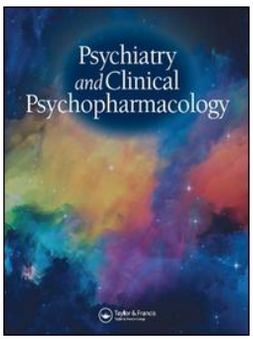

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Possible association between DNA repair gene variants and cannabis dependence in a Turkish cohort: a pilot study

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ABSTRACT

OBJECTIVE: Substance use disorder (SUD) has important effects on health and well-being. It is well known that genetic factors play a role in SUD. The purpose of this research was to investigate whether functional variants of DNA repair genes might be a risk factor for cannabis and/or synthetic cannabis dependence in a Turkish cohort.

METHODS: In total, 131 patients with cannabis and/or synthetic dependence and 70 healthy controls were included in this case–control study. *XRCC1* codon 399 (rs25487) and *XRCC4* G1394 T (rs6869366), and XPD (rs13181) variants were determined by the polymerase chain reaction-restriction fragment length polymorphism assay (PCR-RFLP).

RESULTS: The *XRCC1* rs25487 GG genotype and G allele were significantly lower in patients compared to controls ($p = 0.005$; $p = 0.002$, respectively). *XRCC4* rs6869366 TT genotype and T allele were more common in patients compared to controls ($p = 0.001$, $p = 0.001$, respectively). It was found that patients with *XPD* rs13181 Lys/Gln had a significantly higher risk of cannabis dependence than control did ($p = 0.00$). The subjects carried *XPD* rs13181 Gln/Gln genotype had a 2.2-fold increased risk for cannabis dependence ($p = 0.010$).

CONCLUSIONS: We demonstrated for the first time that DNA repair gene variants may alter individual vulnerability for SUD. This observation could be of further interest to researchers, as it could suggest new candidate genes, presumably crucial for the etiopathogenesis of the cannabis and/or synthetic cannabis dependence.

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Substance use disorder; cannabis; DNA repair; *XRCC1*; *XRCC4*; *XPD*

Introduction

Substance use disorder (SUD) present a worldwide danger to public health and have a severe social and economic effect on individuals and society. Among these substances, cannabis and marijuana are terms related to the plant *Cannabis sativa* and currently are the second most frequently smoked substance following tobacco [1]. This plant contains more than 400 chemical substances, and 60 of them account for its distinctive effect. D-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two main ingredients of the *C. sativa* plant [2]. Nowadays, synthetic cannabinoids (SCs; e.g. Spice in Europe, K2 in the United States and Bonsai or Jamaica in Turkey) are among the most common substances of drug abuse in young adults in Turkey due to its euphoric and addictive effects.

Oxidative stress refers to an imbalance between the generation of free radicals and antioxidant defenses for repair. It has been proposed that oxidative stress plays a role in the pathogenesis of several distinct diseases, and may also be a part of the common pathogenic mechanism in numerous major mental disorders since the brain has relatively more vulnerability to oxidative damage [3]. Numerous studies have searched for the relation between oxidative stress and psychiatric diseases [4,5]; however, few have assessed the possible role of oxidative stress in SUDs. Oxidative stress can induce damage to DNA. Multiple, complementary DNA repair systems have evolved to protect the genome against the harmful effects of DNA lesions [6]. X-ray repair cross-complementing group 1 (*XRCC1*) is one of the essential genes in the base-excision repair pathway, encodes a protein that plays a role in the repair of DNA single-strand breaks [7]. *XRCC4* is found on the chromosomal 5q14.2 and restores DNA double-strand breaks (DSBs) repair. Xeroderma pigmentosum group D (*XPD*, also referred as *ERCC2*) encodes a helicase that is a component of the transcription factor TFIIH. This factor is a key member of the nucleotide-excision repair pathway that accounts for influencing repairs to bulky adducts and UV-induced DNA damage [8]. DNA repair gene changes were shown to result in a decrease in DNA repair capacity. Therefore, we hypothesized that the *XRCC1* Arg399Gln

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(rs25487), and *XRCC4* G1394 T (rs6869366), and XPD (rs13181) variants play a role in SUD. To test this hypothesis, we aimed to investigate whether functional variants of DNA repair gene might be a risk factor for SUD in a Turkish cohort.

