Non-replication of Association between MAPT-SNCA Synergistical Interaction and Susceptibility to Parkinson’s Disease in a Southern European population

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Key words: Parkinson’s disease, MAPT, SNCA, a-synuclein, Case-control study

SUMMARY. The combination of MAPT H1H1 genotype and SNCA (rs356219) GG genotype interaction has recently been identified as a possible factor to approximately double the risk for development of PD. The objective of our study was to test the association of the interaction of these two genetic variants with Parkinson’s disease in a southern European case-control study. We analysed MAPT haplotypes and performed SNP genotyping with Taqman assays for the SNCA rs356219 marker in cohorts of 352 patients and 417 controls of Greek and Italian origin, respectively. Cases (n=352) were more often homozygotes for the MAPT H1 haplotype than controls (n=417). However, the association of the SNCA rs356219 G allele or GG homozygotes with Parkinson’s disease was not confirmed. Furthermore the interaction of the SNCA GG genotype with MAPT H1H1 genotype was not proved to be increased among cases with Parkinson’s disease compared to the controls. The data suggest that increase of PD risk by this specific combination of genotypes is not reproducible to all PD populations.

INTRODUCTION

One of the main neuropathological features of the disease consists of intracellular proteinaceous inclusions called Lewy bodies (1). Aggregation and fibrillation of the α-synuclein protein, which is the main component of Lewy bodies, represent key events in the pathogenesis of PD (2) and the disease is classified as an α-synucleinopathy.

Subsequently, the genetic association between the overall SNCA locus and PD has been examined in order to confine the genetic polymorphisms within the SNCA locus that may be associated with increased levels of a-synuclein protein and affect susceptibility to Parkinson’s disease (PD). To that point, data from many studies add to the accumulating evidence that SNP rs356219 (A/G) in the 3’ region of the SNCA gene confers increased risk to PD (3).

In addition, a disease mechanism based on the protein tau has been proposed in PD (4,5). Tau proteins are a group of phosphorylated neuronal microtubule-associated proteins that bind to microtubules and promote microtubule assembly and stabilization. They are expressed in neurons and they are particularly abundant in axons.[6] Due to the proposed interactions of α-synuclein and tau protein and their abnormal intracellular aggregation in neurodegenerative diseases (4,5), the genetic association of microtubule-associated protein tau (MAPT) gene and PD has been examined and the studies confirmed the significant effect of the H1 haplotype of MAPT gene on PD risk.

Furthermore, the combination of the SNCA rs356219 GG and MAPT H1H1 risk genotypes has been recently shown to approximately double the risk for development of PD [3] supporting the
hypothesis that tau and a-synuclein proteins might be implicated in a common PD pathogenetic pathway.

Since the meta analysis of previous studies in PD patients gave supporting results, (3) concerning the previously referred interaction between SNCA rs356219 and MAPT H1 haplotype we tested whether this interaction is associated with PD in a southern European group of patients. We conducted a study in a cohort of PD patients and controls from two sites, Greece (Athens) and Italy (Rome), and sought to add more data to the previous studies which were based on samples from Northern and Central Europe.

METHODS

We recruited 352 unrelated sporadic PD patients (mean age: 67.3±10.7 years, 37% female, mean age of diagnosis: 54.8 years). The patients were of Greek and Italian ancestry. The 122 PD Greek samples were selected from the Department of Neurology, G. Genimnitas General Hospital, Athens, Greece. A total of 230 Italian patients were recruited from a center in Rome (Centro Europeo di Ricerca sul Cervello (CERC) - Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS). The patients had idiopathic PD and did not suffer from other neurological diseases. The process of sample collection did not include any intervention that is not part of any common clinical practice. Idiopathic Parkinson’s disease (PD) was diagnosed according to the criteria of the UK Parkinson’s Disease Society Brain Bank. The use of the UKPDS standard diagnostic criteria has been shown to increase diagnostic accuracy reaching levels of up to 90% (7). The PD symptoms were quantified by applying Part III of the Unified Parkinson’s Disease Rating Scale (UPDRS) (8) score. The control group consisted of 417 unrelated individuals (mean age: 65.8±17.2, 33.3% female) who were as well of Greek and Italian ancestry. The Greek control subjects donated blood during their treatment in Athens Trauma Hospital KAT, and in the Onasis Cardiac Surgery Center, Athens, Greece. The Italian control subjects were again recruited from Rome.

