# Association between polymorphisms of the DNA repair genes RAD51 and OGG1 and risk of cardiovascular disease

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**Abstract.** Cardiovascular disease (CVD) is one of the leading causes of mortality worldwide, and multiple single-nucleotide polymorphisms of DNA repair genes have been found to be associated with CVD. The aim of the present study was to assess the effects of the genetic variants of RAD51 recombinase (RAD51) and 8-oxoguanine DNA glycosylase (OGG1) on CVD through genotyping and statistical analysis. Regardless of whether there is a significant association or not, the genotyping data on these two polymorphisms are valuable, because there is limited availability of it in certain populations. A total of 240 blood samples were analyzed and genotyped using TaqMan genotyping; 120 were obtained from cases with a history of CVD, and 120 from cases with no history of CVD. A questionnaire was administered to gather information on age, demographics, sex and clinical features, and confirmation was carried out using medical records. The results of the present study confirmed that the polymorphism rs1052133 in OGG1 had no significant association with CVD. On the other hand, the polymorphism rs1801321 in RAD51 exhibited a significant association with CVD. Collectively, the results of the present study revealed that the polymorphism rs1801321 in RAD51 exhibited a significant association with CVD, however a larger sample size to confirm the present findings, may allow for the early identification of CVD and may aid in the decision-making process concerning treatments for CVD.

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## Introduction

Cardiovascular disease (CVD) is a general term for numerous heart conditions. It can refer to several conditions: Coronary heart disease (CHD), peripheral arterial disease, cerebrovascular disease, rheumatic and congenital heart diseases and venous thromboembolism. CVD is responsible for 31% of all deaths and is the leading cause of mortality globally. Each year, 17.9 million people succumb to CVD; the majority of this is in the form of CHD and cerebrovascular disease (1).

Over the past few years, there has been a growing body of evidence that suggests that cancer and CVD share numerous molecular pathways (2). This interaction between different biological pathways indicates that the same genes and proteins are often involved in developing both diseases (2). Cancer and CVD share a number of risk factors and pathogenic processes, including chronic inflammation, oxidative stress and genetic instability (3). There is evidence that DNA damage and oxidative stress play a significant role in the development of CVD (4). For example, people with coronary artery disease have higher levels of DNA damage, which is directly associated with atherosclerosis severity (5).

Reactive oxygen species (ROS) are free radicals that can damage DNA. ROS are produced as a byproduct of cellular respiration and can also be produced by other processes, such as inflammation (6). ROS can damage DNA by causing single-strand breaks, double-strand breaks and base modifications. These types of damage can lead to mutations, cancer and other health problems (6). ROS are essential for cellular functions at low levels, such as serving as cellular messengers in redox signaling reactions (7). Cells have a variety of mechanisms to regulate the levels of ROS. One such mechanism is the restriction of respiration in the mitochondrial inner membrane to prevent the production of ROS and protect other cellular components (7). Another manner by which to regulate the levels of ROS is to protect DNA by complexing it with histones. This prevents ROS from reaching the DNA and damaging it. Finally, cells can also quench ROS by using antioxidant enzymes. These enzymes neutralize ROS, rendering them harmless (7). ROS can damage DNA in two ways (8). First, they can attack the DNA bases, causing mutations. Second, they can also damage the DNA backbone, causing

breaks in the DNA strands (8). These breaks can be repaired by two different pathways: The single-strand break repair (SSBR) pathway and the double-strand break repair (DSBR) pathway (9).

The SSBR pathway repairs single-strand breaks in the DNA backbone. The DSBR pathway repairs double-strand breaks in the DNA backbone. Both of these pathways are important for maintaining the integrity of DNA. Immediately following DNA damage, lesion-specific proteins initiate the DNA damage response, a collection of mechanisms that detect DNA damage, signal its presence and promote DNA repair according to the type of damage (10). Furthermore, cells can also encounter DSBs, which are repaired by the homologous recombination (HR) pathway (11).

From observation of the effects of ROS on DNA during oxidative stress, it is considered that there is an organized and sophisticated system to remove the effects of oxidative damage. In human cells, the repair of oxidatively damaged DNA bases is primarily carried out by the base excision repair mechanism (BER).

