SINGLE NUCLEOTIDE VARIANT *rs293795 OGG1* AS A GENETIC RISK FACTOR FOR DIABETIC NEPHROPATHY

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Diabetic nephropathy (DNP) is a serious complication of type 2 diabetes mellitus (T2DM), leading to early disability and mortality from end-stage renal failure. Experimental and clinical studies have shown the leading role of oxidative stress-induced damage to macromolecules, including DNA, in the development and progression of DNP against the background of hyperglycemia. On the contrary, repair of this damage serves as a signal to stop ongoing oxidative stress. The key enzyme in DNA repair is 8-oxoguanine DNA glycosylase, encoded by the *OGG1* gene. The aim of this study was to analyze the associations of five polymorphic variants rs2072668, rs1052133, rs293795, rs2304277, rs6443265 of the *OGG1* gene with the risk of developing DNP in patients with T2DM. The study included 1461 patients with type 2 diabetes, 577 of whom were diagnosed with DNP. DNA genotyping was performed using real-time polymerase chain reaction (RT-PCR) with allele-specific fluorescent probes. Associations were established between the rs293795-G/G genotype (OR = 1.97, 95% CI = 1.23–3.16, p = 0.007) and the rs2072668C-rs1052133C-rs293795G-rs2304277G-rs6443265C haplotype (OR = 1.30, 95% CI = 1.06–1.60, p = 0.012) of the *OGG1* gene with a predisposition to DNP in patients with T2DM. In addition, 6 *OGG1* diplotypes associated with an increased risk of DNP and one diplotype associated with a reduced risk of DNP in patients with T2DM were identified. Thus, the study presents for the first time data on the association of the *OGG1* gene polymorphism with DNP, which creates a scientific foundation for further research on the contribution of disturbances in the DNA oxidative damage repair system to the development of microvascular complications of T2DM.

Keywords: DNA glycosylases, DNA repair, *OGG1*, genetic predisposition, genotyping methods, real-time PCR, type 2 diabetes mellitus, diabetic nephropathy

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Compliance with ethical standards: the study was approved by the Regional Ethics Committee at Kursk State Medical University (meeting minutes No. 1 dated January 20, 2025).

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ОДНОНУКЛЕОТИДНЫЙ ВАРИАНТ *rs293795 OGG1* КАК ГЕНЕТИЧЕСКИЙ ФАКТОР РИСКА ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ

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Диабетическая нефропатия (ДНФ) — грозное осложнение сахарного диабета 2-го типа (СД2), приводящее к ранней инвалидности и смертности от терминальной почечной недостаточности. В экспериментальных и клинических исследованиях показана ведущая роль индуцированных окислительным стрессом повреждений макромолекул, в том числе ДНК, в развитии и прогрессировании ДНФ на фоне гипергликемии. Восстановление этих повреждений служит сигналом для прекращения продолжающегося окислительного стресса. Ключевым ферментом репарации ДНК является 8-оксогуанин-ДНК-гликозилаза, кодируемая геном *OGG1*. Целью работы было провести анализ ассоциаций пяти полиморфных вариантов rs2072668, rs1052133, rs293795, rs2304277, rs6443265 гена *OGG1* с риском развития ДНФ у пациентов с СД2. В исследование включен 1461 пациент с СД2, у 577 из которых диагностирована ДНФ. Генотипирование ДНК выполнено методом полимеразно-цепной реакции в реальном времени с использованием аллель-специфичных флуоресцентно-меченых зондов. Установлены ассоциации генотипа rs293795-G/G (OR = 1,97, 95% CI = 1,23-3,16; p = 0,007) и гаплотипа rs2072668C-rs1052133C- rs293795G-rs2304277G-rs6443265C (OR = 1,30, 95% CI = 1,06–1,60; p = 0,012) гена *OGG1* с предрасположенностью к ДНФ на фоне СД2. Кроме того, установлено шесть диплотипов *OGG1*, ассоциированных с повышенным риском ДНФ, и один диплотип, ассоциированный с пониженным риском ДНФ у пациентов с СД2. Таким образом, в проведенном исследовании представлены данные об ассоциации полиморфизма гена *OGG1* с ДНФ, что создает научный потенциал для дальнейших работ по изучению вклада нарушений системы репарации окислительных повреждений ДНК в развитие микрососудистых осложнений СД2.

Ключевые слова: ДНК-гликозилазы, репарация ДНК, *OGG1*, генетическая предрасположенность, методы генотипирования, ПЦР в реальном времени, сахарный диабет 2-го типа, диабетическая нефропатия

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Type 2 diabetes mellitus (T2DM) is the most common endocrine metabolic disorder worldwide [1]. Over the past 20 years, the number of people with T2DM worldwide has increased almost fourfold, from 151 million in 2000 to 589 million in 2025. More than 8.2 million people with T2DM live in the Russian Federation [2].

