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Association between single nucleotide polymorphisms of MUTYH, hOGG1 and NEIL1 genes, and depression

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ABSTRACT

Background: An elevated levels oxidative modified DNA bases and a decreased efficiency of oxidative DNA damage repair were found in patients with depression disorders, including recurrent type (rDD). The glycosylases are involved in base excision repair (BER), which eliminates oxidative DNA damage. Therefore, we genotyped the single nucleotide polymorphisms (SNPs) of genes encoding three glycosylases: hOGG1, MUTYH and NEIL1.

Methods: We selected three polymorphisms: c.977C > G – *hOGG1* (rs1052133), c.972G > C – *MUTYH* (rs3219489) and c.*589G > C – *NEIL1* (rs4462560). A total of 555 DNA samples (257 cases and 298 controls) were genotyped using TaqMan probes.

Results: The C/C genotype and allele C of the c.*589G > C decreased the risk of rDD occurrence, while the G/G genotype and allele G of the same SNP increased the risk. This polymorphism had a stronger association with early-onset depression (patients with first episode < 35 years of age) than with late-onset depression (first episode ≥ 35 years of age). We did not find any significant differences in distribution of alleles and genotypes of other SNPs; however, the G/G genotype of the c.972G > C increased the risk of late-onset rDD. We also found that combined genotype C/C–C/C of c.977C > G and c.*589G > C significantly reduced the risk of rDD.

Limitations: Limited sample size and ethnic homogeneity of the studied population.

Conclusion: This is the first study to show that SNPs of genes involved in DNA repair, particularly in BER pathway, may modulate the risk of rDD. These results further support the hypothesis on the involvement of DNA repair mechanisms in pathogenesis of depression.

1. Background

A growing body of evidence indicates that inflammation may play an important role in pathogenesis of depression disorder (including recurrent depressive disorder [rDD]) (Gardner and Boles, 2011). Increased levels of pro-inflammatory cytokines were found in the depressed patients (Maes et al., 1993; Rawdin et al., 2013). Activation of two of those cytokines, interleukin-1b (IL-1β) and interleukin-8, is done by the inflammasome – a complex of proteins containing Nod-like receptor (NLR) – and elevated expression of one of the NLRs – NLRP3 – was detected in peripheral blood mononuclear cells (PBMCs) of depressed patients (Leemans et al., 2011; Alcocer-Gómez et al., 2014).

Abbreviations: RDD, recurrent depression disorder; IL-1β, interleukin-1b; IL-8, interleukin-8; NLR, Nod-like receptor; PBMCs, peripheral blood mononuclear cells; mtROS, mitochondrial reactive oxygen species; 8-oxoG, 8-oxoguanine; SNPs, single nucleotide polymorphisms; hOGG1, human 8-oxoguanien glycosylase 1; MUTYH, MutY E. coli homolog; NEIL1, nei endonuclease VIII-like 1; HDRS, Hamilton Depression Rating Scale; CIDI, Composite International Diagnostic Interview; NCBI dbSNP, National Center for Biotechnology Information the Single Nucleotide Polymorphisms database; RT-PCR, real-time polymerase chain reaction; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval; AP, apurinic/apyrimidinic site; FapyG, 6-diamino-4-hydroxy-5-formamidopyrimidine; FapyA, 4,6-diamino-5-formamidopyrimidine; NTH1, neutral trehalase 1

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It has been suggested that NLRP3 may be involved in DNA damage response (DDR). Its knock-out increased expression of BER and double-strand repair genes, and decreased apoptosis in murine dendritic cells exposed to genotoxic and oxidative stress, thus NLRP3 can suppress DNA damage repair and induce apoptosis mediated by p53 (Licandro et al., 2013). In agreement with this, an elevated level of 8-oxoguanine (8-oxoG), which is a marker of oxidative DNA damage, was found in serum, urine and lymphocytes of the patients with clinical depression as well as depression coexisting with other non-mental diseases (Irie et al., 2001; Forlenza and Miller, 2006; Irie et al., 2003; Maes et al., 2009; Wei et al., 2009; Kupper et al., 2009). On the other hand, urinary levels of 8-oxoG of Japanese office workers were not associated with mild depression symptoms (Yi et al., 2012). Our results obtained by using comet assay showed that PBMCs isolated from patients with rDD had more DNA damage, including oxidative modification of purine and pyrimidines, when compared to PBMCs of the control group (Czarny et al., 2015). Moreover, we also revealed that the patients' cells repair of oxidative DNA damage induced by hydrogen peroxide in less efficient way than the controls' cells.

The impairment of DNA base excision repair (BER) pathway, which is responsible for repair of oxidative DNA damage, might be associated with pathological neurophysiology of depression. Therefore, in this paper we examine the relationship between single nucleotide polymorphisms (SNPs) of glycosylases involved in BER: c.977C > G (rs1052133) of *hOGG1* (human 8-oxoguanien glycosylase 1), c.972G > C (rs3219489) of *MUTYH* (MutY *E. coli* homolog, encoding MUTYH protein), c.*589G > C (rs4462560) of *NEIL1* (nei endonuclease VIII-like 1) and incidence of depression, as well as age at which the first episode occurred.

