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Single-Nucleotide Polymorphisms of Genes Involved in Repair of Oxidative DNA Damage and the Risk of Recurrent Depressive Disorder

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Background: Depressive disorder, including recurrent type (rDD), is accompanied by increased oxidative stress and activation of inflammatory pathways, which may induce DNA damage. This thesis is supported by the presence of increased levels of DNA damage in depressed patients. Such DNA damage is repaired by the base excision repair (BER) pathway. BER efficiency may be influenced by polymorphisms in BER-related genes. Therefore, we genotyped nine single-nucleotide polymorphisms (SNPs) in six genes encoding BER proteins.

Material/Methods: Using TaqMan, we selected and genotyped the following SNPs: c.-441G>A (rs174538) of *FEN1*, c.2285T>C (rs1136410) of *PARP1*, c.580C>T (rs1799782) and c.1196A>G (rs25487) of *XRCC1*, c.*83A>C (rs4796030) and c.*50C>T (rs1052536) of *LIG3*, c.-7C>T (rs20579) of *LIG1*, and c.-468T>G (rs1760944) and c.444T>G (rs1130409) of *APEX1* in 599 samples (288 rDD patients and 311 controls).

Results: We found a strong correlation between rDD and both SNPs of *LIG3*, their haplotypes, as well as a weaker association with the c.-468T>G of *APEXI* which diminished after Nyholt correction. Polymorphisms of *LIG3* were also associated with early onset versus late onset depression, whereas the c.-468T>G polymorphism showed the opposite association.

Conclusions: The SNPs of genes involved in the repair of oxidative DNA damage may modulate rDD risk. Since this is an exploratory study, the results should to be treated with caution and further work needs to be done to elucidate the exact involvement of DNA damage and repair mechanisms in the development of this disease.

MeSH Keywords: Depression • DNA Repair • Inflammation • Oxidative Stress • Polymorphism, Single Nucleotide

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Background

Inflammation is present in patients with depressive disorders, including recurrent depressive disorder (rDD), and is thought to play an important role in the risk for and pathogenesis of this disease [1,2]. The presence of inflammation is indicated by the elevated levels of pro-inflammatory cytokines such as interleukin-1b (IL-1β) and interleukin-8 (IL-8), and by increased expression of NOD-like receptor family, pyrin domain containing 3 (NLRP3), one of the NOD-like receptors, which is a component of inflammasome which is necessary for the release of IL-1β and IL-18 [3–6]. In depression, inflammation is often accompanied by increased oxidative stress, since increased lipid peroxidation and production of mitochondrial reactive oxygen species (mtROS) are found in depressed patients [6,7]. ROS may damage biomolecules, including genetic material, as indicated by elevated levels of 8-oxoguanine (8-oxoG), a marker of oxidative DNA damage, in patients with clinical depression as well as depression that coexists with other non-mental diseases [8–13]. Depression severity may be a factor as well in milder, non-clinical depression, although 8-oxoG levels do not differ from controls [14]. Our team has confirmed previous study results that showed increased levels of oxidatively modified purines and pyrimidines, as well as DNA strand breaks and alkali labile sites in peripheral blood mononuclear cells (PBMCs) isolated from patients with rDD, using comet assay [15]. Furthermore, a recent report showed that NRLP3 may regulate the DNA damage response, with NRLP3 knockout increasing the expression of proteins involved in base-excision repair (BER) in murine dendritic cells exposed to genotoxic and oxidative stress [16]. In a previous study, we showed that PBMCs of rDD patients' cells repaired DNA damage induced by hydrogen peroxide (H_2O_2) less efficiently than in control patients' cells [15]. Finally, our team genotyped single nucleotide polymorphism (SNPs) of glycosylases involved in the first step of BER, finding that their polymorphisms may modulate rDD risk [17].

The aforementioned studies indicate that depression may be associated with impairment of the DNA damage repair mechanism, more particularly the pathways involved in the repair of oxidative DNA damage such as BER. Accordingly, we chose to study the relationship between rDD occurrence and SNPs of genes encoding proteins involved in BER, namely: c.-441G>A (rs174538) of *FEN1* (flap structure-specific endonuclease 1); c.2285T>C (rs1136410) of *PARP1* (poly [ADP-ribose] polymerase 1); c.580C>T (rs1799782) and c.1196A>G (rs25487) of *XRCC1* (X-ray repair cross-complementing protein 1); c.*83A>C (rs4796030) and c.*50C>T (rs1052536) of *LIG3* (DNA ligase 3); c.-7C>T (rs20579) of *LIG1* (DNA ligase 1); and c.-468T>G (rs1760944) and c.444T>G (rs1130409) of *APEX1* (APEX nuclease 1, DNA-[apurinic or apyrimidinic site] lyase).

Material and Methods

Study subjects

The study included 599 participants: patients with rDD (n=288, 140 women and 148 men; mean age 49.3±10.2) and healthy controls (n=311, 153 women and 158 men; mean age 51.2±13.3). All patients were hospitalized at the Department of Adult Psychiatry of the Medical University of Lodz (Poland) and were randomly recruited for this study without replacement sampling, based on the inclusion criteria for a current episode of depression and rDD outlined in ICD-10 (F32.0–7.32.2, F33.0–F33.8) [18] and a written informed consent to participate in the study. The diagnosis of rDD was established according to ICD-10 criteria. In all qualified cases, medical history was obtained using the standardized Composite International Diagnostic Interview (CIDI) [19]. Exclusion criteria included: the presence of axis I and II disorders other than depressive episodes, a diagnosis of severe and chronic somatic diseases or worsening of symptoms, injuries of the central nervous system, and inflammatory or autoimmune disorders. The control group was selected randomly from respondents with a negative history of mental illness. The control group included community volunteers enrolled in the study following the criteria of the psychiatric CIDI interview as well as depressed patients who were not treated for any severe and chronic diseases or worsening of symptoms, injuries of the central nervous system, or inflammatory or autoimmune disorders. An informed, written consent for participation in the study was obtained from each participant, according to the protocol approved by the Bioethics Committee of the Medical University of Lodz (No. RNN/70/14/KE).

Selection of single-nucleotide polymorphisms

We selected the studied polymorphisms from the public domain of the National Center for Biotechnology Information, Single Nucleotide Polymorphisms database (NCBI dbSNP) at *http://www.ncbi.nlm.nih.gov/snp* (Bethesda, MD, USA). We chose SNPs with a minor allele frequency larger than 0.05 in a European population (submitter population ID: HapMap-CEU), that are frequently studied in the literature and which are either localized in coding regions causing non-synonymous substitution or in regulatory regions. Finally, we selected nine polymorphisms:

- c.-441G>A localized near 5' end of *FEN1*;
- c.2285T>C localized in exon of *PARP1* causing valine to alanine substitution in codon 762;
- c.580C>T and c.1196A>G localized in exon of *XRCC1* causing arginine to tryptophan substitution in codon 194 and glutamine to arginine substitution in codon 399, respectively;
- c.*83A>C and c.*50C>T localized in untranscribed region at 3' end (UTR-3) of *LIG3*;
- c.-7C>T localized in untranscribed region at 5' end (UTR-5) of *LIG1*;

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- c.-468T>G and c.444T>G localized near 5' end and in exon causing asparagine to glutamic acid in codon 148, respectively, in *APEX1*.

Extraction of DNA and genotyping

Blood Mini Kit (A&A Biotechnology, Gdynia, Poland) was used to extract genomic DNA from venous blood. Sample purity was obtained by calculating absorbance ratio at 260 nm and 280 nm.

Chosen SNPs were genotyped using TaqMan® SNP Genotyping Assay and TaqMan Fast Universal PCR Master mix (Life Technologies, Carlsbad, CA, USA) in conditions recommended by the manufacturer. We used Bio-Rad CFX96 Real-Time PCR Detection System to carry out reactions. The analysis was done with CFX Manager Software (both from Bio-Rad Laboratories Inc., Hercules, California, USA).

Statistical analysis

Analysis of gathered data was performed in SigmaPlot 11.0 and Statistica 12 (Systat Software Inc., San Jose, CA, USA and Statsoft, Tulsa, OK, USA, respectively). Agreement with Hardy-Weinberg equilibrium (HWE) of the studied SNPs' genotype frequencies was checked using the chi-square test. An unconditional multiple logistic regression model was used to evaluate the association between case/control and each polymorphism or the gene–gene interactions by measuring the odds ratio (OR) and its corresponding 95% confidence interval (CI). We used multi-variable logistic regression model (fractional polynomials) to evaluate the independent relationship between the studied variants and the presence of depression disorder adjusting for age covariates to prevent loss of information resulting from age dichotomization. For multiple testing correction, we calculated the effective number of independent tests using Single Nucleotide Polymorphism Spectral Decomposition (SNPSpD) method which is based on the spectral decomposition (SpD) of matrices of pair-wise linkage disequilibrium values between SNPs [20] applying significance threshold ($p<0.012$) calculated by the method described by Li and Ji [21]. Although the distribution of male and female did not differ between the patients and controls ($p=0.951$; $\chi^2=0.004$), the OR was adjusted for gender, given that women have a doubled risk of depression compared to men [22].

Results

Single-nucleotide polymorphisms of studied genes and the risk of recurrent depressive disorder

The genotyping of the studied SNPs are presented in Table 1. The distribution of all genotypes was in agreement with HWE, with the exception of the c.-441G>A – *FEN1*. We did not find any statistically significant differences in the distribution of alleles and the genotype of c.-441G>A – *FEN1*, c.2285T>C – *PARP1*, c.580C>T – *XRCC1*, c.1196A>G – *XRCC1*, c.-7C>T – *LIG1*, and c.444T>G – *APEX1* between cases and controls. However, genotype A/A and allele A of the c.*83A>C – *LIG3* was associated with an increased risk of depression occurrence, whilst allele C was associated with decreased risk. Furthermore, genotype C/C and allele C of the c.*50C>T – *LIG3* were positively associated with rDD, with allele T being negatively correlated with rDD. Finally, we found that genotype T/G of the c.-468T>G – *APEX1* was associated with an increased risk of depression. It must be noted, that the *p* values for alleles of c.*50C>T – *LIG3* and heterozygotes of c.-468T>G – *APEX1* were greater that the statistical significance calculated by the Nyholt correction ($p=0.012$).

