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Association of the Ser326Cys polymorphism in the OGG1 gene with type 2 DM ☆

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ABSTRACT

The association of the Ser326Cys polymorphism of the 8-oxoguanine glycosylase 1 (OGG1) gene with type 2 diabetes was examined using a Japanese population (n (M/W): 4585 (2085/2500); age: 62.6 ± 10.9 years). HbA1c levels and frequency of diabetic subjects were significantly higher in subjects with genotypes with Cys allele than in those without ($p = 0.032$ and 0.037, respectively). Multiple logistic regression analysis showed that genotypes with Cys allele were significantly associated with diabetes (OR: 1.32, $p = 0.0289$). In subjects whose glucose tolerance was classified by FPG and 2-h PG ($n = 1.634$), the association was more substantial (genotypes with Cys allele vs. without, OR: 1.70, $p = 0.0059$; genotypes Cys/Cys vs. Ser/Ser, OR: 2.19, $p = 0.0008$). In subjects with genotype Ser/Ser, the insulin secretion index, HOMA-β, increased in the subjects with glucose intolerance and decreased in the subjects with diabetes, while, in subjects with genotypes Ser/Cys + Cys/Cys, HOMA-β decreased as the glucose tolerance progressed (p for trend = 0.010).

Hyperglycemia, which is the most prominent feature of diabetes, has been shown to augment free-radical production, probably due to the mitochondrial oxidative metabolism caused by a high intracellular glucose concentration and the increased production of advanced glycation end products [1–3]. Increased free radicals cause DNA damage, resulting in diminished proliferative capacity, premature senescence, and impaired mitochondrial function [4,5]. The role of free radicals in complications of diabetes has been well studied [6,7]. Free radicals has also been shown to play a central role in the islet β-cell destruction in type 1 diabetes [8,9]; however, the role of free radicals in relation to the pathophysiology of the islet β-cell failure in type 2 diabetes has not been well studied.

DNA repair enzymes modulate free-radical production after DNA damage. Among such enzymes, 8-oxoguanine glycosylase 1 (OGG1) seems to be most important since OGG1 is primarily responsible for removing 8-oxoguanine in DNA, which is a major product of DNA damage formed by free radicals, and can mispair with adenine residues instead of the usual cytosine residues, leading to an increased frequency of G:C to T:A transversion mutations [10,11]. Therefore, decreased function of OGG1 seemed to play a major role in tumorigenesis, and, thus, the OGG1 gene has been studied extensively as a candidate gene for many types of tumors [12]. Although the OGG1 gene is highly polymorphic, the gene polymorphism Ser326Cys has been the most studied as a candidate polymorphism susceptible for many types of tumors [13,14], since the Ser326Cys polymorphism has been shown to be associated with the difference in the enzyme activity with the low-expression Cys allele [15].

Although association of the OGG1 gene polymorphism with diabetes has not been reported, a significant reduction of free fatty acid-induced apoptosis by the overexpression of OGG1 in mitochondria of INS-1 cells [16] seemed to indicate an involvement of the gene in the pathophysiology of the islet β-cell function. We here hypothesized that the OGG1 gene is a candidate susceptible for diabetes; thus, we examined the association of the Ser326Cys polymorphism with diabetes in a large population-based Japanese sample.

Materials and methods

Subjects. Subjects ($n = 4585$) from two distinct epidemiological studies, the Funagata (those attending in 2001, 2002 and 2005; $n = 1634$) and the Takahata (those attending in 2004 and 2005; $n = 2951$) studies, were together enrolled in the present study.

☆ OGG1, 8-oxoguanine glycosylase 1; DM, diabetes.

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The Funagata and Takahata studies are Japanese population-based studies held in agricultural area located about 400 and 300 km north of Tokyo, respectively [17,18]. The details of these studies and their clinical characteristics have been reported previously [17,18].

