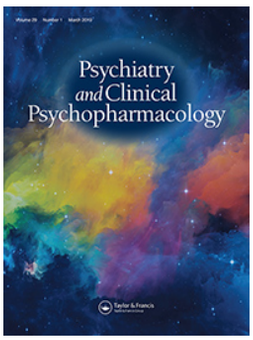

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Association of XRCC1 and XPD functional gene variants with nicotine dependence and/or schizophrenia: a case-control study and in silico analysis

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ABSTRACT

OBJECTIVE: The role of DNA repair mechanisms has received attention recently in schizophrenia (Sch). Sch patients show an increased prevalence of nicotine dependence (ND). This study aimed to find out whether functional SNP variants in the *XRCC1* and the *XPD* play any role both in ND and Sch + ND etiopathogenesis in a Turkish population which was followed up with an in silico analysis approach.

METHODS: *XRCC1* rs25487 and *XPD* rs13181 variants were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). In the prediction of pathogenic effect of rs25487 and rs13181 SNPs, the PANTHER and SNPs&GO programs were used. Also, the protein–protein interaction analysis was performed to retrieve functional partners of the XRCC1 and XPD protein.

RESULTS: *XRRC1* rs25487 GG genotype was significantly lower in both ND and Sch + ND groups than the controls ($p = .001$, $p = .006$) while G allele was lower only in Sch + ND group comparison to controls ($p = .034$). *XPD* rs13181 Lys/Lys genotype was more lower in both Sch + ND and ND groups than in controls ($p = .007$; $p = .001$). XPD rs13181 Gln allele was lower in Sch + ND group compared to controls while Lys allele was higher in ND group than controls, respectively ($p = .034$; $p = .008$). The results of in silico prediction analysis showed that the rs25487 had neutral effect while the rs13181 had a disease-related effect.

CONCLUSIONS: The results of the current study revealed a possible genetic association between *XRCC1/XPD* variants and both in ND and Sch + ND. We think that analysis of this missense SNPs using bioinformatics methods would help diagnosis of *XRCC1* and *XPD*-related diseases.

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Schizophrenia; nicotine dependence; *XRCC1*; *XPD*; DNA repair

Introduction

Schizophrenia (Sch) is a serious and disabling chronic neuropsychiatric illness. It has a high recurrence rate and morbidity [1]. Sch is manifested by cognitive deterioration and disorganized behaviour, which may lead to disability and require highly expensive care. The worldwide prevalence of Sch differs among the countries; the median incidence and the median lifetime morbidity risk of the disease are 15.2/100,000 and 7.2/1000, respectively [2]. Although notable progress in research was achieved on this illness during past decades, many major factors associated with the aetiology and pathophysiology have not yet been clearly established. Nicotine dependence (ND) plays a role in displaying smoking behaviour. Even though the smoking behaviour is influenced by a several genetic and environmental factors, genetic factors are involved in certain aspects of smoking behaviour. The frequency of smoking in patients with Sch was reported to be three to four times higher than the general population [3]. Cigarette smoke has a large amount of carcinogens, such as polycyclic aromatic hydrocarbons, that damage DNA structure by covalent binding or oxidation [4].

DNA damage occurs primarily as oxidative DNA damage and cytogenetic damage. It refers to any alteration in DNA structure which causes changes of its coding features and functions. DNA damage can occur through intracellular and extracellular events following exposure to several exogenous and endogenous factors. Unrepaired damaged DNA accumulates as a result and causes final neuronal loss along with neural impairment [5]. Distinct DNA repair mechanisms keep the unity of the human genome; therefore, loss of repair capacity due to mutations or variations in genes responsible for DNA repair can result in genomic instability.

X-ray repair cross-complementing group 1 (*XRCC1*) gene, found at chromosome 19q13.2, is a

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major component of base excision repair (BER) and is necessary for genetic stability [6]. *Xeroderma pigmentosum* complementation group D (*XPD*) is among the crucial DNA repair genes [7]. This is also called as the excision repair cross-complementing complementation group 2 (*ERCC2*) gene and located in chromosome 19q13.2–13.3 and codes for an evolutionally conserved helicase which plays a key role in transcription and nucleotide excision repair (NER) [7]. Genetic variation in DNA repair genes can have an impact on the activity of DNA repair enzymes, thus modifying the DNA repair ability. This study aimed to find out whether functional SNP variants in the *XRCC1* Arg399Gln (rs25487), *XPD* Lys751Gln (rs13181) variants play any role in both ND and Sch + ND etiopathogenesis in a Turkish population, which was followed up with an in silico analysis approach.