Single-nucleotide polymorphisms of studied genes and onset age of first episode of recurrent depressive disorder

In order to evaluate if the studied SNPs were associated with the age of the first rDD episode, we used multivariable logistic regression for analyzing fractional polynomials. We found that lower age of onset of depression was associated with the presence of G/G polymorphic variant of c.-441G>A *FEN1* polymorphism ($\chi^2=8.47$, $p=0.042$) and G/G variant of c.-7C>T *LIG1* polymorphism ($\chi^2=6.45$, $p=0,045$). For the other study SNPs, we did not find statistically significant correlations with age of onset. Moreover, we analyzed the relationship between the presence of polymorphic variants and age of onset by dividing the patients into two groups, with first episode before the age 35 years and first episode after the age of 35 years (optimal cutpoint in a univariate analysis); results are shown in Table 2. Thirty patients for whom age of first episode was unknown were not included in the analysis. As with the population of patients as a whole, no statistically significant differences were found in the distribution of genotypes and alleles of the c.-441G>A – *FEN1*, c.2285T>C – *PARP1*, c.580C>T – *XRCC1*, c.1196A>G – *XRCC1*, c.-7C>T – *LIG1*, and c.444T>G – *APEX1* between the controls and either early or late onset depression. Genotype A/A of the c.*83A>C – *LIG3* was associated with increased risk of both early and late onset depression, whilst allele A was associated with an increased risk of early onset depression only. Furthermore, genotype C/C and allele C of the same SNP was associated with a decreased risk of early onset depression. In the case of the c.*50C>T – *LIG3*, genotype C/C and allele C were positively correlated with early onset rDD, and allele T negatively correlated. Finally, the T/G genotype of the c.-468T>G – *APEX1* increased the risk of early onset depression, while allele T increased the risk of late onset depression, with the G/G genotype and allele G decreasing this risk.

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Table 1. Distribution of genotypes and alleles of the studied single-nucleotide polymorphism and the risk of recurrent depression disorder.

Genotype /Allele	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR (95% CI)*	*p*
	Number	Frequency	Number	Frequency				
c.-441G>A – *FEN1* (rs174538)								
A/A	0	–	0	–	–	–	–	–
A/G	151	0.486	119	0.413	0.746 (0.540–1.031)	0.076	0.746 (0.540–1.030)	0.075
G/G	160	0.514	169	0.587	1.340 (0.970–1.852)	0.076	1.341 (0.970–1.852)	0.075
					χ^2=2.875; *p*=0.090			
A	151	0.243	119	0.207	0.746 (0.540–1.031)	0.076	0.746 (0.540–1.030)	0.075
G	471	0.757	457	0.793	1.340 (0.970–1.852)	0.076	1.341 (0.970–1.852)	0.075
c.2285T>C – *PARP1* (rs1136410)								
A/A	201	0.646	191	0.663	1.078 (0.769–1.510)	0.664	1.074 (0.767–1.509)	0.670
A/G	103	0.331	82	0.285	0.804 (0.567–1.139)	0.219	0.804 (0.567–1.141)	0.222
G/G	7	0.023	15	0.052	2.384 (0.959–5.939)	0.062	2.385 (0.958–5.936)	0.062
					χ^2=4.672; *p*=0.097			
A	505	0.812	462	0.806	0.960 (0.720–1.280)	0.780	0.959 (0.718–1.279)	0.774
G	117	0.188	112	0.194	1.042 (0.781–1.389)	0.780	1.043 (0.782–1.392)	0.774
c.580C>T – *XRCC1* (rs1799782)								
GG	274	0.881	244	0.847	0.749 (0.468–1.198)	0.228	0.749 (0.467–1.201)	0.231
GA	36	0.116	42	0.146	1.304 (0.809–2.102)	0.275	1.303 (0.807–2.104)	0.279
AA	1	0.003	2	0.007	2.168 (0.196–24.036)	0.528	2.161 (0.191–23.970)	0.530
					χ^2=1.652; *p*=0.438			
G	584	0.939	530	0.920	0.750 (0.480–1.171)	0.206	0.750 (0.479–1.174)	0.208
A	38	0.061	46	0.080	1.334 (0.854–2.084)	0.206	1.33 (0.852–2.087)	0.208
c.1196A>G – *XRCC1* (rs25487)								
C/C	130	0.418	108	0.375	0.835 (0.602–1.160)	0.283	0.834 (0.600–1.158)	0.279
C/T	138	0.444	145	0.503	1.271 (0.922–1.753)	0.144	1.272 (0.922–1.755)	0.142
T/T	43	0.138	35	0.122	0.862 (0.535–1.391)	0.543	0.863 (0.535–1.392)	0.546
					χ^2=2.147; *p*=0.342			
C	398	0.640	361	0.627	0.944 (0.745–1.197)	0.634	0.943 (0.744–1.196)	0.629
T	224	0.360	215	0.373	1.059 (0.835–1.343)	0.634	1.060 (0.836–1.345)	0.629
c.*83A>C – *LIG3* (rs4796030)								
A/A	31	0.100	53	0.184	***2.037 (1.266–3.279)***	***0.003***	***2.042 (1.268–3.288)***	***0.003***
A/C	135	0.434	120	0.417	0.931 (0.673–1.288)	0.667	0.932 (0.674–1.289)	0.670
C/C	145	0.466	115	0.399	0.761 (0.550–1.053)	0.099	0.759 (0.548–1.051)	0.097
					χ^2=9.236; ***p=0.010***			
A	197	0.317	226	0.392	***1.366 (1.083–1.723)***	***0.008***	***1.369 (1.085–1.728)***	***0.008***
C	425	0.683	350	0.608	***0.732 (0.580–0.923)***	***0.008***	***0.730 (0.579–0.921)***	***0.008***

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Table 1 continued. Distribution of genotypes and alleles of the studied single-nucleotide polymorphism and the risk of recurrent depression disorder.

Genotype /Allele	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR (95% CI)*	*p*
	Number	Frequency	Number	Frequency				
c.*50C>T – *LIG3* (rs1052536)								
CC	56	0.180	79	0.274	***1.721 (1.168–2.538)***	***0.006***	***1.721 (1.167–2.537)***	***0.006***
CT	166	0.534	136	0.472	0.782 (0.567–1.078)	0.133	0.781 (0.566–1.077)	0.131
TT	89	0.286	73	0.253	0.847 (0.590–1.216)	0.368	0.848 (0.590–1.218)	0.371
					χ^2=7.607; ***p*=0.022**			
C	278	0.447	294	0.510	**1.295 (1.029–1.630)**	**0.028**	**1.295 (1.029–1.629)**	**0.028**
T	344	0.553	282	0.490	**0.772 (0.614–0.972)**	**0.028**	**0.772 (0.614–0.972)**	**0.028**
c.-7C>T – *LIG1* (rs20579)								
A/A	3	0.010	7	0.024	2.558 (0.655–9.986)	0.177	2.566 (0.657–10.026)	0.175
A/G	73	0.235	65	0.226	0.950 (0.649–1.391)	0.793	0.950 (0.649–1.390)	0.792
G/G	235	0.756	216	0.750	0.970 (0.669–1.407)	0.873	0.970 (0.669–1.407)	0.874
					χ^2=1.984; *p*=0.371			
A	79	0.127	79	0.137	1.093 (0.781–1.530)	0.603	1.093 (0.781–1.530)	0.603
G	543	0.873	497	0.863	0.915 (0.654–1.280)	0.603	0.915 (0.654–1.280)	0.603
c.-468T>G – *APEX1* (rs1760944)								
T/T	56	0.180	48	0.167	0.911 (0.596–1.392)	0.665	0.910 (0.596–1.391)	0.664
T/G	142	0.457	157	0.545	**1.445 (1.047–1.994)**	**0.025**	**1.444 (1.047–1.993)**	**0.025**
G/G	113	0.363	83	0.288	0.709 (0.503–1.001)	0.051	0.710 (0.503–1.002)	0.051
					χ^2=5.084; *p*=0.079			
T	254	0.408	253	0.439	1.146 (0.908–1.445)	0.251	1.145 (0.908–1.445)	0.253
G	368	0.592	323	0.561	0.885 (0.702–1.116)	0.302	0.885 (0.702–1.117)	0.304
c.444T>G – *APEX1* (rs1130409)								
G/G	71	0.228	64	0.222	0.966 (0.658–1.418)	0.859	0.967 (0.658–1.419)	0.862
G/T	164	0.527	150	0.521	0.974 (0.707–1.343)	0.874	0.974 (0.706–1.342)	0.870
T/T	76	0.244	74	0.257	1.069 (0.739–1.548)	0.723	1.069 (0.739–1.548)	0.722
					χ^2=0.131; *p*=0.937			
G	306	0.492	278	0.483	0.962 (0.762–1.213)	0.741	0.962 (0.762–1.214)	0.743
T	316	0.508	298	0.517	1.040 (0.824–1.312)	0.741	1.040 (0.824–1.312)	0.743

* OR adjusted for sex. *p*<0.050 along with corresponding ORs are in bold; *p*<0.012 along with corresponding ORs are in bold and italic.

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Table 2. Distribution of genotypes and alleles of the studied single-nucleotide polymorphism and the age of recurrent depression disorder onset.

