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Association of the *XRCC1* Arg194Trp and Arg399Gln polymorphisms with depression and hopelessness levels in individuals exposed to sour gas

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ABSTRACT

Some parts of Masjid-i-Sulaiman (MIS; southwest of Iran) are polluted by natural sour gas. Previously it has been shown that among MIS citizens the incidence of suicide attempts and self-burning and the frequency of depression and hopelessness are remarkably high. In order to investigate the association of the *XRCC1* genetic polymorphisms (at codons 194 and 399) with depression and hopelessness levels of participants exposed to sour gas, the present cross-sectional study was carried out on 206 healthy persons living in the contaminated areas of MIS. The genotypes of *XRCC1* were determined using PCR based method. Depression and hopelessness scores were determined using Beck's depression inventory and Beck's hopelessness scale, respectively. The "Arg/Trp + Trp/Trp" genotypes of Arg194Trp polymorphism were positively correlated with hopelessness and depression levels. However there was no statistical association between the genotypes of Arg399Gln polymorphism and the hopelessness and depression levels. Our data indicated that the Trp194-Arg399 haplotype was significantly associated with the higher hopelessness (OR = 3.95, 95% CI = 1.34–11.5, $P = 0.012$) and depression levels (OR = 2.55, 95% CI = 1.15–5.66, $P = 0.021$). The Trp194 *vs* Arg194 allele (OR = 4.49, 95% CI = 1.33–15.1, $P = 0.008$) and the Trp194-Arg399 *vs* Arg194-Arg399 haplotype (OR = 4.66, 95% CI = 1.35–16.1, $P = 0.015$) significantly increased in "hopeless and depressed persons" compared with the "without hopelessness and depression" group. The impact of polymorphisms on the function of XRCC1 deserve more attention and also further studies are required to conclude clinical diagnosis of depressive disorders in polluted areas of MIS and study the adverse effects of H_2S on brain function.

1. Introduction

Masjid-i-Sulaiman (MIS) is a city located in the Khozestan province, southwest of Iran. Several areas of the MIS are polluted by subsurface leakage of natural sour gas containing H_2S. Previously, it has been shown that contamination with sour gas alters several biological aspects of individuals resident in the contaminated areas of MIS (Saadat and Bahaoddini, 2004; Saadat et al., 2002, 2004a). Also the association of genetic variations of glutathione S-transferse M1 (*GSTM1*) and T1 (*GSTT1*) on the observed alterations in MIS has been reported (Saadat, 2004; Saadat et al., 2003, 2004b). Previously, it has been reported that the incidence of self-burning is remarkably high (the highest incidence in the world) among MIS citizens (Saadat et al., 2004c). Also it is show that in MIS the frequencies of depression and hopelessness are very high (Saadat et al., 2006) and the null genotype of *GSTT1* is associated with the depression level (Saadat and Zendeh-Boodi, 2008). Moreover, higher mortality due to psychiatric disorder is reported from MIS (Saadat, 2006).

The imbalance between oxidant and antioxidant levels may play a fundamental role in development of depression (Czarny et al., 2017a). There is a significant association between psychological stress and DNA repair gene expressions (Forsberg et al., 2015; Szebeni et al., 2017). The X-ray repair cross-complementation group 1 (*XRCC1*, OMIM: 194360) plays a central role in the base excision repair (BER) pathway. Although many genetic variations in the *XRCC1* are listed in the Ensembl database, the most comprehensively studied its polymorphisms are Arg194Trp (rs.1799782) and Arg399Gln (rs.25487). There are significant associations between the genetic variations in genes of the DNA repair systems (including the *XRCC1*) and the risk of depressive disorder (Czarny et al., 2015, 2017b; Norjmaa et al., 2016).

Natural sour gas contains a lot of compounds; some of those probably are toxic for brain cells and it may lead to increase depression in persons living in the polluted area. Considering that the XRCC1 is expressed in brain (Yoo et al., 1992; Zhou and Walter, 1995), it may

Abbreviations: BDI, Beck depression inventory; BER, base excision repair; BHS, Beck hopelessness scale; GSTM1, glutathione *S*-transferse M1; GSTs, glutathione *S*-transferases; GSTT1, glutathione *S*-transferse T1; HWE, Hardy-Weinberg equilibrium; MIS, Masjid-i-Sulaiman; XRCC1, X-ray repair cross-complementation group 1

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Table 1
Association between hopelessness levels in persons living in the contaminated areas of MIS and their Arg194Trp and Arg399Gln genetic polymorphisms of *XRCC1*.

Genotypes	Group I	Group II	OR	95%CI OR	P	OR*	95%CI OR	P
Arg194Trp								
Arg/Arg	52	118	1.0	–	–	1.0	–	–
Arg/Trp	4	29	3.19	1.07–9.55	0.038	3.50	1.15–10.6	0.027
Trp/Trp	0	3	–	–	–	–	–	–
Trp/−**	4	32	3.52	1.18–10.4	0.023	3.96	1.31–11.9	0.015
Arg399Gln								
Arg/Arg	23	53	1.0	–	–	1.0	–	–
Arg/Gln	24	70	1.26	0.65–2.48	0.493	1.34	0.67–2.69	0.400
Gln/Gln	9	27	1.30	0.53–3.20	0.565	1.26	0.50–3.20	0.614

Groups I and II have 0–3 and 4–20 scores using the Beck hopelessness scale (BHS), respectively.
* Adjusted OR for age and gender of participants.
** Arg/Trp + Trp/Trp genotypes.

contribute to DNA-damage of neuronal cells (Fujimura et al., 2000; Ghosh et al., 2015) and the rs.1799782 and rs.25487 polymorphisms are associated with alterations in the XRCC1 biological functions (Hanssen-Bauer et al., 2012; Monaco et al., 2007), we hypothesized that variant alleles of the above-mentioned polymorphisms might be associated with depression and hopelessness levels of persons living in the contaminated areas of MIS, as a result, the present study was carried out.