In the first step of BER, a damage-specific DNA glycosylase identifies the damaged base and removes it from the DNA. In general, glycosylases are classified depending on their function; they are either monofunctional or bifunctional (12).

An example of a DNA glycosylase in the first step of BER is 8-oxoguanine DNA glycosylase (OGG1). It is located at chromosome 3p25.3 and plays a significant role in the repair of 8-hydroxyguanine. The polymorphism rs1052133 in OGG1 leads to substitution of the amino acid serine for cysteine at codon 326, which shows a decrease in enzyme activity in OGG1-Ser326Cys (13). Moreover, the polymorphism rs1052133 is one of the common SNPs in the OGG1 gene and has been linked to numerous different biological diseases such as breast cancer (14-17), prostate cancer (18,19), gastric cancer (20), colorectal cancer (21), lung cancer (22) and esophageal cancer (23). Judging by the findings of the previous studies, it is clear that polymorphism rs1052133 has a considerable effect on enzyme activity, which might lead to more oxidative damage (13).

In non-homologous end joining, the break is simply joined together by ligation. The break is repaired in HR by copying the homologous DNA sequence from a sister chromatid or another homologous chromosome. In single-strand annealing (SSA), the break is repaired by annealing the two DNA strands together (24). If the DSB occurs between direct repeats, SSA is the only possible repair pathway. Otherwise, the resected 3' end of the broken DNA strand can invade the homologous template to start the repair synthesis (24). There are two other mechanisms that can occur after this step: Synthesis-dependent strand annealing (SDSA) and break-induced repair (BIR) (24). SDSA is a type of HR repair in which the invading 3' end anneals to the homologous template and DNA synthesis is used to fill in the gap. BIR is a type of HR repair in which the invading 3' end anneals to the homologous template, and subsequently, a double Holliday junction is formed. The double Holliday junction is then resolved, resulting in the repair of the DSB (24).

HR is predominant in the $G_2$ phase, and BRCA1 initiates the ubiquitination of the downstream component. Once the DSB is detected, other proteins called replication protein A (RPA) and RAD51 recombinase (RAD51) bind to the DNA. RPA coats the 3' overhang of the broken DNA strand, while RAD51 forms a nucleoprotein filament. This filament then invades the homologous DNA strand, the other copy of the damaged gene. Several other proteins, such as CtBP-interacting protein, breast cancer susceptibility protein 2 and RAD52 homolog, help to facilitate this process. Once the invading strand is in place, polymerases can add new DNA nucleotides to fill in the gap, repairing the DSB (7,24).

As aforementioned, RAD51 has a crucial role in DSBR, specifically in HR. RAD51, in eukaryotes, is a homolog of the RecA protein, and it contains 339 amino acids. It is located at human chromosome 15q15.1 and is highly polymorphic (25). There are five RAD51 paralogs, RAD51B, RAD51C, RAD51D, X-ray repair cross complementing 2 (XRCC2) and XRCC3, in the human genome. They play an essential role in HR, and any loss of function would result in genomic instability (25). RAD51 polymorphism rs1801321; 172G>T is one of the most common polymorphisms located at the 5'UTR (26). In terms of clinical significance, rs1801321 has been linked with endometrial cancer (27) and there is a significant association with breast cancer (28,29). At the same time, a number of studies have suggested no association with ovarian cancer (30,31).

The present study aimed to provide data and evaluate the significant association between CVD and the SNPs in OGG1 rs1052133 and RAD51 rs1801321 in a Saudi population.

## Materials and methods

*Patient population and ethics statement*. The present study included 240 individuals from King Khalid University Hospital (KKUH; Riyadh, Kingdom of Saudi Arabia), of which 120 were clinically hospitalized for CVD and 120 were healthy, age- and sex-matched blood donors considered the control group. Samples were collected from March to December 2021. Their ethnicities were verified since the parents and grandparents of the patients and controls were born in Saudi Arabia. The study was reviewed and approved by the local committee from King Khaled University Hospital and all patients provided written informed consent. The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board (approval no. IRB-HAPO-01-R-011) of Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia. A questionnaire was administered to gather information on age, demographics, sex, clinical features (such as disease duration) and behavioral (such as smoking) factors. Data pertaining to hypotension and hypertension events and pharmacological treatments were also collected in the questionnaire and were then confirmed using medical records. The clinical data are summarized in Table I.