The present study was approved by the Ethics Committee of the Yamagata University School of Medicine, and informed consent to participate was obtained from all the participants. The clinical characteristics of the study population are shown in Table 1. Diabetic conditions of the subjects were classified according to the fasting plasma glucose (FPG) criteria of the 1998 WHO criteria [19]. Those on medication for diabetes were diagnosed as diabetic. Subjects known to have type 1 diabetes were excluded. The numbers of subjects with normal fasting glucose (NFG), impaired fasting glucose (IFG) and diabetes were 3942, 259 and 384, respectively. In the Funagata study, a 75-g oral glucose tolerance test (OGTT) was conducted in all the participants; thus, the Funagata subjects (n = 1634) were classified according to the 1998 WHO criteria with both FPG and 2-h plasma glucose (2-h PG) [19] as well. The numbers of subjects with normal glucose tolerance (NGT), glucose intolerance (GI) and diabetes were 1163, 276 and 195, respectively.

Differences in insulin resistance and secretion indexes assessed by homeostasis model assessment using FPG and serum insulin (FI) levels (HOMA-α and HOMA-β, respectively) among the genotype groups were examined. In the Funagata subjects, these differences among subjects with NGT, GI and diabetes for each genotype group of the Ser326Cys polymorphism of the OGG1 gene were also examined. In the Funagata study, FI levels were not measures in 2001 and 2002; thus, the number of the subjects with FI levels was only 570. However, about half of the subjects who attended the health care examinations in 2001 and 2002 also attended in 2006 and 2007, respectively; thus, for the analysis mentioned above in the Funagata subjects, the clinical data obtained in 2006 or 2007 were substituted for the original clinical data in these subjects (n = 531). To evaluate HOMA indexes precisely, subjects on medication for diabetes were excluded from the analysis of the differences in HOMA-β (n = 32), and, those on medication for diabetes and with FPG levels >140 mg/dl were excluded from the analysis of the differences in HOMA-α (n = 41).

Hypertension was defined as blood pressure ⩾140/90 mm Hg or as being on treatment for hypertension. Hyperlipidemia was defined as total cholesterol ⩾240 mg/dl, TG ⩾150 mg/dl, or as being on treatment for hyperlipidemia.

Genotyping. The Ser326Cys polymorphism of the OGG1 gene (db SNP ID: rs1052133) was analyzed. Genomic DNA was extracted from peripheral blood leukocytes. The genotyping was conducted with a fluorogenic polymerase chain reaction as described previously. The study population was divided into three groups according to genotype: Ser/Ser (n = 1315), Ser/Cys (n = 2286), and Cys/Cys (n = 984). The mean age (±SD) and the sex ratio (female/male) of the groups (Ser/Ser, Ser/Cys, and Cys/Cys) were 62.8 ± 10.8 and 592/726, 62.5 ± 11.1 and 1064/1222, and 62.7 ± 10.8 and 429/555, respectively. No statistical differences in age or sex ratio were observed among the groups.

Statistical analysis. Data are given as means ± SD. A quantitative association between the genotypes and the trait values (parametric) and a case-control association between the genotypes and the frequencies of the condition (non-parametric) were analyzed by analysis of variance (ANOVA) and chi-square tests, respectively. The independent association of the Ser326Cys polymorphism with diabetes from age, gender, body mass index (BMI) and serum triglyceride was examined by multiple logistic regression analysis. $p < 0.05$ was accepted as significant.

Results

Association of the Ser326Cys polymorphism of the OGG1 gene with diabetes

As shown in Table 1, serum triglyceride and HDL cholesterol levels were significantly different among the genotype groups. However, these differences did not have any allele-specific trend and so could not be explained as the effect of the polymorphism. FPG and HbA1c levels tended to increase toward the genotype Cys/Cys and, when the differences were examined between the

Table 1
Differences in clinical characteristics according to the Ser326Cys polymorphism of the OGG1 gene.

