Association between hOGG1 Sequence Variants and Prostate Cancer Susceptibility


Introduction

The DNA repair enzyme OGG1 is a DNA glycosylase/AP lyase that has been hypothesized to play an important role in preventing carcinogenesis by repairing oxidative damage to DNA (1). Specifically, glycosylase/AP lyase can efficiently repair 8-OH-G, a major base lesion produced by ROS, formed as a byproduct of endogenous metabolism or exposure to environmental oxidizing agents, such as ionizing radiation or chemical genotoxic compounds. 8-OH-G is highly mutagenic and, if not excised on DNA replication, can cause GC to TA transversions, which occur frequently in several oncogenes and tumor suppressor genes (2).

The genomic DNA of hOGG1, with eight exons, spans ~16.7 kb on 3p25. Several SNPs in the hOGG1 gene have been identified, and the repair activities of the variant proteins have been evaluated in many studies (3–6). However, in contrast to these extensive functional studies, limited knowledge is available on the association between cancer susceptibility and SNPs in this critical DNA repair gene. To date, only five studies have been reported on the association between hOGG1 SNPs and cancer susceptibility, and all of these have focused on a frequently observed missense change at codon 326 in exon 7 (Ser326Cys). Although three of these previous studies did not find statistically significant differences in the genotype distributions of the SNP between cancer cases and normal controls (3, 7–8), two studies found a significantly increased frequency of Cys/Cys in lung and esophageal cancer cases (9–10). Furthermore, a significant difference in the distribution of Ser326Cys was observed between ethnicities, with the frequency of Ser326 being 0.78 and 0.59 in Caucasian and Asian controls, respectively.

Although sequence variants in genes involved in DNA repair may be an important determinant of inherited susceptibility to cancer in humans (11), this could be particularly relevant for prostate cancer, in which oxidative damage has been proposed to play a critical role in cancer formation. Indeed, the preventative effect of antioxidants and the cancer-associated induction and molecular inactivation of components of the cellular defense system for oxidative stress have been cited as evidence of the important procarcinogenic aspect of ROS in the human prostate (12). In addition, the hOGG1 gene is abundantly expressed in prostate tissue. Finally, a study by Osterod et al. (13) found that the accumulation of oxidative DNA base damage in OGG1-deficient mice is age related and tissue specific. Although we do not know whether this model is directly applicable to prostate, we can hypothesize that the accumulated effect of altered DNA repair activities associated with sequence variants has a larger impact on this late age of onset cancer.

On the basis of the present understanding of the hOGG1 gene function in the DNA repair pathway and the existing epidemiological data, we hypothesized that sequence variants of the hOGG1 gene confer risk to prostate cancer. Therefore, we tested the following four subhypotheses: (a) the missense change Ser325Cys is associated with increased risk to prostate cancer; (b) other sequence variants in the hOGG1 gene are associated with prostate cancer risk; (c) sequence variants of hOGG1 may produce a different risk to hereditary versus sporadic prostate cancer; and (d) clinical characteristics of sporadic prostate cancer are associated with sequence variants of hOGG1.

Subjects and Methods

Subjects. A detailed description of the study sample was presented previously (14). HPC families (n = 159) were ascertained at the Brady Urology Institute at Johns Hopkins Hospital (Baltimore, MD), through referrals, review of medical records for patients seen at Johns Hopkins Hospital for treatment of prostate cancer, and respondents to various lay publications describing our studies. Each family had at least three men affected with prostate cancer. The mean number of affected men per family was 5.1, and the mean age at diagnosis for these cases was 68.1 years. The majority of HPC families were Caucasians (n = 133; 84%), and there were 14 (8.8%) African-American families. For the 159 probands of these families, the mean age at diagnosis was 61 years. The diagnosis of prostate cancer was verified by medical records. All of the 245 unrelated prostate cancer cases were recruited from patients who underwent treatment for prostate cancer at the Johns Hopkins Hospital and did not have first-degree relatives affected with prostate cancer. For each subject, the diagnosis of prostate cancer was confirmed by pathology reports. Preoperative PSA levels, Gleason score, and pathological stages were available for 202, 240, and 241 cases, respectively. Mean age at diagnosis for these cases was 68.1 years. More than 95% of the cases were Caucasian, and 3.2% were African American.