Methods

Subjects

This case–control study included 131 patients with cannabis and/or SC dependence (the mean age ± SD: 29.7 ± 7.9 years) and 70 healthy control subjects (the mean age ± SD: 31.01 ± 10.7). The subjects were recruited among the individuals from Bakirkoy Research and Training Hospital for Psychiatry, Istanbul, Turkey, between September 2015 and December 2016. Patients presenting with dependence were screened to determine eligibility for the study. Eligible patients were Turkish in origin, aged between 18 and 65 who regularly consulted in Addictology Departments for dependence. The patients diagnosed with cannabis and/or synthetic cannabis dependence based on DSM-5 criteria, interviewed by two independent psychiatrists. Exclusion criteria were as follows: the existence of axis I and II disorders other than depressive attacks, a diagnosis of severe and chronic somatic illnesses or worsening of symptoms, injuries of the central nervous system, and inflammatory or autoimmune diseases. The control group was recruited randomly from respondents who had no history of psychiatric disease and current psychoactive medications. All subjects signed a written informed consent form. This study protocol was approved by the Local Ethics Committee (Istanbul Medical Faculty/2015-1945), and the experiment was performed in accordance with relevant guidelines and regulations.

Genotyping

A 5-ml venous blood sample was collected in EDTA vacuum tubes. Genomic DNA was extracted from each blood sample using the salting out procedure [9]. Genotyping was performed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method previously described [10]. PCR was performed in a final volume of 25 µl containing 65 mM tris-HCl (pH 8.9), 24 mM $(NH_4)_2SO_4$, 3 mM $MgCl_2$, 0.05% Twin-20, 0.2 mM deoxynucleoside triphosphate solution, 0.3 µM solution of oligonucleotide primers [*XRCC1* Arg399Gln (rs25487): F5′-AGT AGT CTG CTG GCT CTG G-3′, R5′-TCT CCC TTG GTC TCC AAC CT-3′; *XRCC4* G1394 T (rs6869366): F5′-GAT GCG AAC TCA AAG ATA CTG A-3′, R5′-TGT AAA GCC AGT ACT CAA ACT T-3′; 13181:F5′-ATC CTG TCC CTA CTG GCC ATT C-3′, R5′-TGT GGA CGT GAC AGT GAG AAA T-3′; *XPD* (rs13181): F5′-ATC CTG TCC CTA CTG GCC ATT C-3′, R5′-TGT GGA CGT GAC AGT GAG AAA T-3′), 20–100 ng DNA, and 2 U TaqDNA polymerase. PCR was performed using ABI-9600 with initial denaturation at 96°C for 3 min, then 32 cycles at 55°C for rs25487 and rs25487; 60°C for rs13181 and then last cycle at 72°C for 8 min. Genotyping for *XRCC1* (rs25487), *XRCC4* (rs6869366), and *XPD* (rs13181) variants involved digestion of PCR products with *MspI*, *HincII*, and *PstI* restriction endonucleases, respectively, at 37°C for overnight incubation. All of the digestion products were visualized by electrophoresis on a 2% agarose gel. The experimental process was repeated twice for each sample.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) software version 15.0 for Windows (SPSS Inc., Chicago, IL). Mean and standard deviation were used for the presentation of continuous quantitative variables. Frequencies and percentages were used for categorical data. The *XRCC1* rs25487, *XRCC4* rs6869366, and *XPD* 13181 overall genotype distribution were compared by the chi-square (χ^2) test, and the specific genotype and allele distributions were compared by using Fisher's exact test. The odds ratios (ORs) and 95% confidence intervals (CIs) were used to determine the relationships between the *variants* allelic and genotypic variants and their occurrence in the patients. The *XRCC1* rs25487, *XRCC4* rs6869366, and *XPD* 13181 genotype distributions in both the patients and the healthy controls were analysed according to the Hardy–Weinberg equilibrium. *p*-Values smaller than 0.05 were considered significant.

