 Genetic architecture of prostate cancer in the Ashkenazi Jewish population

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BACKGROUND: Recently, numerous prostate cancer risk loci have been identified, some of which show association in specific populations. No study has yet investigated whether these single nucleotide polymorphisms (SNPs) are associated with prostate cancer in the Ashkenazi Jewish (AJ) population.

METHODS: A total of 29 known prostate cancer risk SNPs were genotyped in 963 prostate cancer cases and 613 controls of AJ ancestry. These data were combined with data from 1241 additional Ashkenazi controls and tested for association with prostate cancer. Correction for multiple testing was performed using the false discovery rate procedure.

RESULTS: Ten of twenty-three SNPs that passed quality control procedures were associated with prostate cancer risk at a false discovery rate of 5%. Of these, nine were originally discovered in studies of individuals of European ancestry. Based on power calculations, the number of significant associations observed is not surprising.

CONCLUSION: We see no convincing evidence that the genetic architecture of prostate cancer in the AJ population is substantively different from that observed in other populations of European ancestry.

Keywords: SNPs; prostate cancer; association studies

Recent studies have identified numerous single nucleotide polymorphisms (SNPs) that modify an individual’s risk of developing prostate cancer (Amundadottir et al, 2006; Eeles et al, 2008; Gudmundsson et al, 2007a; Haiman et al, 2007; Thomas et al, 2008). Although some investigators have considered the possibility of heterogeneity between ethnic groups, where a SNP shows a different effect on prostate cancer risk depending on the population being studied, these studies only considered ethnic groups with different continents of ancestral origins (Haiman et al, 2007; Waters et al, 2009; Yamada et al, 2009; Hooker et al, 2010; Zheng et al, 2010). As alleles of numerous SNPs are known to vary in frequency across Europe (Bersaglieri et al, 2004), and population substructure is consistently observed in Americans with ancestry from different locations in Europe (Price et al, 2008; Tian et al, 2008), there is a possibility that prostate cancer risk alleles may have different effects in different populations of European ancestry.

Ashkenazi Jews are Jews whose ancestors come primarily from central and eastern Europe; the majority of North American Jews and a large proportion of Israeli Jews are of Ashkenazi ancestry. The global linkage disequilibrium (LD) profiles of the Ashkenazi Jewish (AJ) population do not seem to differ significantly from that of other populations of European ancestry. However, it has been suggested that there may be significant local differences in allele frequencies and haplotype structure between the Ashkenazi population and other European populations, including at loci associated with common cancer (Gold et al, 2008; Olshen et al, 2008; Price et al, 2008; Tian et al, 2008). Therefore, examination of known prostate cancer risk SNPs in the AJ population provides a unique opportunity to test for genetic heterogeneity at these loci among individuals of European ancestry.

Here, we report the results of a case–control association study in the AJ population of 29 previously identified prostate cancer SNPs. Our data argue against the hypothesis that risk alleles for prostate cancer generally have different effects in the Ashkenazi and non-Ashkenazi European ancestry populations.

MATERIALS AND METHODS

Case and control DNA samples were obtained under IRB-approved protocols. Specifically for the samples from the Israeli blood bank,
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Table 1: Known prostate cancer risk SNPs successfully tested in this study

