Investigation of DNA repair genes in patients with obsessive-compulsive disorder

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Abstract

Background. Obsessive-compulsive disorder (OCD) is a major psychiatric disorder identified mostly by obsessions and compulsions. Molecular genetic and gene-expression studies focused on familial and twin cases have shown a wide variety of variant genes related to OCD.

Objectives. The aim of the study was to investigate DNA repair genes as potential molecular markers in OCD by evaluating the distribution of polymorphisms of DNA repair genes in OCD patients.

Material and methods. The study included 100 case subjects with OCD and 122 unrelated healthy controls. Genotyping of XRCC1, XRCC3, XPD, XPG, APE1 and HOGG1 was performed by polymerase chain reaction-restriction fragment length polymorphism.

Results. Significant differences were found for XPD and genotype frequencies. Likewise, the frequency of the XPD Lys+ genotype was significantly increased in the patients as compared to the controls, and carriers of the Lys+ genotype had an increased risk for OCD (p = 0.027). The XPD Gln+/Lys genotype frequency was also increased in the patients in comparison to the controls (p < 0.001). XPD Gln+ frequencies were higher in the controls than in the patients, and carriers of the Gln+ genotype showed decreased levels of OCD risk (p < 0.001). XPD Lys+/Lys genotype frequency and XPD Gln+ frequency are also significantly associated even after Bonferroni correction (p < 0.008).

Conclusions. The findings suggest that XPD Lys+/Lys might play a facilitating role in the development of OCD.

Key words: polymorphism, obsessive-compulsive disorder, DNA repair, XPD
Obsessive-compulsive disorder (OCD) is a major psychiatric disorder characterized by obsessive thoughts of an intrusive and disturbing nature, and compulsions – repetitive stereotypic behaviors usually associated with anxiety or dread.1–3

There is considerable evidence suggesting that OCD may have a biological basis. OCD shares similar features with some neurological diseases, such as Huntington's chorea, encephalitis lethargica (von Economo's encephalitis), Parkinson's disease, Tourette syndrome, schizophrenia, Sydenham's chorea, certain epilepsy types and organic brain disorders such as those caused by trauma, ischemia and tumors.4–7

Numerous family studies, segregation analyses, twin and linkage studies have been conducted to understand the genetic and molecular mechanisms of OCD.8–11 These studies have led to a better understanding of the genetic and environmental factors leading to the development of OCD. However, the impact of DNA repair genes on OCD development has not been investigated. DNA damage resulting from alkylation, deamination and oxidative stress is mainly reversed by the base excision repair (BER) pathway to ensure genome integrity. The human oxoguanine glycosylase 1 (HOGG1), AP endonuclease 1 (APE1) and X-ray repair cross-complementing 1 (XRCC1) genes are involved in the BER pathway. HOGG1 is a BER enzyme that recognizes and excises 8-hydroxydeoxygau- nine (8-oxo-dG), whereas APE1 is the rate-limiting en- zyme in the BER pathway.12–15 It cleaves 50 DNA abasic sugar residues generated from ionizing radiation and environmental carcinogens.16–18 The XRCC genes are involved in different DNA repair processes contribut- ing to genetic stability.19,20 XRCC1 acts as a scaffold for other BER enzymes, while XRCC3 encodes RAD-51-like proteins, and is necessary for homologous recombination DNA repair.21

The authors hypothesized that genetic alterations in the components of the DNA repair system could be used as a molecular marker for OCD prognosis. This study was aimed at evaluating the distribution of polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, XPG, APE1 and HOGG1 in OCD patients.

Material and methods

The study population

OCD subjects were diagnosed according to the criteria in the 1994 American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and were recruited at the Psychiatric Department of Istanbul Erenkoy Psychiatric and Neurological Disorders Hospital (Turkey), which has an inpatient ward for acute psychiatric patients. All the patients' medical histories were taken upon their first admission. Assessments for the diagnosis of OCD were performed by 2 psychiatrists using cross-sectional interviews and case records. All the patients had active symptoms at the time of the study. Patients with a history of neurological or medical disorders that would affect neuropsychological function (i.e., seizures, head trauma, stroke, brain tumor, meningitis) or with a recent history of alcohol or psychoactive drug abuse were excluded. A total of 100 OCD patients were included in the study.

Normal control participants were recruited from a large medical outpatient clinic. Their demographic data, medical and psychiatric history were investigated, and subjects with a diagnosis of any DSM-IV axis I or axis II disorders were excluded. None of the control subjects had a history of medical illness, head injury, neurological disorder, psychiatric disorder or alcohol or substance abuse, and none had a family history of any psychiatric disorder. A total of 122 unrelated healthy controls were included the study.