Two hundred twenty-two non-prostate cancer controls were selected from men participating in screening programs for prostate cancer. By applying the
ASSOCIATION OF hOGG1 SNPS AND PROSTATE CANCER

Table 1  PCR primers for the SNPs in hOGG1 gene

<table>
<thead>
<tr>
<th>SNP</th>
<th>Group</th>
<th>Forward</th>
<th>Reverse</th>
<th>Extension (direction)</th>
</tr>
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<tbody>
<tr>
<td>a–627T/C</td>
<td>1</td>
<td>TTGTTGACAGCGGCTTCTG</td>
<td>TCTCCGAGCCGGTTCTCC</td>
<td>AGGGCAAGGGCGGCGGTCC (R)</td>
</tr>
<tr>
<td>a–23A/G</td>
<td>2</td>
<td>GGGTTGAGGCTTCTGCTG</td>
<td>TTCTCAGGCAGAAGCTCG</td>
<td>TCTCCGAGCCGGTTCTCC (R)</td>
</tr>
<tr>
<td>a–18G/T</td>
<td>5</td>
<td>AGACAGGCTGAGGGGACAG</td>
<td>GGGTTGAGGCTTCTGCTG</td>
<td>TTCTCAGGCAGAAGCTCG (R)</td>
</tr>
<tr>
<td>2550C/A</td>
<td>3</td>
<td>ATCTTCCTGTTGAGGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>3224A/C</td>
<td>3</td>
<td>ATCTTCCTGTTGAGGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>3400G/A</td>
<td>5</td>
<td>GTGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>3547G/A</td>
<td>2</td>
<td>GGCTGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>4540G/A</td>
<td>3</td>
<td>ATCTTCCTGTTGAGGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>6170G/C</td>
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<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
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<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>6939C/A</td>
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<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>7143G/A</td>
<td>4</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>9110A/G</td>
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<td>AGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
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<td>AGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>11657A/G</td>
<td>6</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
<tr>
<td>11826A/T</td>
<td>7</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>AGGTCTGAGGCTTCTGCTG</td>
<td>CTGGTCTGAGGCTTCTGCTG (R)</td>
</tr>
</tbody>
</table>

* Numerical values represent the position (measured in base pairs) from the transcription site. The letters represent nucleotide change.

a Multiplex PCR group.

b All have the ACGTTGGATG tag in the front, except for the SNP 6803C/G (by direct sequencing). R, reverse; F, forward.

exclusion criteria of abnormal DRE and abnormal PSA level (i.e., ≥ 4 ng/ml), 211 were eligible for the study. The mean age at examination was 58 years. More than 86% of the eligible controls were Caucasian and 7.1% were African American. On the basis of interviews of the subjects, we learned that 5.6% of the eligible controls had brothers or their father affected with prostate cancer.

The Institutional Review Board of Johns Hopkins University approved the protocols for subject recruitment. After each participant was guided through an informed consent process, they completed and signed a consent form as a record of this process.

Sequencing Methods and SNP Genotyping. SNPs information was obtained from the Celera database. All of the SNPs, except one, were genotyped using the MassARRAY system (SEQUENOM, Inc., San Diego, CA). Table 1 lists the PCR primers and extension primers for all of the SNPs. SNP Ser326Cys was genotyped using direct sequencing. Sequence reaction was run in the ABI 3700 DNA analyzer and analyzed using Sequencer computer software (Gene Codes Corporation, Ann Arbor, MI).

Statistical Methods. HWE tests for all SNPs and LD tests for all pairs of SNPs were performed using the method of exact tests as implemented in the Genetic Data Analysis (GDA) computer program (15). The empirical P was based on 10,000 replicate samples for Monte Carlo simulations.

Genotypic frequencies of each SNP were compared between cases and controls. The hypotheses of differences in genotypic frequencies (three genotypes) between cases and controls were tested using the FET. ANOVA was used to test for association between genotype distributions and prostate cancer and to estimate the age-adjusted RR of risk genotypes (homzygous variant genotype versus homozygous wild-type genotype). ANOVA was used to test for differences in mean log PSA levels (log 10 transformed) among men with different genotypes.

Family-based association tests were performed for a subset of SNPs in the 159 HPC families, using the FBAT software program (16). Briefly, FBAT calculates observed S statistics from the data, which is the linear combination of offspring genotypes and phenotypes. The distribution of the S statistics is generated by treating the offspring genotype data as random and conditioning the phenotypes and parental genotypes. A Z statistic and its corresponding P or an empirical P is calculated. The test for association is valid if the empirical variance is used to account for the correlation between transmissions in families when linkage is present.