Trait	Total	Genotype (OGG1:Ser326Cys)			p	
		Ser/Ser	Ser/Cys	Cys/Cys	Amang 3 groups[#1]	Ser/Ser vs X/Cys
Number (Gender: M/F)	4585 (2085/2500)	1315 (592/723)	2286 (1064/1222)	984 (429/555)	0.278	0.695
Age (yr)	62.6 ± 10.9	62.8 ± 10.8	62.5 ± 11.1	62.7 ± 10.8	0.741	0.526
Height (cm)	156.2 ± 9.1	156.0 ± 9.1	156.3 ± 9.2	156.1 ± 9.0	0.689	0.541
Body weight (kg)	57.7 ± 10.4	57.8 ± 10.6	57.9 ± 10.5	57.2 ± 9.9	0.225	0.672
Body mass index (kg/m^2)	23.6 ± 3.3	23.7 ± 3.5	23.6 ± 3.3	23.4 ± 3.1	0.168	0.275
FPG (mg/dl)[#2]	95.0 ± 16.4	94.4 ± 14.4	95.2 ± 17.1	95.3 ± 17.2	0.343	0.150
HbA1c (%)	5.24 ± 0.71	5.20 ± 0.68	5.25 ± 0.69	5.27 ± 0.78	0.068	0.032*
F-insulin (μU/ml)[#3]	5.4 ± 3.3	5.4 ± 3.2	5.4 ± 3.4	5.4 ± 3.3	0.829	0.551
HOMA-α[#4]	1.26 ± 0.85	1.24 ± 0.80	1.26 ± 0.87	1.27 ± 0.85	0.777	0.480
HOMA-β[#3]	70.4 ± 45.4	68.9 ± 43.2	71.0 ± 46.6	71.2 ± 45.6	0.492	0.235
S-BP (mm Hg)	132.7 ± 16.7	132.7 ± 16.9	132.6 ± 16.5	132.8 ± 17.1	0.947	0.923
D-BP (mm Hg)	78.2 ± 10.3	78.2 ± 10.1	78.4 ± 10.4	78.0 ± 10.4	0.470	0.798
Total cholesterol (mg/dl)	200.7 ± 32.0	201.8 ± 31.3	200.3 ± 32.6	200.5 ± 31.7	0.389	0.175
Triglyceride (mg/dl)	111.3 ± 94.2	106.3 ± 66.2	116.2 ± 113.0	106.6 ± 75.9	0.002**	0.022*
HDL cholesterol (mg/dl)	59.0 ± 14.5	59.8 ± 14.3	58.5 ± 14.5	59.4 ± 14.8	0.022*	0.027*
Hypertension: n (%)	2349 (51.2)	673 (51.2)	1185 (51.8)	491(49.9)	0.595	0.963
Hyperlipidemia: n (%)	1429 (31.2)	394 (30.0)	724 (31.2)	311 (31.6)	0.548	0.273
Diabetes[#5]: n (%)	384(8.4)	93(7.1)	201(8.8)	90(9.1)	0.109	0.037*
Diabetes/IFG[#5]: n (%)	384(8.4)/259(5.6)	93(7.1)/68(5.2)	201(8.8)/138(6.0)	90(9.1)/53(5.4)	0.213	0.075

p Values compared the DM or the IGT groups with the NGT group. $p < 0.05$ and <0.01 are indicated by * and **, respectively. #1: Differences were analyzed using ANOVA. #2: Data were not obtained from some of the subjects, most of which was known to be diabetic prior to the examination (n; Ser/Ser, Ser/Cys Cys/Cys: 1248, 2,146, 925). #3: Data were not obtained from those attended Funagata study in 2001 and 2002, and those on treatment for DM were excluded (n; Ser/Ser, Ser/Cys Cys/Cys: 919, 1568, 676). #4:The subjects whose fasting plasma glucose levels (FPG) were more than 140 mg/dl, and those on treatment for DM were excluded (n; Ser/Ser, Ser/Cys Cys/Cys: 912, 1555, 670). #5: Classified according to the FPG criteria of the 1998 WHO criteria (19). BMI, body mass index; F-insulin, fasting serum insulin; S-BP, systolic blood pressure; D-BP, diastolic blood pressure. X/Cys:Ser/Cys + Cys/Cys.

genotype Ser/Ser and the genotypes Ser/Cys + Cys/Cys, HbA1c levels were significantly higher in the genotypes with Cys allele than in those without ($p = 0.032$).