Genetic analysis of H1 and H2 haplotype

Blood samples were drawn for DNA extraction, using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) and following the manufacturer’s protocol, from patients and controls. The H1/H2 haplotype differentiation was based on the insertion/deletion polymorphism and has been performed as reported by Baker et al. (9) with minor modifications (Table 1).

Marker rs356219 was genotyped using Taqman SNP genotyping assay. The ABI Prism® 7000 SDS instrument in conjunction with the ABI TaqMan Universal Master Mix was used to perform the assay obtained from Applied Biosystems (Applied Biosystems, Foster City, CA, USA). Data were analyzed using the ABI Prism® 7000 SDS 1.0 Software (Perkin-Elmer, Applied Biosystems Division).

RESULTS

The MAPT and SNCA genotype distribution in PD patients and controls is summarized in Table 1. The two markers were in Hardy-Weinberg equilibrium. Overall the frequency of the H1H1 genotype was 63.35% in PD cases and 56.6% in controls. H1H1 homozygotes had a greater risk of PD than H1/H2 and H2H2 carriers (Table 1). The G allele for the SNP rs356219 was not associated with an increased risk of the disease (prevalence: 40% in patients, 38.3% in controls) and moreover patients homozygous for the G allele did not have an increased disease risk (Table 1). The combination of MAPT H1H1 genotype and SNCA GG genotype did not also have any effect on disease susceptibility (Table 1), in contrary with Goris et al. study where these specific two genotypes were observed to interact, with the combination of both doubling the risk for PD.

Table 1

Table 1: Genotype Analysis for MAPT and SNCA and their Interaction

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MAPT</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1/H1</td>
<td>63.35%</td>
<td>56.6%</td>
</tr>
<tr>
<td>H1/H2</td>
<td>39.97%</td>
<td>38.85%</td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>417</td>
</tr>
<tr>
<td>SNCA (rs356219)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>15.34</td>
<td>15.59</td>
</tr>
<tr>
<td>A/G</td>
<td>49.43</td>
<td>45.32</td>
</tr>
<tr>
<td>A/A</td>
<td>35.22</td>
<td>39.09</td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>417</td>
</tr>
<tr>
<td>MAPT-SNCA Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1/H1</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>9.09</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>54.27</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>6.25</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>30.4</td>
</tr>
<tr>
<td>Total</td>
<td>+</td>
<td>352</td>
</tr>
</tbody>
</table>

DISCUSSION
Our study using a Southern European population provided some negative evidence for the possible SNCA rs356219 GG and MAPT H1H1 synergistic interaction which was found to increase PD risk in Goris et al. study. We report that in our population the SNCA rs356219 GG genotype and the G allele for the same SNP did not confer risk to PD. However our results confirm that the distribution of the H1 haplotype of MAPT is an important risk factor of PD, something observed by nearly all relevant studies (summarized in Refenes et al) (10).

Generally, data obtained from statistical analysis cannot alone be efficient to interpret complicated and multifactor biological phenomena. Another explanation for the differing results concerning the same examined associations is ethnic background influence. Our study was the first conducted in a Southern European population concerning the previously referred synergistic interaction and the SNCA rs356219 GG genotype role in PD. Even if the incidence of a disease is geographically rather uniform, the importance of different genetic factors could vary between different populations. The possibility of ethnic background influence among white Caucasians to explain the contradictory results have been discussed previously (11).

REFERENCES