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A Novel Mutation in the GIGYF2 Gene in a Patient with Parkinson's Disease

Nová mutace v genu GIGYF2 u pacienta s Parkinsonovou chorobou

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 all currently known PARK diseases, we do not yet know all of their causative genes.

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 schizoaffective disorder), treated with various types of antidepressants and antipsychotics, including clonazepam, cinolazepam, 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. Initially, we suggested a neuroleptic-induced parkinsonism. However, the patient referred to a history of adult-onset parkinsonism in more family members on her mother's side, some with clear benefit after levodopa treatment (Fig. 1). On examination, there was a hypokinetic-rigid syndrome, more on the left side, with slight postural tremor of the left hand, hypomimia, seboroic dermatitis and positive Babinski sign on the left. Magnetic resonance imaging of the brain displayed slightly asymmetric frontoparietal atrophy (more on the left) and incipient leukoencephalopathy. Electroencephalography showed theta activity with sporadic delta dysrhythmia on the right side. Dopamine transporter single-photon emission computed tomography (DaT-SPECT) confirmed the reduced uptake of presynaptical dopaminergic neurons, thus a neurodegenerative parkinsonism. A slit-lamp examination for the presence of a Kayser-Fleischer ring was negative. The patient was extensively tested neurologically and neuropsychologically (Tab. 1). She started to take rasagiline, with no subjective improvement. A levodopa trial was then initiated with improvement of her parkinsonism at a dose of 750 mg daily. Owing to suspicion of having a familial form of parkinsonism, we conducted genetic testing.

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, HTRA2, 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 coil 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

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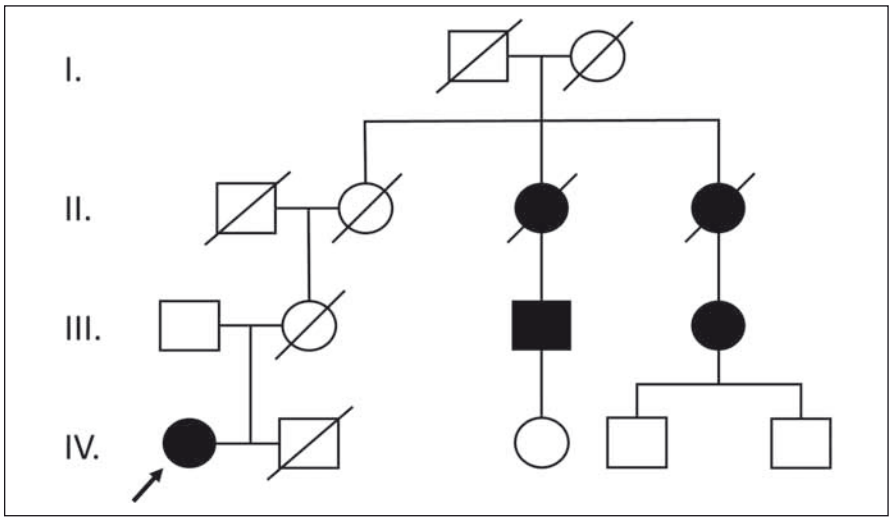


Fig. 1. Four-generation pedigree chart which demonstrates autosomal dominant trait with incomplete penetrance. The patient is indicated by the arrow.
Clinical data in generation I are missing.

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

Tab. 1. Summary of patient´s clinical and genetic characteristics.

Clinical characteristics						
	H-Y stage	MDS--UPDRS III	BDI	MOCA	FAB	NMSQuest (main problems)
total	2	27/132	19/66	23/30	13/18	13/30
subtotal	–	pull test 0	–	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 ingrestless legs symptoms

Genetic analysis			
	HTRA2	GIGYF2	EIF4G1
location (Hg19)	chr.2: 74757554	chr.2: 233684550	chr.3: 184049382
genotype	G/T	G/A	C/T
dbSNP	rs72470544	rs200601366	rs111921843
transcript	NM_0132474	NM_00110314610	NM_0011949471
coding	c.421G > T	c.2384G > A	c.4404C > T
amino acid change	p.Ala141Ser	p.Arg795His	p.Phe1468Phe
PhyloP	0.04	2.33	–1.12
PolyPhen	0	0.998	–
SIFT	0.46	0	–
MAF 1000 G	0.0122	0.0002	0.0046

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 Nucleotid Polymorphism database; PhyloP – bioinformatic tool for evaluating of phylogenetic conservation; PolyPhen – bioinformatic tool for prediction of nonsynonymous variants (Polymorphism 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

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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.

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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.

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