Genotype /Allele	Control (n=298)	Early onset depression (n=130)	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p	Late onset depression (n=128)	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
	N (Freq.)	N (Freq.)					N (Freq.)				
c.-441G>A – *FEN1* (rs174538)											
A/A	0 (–)	0 (–)	–	–	–	–	0 (–)	–	–	–	–
A/G	151 (0.49)	59 (0.45)	0.88 (0.58–1.33)	0.544	0.88 (0.58–1.33)	0.549	50 (0.39)	0.68 (0.45–1.03)	0.070	0.68 (0.45–1.04)	0.073
G/G	160 (0.51)	71 (0.55)	1.14 (0.75–1.71)	0.544	1.13 (0.75–1.71)	0.549	78 (0.61)	1.47 (0.97–2.24)	0.070	1.47 (0.96–2.23)	0.073
			χ^2=0.253; p=0.615					χ^2=2.919; p=0.088			
A	151 (0.24)	59 (0.23)	0.88 (0.58–1.33)	0.544	0.88 (0.58–1.33)	0.549	50 (0.19)	0.68 (0.45–1.03)	0.070	0.68 (0.45–1.04)	0.073
G	471 (0.76)	201 (0.77)	1.14 (0.75–1.71)	0.544	1.13 (0.75–1.71)	0.549	206 (0.81)	1.47 (0.97–2.24)	0.070	1.47 (0.96–2.23)	0.073
c.2285T>C – *PARP1* (rs1136410)											
A/A	201 (0.65)	85 (0.65)	1.03 (0.67–1.59)	0.880	1.03 (0.67–1.58)	0.898	86 (0.67)	1.12 (0.72–1.73)	0.609	1.13 (0.73–1.75)	0.590
A/G	103 (0.33)	39 (0.30)	0.86 (0.56–1.35)	0.523	0.87 (0.56–1.36)	0.542	35 (0.27)	0.76 (0.48–1.12)	0.237	0.75 (0.48–1.19)	0.219
G/G	7 (0.02)	6 (0.05)	2.10 (0.69–6.38)	0.190	2.08 (0.68–6.31)	0.197	7 (0.06)	2.51 (0.86–7.31)	0.091	2.60 (0.89–7.60)	0.081
			χ^2=2.024; p=0.364					χ^2=3.997; p=0.136			
A	505 (0.81)	209 (0.80)	0.95 (0.65–1.38)	0.776	0.94 (0.65–1.37)	0.766	207 (0.81)	0.98 (0.67–1.42)	0.908	0.98 (0.67–1.43)	0.914
G	117 (0.19	51 (0.20)	1.06 (0.73–1.54)	0.776	1.06 (0.73–1.54)	0.766	49 (0.19)	1.02 (0.70–1.49)	0.908	1.02 (0.70–1.49)	0.914
c.580C>T – *XRCC1* (rs1799782)											
G/G	274 (0.88)	108 (0.83)	0.66 (0.37–1.18)	0.159	0.67 (0.38–1.19)	0.174	110 (0.86)	0.83 (0.45–1.51)	0.534	0.79 (0.43–1.46)	0.459
G/A	36 (0.12)	21 (0.16)	1.47 (0.82–2.63)	0.193	1.45 (0.81–2.61)	0.210	17 (0.13)	1.17 (063–2.17)	0.618	1.21 (0.65–2.26)	0.547
A/A	1 (0.00)	1 (0.01)	2.40 (0.15–38.7)	0.536	2.41 (0.15–38.9)	0.535	1 (0.01)	2.44 (0.15–39.3)	0.529	2.71 (0.17–43.9)	0.484
			χ^2=2.159; p=0.334					χ^2=0.688; p=0.709			
G	584 (0.94)	237 (0.91)	0.67 (0.39–1.15)	0.146	0.68 (0.39–1.17)	0.159	237 (0.93)	0.81 (0.46–1.44)	0.475	0.78 (0.44–1.39)	0.400
A	38 (0.06)	23 (0.09)	1.49 (0.87–2.57)	0.146	1.48 (0.86–2.55)	0.159	19 (0.07)	1.23 (0.70–2.18)	0.475	1.28 (0.72–2.28)	0.400
c.1196A>G – *XRCC1* (rs25487)											
C/C	130 (0.42)	52 (0.40)	0.93 (0.61–1.41)	0.736	0.92 (0.61–1.40)	0.706	50 (0.39)	0.89 (0.59–1.36)	0.596	0.91 (0.59–1.38)	0.642
C/T	138 (0.44)	65 (0.50)	1.25 (0.83–1.89)	0.208	1.26 (0.84–1.90)	0.268	60 (0.47)	1.11 (0.73–1.67)	0.632	1.10 (0.73–1.66)	0.654
T/T	43 (0.14)	13 (0.10)	0.69 (0.36–1.34)	0.273	0.69 (0.36–1.34)	0.273	18 (0.14)	1.02 (0.56–1.85)	0.948	1.01 (0.55–1.82)	0.987
			χ^2=1.760; p=0.415					χ^2=0.295; p=0.863			
C	398 (0.64)	169 (0.65)	1.05 (0.77–1.42)	0.774	1.04 (0.77–1.41)	0.789	160 (0.63)	0.94 (0.70–1.27)	0.681	0.95 (0.70–1.28)	0.734
T	224 (0.36)	91 (0.35)	0.96 (0.71–1.30)	0.774	0.96 (0.71–1.30)	0.789	96 (0.37)	1.06 (0.79–1.43)	0.681	1.05 (0.78–1.42)	0.734
c.*83A>C – *LIG3* (rs4796030)											
A/A	31 (0.10)	28 (0.21)	***2.48 (1.42–4.34)***	***0.001***	***2.48 (1.42–4.34)***	***0.001***	**24 (0.19)**	**2.08 (1.17–3.72)**	**0.013**	**2.06 (1.15–3.67)**	**0.015**
A/C	135 (0.43)	58 (0.45)	1.05 (0.69–1.59)	0.816	1.06 (0.70–1.60)	0.792	46 (0.36)	0.73 (0.48–1.12)	0.149	0.73 (0.47–1.11)	0.141
C/C	145 (0.47)	44 (0.34)	**0.59 (0.38–0.90)**	**0.014**	**0.58 (0.38–0.89)**	0.013	58 (0.45)	0.95 (0.63–1.43)	0.802	0.96 (0.64–1.46)	0.851
			χ^2=12.697; ***p*=0.002**					χ^2=6.844; ***p*=0.033**			
A	197 (0.32)	114 (0.44)	***1.66 (1.23–2.23)***	***<0.001***	***1.67 (1.24–2.24)***	***<0.001***	94 (0.37)	1.23 (0.92–1.66)	0.164	1.22 (0.91–1.65)	0.184
C	425 (0.68)	146 (0.56)	***0.60 (0.45–0.81)***	***<0.001***	***0.60 (0.45–0.81)***	***<0.001***	162 (0.63)	0.81 (0.60–1.09)	0.164	0.82 (0.61–1.10)	0.184

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Table 2 continued. Distribution of genotypes and alleles of the studied single-nucleotide polymorphism and the age of recurrent depression disorder onset.

Genotype /Allele	Control (n=298)	Early onset depression (n=130)	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p	Late onset depression (n=128)	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
	N (Freq.)	N (Freq.)					N (Freq.)				
c.*50C>T – *LIG3* (rs1052536)											
C/C	56 (0.18)	40 (0.31)	***2.02 (1.26–3.24)***	***0.003***	***2.02 (1.26–3.24)***	***0.003***	32 (0.25)	1.52 (0.93–2.49)	0.098	1.53 (0.93–2.50)	0.094
C/T	166 (0.53)	64 (0.49)	0.85 (0.56–1.28)	0.427	0.84 (0.56–1.27)	0.408	58 (0.55)	0.72 (0.48–1.09)	0.125	0.73 (0.48–1.10)	0.133
T/T	89 (0.29)	26 (0.20)	0.62 (0.38–1.02)	0.062	0.63 (0.38–1.03)	0.066	38 (0.30)	1.05 (0.67–1.66)	0.822	1.04 (0.66–1.64)	0.863
			χ^2=9.773; ***p=0.008***					χ^2=3.404; *p*=0.182			
C	278 (0.45)	144 (0.55)	***1.58 (1.16–2.13)***	***0.003***	***1.57 (1.16–2.13)***	***0.003***	122 (0.48)	1.13 (0.84–1.52)	0.417	1.14 (0.85–1.53)	0.392
T	344 (0.55)	116 (0.45)	***0.64 (0.47–0.86)***	***0.003***	***0.64 (0.47–0.86)***	***0.003***	134 (0.52)	0.88 (0.66–1.19)	0.417	0.88 (0.65–1.18)	0.392
c.-7C>T – *LIG1* (rs20579)											
A/A	3 (0.01)	3 (0.02)	2.43 (0.48–12.2)	0.282	2.43 (0.48–12.2)	0.281	4 (0.03)	3.31 (0.73–15.0)	0.120	3.20 (0.70–14.6)	0.132
A/G	73 (0.23)	25 (0.19)	0.78 (0.47–1.29)	0.329	0.78 (0.47–1.29)	0.328	32 (0.25)	1.09 (0.67–1.75)	0.733	1.09 (0.68–1.76)	0.718
G/G	235 (0.76)	102 (0.79)	1.18 (0.72–1.93)	0.513	1.18 (0.72–1.93)	0.512	92 (0.72)	0.83 (0.52–1.32)	0.421	0.83 (0.52–1.31)	0.417
			χ^2=2.059; *p*=0.357					χ^2=2.908; *p*=0.234			
A	79 (0.13)	31 (0.12)	0.93 (0.59–1.45)	0.748	0.93 (0.59–1.45)	0.747	40 (0.16)	1.28 (0.84–1.94)	0.246	1.28 (0.84–1.94)	0.249
G	543 (0.87)	229 (0.88)	1.08 (0.69–1.68)	0.748	1.08 (0.69–1.68)	0.747	216 (0.84)	0.78 (0.52–1.19)	0.246	0.78 (0.52–1.19)	0.249
c.-468T>G – APEX1 (rs1760944)											
T/T	56 (0.18)	16 (0.12)	0.64 (0.35–1.16)	0.142	0.64 (0.35–1.16)	0.137	29 (0.23)	1.33 (0.81–2.21)	0.263	1.34 (0.81–2.23)	0.254
T/G	142 (0.46)	73 (0.56)	**1.52 (1.01–2.30)**	**0.045**	**1.52 (1.01–2.29)**	**0.047**	66 (0.52)	1.27 (0.84–1.91)	0.261	1.27 (0.84–1.92)	0.253
G/G	113 (0.36)	41 (0.32)	0.81 (0.52–1.25)	0.336	0.81 (0.53–1.26)	0.353	33 (0.26)	**0.61 (0.39–0.96)**	**0.034**	**0.60 (0.38–0.95)**	**0.031**
			χ^2=2.908; *p*=0.234					χ^2=4.716; *p*=0.095			
T	254 (0.41)	105 (0.40)	0.98 (0.73–1.32)	0.900	0.98 (0.73–1.31)	0.872	124 (0.48)	**1.35 (1.01–1.80)**	**0.043**	**1.36 (1.01–1.82)**	**0.039**
G	368 (0.59)	155 (0.60)	1.02 (0.76–1.37)	0.900	1.03 (0.76–1.38)	0.872	132 (0.52	**0.74 (0.56–0.99)**	**0.043**	**0.74 (0.55–0.98)**	**0.039**
c.444T>G – *APEX1* (rs1130409)											
G/G	71 (0.23)	27 (0.21)	0.89 (0.54–1.46)	0.635	0.89 (0.54–1.48)	0.664	33 (0.26)	1.17 (0.73–1.89)	0.509	1.17 (0.73–1.89)	0.517
G/T	164 (0.53)	68 (0.52)	0.98 (0.65–1.48)	0.935	0.98 (0.65–1.47)	0.914	66 (0.51)	0.95 (0.63–1.44)	0.823	0.96 (0.64–1.45)	0.844
T/T	76 (0.24)	35 (0.27)	1.14 (0.72–1.82)	0.584	1.14 (0.71–1.81)	0.590	29 (0.23)	0.91 (0.55–1.48)	0.691	0.90 (0.55–1.47)	0.677
			χ^2=0.403; *p*=0.817					χ^2=0.477; *p*=0.788			
G	306 (0.49)	122 (0.47)	0.91 (0.67–1.22)	0.527	0.91 (0.68–1.23)	0.547	132 (0.52)	1.11 (0.82–1.49)	0.514	1.11 (0.82–1.49)	0.512
T	316 (0.51)	138 (0.53)	1.10 (0.82–1.48)	0.527	1.10 (0.81–1.48)	0.547	124 (0.48)	0.91 (0.67–1.22)	0.514	0.91 (0.67–1.22)	0.512

Early onset depression – the first episode occurred at or before 35 years of age. Late onset depression – the first episode occurred after 35 years of age. * OR adjusted for sex. *p*<0.050 along with corresponding ORs are in bold; *p*<0.012 along with corresponding ORs are in bold and italic.

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Table 3. Gene-gene interactions of the studied polymorphisms and the risk of rDD.

Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
	Number	Frequency	Number	Frequency				
c.444T>G – *APEX1* (rs1130409) and c.1196A>G – *XRCC1* (rs25487)								
G/T-C/C	75	0.241	48	0.167	**0.629 (0.420–0.943)**	**0.025**	**0.627 (0.418–0.940)**	**0.024**
G/T-C/T	68	0.219	88	0.306	**1.572 (1.089–2.271)**	**0.016**	**1.573 (1.089–2.272)**	**0.016**
c.-468T>G – *APEX1* (rs1760944) and c.*50C>T – *LIG3* (rs1052536)								
G/G-C/T	66	0.212	37	0.128	***0.547 (0.353–0.849)***	***0.007***	***0.547 (0.353–0.850)***	***0.007***
c.-468T>G – *APEX1* (rs1760944) and c.*83A>C – *LIG3* (rs4796030)0								
G/G-A/C	53	0.170	28	0.097	***0.524 (0.321–0.855)***	***0.010***	***0.524 (0.321–0.856)***	***0.010***
c.-468T>G – *APEX1* (rs1760944) and c.580C>T – *XRCC1* (rs1799782)								
G/G-G/G	99	0.318	69	0.240	**0.675 (0.470–0.968)**	**0.033**	**0.675 (0.470–0.969)**	**0.033**
c.-468T>G – *APEX1* (rs1760944) and c.1196A>G – *XRCC1* (rs25487)								
T/G-C/T	62	0.199	80	0.278	**1.545 (1.057–2.257)**	**0.025**	**1.546 (1.058–2.260)**	**0.024**
c.-468T>G – *APEX1* (rs1760944) and c.-441G>A – *FEN1* (rs174538)								
T/G-G/G	75	0.241	93	0.323	**1.501 (1.049–2.148)**	**0.026**	**1.500 (1.048–2.148)**	**0.027**
G/G-A/G	55	0.177	32	0.111	**0.582 (0.364–0.930)**	**0.024**	**0.582 (0.364–0.931)**	**0.024**
c.-7C>T – *LIG1* (rs20579) and c.*50C>T – *LIG3* (rs1052536)								
G/G-C/C	44	0.141	59	0.205	**1.563 (1.019–2.400)**	**0.041**	**1.564 (1.019–2.400)**	**0.041**
c.-7C>T – *LIG1* (rs20579) and c.*83A>C – *LIG3* (rs4796030)								
G/G-A/A	25	0.080	40	0.139	**1.845 (1.088–3.128)**	**0.023**	**1.851 (1.091–3.139)**	**0.022**
c.-7C>T – *LIG1* (rs20579) and c.-441G>A – *FEN1* (rs174538)								
A/G-A/G	37	0.119	19	0.066	**0.523 (0.293–0.933)**	**0.028**	**0.523 (0.293–0.932)**	**0.028**
c.*50C>T – *LIG3* (rs1052536) and c.580C>T – *XRCC1* (rs1799782)								
C/C-G/G	47	0.151	63	0.219	**1.573 (1.036–2.388)**	**0.034**	**1.572 (1.036–2.387)**	**0.034**
c.*50C>T – *LIG3* (rs1052536) and c.2285T>C – *PARP1* (rs1136410)								
C/C-A/A	39	0.125	57	0.198	**1.721 (1.105–2.681)**	**0.016**	**1.720 (1.104–2.681)**	**0.017**
c.*50C>T – *LIG3* (rs1052536) and c.-441G>A – *FEN1* (rs174538)								
C/C-G/G	27	0.087	48	0.167	***2.104 (1.274–3.475)***	***0.004***	***2.104 (1.274–3.475)***	***0.004***
C/T-A/G	86	0.277	58	0.201	**0.660 (0.451–0.965)**	**0.032**	**0.658 (0.449–0.963)**	**0.031**
c.*83A>C – *LIG3* (rs4796030) and c.580C>T – *XRCC1* (rs1799782)								
A/A-G/G	25	0.080	43	0.149	***2.008 (1.192–3.383)***	***0.009***	***2.015 (1.195–3.398)***	***0.009***
c.*83A>C – *LIG3* (rs4796030) and c.1196A>G – *XRCC1* (rs25487)								
A/A-C/T	13	0.042	27	0.094	**2.371 (1.199–4.691)**	**0.013**	**2.374 (1.200–4.698)**	**0.013**
c.*83A>C – *LIG3* (rs4796030) and c.2285T>C – *PARP1* (rs1136410)								
A/A-A/A	19	0.061	37	0.128	***2.265 (1.271–4.039)***	***0.006***	***2.268 (1.272–4.044)***	***0.006***
C/C-A/G	54	0.174	31	0.108	**0.574 (0.357–0.922)**	**0.022**	**0.574 (0.357–0.922)**	**0.022**
c.*83A>C – *LIG3* (rs4796030) and c.-441G>A – *FEN1* (rs174538)								
A/A-G/G	13	0.042	35	0.122	***3.171 (1.642–6.125)***	***< 0.001***	***3.171 (1.642–6.124)***	***<0.001***
c.580C>T – *XRCC1* (rs1799782) and c.-441G>A – *FEN1* (rs174538)								
G/G-A/G	135	0.434	101	0.351	**0.704 (0.506–0.979)**	**0.037**	**0.704 (0.506–0.979)**	**0.037**
c.1196A>G – *XRCC1* (rs25487) and c.2285T>C – *PARP1* (rs1136410)								
C/T-G/G	3	0.010	10	0.035	**3.693 (1.006–13.556)**	**0.049**	**3.691 (1.006–13.549)**	**0.049**
c.2285T>C – *PARP1* (rs1136410) and c.-441G>A – *FEN1* (rs174538)								
G/G-G/G	3	0.010	10	0.035	**3.693 (1.006–13.556)**	**0.049**	**3.699 (1.007–13.578)**	**0.049**

* OR adjusted for sex. $p<0.05$ along with corresponding ORs are in bold; $p<0.012$ along with corresponding ORs are in bold and italic.

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Table 4. Distribution of haplotypes of in the studied SNPs.

Haplotypes	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*
	Number	Frequency	Number	Frequency		
c.*50C>T – *LIG3* (rs1052536) and c.*83A>C – *LIG3* (rs4796030)						
CA	264	0.212	350	**0.304**	**1.620 (1.346–1.949)**	**<0.001**
CC	292	0.235	238	0.207	0.849 (0.699–1.030)	0.098
TA	130	0.105	102	0.089	0.832 (0.634–1.093)	0.187
TC	558	0.449	462	**0.401**	**0.818 (0.696–0.963)**	**0.016**

p<0.05 along with corresponding ORs are in bold.

Gene-gene interactions and the risk of recurrent depression disorder

Additionally, we evaluated whether the gene-gene combinations can modulate the risk of depression. The results of this analysis are shown in Table 3 which presents only statistically significant results, and Supplementary Table 1 which presents all results. We found several significant associations, some of which were for genes that alone did not modulate rDD risk. Combined genotype G/T-C/C of the c.444T>G – *APEX1* and the c.1196A>G – *XRCC1* was positively correlated with rDD, while the combined genotype G/T-C/T negatively correlated with rDD. Additionally, the combined genotype A/G-A/G of the c.-7C>T – *LIG1* and the c.-441G>A – *FEN1* was associated with a decreased risk of depression.

Haplotypes of the studied single-nucleotide polymorphism and the risk of recurrent depression disorder

The distribution of haplotypes of the studied SNPs are presented in Table 4 and Supplementary Table 2. We only found statistically significant results for the haplotypes of c.*50C>T – *LIG3* and c.*83A>C – *LIG3* – haplotype CA, which were associated with an increased rDD risk, while haplotype TC was associated with a decreased rDD risk.

Discussion

As indicated in the introduction, depression is accompanied by inflammation and increased oxidative stress, both of which may be important in its pathogenesis [2]. Oxidative stress may induce DNA damage, and our team and others have found increased levels of oxidatively modified DNA bases, especially 8-oxoG, DNA breaks, and an alkali labile site in depressed patients [8–13,15]. This kind of DNA damage is mainly repaired by the BER. PBMCs isolated from cells of rDD patients repaired hydrogen peroxide-induced oxidative DNA damage less efficiently than from the cells of controls, which may indicate impairments in this repair pathway [15]. Furthermore, recent studies have shown that some polymorphic variants of the BER genes may negatively impact the repair of oxidative DNA damage, and our team found that glycosylase SNPs can modulate rDD risk [17,23,24]. Therefore, in this study, nine SNPs of the six genes encoding proteins involved in later steps of BER were genotyped; and to our knowledge, none of them have been studied in the context of mental illnesses.

One of the selected genes was *LIG3*, which encodes ligase, an essential component of BER, sealing in place the new base in the final step of this pathway [25,26]. It is mainly utilized in short-patch BER, but it can be used as a "back-up" ligase in the long-patch sub-pathway [27]. *LIG3* also plays a major role in mitochondrial BER (mtBER), since its depletion by siRNA leads to the reduction of mitochondrial DNA (mtDNA) copy number and elevations in DNA single-strand breaks [28,29]. We examined the c.*50C>T and the c.*83A>C, both localized in UTR-3, where they can alter gene expression by affecting mRNA stability, half-life, and degradation [30]. Indeed, the c.*83A>C affects the binding site of microRNA, modulating the risk of bladder cancer, whilst the c.*50C>T modulates the risk of young-onset lung cancer [31,32]. Here, both SNPs showed a significant association with rDD (Table 1). We found that the AA genotype of the c.*83A>C and the CC genotype of c.*50C>T increased the risk of depression, with these genotypes also increasing cancer risk [31,32]. These SNPs are also associated with rDD onset with the c.*50C>T variant modifying the risk of early onset rDD only, with the c.*83A>C variant also being more associated with early rather than late onset depression (Table 2). Such data indicates that these SNPs are linked to early incidence of rDD, possibly being less related to non-genetic factors, which may have a greater role in late-life depression. Finally, we found that the haplotype C/A of the c.*50C>T and the c.*83A>C were associated with a significantly increased rDD risk, in contrast to the haplotype T/C, which was associated with decreased risk (Table 4).

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The next gene studied was *APEX1*. *APEX1* encodes endonuclease, which recognizes the apurinic/apyrimidinic (AP) site arising from the actions of glycosylases after the first BER step, but is also responsible for RNA processing and the regulation of transcription [33,34]. This protein takes part in mtBER, although its role is still the subject of investigation. On the one hand, overexpression of mitochondrial APEX1 in human umbilical vein endothelial cells decreases apoptosis after H_2O_2-induced oxidative stress, probably by enhancing mitochondrial DNA repair. However, on the other hand, expression of exonuclease III (with which *APEX1* has significant homology) in the mitochondria of a malignant breast epithelial cell line caused cells to be more sensitive to oxidative stress due to deficient mtDNA repair [35,36]. We genotyped two polymorphisms in this gene: the c.-468T>G and the c.444T>G. The latter, located near the 5' end of the gene, was found to affect the promoter strength and by this may modulate the risk of lung cancer [37,38]. The former causes amino acid substitution of asparagine to glutamic acid in codon 148 and although it did not alter the *in vitro* activity of *APEX1*, it modulated the risk of cancer and was associated with Parkinson's disease, probably by affecting interactions of the enzyme with other BER proteins [39–42]. Data in our study showed that the heterozygote of the c.-468T>G increased rDD risk (Table 1). This SNP was more associated with late onset rather than with early onset depression, which could mean that the c.-468T>G has lower penetration than the *LIG3* polymorphisms and needs other factors to induce rDD later in life (Table 2). Although the heterozygote increased the risk only of early onset depression, the A allele homozygote and the A allele alone decreased late onset rDD risk, while the T allele increased this risk. These results are consistent with the work of Lo and colleagues that showed that the G allele increased luciferase reported gene expression in several adenocarcinoma cell lines [38]. The hypothesis that this polymorphism had less impact on depression occurrence was confirmed by the fact that, only together with heterozygotes of *LIG3* SNPs genotype GG, was the risk for the disease decreased (Table 3). In the case of c.444T>G as well as haplotypes of these two *APEX1* polymorphisms, we did not find any statistically significant results (Tables 1, 4).

