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Short communication

# Familial early onset Parkinson's disease caused by a homozygous frameshift variant in PARK7: Clinical features and literature update

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ABSTRACT

*Background:* Bi-allelic mutations in *PARK7* are a rare cause of autosomal recessive early onset Parkinson's disease (EO-PD). To date, 30 individuals harbouring 20 unique causative variants have been described. Understanding of the spectrum of clinical features and natural history of *PARK7* mediated EO-PD remain limited.
*Methods:* We studied a family with three offspring, two of whom were affected with EO-PD. Family members underwent detailed clinical examination and DNA samples from both affected individuals and parents were analysed by exome sequencing.
*Results:* Two brothers of Iranian descent presented at age 29 years with Parkinsonism associated with high-pitched voice and hypomimia. The brothers were followed over a six and fifteen-year period and displayed typical levodopa responsive slowly-progressive Parkinsonism. A novel homozygous frameshift mutation in *PARK7* [NM_007262.4:c.90dupG, p(Ile31Aspfs*2)] was identified.
*Conclusions:* Here we report the clinical presentation and progression of EO-PD in brothers with a novel pathogenic *PARK7* variant. We expand the clinical phenotype and provide an update of clinical and pathological features of the disorder.

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder affecting > 1% of individuals over 60 years of age [1,2]. The primary pathological hallmarks of PD are the specific loss of dopaminergic (DA) neurons in the Substantia nigra (SN) pars compacta (SNpc) and the presence of intracellular inclusions termed Lewy bodies in surviving DA neurons [3]. Loss of DA neurons underpins the clinical presentation, which can include motor symptoms such as resting tremor, joint and muscular rigidity, postural instability and bradykinesia [4]. The clinical features of PD vary between affected individuals due to disease heterogeneity, impacting prognostication and clinical management.

The majority of affected individuals have idiopathic PD, likely mediated by the interaction of environmental and genetic susceptibility factors. However, a direct genetic aetiology can be identified in 5–10% of patients. These monogenic forms of the disease can be autosomal dominant (e.g. *SNCA*, *LRRK2*), autosomal recessive (e.g. *PRKN*, *PINK1*, *DJ-1*) or X-linked (*RAB39B*), and typically present earlier than sporadic disease, with the earliest onset observed in the autosomal recessive forms. The phenotypic similarities between genetic and idiopathic PD suggest they share key pathological pathways; therefore understanding the spectrum of clinical features, natural history and pathogenic mechanisms underlying rare monogenic forms of PD will inform management and potentially the development of new therapies for idiopathic PD [5].

Individuals with pathogenic variants in the genes encoding parkin (*PRKN*), PTEN Induced Putative Kinase 1 (*PINK1*) and Parkinsonism associated deglycase (*PARK7*) present with typical early onset PD (EO-PD) with slow progression and account for ~13% of all EO-PD, defined as onset occurring before age of 40 years. *In vitro* and *in vivo* studies have demonstrated the key role these proteins play in neuroprotection and preventing oxidative stress. There is strong evidence that PRKN and

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PINK1 are involved in mitochondrial quality control via mitochondrial homeostasis and mitophagy, and that PARK7 functions as a redox sensitive chaperone [6].

To date, 18 families and 30 individuals with pathogenic variants in *PARK7* (76% male) have been described and key clinical features were recently summarised [7]. All index cases carried a different mutation, with in total 20 disease-causing sequence variants identified. The majority of affected individuals have originated from Italy, Iran or Turkey. Here we report the clinical features and disease progression over a six and fifteen year period in two affected individuals with EO-PD caused by a novel pathogenic frameshift variant [p(Ile31Aspfs*2)] in *PARK7*.

## 2. Methods

Study approval was provided by the Royal Children's Hospital Research Ethics Committee (HREC#28097) with informed consent provided by participants or their guardians. Genomic DNA derived from the two affected brothers and their parents underwent exome sequencing. Exons were captured using the SureSelect Human All Exon V5 + UTRs (Agilent) and sequencing data was analysed using standard methods. Briefly, raw reads were aligned to the UCSC hg19 reference genome using BWA-MEM [8]. Local re-alignment was performed with Genome Analysis Toolkit (GATK) [9]. Single nucleotide variants and small indels were called with GATK-Haplotype Caller for all individuals (simultaneously) and peddy [10] was used to determine relatedness using identity by state between all individuals. SNP data was assessed for CNVs using an in-house bioinformatics pipeline and early-onset PD-associated loci, including *PRKN*, were visually assessed using the Integrative Genomics Viewer. Variants were filtered against population databases and rare variants (MAF < 1%) within homozygous regions were assessed for pathogenicity using VarSome [11]. Sanger sequencing using primers DJ-1 E2F (5′-TCTGCTTGAAAATGCTCC-3′) and DJ-1 E2R (5′-GGCAAGACATTAACAAGCG-3′) confirmed segregation.