Measurements, protocol and procedure

All the subjects were examined using a standardized interview. Assessments were done on a semi-structured socio-demographic form that required patient information regarding the demographic and personal details of the patients and informants, the patients' complaints, the history of the present illness, details of medical or surgical interventions, past history, family history, premorbid personality, physical examination details, a mental status examination, and a diagnostic formulation. The potential cases were interviewed by a psychiatrist, and their medical records were reviewed whenever relevant. Secondly, a consultant psychiatrist audited the 1st phase results, and confirmed or rejected the diagnosis.

To minimize the effect of ethnic differences in gene frequencies, the study participants were chosen from the Turkish population living in the western region of Turkey. The study was approved by the Medical Ethics Committee of Istanbul Medical Faculty, and all the participants gave written informed consent.

Polymorphism analysis

Blood samples from all the study participants were collected in EDTA-containing tubes. Genomic DNA was extracted from peripheral whole blood using a commercially available kit according to the manufacturer's instructions (PureLink Genomic DNA Mini Kit, Thermo Fisher Scientific Inc., Waltham, USA). Polymerase chain reaction (PCR)/restriction fragment length polymorphism (RFLP) analysis was performed to detect variations in DNA repair genes APE1, HOGG1, XRCC1, XRCC3, XPD and XPG. Appropriate primers were used to amplify the subjects' corresponding gene by PCR, and the reaction products were digested using the appropriate
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The statistical analyses were performed using SPSS software (v. 11.5, SPSS Inc., Chicago, USA). Differences in the distribution of DNA repair genotypes or alleles between the patient group and the control group were tested using the χ² test; the data was expressed as means ± standard deviation (SD). Demographic data was compared using Student’s t-test and the χ² test, as required. Relative risk with 95% confidence intervals (CI) was calculated as the odds ratio (OR). An OR > 1 is associated with higher odds of the outcome; an OR < 1 is associated with lower odds of the outcome; and an OR = 1 does not affect the odds of the outcome.22

In addition to this, minor allele frequency and Hardy-Weinberg equilibrium were calculated by Haplovie 4.2 software (The Broad Institute, Cambridge, USA). Linkage disequilibrium among DNA repair gene polymorphisms was assessed using D’ and r² values obtained through the Haplovie program. Multiple comparisons were controlled using the Bonferroni correction. P-values < 0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of the patient and control groups. The controls and patients were adjusted for age, sex, smoking habit, and alcohol use (p < 0.05).

The distribution of APE1, XRCC1, XRCC3, XPD, XPG and HOGGI genotype frequencies in the OCD patients and controls is shown in Table 2. Significant differences were found only for the XPD Lys751Gln and XRCC3 Thr241Met (p < 0.05) genotype frequencies. As compared to the controls, the OCD patients had statistically higher frequencies of the XRCC3 Thr+ genotype (88% vs 77.1%, p = 0.03, χ² : 4.46, OR: 2.18, 95% CI: 1.04–4.56) and XRCC3 Thr241Met genotype frequency (83% vs 64.8%, p = 0.002, χ² : 9.27, OR: 2.65, 95% CI: 1.40–5.04). Likewise, XPD Lys+ genotype frequency was significantly higher in the patients (95%) than in the controls (86%); and carriers of the Lys+ genotype (p = 0.027, χ²: 4.91, OR: 3.07, 95% CI: 1.09–8.66) had a 3 times higher risk of OCD. Also, Lys/Lys genotype frequency (p = 0.000, χ²:14.72, OR: 2.85, 95% CI: 1.65–4.93) was higher in the patients (60%) than in the controls (34.4%). Although the OCD patients showed trends toward displaying higher frequencies of XRCC1, Thr241Met with 95% confidence intervals (CI) was calculated as the odds ratio (OR). An OR > 1 is associated with higher odds of the outcome; an OR < 1 is associated with lower odds of the outcome; and an OR = 1 does not affect the odds of the outcome.22

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TABLE 3. Minor allele frequencies and the distribution of APE1, XRCC1, XRCC3, XPD, XPG and HOGG1 allele frequencies in the OCD patients and the controls

