Ser9Gly polymorphism of the DRD3 gene is associated with worse premorbid social functioning and an earlier age of onset in female but not male schizophrenic patients

To the Editors:

Social deficits have been proposed as a core feature of the predisposition to schizophrenia, correlated with the age of onset (Faraone et al., 2001). Although social function is thought to be influenced by genetic factors, the studies in this area are scarce. One of the plausible candidates might be the dopamine D3 receptor (DRD3) gene as suggested by improvement in social interactions by selective DRD3 antagonists (Joyce and Millan, 2005), and its functional polymorphism Ser9Gly (rs 6280) for which an association with social functioning in schizophrenia was found (Lane et al., 2005). The affinity of the receptor for dopamine is significantly higher in the case of genotypes containing the Gly allele (Gly (+) compared with the Ser/Ser genotype (Lundstrom and Turpin, 1996).

The present study addressed a possible association between the above variant and both social functioning in the premorbid period and age of schizophrenia onset. The study group included 72 men and 69 women with schizophrenia (DSM-IV criteria, SCID-I), independently diagnosed by two psychiatrists. The study was approved by the Local Ethics Committee, and informed consent was obtained.

Premorbid social functioning was assessed using a specific scale (Subscale I of the Phillips Scale (Phillips, 1953); a higher score corresponded to poorer functioning. The age of onset was defined by the first appearance of schizophrenia symptoms. To increase reliability, information was collected from the patients and third parties. Variants were analyzed by PCR-RFLP (Lannfelt et al., 1992). The data were analyzed with Statistica 7.0 software (Statsoft).

The polymorphism was in the Hardy–Weinberg equilibrium ($P=0.05$). Significantly lower scores on Subscale I of the Phillips Scale and a later age of onset were seen for the Gly(−) genotype ($Z=−2.12$, $P=0.03$ and $Z=−2.07$, $P=0.04$, respectively); however, these differences were confined to women and absent for men. Women lacking the Gly allele scored lower on Subscale I of the Phillips scale compared with both women with one of the Gly(+) genotypes ($Z=2.63$; $P=0.008$), and men with Gly(+) ($Z=2.64$; $P=0.008$) and Gly(−) ($Z=2.52$; $P=0.01$) genotypes (Supplementary Fig. 1). Similarly, they had a later age of onset than women with one of the Gly(+) genotypes ($Z=−2.07$, $P=0.04$) and men with Gly(+) ($Z=2.48$, $P=0.01$) and Gly(−) genotypes ($Z=3.07$, $P=0.002$) (Supplementary Fig. 2). The results were not significant for the Ser allele. Scores on Subscale I of the Phillips Scale and the age of onset according to the Gly allele status are shown in Table 1. Additionally, a lower level of premorbid functioning was associated with an earlier age of schizophrenia onset ($R^2=−0.31$).

These results are in line with studies in which a decrease in DRD3 sensitivity (corresponding to the absence of glycine) improved social functioning in animals (Joyce and Millan, 2005), and they might point to an impairing influence of glycine in this area. However, this effect was seen only in women. Hypothetically, the findings might reflect, for example, the existence of protective factors specific to women, counteracting to some extent dopaminergic hypertransmission but only in the presence of the Gly(−) genotype, or a reduced penetrance of the Gly(−) allele in women. Limitations need to be considered, especially the group size, further reduced by subdivision by gender.

Appendix A. Supplementary data


References


Table 1

Scores on Subscale I of the Phillips Scale and age of schizophrenia onset in the examined groups of patients according to the presence of the Gly allele of the Ser9Gly polymorphism of the DRD3 gene.

<table>
<thead>
<tr>
<th>Genotype/group</th>
<th>N</th>
<th>Phillips Scale, Subscale I, score (median, min-max)</th>
<th>Age, years (median, min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly (+)</td>
<td>75</td>
<td>15.0 (2.0–30.0)</td>
<td>22.0 (7.0–45.0)</td>
</tr>
<tr>
<td>Gly (−)</td>
<td>62</td>
<td>12.0 (2.0–29.0)</td>
<td>22.0 (13.0–42.0)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly (+)</td>
<td>33</td>
<td>14.0 (2.0–29.0)</td>
<td>22.0 (15.0–29.0)</td>
</tr>
<tr>
<td>Gly (−)</td>
<td>37</td>
<td>13.0 (4.0–29.0)</td>
<td>21.0 (13.0–39.0)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly (+)</td>
<td>42</td>
<td>15.0 (2.0–30.0)</td>
<td>22.0 (7.0–45.0)</td>
</tr>
<tr>
<td>Gly (−)</td>
<td>25</td>
<td>7.0 (2.0–27.0)</td>
<td>27.0 (16.0–42.0)</td>
</tr>
</tbody>
</table>

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