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Original Article

Genetic polymorphisms of DNA repair enzymes in dilated cardiomyopathy

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Abstract: The association between the polymorphisms in DNA repair enzymes: 8-oxoguanine glycosylase-1 (OGG1), AP endonuclease-1 (APE1), DNA polymerase β (POLβ), X-ray cross-complementing group 1 (XRCC1) in the base excision repair (BER) pathway and xeroderma pigmentosum complementation group D (XPD) genes in the nucleotide excision repair (NER) pathways and the risk of dilated cardiomyopathy (DCM) in the Chinese population is not known. Therefore, we investigate the possible association between polymorphisms of these genes and DCM development. The study included 502 DCM patients and 520 controls. 8-OHdG levels were measured by ELISA methods. Genotyping was conducted using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Significantly higher 8-OHdG concentrations were detected in the blood in DCM cases than the controls. POLβ Met/Met genotype frequency was significantly higher in DCM patients (P = 0.005, odds ratio (OR) = 1.977, 95% confidence intervals (CI) = 1.237-3.160), the Met allele (P = 0.002, OR = 1.370, 95% CI = 1.125-1.669) seemed to have a deleterious role in the development of DCM. In OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, XRCC1-Arg194Trp, XRCC1-Arg399Gln, and XPD-Lys751Gln, XPD-Asp312Asn polymorphisms, there were no significant differences in the frequency of the homozygous variant between the patients and the controls. The results suggest that the Met/Met genotype of the POLβ-Lys289Met polymorphism might be associated with increased risk of DCM.

Keywords: Dilated cardiomyopathy, DNA repair enzymes, polymorphisms

Introduction

Dilated cardiomyopathy (DCM), which is characterized by left ventricular dilation, myocyte death, myocardial fibrosis and systolic dysfunction, is the most common form of heart muscle disease [1]. The etiology of DCM is multifactorial and many clinical conditions can lead to DCM. The pathogenesis of DCM has been extensively studied, and many studies have found that genetic factors play important role in its etiology and pathogenesis of DCM [2, 3].

Oxidative damage to DNA has been implicated as a dangerous factor in degenerative diseases, and in cancer [4, 5]. DNA damage results in many abnormal responses, such as inhibition of transcription and replication, impairment of cell cycle progression, senescence, cell death, and other processes [6-8]. Reactive oxygen species (ROS) can lead to nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) damage, which can be rapidly repaired by the DNA repair pathway. Most oxidative DNA lesions are repaired by base excision repair (BER) and nucleotide excision repair (NER) pathways [9, 10]. The BER pathway involves a highly coordinated process integrated by the sequential actions of DNA repair enzymes, which plays an important role in maintaining genome stability and integrity. The NER pathway repairs bulky lesions, such as pyrimidine dimers, other photo-products, larger chemical adducts, and crosslinks. Polymorphisms in BER or NER pathway genes reduce the capacity to repair DNA damage, and thus leading to a greater susceptibility to cancer or degenerative diseases [11, 12].

Table 1. Demographic data of the patients and controls

	DCM Group	*Control Group*	*P-value*
Number of patients	502	520	
Gender			0.234
Male, n (%)	243 (48.4%)	272 (52.3%)	
Female, n (%)	259 (51.6%)	248 (47.7%)	
Age (years)			0.078
Mean ± SD	54.86 ± 10.44	53.71 ± 10.43	
Systolic blood pressure (mmHg)	116 ± 21	131 ± 22	
Diastolic blood pressure (mmHg)	68 ± 10	74 ± 11	
NYHA (I/II/III/IV)	84/120/148/150		
LVEDD, mm	67.4 ± 5.36		
LVESD, mm	41.28 ± 4.25		
LVFS, %	20.11 ± 3.15		
LVEF, %	38.05 ± 4.23		
IVST, mm	8.82 ± 1.83		
PWT, mm	7.05 ± 0.75		
8-OHdG (ng/ml)	9.50 ± 0.92	9.33 ± 0.90	0.002

NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; IVST, interventricular septal wall thickness; PWT, posterior wall thickness; SD = Standard Deviation.