| SNP          | Chr. | Gene             | Alleles (Maj/Min) | MAF     | Prev. OR | Citation                        |
|--------------|------|------------------|-------------------|---------|----------|---------------------------------|
| rs721048     | 2    | EHBP1            | G/A               | 0.19    | 1.15     | Gudmundsson et al (2008)         |
| rs5660753    | 3    | CTBP2            | C/T               | 0.11    | 1.18     | Eeles et al (2008)              |
| rs9364554    | 6    | SLCT2A3; SLCT2A2; LPAL2; LPA | C/T | 0.29 | 1.17 | Eeles et al (2008) |
| rs10942567   | 6    | JAZF1            | C/T               | 0.23    | 1.74     | Thomas et al (2008)            |
| rs6456657    | 7    | LMTK2; BH4L88    | T/C               | 0.46    | 1.12     | Eeles et al (2008)             |
| rs7008482    | 8    | —                | T/G               | 0.83    | 1.8      | Robbins et al (2007)           |
| rs1016343    | 8    | —                | C/T               | 0.18    | 1.37     | Eeles et al (2008)             |
| rs13254738   | 8    | —                | A/C               | 0.34    | 1.11     | Haiman et al (2007)            |
| rs16501979   | 8    | —                | C/A               | 0.031   | 1.79     | Gudmundsson et al (2007a)       |
| rs6983267    | 8    | —                | G/T               | 0.50    | 0.8      | Yeager et al (2007)            |
| rs7000448    | 8    | —                | C/T               | 0.39    | 1.14     | Haiman et al (2007)            |
| rs4242382    | 8    | —                | G/A               | 0.12    | 1.41     | Thomas et al (2008)           |
| rs4242384    | 8    | —                | A/C               | 0.09    | 1.88     | Eeles et al (2008)             |
| rs7920517    | 10   | MSMB             | G/A               | 0.48    | 0.82     | Eeles et al (2008)             |
| rs10993994   | 10   | MSMB             | T/C               | 0.60    | 0.8      | Eeles et al (2008)             |
| rs9462146    | 10   | CTBP2            | T/C               | 0.27    | 1.2      | Thomas et al (2008)            |
| rs7931342    | 11   | —                | G/T               | 0.49    | 0.84     | Eeles et al (2008)             |
| rs10896449   | 11   | —                | G/A               | 0.48    | 0.78     | Thomas et al (2008)            |
| rs4430796    | 17   | TCF2             | G/A               | 0.49    | 1.24     | Gudmundsson et al (2007b)     |
| rs7501939    | 17   | TCF2             | G/A               | 0.42    | 0.83     | Gudmundsson et al (2007b)     |
| rs859962     | 17   | —                | G/T               | 0.34    | 1.24     | Gudmundsson et al (2007b)     |
| rs2735839    | 19   | KLK2; KLK3       | G/A               | 0.15    | 0.83     | Eeles et al (2008)             |
| rs8954372    | X     | NUDT1; NUDT10    | G/A               | 0.35    | 1.24     | Gudmundsson et al (2008)       |

Abbreviations: alleles = major/minor alleles; chr. = chromosome; gene = nearby gene as reported in the cited literature; MAF = allele frequency in the controls of the cited paper for the minor allele as observed in the Ashkenazi Jewish population; prev. OR = previous odds ratio for the SNP as cited by the given paper; SNP = single nucleotide polymorphism. When MAF is > 0.5, it indicates that the minor allele in the Ashkenazi Jewish population is the major allele in the study that initially reported the SNP.
remaining three SNPs were analysed only with the data from the Sequenom genotyping. Association analysis was performed in PLINK using logistic regression. Replication was performed twice, once without an adjustment for age and once with an adjustment for age of either diagnosis (cases) or sample collection (controls). Multiple testing was accounted for by holding the false discovery rate to be 5% using the Benjamini–Hochberg procedure (Benjamini and Hochberg, 1995).

To compute the power to detect association for each SNP, we assumed the previously reported odds ratio (OR), allele frequencies in our control population, and a sample size based on the number of successfully genotyped cases and controls. We used a previously reported method to compute the power at a significance level of 0.05 (Klein, 2007).

As a reference population of non-Ashkenazi white Americans, we used the GWAS data from the CGEMS Prostate Cancer GWAS – Stage 1 – PLCO (phs000207.v1.p1) in dbGaP (http://www.ncbi.nlm.nih.gov/gap), removing duplicate individuals. To test for the heterogeneity of the OR between the CGEMS data and our data, we used the Breslow–Day test as implemented in PLINK.

### RESULTS

In the current study, we genotyped 29 SNPs previously reported as being associated with prostate cancer risk in 963 AJ prostate cancer cases and 613 AJ controls. The overall genotype call rate (fraction of genotypes for which a call was made) was 95%. After quality control (QC) filtering the Sequenom data as described in the methods, resulting in 23 SNPs that pass QC, we added data from 20 SNPs in 1241 male AJ controls genotyped with the Illumina Omni-1 Quad platform. As some controls came from Israel and some from the United States, we first queried if we observed allele frequency differences between AJ controls based on origin. Although two SNPs showed nominal differences in allele frequencies (rs9364554 and rs4242384; P < 0.05), neither of these differences were significant after correcting for multiple testing.

