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Associations between *hOGG1* Sequence Variants and Prostate Cancer Susceptibility[1]

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Abstract

8-Hydroxyguanine is a mutagenic base lesion produced by reactive oxygen species. The *hOGG1* gene encodes a DNA glycosylase/AP lyase that can suppress the mutagenic effects of 8-hydroxyguanine by catalyzing its removal from oxidized DNA. A population-based (245 cases and 222 controls) and family-based (159 hereditary prostate cancer families) association study was performed to test the hypothesis that sequence variants of *hOGG1* increase susceptibility to prostate cancer. We found that the genotype frequency of two sequence variants (11657A/G and Ser326Cys) was significantly different between cases and controls. The association with 11657A/G is confirmed and strengthened by our family-based association study. These results suggest that sequence variants in this gene are associated with prostate cancer risk, presumably through defective DNA repair function of *hOGG1*.

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[3] 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 statistical 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 was 64.3 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 58.7 years. More than 93% 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

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[3] The abbreviations used are: 8-OH-G, 8-hydroxyguanine; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; HPC, hereditary prostate cancer; PSA, prostate-specific antigen; DRE, digital rectal examination; HWE, Hardy-Weinberg equilibrium; LD, linkage disequilibrium; FET, Fisher's exact test; CI, confidence interval; RR, relative risk.

Table 1 *PCR primers for the SNPs in hOGG1 gene*

SNP[a]	Group[b]	Primers[c]		
		Forward	Reverse	Extension (direction)
−627T/C	1	TGGTGAAGACAGGGTTCGTG	TTCTCCGAGAGCCGTTCTCC	CTCCCCCGAGCCTTTGCA(R)
−23A/G	1	GCATTTCCACAGCAGGCACC	AAGGGTCGTGGTCCTTGTCTG	CTGGGTAGGCGGGGCTACT(F)
−18G/T	5	TTGTCTGGGCGGGGTCTTTG	GGCAGGCATTTCCACAGCAG	ATTTCCACAGCAGGCACCG(R)
2550A/C	1	GAGGTCGAGGCAGGCAGAT	GGTTTCACCATGTTGGCCAG	CTGGTCTTGAACTCCTGACC(R)
3224A/C	3	CCCCGTCTCTACTAAAAATAC	TTCACGCCATTCTCCTGCCT	CGCCCACCACCACACCC(R)
3402G/A	2	ACAGAGTGAGACTCTGTCTC	GCCTTATGACTAACTAAGCC	TGACTAACTAAGCCAGGAGC(R)
3574G/A	2	GCAATCATGAGGCAGTGTAG	GCTGAAATTACCAGCATGAG	CAGCATGAGCTACCCCACC(R)
4540G/A	2	GAGCCATCCTGGAAGAACAG	CTTGTGGGCCTCCTCATATG	GGCCTCCTCATATGAGGACTCT(R)
6170G/C	3	GCTATAAGCAAGATGCTGGC	TGCAGTCAGCCACCTTTGAC	AGCCACCTTTGACAGACACA(R)
6803C/G		TGCCCAACGTGACTACAGC	GAGGTAGTCACAGGGAGGCC	
6876T/A	5	AGAGAAGTGGGGAATGGAGG	AGAAAGGGTTCCAAAGGGCC	AGGCTAGATGGGGCACCC(F)
6893T/C	4	AGAAAGGGTTCCAAAGGGCC	AGAGAAGTGGGGAATGGAGG	GAATGGAGGGGAAGGTGCTT(R)
7143A/G	3	CTGAACCGGGAGTTTCTCTG	GGAAAATGCAGTGAGGAGTG	ATGCAGTGAGGAGTGGTAGGGA(F)
9110A/G	4	TACCCAGGCTCAGCTTGCAC	AGTCCTTCAGTAAGGATCCC	AAGCAGTTACTGTGTGCCCA(F)
10629C/G	4	GGAGTTCCCCCTTTATAAAC	CAAGGAACAGAAAGGATAATG	CAGAAAGGATAATGTAGCTAGAA(R)
10660A/T	5	CTAGCTACATTATCCTTTCTG	AAGCAATGGCAAGTGCAAAG	GAGGGCAAGATGGCGGCACAT(R)
11657A/G	6	AGGTTTAGAGACAGTTCCCC	CAAGGAAGCTCTCAAGAAGG	CCAGGAAGGACAAGGCTCA(F)
11826A/T	7	AATGCCATCCTCACTGCTTC	AGTCACTTTGCCTCCAAAGG	TGCCTCCAAAGGCATCAGTT(R)

[a] Numerical values represent the position (measured in base pairs) from the transcription site. The letters represent nucleotide change.
[b] Multiplex PCR group.
[c] 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 Sequencher 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* were 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. An unconditional logistic regression was used to test for association between genotypes and prostate cancer and to estimate the age-adjusted RR of risk genotypes (homozygous 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 package (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 *GG* homozygotes for the 11657A/G and 7143A/G in cases compared with controls. For example, there were 17 *GG* 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, 13.89 (95% CI, 1.57–125) for hereditary prostate cancer, and 9.80 (95% CI, 1.30–76.92) for either type of 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

