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hOGG1 gene polymorphisms and susceptibility to polycystic ovary syndrome

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Abstract. Oxidative stress generates 8-hydroxy-2'-deoxyguanine (8-oxodG), which can structurally modify DNA. Glycosylase hOGG1 can remove the mutagenic lesion 8-oxodG from DNA. The aim of the present study was to determine whether polymorphisms in hOGG1 were associated with the risk of polycystic ovary syndrome (PCOS). One common single-nucleotide polymorphism (Ser326Cys) in exon 7 and four rare polymorphisms (c.-18G>T, c.-23A>G, c.-45G>A and c. -53G>C) were screened in the 5' untranslated region of the *hOGG1* gene. No such distributional differences were observed between the PCOS patients and controls either in the genotype frequency or in the allele frequency. There were no differences in the clinical variables among the different genotypes in all the variants, except that the follicle-stimulating hormone level was elevated in the GC genotype of c. -53G>C in PCOS patients (P=0.002). These results suggest that the polymorphisms in *hOGG1* may not be an independent risk factor for PCOS.

Introduction

In the living cells of aerobic organisms, reactive oxygen species (ROS) are continuously produced in various physiological processes, such as metabolic and other biochemical reactions. A low level of ROS is essential for maintaining physiological function and biochemical pathway processing, including intracellular signaling pathways in cell differentiation, proliferation, apoptosis (1) and immunity (2). By contrast, high levels of ROS can cause oxidative stress damaging biological macromolecules, such as membrane lipids, proteins and DNA, which may lead to metabolic malfunctions (3-5). 8-Hydroxy-2'-deoxyguanine (8-OHdG) induces ROS-mediated oxidative damage by promoting the transversion of G/C to A/T, as it has a higher affinity for pairing with adenine (A) rather than cytosine (C) (6). Base excision repair (BER) of DNA reverses a number of spontaneous and environmentally induced genotoxic or miscoding base lesions in a process initiated by DNA glycosylases (7). Human OGG1 (hOGG1) efficiently repairs the incorrect or damaged bases by removing 8-OHdG, as part of the BER pathway (8).

Previous studies have reported several polymorphisms in the *hOGG*1 gene (9,10). *In vitro* activity assays confirmed that some of the variants affect hOGG1 expression resulting in a substantially higher DNA repair activity. Variants in the *hOGG1* gene have been investigated in numerous diseases (11-13). A number of genetic variants in the *hOGG1* gene may alter the repair function and thus contribute to the development of ROS-related diseases.

PCOS is one of the most common reproductive endocrine disorders, affecting 5-10% of women of reproductive age (14). PCOS is a heterogeneous syndrome characterized by clinical and/or biochemical androgen excess, polycystic ovaries and ovulatory dysfunction (15). While the etiology of PCOS remains to be elucidated, accumulating evidence suggests that chronic low-grade inflammation strengthens the development of metabolic aberration and ovarian dysfunction in this disorder (16,17). Circulating TNF-α levels are elevated in PCOS patients (18). TNF-α is mainly derived from mononuclear cells (MNCs), and hyperglycemia can further induce MNCs to produce TNF-α and ROS (18,19). TNF-α and ROS in turn exacerbate the inflammatory process, resulting in chronic inflammation in PCOS patients. The *hOGG1* gene is associated with decreased insulin sensitivity (20), a common feature of certain PCOS patients. Therefore, we hypothesize that a link between the *hOGG1* gene and PCOS may exist.

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Table I. Clinical and endocrine characteristics of PCOS patients and controls.

Patients	Total, n	Age, years	BMI[a], kg/m^2	FSH[a], IU/l	LH[a], IU/l	LH/FSH[a]	E2[a], pg/ml	T[a], nmol/l
Control	440	33.02±5.39	21.95±3.91	8.36±8.32	5.62±4.86	0.75±0.50	65.33±58.40	2.45±1.75
PCOS	425	26.95±6.79	22.96±6.13	5.97±3.22	11.77±8.96	2.26±3.04	79.3±69.22	2.7±6.02

[a]P<0.05 between the PCOS and control groups. Data are mean ± standard deviation. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone; PCOS, polycystic ovary syndrome.

