Role of the dopamine D5 receptor (DRD5) as a susceptibility gene for cervical dystonia

F Brancati, E M Valente, M Castori, N Vanacore, M Sessa, G Galardi, A Berardelli, A R Bentivoglio, G Defazio, P Girlanda, G Abbruzzese, A Albanese, B Dallapiccola, and the Italian Movement Disorder Study Group

Cervical dystonia (CD) is one of the most common forms of primary dystonia. The pathogenesis of the disease is still unknown, although evidence suggests a role for genetic factors. Recently, a polymorphism in the dopamine D5 receptor (DRD5) gene has been associated with the disease in a British population, suggesting that DRD5 is a susceptibility gene for CD. To confirm these data, we performed a case-control study of the microsatellite (CT/GT/GA) at the DRD5 locus in 104 Italian CD patients and 104 healthy controls. The frequency of allele 4 was higher in the CD patients compared to the controls. This resulted in a twofold increased risk of developing the disease. These results provide further evidence of an association between DRD5 and cervical dystonia, supporting the involvement of the dopamine pathway in the pathogenesis of CD.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the \( \chi^2 \) test, and odds ratios (OR) with relative 95% confidence intervals (CI). Statistical procedures were performed using the BMDP New System software.

RESULTS

Female to male ratio was 1.08 in both patients and controls. The mean age of cases and controls was 49.6 (14.9) years and 49.5 (15.0) years respectively. The mean age at onset of dystonia was 45.2 (10.7).

Table 1 presents the results of (CT/GT/GA) microsatellite genotyping in patients and controls. A total of 12 alleles were detected for the (CT/GT/GA) microsatellite. A significant association was found for allele 4 (bp 150), more frequent in patients than in control subjects. This resulted in a twofold increased risk of developing the disease (OR 2.44; 95% CI 1.14 to 5.27; \( p = 0.01 \)). Conversely, allele 10 (bp 138) was more common in controls than in patients, but the difference did not reach statistical significance (OR 0.56; 95% CI 0.30 to 1.06; \( p = 0.06 \)).

DISCUSSION

The aim of this study was to evaluate the previously reported association between DRD5 and sporadic adult onset cervical dystonia in an Italian population. In our study, allele 4 was significantly associated with CD, resulting in a twofold increased risk of developing the disease. The frequency distribution of allele 10 in cases and controls suggests a protective
role for this allele, but lack of statistical significance does not allow confirmation of this data. Both susceptibility and protective DRD5 alleles in the present study are different to those described in the British study. This could be explained by the fact that the (CT/GT/GA)n microsatellite is located at 5′ outside the DRD5 coding region, making a functional role for this polymorphism very unlikely. Therefore, we suggest that a functional, still unidentified variant in DRD5, identical in the two populations, could be in linkage disequilibrium with two different (CT/GT/GA)n alleles, depending on the different genetic background of the Italian and British populations.

The DRD5 gene codes for a dopamine receptor included in the D1 super family. The involvement of the dopamine pathway in the pathogenesis of PTD is particularly intriguing. It has been recently suggested that dopamine D1/5 receptors could play a role in the so called indirect pathway of the basal ganglia circuitry. Moreover, DRD5 has been recently associated with blepharospasm, another common form of adult onset focal PTD. Other evidence supports a link between dopamine and dystonia. The protein encoded by the DYT1 gene, torsin A, mutated in early onset generalised PTD, is a member of the AAA+ super family of chaperone proteins and is highly expressed in dopaminergic neurones in human brain. Autosomal dominant dopa responsive dystonia is caused by mutations in the GTP cyclohydrolase I gene, whose protein is involved in dopamine synthesis. Patients affected by Parkinson’s disease, when treated with L-dopa, can develop dystonic dyskinesias, and antipsychotic drugs which inhibit dopamine receptors can produce dystonia.

The multifactorial inheritance of CD has been already suggested, based on the observation of familial clustering. The association between DRD5 and CD in two independent studies hints towards a putative role of DRD5 as a susceptibility gene for primary cervical dystonia. Nevertheless, these results must be interpreted with some caution and further studies are needed to confirm the involvement of DRD5 in CD and other forms of PTD. In particular it would be useful to identify the functional variant, in order to better understand the role of this receptor in the pathogenetic mechanism leading to the disease.

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Table 1  Distribution of the (CT/GT/GA)n microsatellite alleles in 104 sporadic CD patients and 104 matched controls

<table>
<thead>
<tr>
<th>Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (156)</td>
<td>3</td>
<td>1</td>
<td>3.03 (0.24 to 159.8)</td>
<td>–</td>
</tr>
<tr>
<td>2 (154)</td>
<td>3</td>
<td>3</td>
<td>1.00 (0.13 to 7.55)</td>
<td>–</td>
</tr>
<tr>
<td>3 (152)</td>
<td>20</td>
<td>24</td>
<td>0.82 (0.42 to 1.59)</td>
<td>–</td>
</tr>
<tr>
<td>4 (150)</td>
<td>27</td>
<td>12</td>
<td>2.44 (1.14 to 5.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>5 (148)</td>
<td>83</td>
<td>76</td>
<td>1.15 (0.76 to 1.75)</td>
<td>–</td>
</tr>
<tr>
<td>6 (146)</td>
<td>18</td>
<td>9</td>
<td>2.09 (0.87 to 5.18)</td>
<td>–</td>
</tr>
<tr>
<td>7 (144)</td>
<td>6</td>
<td>14</td>
<td>0.57 (0.21 to 2.49)</td>
<td>–</td>
</tr>
<tr>
<td>8 (142)</td>
<td>6</td>
<td>14</td>
<td>0.41 (0.13 to 1.17)</td>
<td>–</td>
</tr>
<tr>
<td>9 (140)</td>
<td>8</td>
<td>15</td>
<td>0.51 (0.19 to 1.33)</td>
<td>–</td>
</tr>
<tr>
<td>10 (138)</td>
<td>20</td>
<td>33</td>
<td>0.56 (0.30 to 1.06)</td>
<td>0.06</td>
</tr>
<tr>
<td>11 (136)</td>
<td>10</td>
<td>5</td>
<td>2.05 (0.62 to 7.77)</td>
<td>–</td>
</tr>
<tr>
<td>12 (134)</td>
<td>4</td>
<td>6</td>
<td>0.66 (0.14 to 2.83)</td>
<td>–</td>
</tr>
</tbody>
</table>

REFERENCES
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