8-oxoguanine glycosylase-1 (OGG1), AP endonuclease-1 (APE1), DNA Polymerase *β* (POLβ), and X-Ray Cross-Complementing Group 1 (XRCC1) genes are the key enzymes of the BER pathway [12]. Xeroderma pigmentosum complementation group D (XPD) is the key enzyme of NER pathway [12]. These DNA repair genes, which carry genetic polymorphisms, have been studied extensively, and many recent studies have focused on the association of these DNA repair genes polymorphisms with cancer and aging [13-15]. OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, POLβ-Lys289Met, XRCC1-Arg194Trp, XRCC1-Arg399Gln, and XPD-Lys751Gln, XPD-Asp312Asn polymorphisms, the most common and important of these genetic polymorphisms, have some phenotypic significance [16, 17].

Recent studies have suggested that DNA mutations may contribute to the development of DCM [18]. DNA repair mechanisms are in place to protect against such damage, suggesting that DNA repair genes have a role in the response of the myocardium to oxidative stress. Accordingly, DNA repair genes are potential candidate genes for further study regarding myocardium damage. The purpose of this study was to evaluate the possible association between these DNA repair genes and risk of DCM in the Chinese population. We analyzed OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, POLβ-Lys289Met, XRCC1-Arg194Trp, XRCC1-Arg399Gln, and XPD-Lys751Gln, XPD-Asp312Asn polymorphisms in 502 patients with DCM and in 520 otherwise healthy, similarly aged control subjects. We hope our work will contribute to a better understanding of its etiology and pathogenesis of DCM.

Materials and methods

Patients

Patients with DCM were recruited from the Department of Cardiology of the Fouth Affiliated Hospital of Harbin Medical University, the Second Affiliated Hospital of Harbin Medical University and the First Hospital of Harbin, between February 2009 and December 2013. All subjects were from a Han population living in HeiLongJiang Province in northeastern China. This case-control study included 502 unrelated DCM patients (mean age 54.86 ± 10.44) and 520 age-matched healthy Chinese controls (mean age 53.71 ± 10.43) were included in this study (**Table 1**). Informed consent was obtained from all patients and controls before blood sampling. The clinical diagnosis of DCM was confirmed according to the report of the 1995 World Health Organization [19]. All of the patients had left ventricular dilatation (end diastolic diameter > 5.5 cm) and showed impaired left ventricular function (left ventricular ejection fraction < 45% or fractional shortening < 25%). The following exclusion criteria were put in place to avoid confounding variables: (1) history of myocardial infarction, (2) history of alcohol abuse, (3) evidence of coronary heart disease or valvular heart disease by cardiac catheterization, (4) active myocarditis or post-myocarditic state, (5) secondary heart muscle diseases [20]. The sex- and age-matched control subjects were recruited collected from unrelated volunteers in the same clinic. The study was approved by

Table 2. Technical details of PCR-RFLP analysis

Gene	Polymorphism	PCR primers	PCR product	Restriction	Fragments identifying
			Size (bp)	Enzyme	Genotypes (bp)
OGG1	Arg229Gln	F: 5-CAGGCTTGGCTCATTTCCTG-3	376	MspI	Arg/Arg = 232, 144
		R: 5-GAGGTAGAGAGCTCACTTAC-3			Arg/Gln = 376, 232, 144
					Gln/Gln = 376
OGG1	Ser326Cys	F: 5-AGTCTCACCAGCCCTGAC-3	338	Fnu4HI	Ser/Ser = 338
		R: 5-CTGTCTCCCTCAATATCCC-3			Ser/Cys = 338, 247, 91
					Cys/Cys = 247, 91
APE1	Asp148Glu	F: 5-CTGTTTCATTTCTATAGGCTA-3	164	FspBI	Asp/Asp=164
		R: 5-AGGAACTTGCGAAAGGCTTC-3			Asp/Glu = 164, 144, 20
					Glu/Glu = 144, 20
POLβ	Lys289Met	F: 5-GTCATTTCCTGCCTGGGCTAAG-3	586	EcoNI	Lys/Lys = 360, 208
		R: 5-ATGCATTAAATCCTCTCTCGT-3			Lys/Met = 586, 360, 208
					Met/Met = 586
XRCC1	Arg399Gln	F: 5-TTGTGCTTTCTCTGTGTCCA-3	242	MspI	Arg/Arg = 148, 94
		R: 5-TCCTCCAGCCTTTTCTGATA-3			Arg/Gln = 242, 148, 94
					Gln/Gln = 242
XRCC1	Arg194Trp	F: 5-GTTCCGTGTGAAGGAGGAG-3	504	PvuII	Arg/Arg = 431
		R: 5-CTTGGAGGTGCTGCCTATG-3			Arg/Trp = 368 + 431
					Trp/Trp = 368
XPD	Asp312Asn	F: 5-AACGTCTGCATCGACTCCATG-3	421	Hpy99I	Asp/Asp = 333
		R: 5-CTCTGCGAGGAGACGCTATC-3			Asp/Asn = 333 + 397
					Asn/Asn = 397
XPD	Lys751Gln	F: 5-GCCCGCTCTGGATTATACG-3	436	PstI	Lys/Lys = 290, 146
		R: 5- CTATCATCTCCTGGCCCCC-3			Lys/Gln = 290, 227, 146, 63
					Gln/Gln = 227, 146, 63