*DNA extraction*. DNA was extracted from 200 $\mu$l of EDTA anticoagulated peripheral blood. The extraction was carried out following the standards and procedures provided by the DNeasy® Blood & Tissue Kit (cat. no. 69504; Qiagen GmbH). The purity and concentration of the DNA were measured using a NanoDrop™ 8000 Spectrophotometer (Thermo Fisher Scientific, Inc.) using the ratio A260/A280. The DNA samples

Table I. Clinical data and characteristics of the patients with CVD.

| Characteristics | CVD | Controls |
|---|---|---|
| N | 120 (50.0%) | 120 (50.0%) |
| Age, years | 62.0±12.0 | 54.8±15.3 |
| Sex | | |
| Male | 85 (70.8%) | 80 (66.0%) |
| Female | 35 (29.2%) | 40 (33.3%) |
| FBS, mmol/l | 8.2±3.9 | - |
| TG, mmol/l | 1.5±0.7 | - |
| TC, mmol/l | 4.2±1.1 | - |
| HDL-c, mmol/l | 1.1±0.9 | - |
| LDL-c, mmol/l | 2.6±0.8 | - |
| Smokers | 54 (45.0%) | 59 (49,2%) |
| Non-smokers | 66 (55.0%) | 61 (50.8%) |
| Hyper and hypotension events | 89 (74.2%) | - |
| | 110 (91.7%) | |
| Pharmacological treatments | | No treatment |
| Yes | 82 (68.3%) | |
| No | 38 (31.7%) | |

CVD, cardiovascular disease; FBS, fasting blood sugar; TG, triglyceride; TC, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein.

were subsequently diluted, with each sample diluted according to its concentration and DNA samples were then stored at -20˚C for genotyping.

*Choice of SNPs*. The two SNPs, rs1052133 in OGG1 and rs1801321 in RAD51, were selected based on their functional properties. The RAD51 polymorphism rs1801321; 172G>T is one of the most common polymorphisms and is located at the 5'UTR (26). The OGG1 polymorphism rs1052133 leads to the substitution of the amino acid serine to cysteine at codon 326 and shows a decrease in enzyme activity in OGG1-Ser326Cys (13).

*TaqMan SNP genotyping*. TaqMan genotyping assay was used to determine whether the SNPs, OGG1 rs1052133 and RAD51 rs1801321, were prevalent in the test samples compared with the control samples. TaqMan genotyping assay (cat. no. 4351379; Applied biosystem, USA) was used for OGG1 rs1052133 [VIC/FAM]5'-CTGTTCAGTGCCGACCTGCGCCAAT[C/G] CCGCCATGCTCAGGAGCCACCAGCA-3') and RAD51 rs1801321 ( [VIC/FAM] 5'-GCCGTGCGGGTCGGGCGCGTG CCAC[GT]CCCGCGGGGTGAAGTCGGAGCGCGG-3'). The genotyping was performed in a 96-well format by applying a QuantStudio 7 Flex Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). To prepare the plates for genotyping, the following were added to each well in a 0.1-ml plate: 5 $\mu$l TaqMan master mix, 0.25 $\mu$l SNP reagent (Applied Biosystems, USA), 2.75 $\mu$l RNase-free water and 2 $\mu$l DNA from each sample. The total volume in each well was 10 $\mu$l. Thermocycling conditions were as follows: 30-sec pre-read phase at 60˚C, a 10-min initial activation step at 95˚C, and then proceeded to 45 cycles of PCR amplification. Each cycle encompassed a 15-sec denaturation period at 95˚C, followed by a 1-min annealing phase at 60˚C, and concluded with a 30-sec extension phase also at 60˚C.

