THE G209A MUTATION IN THE α-SYNUCLEIN GENE IN BRAZILIAN FAMILIES WITH PARKINSON’S DISEASE

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ABSTRACT - A missense G209A mutation of the alpha-synuclein gene was recently described in a large Contursi kindred with Parkinson’s disease (PD). The objective of this study is to determine if the mutation G209A of the alpha-synuclein gene was present in 10 Brazilian families with PD. PD patients were recruited from movement disorders clinics of Brazil. A family history with two or more affected in relatives was the inclusion criterion for this study. The alpha-synuclein G209A mutation assay was made using polymerase chain reaction and the restriction enzyme Tsp45I. Ten patients from 10 unrelated families were studied. The mean age of PD onset was 42.7 years old. We did not find the G209A mutation in our 10 families with PD. Our results suggest that alpha-synuclein mutation G209A is uncommon in Brazilian PD families.

KEY WORDS: Parkinson’s disease, alpha-synuclein, genetics.

Mutação G209A no gene da alfa-sinucleína em famílias brasileiras com doença de Parkinson


PALAVRAS-CHAVE: doença de Parkinson, alfa-sinucleína, genética molecular.

Parkinson’s Disease (PD) is one of the most common neurodegenerative diseases and its diagnosis is based on the presence of at least two of its cardinal signs: bradikinesia, rigidity, resting tremor, and postural instability. In 1997 Polymeropoulos et al. found a missense G209A mutation in the alpha-synuclein gene in a large family diagnosed with PD from Contursi, Italy and in another 3 Greek families with an autosomal dominant pattern. This point mutation leads to the substitution of alanine by threonine at the 53 position in the aminoacid sequence of the alpha-synuclein (Ala53Thr). Later, Kruger et al. described a second point mutation that leads to the substitution of alanine by proline at the 30 position in the aminoacid sequence. Nevertheless, mutations in the alpha-synuclein gene are a rare cause of PD in families from North America, Europe and China.

In Brazil there are no studies focusing on the mutations of the alpha-synuclein in families with PD and our study’s objective is to determine whether the G209A mutation can be found among 10 Brazilian families with PD.

METHOD

Patients with PD from different Brazilian Movement Disorders study centers were enrolled for the study. Patients were included if there was at least one relative who had been also diagnosed with PD. We studied 10 index patients from 10 different, unrelated Brazilian families. In 4 families the inheritance pattern was clearly autosomal recessive (index-cases 1, 7, 8 and 10) and among the oth-

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ers a clear genetic transmission pattern could not be established. The mean age at onset of symptoms was 42.7 years of age, ranging from 11 to 65 years (Table 1).

DNA from the index cases was extracted from peripheral blood leukocytes at the Laboratório Genética (Dr. Salmo Raskin). Genetic analysis was later performed at the National Human Genome Research Institute, National Institute of Health, Bethesda, MD, USA (Dr. Michael Polymepropoulos), using previously described primers for DNA amplification through polymerase chain reaction. The G209A mutation of the alpha-synuclein gene was detected by using the Tsp451 restriction enzyme, as previously described1.

RESULTS
We could not find the G209A mutation in the exon 4 of the alpha-synuclein gene in the families studied.

DISCUSSION
It has previously been established that a certain percentage of PD has a genetic origin, more so if onset of the disease is before 50 years of age. Mutations of the alpha-synuclein gene at 4q chromosome (PARK7) were reported in families with autosomal dominant inheritance pattern from Italy, Greece and Germany2,3. Other two loci related to autosomal dominant parkinsonism were found at the 2p (PARK3)8 and at the 4p8 chromosomes. In addition, a missense mutation at the ubiquitine carboxi-terminal hydrolase L1 (UCH-L1) gene on chromosome 4p was linked to parkinsonism in one family10. Mutations in another gene for parkinsonism on chromosome 6q, parkin (PARK2), were detected in families that had autosomal recessive juvenile parkinsonism11.