the Bioethics Committee of the Harbin Medical University.

Blood samples and DNA isolation

We collected 2 ml of venous blood into ethylene diamine tetraacetic acid tubes from all of the patients and controls, these subjects having had no food or drink. Samples (1 mL) of venous blood samples were centrifuged at 1000×g for 10 min. The serum samples were stored at -80°C until assayed. 8-OHdG levels were measured using a commercially available kit by ELISA methods (Cell Biolabs, Inc., San Diego, CA) according to the manufacture's instructions. Genomic DNA was extracted from leukocytes using a DNA purification kit (WatsonBio, China).

Genotyping

These genotypes were detected using the PCR-RFLP method and primers are given in **Table 2**.

An Arg→Gln in OGG1 codon 229 was amplified to form undigested fragments of 376 bp. The 376 bp PCR products were digested with MspI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 1.5% agarose gels. A Ser→Cys in OGG1 codon 326 was amplified to form undigested fragments of 338 bp. The 338 bp PCR products were digested with Fnu4HI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 1.5% agarose gels.

An Asp→Glu in APE1 codon 148 was amplified to form undigested fragments of 164 bp. The 164 bp PCR products were digested with FspBI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 2.5% agarose gels.

A Lys→Met in POLβ codon 289 was amplified to form undigested fragments of 586 bp. The 586 bp PCR products were digested with EcoNI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 1.5% agarose gels.

Table 3. Polymorphisms in DNA repair genes OGG1-*Arg229Gln,* OGG1-Ser326Cys, *APE1*-Asp148Glu, POLβ-Lys289Met, XRCC1-Arg194Trp, *XRCC1*-Arg399Gln, *XPD*-Lys751Gln, XPD-Asp312Asn, and risk of DCM