It is known that type 2 diabetes is one of the leading risk factors for the development of stroke and myocardial infarction, and is also the main cause of vision loss, non-traumatic amputations and the development of end-stage renal failure [3]. Diabetic nephropathy (DNP) is a clinical syndrome characterized by persistent albuminuria and progressive decline in renal function [4]. The mechanisms of DNP development are very complex, and despite decades of intensive research, the pathogenesis of this complication is still not fully understood [5–7]. It is known that numerous pathways and processes, such as oxidative stress, activation of the renin-angiotensin-aldosterone system, mitogen-activated protein kinases, formation of advanced glycation end products, excessive production of connective tissue growth factors and proinflammatory cytokines contribute to the development and progression of kidney damage in type 2 diabetes [8].

Recent genetic and biochemical studies in humans and animal models have confirmed the necessity of coordinated work of repair enzymes for cell survival under conditions of oxidative stress [9–12]. Excessive production of reactive oxygen species in the context of nutrient overload in overweight and obese patients can cause significant damage to any cellular macromolecules, especially DNA: It has been estimated that on average, 10,000 DNA damages occur per cell in the human body in 24 hours, with oxidative DNA damage being the most prevalent [13]. The structures of all four DNA nitrogenous bases are susceptible to oxidative damage when exposed to reactive oxygen species, and more than one hundred different types of oxidative base damage have been identified, including products with cleavage of heterocycles and the formation of oxidized aromatic derivatives [14–15]. Changes in the structure of nitrogenous bases as a result of oxidative damage alter their ability to form hydrogen bonds with a partner base during the synthesis of a complementary chain, which serves as a major source of mutations and the cause of disruption of gene expression [16].

In most cases, DNA repair mechanisms, including base excision repair, nucleotide excision repair, direct reversible repair, mismatch repair, and homologous recombination, correct the damage that has occurred and maintain cellular homeostasis [17]. Base excision repair is most effective in repairing endogenous oxidative damage to purines or pyrimidines of DNA and occurs with the use of DNA glycosylases such as mutY DNA glycosylase *MUTYH*, nth-like DNA glycosylase 1 *NTHL1*, 8-oxoguanine DNA glycosylase *OGG1* or nei-like DNA glycosylase 1 *NEIL1*, which recognize the aberrant nitrogenous base and excise it [18].

Of the four nitrogenous bases in DNA, guanine is the most frequently subject to oxidation [19]. The enzyme 8-oxoguanine DNA glycosylase *OGG1* has the ability to remove 8-oxoguanine and 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine, being part of a complex system for repairing oxidative damage to guanine in DNA [20–21]. In an experimental study by Kumar V., a decrease in the efficiency of reparation processes in type 2 diabetes was demonstrated, which leads to cell aging, activation of inflammation, and ultimately, to fibrosis of the kidneys and lungs [22]. A genetically determined defect in the elimination of aberrant guanine in carriers of the 8-oxoguanine DNA glycosylase gene rs1052133 is associated with T2DM in Mexican Americans [23] and Japanese [24], however, in general, studies of the role of genes for the repair of oxidative DNA damage in the development of T2DM and its complications are few in number, contradictory, lack systemic coverage, were performed on small samples, and are poorly reproducible in replicative studies.

The aim of this study is to analyze the associations of five polymorphic variants rs2072668, rs1052133, rs293795, rs2304277, rs6443265 of the *OGG1* gene with the risk of developing DNP in patients with T2DM.

METHODS

Characteristics of the Study Subjects

The study was conducted in accordance with the international STREGA (STrengthening the REporting of Genetic Association Studies) guidelines on an ethnically homogeneous sample (1,461 individuals) of unrelated residents of Central Russia (primarily natives of the Kursk region) of Slavic origin. The study was carried out in accordance with the international STREGA (STrengthening the REporting of Genetic Association Studies) recommendations on an ethnically homogeneous sample (1461 people) of unrelated residents of Central Russia (mainly natives of the Kursk region) of Slavic origin. Based on written informed consent, 1,461 patients with type 2 diabetes (486 men and 975 women) were included in the study, receiving inpatient treatment in the endocrinology department of the Kursk City Clinical Emergency Hospital. The diagnosis of type 2 diabetes was established based on WHO criteria [25]. The inclusion criteria for the patient group were: a physician-verified diagnosis of the disease, confirmed by clinical and laboratory-instrumental methods, age over 35 years, and written informed consent to participate in the study. The criteria for exclusion of patients from the main sample were: severe decompensation of type 2 diabetes or coma, the presence of immune-mediated or idiopathic type 1 diabetes, the presence of gestational diabetes, the presence of specific types of diabetes, such as MODY, diseases of the exocrine pancreas — pancreatitis, trauma or pancreatectomy, pancreatic tumors, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma), hereditary diseases combined with diabetes (Down syndrome, Friedreich's ataxia, Huntington's chorea, Klinefelter syndrome, Lawrence–Moon–Biedl syndrome, myotonic dystrophy, porphyria, Prader–Willi syndrome, Turner syndrome), the onset of the disease before the age of 35, as well as the absence of written informed consent to participate in the project, were excluded. 577 patients with type 2 diabetes (110 men and 467 women) were diagnosed with DNP. Clinical and laboratory characteristics of the study participants are presented in Table 1.