*Protein-protein interaction (PPI) network*. The PPI network was generated using GENEMANIA (http://www.genemania.org/), which is a database and a tool that predicts gene functions based on different sources and databases (32). The network showed physical interaction if two gene products were found to interact in a PPI study, co-expression if two genes were linked and their expression levels were similar in a gene expression study, predictions if there were functional relationships between genes (often protein interactions) and co-localization if genes were expressed in the same tissue or if their products were found in the same cellular location. The network also revealed pathway data if two gene products participated in the same reaction in a pathway, genetic interaction if two genes were functionally associated (for example, if the effects of perturbing one gene were found to be modified by perturbations to a second gene) and shared protein domains if two gene products had the same protein domain. In total, the network demonstrated seven categories to detect related genes: Physical interaction, co-expression, predicted, co-localization, pathway, genetic interactions and shared protein domains.

*Statistical analysis*. The genotype frequencies were tested using the Hardy-Weinberg exact test. The significant differences between the controls were calculated using the chi-square test. The odds ratio (OR) and 95% confidence interval were calculated using Fisher's exact test and SPSS version 16.0 statistical package (SPSS, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Analysis of clinical characteristics as well as identification of the risk for CVD related to RAD51 SNP and OGG1 SNP in patients from Saudi Arabia*. The clinical characteristics of the 120 cases of CVD and matched controls, with the same age, sex, ethnicity, smoking habits and pharmacological treatments are presented in Table I.

A total of 70.8% of the patients with CVD were male and 29.2% were female patients, whereas, in the control group, 66% were men and 33.3% were women. Most of the patients were men due to the availability of blood samples. Thus, the authors tried to match the ratio of CVD cases and the control group. It is worth stating that the ethnic distribution was 100% Saudi Arabian for all of the patients of the study. The mean age of the study population was 62±12 and 54.8±15.3 years for patients with CVD and healthy subjects, respectively.

*Genotype frequencies of OGG1 gene rs1052133 and RAD51 gene rs1801321 in CVD and control groups*. To analyze the role of the two polymorphisms of OGG1 and RAD51 in the pathophysiology of CVD, the association between the patients with CVD and healthy controls were investigated by comparing the allele frequencies of the two SNPs. The distributions of the

Table II. Genotype frequencies of OGG1 gene polymorphism and RAD51 gene polymorphism in patients with CVD and controls.

| Gene | SNP ID | Genotype | CVD (%) | Control (%) | OR | 95% CI | $\chi^2$-value | P-value |
|---|---|---|---|---|---|---|---|---|
| OGG1 | rs1052133 | CC | 48 (40%) | 50 (42%) | Ref | | | |
| | | CG | 57 (47%) | 58 (48%) | 1.02 | 0.5972-1.7549 | 0.01 | 0.920344 |
| | | GG | 15 (12.5%) | 10 (8%) | 1.56 | 0.6398-3.8156 | 0.97 | 0.325 |
| | | CG + GG | 72 (60%) | 68 (57%) | 0.91 | 0.5410-1.5196 | 0.14 | 0.709 |
| | | C | 153 (64%) | 158 (66%) | Ref | | | |
| | | G | 87 (36%) | 78 (32%) | 0.87 | 0.5949-1.2669 | 0.54 | 0.463 |
| RAD51 | rs1801321 | GG | 15(12.5%) | 59 (49%) | Ref | | | |
| | | GT | 2 (2%) | 0 | 0.14 | 0.0115-1.5923 | 3.34 | 0.0076[a] |
| | | TT | 103 (86%) | 60 (50%) | 0.16 | 0.0835-0.2989 | 36.0 | $1.98x10^{-9}$[a] |
| | | GT + TT | 105 (87%) | 60 (50%) | 0.16 | 0.0834-0.2977 | 36.3 | $1.24x10^{-9}$[a] |
| | | G | 32 (26.6%) | 118 (98%) | Ref | | | |
| | | T | 208 (87%) | 120 (100%) | 0.17 | 0.1068-0.2586 | 70.22 | $5.92x10^{-17}$[a] |

[a]P<0.05. OGG1, 8-oxoguanine DNA glycosylase; RAD51, RAD51 recombinase; CVD, cardiovascular disease; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; Ref, Reference.