Patients with mutations of the alpha-synuclein gene present with early onset PD (mean age of onset of 46 years, whereas patients with sporadic PD have a mean age of onset of 59.7), a rather fast course from onset to death, a higher incidence of dementia and other signs non-related to parkinsonism (aphasia, myoclonus and palilalia) and a worse response to levodopa therapy than patients with classic PD. Brain pathology is the same in both classic PD and PD related to mutations of the alpha. The G209A mutation in the α-synuclein gene is not detected in familial cases of Parkinson α-synuclein gene, making them indistinguishable on a pathological basis. Both present with neuronal degeneration of the substantia nigra and Lewy bodies12,13.

Alpha-synuclein is a protein that can be found in great amounts in the brain, mainly at the medulla, olfactory tract, hypothalamus and the substantia nigra. Its exact function and its role in the pathogenesis of PD are still unclear. However, immunocytochemical studies have shown that the alpha-synuclein protein is an important component of the Lewy bodies, even in those cases of patients without mutations of the alpha-synuclein gene1.

In order to evaluate the prevalence of familiar PD linked to mutations of the alpha-synuclein gene, Gasser et al. studied 13 families with an autosomal dominant inheritance pattern and excluded, through linkage and sequencing studies, mutations of the

Table 1. Clinical features and family history of patients with PD.

<table>
<thead>
<tr>
<th>Index case</th>
<th>Age and gender</th>
<th>Age of onset</th>
<th>Number of affected relatives</th>
<th>Relationship of affected relatives</th>
<th>H-Y</th>
<th>Ethnic background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64 (F)</td>
<td>58</td>
<td>4</td>
<td>4 sisters</td>
<td>2,5</td>
<td>Italian</td>
</tr>
<tr>
<td>2</td>
<td>66 (M)</td>
<td>56</td>
<td>2</td>
<td>Father</td>
<td>2,5</td>
<td>Italian</td>
</tr>
<tr>
<td>3</td>
<td>46 (M)</td>
<td>38</td>
<td>4</td>
<td>Paternal cousin</td>
<td></td>
<td>Polish</td>
</tr>
<tr>
<td>4</td>
<td>67 (M)</td>
<td>65</td>
<td>2</td>
<td>Father</td>
<td>2</td>
<td>Portuguese</td>
</tr>
<tr>
<td>5</td>
<td>61 (M)</td>
<td>54</td>
<td>1</td>
<td>Father</td>
<td>3</td>
<td>Brazilian</td>
</tr>
<tr>
<td>6</td>
<td>40 (M)</td>
<td>31</td>
<td>1</td>
<td>Mother</td>
<td>3</td>
<td>German</td>
</tr>
<tr>
<td>7</td>
<td>39 (M)</td>
<td>17</td>
<td>2</td>
<td>2 Brothers</td>
<td>2,5</td>
<td>Italian</td>
</tr>
<tr>
<td>8</td>
<td>67 (M)</td>
<td>55</td>
<td>2</td>
<td>Brother</td>
<td>2</td>
<td>Italian</td>
</tr>
<tr>
<td>9</td>
<td>43 (M)</td>
<td>42</td>
<td>1</td>
<td>Maternal uncle</td>
<td>1,5</td>
<td>Italian</td>
</tr>
<tr>
<td>10</td>
<td>31 (F)</td>
<td>11</td>
<td>2</td>
<td>Sister</td>
<td>5</td>
<td>Brazilian</td>
</tr>
</tbody>
</table>

alpha-synuclein gene. Later studies with both familial and sporadic cases of PD, with and without early onset, in many countries of Europe, North America and Asia using different techniques for the detection of point mutations or genetic sequencing could not find any mutation of the alpha-synuclein gene (Table 2).

In spite of the small size of our sample, our results suggest that the G209A mutation is uncommon among Brazilian families with PD, results similar to those found in other countries. Truthfully, in none of the studied families we could establish an autosomal dominant inheritance pattern.

Mutations at the other gene linked to PD, which is located in the 6q chromosome (parkin), were first described in Japan and later in several other countries. Mutations of the parkin gene seem to have a worldwide distribution, whereas alpha-synuclein mutations are restricted to a few European families. Further studies are still necessary to identify the gene or genes that play a role in the etiology of PD in these 10 Brazilian families.

REFERENCES