Patients with DNP had higher body mass index, fasting blood glucose, and a longer duration of T2DM. The glomerular filtration rate (GFR), calculated using the CKD-EPI formula, was significantly lower in this group of patients than in patients with T2DM without DNP ($p < 0.0001$). DNA extraction and genotyping. A 5 ml sample of fasting venous blood was collected from all study participants into Vacuette tubes containing EDTA as an anticoagulant. Genomic DNA of 1461 blood samples of patients with type 2 diabetes from the biobank of the Research Institute of Genetic and Molecular Epidemiology of KSMU was isolated by the column method using Biolabmix reagent kits (Russia). The quality of the isolated DNA was assessed by the degree of purity and concentration of the solution using a

Table 1. Demographic, clinical and biochemical characteristics of patients with type 2 diabetes

Basic characteristics	Patients with type 2 diabetes without DNP, *n* = 884	Patients with type 2 diabetes with DNP, *n* = 577	*p*
Age, average ± SD	58.88 ± 10.31	66.21 ± 8.54	< 0.0001
Men, *n* (%)	376 (42.5)	110 (19.1)	< 0.0001
Women, *n* (%)	508 (57.5)	467 (80.9)	
ИBody mass index (kg/m^2), average value ± SD	31.65 ± 6.87	33.18 ± 6.30	< 0.0001
Duration of diabetes, Me (Q_1; Q_3)	7.0 (2.0; 12.0)	11.0 (6.0; 17.0)	< 0.0001
HbA_{1c} (%), Me (Q_1; Q_3)	9.0 (7.7; 10.5)	9.2 (7.8; 11.0)	0.09
Fasting blood glucose (mmol/L), Me (Q_1; Q_3)	12.0 (9.5; 15.0)	12.6 (10.0; 15.9)	0.026
Total cholesterol (mmol/L), Me (Q_1; Q_3)	5.02 (4.18; 5.90)	5.24 (4.33; 6.31)	0.0047
LDL (mmol/L),Me (Q_1; Q_3)	3.17 (2.50; 4.11)	3.10 (2.40; 4.07)	0.51
HDL (mmol/L), Me (Q_1; Q_3)	0.84 (0.72; 1.03)	0.85 (0.74; 1.03)	0.18
Triacylglycerols (mmol/l),Me (Q_1; Q_3)	2.12 (1.54; 2.82)	2.25 (1.55; 3.10)	0.14
SCF, ml/min /1,72м^2, Me (Q_1; Q_3)	73.7 (65.0; 83.6)	48.47 (43.0; 54.1)	< 0.0001

Note: Me (Q_1;Q_3) — median, first and third quartiles; GFR — glomerular filtration rate (CKD-EPI); LDL — low-density lipoproteins; HDL — high-density lipoproteins.

NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). All analyzed DNA samples were diluted with deionized water to a concentration of 10 ng/µl at A260/280 = 1.5–2.0.

The selection of single nucleotide polymorphisms (SNPs) in the *OGG1* DNA glycosylase gene was performed using the Ensembl genome browser (https://www.ensembl.org/index.html) and the bioinformatics tools of the SNPinfo web server (https://snpinfo.niehs.nih.gov/), including GenePipe, FuncPred and TagSNP, the atSNP resource (http://atsnp.biostat.wisc.edu/) and was based on the assessment of the haplotype structure of the gene (selection of tagSNPs, r2 ≥ 0.8), the minor allele frequency (MAF > 5%) in the European populations of the HapMap project, parameters necessary for the most complete coverage of gene variability and the inclusion of functionally significant polymorphic loci that have regulatory potential and are capable of influencing the binding of transcription factors and microRNAs, splicing and/or the activity of the protein product of the *OGG1* gene. All five selected variants rs2072668, rs1052133, rs293795, rs2304277, rs6443265 affected the affinity of transcription factors in the corresponding DNA regions, rs1052133 and rs293795 are located in the microRNA binding sites. SNP rs2072668 (C>G) is a splicing variant of the polypyrimidine tract, rs1052133 (C>G) is a missense variant resulting in the substitution of serine for cysteine at position 326 of the protein, rs293795 (A>G) and rs6443265 (T>C) are located in the introns of the *OGG1* gene, rs2304277 (G>A) is in the non-coding transcript exon of *OGG1*.

