A Case Report on a Novel *PINK1* Gene Mutation in a Female with a Neurodegenerative Disorder

Authors: Shaile Sudha Bandla, Avvari Srilekha, Poojita Karchalkar, Sowmya Gayatri, *Ananthapur Venkateshwari

Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Hyderabad, India

*Correspondence to venkateshwari@yahoo.com

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Abstract

Introduction: Parkinson's disease (PD) is a progressive neurological disorder that affects both motor and non-motor skills in an individual. Both familial and sporadic cases of PD can be caused by mutations in the *LRRK2, PARK7, PINK1, PRKN*, or *SNCA* genes. However, mutations in genes *PINK1* and *LRRK2* are associated with early onset PD.

Case presentation: This study reports an 18-year-old female with early onset PD, where whole-exome sequencing showed a pathogenic missense variant p.R88W in the *PINK1* gene (NM_032409.2) resulting in the disease condition.

Conclusion: For cases like neurodegenerative disorders confirmed by an MRI or CT scan, it is always advisable to perform whole-exome sequencing or next-generation sequencing to detect the genes associated with the disease. Depending on the type of the symptoms, medication along with physical therapy can be advised to manage the condition.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder attributed to the loss of dopaminergic neurons in the substantia nigra.[1] PD is considered to be the second most common neurodegenerative disease, affecting 4.6 million people worldwide.[2] Depending on the type of gene mutation, the inheritance pattern could be either autosomal dominant or autosomal recessive. The literature has shown 27 genes identified to be associated either with autosomal dominant, autosomal recessive, or with X-linked transmission.[3] However, *PINK1* mutations are the most common prevalent genetic cause of autosomal recessive early onset PD.[4,5]

The *PINK1* gene, located on chromosome 1 (*PARK6* locus), contains eight exons and encodes for a 581-amino acid protein that targets both mitochondrial and serine/threonine

kinase domains, which were identified to be a cause of autosomal recessive PD.[6,7] The gene is, therefore, responsible for fine-tuning the network and energy metabolism of the mitochondria. It regulates parkin translocation in impaired mitochondria and drives their removal via selective autophagy.[2,8] The mutations in the *PINK1* gene result in the malfunctioning of the mitochondria, particularly when cells are stressed, causing neurodegeneration such as inflammation, apoptosis, or dendritic morphogenesis in humans.[9,10]

The purpose of the case study is to evaluate an 18-year-old female with an early onset neurodegenerative disease and a heterozygous gene mutation in the *PINK1* gene, which is reported here for the first time in India to the best of the authors' knowledge.

CASE PRESENTATION

History and Examination

An 18-year-old female, born to a non-consanguineous couple, was referred to the authors' institute for genetic evaluation. On clinical examination, the patient presented with left hand dystonia, progressive flexion contracture of the left hand and leg, difficulty writing, left hemi-dystonia, and left leg gait abnormality. Since the subject was 12 years old, their pupils have remained reactive to light and no Kayser–Fleischer rings have been observed under slit-lamp examination. MRI and CT scan evaluations showed normal reports. The levels of serum copper (136.5 µg/dL), serum ceruloplasmin (27.2 µg/dL), and urine copper (11.5 µg/day) were within normal range. Both parents of the index case and their sibling exhibited normal behaviour with no history of genetic disease.

Complimentary Examination

The index case was evaluated for whole-exome sequencing, using this massively parallel sequencing method to identify the molecular and genetic basis of suspected genetic conditions. Genomic DNA was enriched for the complete coding regions and splice site junctions of the genes of the specimen. Paired-end sequencing was performed with 2x100 and 2x150 chemistry on an Illumina platform (San Diego, California, USA). Reads were assembled and aligned to reference sequences based on National Center for Biotechnology Information (NCBI) RefSeq transcripts and the human genome build GRCh37 (hg19). Data was filtered and analysed to identify variants of interest and interpreted in the context of a single most damaging, clinically relevant transcript for the report, indicated as a part of variant details. Variant calling and filtering were performed by the OrionSeek algorithm (St. Louis, Missouri, USA), which is currently benchmarked to the Genome in a Bottle (GIAB) variant callset for these target regions.

