New Mutations Causing Familial Parkinsonism

Dear Editor,

Parkinson's disease (PD) is a neurodegenerative movement disorder caused by a loss in the number of dopamine producing nerve cells. In the majority of cases PD is a multifactorial condition, with both genetic and environmental factors contributing to its pathogenesis.[1] The frequency of PD among first degree relatives of classic idiopathic PD patients is known to be higher than the general population.[2] About 10% to 15% of patients with PD have a positive family history of PD compatible with Mendelian inheritance and 85% to 90% are sporadic in nature.[3] A number of susceptibility genes and markers for idiopathic PD have been identified. This has been achieved with the help of genome-wide association studies (GWAS) which help to illustrate potential genetic associations with certain disease pathology.[4] For example, it was recently found that a genetic marker might cause inflammation leading to an increased risk of acquiring PD.[5] Most experts agree that Familial Parkinsonism (FP) involves a diagnosis of PD in the presence of an inherited mutation. FP can be further classified into Juvenile Parkinsonism, which includes PD cases up to age of 20 years, Young-Onset, from age 20 to 40 years and Adult FP which includes cases age of 40 years and above.

Both autosomal dominant (AD) and recessive inheritance has been seen in FP. The most common mutations in an AD gene involved in FP is the LRRK2 gene whereas mutations in several other genes including the Parkin gene causes an autosomal recessive inherited form of PD.[6] Here we describe 3 cases of FP to illustrate the unique interplay of genetics and the PD process.

Case 1

First patient was a 39-year-old right-handed man of Middle Eastern descent who initially noticed slowing of movements several years before seeking medical attention. He had trouble with his dexterous movement, including fastening buttons and tying his shoe laces. He also felt that his right hand was not able to coordinate well. His parents were first cousins and he had 4 brothers, 2 sisters and 3 children. His birth, developmental and family history was unremarkable.

On examination, he had decreased facial expressions, 2 out of 4 bradykinesia on the UPDRS-III scale on rapid alternating movements on his right side and 1/4 bradykinesia on the left side. He had 1/4 rigidity and decreased arm swing on the right side of his body, but no resting or action tremor present. The patient also had a shuffling gait which was unique because gait abnormalities are often seen in later stages of PD. The rest of the neurological examination was unremarkable and his brain MRI imaging was normal. Routine serological investigations which included a complete blood count, serum electrolytes including calcium, magnesium and phosphorus, liver function tests and a complete thyroid panel were also unremarkable.

A diagnosis of PD was considered and he was started on Levodopa/Carbidopa 100/25mg 3 times a day in which he responded very well. Genetic testing was performed by PCR amplification and sequencing analysis of the exon 41 which harbours 2 of the most common mutations (*p.Gly2019Ser* and *p.Ile2020Thr*). However, this was reported to be negative. PCR amplification and sequencing analysis of the coding region and exon-intron splice junctions of the LRRK2 gene showed a heterozygous mutation, *c.2697A>C* (*p.Glu899Asp*), a novel variant which has not been reported in the literature.

Case 2

A right-handed female of Middle Eastern descent presented with slowness of movements at the age of 28 years. She had difficulty controlling her balance and developed gait problems in the previous 6 months. Initially, she was diagnosed with depression by her general practitioner. She was single and worked as a nurse. Her parents were first cousins and she had 4 brothers. Her birth, developmental and family histories were unremarkable.

On examination, she had decreased facial expression and 1/4 hypophonia. There was 2/4 bradykinesia and 1/4 rigidity bilaterally. These symptoms were more prominent on the right side with no tremor.

Her brain MRI, EEG and serological investigations including 24 hour urine copper and serum ceruloplasmin were unremarkable. Genetic testing for LRRK2 showed

2 variants: *c.2501-10dupT* and *c.4939T>A*. The latter is a known pathogenic variant that has been previously described in patients with FP and is considered a risk factor for PD.

Case 3

This patient was a 15-year-old left-handed female of Canadian South Asian descent who was seen for a neurology consultation for an action tremor of both upper extremities. The finding of a tremor is unique and not usually seen in this age group. Her birth and developmental histories were normal. Her age of onset was at 5 years old when her parents noticed a tremor in both of her hands when she was holding various items. There was no significant progression until she reached 16 years of age where she started noticing slowness and fatigue, while the tremor of the upper extremities worsened.

She was a high school student with no family history of PD, essential tremor or any other neurological disorder. On examination, there was no resting tremor; she had 1/4 amplitude, low frequency postural and kinetic tremors of both upper extremities, more prominent on the right side. There was 1/4 rigidity in both upper extremities, more evident on the right. There was also 1/4 bradykinesia on the right and 2/4 reduced right arm swing. Brain MRIs and serological investigations including serum and urine copper and ceruloplasmin were normal. Genetic testing for Parkin gene mutations revealed a heterozygous Parkin gene mutation consisting of a whole exon 3 deletion. There were no mutations in LRRK2 or other genes detected.

Although it can be challenging to distinguish FP from idiopathic PD, there are certain clinical features that should raise a clinician's suspicion as to a potential genetic aetiology. A patient with an early age of onset, usually less than 40 years of age and a positive family history of PD in at least one first degree relative, should undergo genetic testing. It is also important to note that a negative family history does not exclude the possibility of FP. Regarding testing, DNA sequencing by the Sanger method in conjunction with PCR analysis is generally used to detect genetic mutations.

A wide range of phenotypic heterogeneity of PD is being increasingly recognised which makes it important for clinicians to keep a genetic etiology as part of their differential. This paper serves to highlight the importance of recognising the involvement of genetics and its role in the understanding and diagnosis of PD.

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Abdul Qayyum Rana, [1]*MD, FRCPC*, Talal Al-Harbi, [2]*MD*, Osama A Khan, [3]*MD*, Ami Patel, [4]*BSc*

[1]Parkinson's Clinic of Eastern Toronto & Movement Disorders Centre, Toronto, Ontario, Canada
[2]King Fahad Specialist Hospital, Dammam, Saudi Arabia
[3]Oakville Bone Centre, Oakville, Ontario, Canada
[4]Department of Life Sciences, University of Toronto, Ontario, Canada

Address for Correspondence: Dr Abdul Qayyum Rana, Parkinson's Clinic of Eastern Toronto and Movment Disorders Centre, 1371 Neilson Rd, Toronto, Canada M1B 4Z8.
Email: ranaaq@yahoo.com