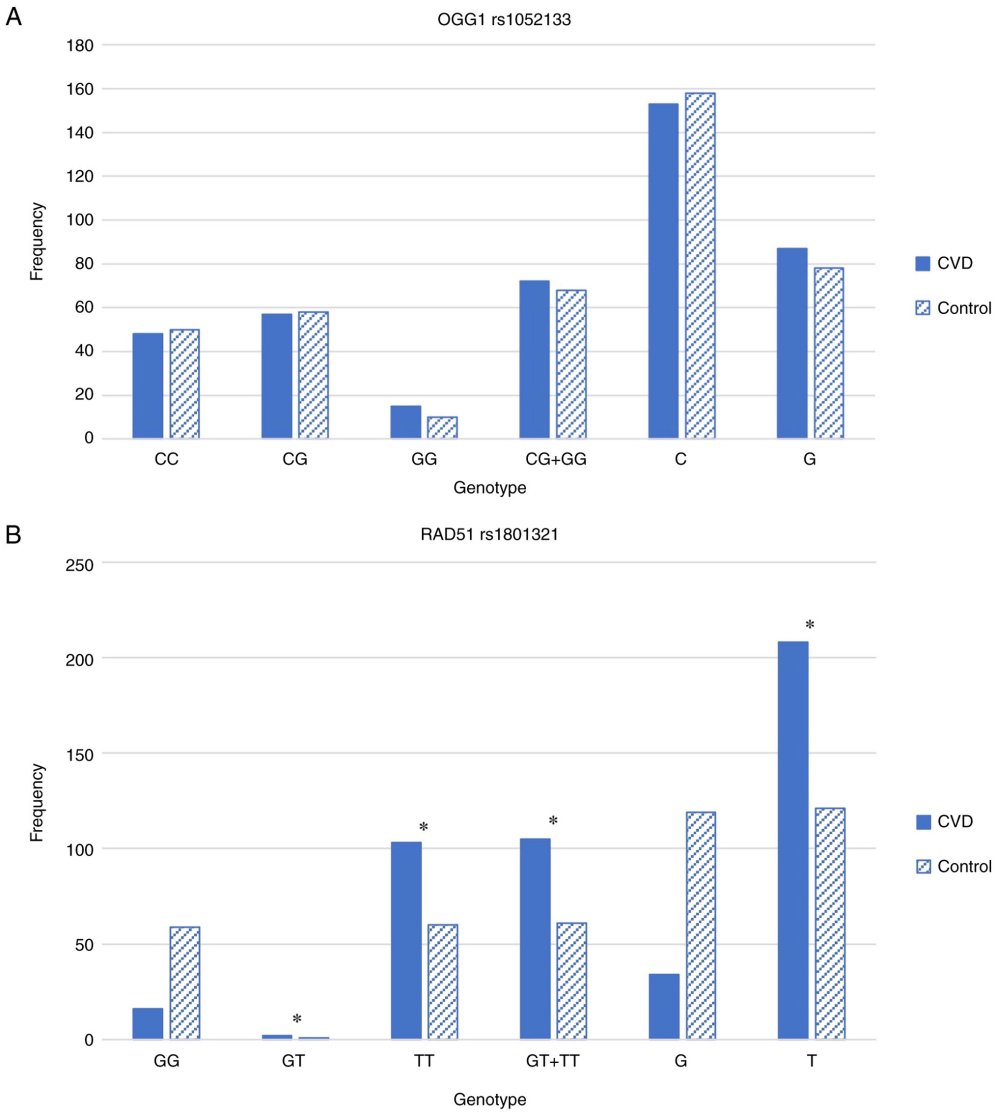


Figure 1. Genotypic frequency in CVD cases and controls. (A) Genotype frequencies of OGG1 gene polymorphism (rs1052133) in patients with CVD and a control group. (B) Genotype frequencies of RAD51 gene polymorphism (rs1801321) in a CVD group and a control group. OGG1, 8-oxoguanine DNA glycosylase; CVD, cardiovascular disease; RAD51, RAD51 recombinase.