Primer3web version 4.1.0 (https://primer3.ut.ee/) was used to design primers. Sequences of allele-specific fluorescently labeled probes were selected based on the nucleotide sequence of the *OGG1* gene (https://www.ensembl.org/Homo_sapiens/Gene/Sequence?db=core;g=ENSG00000114026; *r* = 3:9749944-9788219). The primers and probes presented in Table 2 were synthesized by Syntol (Moscow).

The total volume of the reaction mixture was 14.25 µl. 13.25 µl of the PCR mixture containing 9.4 µl of ddH2O, 1.3 µl of $MgCl_2$ solution (Eurogen, mass concentration 2.5%), 1.3 µl of PCR buffer (Biolabmix), 0.2 µl of dNTP mixture (Eurogen, concentration 2 mmol/l) were added to 1 µl of DNA solution with a concentration of 10 ng/µl., 0.05 µl of forward and reverse primer solution (concentration 100 pmol/µl), 0.025 µl of each TaqMan probe solution (concentration 100 pmol/µl) and 0.11 µl of Taq DNA polymerase (Biolabmix) with hot start (concentration 5 U/µl). PCR was performed using a CFX96 Real-Time System (Bio-Rad) using the following mode: 10 min at 95 °C, amplification of 38 cycles, including 15 sec at 95 °C, 30 s at *t* = 53 °C and 60 s at an experimentally selected annealing temperature, individual for each SNP (Table 2).

Identification of the reference and minor alleles of the studied SNPs was carried out based on a comparison of the fluorescence intensity of FAM and ROX dyes, respectively. The analysis of genotyping results was performed using the software for the CFX96 Real-Time System (Bio-Rad) amplifier, version Bio-Rad CFX Manager 2.1, which presents the genotyping results as an allele distribution. Figure 1 shows an example of genotype detection for the rs2304277 locus of the *OGG1* gene: rs2304277-G/G genotypes are shown in orange, rs2304277-G/A genotypes are shown in green, rs2304277-A/A genotypes are shown in blue, and the negative control is shown in black diamond.

Concentrations of glucose, glycated hemoglobin, creatinine, triglycerides, total cholesterol and its subfractions were determined using Diakon-DS kits on a Clima MC-15 semi-automatic biochemical analyzer (RAL, Spain). For functional annotation of DNA variants, the following online resources were used: GTEx Portal (https://www.gtexportal.org/home/), atSNP (http://atsnp.biostat.wisc.edu/), Gene Ontology Resource (https://geneontology.org/), mQTLdb [https://www.mqtldb.org/] and VannoPortal (http://www.mulinlab.org/vportal/index.html).

Statistical data processing. The analysis of associations of the studied SNPs and haplotypes with the risk of DNP was performed using the logistic regression method with adjustment for gender, age, and BMI using the SNPStats program [26]. The analysis of associations of *OGG1* diplotypes with DNP, as well as the calculation of quantitative indicators, was carried out using the STATISTICA v10.0 program. An association was considered significant at $p < 0.05$. The Kolmogorov–Smirnov test was used to test the normal distribution of biochemical parameters. Normally distributed variables were described using the mean and standard deviation. The Student's *t*-test was used to test statistical significance. Non-normally distributed variables were described using the median (Median), first (Q_1), and third (Q_3) quartiles, as follows: Median [Q_1; Q_3]. The Mann–Whitney test was used to test statistical significance in such cases. Differences between groups were considered statistically significant at $p < 0.05$.

RESULTS

The studied SNPs were in accordance with the Hardy–Weinberg equilibrium ($p > 0.05$). The results of the association analysis of

Table 2. Sequences of primers and allele-specific fluorescent probes for genotyping by real-time PCR

