Dear editor,

Although Parkinson’s disease (PD) is mainly a sporadic disorder, there is a demonstrable familial occurrence in up to 30% of cases [1]. Thanks to the improving of molecular genetics technologies, the list of identifiable genetic mutations related to genetic forms of PD is ever broader. In general, these are labelled with the abbreviation PARK with a number reflecting the chronological order in which they were discovered (to date PARK 1–23) [2]. Although we know the gene loci of in which they were discovered (to date PARK 1–23) [2]. Although we know the gene loci of PD is ever broader. In general, these are genetic mutations related to genetic forms of PD a sporadic disorder, there is a demonstrable familial occurrence in up to 30% of cases [1]. Thanks to the improving of molecular genetics technologies, the list of identifiable genetic mutations related to genetic forms of PD is ever broader. In general, these are labelled with the abbreviation PARK with a number reflecting the chronological order in which they were discovered (to date PARK 1–23) [2]. Although we know the gene loci of

We describe a 59-year-old woman with a history of 7 years of anxious depressive disorder, insomnia and personality disorder with paranoid behaviour (documented as a depressive type of schizoaffecitive disorder), treated with various types of antidepressants and antipsychotics, including clonazepam, cinnolazepam, mirtazapine, venlafaxine, alprazolam and risperidone. She is currently taking olanzapine, venlafaxine and alprazolam. Her psychological assessment showed cognitive decline and organicity, without significant evidence of psychosis. She was examined for the first time at the age of 57, when she complained of left hand clumsiness and nonspecific leg weakness when walking, occurring for about 2 years, short-term memory loss, urinary frequency and orthostatic problems.

The patient’s DNA was isolated from peripheral blood. The amplicon library was in-silico-, designed by Ion AmpliSeq Designer (Thermo Fisher Scientific, Waltham, USA) for the ADH1C, EIF4G1, FBXO7, GBA + + GBAP1, GIGYF2, HTA2, LRRK2, MAPT, PARK2, PARK7, PINK1, PLA2G6, SNCA, UCHL1 and VPS35 genes. In total 617 amplicons covered 92.59% of the coding DNA sequence, including 100 bp into the introns and both 5’ and 3’ UTRs of the particular gene regions. After filtering the variants, two missense and one synonymous rare mutation were found (Tab. 1). The most important mutation was found in exon 21 in a coiled coiled domain of the GIGYF2 gene on chromosome 2 (c.2384G>A; p.Arg795His), which has not been published until now. Since the majority of symptomatic family members including the patient’s brother have died, the patient is childless and cooperation with her is quite difficult, extensive genetic family testing is, unfortunately, not possible.

In 2002, Pankratz et al identified, by way of whole-genome linkage analysis, a locus for a new genetic form of PD [3]. The locus on chromosome 2 (2q36–37) corresponds with the 18-cM interval between the
microsatellite markers D2S396 and D2S338, which contains 73 potential candidate genes. In this region, the gene encoding a protein with 1,299 amino acids, named GIGYF2 (Grb10-Interacting GYF protein 2), was found. Both known homologues, GIGYF1 and GIGYF2, interact by their GYF domain with the proline-rich region of Grb10 adaptor protein [4,5]. Although it is hypothesized that GYF-domain-containing proteins take part in mRNA splicing or other steps of mRNA processing, the exact function of the GIGYF2 protein is not yet known [4]. Lautier et al. [4] have studied all 27 exons of the GIGYF2 gene in 249 PD patients with at least one affected first-degree relative in comparison to 227 control subjects. In the PD group there were seven heterozygous mutations in 12 unrelated identified cases. These mutations were consistent with autosomal dominant adult onset levodopa-responsive PD with incomplete penetrance. The GIGYF2 gene was then added to the candidate genes for a monogenic form of PD, later designated as PARK 11. Nichols et al. carefully examined a sample of 566 familial PD cases with nearly 1,500 affected individuals for these seven variants. Additionally, another three new mutations were discovered. All these variants

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>H-Y stage</th>
<th>MDS-UPDRS III</th>
<th>BDI</th>
<th>MOCA</th>
<th>FAB</th>
<th>NMSQuest (main problems)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2</td>
<td>27/132</td>
<td>19/66</td>
<td>23/30</td>
<td>13/18</td>
<td>13/30</td>
</tr>
<tr>
<td>Subtotal</td>
<td>–</td>
<td>pull test 0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

- visuospatial naming
- attention
- language
- abstraction (–1)
- memory (–5)
- orientation (–1)