Methods

Study population

This case-control association study investigated *XRCC1* rs25487 variant (140 subjects with ND, 103 patients with Sch + ND, and 70 healthy controls) and *XPD* rs13181 variant (99 subjects with ND, 142 patients with Sch + ND, and 70 healthy controls). The subjects were selected among the individuals from Bakirkoy Research and Training Hospital for Psychiatry, Istanbul Turkey and Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul Turkey. The subjects were recruited among the individuals from Bakirkoy Research and Training Hospital for Psychiatry, Istanbul Turkey between December 2015 and December 2016. Clinical diagnosis of Sch was made according to 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) [8] by a psychiatrist. 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 and the Fagerström Test for ND [9]. The healthy controls were randomly recruited from relatives of other patients in the Internal Medicine Department, outpatient clinic, in the same hospital. Control subjects had no family or past history of any psychiatric disorders and no kinship to the study patients. All subjects signed informed consent. The experimental study was performed in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee (Istanbul Medical Faculty/2015–1945).

Genotyping

Genomic DNA was isolated from blood granulocytes by using standard salting-out procedure [10] and stored at −20°C until being processed with these applications. The *XRCC1* rs25487 and *XPD* rs13181 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay previously described [11]. The *XRCC1* rs25487 variant, a G→A transition in exon 10 (position 28 152) was determined using the following primers: 5′-AGT AGT CTG CTG GCT CTG G-3′ and 5′-TCT CCC TTG GTC TCC AAC CT-3, 55°C annealing temperature for the PCR reaction. The 248 bp PCR product was digested with *Msp*I restriction enzyme. The *XPD* variant was determined using the following primers: 5′-ATC CTG TCC CTA CTG GCC ATT C-3′ and 5′-TGT GGA CGT GAC AGT GAG AAA T-3′. PCR product was digested with *Pst1* restriction enzyme. The digested PCR products were separated on a 2% agarose gel and stained with ethidium bromide for visualization.

The prediction of polymorphisms via bioinformatics algorithms

Human *XRCC1* and *XPD* genes information data were collected from Ensembl release 89 [12], National Centre for Biological Information dbSNP Short Genetic Variations Database [13], 1000 Genomes Browser [14], and NHLBI Exome Sequencing Project Exome Variant Server [15]. The structure of the XRCC1 protein was visualized by the Java Viewer for Chemical Structures in 3D (Jmol) (Figure 1) [16]. To visually reveal structural effects of *XPD* gene SNPs, the web-tool of Radboud University Medical Centre was used. This visualization tool collects structural information from a series of sources, including calculations on the 3D protein structure, sequence annotations in UniProt and predictions from DAS-servers. The tool combines this information for analysing the effect of a certain mutation on the protein structure.

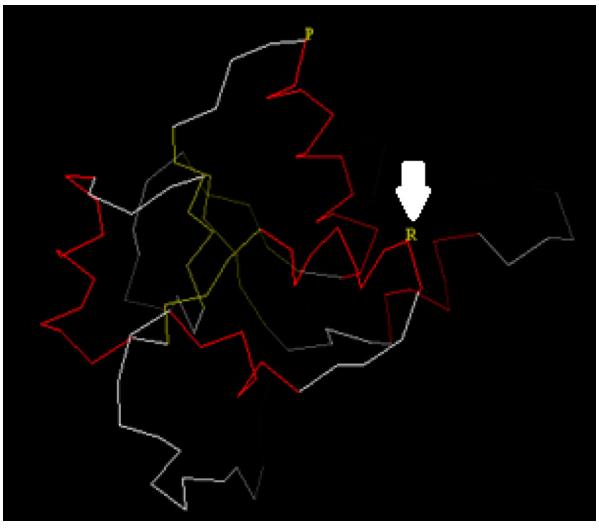

Figure 1. 2d8m structure of XRCC1 protein is visualized with STRAP multiple alignment viewer. Amino acid residue that is changed due to missens mutation is pointed with white arrow.

In the protein–protein interaction analysis, the search tool for the retrieval of interacting genes/proteins online database was used to retrieve functional partners of XRCC1 and XPD proteins. The analyses were performed according to several parameters of the FMR1 protein such as neighbourhood, fusion, and occurrence of co-expression, experiments, database, and text mining. Additionally, predictions with a confidence score higher than 0.9 were included in this study.

