XRCC4 rs6869366 polymorphism is associated with susceptibility to both nicotine dependence and/or schizophrenia

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Abstract

Background: Oxidative stress induced DNA damage has been assumed to contribute to the etiopathogenesis of schizophrenia (Sch). Smoking prevalence was more common in patients with Sch. The X-ray repair cross-complementation group 4 (*XRCC4*) gene plays an important role in the repair of DNA double-strand breaks. **Objective:** The purpose of this study was to investigate whether *XRCC4* rs6869366 polymorphism has a relationship both in nicotine dependence (ND) and Sch+ND risk. **Methods:** One hundred and four patients with Sch+ND, 133 subjects with ND only and 70 healthy controls were enrolled in the study. *XRCC4* rs6869366 polymorphism was analyzed using PCR-RFLP assay. **Results:** The frequency of *XRCC4* rs6869366 GG genotype was more common in the ND and Sch+ND group than controls (p = 0.001 and p = 0.001, respectively). *XRCC4* rs6869366 TT genotype was lower in both ND and Sch+ND group compared to controls (p = 0.001 and p = 0.001, respectively). Also, *XRCC4* rs6869366 G allele was higher in Sch+ND group than controls (p = 0.001) while *XRCC4* rs6869366 T allele was lower in ND group than healthy controls (p=0.001). *XRCC4* rs6869366 GT genotype was lower in ND group than control group (p = 0.003). **Discussion:** These results suggested that the *XRCC4* rs6869366 polymorphism G related genotype/allele was associated with susceptibility to both ND and Sch+ND in a Turkish population.

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Keywords: DNA repair, Schizophrenia, nicotine dependence, *XRCC4*.

Introduction

Schizophrenia (Sch, OMIM181500), manifested by delusions, hallucinations, altered cognition, emotional reactivity, and disorganized behavior[1], is one of the most debilitating and heterogeneous neuropsychiatric diseases. It occurs in about 1% of the population worldwide. Scientific evidence suggests that environmental factors are not solely accused for the development of this disease, genetic factors also play crucial role in predisposition to Sch. Conventional twin studies and population based family trials have already implicated the heredity in Sch with a frequency exceeding 80% and 60% respectively, establishing genetic traits underlying Sch[2]. Smoking is an important public health problem all around the world, causing death of almost six million people annually. Evidence supports that patients with severe psychiatric disorders tend to suffer from nicotine dependence (ND)[3,4].

Oxidative stress occurs as a result of an abnormal redox regulation in which the intracellular concentrations of reactive oxygen species (ROS), exceed the antioxidant capacity[5]. It is generally assumed that a surplus of ROS is highly toxic and harms cellular elements, such as nucleic acids, proteins and lipids[6]. Oxidative damage leads to DNA base alterations, such as abasic sites, oxidized base modification, deamination, methylation, nucleotide deletion, nucleotide insertion, bulky abducts, single-strand breaks (SSBs), double-strand breaks (DSBs), inter- and intra-strand cross-links (ICLs), and DNA-protein cross-links[7].

In vivo studies have reported that chronic administration of nicotine leads to the instability of pro-oxidant/antioxidant equilibrium in blood cells, blood plasma and tissues of rats[8], while *in vitro* studies showed that nicotine heavily harms DNA and damages the prooxidant/antioxidant equilibrium in lymphocytes[9]. In addition, various experiments have also shown the relation between antioxidant status and symptom severity or psychosis ratings, that may associate the antioxidant defense system defects with Sch pathogenesis[10]. In mammalian cells, numerous predominant DNA repair mechanisms are well analyzed, such as direct repair, base excision repair (BER), nucleotide excision repair (NER), mismatch repair, homologous recombination repair (HR), and non-homologous end-joining repair (NHEJ)[11]. *XRCC4* gene is found on the chromosomal 5q14.2 and it is involved in precise end-joining of blunt DNA double strand breaks (DSBs)[12]. It was reported that genetic polymorphisms in DNA repair genes affect DNA repair ability and result in tendency to various disease types. Therefore, the purpose of this study was to investigate whether there is a relationship between *XRCC4* rs6869366 variant and ND and Sch+ND risk.