## 3. Results

### 3.1. Case presentation

The affected individuals were male siblings born to Jewish parents of Iranian origin (city of Amaden) with reported consanguinity, confirmed as first-degree by Peddy analysis of the exome data (Fig. 1A). The family history was negative for Parkinson's disease. The patients were diagnosed at a similar age of onset and had similar initial parkinsonian symptomatology. The clinical features are summarised in Table 1.

#### 3.1.1. Clinical history

Patient I: The patient presented at age 29 years with a one-year history of high-pitched voice and hypomimia. Physical examination revealed hypomimia with almost no blinking, mild limitation of upward gaze, and slow saccades. Symmetric bradykinesia, rigidity, and rest and postural tremor were observed in addition to a reduced arm swing bilaterally. Postural reflexes were intact. The score on the motor part of the UPDRS was 31. Motor examination revealed no abnormalities except for decreased tendon reflexes in both hands. There were no cerebellar signs and no non-motor symptoms (case-reported hyposmia, constipation, urinary symptoms, dysphagia). Cognition was intact (MOCA 29/30). Brain MRI scan was normal. Initially, the patient was treated with rasagiline. By the 3-year follow-up, the motor symptoms had progressed and treatment with pramipexole was initiated. Two years later, impulse control disorder developed with hypersexuality and compulsive shopping. At that time, the score on part III of the UPDRS was 42. Pramipexole treatment was discontinued and replaced with carbidopa-levodopa (Sinemet) 100 mg TID, with improvement of the motor symptoms and of the compulsive behaviour. There was no change in the intonation of speech and pitch of voice though the pronunciation of words became slurred. After one year of levodopa treatment motor fluctuations or dyskinesias did not emerge.

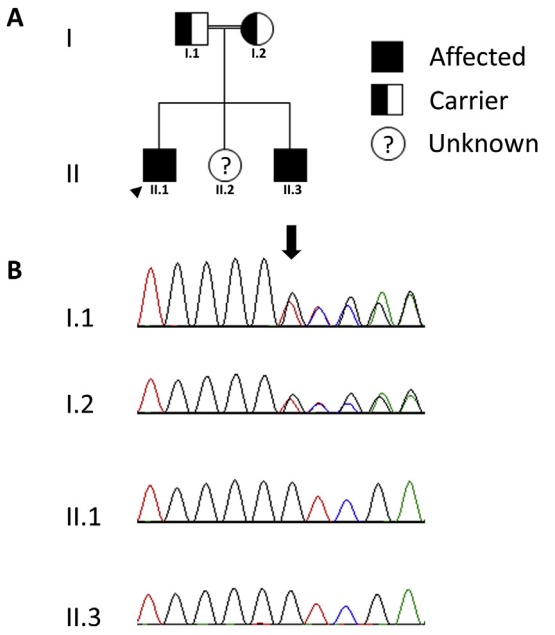


**Fig. 1.** Parkinson's disease caused by PARK7 p(Ile31Aspfs*2). A. Pedigree of the family with clinical status, arrow indicates index case. B. Chromatographs confirming the c.90dupG variant. Traces for unaffected parents (I.1 & I.2) demonstrate heterozygous T/G while affected individuals (II.1 & II.3) show a homozygous dupG variant. Chromatogram: T (red), G (black), C (blue), A (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

**Table 1**
Clinical features of PARK7 associated PD.

| Motor signs | This study | | Summary data from Kasten et al., 2018[7] | | |
|---|---|---|---|---|---|
| | II.1 | II.3 | Yes | No | Not reported |
| Parkinsonism | ✓ | ✓ | 30 (100%) | 0 (0%) | 0 (0%) |
| Bradykinesia | ✓ | ✓ | 27 (90%) | 1 (3%) | 2 (7%) |
| Rigidity | ✓ | ✓ | 21 (70%) | 0 (0%) | 9 (30%) |
| Tremor | ✓ | ✓ | 19 (63%) | 5 (17%) | 6 (20%) |
| Postural instability | ✗ | ✗ | 12 (40%) | 5 (17%) | 13 (43%) |
| Dyskinesia | ✗ | ✗ | 7 (23%) | 4 (13%) | 19 (64%) |
| Dystonia | ✗ | ✓ | 14 (46%) | 5 (17%) | 11 (37%) |
| Hyperreflexia | ✗ | ✗ | 4 (13%) | 6 (20%) | 20 (67%) |
| Diurnal fluctuations | ✗ | ✗ | 1 (3%) | 3 (10%) | 26 (87%) |
| Sleep benefit | ✗ | ✗ | 1 (3%) | 0 (0%) | 29 (97%) |
| Motor fluctuations | ✗ | ✗ | 4 (13%) | 0 (0%) | 26 (87%) |
| Atypical | ✗ | ✗ | 4 (13%) | 8 (27%) | 18 (60%) |
| **Nonmotor signs** | | | 17 (57%) | 0 (0%) | 13 (43%) |
| Depression | ✓ | ✓ | 4 (13%) | 1 (3%) | 25 (84%) |
| Anxiety | ✓ | ✓ | 4 (13%) | 2 (7%) | 24 (80%) |
| Psychotic | ✓ | ✓ | 6 (20%) | 3 (10%) | 21 (70%) |
| Sleep disorder | ✗ | ✗ | 3 (10%) | 2 (7%) | 25 (83%) |
| Cognitive decline | ✗ | ✗ | 5 (17%) | 6 (20%) | 19 (63%) |
| Autonomic | ✗ | ✗ | 4 (13%) | 7 (23%) | 19 (64%) |
| Hypomimia | ✓ | ✓ | NA | NA | NA |
| **Unique features** | | | | | |
| High pitched voice | ✓ | ✓ | NA | NA | NA |