Table 2 *Genotype frequencies of sequence variants of hOGG1 in cases and controls (Caucasians only)*

SNPs	Genotype	No. of subjects (%)			*P*s (*vs.* control)[a]	
		Controls	Sporadic	HPC	Sporadic	HPC
3402G/A	*AA*	79 (43)	73 (40)			
	AG	83 (45)	81 (44)			
	GG	23 (12)	29 (16)		N.S.[b]	
3574G/A	*AA*	104 (60)	128 (67)			
	AG	58 (34)	54 (28)			
	GG	11 (6)	10 (5)		N.S.	
6170G/C	*CC*	101 (58)	130 (63)			
	CG	60 (34)	69 (33)			
	GG	13 (7)	8 (4)		N.S.	
6803C/G (Ser326Cys)	*CC*	96 (55)	122 (61)	60 (61)		
	CG	63 (36)	71 (36)	35 (35)		
	GG	15 (9)	6 (3)	4 (4)	0.055	0.34
7143A/G	*AA*	130 (71)	153 (68)	83 (64)		
	AG	52 (28)	59 (26)	41 (32)		
	GG	2 (1)	12 (5)	6 (5)	0.059	0.11
9110A/G	*GG*	110 (60)	138 (66)			
	GA	62 (34)	66 (31)			
	AA	12 (7)	6 (3)		N.S.	
10629C/G	*CC*	53 (30)	54 (28)			
	CG	73 (41)	84 (44)			
	GG	53 (30)	51 (27)		N.S.	
10660A/T	*TT*	111 (61)	140 (65)			
	TA	59 (32)	69 (32)			
	AA	12 (7)	8 (4)		N.S.	
11657A/G	*AA*	139 (74)	158 (70)	88 (67)		
	AG	47 (25)	56 (25)	38 (29)		
	GG	1 (1)	11 (5)	6 (5)	0.028	0.03
11826A/T	*AA*	110 (60)	138 (66)			
	AT	60 (33)	64 (31)			
	TT	12 (7)	7 (3)		N.S.	

[a] FET.
[b] N.S., not significant.

11657A/G and 7143A/G were genotyped in all of the available family members of HPC families because the distribution of these two SNPs in the probands were significantly different from those in the controls. Parents who are heterozygous *A/G* for 11657A/G preferably transmit the *G* allele to affected sons (observed and expected *S* of 91 and 81, respectively; $Z = 2.28$, $P = 0.02$). A similar trend was observed for 7143A/G, although it was not statistically significant ($Z = 1.36$, $P = 0.17$). These results suggest that the observed differences of genotype distributions at 11657A/G between cases and controls are not solely attributable to the impact of population stratification.

We also tested the hypotheses that the sequence variants in *hOGG1* are associated with clinical characteristics of prostate cancer or preoperative PSA levels. When we compared the distributions of the 10 SNPs in sporadic cases with high ($\geq$7) or low ($\leq$6) Gleason scores and with a confined or nonlocalized tumor, no statistically significant difference in the genotypic frequencies of these SNPs was found between any of these groups (data not shown). We also compared the mean $\log_{10}$ PSA levels by the genotypes in these 10 SNPs among cases (preoperative) and controls, respectively. No significant difference was found in any of the groups.

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* 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 preferably 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 3 *Estimated RR of hOGG1 SNPs for prostate cancer (Caucasians only)*

SNPs	Genotype	RR (95% CI),[a] FET *P*		
		Sporadic	Hereditary	Either type of prostate cancer
6803C/G (Ser326Cys)	*GG*	1	1	1
	CC	3.23 (1.19–8.73) FET $P = 0.02$	2.07 (0.65–6.62) FET $P = 0.21$	2.72 (1.17–6.32) FET $P = 0.02$
7143A/G	*AA*	1	1	1
	GG	5.12 (1.12–23.25) FET $P = 0.03$	8.19 (1.51–45.45) FET $P = 0.06$	5.21 (1.18–22.73) FET $P = 0.03$
11657A/G	*AA*	1	1	1
	GG	9.80 (1.25–76.92) FET $P = 0.008$	13.89 (1.57–125.00) FET $P = 0.02$	9.80 (1.30–76.92) FET $P = 0.009$

[a] Adjusted for age.

risk population because of self-selection. This potential bias, however, 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, all of 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 frequency 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 epidemiological studies. The exact repair function associated with this sequence variant is unknown. Whereas Kohno *et al.* (3) demonstrated 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 sequence 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, Sugimura *et al.* (9) found that individuals homozygous for *G* (Cys326) were at significantly increased risk for lung squamous cell carcinoma and nonadenocarcinoma in a Japanese population. However, two other studies did not confirm this association (3, 7). In 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 Wikman'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 homozygous *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 prevalence 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 promoter 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 between sequence variants of *hOGG1* and prostate cancer risk. Considering 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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