The pathogenic and disease-related effects of rs25487 and rs13185 numbered missense SNPs were predicted via six bioinformatics algorithms (SIFT [17], PolyPhen [18], PANTHER [19], PhD-SNP [20], SNPs&GO [21], and I-Mutant2.0 [22]).

Statistical analysis

The SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The results were statistically analysed by calculating the odds ratios (OR) and 95% confidence intervals (CI) using the chi-square (χ^2) test. The genotypes and allele distribution of the *XRCC1* rs25487 and *XPD* rs13181 were compared between patients and controls using chi-square test and Fisher's exact test was used when needed. The Hardy-Weinberg Equation 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 .05.

Results

The genotype distributions of *XRCC1* rs25487 and *XPD* rs13181 polymorphisms among the groups are shown in Tables 1 and 2.

XRRC1 *genotyping*

A significant difference was found between the cases (ND/Sch + ND) and control group as for genotype distribution of *XRRC1* rs25487 variant. *XRRC1* rs25487 GG genotype was significantly lower in cases with ND and Sch + ND groups than the healthy controls, respectively ($p = .001$, OR: 4.187, 95% Cl: 1.946–9.008; $p = .006$, OR: 2.967, 95% Cl: 1.368–6.436).

There was a significant difference between the patients with Sch + ND and the controls with respect to the frequencies of alleles in *XRRC1* rs25487 variant. *XRRC1* rs25487 G allele was lower in Sch + ND group comparison to control group ($p = .034$, OR: 1.625, 95% Cl: 1.049–2.517). The frequency of the A allele was more common in ND group compared to the healthy controls ($p = .008$, OR: 1.793, 95% Cl: 1.185–2.715).

XPD *genotyping*

Genotype and allele frequencies of *XPD* rs13181 variant are shown in Table 2. There was a significant difference for genotype distribution *XPD* rs13181 variant between groups. *XPD* rs13181 homozygous wild-type genotype (AA or Lys/Lys) was more lower in both Sch + ND and ND groups than in controls ($p = .007$, OR: 2.459, 95% Cl: 1.306–4.632; $p = .001$, OR: 2.762, 95% Cl: 1.526–4.999). *XPD* rs13181 Gln/Lys genotype was higher in ND group compared to controls ($p = .009$, OR: 0.453, 95% Cl: 0.250–0.820).

XPD rs13181 variant allele frequency was statistically different among the groups. *XPD* rs13181 Lys allele was lower in ND group compared to controls while Gln allele was higher in Sch + ND group than controls, respectively ($p = .008$, OR: 1.793, 95% Cl: 1.185–2.715; $p = .034$, OR: 0.625, 95% Cl: 1.049–2.517).

No significant enrichment was detected in between XRCC1 and XPD proteins in terms of text mining, experiments, databases, co-expression, neighbourhood, gene fusion, and co-occurrence. Also, in the rs13181 numbered SNP of the *XPD* gene, the mutant residue was bigger than the wild-type residue. The wild-type residue charge was negative and the mutant residue charge was neutral. In the 3D-structure, it could be seen that the wild-type residue was located in its preferred secondary structure, a turn. The mutant residue prefers to be in another secondary structure; therefore, the local conformation would be slightly destabilized

Table 1. Genotype and allele distribution of *XRCC1 rs25487 variant* in Sch + ND, ND, and healthy control groups.

XRCC1	Sch + ND group	ND group	Control group	OR*	95% CI*	*p*
Genotypes	*n* = 103 (%)	*n* = 140 (%)	*n* = 70 (%)			
GG	13 (12.62)	13 (9.28)	21 (30.0)	2.967[a]	1.368–6.436[a]	**.006***[a]
				4.187[b]	1.946–9.008[b]	**.001***[b]
GA	47 (45.63)	68 (48.57)	24 (34.28)	0.622[a]	0.332–1.164[a]	.158[a]
				0.552[b]	0.305–1.001[b]	.056[b]
AA	43 (41.75)	59 (42.15)	25 (35.72)	0.775[a]	0.414–1.450[a]	.525[a]
				0.736[b]	0.422–1.380[b]	.455[b]
Alleles						
G	73 (35.43)	94 (33.58)	66 (46.43)	1.625[a]	1.049–2.517[a]	**.034***[a]
A	133 (64.57)	186 (66.42)	75 (53.57)	1.793[b]	1.185–2.715[b]	**.008***[b]

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.

Table 2. Genotype and allele distributions of *XPD* rs13181*variant* in Sch + ND, ND, and healthy control groups.

