Abstract

NR4A2 (also known as Nurr1) is a nuclear transcription factor important for the differentiation and survival of midbrain dopaminergic neurons. Recently, it has been reported several mutations in this gene, suggesting that Nurr1 may play a role in the cause and pathogenesis of PD. The genetic study in ethnic Chinese is still lacking. To address this issue, we performed a mutation screen of Nurr1 in 679 PD patients and 889 control subjects in Chinese population, and identified a new single-nucleotide polymorphism (SNP) -35 A-G located in exon2 and two novel nonsense mutations (711C-A and 21 point mutations) in exon2 respectively. The case-control study results suggest that the 711C-A and 21 point mutations are specific for PD while -35 A-G variant in exon2 may protect the carrier from the risk of PD. We identified novel mutations of Nurr1 in ethnic Chinese population for the first time. The exon2 sequence of PD patients carrying the -35 A-G mutation. Analysis of the -35 A-G mutation in exon2 in patients with PD. The panel above showed the DNA sequence of control. The other panel showed the DNA sequence of PD patients carrying the -35 A-G mutation. Arrows showed the position of the mutation.

Objective

To identify whether there is any mutations in NR4A2 gene associated with Parkinson’s disease in ethnic Chinese population.

Background

NR4A2 (Nurr1) encodes a transcription factor regulating the expression of genes including tyrosine hydroxylase and is required for the development of midbrain dopaminergic neurons. NR4A2 gene maps to chromosome Xq22-23 and is about 8.3 kb long and consists of eight exons. Several mutations have been identified in exon2 and exon3, and identified a new single-nucleotide polymorphism (SNP) -35 A-G located in exon2 and two novel nonsense mutations (711C-A and 21 point mutations) in exon2 respectively. The case-control study results suggest that the 711C-A and 21 point mutations are specific for PD while -35 A-G variant in exon2 may protect the carrier from the risk of PD. We identified novel mutations of Nurr1 in ethnic Chinese population for the first time. The genetic study in ethnic Chinese is still lacking.

Materials and Methods

Patients and Controls: In this study, 679 patients with sporadic and familial PD were included. All the ethnic Chinese patients signed an informed consent, which was approved by our three collaborator’s Institutional Review Board for Human Research. Among the research subjects, 689 patients are sporadic PD and 30 patients have at least one relative with PD. The age ranged from 21 to 81 years with a mean of 64.1 ± 10.6 years and the onset of disease ranged from 15 to 78 years with a mean of 61.7 ± 11.8 years. A total of 431 PD patients were men, whereas 268 patients were women. 689 healthy controls with the age, sex, and origins similar to the PD patients were also collected.

Mutational analysis: The designed primers amplifying the whole exon regions of Nurr1 (Bio-Rad Cycler Optical Module). The PCR product was then purified by a purification kit (Sangon, Shanghai, China) and then sequenced using an ABI 3730 automated DNA sequence (Applied Biosystem, Foster city, CA).

Statistical analysis: The software SPSS 13.0 was used for statistical analysis. Data were analyzed by means of the Pearson’s chi-square test. Relative risk for the variants was calculated by the odds ratio (OR) for the disease. Data were expressed as mean ± SEM. Statistical significance was considered at the P < 0.05 level.

Results

Table 1. Association of novel mutation SNP with Parkinson’s disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>N</th>
<th>PD (2010)</th>
<th>Control (2010)</th>
<th>OR</th>
<th>OR (95% CI)</th>
</tr>
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<tr>
<td>SNP1</td>
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<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>SNP2</td>
<td>22</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Conclusions

Our data suggest the notion that Nurr1 mutations are a rare cause of PD in Asian cohort and as well as in Caucasian PD patient, and some other kind of Nurr1 mutation likely displayed protective effect. Identifying the new mutation and greater understanding of the novel mutation will shed light to the study of pathogenesis of PD and help us to develop new strategies against neurodegenerative diseases.

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References