Gene	SNP	Oligo-nucleotide	Primer/probe sequence	*t* annealing in PCR
OGG1	rs2072668 C>G	F	5'-ACAGTAACCCCAGAGTGAAGG-3'	55 °C
		R	5'-CCTGGGGCTTGTCTAGGG-3'	
		FAM	5'-FAM-CCACAAGGGCTCATTC-RTQ1-3'	
		ROX	5'-ROX-CCACAAGGGCTCATTG-BHQ-3'	
	rs1052133 C>G	F	5'-CTAGTCTCACCAGCCCTGAC-3'	56 °C
		R	5'-GTGCCCCATCTAGCCTTCC-3'	
		FAM	5'-FAM-CCGACCTGCGCCAATC-RTQ1-3'	
		ROX	5'-ROX-CCGACCTGCGCCAATG-BHQ-3'	
	rs293795 A>G	F	5'-AGACAGCGCTAAGGATGGTT-3'	56 °C
		R	5'-CTCCCCTTCCCTCCCTGAA-3'	
		FAM	5'-FAM-TGAGGAGTGGTAGGGAA-RTQ1-3'	
		ROX	5'-ROX-TGAGGAGTGGTAGGGAG-BHQ-3'	
	rs2304277 G>A	F	5'-TCTGGAATAGAGAAGGTGTTGGG-3'	56 °C
		R	5'-GGACTCCTCCCCATCCCTA-3'	
		FAM	5'-FAM-AGTTACTGTGTGCCCAG-RTQ1-3'	
		ROX	5'-ROX-AGTTACTGTGTGCCCAA-BHQ-3'	
	rs6443265 T>C	F	5'-AGAGACTTGTTCGGGTTGCT-3'	54 °C
		R	5'-GGGAATCCATCACAGTGCCT-3'	
		FAM	5'-FAM-ATGTCACCTATACCCTT-RTQ1-3'	
		ROX	5'-ROX-ATGTCACCTATACCCTC-BHQ-3'	

Note: F — forward primer, R — reverse primer, FAM — reference allele-specific fluorescently labeled probe, ROX — minor allele-specific fluorescently labeled probe.

polymorphic variants of the *OGG1* gene with DNP are presented in Table 3. As can be seen from Table 3, the rs293795-G/G genotype (OR = 1.97, 95% CI = 1.23–3.16, $p = 0.007$) of OGG1 was associated with an increased risk of DNP in the background of T2DM, regardless of the gender, age, and body mass index of patients.

At the next stage, an analysis of associations of paired combinations of *OGG1* genotypes (diplotypes) with predisposition to DNP was performed, the statistically significant results of which are presented in Table 4.

It was found that carriage of the G/G genotype of rs293795 was associated with an increased risk of DNP in combination with the genotypes rs2072668-C/C (OR = 1.68, 95% CI = 1.10–2.56, $p = 0.015$), rs1052133-C/C (OR = 1.64, 95% CI = 1.07–2.51, $p = 0.021$), rs2304277-G/G (OR = 1.68, 95% CI = 1.10–2.56, $p = 0.015$) and rs6443265-C/C (OR = 1.64, 95% CI = 1.06–2.54, $p = 0.025$). The heterozygous genotype rs293795-A/G also determined the risk of DNP in combination with the genotypes rs2072668-C/G (OR = 1.48, 95% CI = 1.06–2.08, $p = 0.022$) and rs1052133-C/G (OR = 1.42, 95% CI = 1.01–1.99, $p = 0.043$), whereas the combination of the homozygous reference allele genotype rs293795-A/A with the genotype rs6443265–T/C had a protective effect against DNP: OR = 0.67, 95% CI = 0.49–0.92, $p = 0.013$ (Table 4).

Linkage disequilibrium (LD) analysis of the studied *OGG1* gene loci (Table 5) showed that rs293795 was in positive linkage disequilibrium with rs6443265 (D = 0.1561, D` = 0.9541, $p < 2 \times 10^{-16}$). At the same time, rs293795 was in negative

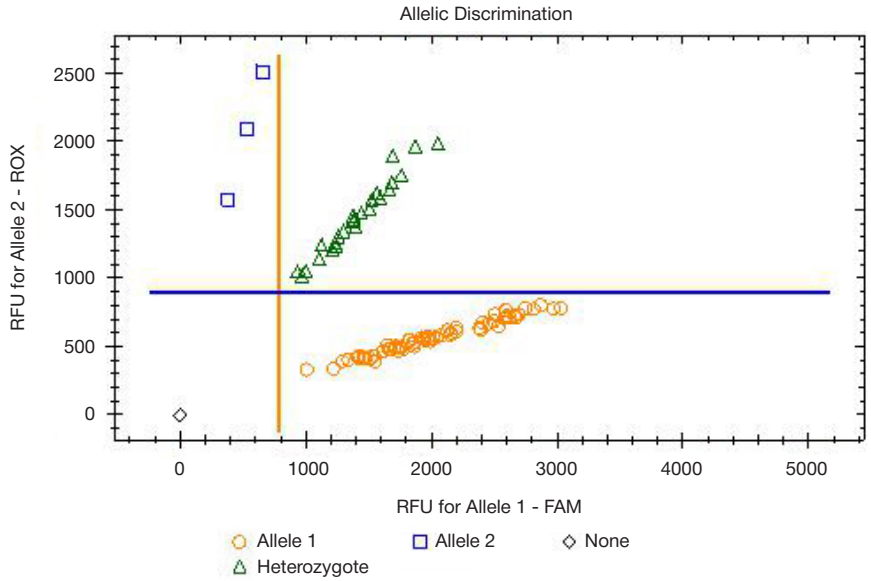

Fig. 1. Distribution of genotypes by locus rs2304277 of the *OGG1* gene

Table 3. Associations of *OGG1* gene polymorphic variants with the risk of developing DNP in patients with type 2 diabetes