XPD	Sch + ND	ND	Controls	OR*	95% CI*	*p*
Genotypes	*n* = 99 (%)	*n* = 142 (%)	*n* = 70 (%)			
Lys/LysAA	31 (31.31)	41 (28.87)	37 (52.85)	2.459[a]	1.306–4.632[a]	**.007***[a]
				2.762[b]	1.526–4.999[b]	**.001***[b]
Gln/LysAC	49 (49.49)	76 (53.52)	24 (34.28)	0.532[a]	0.283–1.001[a]	.059[a]
				0.453[b]	0.250–0.820[b]	**.009***[b]
Gln/GlnCC	19 (19.19)	25 (17.60)	9 (12.85)	0.621[a]	0.263–1.468[a]	.302[a]
				0.690[b]	0.303–1.571[b]	.431[b]
Alelles						
LysA	111 (56.1)	158 (55.6)	74 (70.0)	1.793[b]	1.185–2.715[b]	**.008***[b]
GlnC	87 (43.9)	126 (44.4)	42 (30.0)	0.625[a]	1.049–2.517[a]	**.034***[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.

(Figures 1 and 2). It was found that while rs25487 variant of the *XRCC1* gene had a neutral effect on the protein, *XPD* gene rs13181 variant would have a disease-related effect on the protein (Table 3).

Discussion

In the present study, we aimed at examining the effects of *XRCC1* and *XPD* variants play any role both in ND and/or ND + Sch risk in a sample of the Turkish population. These results showed that these variants may be associated with ND and/or Sch + ND in our population. Tobacco smoking exerts a serious threat to human health. The main alkaloid found in cigarettes is nicotine. Its concentration is about 1–2 mg/ml and is detected in the blood of cigarette smokers [23]. Nicotine accounts for the addictive characteristics of tobacco [24]. Nicotine has been shown to influence numerous biological functions such as gene expression, regulation of hormone secretion and enzyme activities.