Two SNPs were also genotyped in *XRCC1*, which encodes a protein that is not only an important component of BER, but also a component of other DNA repair pathways, such as single-strand break repair and non-homologous end joining [43,44]. In BER, XRCC1 is involved in each of these pathway steps due to its function as a scaffold protein, which physically associates with repair enzymes [45]. Its polymorphisms are associated with cancers and neurodegenerative diseases such as Alzheimer's disease [46–48]. Again two SNPs were genotyped: the c.580C>T, which is localized in a region that coordinates protein integrations, whereas the c.1196A>G is positioned in the breast cancer 1 C terminus (BRCT1) domain, which is responsible for interactions with PARP [48–50]. No significant associations of depression with either genotypes, alleles, nor haplotypes of *XRCC1* SNPs were found (Tables 1, 2, and Supplementary Table 1). However, combined genotypes of this gene with genes encoding proteins interacting with XRCC1 provided some statistically significant results. The most interesting being the combination of the c.1196A>G – *XRCC1* and the c.444T>G – *APEX1*, which alone were not rDD associated. In this gene-gene interaction, the latter SNP is more important due to changes of this polymorphism's genotype causing either a decrease (homozygote CC) or an increase (heterozygote) in rDD risk (Table 3). Moreover, this heterozygote increased the risk of rDD in combination with the TG genotype of the c.-468T>G – *APEX1* and AA genotype of the c.*83A>C – *LIG3*. Such results suggest that this SNP may have little if any impact on the development of depression. Similarly, the two polymorphisms of *FEN1* and *LIG1*, although neither alone influenced rDD risk, the combined genotype consisting of heterozygotes decreased rDD risk (Tables 1, 3). *FEN1* encodes structure specific endonuclease that removes the 5'-flap structures arising during long-patch BER and is involved in maturation of Okazaki fragments, as well as releasing stalled replication forks [51–53]. It also participates in maintaining the mitochondrial genome [54]. A polymorphism of this gene, the c.-441G>A, reduced expression of *FEN1*, elevated levels of DNA damage, and increased risk of lung cancer in individuals carrying the GG genotype [55]. In our study, this SNP was associated with depression in combination with other SNPs, most notably the combination of its GG genotype with the homozygote AA of the c.*83A>C – *LIG3* or the homozygote CC of the c.*50C>T – *LIG3* significantly increased rDD risk (Table 4). The product of *LIG1* is also involved in long-patch BER and maturation of Okazaki fragments [56]. The SNP located in the 5'-UTR of this gene is associated with lung cancer in heterozygote carriers, although its influence on gene expression is unknown [32]. We found that its heterozygote in combination with the homozygote AA of the c.*83A>C – *LIG3* or the homozygote CC of the c.*50C>T – *LIG3* was correlated with rDD (Table 4). It must be noted that this association was weaker than in the case of the c.-441G>A – *FEN1*, which could indicate that the latter SNP is more involved in the pathogenesis of rDD than the former. Finally, we genotyped one SNP in *PARP1*, which encodes protein involved not only in DNA damage, including the BER, but also in the inflammation response, transcription, and apoptosis [57,58]. This SNP was found to reduce enzyme activity by about 40% [59]. However, no significant correlation was found between this polymorphisms and depression (Tables 1, 2).

The results showing a strong association between depression and some polymorphism variants of *LIG3*, their haplotypes, or their interactions with other SNPs of BER genes are especially interesting in the context of recent work demonstrating impairments in oxidative DNA damage repair in rDD

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patients [15]. DNA damage repair kinetics in the aforementioned study revealed that the differences between controls and cases were more likely to be present in the later stages of BER, as initial DNA damage caused by the actions of DNA glycosylases in both groups occurred at the same time. As such, it can be speculated that this difference may arise, at least partly, by the more frequent occurrence of a specific variant of *LIG3* and others genes involved in the later steps of BER in depressed patients versus controls. Furthermore, as indicated earlier, *LIG3* plays an important role in the maintenance of the mitochondrial genome and a growing number of reports indicate the importance of mitochondrial dysfunctions in depression [28,29]. Depressed patients have lower mitochondrial ATP production, lower CoQ10 levels and increased mitochondrial ROS, all of which indicate mitochondrial damage [60–63]. The mitochondrial impairments may be due to increased mtDNA damage, and elevated levels of mtDNA deletions are found in depressed patients' muscles and PBMCs [61,62]. Such deletions can be triggered by DNA damage, and one of the most frequently occurring deletions, called "common deletion", is triggered by a single-strand break following incomplete DNA damage repair, when ligase does not seal the nick in the last step of BER [64]. Given the classical decrease in serotonin in depression, and its role as a precursor for melatonin and a significant regulator of mitochondrial functioning as well as an inhibitor of oxidative damage and inflammation, it is not unlikely that variations in melatonin availability will interact with genes regulating the BER [65].

Our work has some limitations. One limitation was a relatively small sample size, although comparable studies concerning depression had similar study group size [66,67]. In addition, our results cannot be generalized to the world population, due to ethnic homogeneity of the studied population.

Conclusions

This study is concordant with the extant literature in showing that SNPs of genes involved in oxidative DNA damage repair may modulate the risk of rDD [17]. Further studies are needed to elucidate the role of nuclear DNA as well as mitochondrial DNA damage and repair in pathogenesis of depression, and the effect on clinical outcome. Aging effects on telomerase, which can be offset by melatonin, would be expected to interact with the genetic susceptibility to rDD, driven partly by BER SNPs.

Statement

The authors declare no conflict of interest.

Supplementary Table 1. Gene-gene interactions of the studied polymorphisms and the risk of rDD.

Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
c.444T>G – *APEX1* (rs1130409) and c.-7C>T – *LIG1* (rs20579)								
G/G-A/A	0	-	1	0.003	–	–	–	–
G/G-A/G	20	0.064	18	0.063	0.970 (0.502–1.873)	0.928	0.970 (0.502–1.873)	0.928
G/G-G/G	51	0.164	45	0.156	0.944 (0.610–1.462)	0.797	0.945 (0.610–1.464)	0.800
G/T-A/A	2	0.006	5	0.017	2.730 (0.525–14.181)	0.232	2.771 (0.531–14.459)	0.227
G/T-A/G	44	0.141	33	0.115	0.785 (0.485–1.273)	0.327	0.785 (0.484–1.272)	0.326
G/T-G/G	118	0.379	112	0.389	1.041 (0.749–1.447)	0.812	1.040 (0.748–1.446)	0.817
T/T-A/A	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.068 (0.066–17.231)	0.963
T/T-A/G	9	0.029	14	0.049	1.715 (0.730–4.024)	0.216	1.713 (0.730–4.021)	0.217
T/T-G/G	66	0.212	59	0.205	0.956 (0.645–1.419)	0.825	0.957 (0.645–1.420)	0.827
c.444T>G – *APEX1* (rs1130409) and c.*50C>T – *LIG3* (rs1052536)								
G/G-C/C	13	0.042	16	0.056	1.348 (0.637–2.855)	0.435	1.348 (0.637–2.854)	0.435
G/G-C/T	35	0.113	26	0.090	0.783 (0.458–1.336)	0.369	0.783 (0.459–1.337)	0.370
G/G-T/T	23	0.074	22	0.076	1.036 (0.564–1.902)	0.910	1.037 (0.565–1.906)	0.906
G/T-C/C	30	0.096	40	0.139	1.511 (0.913–2.499)	0.108	1.510 (0.912–2.498)	0.109
G/T-C/T	91	0.293	76	0.264	0.867 (0.606–1.240)	0.434	0.866 (0.605–1.240)	0.433
G/T-T/T	43	0.138	34	0.118	0.834 (0.515–1.350)	0.461	0.834 (0.516–1.350)	0.461
T/T-C/C	13	0.042	23	0.080	1.990 (0.988–4.006)	0.054	1.994 (0.990–4.018)	0.053

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
	Number	Frequency	Number	Frequency				
T/T-C/T	40	0.129	34	0.118	0.907 (0.557–1.478)	0.695	0.905 (0.555–1.476)	0.690
T/T-T/T	23	0.074	17	0.059	0.785 (0.411–1.502)	0.466	0.786 (0.411–1.505)	0.468
c.444T>G – *APEX1* (rs1130409) and c.*83A>C – *LIG3* (rs4796030)								
G/G-A/A	5	0.016	12	0.042	2.661 (0.926–7.649)	0.069	2.658 (0.924–7.642)	0.070
G/G-A/C	32	0.103	26	0.090	0.865 (0.502–1.491)	0.602	0.866 (0.503–1.494)	0.606
G/G-C/C	34	0.109	26	0.090	0.808 (0.472–1.384)	0.439	0.809 (0.472–1.385)	0.440
G/T-A/A	17	0.055	27	0.094	1.789 (0.953–3.357)	0.070	1.790 (0.954–3.358)	0.070
G/T-A/C	70	0.225	64	0.222	0.984 (0.670–1.445)	0.933	0.984 (0.670–1.447)	0.936
G/T-C/C	77	0.248	59	0.205	0.783 (0.533–1.151)	0.213	0.781 (0.531–1.148)	0.208
T/T-A/A	9	0.029	14	0.049	1.715 (0.730–4.024)	0.216	1.730 (0.735–4.072)	0.210
T/T-A/C	33	0.106	30	0.104	0.980 (0.581–1.652)	0.938	0.979 (0.580–1.651)	0.936
T/T-C/C	34	0.109	30	0.104	0.947 (0.564–1.593)	0.838	0.946 (0.563–1.591)	0.835
c.444T>G – *APEX1* (rs1130409) and c.580C>T – *XRCC1* (rs1799782)								
G/G-G/G	62	0.199	51	0.177	0.864 (0.573–1.304)	0.784	0.865 (0.573–1.306)	0.491
G/G-G/A	9	0.029	13	0.045	1.586 (0.668–3.769)	0.296	1.583 (0.666–3.766)	0.299
G/G-A/A	0	–	0	–	–	–	–	–
G/T-G/G	142	0.457	130	0.451	0.979 (0.710–1.351)	0.898	0.979 (0.710–1.351)	0.899
G/T-G/A	22	0.071	19	0.066	0.928 (0.491–1.752)	0.817	0.925 (0.489–1.749)	0.810
G/T-A/A	0	–	1	0.003	–	–	–	–
T/T-G/G	70	0.225	63	0.219	0.964 (0.655–1.418)	0.852	0.964 (0.656–1.419)	0.854
T/T-G/A	5	0.016	10	0.035	2.201 (0.743–6.520)	0.154	2.198 (0.742–6.512)	0.155
T/T-A/A	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.080 (0.067–17.354)	0.956
c.444T>G – *APEX1* (rs1130409) and c.1196A>G – *XRCC1* (rs25487)								
G/G-C/C	28	0.090	30	0.104	1.175 (0.684–2.021)	0.559	1.177 (0.684–2.024)	0.556
G/G-C/T	36	0.116	27	0.094	0.790 (0.467–1.338)	0.381	0.791 (0.467–1.339)	0.382
G/G-T/T	7	0.023	7	0.024	1.082 (0.375–3.123)	0.884	1.082 (0.375–3.124)	0.884
G/T-C/C	75	0.241	48	0.167	**0.629 (0.420–0.943)**	**0.025**	**0.627 (0.418–0.940)**	**0.024**
G/T-C/T	68	0.219	88	0.306	**1.572 (1.089–2.271)**	**0.016**	**1.573 (1.089–2.272)**	**0.016**
G/T-T/T	21	0.068	14	0.049	0.706 (0.352–1.415)	0.326	0.706 (0.352–1.417)	0.328
T/T-C/C	27	0.087	30	0.104	1.223 (0.708–2.113)	0.470	1.222 (0.707–2.111)	0.472
T/T-C/T	34	0.109	30	0.104	0.947 (0.564–1.593)	0.838	0.948 (0.564–1.594	0.840
T/T-T/T	15	0.048	14	0.049	1.008 (0.478–2.127)	0.983	1.009 (0.478–2.129)	0.981
c.444T>G – *APEX1* (rs1130409) and c.2285T>C – *PARP1* (rs1136410)								
G/G-A/A	44	0.141	48	0.167	1.214 (0.778–1.893)	0.393	1.214 (0.778–1.893)	0.393
G/G-A/G	25	0.080	16	0.056	0.673 (0.352–1.288)	0.232	0.674 (0.352–1.291)	0.234
G/G-G/G	2	0.006	0	–	–	–	–	–
G/T-A/A	104	0.334	96	0.33	0.995 (0.708–1.398)	0.978	0.993 (0.706–1.397)	0.967
G/T-A/G	57	0.183	46	0.160	0.847 (0.553–1.298)	0.446	0.848 (0.553–1.301)	0.450
G/T-G/G	3	0.010	8	0.028	2.933 (0.771–11.166)	0.115	2.938 (0.772–11.186)	0.114
T/T-A/A	53	0.170	47	0.163	0.949 (0.617–1.460)	0.813	0.950 (0.618–1.461)	0.816
T/T-A/G	21	0.068	20	0.069	1.031 (0.546–1.944)	0.926	1.029 (0.546–1.942)	0.929
T/T-G/G	2	0.006	7	0.024	3.849 (0.793–18.681)	0.094	3.845 (0.792–18.666)	0.095

