**Background**

- Several studies were performed with GBA variant carrier individuals to uncover accompanying mutations causing or preventing Parkinson’s Disease (PD) phenotype within these patients.
- Usually, these studies have been performed with a very limited number of samples. Therefore, results were useful but incomplete in terms of explaining the mechanisms underlying GBA-related Parkinsonism.
- We hypothesized that the commonality of GBA polymorphic alleles within PD patients might suggest the presence of at least one modifier mutation in a different gene to cause the PD phenotype in these patients.

**Methods**

- We included 188 patients with PD and 83 age-matched healthy controls in the study.
- We analyzed whole-exome sequencing (WES) for 20 GBA variant carriers using an in-house workflow based on GATK best practices, and variants were filtered based on allele frequency (<0.05), allele depth (DP >10), and genotyping quality (>30). CNVs were called using GATK GermlineCNVCaller and compared against DGV, DECIPHER, and ClinDB databases for the phenotypic association.

**Results**

- Genes related to neuroprotection, transcriptional regulation, autophagy, RNA processing, ion channels, signaling proteins, and membrane dynamics were researched for rare SNPs, INDELs, and CNVs from WES data. We detected changes in the SPEN gene, which is related to neuroprotection.
- Three variants of the SPEN gene in 20 exome cases were detected (Table 1). All of these variants are very rare in the GnomAD database. We checked these variants and variant frequencies of any variant in this gene in 2029 exomes done in the Turkish population (Intergen Genetics and Rare Diseases Diagnosis Research & Application Center database) and found no benign or pathogenic variant in control cases.
- The patients carrying SPEN variants were female. There was no significant difference between patients with and without SPEN in the age of diagnosis, UPDRS 1, UPDRS 3, Hoehn Yahr, LEDD scores which indicate disease severity.
- When genes known to be associated with PD or any movement disorder are investigated, heterozygous variants of DNAJC6 and PINK1 genes were observed in two different individuals. Both genes are related to the autosomal recessive form of the PD, thus, not enough to cause any disorder as heterozygous, even if the mutation is pathogenic. The patients carrying variants of DNAJC6 and PINK1 genes were male.
- The other most common Parkinson’s genes (LRRK2, PARK7, PRKN, ATP13A2) were excluded in all patients.

**Table 1. Whole exome sequencing results of GBA carrier patients with PD.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>UPDRS-1 (non-motor)*</th>
<th>UPDRS-3 (motor)*</th>
<th>Hoehn Yahr scale</th>
<th>Levodopa equivalent daily dose*</th>
<th>Gene/Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>61</td>
<td>Female</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>100</td>
<td>SPEN:NM_015001.3:exon11:c.2351G&gt;A:p.R784H</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>43</td>
<td>Female</td>
<td>0</td>
<td>18</td>
<td>5</td>
<td>525</td>
<td>SPEN:NM_015001.3:exon11:c.2429G&gt;A:p.R810Q</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>57</td>
<td>Female</td>
<td>10</td>
<td>67</td>
<td>4</td>
<td>1314</td>
<td>SPEN:NM_015001.3:exon11:c.7135G&gt;A:p.E2379K</td>
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</tr>
<tr>
<td>P4</td>
<td>53</td>
<td>Male</td>
<td>8.5</td>
<td>24</td>
<td>3</td>
<td>1731.5</td>
<td>DNAJC6:NM_014787.4:exon12:c.1646A&gt;C:p.H549P</td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>66</td>
<td>Male</td>
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<td>43</td>
<td>2</td>
<td>1218.5</td>
<td>PINK1:NM_032409.3:exon5:c.976C&gt;T:p.R326C</td>
<td></td>
</tr>
</tbody>
</table>

*higher scores indicate more severe disease

**Conclusion**

- We suggest that the presence of rare heterozygous polymorphisms of autosomal recessive PD genes may influence the outcome of the phenotype in a GBA-sensitive genetic background.
- As we detected in an exome study of three of 20 patients with GBA variant, and the SPEN gene can be speculated as a causative or modifier gene for PD clinical picture in GBA carriers.
- These results may explain why only some of the GBA variant carrier individuals develop PD. This study will contribute to understanding the effects of GBA on the PD phenotype.

**References**