Results

In this study, a total of 131 unrelated Turkish patients with cannabis and/or SC dependence and 70 individuals without any established disease diagnoses were evaluated for the *XRCC1* rs25487/*XRCC4* rs6869366/*XPD* rs13181 variants. The distributions of the genotypes and alleles of the patients and healthy controls for *XRCC1* rs25487/*XRCC4* rs6869366/*XPD rs13181* variants are presented in Tables 1–3.

XRRC1 genotyping

For the *XRRC1* rs25487 variant, the frequencies of the GG, GA, and AA genotypes are 12.9%, 37.4%, and 49.7% in the patients and 30%, 34.3%, and 35.7%, respectively, among the controls; the differences were statistically significant. The *XRCC1* rs25487 GG genotype was significantly decreased in patients than in controls (12.9% versus 30%, $p = 0.005$, OR: 2.874, 95CI%: 1.396–5.915). *XRRC1* rs25487 G allele was

Table 1. Genotype and allele frequencies of *XRCC1* rs25487 variant.

XRCC1	Cannabis dependence group	Control group	OR*	%95 CI*	*p*
Genotypes	*n* = 131 (%)	*n* = 70 (%)			
GG	17 (12.9)	21 (30)	2.874	1.396–5.915	**0.005**
GA	49 (37.4)	24 (34.3)	0.873	0.476–1.603	0.758
AA	65 (49.7)	25 (35.7)	0.564	0.311–1.025	0.074
Alleles					
G	83 (31.8)	66 (47)			
A	179 (68.2)	75 (53)	1.923	1.262–2.933	**0.002**

Note: Fisher's exact test, the results that are statistically significant are shown in boldface.

Table 2. Genotype and allele frequencies of *XRCC4* rs6869366.

XRCC4	Cannabis dependence group	Control group	OR*	%95 CI*	*p*
Genotypes	*n* = 131 (%)	*n* = 70 (%)			
GG	2 (1.5)	17 (24.3)	19.111	4.248–85.885	**0.001**
GT	25 (19.1)	26 (37.1)	2.505	1.306–4.808	**0.007**
TT	104 (79.4)	27 (38.6)	0.179	0.095–0.336	**0.001**
Alleles					
G	29 (11.1)	60 (42.9)			
T	233 (88.9)	80 (57.1)	6.026	3.615–10.044	**0.001**

Note: Fisher's exact test, the results that are statistically significant are shown in boldface.

Table 3. Genotype and allele frequencies of *XPD* 13181 variant.

XPD	Cannabis dependence group	Control group	OR*	%95 CI*	*p*
Genotypes	*n* = 130 (%)	*n* = 70 (%)			
Lys/Lys	16 (12.3)	9 (12)	1.051	0.439–2.519	1.000
Lys/Gln	71 (54.6)	24 (37.1)	0.434	0.237–0.792	**0.007**
Gln/Gln	43 (33.1)	37 (38.6)	2.268	1.252–4.112	**0.010**
Alleles					
Lys	103 (39.6)	42 (30)			
Gln	157 (60.4.9)	98 (70)	0.653	0.421–1.013	0.064

Note: Fisher's exact test, the results that are statistically significant are shown in boldface.

lower in cannabis dependence patients compared to the control group, while *XRRC1* rs25487 A allele was more common in the control group than the patients ($p = 0.002$, OR: 1.923, 95CI%: 1.262–2.933).

XRRC4 *genotyping*

For the *XRCC4* rs6869366 variant, the frequencies of the GG, GT, and TT genotypes are 1.5%, 19.1%, and 79.4% in the patients and 24.3%, 37.1%, and 38.6% among the controls, respectively; these differences were statistically significant. *XRCC4* rs6869366 homozygous wild-type genotype (GG) and heterozygous genotype (GT) were significantly decreased in patients compared to the controls ($p = 0.001$, OR: 19.111, 95CI%: 4.248–85.885; $p = 0.007$, OR: 2.505, 95CI%: 1.306–4.808, respectively). *XRCC4* variant TT genotype was higher in the control group compared to those in the patient group ($p = 0.001$, OR: 0.179, 95CI%: 0.095–0.336). Also, the frequency of the *XRCC4* rs6869366T allele was found to be significantly higher in the control group compared to the patients ($p = 0.001$, OR: 6.026, 95CI%: 3.615–10.044).