	Patients (%)	Controls (%)	OR (95% CI)	*P*-value
OGG1-*Arg229Gln*	502	520		
Arg/Arg	201 (40.1)	230 (44.2)	Reference	
Arg/Gln	220 (43.8)	220 (42.3)	1.144 (0.877-1.493)	0.343
Gln/Gln	81 (16.1)	70 (13.5)	1.324 (0.913-1.920)	0.156
Arg allele frequency	62.0%	65.4%		
Gln allele frequency	38.0%	34.6%	1.160 (0.969-1.389)	0.108
OGG1-Ser326Cys				
Ser/Ser	214 (42.6)	242 (46.5)	Reference	
Ser/Cys	213 (42.5)	213 (41.0)	1.131 (0.868-1.473)	0.381
Cys/Cys	75 (14.9)	65 (12.5)	1.305 (0.893-1.907)	0.177
Ser allele frequency	63.8%	67.0%		
Cys allele frequency	36.2%	33.0%	1.151 (0.959-1.381)	0.137
APE1-Asp148Glu				
Asp/Asp	158 (31.5)	189 (36.3)	Reference	
Asp/Glu	250 (49.8)	251 (48.3)	1.191 (0.906-1.568)	0.235
Glu/Glu	94 (18.7)	80 (15.4)	1.406 (0.975-2.026)	0.077
Asp allele frequency	56.4%	60.5%		
Glu allele frequency	43.6%	39.5%	1.184 (0.993-1.412)	0.066
POLβ-Lys289Met				
Lys/Lys	258 (51.4)	308 (59.2)	Reference	
Lys/Met	191 (38.0)	180 (34.6)	1.267 (0.974-1.647)	0.082
Met/Met	53 (10.6)	32 (6.2)	1.977 (1.237-3.160)	0.005
Lys allele Frequency	70.4%	76.5%		
Met allele Frequency	29.6%	23.5%	1.370 (1.125-1.669)	0.002
XRCC1-Arg194Trp				
Arg/Arg	184 (45.4)	205 (51.0)	Reference	
Arg/Trp	252 (46.6)	251 (42.5)	1.119 (0.858-1.458)	0.418
Trp/Trp	66 (8.0)	64 (6.5)	1.149 (0.772-1.709)	0.543
Arg allele frequency	61.8%	63.6%		
Trp allele frequency	38.2%	36.4%	1.080 (0.903-1.292)	0.411
XRCC1-Arg399Gln				
Arg/Arg	228 (45.4)	265 (51.0)	Reference	
Arg/Gln	234 (46.6)	221 (42.5)	1.231 (0.953-1.588)	0.119
Gln/Gln	40 (8.0)	34 (6.5)	1.367 (0.837-2.233)	0.215
Arg allele frequency	68.7%	72.2%		
Gln allele frequency	31.3%	27.8%	1.183 (0.978-1.430)	0.090
XPD-Lys751Gln				
Lys/Lys	221 (45.4)	253 (51.0)	Reference	
Lys/Gln	226 (46.6)	216 (42.5)	1.198 (0.924-1.553)	0.186
Gln/Gln	55 (8.0)	51 (6.5)	1.235 (0.810-1.882)	0.335
Lys allele frequency	66.5%	69.4%		
Gln allele frequency	33.5%	30.6%	1.144 (0.950-1.378)	0.169
XPD-Asp312Asn				
Asp/Asp	255 (50.8)	294 (56.5)	Reference	
Asp/Asn	202 (40.2)	186 (35.8)	1.252 (0.965-1.625)	0.097

Asn/Asn	45 (9.0)	40 (7.7)	1.297 (0.821-2.050)	0.294
Asp allele frequency	70.9%	74.4%		
Asn allele frequency	29.1%	25.6%	1.193 (0.982-1.450)	0.082

OR = Odds Ratio; CI = Confidence Intervals.

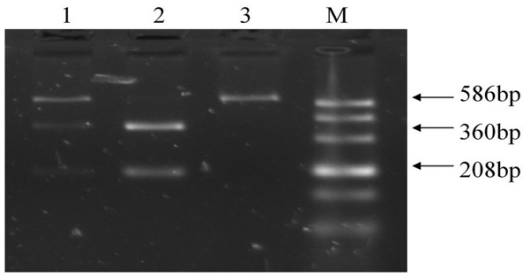

Figure 1. PCR analysis of POLβ gene polymorphism. two fragments of 360 and 208 bp fragments for wild-type (Lys/Lys); three fragments of 586, 360 and 208 bp for heterozygous (Lys/Met); and one fragment of 586 bp for variant homozygous (Met/Met). Columns show the following: M column, DL500 DNA marker; 1 column, POLβ heterozygous (Lys/Met); 2 column, POLβ wild-type (Lys/Lys); 3 column, POLβ variant homozygous (Met/Met).

An Arg→Gln in XRCC1 codon 399 was amplified to form undigested fragments of 242 bp. The 242 bp PCR products were digested with MspI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 2% agarose gels. An Arg→Trp in XRCC1 codon 194 was amplified to form undigested fragments of 504 bp. The 504 bp PCR products were digested with PvuII (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 2% agarose gels.

An Asp→Asn in XPD codon 312 was amplified to form undigested fragments of 421 bp. PCR products were digested with Hpy99I (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 1.5% agarose gels. A Lys→Gln in XPD codon 751 was amplified to form undigested fragments of 436 bp. PCR products were digested with PstI (MBI Fermentas, Burlington, CA) 37°C for 5 h and analyzed with 2% agarose gels.

Statistical analysis

Statistical analyses were performed with SPSS 17.0 for Windows. Differences between the means of the two continuous variables were evaluated by the Student's *t*-test. The Chi-square (χ^2) or Fischer's exact test (two-sided) was used to compare gender distribution, test the association between the genotypes and alleles in relation to the cases and controls, and test for deviation of genotype distribution from the Hardy-Weinberg Equilibrium (HWE). The odds ratio (OR) and their 95% confidence intervals (CI) were calculated to estimate the strength of the association between the polymorphism genotype alleles of the patients and controls. A p value < 0.05 was considered statistically significant.