Materials and methods

Subjects. A total of 865 individuals, consisting of 425 PCOS patients and 440 non-PCOS control women, were involved in the present study. All the participants were of Han Chinese origin. Peripheral venous blood samples were collected at Nanjing Drum Tower Hospital of Nanjing University, Memorial Hospital of Sun Yat-Sen University (Nanjing, Jiangsu, China), and at the Department of Obstetrics and Gynecology of Anhui Medical University (Hefei, Anhui, China) between 2004 and 2013. The PCOS patients were diagnosed based on the 2003 Rotterdam Criteria (15). All the controls had normal ovulatory menstrual cycles and did not show hirsutism or other manifestations of hyperandrogenism. Serum hormone levels and clinical variables [including age and body mass index (BMI)] were measured as previously described (21). The study was approved by the Ethics Committee of Nanjing University and informed consent was obtained from each participant.

Polymorphism genotyping analysis in the hOGG1 gene. Genomic DNA was isolated from peripheral blood leukocytes using an UltraPure™ Genome DNA kit (SBS Genetech Co., Ltd., Shanghai, China) and stored at -80˚C. A DNA fragment containing part of the 5' untranslated region (UTR) and the full region of exon 1 was amplified with the primers: Forward, 5'-AGG AGG TGG AGG AAT TAA GT-3' and reverse, 5'-GGC TTC TCA GGC TCA GTC A-3', as described previously (9,11). Amplification of DNA sequences, including Ser326Cys polymorphism in exon 7, was carried out with: Forward primer, 5'-GGA AGG TGC TTG GGG AAT-3' and reverse primer, 5'-ACT GTC ACT AGT CTC ACC AG-3'. Polymorphism chain reaction (PCR) was run in a total volume of 25 μl containing 50 ng of genomic DNA, 6 pmol of each primer, 2.5 μl short tandem repeat 10X buffer (Promega, Madison, WI, USA) and 0.75 units of GoTaq DNA polymerase (Promega). The PCR protocol was conducted as follows: Denaturing at 95˚C for 5 min, followed by 30 cycles consisting of 30 sec of denaturation at 94˚C, 30 sec of annealing at 60˚C for 5'-UTR or 58˚C for exon 7, and 30 sec of extension at 72˚C; and a final single extension of 10 min at 72˚C. For 5'-UTR, the genotyping was carried out by direct sequencing on an ABI 3130 automated sequencer at Nanjing Springen Bio-Technique Corp. (Nanjing, China). Genotyping for the *hOGG1* Ser326Cys polymorphism was performed by the PCR-restriction fragment length polymorphism (RFLP) assay. Briefly, a 200-base pair (bp) PCR product was digested at 37˚C with *Fnu*4HI (Thermo Fisher Scientific, Inc., San Jose, CA, USA) for 16 h resulting in a single 200-bp band for the homozygous Ser/Ser *hOGG1* variant, a single 100-bp band for the homozygous Cys/Cys *hOGG1* variant, and double bands of 200 and 100 bp for the heterozygous Ser/Cys *hOGG1* variant. Digestion was visualized following electrophoresis on a 3% agarose gel containing ethidium bromide. Finally, 100 DNA samples were randomly selected for direct sequence to validate Ser326Cys.

Serum hormone determination. Venous blood samples were collected in the early follicular phase (days 3-5) of the menstrual cycle for those who had menstrual cycles and at any time for those who were amenorrheic. Prior to sample collection, all participants went through a 12-h overnight fast. Serum estradiol (E2), testosterone (T), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were determined by radioimmunoassay (Beijing North Institute of Biological Technology of China, Beijing, China and the CIS Company of France, Gif-sur-Yvette, France). The intra-assay and inter-assay coefficients of variation were <10% for all the assays.

Statistical analysis. Fisher's exact test or χ^2 test was used when appropriate to detect the association between genotypic variants in the *hOGG1* gene. The PCOS risks were determined by the odds ratio (OR) and its corresponding 95% confidence intervals (CIs). Genotype frequencies for each single-nucleotide polymorphism (SNP) were determined for Hardy-Weinberg equilibrium in the control group. The results of serum hormone levels, age and BMI are reported as the mean ± standard deviation. Genotypic distribution analysis between PCOS and control was carried out by Fisher's exact test. Biochemical steroid levels among different genotypes were compared by analysis of covariance to correct for age and BMI. All the statistical analysis was performed using the statistical program SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of PCOS and control subjects. Clinical variables and serum steroid hormone levels were compared between women with PCOS and controls (Table I). PCOS patients had significantly higher BMI, testosterone levels and LH/FSH ratios as compared with healthy control women.

Distribution of the hOGG1 gene variants. Five variants were screened in a case-control study that included 425 PCOS

Table II. Germline *hOGG1* variations and genotype/allele frequencies in the case-control study.