We were also concerned that the use of different genotyping platforms could lead to errors in our results. To test for this, we compared allele frequencies between individuals genotyped on the Illumina and Sequenom platforms and observed no differences (all nominal P > 0.3).

We tested for association in 875 cases and 1810 controls total under an additive model. Before adjusting for age, 12 SNPs were nominally associated with prostate cancer risk (P < 0.05; Table 2). Of these, 10 were significant at a false discovery rate of 5%. Among the 12 significant SNPs, only one – rs7008482 – shows a direction of effect opposite from that which was previously reported. As the SNP was identified in a case–control study of African-American men, we queried what effect this SNP had in the stage 1 data from the CGEMS prostate cancer GWAS of white Americans (Yeager et al, 2007). Although not significantly associated with risk (P = 0.2), this SNP has the same direction of effect that we observe in the Ashkenazi population (OR = 0.92; 95% CI = 0.81–1.04). We next queried whether adjusting for age would influence these results. After removing 26 individuals without age information and adjusting for age as a covariate, nine SNPs were nominally significant (P < 0.05), of which three are significant at a false discovery rate of 5% (Table 3). Notably, seven SNPs are nominally significant both with and without age adjustment.

We next wished to query if we could observe any heterogeneity between the size effect we observed in the Ashkenazi population and the effects observed in other populations of European ancestry. To do so in a systemised way, we used the stage 1 CGEMS data. There are 18 SNPs that we tested here that are also present in the CGEMS data. Of these, only one (rs4962416) shows heterogeneity (P = 0.002). Although this SNP is associated with prostate cancer risk in the CGEMS stage 1 study (OR = 1.3; 95% CI = 1.2–1.5), we observe no evidence for association in the AJ population (OR = 1.0; 95% CI = 0.9–1.1).

For several of the SNPs, we did not replicate the association with prostate cancer risk observed in a number of prior studies (Kim...
DISCUSSION

Here, in the AJ population, we have replicated the association with prostate cancer risk for many of the prostate cancer risk SNPs tested. Overall, the effect of these SNPs in the AJ population is similar to that previously reported with the discovery of the SNPs. However, there are some SNPs for which we did not replicate the previously reported association despite having adequate power to do so. One potential explanation is the ‘winner’s curse’, in which the first report of an association overestimates the magnitude of effect, leading to an inflated power estimation. In fact, for rs10486567, our first report of an association overestimates the magnitude of effect, similar to that previously reported with the discovery of the SNPs.

Furthermore, our sample size is likely too small to distinguish more prostate cancer associations will be necessary to answer this question. Of the significant results, only one SNP – rs700482 – showed a different direction of effect than that which has been previously reported. This SNP was first identified as a prostate cancer risk allele in the African-American population (Robbins et al., 2007). A more recent replication study found that this SNP is not associated with prostate cancer in the AJ population, illustrating population heterogeneity, or that our sample size is simply not large enough. Larger studies in which we are well powered to replicate the known prostate cancer risk SNPs are needed to determine if this is a real prostate cancer risk SNP, perhaps tagging different functional alleles in different populations.

RS16901979 and prostate cancer in the AJ population, as observed for this rare SNP was 1.0 in our study.

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We used controls from both the United States and Israel. Although we have previously found that AJ individuals from these two countries cluster similarly using principal components analysis (Gold et al., 2008), we nevertheless tested each SNP for...
allele frequency differences between Israeli and United States controls. As we did not find any significant difference, we do not think this is a major source of potential error in our study.

These results provide evidence of some differences in the genetic architecture of prostate cancer between the AJ population and other populations of European ancestry. However, these few differences are not enough evidence to argue that there are substantive differences in genetic susceptibility to prostate cancer between these populations. Further study of the genetics of prostate cancer in this unique population will be needed to understand to what extent genetic risk to prostate cancer is similar to that in other European populations and to what extent it is different.

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