2. Methods

2.1. Study subjects and data collection

The study was carried out in a group of 555 subjects: patients with rDD ($n=257$, age 51.9 ± 12.9) and a matched group of healthy controls ($n=298$, age 49.1 ± 10.4).

All patients were hospitalized at the Department of Adult Psychiatry of the Medical University of Lodz, Poland. The selection of individuals for the study group was performed randomly without replacement sampling.

The patients were selected based on the inclusion criteria for ED and rDD outlined in ICD-10 (F32.0-7.32.2, F33.0-F33.8) (World Health Organization, 1992). The presence of axes I and II disorders, other than depressive episodes, and the diagnosis of somatic diseases and injuries of the central nervous system were regarded as exclusion criteria. Other exclusion criteria included: inflammatory or autoimmune disorders and unwillingness to give informed consent. For all the subjects, a case history was obtained prior to participation using the standardized Composite International Diagnostic Interview (CIDI) (Patten, 1997).

All the subjects were free from medical illnesses, including infectious and inflammatory or allergic reactions. None of the control subjects or depressed patients was treated with drugs known to influence lipid metabolism, immune response or endocrine function. None of the participants were drinkers or heavy smokers, and none had ever taken psychotropic drugs.

An informed, written consent for participation in the study was obtained from each subject, according to the protocol approved by the Bioethics Committee of the Medical University of Lodz (No. RNN/70/14/KE).

2.2. Selection of single-nucleotide polymorphisms

To choose the SNPs we used the public domain of National Center for Biotechnology Information the Single Nucleotide Polymorphisms database (NCBI dbSNP) at http://www.ncbi.nlm.nih.gov/snp (Bethesda, MD, USA). We selected polymorphisms that have known distribution in European population, their minor allele frequency is larger than 0.05 (submitter population ID: HapMap-CEU) and are localized either in the coding or regulatory region of the genes: c.977C > G is localized in coding region of *hOGG1* gene and causing serine to cysteine substitution at codon 326 of the protein, c.972G > C is localized in exon of *MUTYH* and causing glutamine to histidine substitution in codon 324, and c.*589G > C is located near 3′ end of *NEIL1*. Another choosing reason

Table 1
Distribution of genotypes and alleles of c.977 C > G, c.972 G > C and c.*589 G > C and the risk of rDD.

Genotype /Allele	Control ($n=298$)		Depression ($n=257$)		Crude OR (95% CI)	p	Adjusted OR*(95% CI)	p
	Number	Frequency	Number	Frequency				
***hOGG1*c.977C > G (rs1052133)**								
C/C	190	0.638	146	0.568	0.748 (0.531–1.052)	0.095	0.744 (0.529–1.048)	0.091
C/G	95	0.319	98	0.381	1.317 (0.928–1.870)	0.123	1.060 (0.758–1.481)	0.120
G/G	13	0.044	13	0.051	1.168 (0.531–2.567)	0.699	1.175 (0.534–2.584)	0.689
$\chi^2=2.795$; $p=0.247$								
C	475	0.797	390	0.759	0.799 (0.600–1.064)	0.124	0.796 (0.597–1.060)	0.119
G	121	0.203	124	0.241	1.252 (0.940–1.667)	0.124	1.257 (0.943–1.675)	0.119
***MUTYH*c.972G > C (rs3219489)**								
C/C	198	0.664	176	0.685	1.097 (0.768–1.567)	0.609	1.098 (0.769–1.568)	0.608
C/G	93	0.312	71	0.276	0.841 (0.583–1.215)	0.357	0.841 (0.583–1.215)	0.356
G/G	7	0.023	10	0.039	1.683 (0.631–4.487)	0.298	1.680 (0.630–4.481)	0.300
$\chi^2=1.986$; $p=0.371$								
C	489	0.820	423	0.823	1.017 (0.746–1.386)	0.914	1.018 (0.747–1.387)	0.911
G	107	0.180	91	0.177	0.983 (0.721–1.340)	0.914	0.983 (0.721–1.339)	0.911
***NEIL1*c.*589G > C (rs4462560)**								
C/C	195	0.654	144	0.560	**0.673 (0.478–0.949)**	**0.024**	**0.669 (0.474–0.944)**	**0.022**
C/G	95	0.319	94	0.344	1.232 (0.867–1.752)	0.245	1.238 (0.870–1,763)	0.235
G/G	8	0.027	19	0.074	**2.894 (1.245–6.728)**	**0.014**	**2.896 (1.246–6.733)**	**0.014**
$\chi^2=9.181$; $\mathbf{p=0.010}$								
C	485	0.814	382	0.743	**0.661 (0.496–0.883)**	**0.005**	**0.658 (0.493–0.879)**	**0.005**
G	111	0.186	132	0.257	**1.512 (1.133–2.017)**	**0.005**	**1.519 (1.137–2.028)**	**0.005**

$p < 0.05$ along with corresponding ORs are in bold.

* OR adjusted for sex.