SNP sites	Genotype/allele	Total, n (%)		P-value[a]	OR (95% CI)[b]
		PCOS (n=425)	Control (n=440)		
c.-53G>C	GC	10 (2.4)	5 (1.1)	0.199	2.096 (0.711-6.185)
	GG	415 (97.6)	435 (98.9)		1
	C	10 (1.2)	5 (0.6)	0.201	2.083 (0.709-6.121)
	G	840 (98.8)	875 (99.4)		1
c.-45G>A	GA	0 (0.0)	2 (0.4)	0.500	-
	GG	425 (100.0)	438 (99.6)		-
	A	0 (0.0)	2 (0.2)	0.500	-
	G	850 (100.0)	878 (99.8)		-
c.-23A>G	AG	7 (1.6)	14 (3.2)	0.185	0.510 (0.204-1.275)
	AA	418 (98.4)	426 (96.8)		1
	G	7 (0.8)	14 (1.6)	0.188	0.514 (0.206-1.279)
	A	843 (99.2)	866 (98.4)		1
c.-18G>T	GT	13 (3.0)	20 (4.5)	0.289	0.663 (0.325-1.350)
	GG	412 (97.0)	420 (95.5)		1
	T	13 (1.5)	20 (2.3)	0.294	0.668 (0.330-1.351)
	G	837 (98.5)	860 (97.7)		1
Ser326Cys	GG	156 (36.7)	141 (32.0)		1.314 (0.878-1.966)
(C>G)	CG	205 (48.2)	223 (50.7)	0.319	1.092 (0.744-1.601)
	CC	64 (15.1)	76 (17.3)		1
	G	517 (60.8)	505 (57.4)	0.146	1.153 (0.952-1.397)
	C	333 (39.2)	375 (42.6)		1

[a]Data were analyzed for the frequencies of genotypes or alleles between cases and controls carried out by Fisher's exact test. [b]OR (95% CI) were calculated as the wild genotype. SNP, single-nucleotide polymorphism; PCOS, polycystic ovary syndrome; OR, odds ratio; CI, confidence interval.

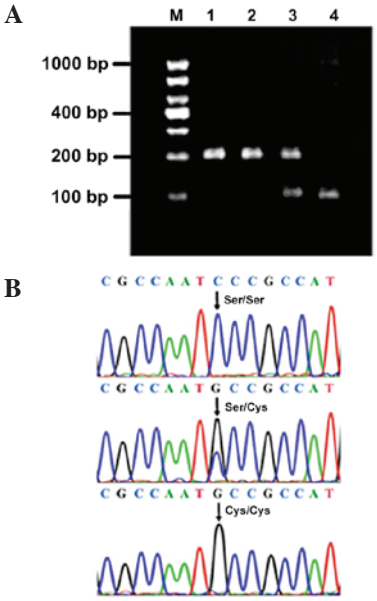

Figure 1. Analyses of the *hOGG1* polymorphism chain reaction products following digestion with *Fnu*4HI by direct sequencing. (A) Identification of different genotypes of *hOGG1* Ser326Cys polymorphisms by electrophoresis of DNA fragments. M, molecular weight marker; lane 1, PCR product without digestion; lane 2, genotype Ser/Ser; lane 3, genotype Ser/Cys; lane 4, genotype Cys/Cys. (B) The Ser326Cys genotypes were identified by DNA direct sequencing. The Ser/Ser, Ser/Cys and Cys/Cys genotypes are indicated by arrows.

patients and 440 age-matched controls by direct sequencing and/or RFLP (Fig. 1A and B). Four of the variants were SNP, namely, c.-18G>T, c.-23A>G, c. -53G>C and Ser326Cys. The genotypic distributions of the four SNPs were consistent with Hardy-Weinberg equilibrium in the control group. A rare variation, c.-45G>A, was only observed in the normal controls with an extremely low allele frequency (<1%), while another previously reported rare variation, c.-63G > C, was not detected in the Chinese population examined in the present study. Of note, the four closely adjacent variants did not appear to belong to an individual linkage disequilibrium block, as there were no combined variants in the whole population investigated.

No significant differences were detected in the genotype frequency or allele frequency in all five variations between patients and control (Table II). There were no differences in the clinical variables and hormone levels among the different genotypes in all the variants, except that the FSH level was elevated in the GC genotype (P=0.002) of c. -53G>C in PCOS patients (Tables III-VII). Furthermore, the potential joint effect between the four rare variants and Ser326Cys was investigated to evaluate the risk of the combined variants in PCOS. However, no significant association was found in each individual allele (Table II) or genotype combinations (data not shown).

Table III. Comparisons of variants at c.-53 G>C for women with or without PCOS in terms of anthropometric characteristics and serum hormone concentrations.