SNP ID of the *OGG1* gene	Genotype	Genotype frequencies in patients with type 2 diabetes		OR[2] (95% CI)	*P*[3]
		without DNP *n* (%)[1]	with DNP *n* (%)[1]		
rs2072668 C>G	C/C	561 (63.7%)	350 (63%)	1.00	0.69
	C/G	274 (31.1%)	184 (33.1%)	1.05 (0.82–1.34)	
	G/G	46 (5.2%)	22 (4%)	0.81 (0.45–1.44)	
rs1052133 C>G	C/C	557 (63.4%)	350 (63.1%)	1.00	0.83
	C/G	278 (31.7%)	185 (33.3%)	1.01 (0.78–1.29)	
	G/G	43 (4.9%)	20 (3.6%)	0.83 (0.46–1.53)	
rs293795 A>G	A/A	517 (59%)	288 (51.8%)	1.00	0.007
	A/G	314 (35.8%)	220 (39.6%)	1.28 (1.00–1.63)	
	G/G	45 (5.1%)	48 (8.6%)	1.97 (1.23–3.16)	
rs2304277 G>A	G/G	619 (70.3%)	399 (71.8%)	1.00	0.68
	G/A	228 (25.9%)	140 (25.2%)	0.90 (0.69–1.18)	
	A/A	33 (3.8%)	17 (3.1%)	0.83 (0.43–1.62)	
rs6443265 T>C	T/T	374 (42.5%)	227 (40.8%)	1.00	0.31
	T/C	415 (47.2%)	258 (46.4%)	1.04 (0.81–1.33)	
	C/C	90 (10.2%)	71 (12.8%)	1.35 (0.92–1.99)	

Note: [1] — Absolute number and percentage of individuals with a particular genotype; [2] — Odds ratio and 95% confidence interval of the SNP association with the phenotype, adjusted for sex, age, and BMI; [3] — Significance level of association according to the codominant model, adjusted for sex, age, and BMI.

linkage disequilibrium with rs2072668 (D = –0.0514, D` = 0.9990, $p < 2 \times 10^{-16}$), rs1052133 (D = –0.0512, D` = 0.9989, $p < 2 \times 10^{-16}$) and with rs2304277 (D = –0.0406, D` = 0.9982, $p < 2 \times 10^{-16}$).

Haplotype analysis of the *OGG1* gene revealed five common haplotypes (Table 6). The H2 haplotype rs2072668C-rs1052133C-rs293795G-rs2304277G-rs6443265C, which contains the minor allele rs293795-G, was associated with an increased risk of DNP: OR = 1.30, 95% CI = 1.06–1.60, $p = 0.012$.

In addition, 12 rare *OGG1* haplotypes with a frequency of less than 1% were identified: H6 CCGGT, H7 GGAGC, H8 GGAAC, H9 GCAAT, H10 CGAGC, H11 CCGAT, H12 GCAGT, H13 CGAAT, H14 GGGGT, H15 CCGAC, H16 CCAAC and H17 CGGAC, which (the "rare" column in Table 6) did not affect the risk of DNP in type 2 diabetes ($p < 0.05$).

DISCUSSION

Recovery of oxidized DNA nitrogenous bases is primarily accomplished through the base excision repair pathway [18]. Due to the diversity of sizes and shapes of DNA lesions caused by oxidative stress, a diverse array of DNA glycosylases has evolved to maintain genomic stability and combat various base modifications. Based on their structural characteristics, DNA glycosylases are divided into four superfamilies: 1) uracil DNA glycosylases (UDG, SMUG1, TDG), 2) helix-hairpin-helix (HhH) glycosylases — NTHL1, OGG1 and MUTYH, 3) 3-methylpurine glycosylases (MPG) and 4) endonuclease VIII-like (NEIL) glycosylases — NEIL1, NEIL2 and NEIL3 [27].

The *OGG1* enzyme belongs to the second family and is a β-eliminating bifunctional DNA glycosylase, since it has both glycosylase and lyase activity and is responsible for the removal of the oxidized form of guanine 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxoG) [28]. The resulting apurinic (AP) site is recognized by the AP endonuclease APEX1, which initiates repair by cleaving the sugar-phosphate backbone. DNA polymerase beta POLB fills the gap and, forming a complex with the XRCC1 protein and DNA ligase 3 LIG3, inserts the desired complementary base into the AP site [9].