All of the hypothesis tests were limited to Caucasians only, to decrease the impact of heterogeneity and potential population stratification.

Results

Eighteen hOGG1 SNPs described in the Celera SNP database were selected for initial screening. Of these, two were not observed at all, and six were infrequently seen (the frequency of the less frequent allele, <0.05) in our first 96 samples and, thus, were not further genotyped in the rest of the samples. The remaining 10 SNPs were genotyped in the total 245 sporadic cases and 222 unaffected controls. All of the 10 SNPs were in HWE (P < 0.05), and all of the pair-wise SNPs were in strong LD (P < 0.00001) both in sporadic cases and in unaffected controls. When the genotype distributions of the 10 SNPs were compared between sporadic cases and controls (Table 2), three had differences in the genotype distributions (Ser326Cys, FET P = 0.055; 7143A/G, FET P = 0.059; 11657A/G, FET P = 0.028), although only the 11657A/G reached statistical significance.

These three SNPs were then further genotyped in 159 HPC probands (Table 2). The genotype distributions of Ser326Cys and 7143A/G in the HPC probands were similar to those in the controls (FET, P = 0.34 and 0.11, respectively). The distribution of 11657A/G in the HPC probands, however, was significantly different from that in the controls (FET, P = 0.03). Exploring the data, we found a higher frequency of CC homozygotes for the Ser326Cys and an especially higher frequency of GC homozygotes for the 11657A/G and 7143A/G in cases compared with controls. For example, there were 17 GC homozygotes at 11657A/G among 357 sporadic or HPC probands and only one GG homozygote in the 187 controls, although the subject had an elevated PSA level (3.9 ng/ml). Compared with men with the AA genotype at 11657A/G, men with the GG genotype were at increased risk for prostate cancer, even after adjustment for age. The point estimate of the RR was 9.80 (95% CI, 1.25–76.92) for sporadic prostate cancer (Table 3). Similar results were observed for the SNP 7143A/G. For the SNP Ser326Cys, men with the CC genotype (Ser326) had an increased risk of prostate cancer, especially sporadic prostate cancer, compared with homozygous GG men (Cys326). The estimated RR was 3.23 (95% CI, 1.19–8.73), 2.07 (95% CI, 0.65–6.62), and 2.72 (95% CI, 1.17–6.32), for sporadic, hereditary, and either type of prostate cancer, respectively.

Because cases and controls may come from different genetic backgrounds, and any observed genotypic difference may reflect variation in genetic characteristics, rather than a difference directly related to the disease phenotype (i.e., a population stratification effect), we performed a family-based association test to further examine the association between the sequence variants and prostate cancer risk, independent of potential population stratification. The SNPs...
and prostate cancer risk using a comprehensive approach. Not only did we evaluate the previously reported missense change (Ser326Cys), but we also screened an additional 17 sequence variants spanning the entire gene, and we evaluated a total of 10 SNPs in the 245 sporadic cases and 222 unaffected controls. Furthermore, based on the results of sporadic cases and controls, we genotyped three SNPs with evidence for association in an additional 159 HPC probands. Most importantly, we applied family-based association tests to evaluate two of the three SNPs, to eliminate any potential impact of population stratification. We found that men with homozygous G at either 11657A/G or 7143A/G or with homozygous C (Ser326) at Ser326Cys, were at increased risk for prostate cancer, especially for sporadic prostate cancer. The finding of significant differences in the genotype distribution of 11657A/G between cases and controls was confirmed and significantly strengthened by the observation that heterozygous parents preferentially transmit the G allele to affected sons, from a family-based association test. Taking these results together, our study provides strong preliminary evidence that sequence variants of hOGG1 are associated with prostate cancer risk.

Although the significantly increased frequency of men homozygous for G at 11657A/G and C (Ser326) at Ser326Cys in both sporadic and hereditary cases, compared with controls, may be potentially attributable to random genotype error and/or population stratification, these confounding factors are unlikely to be major problems in our study for the following reasons: (a) the genotyping error rate should be very low in our study. A rigorous quality control is implemented in our genotyping laboratory by including both case and control samples in the same 384-well plates, the incorporation of multiple Centre d’Etude du Polymorphisme Humain (CEPH) controls in each plate, the use of robots in each step, and allele determination by a computer program. If genotyping error exists after these steps, it should be random to cases and controls. Furthermore, almost complete matching of the genotypes at 11657A/G and 7143A/G (caused by almost complete LD between these two SNPs) suggests a high quality of genotyping; and (b) potential population stratification, which is an inherent problem of any case-control study, is unlikely to play a major role in our findings. Our family-based linkage disequilibrium test, which is not susceptible to this confounding factor, provided the same significant finding for the SNP 11657A/G.