Table III. Genotype frequencies of OGG1 gene polymorphism and RAD51 gene polymorphism in patients with CVD and controls based on age.

| Gene | SNP ID | Genotype | CVD <60 | CVD >60 | OR | 95% CI | $\chi^2$-value | P-value |
|---|---|---|---|---|---|---|---|---|
| OGG1 | rs1052133 | CC | 24 | 37 | Ref | | | |
| | | CG | 26 | 31 | 1.19 | 0.5524-2.5733 | 0.20096 | 0.65395 |
| | | GG | 7 | 8 | 1.14 | 0.3577-3.6512 | 0.05081 | 0.82167 |
| | | CG + GG | 33 | 39 | 1.18 | 0.5687-2.4560 | 0.2005 | 0.65432 |
| | | C | 74 | 79 | Ref | | | |
| | | G | 40 | 47 | 1.1 | 0.6494-1.8653 | 0.12693 | 0.72163 |
| RAD51 | rs1801321 | GG | 9 | 7 | Ref | | | |
| | | GT | 1 | 1 | 1.29 | (0.0678-24.3835) | 0.0281 | 0.8668 |
| | | TT | 45 | 58 | 1.66 | (0.5731-4.7914) | 0.8815 | 0.34779 |
| | | GT + TT | 46 | 59 | 0.5711 | (0.5711-4.7613) | 0.8667 | 0.35187 |
| | | G | 19 | 15 | Ref | | | |
| | | T | 91 | 117 | 1.63 | (0.7846-3.3804) | 1.7349 | 0.18778 |

OGG1, 8-oxoguanine DNA glycosylase; RAD51, RAD51 recombinase; CVD, cardiovascular disease; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table IV. Genotype frequencies of OGG1 gene polymorphism and RAD51 gene polymorphism in patients with CVD and controls based on sex.

| Gene | SNP ID | Genotype | Male patients with CVD | Female patients with CVD | OR | 95% CI | $\chi^2$-value | P-value |
|---|---|---|---|---|---|---|---|---|
| OGG1 | rs1052133 | CC | 38 | 10 | Ref | | | |
| | | CG | 37 | 20 | 2.05 | (0.8487-4.9711) | 2.5943 | 0.10725 |
| | | GG | 9 | 6 | 2.53 | (0.7288-8.8064) | 2.2159 | 0.1366 |
| | | CG + GG | 46 | 26 | 2.15 | (0.9213-5.0075) | 3.2011 | 0.07359 |
| | | C | 113 | 40 | Ref | | | |
| | | G | 55 | 32 | 1.64 | (0.9336-2.8937) | 2.9887 | 0.08385 |
| RAD51 | rs1801321 | GG | 14 | 2 | Ref | | | |
| | | GT | 1 | 0 | - | - | 0.46667 | 0.49452 |
| | | TT | 70 | 33 | 0.94 | 0.1643-5.4103 | 0.00436 | 0.94736 |
| | | GT + TT | 71 | 33 | 0.93 | 0.1620-5.3329 | 0.00672 | 0.93469 |
| | | G | 29 | 4 | Ref | | | |
| | | T | 141 | 66 | 3.39 | 1.1461-10.0483 | 5.902 | 0.01512[a] |

[a]P<0.05. OGG1, 8-oxoguanine DNA glycosylase; RAD51, RAD51 recombinase; CVD, cardiovascular disease; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

alleles and genotypes with significances and OR are reported in Table II. Hardy-Weinberg equilibrium was used to measure the genotype frequencies of all SNPs.

For OGG1 rs1052133C>G, the genotype frequencies of the OGG1 gene in the patients with CVD and controls are shown in Fig. 1A. No significant differences were observed in the genotype and allele frequencies for the C and G alleles between the patients with CVD and normal controls. For RAD51 rs1801321G>T, the genotype frequencies of the RAD51 gene in the patients with CVD and controls are illustrated in Fig. 1B. The controls were homozygous for either the G allele or T allele, while the CVD samples revealed a strong association with rs1801321G>T polymorphism. The TT genotype was strongly associated with CVD in the Saudi population with $P<1.98x10^{-9}$. It appears that heterogenicity is not common in RAD51, as there were only three samples (two CVD and one control) that showed a GT genotype. The frequency of the wild-type GG genotype was higher in the controls than in the CVD samples. By contrast, the TT genotype was found to be more frequent in the CVD samples than in the controls.