Results

There were no significant differences in sex, age, or ethnicity, suggesting that the data of the DCM patients is comparable to that of the controls, as shown in **Table 1**. Significantly higher 8-OHdG concentrations were detected in the blood in DCM cases than the controls (P < 0.01). Four genotypes were determined for all DCM cases and controls. For all polymorphisms, the more common allele was considered the reference genotype, whereas the less common allele was examined as the variant. The distributions of the OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, POLβ-Lys289Met, and XRCC1-Arg194Trp, XRCC1-Arg399Gln, XPD-Lys751Gln, XPD-Asp312Asn, genotypes were in accordance with the HWE among the controls (P = 0.136, P = 0.094, P = 0.824, P = 0.410, and P = 0.338, P = 0.179, P = 0.623, P = 0.168, respectively) and the patients (P = 0.115, P = 0.069, P = 0.780, P = 0.052, and P = 0.160, P = 0.059, P = 0.806, P = 0.583, respectively). The frequencies of the genotypes and alleles of the OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, POLβ-Lys289Met, and XRCC1-Arg194Trp, XRCC1-Arg399Gln, XPD-Lys751Gln, XPD-Asp312Asn, polymorphisms in the DCM group and control group are shown in **Table 3**.

As shown in **Figure 1**, Columns show the following: M column, DL500 DNA marker; 1 column, POLβ heterozygous (Lys/Met); 2 column, POLβ wild-type (Lys/Lys); 3 column, POLβ variant homozygous (Met/Met). The analysis of the

polymorphisms located at POLβ codon 289 in the DCM group showed that 258 (51.4%) were homozygous for the Lys/Lys genotype, 53 (10.6%) were variant homozygous for the Met/Met genotype, and 191 (38.0%) were heterozygous for the Lys/Met genotype. There was a significant difference in the POLβ Met/Met genotype between the case and control groups (P = 0.005). The statistical analysis revealed a possible deleterious effect of the POLβ-289 Met/Met genotype (OR = 1.977, 95% CI = 1.237-3.160) in the development of DCM. When compared to the healthy controls, the Met allele frequency of POLβ-Lys289Met was significantly different in the DCM group (P = 0.002, OR = 1.370, 95% CI = 1.125-1.669). However, no statistically significant differences were observed in the alleles or in the genotype frequencies of the OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, XRCC1-Arg194Trp, XRCC1-Arg399Gln, XPD-Lys751Gln, XPD-Asp312Asn gene polymorphisms between the control group and the DCM patients (**Table 3**).

Discussion

In this study, we analyzed the association between OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148Glu, POLβ-Lys289Met, XRCC1-Arg194Trp, XRCC1-Arg399Gln, and XPD-Lys-751Gln, XPD-Asp312Asn polymorphisms and the risk of DCM in the Chinese population, as these gene polymorphisms may alter DNA repair capacity and lead to synergistic effects with DCM induced by DNA damage. In our experiments, we found higher 8-OHdG concentrations in DCM cases, and the POLβ-Lys-289Met polymorphism may be associated with an increased risk of DCM, but we did not find a statistically significant association in the OGG1-Arg229Gln, OGG1-Ser326Cys, APE1-Asp148-Glu, and XRCC1-Arg194Trp, XRCC1-Arg399Gln, XPD-Lys751Gln, XPD-Asp312Asn, polymorphisms between the controls and patients.

No studies have investigated the role of these DNA repair gene polymorphisms in DCM patients. We choose these key DNA repair enzymes for this study because they play vital role in BER and NER pathways [21]. We found a possible deleterious effect of the POLβ-289Met/Met genotype in the development of DCM. The genetic effect of an individual SNP is generally small, but this effect of combinations with relevant SNPs may additively or synergistically contribute to increased DCM risk [22]. The POLβ gene is located on chromosome 8p11.2 and spans 33 kb, which includes 14 exons and 13 introns. The gene encodes a 335 amino acid protein that is approximately 39 kDa in size and is restricted to the nucleus [23]. POLβ is a key enzyme in BER pathways, and any perturbations in its expression or function can lead to increased mutation frequency and genomic instability [24].