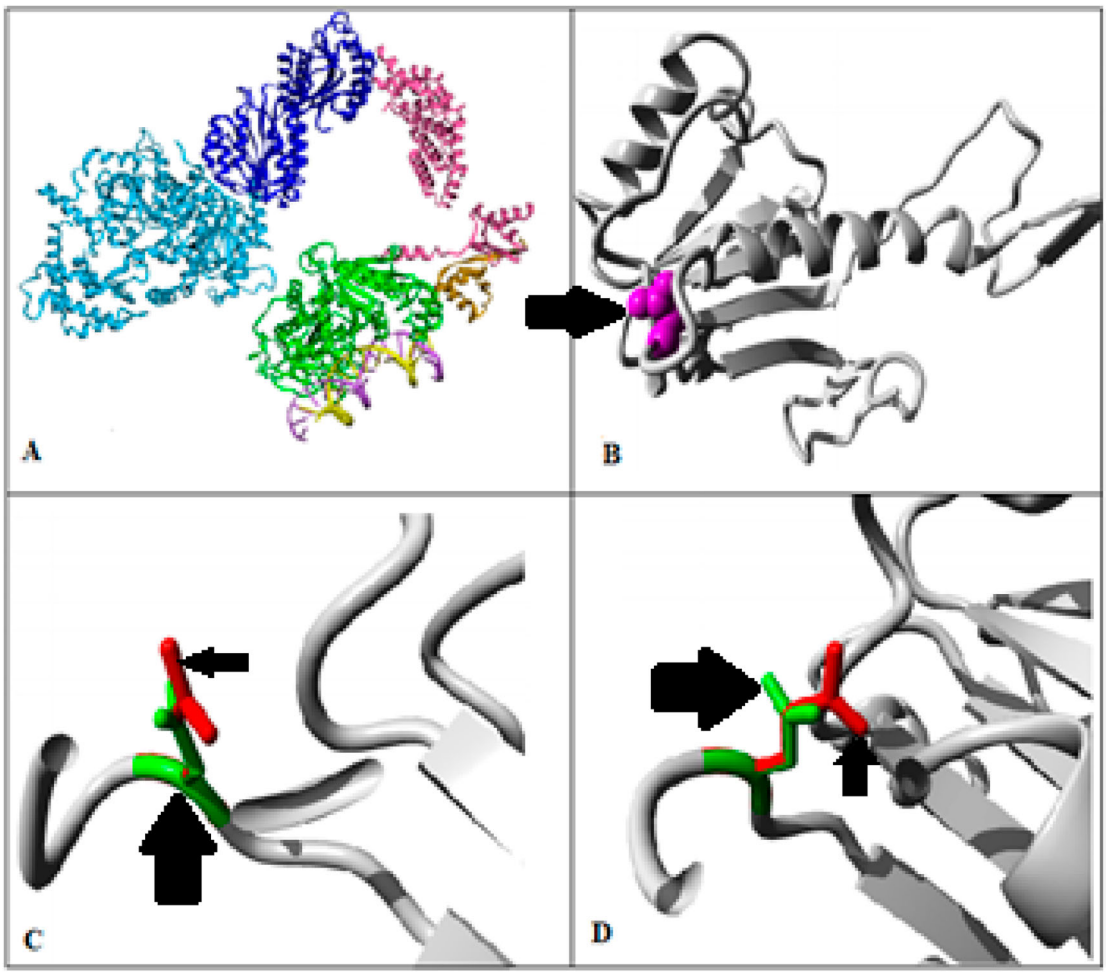

Figure 2. (A) 5ivw structure of XPD protein is visualized with 3Dmol viewer. (B) The XPD protein is coloured grey, the side chain of the mutated residue is pointed with arrow. (C,D) The side chains of both the wild-type and the mutant residue are shown and pointed with thick arrow and thin arrow, respectively. The structural differences are seen between the mutated and wild-type amino acid residues in this figure.

Table 3. Results of the prediction and protein stability analysis methods obtained by analysis of known missense mutations and SNPs of *XRCC1* and *XPD* genes, respectively.

Mutation	Type	AA	SIFT (score)	PolyPhen (score)	PANTHER (score)	PhD-SNP (score)	SNPs&GO (score)	I-Mutant 2.0 protein stability
rs25487	SNP	R399Q	Tolerated (0.6)	Benign (0)	Probably Benign (0.37)	Neutral (0.33)	Neutral (0.11)	Decrease
rs13181	SNP	K673Q	Tolerated (0.6)	Benign (0)	Disease (0.80)	Disease (0.96)	Disease (0.89)	Decrease

Sch is associated with altered neurodevelopmental along with structural and behavioural abnormalities. It has been suggested that these abnormalities could arise from malfunctioning genes and/or non-genetic factors. Patients with Sch are known to exhibit a high prevalence of ND [25]. It has been reported that smoking is an attempt to self-medicate in Sch patients, with regard to reduce extrapyramidal symptoms related with antipsychotic treatment, and relieving cognitive deficits seen with Sch.

Lowered antioxidants and/or high synthesis of reactive oxygen species will lead to oxidative damage of cell lipids, proteins, enzymes, carbohydrates, and DNA structures [26]. Oxidative stress plays an important role in pathophysiology of certain psychiatric disorders. Poor prognosis and progressive course of deterioration occurring in these patients are in part due to oxidative stress [27]. Some studies suggested that changes in Thiobarbituric acid reactive substances, superoxide dismutase and nitric oxide have also been well defined in Sch [28–30].

The DNA damage induced oxidatively occur in apurinic/apyrimidinic DNA sites, oxidized purines and pyrimidines, single strand (SSBs) and double strand DNA breaks. DNA damage accounts for cellular dysfunction and death, carcinogenesis, and the ageing process. The cells in nervous system are very vulnerable to DNA damage, especially compared to other non-replicating cell types. DNA damage can be fixed by various mechanisms and these are essential for the survival. DNA repair mechanisms are involved in sustaining the genomic stability. Disturbances in DNA repair mechanisms can lead to a change in DNA repair capacity of the relevant cell or tissue that might exhibit itself in higher levels of DNA damage. This, in turn, makes cells more vulnerable to progressive DNA damage. This damage has been aetiologically associated with the occurrence of several human disorders. ND also may cause DNA damage in individuals with a decreased capacity of DNA repair. Afflicted DNA damage repair in patients with Sch has been investigated in numerous studies [31,32].

XRCC1 plays a pivotal role in the DNA repair pathway since it could specifically interact with nicked and gapped DNA, promptly and temporarily responds to DNA damage in cells, thereby may act as a strand-break sensor [33]. Furthermore, *XRCC1* could interact with many proteins known to take part in BER and SSBs; so it has been suggested that XRCC1 may act as a scaffold protein able to modulate the steps of several DNA repair pathways [34]. Cells that carry a mutant *XRCC1* gene have a higher sensitivity to ionizing radiation and alkylating agents [35]. XRCC1 codon 399 is found within the BRCT domain (amino acids 301–402) that collaborates with poly (ADP-ribose) polymerase (PARP) [36]. The Arg399Gln variant in exon 10 of the *XRCC1* plays a role in the amino acid substitution (glutamine to arginine). The action of *XRCC1* in BER gathers DNA polymerase, DNA ligase III, and PARP at the site of DNA damage; so the rs25487 variant could have an altered repair activity [36]. Also, this variant may be related with some phenotypic changes, such as elevated sister chromatid exchange, glycophorin A mutations, polyphenol DNA adducts, aflatoxin B1–DNA adducts, and prolonged cell cycle delay [37]. Relation of the *XRCC1* variants with various cancer types and in various populations has been studied [35].