Disruptions in the described reparation process aggravate metabolic disorders that develop during oxidative stress under conditions of chronic hyperglycemia and contribute to cell death. Thus, an immunohistochemical study of autopsy material from the pancreas of patients with type 2 diabetes revealed that a decrease in the volumetric density of beta cells significantly correlated with markers of oxidative DNA damage — 8-oxodG and histone γH2AX phosphorylated at the 139th serine residue, whereas associations with endoplasmic reticulum stress markers C/EBP-β and autophagy impairment

Table 4. Statistically significant associations of *OGG1* gene diplotypes with the risk of developing DNP in patients with type 2 diabetes

Genotype combinations	Patients with type 2 diabetes and DNP[1]		Patients with type 2 diabetes without DNP[1]		*p*[2]	OR (95% CI)[3]
	n	%	*n*	%		
rs293795-G/G × rs2072668-C/C	48	8.35	45	5.14	0.015	1.68 (1.10–2.56)
rs293795-G/G × rs1052133-C/C	47	8.19	45	5.15	0.021	1.64 (1.07–2.51)
rs293795-G/G × rs2304277-G/G	48	8.35	45	5.14	0.015	1.68 (1.10–2.56)
rs293795-G/G × rs6443265-C/C	44	7.65	42	4.81	0.025	1.64 (1.06–2.54)
rs293795-A/G × rs2072668-C/G	72	12.52	77	8.8	0.022	1.48 (1.06–2.08)
rs293795-A/G × rs1052133-C/G	71	12.37	79	9.05	0.043	1.42 (1.01–1.99)
rs293795-A/A × rs6443265-T/C	67	11.65	143	16.36	0.013	0.67 (0.49–0.92)

Note: [1] — Absolute number and percentage of individuals with a particular genotype; [2] — Significance level; [3] — Odds ratio and 95% confidence interval. Minor alleles are underlined.

Table 5. Linkage disequilibrium analysis of the studied loci of the *OGG1* gene

SNP	rs2072668	rs1052133	rs293795	rs2304277	rs6443265
rs2072668	–	0.1613	–0.0514	0.1275	–0.0665
	–	0.9898	0.9990	0.9854	0.9373
rs1052133	–	–	-0.0512	0.1263	–0.065
	–	–	0.9989	0.9758	0.9206
rs293795	–	–	–	–0.0406	0.1561
	–	–	–	0.9982	0.9541
rs2304277	–	–	–	–	–0.0527
	–	–	–	–	0.9402

Note: The gray cells show the D values, the white ones show the D` values. $p < 2 \times 10^{-16}$.

P62 were absent [29–30]. The danger of 8-oxoG accumulation is that it can pair with cytosine similarly to guanine, while rotation around its N-glycosidic bond allows pairing with adenine [31]. The stability of the 8-oxoG syn conformation in duplex DNA leads to an increase in G:C → T:A transversion mutations during subsequent rounds of replication. Another oxidative lesion of guanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), results from fragmentation of the imidazole ring of the purine and is more likely than 8-oxoG to result in a G:C → T:A transversion [32–33]. The influence of the prooxidative status of the cell on the expression of DNA glycosylases is noteworthy: hydrogen peroxide reduces the expression of *OGG1*, while N-acetylcysteine reduces the amount of the oxidation product 8-oxodG and increases the expression of the *OGG1* enzyme [34–36].

According to clinical and experimental studies, loss-of-function single nucleotide variants of the *OGG1* gene are associated with reduced genetic stability and a high risk of carcinogenesis [21]. In particular, rs1052133 is associated with a predisposition to chronic myeloid leukemia [37], rs1052133 and rs2072668 — to breast cancer [38–39], rs2304277 — to ovarian cancer [40]. The rs1052133 polymorphism of the *OGG1* gene is associated with T2DM in Mexican Americans [23] and Japanese [24]. *OGG1* deficiency in mice results in obesity, fatty liver, impaired glucose tolerance and metabolic dysfunction [41].