The clinical features of the Iranian family are described in detail and compared to all previously reported cases [7].

Patient II: The patient presented at age 29 years with high-pitched voice and hypomimia. At the most recent follow-up, 15 years later, severe hypomimia, unintelligible speech, and slowness of eye movements and saccades were noted. There was a mild rest tremor of both

hands but no postural tremor, and rigidity and slowness of all limbs, slightly more on the left side. Foot dystonia was present in both legs. The patient had no abnormalities of posture, and postural reflexes remained intact. He was being treated with levodopa, but despite high doses (1250 mg/d) he did not develop motor fluctuations or dyskinesias. Cognitive functions were normal (MOCA 28/30). Interestingly, there was anecdotal evidence from the carer of the patient that speech was clearer with mannitol, though the articulation and high pitch voice remained unchanged.

### 3.2. Genetic analysis

WES and *in silico* filtering identified 24 variants within regions of homozygosity shared by the affected brothers. Twenty three variants were classified as benign or of uncertain significance. Only one variant, a novel homozygous frameshift variant (NM_007262.4:c.90dupG, p (Ile31Aspfs*2)) in *PARK7*, was classified as pathogenic utilizing the American College of Medical Genetics and Genomics guidelines [12]. This variant was homozygous in both affected brothers and present in the heterozygous state in both unaffected parents. Sanger sequencing of all available individuals confirmed the c.90dupG variant (Fig. 1B).

## 4. Discussion

We describe the clinical features and disease progression in two individuals of Jewish Iranian ethnicity with a novel pathogenic *PARK7* variant. The affected individuals displayed a natural history of the disease broadly similar to other affected individuals with PARK7 mediated EO-PD. Disease onset occurred at a very early age and notable clinical features included high-pitched voice at presentation, symmetric motor symptoms (in one sibling), and absence of motor fluctuations. In both individuals posture, postural reflexes and cognition were intact.

The clinical features and natural history of *PARK7* mediated PD have not been thoroughly described, in part due to the rarity of the disorder. Most cases are characterized by very early age of PD onset (range 10–34 years), absence of atypical PD features, very good response to dopaminergic treatment, slow disease progression, focal dystonia, hyperreflexia, prominent motor fluctuations, and psychiatric symptoms, especially anxiety (Table 1) [7,13–15]. Novel features reported in one or a small number of individuals have included a very severe form of Parkinson-dementia-motor neuron disease or unresponsive disease complicated by dystonia, bulbar signs, and dementia [16–18]. An Iranian kindred presented with early onset, oromandibular dystonia, and psychosis. The condition was slowly progressive and symmetric, with frequent falls but no significant tremor and good response to levodopa [19]. In one Iranian family, voice change is mentioned as one of the symptoms but was not characterized in detail [20].

The first pathological examination of an individual with PARK7 mediated EO-PD was recently reported [18]. The case had a rapid and complex progression of the disease with dementia. Severe dopaminergic neuronal loss within the substantia nigra pars compacta (SNpc) was accompanied by gliosis; extracellular pigment and classical Lewy bodies were readily visible. Additional severe neuronal loss of the Locus coeruleus, moderate neuronal loss of the globus pallidus and mild neuronal loss of the putamen were also identified. Widespread alpha-synuclein positive diffuse Lewy body, Lewy neurites, spheroids and glial inclusions were identified throughout the midbrain and cortices varying in degree of severity but absent from the cerebellum. Scattered tau positive neurofibrillary tangles and dystrophic neurites consistent with Braak neurofibrillary stage I were observed, but there were no abnormal amyloid β or TDP-43 inclusions. Although based on a single case study these observations suggests that loss of PARK7 function results in α-synucleinopathy.

In conclusion, studies of the clinical, genetic and neuropathological features of rare genetic forms of EO-PD are facilitating understanding of Parkinson's disease pathophysiology. For example, PARK7 was recently shown to play a key role in guanine glycation repair [21], potentially implicating this novel nucleotide repair system in disease development and progression. These and similar studies identifying pathways involved in the neurodegeneration process will aid in the development of new therapeutic targets and interventions.

## Declarations of interest

None.

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