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
c.444T>G – *APEX1* (rs1130409) and c.-441G>A – *FEN1* (rs174538)								
G/G-A/A	0	–	0	-	–	–	–	–
G/G-A/G	38	0.122	24	0.083	0.653 (0.381–1.119)	0.121	0.653 (0.381–1.119)	0.121
G/G-G/G	33	0.106	40	0.139	1.359 (0.831–2.222)	0.222	1.361 (0.832–2.226)	0.220
G/T-A/A	0	–	2	–	–	–	–	–
G/T-A/G	75	0.241	61	0.212	0.846 (0.576–1.241)	0.392	0.845 (0.575–1.240)	0.389
G/T-G/G	89	0.286	89	0.309	1.116 (0.786–1.584)	0.541	1.115 (0.785–1.584)	0.542
T/T-A/A	0	–	0	–	–	–	–	–
T/T-A/G	38	0.122	34	0.118	0.962 (0.587–1.575)	0.877	0.692 (0.587–1.575)	0.877
T/T-G/G	38	0.122	40	0.139	1.159 (0.720–1.865)	0.544	1.159 (0.720–1.865)	0.544
c.-468T>G – *APEX1* (rs1760944) and c.-7C>T – *LIG1* (rs20579)								
T/T-A/A	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.080 (0.067–17.354)	0.956
T/T-A/G	11	0.035	11	0.038	1.083 (0.462–2.538)	0.854	1.086 (0.463–2.546)	0.850
T/T-G/G	44	0.141	36	0.125	0.867 (0.540–1.391)	0.554	0.865 (0.539–1.389)	0.550
T/G-A/A	2	0.006	4	0.014	2.176 (0.396–11.971)	0.371	2.187 (0.397–12.046)	0.369
T/G-A/G	32	0.103	33	0.115	1.128 (0.674–1.888)	0.646	1.128 (0.674–1.888)	0.647
T/G-G/G	108	0.347	120	0.417	1.343 (0.965–1.869)	0.081	0.856 (0.614–1.192)	0.356
G/G-A/A	0	-	2	0.007	–	–	–	–
G/G-A/G	30	0.096	21	0.073	0.737 (0.412–1.319)	0.304	0.735 (0.411–1.317)	0.301
G/G-G/G	83	0.267	60	0.208	0.723 (0.495–1.057)	0.094	0.723 (0.494–1.058)	0.095
c.-468T>G – *APEX1* (rs1760944) and c.*50C>T – *LIG3* (rs1052536)								
T/T-C/C	12	0.039	19	0.066	1.760 (0.839–3.693)	0.135	1.759 (0.838–3.691)	0.136
T/T-C/T	25	0.080	18	0.063	0.763 (0.407–1.430)	0.398	0.760 (0.405–1.426)	0.392
T/T-T/T	19	0.061	11	0.038	0.610 (0.285–1.306)	0.203	0.611 (0.285–1.310)	0.205
T/G-C/C	28	0.090	39	0.125	1.444 (0.857–2.434)	0.168	1.443 (0.855–2.433)	0.169
T/G-C/T	75	0.241	81	0.281	1.231 (0.854–1.774)	0.264	1.231 (0.854–1.774)	0.265
T/G-T/T	39	0.125	40	0.139	1.125 (0.701–1.806)	0.626	1.021 (0.636–1.639)	0.931
G/G-C/C	16	0.051	24	0.083	1.676 (0.872–3.224)	0.122	1.682 (0.874–3.237)	0.120
G/G-C/T	66	0.212	37	0.128	***0.547 (0.353–0.849)***	***0.007***	***0.547 (0.353–0.850)***	***0.007***
G/G-T/T	31	0.100	22	0.076	0.747 (0.422–1.323)	0.317	0.747 (0.422–1.324)	0.318
c.-468T>G – *APEX1* (rs1760944) and c.*83A>C – *LIG3* (rs4796030)0								
T/T-A/A	4	0.013	10	0.035	2.761 (0.856–8.903)	0.089	2.768 (0.858–8.930)	0.088
T/T-A/C	18	0.058	18	0.063	1.085 (0.553–2.129)	0.812	1.083 (0.552–2.126)	0.816
T/T-C/C	34	0.109	20	0.069	0.608 (0.341–1.083)	0.091	0.608 (0.341–1.083)	0.091
T/G-A/A	17	0.055	24	0.083	1.572 (0.826–2.991)	0.168	1.572 (0.826–2.991)	0.168
T/G-A/C	64	0.206	74	0.257	1.335 (0.911–1.954)	0.138	1.335 (0.912–1.955)	0.138
T/G-C/C	61	0.196	59	0.205	1.056 (0.708–1.576)	0.790	1.054 (0.706–1.574)	0.796
G/G-A/A	10	0.032	19	0.066	2.126 (0.971–4.653)	0.059	2.134 (0.975–4.674)	0.058
G/G-A/C	53	0.170	28	0.097	***0.524 (0.321–0.855)***	***0.010***	***0.524 (0.321–0.856)***	***0.010***
G/G-C/C	50	0.161	36	0.125	0.746 (0.470–1.184)	0.213	0.745 (0.469–1.183)	0.212
c.-468T>G – *APEX1* (rs1760944) and c.580C>T – *XRCC1* (rs1799782)								
T/T-G/G	45	0.145	41	0.142	0.981 (0.621–1.550)	0.935	0.982 (0.621–1.551)	0.937

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
T/T-G/A	10	0.032	7	0.024	0.750 (0.282–1.997)	0.565	0.745 (0.279–1.989)	0.557
T/T-A/A	1	0.003	0	–	–	–	–	–
T/G-G/G	130	0.418	134	0.465	1.211 (0.877–1.674)	0.244	1.211 (0.877–1.673)	0.245
T/G-G/A	12	0.039	21	0.073	1.960 (0.946–4.059)	0.070	1.958 (0.945–4.058)	0.071
T/G-A/A	0	–	2	0.007	–	–	–	–
G/G-G/G	99	0.318	69	0.240	**0.675 (0.470–0.968)**	**0.033**	**0.675 (0.470–0.969)**	**0.033**
G/G-G/A	14	0.045	14	0.049	1.084 (0.508–2.315)	0.835	1.082 (0.506–2.311)	0.840
G/G-A/A	0	–	0	–	–	–	–	–
c.-468T>G – *APEX1* (rs1760944) and c.1196A>G – *XRCC1* (rs25487)								
T/T-C/C	27	0.087	19	0.066	0.743 (0.404–1.368)	0.340	0.741 (0.402–1.365)	0.336
T/T-C/T	25	0.080	23	0.080	0.993 (0.550–1.792)	0.981	0.993 (0.550–1.792)	0.982
T/T-T/T	4	0.013	6	0.021	1.633 (0.456–5.847)	0.451	1.638 (0.457–5.868)	0.448
T/G-C/C	58	0.186	57	0.198	1.076 (0.717–1.617)	0.723	1.075 (0.715–1.615)	0.728
T/G-C/T	62	0.199	80	0.278	**1.545 (1.057–2.257)**	**0.025**	**1.546 (1.058–2.260)**	**0.024**
T/G-T/T	22	0.071	20	0.069	0.980 (0.523–1.837)	0.951	0.979 (0.522–1.835)	0.947
G/G-C/C	45	0.145	32	0.111	0.739 (0.455–1.200)	0.221	0.739 (0.455–1.201)	0.222
G/G-C/T	51	0.164	42	0.146	0.870 (0.558–1.357)	0.540	0.871 (0.558–1.357)	0.541
G/G-T/T	17	0.055	9	0.031	0.558 (0.245–1.272)	0.165	0.559 (0.244–1.276)	0.167
c.-468T>G – *APEX1* (rs1760944) and c.2285T>C – *PARP1* (rs1136410)								
T/T-A/A	31	0.100	29	0.101	1.011 (0.593–1.725)	0.967	1.011 (0.593–1.724)	0.969
T/T-A/G	23	0.074	16	0.056	0.737 (0.381–1.424)	0.363	0.736 (0.381–1.423)	0.362
T/T-G/G	2	0.006	3	0.010	1.626 (0.270–9.803)	0.596	1.631 (0.270–9.835)	0.594
T/G-A/A	96	0.309	105	0.365	1.285 (0.915–1.805)	0.148	1.285 (0.913–1.808)	0.150
T/G-A/G	44	0.141	45	0.156	1.124 (0.716–1.763)	0.612	1.128 (0.718–1.772)	0.603
T/G-G/G	2	0.006	7	0.024	3.849 (0.793–18.681)	0.094	3.845 (0.792–18.666)	0.095
G/G-A/A	74	0.238	57	0.198	0.790 (0.535–1.167)	0.237	0.791 (0.535–1.169)	0.239
G/G-A/G	36	0.116	21	0.073	0.601 (0.342–1.056)	0.077	0.601 (0.342–1.057)	0.077
G/G-G/G	3	0.010	5	0.017	1.814 (0.430–7.659)	0.418	1.810 (0.428–7.645)	0.420
c.-468T>G – *APEX1* (rs1760944) and c.-441G>A – *FEN1* (rs174538)								
T/T-A/A	0	–	0	–	–	–	–	–
T/T-A/G	29	0.093	23	0.080	0.844 (0.476–1.496)	0.561	0.838 (0.471–1.491)	0.548
T/T-G/G	27	0.087	25	0.087	1.000 (0.566–1.767)	1.000	1.004 (0.567–1.777)	0.990
T/G-A/A	0	–	0	–	–	–	–	–
T/G-A/G	67	0.215	64	0.222	1.041 (0.706–1.533)	0.841	1.041 (0.706–1.534)	0.840
T/G-G/G	75	0.241	93	0.323	**1.501 (1.049–2.148)**	**0.026**	**1.500 (1.048–2.148)**	**0.027**
G/G-A/A	0	–	0	–	–	–	–	–
G/G-A/G	55	0.177	32	0.111	**0.582 (0.364–0.930)**	**0.024**	**0.582 (0.364–0.931)**	**0.024**
G/G-G/G	58	0.186	51	0.177	0.939 (0.619–1.423)	0.765	0.939 (0.619–1.423)	0.766
c.-7C>T – *LIG1* (rs20579) and c.*50C>T – *LIG3* (rs1052536)								
A/A-C/C	0	–	0	–	–	–	–	–
A/A-C/T	2	0.006	4	0.014	2.176 (0.396–11.971)	0.371	2.187 (0.397–12.046)	0.369
A/A-T/T	1	0.003	3	0.010	3.263 (0.338–31.550)	0.307	3.264 (0.338–31.560)	0.307