However, caution should be used when interpreting and generalizing these findings. The study subjects were recruited primarily for genetic studies rather than for a rigorously designed epidemiological study, thus making it difficult to generalize the point estimates of the RR. Furthermore, the control subjects, who were recruited from a prostate cancer screening population, are subject to potential misclassification in that they may represent a higher

### Table 2

Genotype frequencies of sequence variants of hOGG1 in cases and controls (Caucasians only)

<table>
<thead>
<tr>
<th>SNPs</th>
<th>No. of subjects (%)</th>
<th>Genotype</th>
<th>Controls</th>
<th>Sporadic HPC</th>
<th>HPC</th>
<th>Sporadic HPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3402G/A</td>
<td>AA</td>
<td>79 (43)</td>
<td>73 (40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>83 (45)</td>
<td>81 (44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>23 (12)</td>
<td>29 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3574G/A</td>
<td>AA</td>
<td>104 (60)</td>
<td>128 (67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>58 (34)</td>
<td>54 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>11 (6)</td>
<td>10 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61700G/C</td>
<td>CC</td>
<td>101 (58)</td>
<td>130 (63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>60 (34)</td>
<td>69 (33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>13 (7)</td>
<td>8 (4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6803C/G (Ser326Cys)</td>
<td>CC</td>
<td>96 (55)</td>
<td>122 (61)</td>
<td>60 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>63 (36)</td>
<td>71 (36)</td>
<td>35 (35)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GG</td>
<td>15 (9)</td>
<td>6 (3)</td>
<td>4 (4)</td>
<td>0.055</td>
<td>0.34</td>
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<td>7143A/G</td>
<td>AA</td>
<td>130 (71)</td>
<td>153 (68)</td>
<td>83 (64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>52 (28)</td>
<td>59 (26)</td>
<td>41 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
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<td>12 (5)</td>
<td>6 (5)</td>
<td>0.059</td>
<td>0.11</td>
</tr>
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<td>9110A/G</td>
<td>GG</td>
<td>110 (60)</td>
<td>138 (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>62 (34)</td>
<td>66 (31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
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<td>6 (3)</td>
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</tr>
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<td>10629G/C</td>
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<td>54 (28)</td>
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<tr>
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<td>51 (27)</td>
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<tr>
<td>10660A/T</td>
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<td>140 (65)</td>
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</tr>
<tr>
<td></td>
<td>TA</td>
<td>59 (32)</td>
<td>69 (32)</td>
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<td></td>
</tr>
<tr>
<td></td>
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<td>8 (4)</td>
<td></td>
<td>N.S.</td>
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<td>139 (74)</td>
<td>158 (70)</td>
<td>88 (67)</td>
<td></td>
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<td>6 (5)</td>
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<td></td>
</tr>
<tr>
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</tr>
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<td>TT</td>
<td>12 (7)</td>
<td>7 (3)</td>
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</table>

* FET.

** N.S., not significant.

### Discussion

Although multiple functional studies have clearly demonstrated that hOGG1 plays a critical role in repairing the major lesion 8-OH-G, limited data are available on the association between the sequence variants of the hOGG1 and cancers. In this study, we provided new data to address this issue in prostate cancer. Our study is the first one to evaluate the sequence variants of hOGG1
risk population because of self-selection. This potential bias, how-
ever, is unlikely to be significant in our study, because very few of
the 182 personally interviewed controls reported a positive family
history (defined as an affected father and/or brothers). In addition,
of all the control subjects were found to have normal DRE and PSA
results at the time of screening. Lastly, we cannot rule out the
impact of random sampling variation as a potential reason for our
significant findings, especially when considering the low fre-
cuency of GG homozygotes for 11657A/G. Although we observed
a higher frequency of GG homozygotes for 11657A/G and CC for
Ser325Cys in both sporadic cases and hereditary cases, they were
both compared with a single control group. Although replication of
these findings in independent studies can definitively address this
issue, the similar results observed in our family-based association
study alleviate this concern substantially.