XPD *genotyping*

For the *XPD* rs13181 variant, the frequencies of the Lys/Lys, Lys/Gln, and Gln/Gln genotypes are 12.3%, 54.6%, and 33.1% in the patients and 12%, 37.1%, and 38.6%, among the controls, respectively; these differences were statistically significant. We found that the patients with *XPD* rs13181 Lys/Gln ($p = 0.007$, OR: 0.434, 95CI%: 0.237–0.792) and *XPD* rs13181 Gln/Gln ($p = 0.010$, OR: 2.268, 95CI%: 1.252–4.112) genotypes had a significantly higher risk of cannabis and/or SC dependence compared to the controls. No statistically significant association was determined between the allele frequencies of the patients and healthy control groups ($p = 0.064$).

Discussion

SUD is a multifactorial disorder; therefore, genetic interactions with factors including behavioral traits and environmental conditions could be involved in the development of addiction. Environmental factors such as peer pressure, parental monitoring, and the accessibility of a substance play a key role in the initial intention to drink, smoke, or take the substance. Family and twin studies have shown that genetic effects are associated with developing vulnerability to substance abuse [11]. Cannabis has been associated with numerous adverse effects in humans. In animal studies, Wolff et al. showed that THC breaks down complexes I, II, and III of the mitochondrial respiratory chain and mitochondrial coupling. It also enhances free radical

generation in the brain and increases mitochondrial free radical leakage [12]. It was reported that THC induces oxidative stress in several cell lines through the central cannabinoid receptor pathway [13]. Also, it was reported that THC caused important imbalances in oxidative status and increased the levels of oxidative stress-induced lipid peroxidation, protein carbonylation, and DNA damage [14]. Sarafian et al. found that cannabis smoke stimulates the production of reactive oxygen species in human endothelial cells [15]. Bayazit et al. reported that the oxidative balance of individuals with cannabis use disorder was impaired [16]. Furthermore, cannabis has about 50% more carcinogenic polycyclic aromatic hydrocarbons than cigarette smoke, including examples like naphthalene, benz[*a*]anthracene, and benzo[*a*]pyrene [17].

DNA damage can be due to exposure to exogenous DNA damaging agents, including tobacco smoke or UV radiation, endogenous sources like oxidative stress originating from the respiratory chain, or it can be caused by a reduction in the repair of normal levels of DNA damage that invariably occurs in our genomes [18]. Failure in DNA repair is another mechanism that can induce DNA damage in general, and in neurodevelopmental disorders. Signs of enhanced oxidative stress and oxidative DNA damage have been found in several tissues of patients with schizophrenia. High levels of oxidative stress and oxidative DNA damage were also seen in autism spectrum disorder patients and in animal models relevant to this condition [18]. Besides, multiple evidence support the role of oxidative and nitrosative stress in the pathophysiology of major depression [19]. Therefore, we hypothesized whether DNA repair gene variants may be a risk factor for SUD. To the best of our knowledge, there is no report on the association between *XRCC1* rs25487/*XRCC4* rs6869366/*XPD* rs13181 gene variants and risk of SUD in a Turkish cohort. Our results show a significant association between these variants and risk of cannabis and/or SC dependence.

XRCC1 is a multi-domain protein which has a "scaffold" effect to attract other parts of the DNA base damage repair pathway. *XRCC1* both interacts with other proteins in the repair process and coordinates with various repair proteins to increase the competence of DNA repair [20]. The significance of *XRCC1* in providing genomic stability is implied by a higher frequency of spontaneous chromosome aberrations and deletions in *XRCC1* mutant cells and by embryonic lethality in *XRCC1* knockout mice [21]. Some previous studies have shown that *XRCC1* polymorphisms are linked with various autoimmune diseases, while other reports have reported no such relations [20]. The most common variant leads to the substitution of a glutamine for the normally occurring arginine at amino acid residue 399 [22]. Some studies have demonstrated that the *XRCC1* rs25487 variant modifies XRCC1 protein function and decreases the ability of DNA damage removal following irradiation and exposure to genotoxic compounds more than threefold. The *Gln* allele of this variant was related to increased levels of DNA adducts and glycophorin A variants, increased sister chromatid exchange frequencies, and enhanced sensitivity to ionizing radiation; however, two other studies reported no association between this polymorphism and increased DNA adduct levels [23]. It was reported that biallelic mutations in human *XRCC1* are associated with ocular motor apraxia, axonal neuropathy, and progressive cerebellar ataxia [24]. It has been reported that *XRCC1* rs25487 Gln/Gln and Arg/Gln genotypes were more common in patients with schizophrenia than healthy controls [25,26]. However, Celik et al. and Czarny et al. showed that *XRCC1* rs25487 variant had no significant association with obsessive-compulsive disorder (OCD) and recurrent depressive disorder [27,28]. In the present study, we found that *XRCC1* rs25487 variant GG genotype and G allele were lower frequency in patients with cannabis dependence ($p < 0.05$) (Table 1). *XRCC1* rs25487 G allele may be a protection from dependence.