- conceptualisation
- verbal fluency
- Luria test (–3)
- conflict instructions (–1)
- Go- No Go test grasping (–1)

- urinary incontinence, urgency
- short-term memory problems
- difficulty with concentration
- feel of anxiety/fear
- orthostatic symptoms
- sleep problems
- intensive dreams/speak
- ingestness
- restless legs symptoms

### Genetic analysis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location chr</th>
<th>Genotype</th>
<th>dbSNP</th>
<th>Transcript</th>
<th>Coding</th>
<th>Amino acid change</th>
<th>PolyPhen</th>
<th>PhyloP</th>
<th>sift</th>
<th>MAF 1000 G</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTRA2</td>
<td>chr.2: 74757554</td>
<td>G/T</td>
<td>rs72470544</td>
<td>NM_0132474</td>
<td>c.421G &gt; T</td>
<td>p.Ala141Ser</td>
<td>0.04</td>
<td>0.0122</td>
<td>0.0022</td>
<td>0.00002</td>
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<tr>
<td>GIGYF2</td>
<td>chr.2: 233684550</td>
<td>G/A</td>
<td>rs200601366</td>
<td>NM_00110314610</td>
<td>c.2384G &gt; A</td>
<td>p.Arg795His</td>
<td>2.33</td>
<td>0.998</td>
<td>0.0002</td>
<td>0.0046</td>
</tr>
<tr>
<td>EIF4G1</td>
<td>chr.3: 184049382</td>
<td>C/T</td>
<td>rs111921843</td>
<td>NM_001194971</td>
<td>c.4404C &gt; T</td>
<td>p.Phe1468Phe</td>
<td>–112</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

H-Y – Hoehn-Yahr stage; MDS-UPDRS III – Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (Motor Examination, on state); BDI – Beck’s Depression Inventory; MOCA – Montreal Cognitive Assessment; FAB – Frontal Assessment Battery; NMSQuest – Non-Motor Symptoms Questionnaire for Parkinson’s Disease; Hg – Human genome reference sequence 19; dbSNP – Single Nucleotide Polymorphism database; PhyloP – bioinformatic tool for evaluating of phylogenetic conservation; PolyPhen – bioinformatic tool for prediction of nonsynonymous variants (Polyorphism Phenotyping v2); SIFT – bioinformatic tool for prediction of nonsynonymous variants (sorts intolerant from tolerant); MAF – minor allele frequency; 1000 G – allele frequency based on 1000 Genomes Project
A NOVEL MUTATION IN THE GIGYF2 GENE IN A PATIENT WITH PARKINSON’S DISEASE

were found in only six PD families, and the authors believe they are not responsible for the heredity of PD at the 2q36–37 locus [5].

Haplotype analysis of the GIGYF2 gene proved that mutations are not associated with a higher risk of sporadic PD [6]. In an animal study, abrogation of GIGYF2 function in zebrafish did not lead to a loss of diencephalic dopaminergic cells, suggesting that this gene is probably not required for dopaminergic differentiation of cells [7]. Afterwards, another study which questioned the role of the GIGYF2 gene in causal relation to familial PD and its association with PARK 11 disease started to appear [8,9]. Therefore in the contemporary literature, the mutations in the GIGYF2 gene no longer appear as a cause of PARK 11 disease [10].

We report here a patient with possible autosomal dominant PD with incomplete penetrance with genetically confirmed mutation in the GIGYF2 gene. Unfortunately, the patient’s symptomatic and asymptomatic relatives were not clinically or genetically tested. In our patient, psychiatric manifestation (depression, paranoid behaviour and cognitive decline) preceded her motor symptoms by some years. They more likely represent associated symptoms in PD rather than simple coexistence of a schizoaffective disorder with PD. Psychiatric symptoms in carriers of the GIGYF2 mutation have thus far not been reported. As previously mentioned, the causality of GIGYF2 mutation in PARK 11 disease has been disproved [10]. However, there is a need to answer two principal questions: 1. What other gene mutation could be responsible for the developing of the disease? 2. What is a result of GIGYF2 mutation in our patient, if it is not pathogenic? Therefore, we believe that further studies to solve this problem are necessary.

References

On the website www.csnn.eu you can find supplemental video. The video demonstrates clinical presentation of the patient; particularly the parkinsonian syndrome with hypomimia, bradykinesia, slight postural tremor predominantly on the left side and her characteristic gait. 1:17 min., 24,6 MB.

Na webových stránkách www.csnn.eu naleznete aktualizované pokyny pro autory.

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