Although our results on the SNP Ser326Cys are unexpected,
they are still consistent with the results from functional and epi-
demiological studies. The exact repair function associated with
this sequence variant is unknown. Whereas Kohno et al. (3) dem-
onstrated that the Cys326 allele was about 7-fold less capable of
complementing a repair deficient strain than the Ser326 allele in an
in vitro functional complementation assay. Dherin et al. (4) did
not observe significant differences in OGG1 activity of OGG1-
glutathione S-transferase (GST) fusion proteins in vitro. A recent
study by Janssen et al. (17) found that DNA repair activity of
OGG1 in human lymphocytes is not dependent on the Ser326Cys
variant. Furthermore, the repair activity associated with this se-
quence variant in vivo in normal human cells is not known.

Paralleling the results of the functional studies, the results from
epidemiological studies on the association between this sequence
variant and cancer risk are inconclusive. The sequence variant
Ser326Cys in germ-line DNA has been studied in several lung,
esophageal, and gastric cancer populations. Two observations can
be summarized from these studies: (a) although inconclusive, there
is evidence that this sequence variant may be associated with
susceptibility to several different cancers. For lung cancer, Sug-
imura et al. (9) found that individuals homozygous for G (Cys326)
were at significantly increased risk for lung squamous cell carci-
noma and nonadenocarcinoma in a Japanese population. However,
the German population, Wikman et al. (7) found a higher proportion
of CC homozygotes (Ser326) among lung cancer patients (64.8%)
than in the controls (57.1%). It is worth noting that the frequency
of CC homozygotes (Ser326) in the cases and controls of Wik-
man’s study (7) are similar to what we observed in our prostate
cancer cases (61.3%) and controls (55.2%), respectively. For
esophageal cancer, Xing et al. (10) found that GG (Cys326)
homozygotes were at significantly increased risk for developing
esophageal squamous cell carcinoma in a Chinese population; and
(b) there are significant differences in the genotype distribution
between different races and ethnicities. The proportion of homozy-
gous C (Ser326) individuals is highest in Melanesians (74.5%),
Hungarians (63.7%), and Germans (57.1%), lower in Australian
Caucasians (39.9%), Japanese (27.7%), and Micronesians (25.8%),
and lowest in Chinese (12%; Refs. 7, 9). With the limited sample
in our study, we observed 13 CC homozygotes out of 15 controls
among African Americans. Interestingly, the proportions of the
homozygous C (Ser326) are coincident with the different preva-
ience rates of prostate cancer in these populations. Furthermore,
from these limited data, it seems that Ser326 confers risk to cancer
in Caucasian populations and Cys326 confers risk to cancer in
Asian populations.

Another potential limitation of this study is the possibility that
some unknown sequence variants were not evaluated. This is
especially true among the HPC cases, because only three SNPs
were evaluated. However, we genotyped 10 SNPs across this gene,
and there is significant pair-wise LD in all of the SNPs. Therefore,
it is reasonable to expect that any increased prostate cancer risk
caused by unknown sequence variants across hOGG1 would most
likely be reflected indirectly by at least one of the genotyped SNPs.
However, we recognize that sequencing the entire gene and pro-
moter region offers a definitive approach to identifying all of the
important sequence variants, independent of the limitations of
genotyping.

The stronger association of hOGG1 SNPs observed in sporadic
cases, compared with hereditary cases, was an unexpected finding.
Although we can hypothesize that these are low-penetrance sequence
variants, this assumption alone is not a sufficient explanation, because
we would expect to observe at least similar risk to sporadic and
hereditary prostate cancer if the inherited sequence variants confer
any risk. Therefore, we think that at least two additional factors may
contribute to this finding. First, competing high-penetrance genes may
account for a significant proportion of the hereditary prostate cancer
cases, such that the contribution of a low-penetrance gene, such as
hOGG1, is relatively small in hereditary prostate cancer. The second
contributing factor may be the unequal statistical power provided by
the relatively small sample size of hereditary prostate cancer probands
included in our study (n = 133, Caucasians), compared with sporadic
cases (n = 229).

In summary, our study provides evidence for an association be-
 tween sequence variants of hOGG1 and prostate cancer risk. Consi-
dering the importance of this gene and the complexities of the available
results, we conclude that additional epidemiological and functional
studies are warranted not only in prostate cancer but also in other
cancers.

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