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
	Number	Frequency	Number	Frequency				
A/G-C/C	12	0.039	20	0.069	1.859 (0.892–3.876)	0.098	1.858 (0.891–3.873)	0.098
A/G-C/T	42	0.135	31	0.108	0.773 (0.471–1.267)	0.306	0.773 (0.471–1.267)	0.307
A/G-T/T	19	0.061	14	0.049	0.785 (0.386–1.597)	0.504	0.785 (0.386–1.597)	0.504
G/G-C/C	44	0.141	59	0.205	**1.563 (1.019–2.400)**	**0.041**	**1.564 (1.019–2.400)**	**0.041**
G/G-C/T	122	0.392	101	0.351	0.837 (0.600–1.166)	0.293	0.836 (0.599–1.165)	0.290
G/G-T/T	69	0.222	56	0.194	0.847 (0.570–1.258)	0.410	0.847 (0.570–1.260)	0.413
c.-7C>T – *LIG1* (rs20579) and c.*83A>C – *LIG3* (rs4796030)								
A/A-A/A	0	–	0	–	–	–		
A/A-A/C	0	–	2	0.007	–	–		
A/A-C/C	3	0.010	5	0.017	1.814 (0.430–7.659)	0.418	1.821 (0.431–7.694)	0.415
A/G-A/A	6	0.019	13	0.045	2.403 (0.901–6.409)	0.080	2.402 (0.901–6.407)	0.080
A/G-A/C	34	0.109	25	0.087	0.774 (0.450–1.333)	0.356	0.775 (0.450–1.335)	0.359
A/G-C/C	33	0.106	27	0.094	0.871 (0.510–1.489)	0.615	0.870 (0.508–1.487)	0.610
G/G-A/A	25	0.080	40	0.139	**1.845 (1.088–3.128)**	**0.023**	**1.851 (1.091–3.139)**	**0.022**
G/G-A/C	101	0.325	93	0.323	0.992 (0.704–1.397)	0.962	0.992 (0.704–1.397)	0.963
G/G-C/C	109	0.350	83	0.288	0.750 (0.531–1.060)	0.103	0.749 (0.530–1.059)	0.101
c.-7C>T – *LIG1* (rs20579) and c.2285T>C – *PARP1* (rs1136410)								
A/A-A/A	1	0.003	2	0.007	2.168 (0.196–24.036)	0.528	2.151 (0.193–23.970)	0.534
A/A-A/G	2	0.006	4	0.014	2.176 (0.396–11.971)	0.371	2.202 (0.399–12.159)	0.365
A/A-G/G	0	–	1	0.003	–	–	–	–
A/G-A/A	49	0.158	46	0.160	1.016 (0.655–1.576)	0.942	1.016 (0.655–1.575)	0.945
A/G-A/G	24	0.077	17	0.059	0.750 (0.394–1.427)	0.381	0.751 (0.395–1.428)	0.382
A/G-G/G	0	–	2	0.007	–	–	–	–
G/G-A/A	151	0.486	143	0.497	1.045 (0.758–1.440)	0.788	1.044 (0.758–1.439)	0.792
G/G-A/G	77	0.248	61	0.212	0.817 (0.557–1.197)	0.299	0.817 (0.557–1.199)	0.302
G/G-G/G	7	0.023	12	0.042	1.888 (0.733–4.864)	0.188	1.886 (0.732–4.859)	0.189
c.-7C>T – *LIG1* (rs20579) and c.-441G>A – *FEN1* (rs174538)								
A/A-A/A	0	–	0	–	–	–	–	–
A/A-A/G	2	0.006	5	0.017	2.730 (0.525–14.181)	0.232	2.730 (0.525–14.181)	0.232
A/A-G/G	1	0.003	2	0.007	2.168 (0.196–24.036)	0.528	2.161 (0.195–23.970)	0.530
A/G-A/A	0	–	0	–	–	–	–	–
A/G-A/G	37	0.119	19	0.066	**0.523 (0.293–0.933)**	**0.028**	**0.523 (0.293–0.932)**	**0.028**
A/G-G/G	36	0.116	46	0.160	1.452 (0.908–2.321)	0.119	1.452 (0.908–2.321)	0.119
G/G-A/A	0	–	0	–	–	–	–	–
G/G-A/G	112	0.360	95	0.330	0.875 (0.624–1.226)	0.437	0.874 (0.624–1.225)	0.435
G/G-C/C	123	0.395	121	0.420	1.107 (0.799–1.535)	0.540	1.108 (0.800–1.535)	0.538
c.*50C>T – *LIG3* (rs1052536) and c.580C>T – *XRCC1* (rs1799782)								
C/C-G/G	47	0.151	63	0.219	**1.573 (1.036–2.388)**	**0.034**	**1.572 (1.036–2.387)**	**0.034**
C/C-G/A	9	0.029	14	0.049	1.715 (0.730–4.024)	0.216	1.714 (0.730–4.023)	0.216
C/C-A/A	0	-	2	0.007	–	–	–	–
C/T-G/G	152	0.489	122	0.424	0.769 (0.557–1.061)	0.110	0.769 (0.557–1.062)	0.110
C/T-G/A	13	0.042	14	0.049	1.171 (0.541–2.536)	0.688	1.167 (0.5358–2.534)	0.696

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
C/T-A/A	1	0.003	0	–	–	–	–	–
T/T-G/G	75	0.241	59	0.205	0.811 (0.551–1.193)	0.287	0.811 (0.551–1.196)	0.291
T/T-G/A	14	0.045	14	0.049	1.084 (0.508–2.315)	0.835	1.081 (0.505–2.311)	0.841
T/T-A/A	0	–	0	–	–	–	–	–
c.*50C>T – *LIG3* (rs1052536) and c.1196A>G – *XRCC1* (rs25487)								
C/C-C/C	23	0.074	32	0.111	1.565 (0.893–2.745)	0.118	1.565 (0.893–2.745)	0.118
C/C-C/T	25	0.080	37	0.128	1.686 (0.988–2.879)	0.056	1.686 (0.988–2.879)	0.056
C/C-T/T	8	0.026	10	0.035	1.362 (0.530–3.501)	0.521	1.361 (0.530–3.498)	0.522
C/T-C/C	65	0.209	46	0.160	0.719 (0.474–1.092)	0.122	0.715 (0.470–1.087)	0.117
C/T-C/T	74	0.238	72	0.250	1.068 (0.735–1.550)	0.731	1.069 (0.736–1.553)	0.726
C/T-T/T	27	0.087	18	0.063	0.701 (0.378–1.303)	0.261	0.702 (0.378–1.303)	0.262
T/T-C/C	42	0.135	30	0.104	0.745 (0.452–1.226)	0.247	0.745 (0.453–1.228)	0.249
T/T-C/T	39	0.125	36	0.125	0.996 (0.614–1.617)	0.988	0.996 (0.614–1.617)	0.987
T/T-T/T	8	0.026	7	0.024	0.944 (0.338–2.636)	0.912	0.947 (0.339–2.651)	0.918
c.*50C>T – *LIG3* (rs1052536) and c.2285T>C – *PARP1* (rs1136410)								
C/C-A/A	39	0.125	57	0.198	**1.721 (1.105–2.681)**	**0.016**	**1.720 (1.104–2.681)**	**0.017**
C/C-A/G	17	0.055	17	0.059	1.085 (0.543–2.168)	0.818	1.086 (0.543–2.170)	0.815
C/C-G/G	0	-	5	0.017	–	–	–	–
C/T-A/A	108	0.347	89	0.309	0.841 (0.597–1.183)	0.320	0.839 (0.595–1.181)	0.314
C/T-A/G	52	0.167	40	0.139	0.803 (0.514–1.257)	0.338	0.804 (0.514–1.259)	0.341
C/T-G/G	6	0.019	7	0.024	1.266 (0.421–3.813)	0.675	1.263 (0.419–3.807)	0.678
T/T-A/A	54	0.174	45	0.156	0.881 (0.572–1.359)	0.567	0.882 (0.572–1.360)	0.570
T/T-A/G	34	0.109	25	0.087	0.774 (0.450–1.333)	0.356	0.775 (0.450–1.335)	0.359
T/T-G/G	1	0.003	3	0.010	3.263 (0.338–31.550)	0.307	3.250 (0.336–31.466)	0.309
c.*50C>T – *LIG3* (rs1052536) and c.-441G>A – *FEN1* (rs174538)								
C/C-A/A	0	–	0	–	–	–	–	–
C/C-A/G	29	0.093	31	0.108	1.173 (0.688–2.000)	0.558	1.172 (0.687–1.999)	0.559
C/C-G/G	27	0.087	48	0.167	***2.104 (1.274–3.475)***	***0.004***	***2.104 (1.274–3.475)***	***0.004***
C/T-A/A	0	–	0	–	–	–	–	–
C/T-A/G	86	0.277	58	0.201	**0.660 (0.451–0.965)**	**0.032**	**0.658 (0.449–0.963)**	**0.031**
C/T-G/G	80	0.257	78	0.271	1.072 (0.746–1.543)	0.706	1.073 (0.746–1.544)	0.704
T/T-A/A	0	-	0	-	–	–	–	–
T/T-A/G	36	0.116	30	0.104	0.888 (0.532–1.484)	0.651	0.890 (0.532–1.489)	0.658
T/T-G/G	53	0.170	43	0.149	0.854 (0.551–1.325)	0.482	0.854 (0.551–1.324)	0.481
c.*83A>C – *LIG3* (rs4796030) and c.580C>T – *XRCC1* (rs1799782)								
A/A-G/G	25	0.080	43	0.149	***2.008 (1.192–3.383)***	***0.009***	***2.015 (1.195–3.398)***	***0.009***
A/A-G/A	6	0.019	9	0.031	1.640 (0.576–4.666)	0.354	1.637 (0.575–4.660)	0.356
A/A-A/A	0	–	1	0.003	–	–	–	–
A/C-G/G	124	0.399	106	0.368	0.878 (0.631–1.222)	0.441	0.879 (0.632–1.223)	0.444
A/C-G/A	10	0.032	13	0.045	1.423 (0.614–3.297)	0.411	1.423 (0.614–3.297)	0.411
A/C-A/A	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.068 (0.066–14.231)	0.963
C/C-G/G	125	0.402	95	0.330	0.732 (0.524–1.023)	0.068	0.732 (0.524–1.023)	0.068