Whole-exome sequencing results showed a heterozygous variant of uncertain significance with the *PINK1* missense variant p.R88W, which had not been previously reported as a pathogenic variant nor as a benign variant, to the authors' knowledge. The variant p.R88W was observed in only two patients with early onset PD. These individuals presented in heterozygote form as per the genome aggregation database data (0.001%). Whole-exome sequencing details of the proband revealed the gene and transcript of *PINK1* (NM_032409.2) at exon 1 location on chromosome 1p36.12, with a variant c.262C>T (p.Arg88Trp). This is classified as a heterozygous variant with an uncertain significance, inherited in an autosomal recessive inheritance pattern, leading to PD-6 with an early onset.

DISCUSSION

PD is the second most common neurodegenerative disease, affecting approximately 1% of people over 50 years of age worldwide.[11] During the fourth decade of life, the prevalence ranges from 41 per 100,000 people, compared with more than 1,900 per 100,000 for those 80 and above. PD is a long-standing progressive neurodegenerative disorder with the involvement of both genetic and non-genetic factors. It is outlined pathologically by the conspicuous and selective loss of dopaminergic neurons, projecting from the *substantia nigra pars compacta* to the striatum, and by the accumulation of intracytoplasmic proteinaceous inclusions known as Lewy bodies.[12] The present study revealed an unreported heterozygous mutation in the *PINK1* gene, causing impaired motor skills in the proband at an early age. The gene mutation at p.Arg88Trp in the *PINK1* gene of the proband may deregulate the protein

synthesis, which could result in dopaminergic neuronal dysfunction.

The clinical features observed in the present study are in accordance with the earlier studies of Ibáñez et al.,[3] where flexion contracture of the left hand was reported. Valente et al.[4] observed that the *PINK1* gene is responsible for *PARK6*-associated autosomal recessive PD, with either a homozygous missense mutation (G309D) or a homozygous truncating mutation (W437X) in Spanish and Italian kindreds, respectively. A study by Gandhi et al.[13] indicated that the *PINK1* gene mutation in parkinsonism highlights two points: the molecular link between mitochondria and neurodegeneration in PD and the importance of the kinase signalling pathway in the pathogenesis of dopaminergic nigral cell death.[13]

Heterozygous mutations in genes causing autosomal recessive forms of parkinsonism (i.e., the *DJ-1*, parkin, and *PINK1* genes) have been identified in cases of sporadic PD where their contribution to disease causation remains unclear. Abou-Sleiman et al.[14] have identified heterozygous mutations in the *PINK1* gene in sporadic PD cases with a higher frequency than in control groups. One important hypothesis is that heterozygous mutations may have a functional effect on the encoded protein as a result of haploinsufficiency. Earlier studies have emphasised that PET scans of clinically unaffected relatives of cases who carry heterozygous mutations in the *PINK1* gene revealed a reduction of 18F-dopa uptake in their nigrostriatal neurons, indicating a degree of dopaminergic dysfunction.[15] Thus, it appears that the presence of a heterozygous mutation of the *PINK1* gene in the proband can exert a functional effect on the PTEN-induced kinase 1 protein and subsequently on dopaminergic neuronal dysfunction.

In a study conducted by Ibáñez et al.,[3] the mutation analysis of 177 cases for both *PINK1* and parkin gene mutations in Europe and North Africa for early onset PD revealed 7 cases with *PINK1* gene mutations with an early onset of the disease, and 90 cases with parkin gene mutation, which was reported to appear in the third decade of life. In comparison, the phenotypic representation of the individuals is similar for both of the gene mutations, except for that of the age of onset.[3] The symptoms observed in the proband may be due to the deregulated expression of the *PINK1* gene, resulting in the neurodegenerative disorder PD-6.

CONCLUSION

The study suggests that comprehensive clinical diagnosis, along with advanced genetic testing procedures in neurodegenerative disorders, will provide further evidence that can be used to understand the role of known and novel gene mutations in the aetiology of PD. Further treatment strategies can then be employed based on the obtained gene mutations, which may also help in offering genetic counselling.

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