Similarly, the frequencies of diabetic subjects were significantly higher in subjects with the genotypes Ser/Cys + Cys/Cys of the Ser326Cys polymorphism than in those with the genotype Ser/Ser. Multiple logistic regression analysis showed that the genotypes Ser/Cys + Cys/Cys were significantly associated with diabetes, with an OR of 1.32 (95% CI, 1.03–1.69; $p = 0.0289$) after adjustment for age, gender, BMI, and triglyceride levels (Table 2). When only the subjects whose glucose tolerance was classified by FPG and 2-h PG were used for the case-control association study, the association of the genotypes was more substantial and significant, even though the number of subjects was smaller (Ser/Cys + Cys/Cys vs Ser/Ser, OR:1.70, $p = 0.0059$; Cys/Cys vs Ser/Ser, OR: 2.19, $p = 0.0008$ (Table 2)).

Effect of the Ser326Cys polymorphism of the OGG1 gene on insulin secretion

We next examined the effect of the polymorphism on insulin resistance and secretion indexes, HOMA-α and HOMA-β. As shown in Fig. 1, HOMA-α increased as the glucose tolerance progressed (NGT to GI to diabetes) in subjects with the genotypes Ser/Ser (p for trend and ANOVA < 0.001) and Ser/Cys + Cys/Cys (p for trend and ANOVA < 0.0001) of the polymorphism. In subjects with the genotype Ser/Ser, HOMA-β seemed to be increased in subjects with GI and decreased in subjects with diabetes, compared with those with NGT; thus, the differences in the values among the subjects based on the glucose tolerance were not significant (p for trend = 0.417, p for ANOVA = 0.474). However, in subjects with the genotypes Ser/Cys + Cys/Cys, HOMA-β decreased as the glucose tolerance progressed (p for trend = 0.010, p for ANOVA = 0.026); namely, HOMA-β was decreased in subjects with GI compared with those with NGT.

Discussion

The association of the Ser326Cys polymorphism of the OGG1 gene with diabetes was shown by both quantitative and case-control association analyses in a relatively large population-based Japanese sample. In this study, diabetic condition was classified by FPG alone; thus, the diagnosis of diabetes did not seem to be accurate. However, as a subanalysis, when only the subjects whose glucose tolerance was classified by both FPG and 2-h PG were included, the association was more substantial and significant, although the number of subjects was smaller. Taken together, these results strongly indicated the association of the Ser326Cys polymorphism of the OGG1 gene with diabetes: thus explaining the functional involvement of the OGG1 in the pathophysiology leading to diabetes.

Table 2
Association of the Ser326Cys polymorphism of the OGG1 gene with diabetes.

Trait	Odds ratio	95% CI	p
With diabetes classified by FPG (n = 4585)			
Ser/Ser vs Ser/Cys + Cys/Cys	1.32	1.03–1.69	0.0289*
Ser/Ser vs Cys/Cys	1.41	1.03–1.92	0.0302*
Age (per 1 year)	1.05	1.04–1.06	<0.0001**
Gender (M vs F)	0.65	0.52–0.81	<0.0001**
BMI (per 1 kg/m^2)	1.12	1.09–1.16	<0.0001**
TG (per 10 mg/dl)	1.01	1.00–1.02	<0.0087**
With diabetes classified by OGTT (n = 1634)			
Ser/Ser vs Ser/Cys + Cys/Cys	1.70	1.17–2.49	0.0059**
Ser/Ser vs Cys/Cys	2.19	1.39–3.46	0.0008**
Age (per 1 year)	1.08	1.06–1.09	<0.0001**
Gender (M vs F)	0.63	0.46–0.87	0.0048*
BMI (per 1 kg/m^2)	1.19	1.14–1.25	<0.0001**
TG (per 10 mg/dl)	1.01	1.00–1.02	0.0277*

Multiple logistic regression analysis was applied. $p < 0.05$ and <0.01 are indicated by * and **, respectively.

