GWAS SNPs has led to establishment of polygenic risk scores that may soon be used in the clinic to tailor early detection strategies. However, in general, GWAS SNPs have been notoriously poor at distinguishing aggressive and/or lethal PCa from more indolent or clinically insignificant disease. For example, a large GWAS study with multiple cohorts (encompassing data from over 24 000 men with PCa) failed to identify a single significant and reproducible association between genetic variants and PCa survival [2].

So, why has it been so challenging to incorporate clinical factors into GWAS studies? First, PCa is a very clinically heterogeneous disease with inherent biological differences that drive clinical outcomes. Second, adoption of prostate-specific antigen screening for PCa varies widely throughout the world and influences both the age of diagnosis and the identification of low grade/stage cancers which may not require treatment. Finally, there are a multitude of treatment choices for men with PCa that range from active surveillance to modalities designed for curative intent. Taken together, these and likely other factors have complicated our ability to consistently identify genetic factors associated with clinical features of PCa.

In this issue of *European Urology*, Li et al [3] performed a GWAS with the goal of identifying SNPs associated with death from PCa. Samples were used from the Malmo Diet and Cancer cohort study, which recruited Swedish men aged 41–73 years. The cohort was established between 1991 and 1996, and over the follow-up period which ended in 2014, 1476 of the 11 506 men were diagnosed with PCa and 317 died of the disease. GWAS was performed using DNA from 1053 men with PCa who had complete clinical data. Two SNPs

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were shown to be associated with PCa-specific survival at genome-wide significance after adjusting for age, stage, and grade at diagnosis: rs73055188 in the *AOX1* gene located on chromosome 2q23.1 ($p = 5.27 \times 10^{-9}$) and rs35105661 in *HERC4* located on chromosome 10q21.3 ($p = 1.10 \times 10^{-8}$). The lead candidate SNP, rs73055188, was validated using an independent Swedish cohort with 1552 PCa cases that was initiated in 1985 with approximately 25 yr of follow up. This SNP, along with five additional SNPs at the same locus, correlated with *AOX1* expression likely through methylation changes. Finally, two separate prostate cancer cohorts with 111 and 140 cases were examined. Low tissue expression of *AOX1* was shown to correlate with shorter time to biochemical recurrence. This finding supports the hypothesis that the minor A allele is associated with lower *AOX1* expression in PCa tissue which correlates with shortened PCa-specific survival. Previous research has implicated *AOX1* gene expression and PCa recurrence. For example, Haldrup et al [4] identified *AOX1* and additional candidate genes as biomarkers for biochemical recurrence by screening PCa tissue for DNA methylation changes compared with benign PCa tissues. The *AOX1* gene encodes the protein aldehyde oxidase which is highly expressed in the liver but is present in many other organs including the prostate gland.

Why were these investigators able to find the needle in the haystack when others have failed? Keeping in mind the aforementioned challenges of GWAS focused on post-diagnostic outcomes, it is likely that discovery was achieved by: (1) reducing genetic variability through the study of a population of common ancestry, and (2) adjusting for clinical predictors of disease progression. The authors also surmise that because the Swedish population participates in a single healthcare system, there was limited variability in both diagnostic procedures and treatment. In other words, by increasing homogeneity in their discovery dataset, the relationship between genetic variation in *AOX1* and PCa clinical outcomes could be detected. This concept is validated by the fact that the association was confirmed using a second Swedish cohort study established and observed during the same time period. However, the obvious tradeoff of this study design is the potential limited generalizability of findings to populations with greater genetic and clinical variability, the latter of which could be due to either inherent biologic differences or issues related to differential access to medical care.

The identification of the PCa susceptibility gene *HOXB13* is an example of a founder allele, probably originating in a Nordic country, which has world-wide impact. Although the *HOXB13* G84E risk allele was identified through linkage analysis using two US cohorts [5], follow-up studies using over 2400 PCa families collected throughout the world confirmed that the G84E mutation contributed to ~5% of PCa families [6]. If the association of the *AOX1* risk allele is associated with PCa survival in additional large PCa cohorts outside of Sweden, *AOX1* SNP genotypes may be added into PCa predictive algorithms since the association of rs73055188 genotype with PCa survival appears independent of cancer stage and grade. This observation may have important implications for health disparities research since the rs73055188 A allele is in higher frequency in African populations than in Nordic populations using data from the 1000 Genomes Project (A allele is 0.06 frequency in FIN [Finnish in Finland], 0.19 in ASW [Americans of African Ancestry], and 0.25 in YRI [Yourba in Ibadan, Nigeria]). Men of African descent living in Africa and in the US experience disproportionate incidence and mortality from PCa and perhaps genetic variation

at the *AOX1* gene is playing a contributing role. Additional research investigating if rs73055188 is related to PCa survival in these and other populations is required to confirm the importance of this mutation for predicting clinical outcome.

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