<table>
<thead>
<tr>
<th>SNP</th>
<th>Rs number</th>
<th>HW p-value</th>
<th>MAF</th>
<th>Associated alleles</th>
<th>Case, control ratios</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ape Asp1104Glu</td>
<td>rs1130409</td>
<td>0.231</td>
<td>0.327</td>
<td>Asp</td>
<td>0.685, 0.664</td>
<td>0.222</td>
<td>0.6377</td>
</tr>
<tr>
<td>XRCC1 Arg399Gln</td>
<td>rs25487</td>
<td>0.806</td>
<td>0.063</td>
<td>Gln</td>
<td>0.085, 0.045</td>
<td>2.964</td>
<td>0.0851</td>
</tr>
<tr>
<td>XRCC3 Thr241Met</td>
<td>rs861539</td>
<td>&lt;0.001</td>
<td>0.455</td>
<td>Thr</td>
<td>0.465, 0.447</td>
<td>0.148</td>
<td>0.7004</td>
</tr>
<tr>
<td>XPD Lys751Gln</td>
<td>rs1052559</td>
<td>0.981</td>
<td>0.32</td>
<td>Lys</td>
<td>0.775, 0.602</td>
<td>15.042</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>XPG Asp1104His</td>
<td>rs17655</td>
<td>0.011</td>
<td>0.311</td>
<td>His</td>
<td>0.360, 0.270</td>
<td>4.111</td>
<td>0.0426</td>
</tr>
<tr>
<td>HOGG1 Ser326Gys</td>
<td>rs1052133</td>
<td>0.004</td>
<td>0.214</td>
<td>Gys</td>
<td>0.220, 0.200</td>
<td>0.079</td>
<td>0.7789</td>
</tr>
</tbody>
</table>

MAF – minor allele frequency; HW – Hardy-Weinberg equilibrium.

TABLE 4. The frequencies of haplotypes of DNA repair genes in the patients and the controls

<table>
<thead>
<tr>
<th>Number of haplotype</th>
<th>Overall Frequency</th>
<th>Patients control</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRCC1 Arg XRCC3 Asp</td>
<td>0.654</td>
<td>0.598</td>
<td>0.701</td>
<td>5.138</td>
</tr>
<tr>
<td>XRCC1 Arg XRCC3 His</td>
<td>0.283</td>
<td>0.317</td>
<td>0.254</td>
<td>2.145</td>
</tr>
<tr>
<td>XRCC1 Gin XRCC3 Asp</td>
<td>0.035</td>
<td>0.042</td>
<td>0.029</td>
<td>0.579</td>
</tr>
<tr>
<td>XRCC1 Gin XRCC3 His</td>
<td>0.028</td>
<td>0.043</td>
<td>0.016</td>
<td>2.839</td>
</tr>
</tbody>
</table>

Discussion

OCD is a widespread psychiatric disorder that is characterized by disabling obsessions and/or compulsions. Originally thought to be rare, OCD is now known to have a lifetime prevalence around 1–3% worldwide, making it one of the most common and serious mental conditions. Although the exact causes of OCD are unknown, data from family studies suggests the presence of a heritable factor, and implies that genetic factors might account for around 50% of OCD symptoms. Moreover, polymorphisms of certain genes have been associated with OCD. The present study attempted to unravel potential association with DNA repair genes and OCD. To the authors’ knowledge, this is the first study focused on the potential contribution of XRCC1, XRCC3, XPD, XPG, APE1 and HOGG1 genotypes to OCD pathogenesis.

The study found that certain XPD gene polymorphisms might have a facilitating or protective role in OCD development. These results not only suggest that DNA repair mechanisms somehow influence the neuronal pathways controlling behaviors, but also lend further support to a biological basis of OCD.

Exposure to certain chemicals such as hydrocarbons, amines and nitrosamines might result in the formation of reactive oxygen species as by-products, which might ultimately affect DNA functions. DNA repair mechanisms are thus of paramount importance in reversing alterations to DNA and providing unmutated DNA during the replication process. More than a hundred genes are known to participate in DNA repair mechanisms. Biological models of OCD propose anomalies in the dopamine and serotonin pathways of the brain. At least in some patients, OCD might plausibly be the end result of mesocortical pathway dysfunction caused by a variety of factors such as trauma, infections and autoimmunity. Increased generation of reactive oxygen species as a result of impaired DNA repair mechanisms might be rendering the dopaminergic mesocortical pathway more susceptible to these environmental factors. Recent findings on the association between DNA repair gene polymorphisms and Parkinson’s disease, which is also related to dopaminergic pathways, support this hypothesis. It is also possible that XPD genes have some yet unknown function in dopamine and/or serotonin metabolism.
According to human brain tissue studies, DNA damage has been found at increasingly high levels in nervous system disorders, adding to the importance of the present study to research investigating OCD mechanisms. It is possible to say that there might be an important relationship between the DNA repair system and neurodegeneration. This area should be investigated further in large-scale studies to focus specifically on identifying which repair system is related to the disease mechanism.

Conclusions

The findings of the current study suggest that certain XPD genotypes are associated with the development of OCD. Further studies with larger sample groups are necessary to clarify the significance of these gene variants. Moreover, the mechanisms by which these genes contribute to OCD pathogenesis need to be clarified.

References