Methods

Subjects

The study population involved a total of 104 patients diagnosed with Sch+ND, 133 subjects with ND and age, gender matched 70 healthy individuals as controls. The subjects were selected among the individuals from Bakirkoy Research and Training Hospital for Psychiatry Hospital, Istanbul Turkey and Yedikule Hospital for Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul Turkey. Clinical diagnosis of Sch were made in strict accordance with DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, the fourth edition) based on SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders) by two independent psychiatrists[13]. The average amount of tobacco consumed per day was recorded for each participant. The severity of ND was evaluated by the scores on Heaviness of Smoking Index (HSI) and the Fagerström Test for Nicotine Dependence (FTND). The healthy control subjects were randomly recruited from relatives of patients in the Medicine Department, outpatient clinic, in the

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same hospital. Control subjects had a negative family or past history of any psychiatric disorders and had no family relationship to the present study patients. Informed written consent was obtained from the patients. The patient's information was anonymized before submission. The work was approved by Local Ethics Committee. All the procedures performed in the study were in accordance with the Declaration of Helsinki.

Genotyping

DNA was isolated with high salt DNA extraction method from peripheral blood samples[14]. Genotyping of *XRCC4* rs6869366 variant was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay according to previous paper[15]. The *XRCC4* rs rs6869366 variant was determined using the following primers: 5′-GAT GCG AAC TCA AAG ATA CTG A-3′, 5′-TGT AAA GCC AGT ACT CAA ACT T-3′, 55°C annealing temperature for the PCR reaction. The PCR product was digested with *HincII* enzyme. The digested PCR products were separated on a 2% agarose gel and stained with ethidium bromide for visualization under ultraviolet light (Figure 1). For quality control, the genotyping analysis was done blind as regards participants.

Statistical analysis

The SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL; USA) was used for statistical analyses. The results were statistically analyzed by calculating the odds ratios (OR) and 95% confidence intervals (CI) using the χ^2 test. Differences in *XRCC4* rs6869366 genotype distribution between the patient and control groups were compared with chi-square test and, Fisher's exact test was used when needed. The Hardy-Weinberg Equilibrium (HWE) test was done to examine whether the allele and genotype frequencies in the studied groups remain constant from generation to generation in the absence of other evolutionary influences or not. All *p*-values were two sided, and a *p*-value was regarded as statistically significant when it less than 0.05.

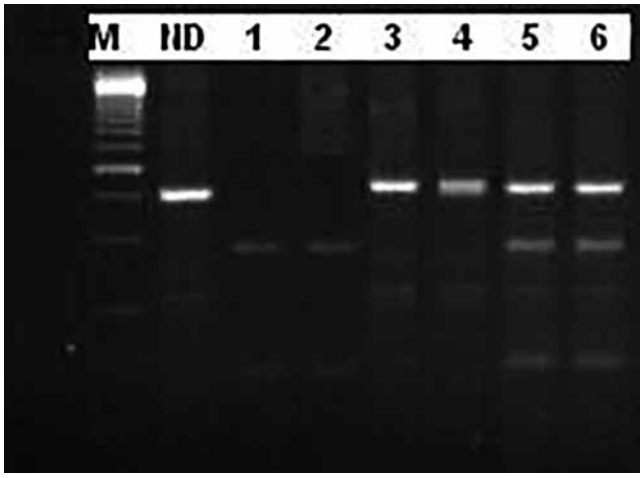

Figure 1. RFLP analysis of PCR products. Lane M: Marker; Lane ND: Non-digest PCR product; Lanes 1 and 2: homozygous TT; Lane 3 and 4: homozygous GG; Lanes 5 and 6: heterozygous GT.

Results

For *XRCC4* rs6869366 variant, 104 Sch+ND patients, 133 subjects with ND and 70 healthy controls were evaluated. The genotype and allele distributions of *XRCC4* rs6869366 among the groups are showed in Table 1. It was found that *XRCC4* rs6869366 TT genotype was significantly lower in Sch+ND and ND group compared to controls (p = 0.001, OR: 28.333, 95% Cl: 6.434–124.762; p = 0.001, OR: 82.884, 95% Cl: 10.936–628.176, respectively). The frequency of *XRCC4* rs6869366 GG genotype was more common in the Sch+ND and ND group than the control group (p = 0.001, OR: 0.112, 95% Cl: 0.056–0.227; p = 0.001, OR: 0.071, 95% Cl: 0.035–0.143, respectively). It was observed that the GT genotype was lower in ND group than the controls (p = 0.003, OR: 0.826, 95% Cl: 1.459–5.474).