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
C/C-G/A	20	0.064	20	0.069	1.086 (0.572–2.063)	0.801	1.082 (0.567–2.061)	0.812
C/C-A/A	0	–	0	–	–	–	–	–
c.*83A>C – *LIG3* (rs4796030) and c.1196A>G – *XRCC1* (rs25487)								
A/A-C/C	13	0.042	22	0.076	1.896 (0.937–3.838)	0.075	1.897 (0.937–3.841)	0.075
A/A-C/T	13	0.042	27	0.094	**2.371 (1.199–4.691)**	**0.013**	**2.374 (1.200–4.698)**	**0.013**
A/A-T/T	5	0.016	4	0.014	0.862 (0.229–3.242)	0.826	0.865 (0.230–3.259)	0.831
A/C-C/C	51	0.164	39	0.135	0.798 (0.508–1.254)	0.329	0.796 (0.507–1.252)	0.324
A/C-C/T	59	0.190	63	0.219	1.196 (0.803–1.781)	0.378	1.199 (0.805–1.787)	0.372
A/C-T/T	25	0.080	18	0.063	0.763 (0.407–1.430)	0.398	0.764 (0.407–1.432)	0.401
C/C-C/C	66	0.212	47	0.163	0.724 (0.478–1.095)	0.126	0.723 (0.478–1.095)	0.126
C/C-C/T	66	0.212	55	0.191	0.876 (0.587–1.308)	0.518	0.875 (0.586–1.306)	0.513
C/C-T/T	13	0.042	13	0.045	1.084 (0.494–2.378	0.841	1.082 (0.493–2.375)	0.844
c.*83A>C – *LIG3* (rs4796030) and c.2285T>C – *PARP1* (rs1136410)								
A/A-A/A	19	0.061	37	0.128	***2.265 (1.271–4.039)***	***0.006***	***2.268 (1.272–4.044)***	***0.006***
A/A-A/G	12	0.039	14	0.049	1.273 (0.579–2.800)	0.548	1.275 (0.579–2.805)	0.546
A/A-G/G	0	–	2	0.007	–	–	–	–
A/C-A/A	93	0.299	78	0.271	0.871 (0.610–1.242)	0.445	0.870 (0.610–1.242)	0.443
A/C-A/G	37	0.119	37	0.128	1.092 (0.671–1.776)	0.724	1.097 (0.672–1.789)	0.712
A/C-G/G	5	0.016	5	0.017	1.081 (0.310–3.774)	0.902	1.079 (0.309–3.768)	0.905
C/C-A/A	89	0.286	76	0.264	0.894 (0.624–1.281)	0.542	0.893 (0.623–1.279)	0.536
C/C-A/G	54	0.174	31	0.108	**0.574 (0.357–0.922)**	**0.022**	**0.574 (0.357–0.922)**	**0.022**
C/C-G/G	2	0.006	8	0.028	4.414 (0.930–20.963)	0.062	4.408 (0.928–20.939)	0.062
c.*83A>C – *LIG3* (rs4796030) and c.-441G>A – *FEN1* (rs174538)								
A/A-A/A	0	–	0	–	–	–	–	–
A/A-A/G	18	0.058	18	0.063	1.085 (0.553–2.129)	0.812	1.089 (0.554–2.139)	0.805
A/A-G/G	13	0.042	35	0.122	***3.171 (1.642–6.125)***	***< 0.001***	***3.171 (1.642–6.124)***	***<0.001***
A/C-A/A	0	–	0	–	–	–	–	–
A/C-A/G	71	0.228	49	0.170	0.693 (0.462–1.040)	0.076	0.692 (0.461–1.039)	0.076
A/C-G/G	64	0.206	71	0.247	1.263 (0.860–1.854)	0.234	1.266 (0.862–1.860)	0.229
C/C-A/A	0	–	0	-	–	–	–	–
C/C-A/G	62	0.199	52	0.181	0.885 (0.588–1.332)	0.558	0.884 (0.587–1.331)	0.555
C/C-G/G	83	0.267	63	0.219	0.769 (0.528–1.120)	0.171	0.768 (0.527–1.119)	0.169
c.580C>T – *XRCC1* (rs1799782) and c.2285T>C – *PARP1* (rs1136410)								
G/G-A/A	178	0.572	160	0.556	0.934 (0.676–1.290)	0.679	0.934 (0.676–1.291)	0.679
G/G-A/G	90	0.289	72	0.250	0.819 (0.570–1.176)	0.279	0.819 (0.570–1.178)	0.282
G/G-G/G	6	0.019	12	0.042	2.210 (0.818–5.968)	0.118	2.208 (0.818–5.964)	0.118
G/A-A/A	22	0.071	30	0.104	1.527 (0.859–2.715)	0.149	1.528 (0.857–2.727)	0.151
G/A-A/G	13	0.042	10	0.035	0.825 (0.356–1.911)	0.653	0.825 (0.356–1.912)	0.654
G/A-G/G	1	0.003	2	0.007	2.168 (0.196–24.036)	0.528	2.161 (0.195–23.970)	0.530
A/A-A/A	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.068 (0.066–17.231)	0.963
A/A-A/G	0	–	0	–	–	–	–	–
A/A-G/G	0	–	1	0.003	–	–	–	–

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Combined genotype	Control (n=311)		Depression (n=288)		Crude OR (95% CI)	*p*	Adjusted OR* (95% CI)	*p*
	Number	Frequency	Number	Frequency				
c.580C>T – *XRCC1* (rs1799782) and c.-441G>A – *FEN1* (rs174538)								
G/G-A/A	0	–	0	–	–	–	–	–
G/G-A/G	135	0.434	101	0.351	**0.704 (0.506–0.979)**	**0.037**	**0.704 (0.506–0.979)**	**0.037**
G/G-G/G	139	0.447	143	0.497	1.220 (0.885–1.683)	0.225	1.224 (0.887–1.689)	0.219
G/A-A/A	0	–	0	–	–	–	–	–
G/A-A/G	16	0.051	17	0.059	1.157 (0.573–2.335)	0.685	1.156 (0.573–2.334)	0.685
G/A-G/G	20	0.064	25	0.087	1.383 (0.751–2.548)	0.298	1.382 (0.747–2.556)	0.303
A/A-A/A	0	-	0	-	–	–	–	–
A/A-A/G	0	-	1	0.003	–	–	–	–
A/A-G/G	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.080 (0.067–17.354)	0.956
c.1196A>G – *XRCC1* (rs25487) and c.2285T>C – *PARP1* (rs1136410)								
C/C-A/A	84	0.270	77	0.267	0.986 (0.687–1.416)	0.940	0.984 (0.685–1.414)	0.930
C/C-A/G	43	0.138	27	0.094	0.645 (0.387–1.074)	0.092	0.645 (0.387–1.075)	0.093
C/C-G/G	3	0.010	4	0.014	1.446 (0.321–6.517)	0.631	1.449 (0.321–6.532)	0.629
C/T-A/A	88	0.283	90	0.313	1.152 (0.811–1.636)	0.429	1.152 (0.811–1.636)	0.429
C/T-A/G	47	0.151	45	0.156	1.040 (0.667–1.622)	0.862	1.042 (0.668–1.625)	0.858
C/T-G/G	3	0.010	10	0.035	**3.693 (1.006–13.556)**	**0.049**	**3.691 (1.006–13.549)**	**0.049**
T/T-A/A	29	0.093	24	0.083	0.884 (0.502–1.557)	0.670	0.884 (0.502–1.557)	0.670
T/T-A/G	13	0.042	10	0.035	0.825 (0.356–1.911)	0.653	0.827 (0.356–1.920)	0.659
T/T-G/G	1	0.003	1	0.003	1.080 (0.067–17.349)	0.957	1.068 (0.066–17.231)	0.963
c.1196A>G – *XRCC1* (rs25487) and c.-441G>A – *FEN1* (rs174538)								
C/C-A/A	0	–	0	–	–	–	–	–
C/C-A/G	66	0.212	48	0.167	0.742 (0.492–1.121)	0.157	0.739 (0.489–1.118)	0.152
C/C-G/G	64	0.206	60	0.208	1.016 (0.684–1.508)	0.939	1.016 (0.684–1.509)	0.937
C/T-A/A	0	–	0	–	–	–	–	–
C/T-A/G	59	0.190	57	0.198	1.054 (0.703–1.581)	0.800	1.055 (0.703–1.583)	0.795
C/T-G/G	79	0.254	88	0.306	1.292 (0.903–1.848)	0.160	1.292 (0.904–1.848)	0.160
T/T-A/A	0	–	0	–	–	–	–	–
T/T-A/G	26	0.084	14	0.049	0.560 (0.286–1.095)	0.090	0.561 (0.287–1.097)	0.091
T/T-G/G	17	0.055	21	0.073	1.360 (0.703–2.633)	0.361	1.360 (0.702–2.632)	0.362
c.2285T>C – *PARP1* (rs1136410) and c.-441G>A – *FEN1* (rs174538)								
A/A-A/A	0	–	0	–	–	–	–	–
A/A-A/G	100	0.322	78	0.271	0.784 (0.551–1.115)	0.175	0.782 (0.550–1.113)	0.172
A/A-G/G	101	0.325	113	0.392	1.343 (0.960–1.877)	0.085	1.342 (0.960–1.876)	0.085
A/G-A/A	0	–	0	–	–	–	–	–
A/G-A/G	47	0.151	36	0.125	0.802 (0.503–1.280)	0.356	0.803 (0.503–1.283)	0.359
A/G-G/G	56	0.180	46	0.160	0.866 (0.564–1.328)	0.508	0.866 (0.565–1.329)	0.511
G/G-A/A	0	–	0	–	–	–	–	–
G/G-A/G	4	0.013	5	0.017	1.356 (0.361–5.100)	0.652	1.352 (0.359–5.088)	0.656
G/G-G/G	3	0.010	10	0.035	**3.693 (1.006–13.556)**	**0.049**	**3.699 (1.007–13.578)**	**0.049**

* OR adjusted for sex. $p<0.05$ along with corresponding ORs are in bold; $p<0.012$ along with corresponding ORs are in bold and italic.

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