There are no data in the literature on the involvement of rs2072668, rs293795, rs2304277, rs6443265 *OGG1* in the development of diabetes mellitus and its complications. Our study was the first to establish associations between the rs293795-G/G genotype, seven diplotypes rs293795-G/G × rs2072668-C/C, rs293795-G/G × rs1052133-C/C, rs293795-G/G × rs2304277-G/G, rs293795-G/G × rs6443265-C/C, rs293795-A/G × rs2072668-C/G, rs293795-A/G × rs1052133-C/G, rs293795-A/A × rs6443265-T/C and the haplotype rs2072668C-rs1052133C-rs293795G-rs2304277G-rs6443265C of the *OGG1* gene with a predisposition to DNP against the background of T2DM. Moreover, an increased risk of DNP was associated with carriage of the minor allele rs293795-G, which, according to the GTEx Portal transcriptome analysis, is associated with a decrease in the expression of the *OGG1* gene (https://www.gtexportal.org/home/). Analysis of transcription factor affinity at SNP sites (http://atsnp.biostat.wisc.edu/) showed that the G allele of rs293795 forms binding sites for 25 proteins — BCL ($p = 0.0021$), BHLHE40 ($p = 0.0045$), CACBP ($p = 0.0014$), CHD2 ($p < 0.0001$), E2F1 ($p = 0.0046$), EGR ($p = 0.0018$), EGR1 ($p = 0.0088$), ELF1 ($p = 0.0012$), MAZ ($p = 0.0081$), MEIS1 ($p = 0.0055$), MYC ($p = 0.0000029$), NFE2 ($p < 0.0001$), PLAG1 ($p = 0.0006$), RAD21 ($p = 0.0068$), REST ($p < 0.0001$), SREBF ($p = 0.002$), TATA ($p = 0.0077$), TBX20 ($p = 0.0069$), TFAP2 ($p = 0.0091$), TLX1:NFIC ($p = 0.0061$), WT1 ($p = 0.0021$), YY1 ($p = 0.0032$), ZNF219 ($p = 0.00043$), ZNF740 ($p = 0.0056$), ZNF784 ($p = 0.0026$). The general terms of the gene ontologies of the listed transcription factors (The Gene Ontology Resource https://geneontology.org/) are regulation of proliferation of mesangial cells of the metanephric glomeruli ($p = 8.97 \times 10^{-7}$), positive regulation of cell proliferation, involved in kidney development ($p = 3.22 \times 10^{-5}$) and negative regulation of gene expression through methylation of CpG islands ($p = 1.07 \times 10^{-4}$). The association of the rs293795-G allele with hypermethylation of CpG islands of the *OGG1* gene (i.e., with low transcriptional activity of the gene) in adults was also established in a methylome analysis, the results of which were deposited in the mQTLdb online database [42].

According to the VannoPortal project (http://www.mulinlab.org/vportal/index.html), in kidney tissue rs293795 serves as a marker of the histone modification H3K36me3, which is involved in the response to DNA damage and maintains the

Table 6. Analysis of associations of *OGG1* haplotypes with the risk of DNP in patients with T2DM

SNPs *H1*	rs2072668	rs1052133	rs293795	rs2304277	rs6443265	Haplotype frequencies in patients with type 2 diabetes		OR[2] (95% CI)	p^3
						without DNP	with DNP		
H1	C	C	A	G	T	0.4522	0.4378	1	–
H2	C	C	G	G	C	0.2231	0.2676	1.30 (1.06– 1.60)	0.012
H3	G	G	A	A	T	0.1609	0.1497	0.99 (0.78–1.26)	0.93
H4	C	C	A	G	C	0.1079	0.08	0.80 (0.58–1.10)	0.17
H5	G	G	A	G	T	0.0384	0.0443	1.29 (0.85–1.96)	0.24
rare	*	*	*	*	*	0.0063	0.0073	1.04 (0.52–2.08)	0.91
General $p = 0.028$									

Note: [1] — Haplotype; [2] — Odds ratio and 95% confidence interval of the haplotype–phenotype association adjusted for sex, age, and BMI; [3] — Significance level of the association adjusted for sex, age, and BMI. Minor alleles are underlined.

repressive status of chromatin regardless of histone acetylation [43]. Another important role of H3K36me3 in gene expression is the regulation of RNA splicing [44], for which H3K36me3 forms an adapter system with the *MRG15* gene, thus recruiting the polypyrimidine tract-binding protein of the splicing regulator PTB [45].

CONCLUSIONS

Thus, the results obtained in the present study indicate the involvement of the polymorphism of the 8-oxoguanine DNA glycosylase gene for the repair of oxidative DNA damage in the development of diabetic nephropathy in patients with type 2 diabetes.

The data from the functional annotation of the polymorphic variant rs293795, associated with an increased risk of DNP, collectively indicate a kidney tissue-specific decrease in the function of the *OGG1* enzyme in carriers of the minor allele rs293795-G, which, under conditions of increased load on the reparation system during hyperglycemia and oxidative stress may contribute to the classic structural and functional damage to vessels and glomeruli characteristic of DNP. Further studies, including those in animal models of T2DM, will allow for a systematic assessment of the role of DNA glycosylase genes in the initiation and progression of diabetic kidney disease, thereby providing a deeper understanding of the pathogenesis of this microvascular complication of diabetes.

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