XRCC4 gene, an essential component of Non-Homologous End-Joining repair pathway, is reported to restore DNA DSBs. Despite numerous studies conducted on *XRCC4* variants and their association with psychiatric diseases, results remain uncertain. We also previously showed that *XRCC4* intron 3 VNTR variant DD genotype was associated with schizophrenia + nicotine dependence [29]. The G1394T variant is located in the promoter region of the *XRCC4* gene, and even the most subtle differences of the promoter region may regulate the biofunction of the gene product by down-regulating its expression. We found that *XRCC4* rs6869366 TT genotype and T allele were higher in patients compared to controls (Table 2). Our results suggest that *XRCC4* promoter −1394T allele might exert a modest positive effect on cannabis dependence risk when two copies of the allele are present. It also provides a valuable insight into the pathogenesis of cannabis and/or SC dependence. We thought this variant may have functional regulatory significance since the nucleotide change from G to T in the promoter region may be susceptible to cannabis and/or SC dependence risk. *XRCC4* rs6869366 G allele may be a protection from dependence.

The *XPD* gene maps to chromosome 19q13.3 and has 22 exons and 21 introns spanning approximately 2.3 kb. Since *XPD* is crucial in the biofunctions of multiple cells and *XPD* mutations have been studied in the pathogenesis of numerous genetic disorders, *XPD* genetic variants may hence be considered as a main genetic susceptibility factor [30]. Some variants in *XPD* gene exons have been described; Lys751Gln variant is one of the most common [31]. The *XPD* Lys751Gln variant is an adenine (A) to cytosine (C) transition, which may

lead to modify from lysine to glutamine in exon 23 of the *XPD* gene. This variant may generate the most relevant alteration in *XPD* function and influence various protein interactions, decrease the activity of TFIIH complexes, affect DNA repair capacity and change the genetic susceptibility to diseases. People with *XPD* 751Gln/Gln have been shown to manifest suboptimal DNA repair capacity to remove UV photoproducts when compared to the *XPD* 751Lys/Lys and Lys/Gln genotypes [8]. Odemis et al. and Celik et al. found that XPD Lys751Gln variant Lys/Lys genotype frequency was increased in patients with schizophrenia and in OCD comparison to controls [26,27]. In the present study, we showed that Gln/Gln genotype was higher in subjects with cannabis and/or synthetic cannabis dependence than in healthy controls. The subjects carrying this genotype had a 2.2-fold increased risk for SUD. Because the *XPD* Lys751Gln variant Gln/Gln genotype reflects insufficient DNA repair, the result emphasizes the importance of DNA repair capacity in SUD.

The limitations of this research study should also be noted. First, we focused on only three variants involved in the DNA repair pathway, other regulatory variants in the DNA repair signalling pathway may also contribute to the pathogenesis of SUD. Second, owing to the relatively small sample size, the frequencies of some homozygous variants were low in groups and therefore reduced the statistical power. Finally, lack of assessment of expression levels of these proteins is also a limitation of this study.

In summary, we demonstrated for the first time a significant association between DNA repair gene functional variants and SUD. Although the size of the investigated sample is small, these original results are promising and could lead to a new pharmacokinetic hypothesis for SUD. Our results support the hypothesis that the *XRCC1*, *XRCC4*, and *XPD* gene variants are important and independent genetic markers for SUD. Further studies with a larger sample size investigating a wider spectrum of *DNA* repair genes variants are needed to support these results and better clarify its role in the genesis of SUD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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