Frequency of *XRCC4* rs6869366 G allele was higher in Sch+ND group than healthy control group (p = 0.001, OR: 0.173, 95% Cl: 0.107–0.281) while that of *XRCC4* rs6869366 T alelle was lower in ND group than controls (p = 0.001, OR:0.074, 95%Cl:0.043–0.127).

Discussion

Cigarette smoke contains more than 7000 chemical compounds, along with a high levels of oxidants[16]. Cigarette smoke holds 10^{17} oxidant molecules per puff[17]. Nicotine is the major alkaloid present in cigarettes. It was first obtained as a distillate from tobacco, is detected in the blood of smokers[18]. Nicotine is among the most addicting substances and can induce oxidative stress in quantities similar to those in cigarette smoke, as shown *in vitro* and *in vivo*[19,20]. Chemical carcinogens and ROS can play a role in the accumulation of bulky adducts, SSBs, and DSBs, and several forms of nucleotide base modification or loss which can result in genomic instability.

Sch is a chronic, severe mental illness. The pathogenesis of this disease is unknown, however one generally accepted hypothesis for the etiology is that variations in more than one risk genes, each with a modest additive consequence, interacting with environmental and developmental factors, are involved in appearance of disease phenotype[21]. Between 40 and 90% of schizophrenics smoke. This ratio is remarkably higher than a several comparison populations such as those with other serious mental diseases[22]. Numerous studies have reported various indices of oxidative stress (increased cellular levels of ROS, disturbed antioxidant balance and increased oxidative damage) in blood, cerebrospinal fluid, and post-mortem brains from Sch patients compared with matched normal controls[23]. Further findings supporting a role of redox imbalances and oxidative stress in the

Table 1. Genotypes and allelic frequencies for *XRCC4* rs6869366 polymorphism in Sch+ND, ND and control groups

XRCC4	Sch+ND	ND	Controls	OR*	%95 CI*	p
Genotypes	**n = 104 (%)**	**n = 133 (%)**	**n = 70 (%)**			
TT	2 (1.93)	1 (0.75)	27 (38.58)	28.333[a] 82.884[b]	6.434-124.762[a] 10.936-628.176[b]	0.001[a] 0.001[b]
GT	25 (24.04)	23 (17.29)	26 (37.14)	1.876[a] 2.826[b]	0.964-3.618[a] 1.459-5.474[b]	0.089[a] 0.003[b]
GG	77 (74.03)	109 (81.96)	17 (24.28)	0.112[a] 0.071[b]	0.056-0.227[a] 0.035-0.143[b]	0.001[a] 0.001[b]
Alleles						
T	29 (13.94)	25 (9.39)	80 (57.14)	0.074[b]	0.043-0.127[b]	0.001[b]
G	179 (86.06)	241 (90.61)	60 (42.86)	0.173[a]	0.107-0.281[a]	0.001[a]

Fisher's Exact Test, [a]:Sch + ND versus control group; [b]: ND versus control group.

The results that are statistically significant are shown in *boldface.

development of Sch arise from several animal models, which imply that increased oxidative stress during sensitive windows of brain development and maturation is related to the subsequent occurrence of Sch-linked brain and behavioral abnormalities[24,25]. Brain tissue is particularly vulnerable to oxidative stress because it has a high rate of oxidative metabolic activity, high oxygen consumption, relatively low concentrations of antioxidant enzymes, and a neural network that is vulnerable to damage[26].

The DNA repair system acts as a cellular defense mechanism against DNA damage due to mostly oxidative stress. Altered or deficient bases and SSBs are usually fixed through the BER. There are two major mechanisms for DSBs repair which are called homologous recombination and NHEJ. The NHEJ is the main pathway to repair DSBs in mammals[27]. To evaluate the cellular ability for DNA repair in Sch patients, DNA damage under basal conditions and due to cellular stressors was measured. Flow cytometric analysis of the DNA DSB marker γH2AX in immortalized lymphoblasts from Sch patients showed a significantly increased baseline levels of γH2AX in untreated cells, and a decreased γH2AX response upon irradiation with 5 Gray[28]. In the NHEJ pathway, a relatively small number of essential repair proteins regulate the DSB repair, such as *XRCC4*.