	Control			PCOS		
Genotypes	*GG*	*GC*	P-value	*GG*	*GC*	P-value
Age, years	32.99±5.35	36.67±10.40	0.240	26.89±6.73	29.33±9.35	0.384
BMI, kg/m^2	21.95±3.92	21.54±1.46	0.856	22.96±6.17	22.97±4.83	0.994
FSH, IU/l	8.33±8.33	11.75±7.98	0.480	5.86±2.77	10.36±11.51	0.002[a]
LH, IU/l	5.63±4.88	4.97±1.79	0.815	11.72±9.04	14.08±4.66	0.562
LH/FSH	0.75±0.50	0.48±0.13	0.356	2.26±3.07	2.17±0.99	0.947
T, nmol/l	2.46±1.74	0.24±0	0.207	2.70±6.09	2.49±1.16	0.938
E2, pg/ml	65.68±58.51	26.83±27.25	0.252	79.18±69.64	84.35±55.60	0.869

[a]P<0.05. Statistical analyses were carried out by analysis of covariance to correct for age and BMI. Data are mean ± standard deviation. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone.

Table IV. Comparisons of variants at c.-45 G>A for women without PCOS in terms of anthropometric characteristics and serum hormone concentrations.

	Control		
Genotypes	*GG*	*AG*	P-value
Age, years	32.92±5.68	33.00±5.65	0.987
BMI, kg/m^2	22.11±3.57	20.45±0.64	0.512
FSH, IU/L	8.37±8.35	7.09±2.11	0.829
LH, IU/L	5.62±4.86	7.24±6.36	0.638
LH/FSH	0.75±0.92	0.50±0.62	0.613
T, nmol/l	2.45±1.75	-	-
E2, pg/ml	65.52±58.52	34.00±14.14	0.448

Statistical analyses were carried out by analysis of covariance to correct for age and BMI. Data are mean ± standard deviation. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone.

Discussion

PCOS is a complex endocrine disease with no clear etiology. Accumulating evidence suggests that genetic and environmental factors contribute to its occurrence and development (22). Familial clustering of PCOS or PCOS-related metabolic symptoms indicates a genetic origin (23,24), although no consensus of the inheritance mode has been reached. To date, significant attention has been focused on the genes involved in the androgen biosynthetic pathways (*CYP11*, *CYP17* and *CYP19*) and insulin-related pathways (*INS* and *INSR*). However, other genes that are crucial in maintaining normal metabolic functions, such as insulin sensitivity preservation may show a link with this metabolic disease. The *hOGG1* gene is critical in BER. Several polymorphisms in *hOGG1* have been identified as associated with insulin sensitivity and type 2 diabetes mellitus (T2MD). The underlying role of ROS-induced oxidative stress in PCOS together with the correlation between ROS and the BER system provide us with a new insight into the possible causes of PCOS. To the best of our knowledge, this is the first time that functional polymorphisms in the *hOGG1* gene in Chinese PCOS patients have been investigated.

The structure and functions of hOGG1 have been well studied and several of its polymorphisms have been identified. Specifically, certain polymorphisms in *hOGG1* that are associated with insulin sensitivity or T2MD have been reported, indicating the functional involvement of *hOGG1* in the maintenance of normal glucose metabolism (9,20,25). Previous studies have reported an association between oxidative stress and insulin resistance not only in the context of diabetes, but also in nondiabetic individuals and in those with metabolic syndromes (26-28). Consequently, increased generation of ROS in response to oxidative stress in metabolic syndromes prompted other investigators to focus on genomic instability and DNA damage that are associated with *hOGG1*.

The present study investigated four rare SNPs in 5'-UTR and a common SNP (Ser326Cys) in exon 7 of the *hOGG1* gene in a case-control study of PCOS. The 5'-UTR region is known to modulate gene expression at the post-transcriptional level by influencing mRNA stability and translational efficiency medicated by transcription factors (TF) (29,30). The inactivation or induction of the corresponding TF can modulate the expression of the *hOGG1* gene, thus influencing the activity of the protein (31,32). Previous studies revealed that certain types of functional variants in the 5'-UTR of the *hOGG1* gene are capable of increasing the risks of diseases, including cancer (9,11,33,34). The present finding suggests that there was no significant correlation between the variants in *hOGG1* and the PCOS risk. Although the FSH level was elevated in the GC genotype of c. -53G>C in PCOS patients, it is difficult to provide any reasonable explanation for this phenomenon. The polymorphism Ser326Cys in the *hOGG1* gene is shown to be associated with OGG1 activity in *in vitro* and *in vivo* studies, and it is suggested that the 326Cys allele may pose a higher risk of 8-oxoG formation in DNA (35,36). The associations between the *hOGG1* Ser326Cys polymorphism and various diseases have been extensively investigated.