2. Materials and methods

2.1. Participants

The present cross-sectional study was perform on 206 (166 females and 40 males) healthy volunteers' with the mean age of 20.7 ± 7.6 (range 14–49 years). They were from contaminated areas of MIS, named: Posht-e-borj, Bibian, Naphton, Napht-khiz, Siberenj and Nomreh-hasht. Participants belong to an ethnic group (Bakhtiyary, Muslim, and Caucasian). It has been reported that Beck depression inventory (BDI) score correlated with a number of factors (Danielson et al., 2003; Hankin, 2009; Korhonen et al., 2006; Prado et al., 2012). Thus, to rule out the potential confounding effect(s) of these factors, just healthy participants, who had no history of alcohol consumption, diagnosed asthma, cancer, and psychiatric diseases were included. Participants with current illness were excluded. The study was approved by the Ethics Committee of the Shiraz University. We obtained informed consent from each subject before the study.

2.2. Measurements

The 21-item BDI and the 20-item of Beck hopelessness scale (BHS) self-report questionnaires were used. The BDI assesses depressive symptoms in the past week and classified their intensity on a scale from 0 to 3 (total score range 0 to 63) (Beck et al., 1975). In order to increase the statistical power of our analysis the participants were categorized into two groups; groups I and II which have no depressed mood and depressed mood, respectively. For BHS, the total scores range from 0 to 20, and high scores indicate high hopelessness levels (Beck et al., 1974). Here also in order to increase the statistical power of our analysis the participants were categorized into two groups: groups I and II which have no hopelessness at all and hopelessness, respectively.

2.3. DNA extraction and genotyping

Genomic DNA for genotyping analysis was extracted from blood samples. To determine the genotypes of the study polymorphisms of *XRCC1*, PCR-RFLP assay was performed, as described previously (Mohamadynejad and Saadat, 2009). For checking the quality control of genotyping analysis, negative controls were applied in every run to check for contamination and samples with unclear result due to low yield, were reexamined and no discrepancy was revealed upon re-testing of 15% of all samples.

2.4. Statistical analysis

Genetic variations were distributed according to Hardy-Weinberg equilibrium (HWE) assessed by the chi-square test. The relative associations between the genotypes and depression or hopelessness groups were evaluated by odds ratios (ORs) and 95% confidence intervals (CI). SPSS statistical software version 11.5 was used for data analysis. The software SNPAlyze(TM) ver. 6 Standard (Dynacom Co, Ltd. Kanagawa, Japan) was used to assess if the studied polymorphisms of *XRCC1* at 194 and 399 codons are in a status of pair wise linkage disequilibrium. All tests were two-tailed and $P < 0.05$ was consider significant.

3. Results

The *XRCC1* genotypes of our participants according to their depression and hopelessness levels are summarized in Tables 1 and 2. The 399Gln and 194Trp allelic frequencies for the study polymorphisms were 0.4029 and 0.0947, respectively. The observed genotypic frequencies did not show significant difference with the expected values based on the HWE (for the Arg399Gln polymorphism: $\chi^2 = 0.54$, df = 1, $P = 0.458$; for the Arg194Trp polymorphism: $\chi^2 = 0.88$, df = 1, $P = 0.348$). In our samples 42.7% of subjects had no depressed mood (group I). Also 27.2% of subjects had no hopelessness at all (group I).

Statistical analysis revealed that the “Arg/Trp + Trp/Trp” genotypes of the Arg194Trp polymorphism were positively associated with hopelessness (OR = 3.52, 95% CI = 1.18–10.4, $P = 0.023$; Table 1). However there was no statistical association between the genotypes of Arg399Gln polymorphism and the BHS score. Although the levels of the BDI depression scores showed significant association with the Trp/− genotypes of the Arg194Trp polymorphism (OR = 2.60, 95% CI = 1.15–5.86, $P = 0.021$), there was no association between depression levels and the Arg399Gln polymorphism (Table 2). Considering that BDI scores were associated with age and gender of participants (Viinamäki et al., 2004), in next step we tried to adjust the ORs for these factors. After the ORs were adjusted for age and gender of the participants, similar results were observed (Tables 1, 2).

The genetic polymorphisms of the *XRCC1* showed strong linkage disequilibrium ($P < 0.0001$). The haplotypic frequencies of Arg194-Arg399, Arg194-Gln399, Trp194-Arg399, and Trp194-Gln399 were 0.5049, 0.4005, 0.0922 and 0.0024, respectively. The association between the haplotypes of the study polymorphisms and levels of hopelessness and depression were summarized in Tables 3 and 4, respectively. Our data indicated that the Trp194-Arg399 haplotype was positively associated with the higher hopelessness (OR = 3.95, 95%