The DNA repair pathway plays an important role in maintaining genetic integrity, and defects in the repair pathways are associated with many different types of diseases. A majority of the 20,000 DNA lesions in each human cell are repaired per day by the BER pathway [25]. In the mammalian BER pathway, OGG1 is responsible for the removal of 8-oxoguanine, which arises through incorporation, during DNA replication, by forming 8-oxo-dGTP from the oxidation of dGTP by ROS. APE1 is an AP endonuclease that bypasses the AP lyase activity of OGG1, enhancing OGG1 turnover and producing a nick in the DNA backbone that allows further processing to repair the DNA [26, 27]. POLβ then adds the first nucleotide to the 3'-end of the incised AP site and removes the 5'-sugar phosphate residue (by the process of *β*-elimination) and a DNA ligase III-XRCC1 heterodimer (or DNA ligase I), and then completes the repair [28, 29]. XPD codes for a DNA helicase subunit of the core transcription factor IIH essential for NER pathway and transcription [30].

8-OHdG is a biomarker of oxidative DNA damage and has been detected in the cardiomyocytes of patients with severe DCM [31]. In this work, we also found higher 8-OHdG concentrations in DCM cases than the controls, which proved increased DNA damage in DCM cases. Oxidative damage to DNA is inevitable consequence of cellular metabolism in the myocardium. In addition, Several reports showed evidence of increased oxidative stress in dilated cardiomyopathy patients [32, 33]. ROS can induce abasic sites, base damage, single-strand breaks, and double-strand breaks in DNA [34]. The vicious cycle of DNA damage and ROS can be established within cells, which leads to loss of the mitochondrial membrane potential and release of cytochrome c, result-

ing in the cell apoptosis and death [35]. Apoptotic myocytes have been observed in failing human hearts with DCM [36]. As the key DNA polymerase in BER pathway, POLβ has been implicated in multiple cellular processes, such as genome maintenance, telomere processing, and is suggested to play an important role in cell viability following stress and the cellular response to radiation, environmental genotoxicants [37]. POLβ mutations have been confirmed in approximately 30% of human tumors [38]. Recent studies have reported important associations of the POLβ-Lys289Met polymorphisms with reduced DNA repair capacity [13]. Furthermore, previous work demonstrated that expression of cancer associated POLβ variants, such as Lys289Met, can induce transformed phenotypes, including foci formation and anchorage-independent growth [39]. The present study shows that the polymorphisms of POLβ-Lys289Met may diminish the capacity to repair DNA damage in myocytes, which can increase oxidant-induced DNA damage and increase the level of 8-OHdG. In turn, DNA damage can increase superfluous radicals, apoptosis or death of cardiomyocytes, myocardial reconstruction, myocardial fibrosis and systolic dysfunction, which may contribute to the onset of DCM.

Previous studies have proved that these genes polymorphisms are risk factors for many diseases. However, we did not find any association between these enzymes polymorphisms and risk of DCM in our study. There are several possible reasons to explain why we did not find a significant relationship between those three enzymes and DCM. Chiefly, DCM is a multifactorial disease, and the pathogenesis is complicated. The myocardium is exposed throughout life to a large number of possibly injurious agents such as autoimmunity, viruses and inflammation, that results in oxidative damage as shown in cardiomyopathy studies in several mammalian species [40]. Second, ethnic differences may be an important factor that affects polymorphisms studies of this type. Third, exposure to and interaction with other genes taking part in DNA damage recognition, repair and cell cycle regulation might alter the effects of OGG1, APE1, XRCC1 and XPD polymorphisms.

This is the first study to evaluate the possible association between DNA repair enzyme genes and DCM. There is a need for studies of other ethnicities and nationalities to confirm our findings, in order to examine the possible relationship between DNA repair gene polymorphisms and DCM more completely. Our data support the importance of DNA repair gene polymorphisms, and DNA repair genes as potential pharmacological targets to promote DNA repair and to maintain genome stability. We will need the next studies regarding the precise mechanisms of how POLβ-Lys289Met polymorphisms affect the development of DCM, which may provide a method for preventing or slowing the progression of DCM.

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Disclosure of conflict of interest

None.

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