XRCC4 encodes a nuclear phosphoprotein that multimerizes and interacts with DNA Ligase 4 and DNA-dependent protein kinase, involving in the NHEJ pathway[29]. The *XRCC4* is expressed in brain. In mice, lack of *XRCC4* is lethal in embryos leading to a massive neuronal apoptosis, and *XRCC4* has been reported to act with p53 in the regulation of apoptosis, suggesting that *XRCC4* is important for genomic stability and for the inhibition of tumors[30]. In the gene-targeting mutation mice model, *XRCC4* gene inactivation results in late embryonic mortality along with defective lymphogenesis and defective neurogenesis characterized by broad apoptotic death of newly produced postmitotic neurons[31]. These results showed that differentiating lymphocytes and neurons rigorously necessitate the *XRCC4* end-joining proteins. Genome-wide scan showed that 5q14.1 is related with Sch risk, and the gene encoding *XRCC4* is found in this region. Several genetic variants in the *XRCC4* have been reported in humans. One of them is a variable number tandem repeat (VNTR) variant in intron 3 of the *XRCC4* gene. The other, the rs6869366 SNP is found at 1394 bp upstream of the *XRCC4* gene, and is involved in regulating gene expression[32].

It is generally believed that variations of the sequence of the promoter region are linked with a altered level of gene expression. Thus, this type of polymorphism may affect the expression level of the gene. Variants of these specific SNPs might result in an abnormal capacity for protein products, causing several deficiencies. When a DNA repair gene is incapable of normal expression, its downstream genes are directly influenced, leading to the dysfunction of the whole pathway. Therefore, these variants result in a decreased capacity of the repair system and increase the risk of cell pathogeneses.

Considering the higher smoking rates among Sch patients and the close association between nicotine and oxidative stress, and the crucial role of free radicals in the pathophysiology of Sch, we hypothesized that whether *XRCC4* rs6869366 variant is related with both ND group and ND+Sch group in a Turkish cohort. As far as we know, there has been no study conducted about the correlation between *XRCC4* rs6869366 variant and both ND and ND+Sch.

Previously, it was shown that frequencies of *XRCC4* rs6869366 TG+GG genotypes were higher in patients with autism spectrum disorder than the controls[33]. He *et al.* reported that patients who smoked and carried the *XRCC4* rs6869366 G allele had an increased risk for non small cell lung cancer (NSCLC)[34]. In a study conducted on the patients with lung cancer, Hsu *et al.* demonstrated that people with rs 6869366 GT genotype and smoking habit present the highest risk of lung cancer than other groups[35]. However in a study investigating urothelial bladder cancer, Mittal *et al.* found no association between *XRCC4* rs6869366 variant and smoking[36]. We have previously demonstrated that *XRCC4* intron 3 VNTR variant ID genotype was higher in ND group than in healthy control group[37]. In present study, we found that the frequency of *XRCC4* rs6869366 GG genotype and G allele were more common in the both ND group and Sch+ND group than the control group ($p = 0.001$ and $p = 0.001$, respectively). *XRCC4* rs6869366 TT genotype and T allele were significantly lower in ND and Sch+ND group compared to the controls ($p = 0.001$ and $p = 0.001$, respectively). Furthermore, we found that *XRCC4* rs6869366 GT genotype was lower in ND group than control group ($p = 0.003$). The absence of this significance in the Sch+ND group was attributed to heterozygous disadvantage.

In conclusion, for the first time, we showed that *XRCC4* functional rs6869366 variant plays a role in the risk of ND and ND+Sch in a Turkish population. Our results suggested that *XRCC4* rs6869366 GG genotype and G allele might be a susceptibility factor for both ND and Sch+ND. It stresses that this DNA repair mechanism has a role in the etiopathogenesis of Sch and ND, and that further studies in this issue should be done in different populations.

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