The samples were categorized into two groups based on patient age: <60 and >60 years of age. No significant differences in terms of the genotype and allele frequencies of

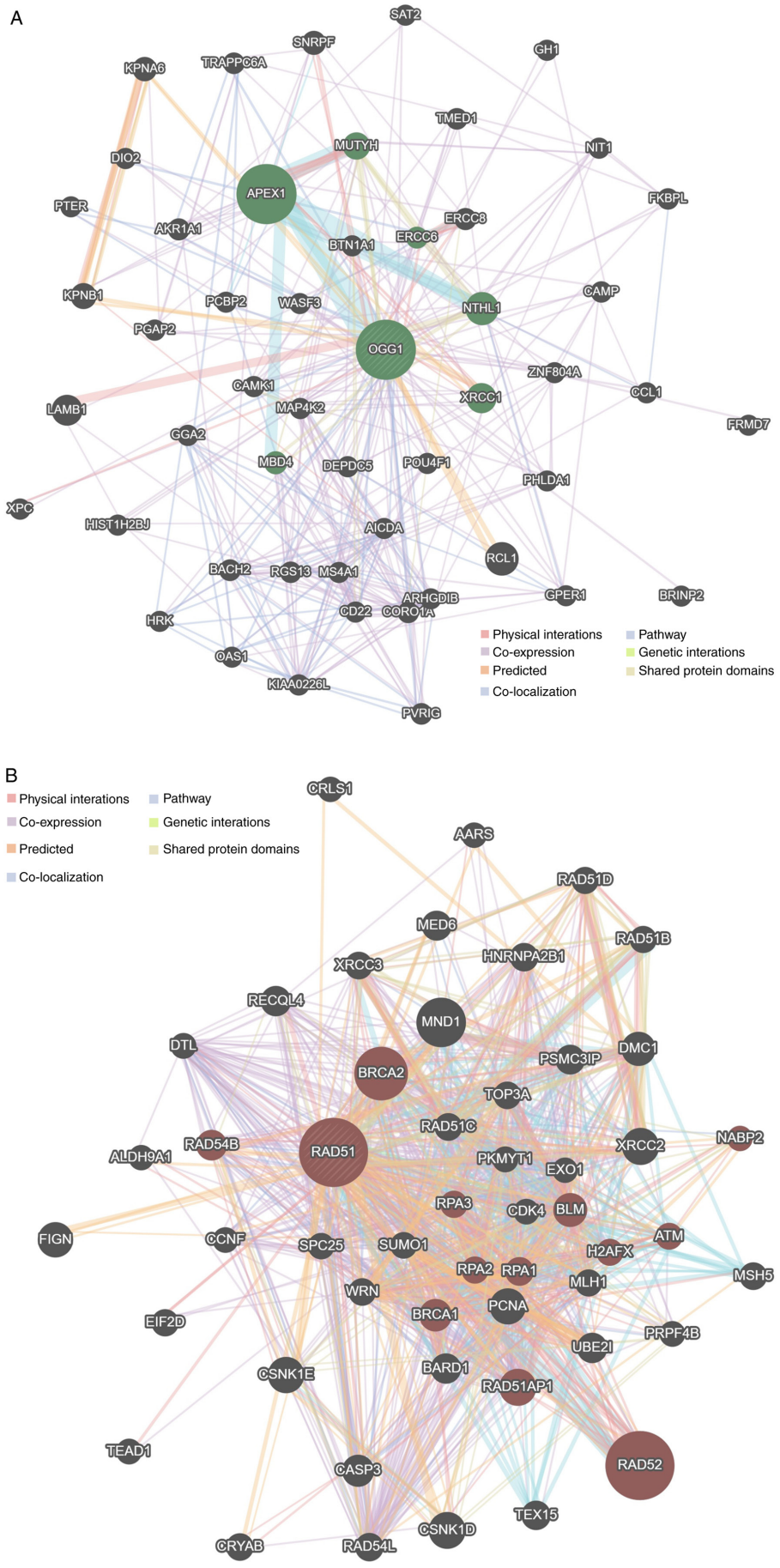


Figure 2. Protein-protein interaction networks of (A) OGG1 and (B) RAD51. A total of 50 genes are shown, which are represented as circles. The line between the circles is given a color based on its categories. The green circles are base excision repair genes while the red circles are homologous recombination genes. OGG1, 8-oxoguanine DNA glycosylase; RAD51, RAD51 recombinase.

