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No TARDBP Mutations in a French Canadian Population of Patients With Parkinson Disease

Parkinson disease (PD) is a neurodegenerative disorder characterized by bradykinesia and at least one of the following primary features: truncal and limb muscle rigidity, resting tremor, and postural instability. Protein aggregates known as Lewy bodies found in dopaminergic neurons of the substantia nigra are deemed to be the major pathological hallmark of this disease. Lewy bodies from several patients with PD have been reported to be positively labeled by an antibody specific to the transactive response (TAR) DNA-binding protein 43 (TDP-43), which is encoded by the TAR DNA-binding protein gene (TARDBP).1 Aggregates positive for TDP-43 were also reported in other neurodegenerative disorders such as frontotemporal dementia, Alzheimer disease, and Lewy body diseases.1 Interestingly, inclusion bodies in a subset of patients with amyotrophic lateral sclerosis (ALS) were also found to be positive for TDP-43.1 Recently, independent studies by our group and others described 15 missense TARDBP mutations in patients with sporadic and familial ALS, further confirming the causative nature of TDP-43 in ALS.2,3 In the present study we sequenced TARDBP in patients with PD to test whether mutations of this gene could also be observed in these patients and consequently be implicated in PD pathogenesis.

Methods. French Canadian patients with PD (n=125) were recruited through 2 designated movement disorder clinics in Quebec City (Quebec, Canada). Every index case was seen by a neurologist (N.D. or E.P.) specialized in movement disorders and met the World Federation of Neurology criteria for PD. Additionally, they had to be dopa-responsive. A detailed standardized clinical assessment form was completed for each subject. All cases signed a consent form approved by local ethics committees prior to being enrolled in the study. Controls (n=360) consist of a group without disease and of similar age and the same ethnicity as the cases.

Cases were all negative for Parkin gene mutations as well as exons 31 and 41 of the LRRK2 gene, which contains a significant proportion of LRRK2 mutations.

On receipt of informed consent, blood samples were obtained from patients and DNA was prepared using standard methods. For each individual, the entire coding sequence (5 exons) of TARDBP (RefSeq NM_007375) was sequenced at the Genome Quebec Innovation Center using a 3730XL DNA analyzer (Applied Biosystems, Foster City, California). Mutation surveyor (v.3.10) was used for mutation detection analyses (SoftGenetics, State College, Pennsylvania).

Results. A summary of the clinical data are presented in the Table. The sequence analysis of all five TARDBP coding exons did not reveal the presence of previously reported or novel mutations, including the C terminus where 14 of 15 of the previously reported mutations of TARDBP in ALS were found.3-5 A variant that encoded for a silent mutation (A66A) of TDP-43 was observed in a single patient with PD. However, this variant was previously reported by us in healthy controls; thus it is likely to be a benign polymorphism.3

Comment. In this study, we evaluated the role of TARDBP in PD pathogenesis by undertaking a sequence analysis of a cohort comprising 125 patients with PD and 360 healthy French Canadian controls. We did not observe

### Table. Characteristics of the PD Population Recruited

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Affected, No. (%) (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>89 (71)</td>
</tr>
<tr>
<td>From Eastern Quebec</td>
<td>125 (100)</td>
</tr>
<tr>
<td>French Canadian</td>
<td>125 (100)</td>
</tr>
<tr>
<td>Juvenile PD (age &lt;40 y)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Family history (first-degree relative)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Positive family history overall</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Average age of onset, y (range)</td>
<td>55.3 (30-79)</td>
</tr>
<tr>
<td>Average duration of symptoms, y</td>
<td>8.0</td>
</tr>
<tr>
<td>Average Hoen &amp; Yahr stage at assessment</td>
<td>1.90</td>
</tr>
</tbody>
</table>

Abbreviation: PD, Parkinson disease.
any evidence that TARDBP is associated with PD. Although the size of the cohort is not sufficient to completely exclude TARDBP as an etiologic cause of PD in French Canadian patients, our data nonetheless indicate that mutations in TARDBP are unlikely to be a common cause of PD in this population. Preliminary studies such as ours in patients with PD and that of a Belgian cohort in patients with frontotemporal dementia have failed to identify TARDBP mutations. These studies suggest that mutations in TARDBP are more strongly associated with ALS than with dementia or movement disorders.

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