The NER pathway is the main pathway for the elimination of bulky DNA lesions which occur as a result of smoking. The XPD enzyme acts dually in this pathway: (1) uncoiling the double helix at the site of DNA lesions and (2) transcription [38]. Certain SNPs in *XPD* gene exons have been defined, and the most common of these was Lys751Gln polymorphism (rs13181) [7]. *XPD* rs13181 in exon 23, manifested by an A to T substitution, leads to a Lys-to-Gln amino acid exchange in the C-terminal part of the protein. This variant may yield alterations in *XPD* function, may affect DNA repair capacity, and may change genetic susceptibility for some disorders [39]. Numerous epidemiological studies aiming at the identification of the role of *XPD* variants in the risk of several cancers have been conducted and different association between rs13181 variant and the risk of lung cancer, glioma, colorectal cancer, breast cancer, and oesophageal squamous cell carcinoma has been reported [40].

In this study, we performed a case-control trial to investigate the possible relationship between variants in the DNA repair genes (*XRCC1/XPD)* and the risk of both in Sch + ND and/or ND. As aforementioned, impaired functioning of DNA repair genes can result in an accumulation of nonrepaired DNA damage and the occurrence of several pathologic conditions. This is also shown by the functional features of the studied genes. In our multicentre study, we collected the samples both ND and Sch + ND groups. More than

300 validated SNPs in the *XRCC1* gene are reported in the dbSNP database [41]. *XRCC1* rs25487 is among the most extensively studied variants in the *XRCC1* gene. Saadat et al. reported that *XRCC1* rs25487 GG and GT genotype were associated with increased risk for Sch [42]. Recently, a study also revealed that an overwhelming presence of GG genotype and G allele existed in the patients with Sch against the controls in South Indian Population [43]. Odemis et al. showed that the carriers of *XRCC1* G allele were significantly more frequent among the cohort of Sch patients than in controls in Turkish population [44]. In the present study, we found that *XRRC1* rs25487 GG genotype was significantly lower in both Sch + ND and ND groups than the healthy controls ($p < .05$) (Table 1). Besides, we found that the frequency of the G allele was lower in Sch + ND group compared to the healthy controls ($p = 0.034$) while the A allele was more common in ND group compared to the healthy controls ($p = .008$). Our findings are not consistent with those found by Saadat et al., Sujitha et al., and Odemis et al. This could be related with the fact that all patients with Sch were smokers and they were ethnically different.

Stern et al. reported that smokers with the Lys/Lys or Lys/Gln genotypes were twice as likely to have bladder cancer than smokers with the Gln/Gln genotype ($p < .05$) [45]. *XPD* rs13181 Lys/Lys genotype (wild type) was significantly lower in both ND and Sch + ND groups than controls, respectively ($p < .05$) (Table 2). Higher frequency of *XPD* rs13181 Gln/Lys genotype in ND group than in the control group was considered as a heterozygote advantage. Also, *XPD* rs13181 Lys allele was lower in ND group compared to healthy controls ($p < .05$). *XPD* rs13181 Gln allele was more common in Sch + ND group than controls ($p < .05$).

This study has some limitations. One of them is that it only reflects the Turkish population and the results may not be generalized to the global population. Secondly, owing to the relatively small sample size, the frequencies of some homozygous variants were low in groups and therefore reduced the statistical power. Finally, evaluation for Sch subtypes and nicotine consumed per day could not be done. However, strenghts of the study include the fact that it was multi-centred and was supported by bioinformatics methods.

In conclusion, our study is the first report that shows an association between the *XRCC1* rs25487 and *XPD* rs13181 variant both in ND and/or Sch + ND subjects in the Turkish population. Our results imply that variants of DNA repair genes may play a crucial role in the ND and/or Sch. Further studies with larger sample size are needed to confirm these results and establish the clear biological basis of these findings.

Disclosure statement

No potential conflict of interest was reported by the authors.

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