OGG1 rs1052133 and RAD1 rs1801321 were revealed between patients <60 and >60 years old (Table III). Conversely, the association between sex, OGG1 and RAD51 variants and the risk of developing CVD was also examined (Table IV). It was revealed that only the rs1801321G>T polymorphism in male patients had a significant association with CVD development.

*PPI network*. Two networks were generated for the OGG1 gene and the RAD51 gene. For each gene, the PPI network revealed a total of 50 interacting genes for the OGG1 gene (Fig. 2A) and the RAD51 gene (Fig. 2B).

## Discussion

DNA damage can be caused by endogenous or exogenous agents. Cells have different mechanisms to repair DNA and continuously monitor chromosomes in an attempt to correct any damage. Thus, DNA repair genes play a critical role in protecting cells from the consequences of genetic mutations. Any damage in DNA repair genes may lead to a failure to maintain the integrity of the genome and the normal function of cells. Several studies have evaluated the association between single-nucleotide polymorphisms (SNPs) and developing several types of cancers and chronic diseases. OGG1 has been revealed to prevent the accumulation of mutations that occur as a result of exposure to reactive oxygen and regulates the transcription of various oxidative stress response genes (33). RADA51 has been demonstrated to be responsible for repairing double-strand DNA breaks (34). Polymorphisms in OGG1 and RADA51 have been linked to the development of several types of cancers, as this mutation alters the functions of proteins (35,36).

In the present study, the association between previously identified SNPs in OGG1 and RAD51 and susceptibility to CVD in individuals from Saudi Arabia was evaluated. The results revealed that for OGG1, there was no significant association between the rs1052133 SNP and the development of CVD, although OGG1 rs1052133 has a carcinogenic role (37). Conversely, the results showed that there was a significant association between RAD51 rs1801321 and CVD. The polymorphism rs1801321 plays a substantial role in promoter activity by substituting G to T on position 172+ (26). Sorting the samples based on age did not reveal a significant association between carrying the RAD51 rs1801321 polymorphism and developing CVD, but the RAD51 rs1801321G>T polymorphism in male patients exhibited a significant association with CVD development.

In terms of the protein-protein network, cooperation between RAD51 and the breast cancer susceptibility protein BRCA2 is crucial for the repair of double-strand DNA breaks by HR (2). BRCA2 plays a role in HR by interacting with RAD51. It captures RAD51, transports it to the damaged site, and subsequently promotes the creation of helical RAD51-single-stranded DNA nucleoprotein filaments. These filaments actively search for a homologous DNA template (38). It has been revealed that promoter activity of RAD51 is significantly enhanced by substituting G at the polymorphic position +172 for T (26). The elevated activity of HR could paradoxically result in genomic instability by causing inappropriate recombination (26). Consequently, accumulation of DNA damage leads to unaffordable sequelae such as senescence, apoptosis and inflammation which in turn could lead to CVD (39).

In conclusion, analyzing the frequencies of RAD51 gene polymorphisms revealed that there was a significant association between CVD and RAD51 rs1801321 for both male and female patients regardless of age, while OGG1 rs1052133 exhibited no significant association with development of CVD in a Saudi population. To the best of our knowledge, no previous research has evaluated the association between CVD and RAD51 rs1801321., thus, more studies with larger sample sizes should be conducted to confirm the findings of the present study.

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## Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

AmA, AbA and MA designed the study. AmA, AbA, JS and SA conducted the experiments. SA contributed new reagents/analytic tools. AmA, AbA, MBA, JS and MA analyzed the data and wrote the paper. MBA and MA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

The protocol of the study was reviewed and approved by the local committee from King Khaled University Hospital and all patients provided written informed consent. The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board of Al-Imam Muhammad Ibn Saud Islamic University (approval no. IRB-HAPO-01-R-011). The samples were originally collected from King Khalid University Hospital (Riyadh, Saudi Arabia) by Dr Mikhlid M. Almutairi, who obtained Institutional Review Board approval from Al-Imam Muhammed Ibn Saud Islamic University.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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