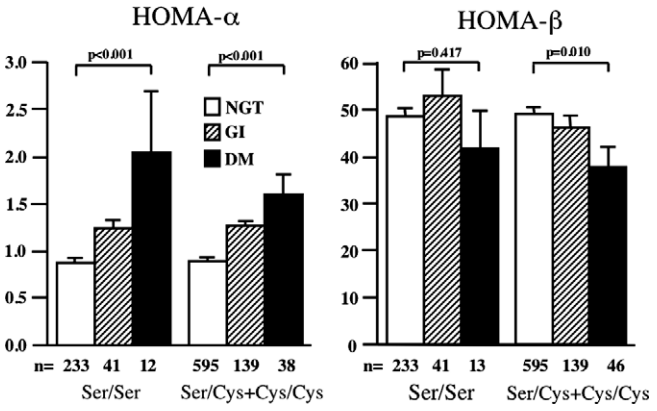

Fig. 1. Effect of the Ser326Cys polymorphism of the OGG1 gene on the insulin resistance and secretion indexes, HOMA-α and HOMA-β. The traits values according to the genotypes of the Ser326Cys polymorphism are shown. Bars above the columns represent standard error (SE). p-Values for trend are shown above each data set. The number of subjects of each group is shown below the columns. NGT: normal glucose tolerance, GI: glucose intolerance, DM: diabetes.

In general, when an increase in insulin resistance occurs, a compensatory increase in insulin secretion occurs concomitantly to maintain plasma glucose levels in a normal range. As this compensatory increase of insulin secretion declines, impairment of glucose tolerance progresses. In this study, in subjects with the genotype Ser/Ser, insulin resistance assessed by HOMA-α was increased in the subjects with GI, and insulin secretion assessed by HOMA-β seemed to be increased as expected. However, in subjects with the genotypes Ser/Cys + Cys/Cys, although HOMA-α was increased in subjects with GI as well, HOMA-β was decreased. This impairment of the compensatory increase in insulin secretion seemed to be responsible for the observed association of the polymorphism with diabetes and probably the pathophysiology of diabetes, in which OGG1 is involved.

Increased numbers of 8-oxoguanosine, a major free radical-derived DNA adduct, positive islet cells have been shown in diabetic humans [20] as well as in diabetic Goto–Kakizaki rats [21]. OGG1, the major repair enzyme involved in the defense against the accumulation of 8-oxoguanune, has also been shown to be increased in both gene and protein expression in islets from diabetic humans [22]. Therefore, it seems that, in diabetes, free radicals cause DNA damage to islet β-cells; subsequently, OGG1 increases to attenuate such DNA damage, which eventually causes the islets β-cell dysfunction and loss. In this respect, the impairment of such attenuation seems to facilitate DNA damage, leading to the islets β-cell dysfunction and loss more easily. The Cys allele of the Ser326Cys polymorphism, shown to be a risk allele of diabetes in this study, has been shown to be associated with low enzyme activity [15]. Therefore, subjects with the Cys allele may not have had a sufficient increase in enzyme activity to attenuate DNA damage, compared with those without. Namely, when plasma glucose levels increased, oxidative stress increase concomitantly, and subjects with the Cys allele may loose islet β-cell function sooner than those without.

Previous genome-wide association studies with analyses of as many as 500 K SNPs revealed several genes to be strongly associated with diabetes [23,24]. The association of the OGG1 gene with diabetes was not extracted in the previous studies; however, no SNP of the OGG1 gene was examined in those studies. The nearest

upstream and downstream SNPs examined (rs159159 and rs6809452, respectively; 21,615 and 25,535 bp from the Ser326Cys polymorphism of the OGG1 gene, respectively) were in the BRPF1 gene and the TADA3L gene, respectively (1 gene upstream and downstream, respectively), and these SNPs were not associated with diabetes (http://www.wtccc.org.uk; http://www.broad.mit.edu/diabets). Furthermore, according to the latest release (#22) of the phased haplotypes for the combined JPT (Japanese) + CHB (Chinese) population of the HapMap database, the Ser326Cys polymorphism of the OGG1 gene composed an linkage disequilibrium (LD) block of 4 kb with another SNP (rs 2072668) of the OGG1, and the above-mentioned SNPs (rs159159 and rs6809452) composed their own LD blocks unlike the LD block composed of the Ser326Cys polymorphism of the OGG1 gene. Therefore, the results of these genome-wide association studies are not in conflict with the present results.

In conclusion, the Ser326Cys polymorphism of the OGG1 gene was associated with diabetes. The increase in insulin secretion to compensate for insulin resistance seemed to be impaired in subjects with the at-risk genotypes, indicating a functional involvement of the OGG1 in the pathophysiology of diabetes.

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