Is the 5-HT<sub>1D</sub> Receptor Gene Implicated in the Pathogenesis of Obsessive-Compulsive Disorder?

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Objective: Obsessive-compulsive disorder (OCD) is a psychiatric condition for which strong evidence of a genetic component and serotonergic system involvement exists. Recent studies have shown that sumatriptan, a selective ligand of the serotonin (5-HT)1D autoreceptor, modifies OCD symptoms. The aim of this study was to investigate the presence of linkage disequilibrium between the 5-HT<sub>1D</sub> receptor gene, which has a variant caused by a silent G to C substitution at nucleotide 861 of the coding region, and OCD.

Method: DNA was collected from 67 probands who met DSM-IV criteria for OCD and from their living parents or siblings. Transmission Disequilibrium Test/sib-Transmission Disequilibrium Test analyses were then conducted with the DNA data.

Results: Thirty-two families were informative for the analysis, which showed a preferential transmission of the G allele to the affected subjects.

Conclusions: If the results are confirmed, there may be important implications for the 5-HT<sub>1D</sub> receptor gene in the pathogenesis and treatment of OCD.

Obsessive-compulsive disorder (OCD) is a psychiatric condition with a lifetime prevalence of up to 3% (1). The etiology of OCD is unknown, but data from challenge studies (2) and from pharmacological trials (3) have supported the involvement of the serotonergic system. Genetic studies have investigated possible variants of serotonergic system genes: the serotonin (5-HT) receptor gene variants 5-1D and serotonergic system involvement exists. Recent studies have shown that sumatriptan, a selective ligand of the serotonin (5-HT) autoreceptor, modifies OCD symptoms. The aim of this study was to investigate the presence of linkage disequilibrium between the 5-HT<sub>1D</sub> receptor gene, which has a variant caused by a silent G to C substitution at nucleotide 861 of the coding region, and OCD.

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TABLE 1. Linkage Disequilibrium for the G861C Variant of the 5-HT_{1D} Receptor Gene in OCD Probands From 32 Families

<table>
<thead>
<tr>
<th>Allele</th>
<th>Transmission/Disequilibrium Test</th>
<th>Transmissions in Sib</th>
<th>Total Transmissions</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transmissions</td>
<td>Nontransmissions</td>
<td>Transmissions/Disequilibrium Test</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>19</td>
<td>10</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>19</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

* Procedure that determines alleles preferentially transmitted from parents to affected offspring.

** Procedure that compares marker genotypes in affected and unaffected siblings.

* Estimated increase of risk associated with the G variant=5.26 (95% confidence interval=1.92–13.10).

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Discussion

Our results indicate a significant linkage disequilibrium between the G861C variant of the 5-HT_{1D} receptor gene and OCD, with preferential transmission of the G allele to the affected subjects. Despite the fact that the silent G861C variant has been claimed to not directly affect the function of the receptor, there are several other possibilities to explain the role of this polymorphism in the pathogenesis of OCD. First, as it has been hypothesized for other serotonin receptor genes (e.g., 5-HT_{2A}) (13), one of the variants of the G861C polymorphism could induce different mRNA secondary structure, thereby affecting the efficiency of translation. Second, other polymorphisms may exist in the gene that could be in linkage disequilibrium with the G861C variant and be functionally relevant. Further investigations should focus on additional markers in the area and other possible variants of the gene. As seen with other complex disorders, more than one gene is expected to be involved in the etiology of OCD in a model in which each gene per se has a relatively small effect in increasing the risk for the disease. In our case, the estimated increase of risk to develop OCD, as an effect of the presence of the G variant, was equal to 5.26 (Table 1). The possibility that the C variant may play a protective role in the development of OCD is also possible.

The OCD phenotype is heterogeneous, as suggested by the variability in the response to medications in both acute and chronic administrations (2, 14). The investigation of the distribution of this and other 5-HT_{1D} receptor gene polymorphisms in OCD patients designated as responsive versus nonresponsive to medication will be useful.

Finally, even though it is impossible at this time to define more precisely the role of the 5-HT_{1D} receptor gene in OCD, the magnitude of the effect that we observed deserves further investigations. Only a combined strategy, which implies an exhaustive exploration of the OCD phenotype and a more extended knowledge of the genetic complexity of the 5-HT_{1D} gene, will be able to shed light on this potential component of the etiology of OCD.

References


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Supported in part by a grant from the Ontario Mental Health Foundation.