Table V. Comparisons of variants at c.-23 A>G for women with or without PCOS in terms of anthropometric characteristics and serum hormone concentrations.

	Control			PCOS		
Genotypes	*AA*	*AG*	P-value	*AA*	*AG*	P-value
Age, years	31.95±7.82	34.50±5.48	0.307	26.98±6.59	31.25±5.44	0.199
BMI, kg/m^2	22.05±3.57	22.70±3.22	0.551	22.91±6.32	20.17±2.08	0.388
FSH, IU/l	8.36±8.44	8.19±2.69	0.949	6.01±3.22	5.31±2.24	0.668
LH, IU/l	5.62±4.92	5.63±2.32	0.997	11.77±8.92	14.57±11.63	0.537
LH/FSH	0.75±0.51	0.75±0.34	0.987	2.26±3.06	2.83±2.19	0.713
T, nmol/l	2.47±1.77	1.91±1.20	0.446	2.51±5.40	2.20±1.67	0.921
E2, pg/ml	65.57±58.88	57.39±41.52	0.663	79.22±69.54	52.86±13.52	0.513

Statistical analyses were carried out by analysis of covariance to correct for age and BMI. Data are mean ± standard deviation, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone.

Table VI. Comparisons of variants at c.-18 G>T for women with or without PCOS in terms of anthropometric characteristics and serum hormone concentrations.

	Control			PCOS		
Genotypes	*GG*	*TG*	P-value	*GG*	*TG*	P-value
Age, years	32.88±5.94	31.81±5.46	0.480	27.18±6.31	26.64±8.03	0.782
BMI, kg/m^2	21.79±3.79	21.67±2.81	0.910	23.56±5.10	22.64±2.78	0.572
FSH, IU/l	8.43±8.49	6.78±1.86	0.469	5.98±3.23	6.31±2.39	0.763
LH, IU/l	5.66±4.74	4.94±2.34	0.488	11.88±9.00	10.59±7.98	0.673
LH/FSH	0.75±0.51	0.77±0.46	0.851	2.30±3.10	1.60±0.89	0.500
T, nmol/l	2.43±1.76	2.92±1.10	0.638	2.70±6.14	2.88±1.63	0.930
E2, pg/ml	65.80±58.32	59.48±61.51	0.693	80.39±69.75	68.86±42.30	0.665

Statistical analyses were carried out by analysis of covariance to correct for age and BMI. Data are mean ± standard deviation. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T, testosterone.

Table VII. Comparisons of Ser326Cys (C>G) for women with or without PCOS in terms of anthropometric characteristics and serum hormone concentrations.

	Control				PCOS			
Genotypes	*CC*	*CG*	*GG*	P-value	*CC*	*CG*	*GG*	P-value
Age, years	31.48±2.65	33.12±5.03	35.88±5.64	0.675	25.95±8.01	28.13±4.03	30.88±6.74	0.468
BMI, kg/m^2	21.46±3.74	21.99±2.33	21.77±3.74	0.897	22.56±5.66	23.43±4.51	22.78±3.78	0.649
FSH, IU/l	7.79±7.49	8.68±2.94	8.29±4.47	0.469	5.78±4.23	6.13±4.46	5.89±2.23	0.657
LH, IU/l	5.67±4.74	5.74±4.04	4.96±3.74	0.658	11.59±6.99	12.84±9.00	8.66±6.74	0.371
LH/FSH	0.78±0.16	0.75±0.69	0.74±0.23	0.865	2.31±1.92	2.27±1.03	1.76±1.89	0.582
T, nmol/l	2.49±1.32	2.32±0.19	2.45±1.96	0.618	2.80±1.64	2.44±1.96	2.68±1.87	0.654
E2, pg/ml	59.90±41.59	65.60±48.22	66.81±48.73	0.413	67.16±48.37	77.80±58.11	81.49±64.77	0.200

Statistical analyses were carried out by analysis of covariance to correct for age and BMI. Data are mean ± standard deviation. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; T testosterone.

However, conflicted results, even in the same disease, have been reported (37,38). The present study does not support an association of this polymorphism with PCOS susceptibility. Given the low allele frequency of the variants in 5'-UTR of

hOGG1, further studies with a larger sample size are required to confirm these findings.

In conclusion, *hOGG1* is not an independent risk factor for PCOS development, and no putative linkage to the syndrome could be established.

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