Clinical, investigational and genetic profiles of seven patients with PARK-*SYNJ1*: An experience from a tertiary care center in India

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Background:

Synaptojanin-1 (**SYNJ1**) is a phosphoinositide phosphatase, critical for synaptic vesicle recycling and membrane dynamics.

It regulates the dephosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2), a lipid important in vesicle trafficking, endocytosis, and actin cytoskeleton remodeling.

Biallelic disease-causing variants involving the ***SYNJ1*** gene are associated with a spectrum of neurological disorders, primarily due to disrupted synaptic transmission and neuronal homeostasis.

Aims and Objectives:

The aim of our study is to describe the clinical-demographical, investigational, and genetic profiles of patients of PARK-*SYNJ1* and to draw a clinico-genetic correlation.

Methodology:

In this retrospective study, from our database, patients who had undergone exome sequencing and were confirmed to have biallelic ***SYNJ1*** variants were recruited.

Detailed demographic, clinical, biochemical, radiological data and genetic details of these selected patients were extracted through a chart review.

Variables	Family-1		Family-2	Family-3	Family-4		Family-5
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Demographics							
Age/AAO/ Gender	36y/31y/F	31y/30y/M	36y/24y/F	24y/18y/M	32y/12y/F	28Y/4Y/M	17y/1.5y/F
FH/Consang	+/+	+/+	+/+	-/-	+/+	+/+	-/-
Clinical picture on presentation							
DD/IDD	-	-	+	-	+	+	+
Parkinsonism	+	+	+	+	+	+	+
Cognitive decline	-	-	+	-	+	+	+
Seizures	-	-	+	-	+	+	+
Examination findings							
Dystonia	+	+	+	+	+	+	+
Parkinsonism	+	+	+	+	+	+	+
UPDRSIII OFF	54	25	60	20	45	NA	54
UPDRS III ON	43	20	48	15	35	NA	45
LID	++	++	+++	+	+	NA	+
Investigations							
Blood W/U	Normal	Normal	Normal	Normal	Normal	NA	Normal
MRI Brain	GPi Mineralization	GPi Mineralization	Cerebral atrophy	Mild GPi Mineralization	Cerebral and cerebellar atrophy	NA	GPi Mineralization
Genetics – SYNJ1 (NM_203446.3)							
Zygosity	Homozygous		Homozygous	Compound heterozygous	Homozygous		Homozygous
Variant	c.3339_3351dup; p.Thr1118GlyfsTer20		c.656G>A; p.Arg219G	c.1717C>T; p.Arg573Ter c.2495A>G; p.Gln832Arg	c.656G>A; p.Arg219Gln		c.1382G>A; p.Arg461Gln
Pathogenicity	P		LP	P/LP	P		VUS
Novel	Yes		No	Yes/No	No		Yes
Treatment and follow-up							
Levodopa	+	+	+	+	+	-	+
ASM	-	-	+	-	+	+	+
TLEDD	650	600	850	400	300	-	450
UPDRS III OFF (F/U)	52	28	60	22	40	-	54
UPDRS III ON (F/U)	35	10	44	9	31	-	45

Abbreviation: +: Present; -: Absent; AAO: Age at onset; ASM: Anti-seizure medications; Consang: Consanguinity; DD: Developmental Delay; F: Female: FH: Family history; F/U: Follow-up; GPi: Globus pallidus interna; IDD: Intellectual disability; LEDD: Total levodopa equivalent daily dose; LID: Levodopa-induced dyskinesia; LP: Likely Pathogenic; M: Male; MRI: Magnetic resonance imaging; NA: Not available; P: Pathogenic; UPDRSIII: Unified Parkinson Disease rating scale Part-III; VUS: Variant of uncertain significance; W/U: Workup.

Results:

7 patients (4 females, 3 males) were recruited from 5 families.

5 patients were born out of Consanguineous parentage

The median age at presentation was 31 (IQR: 24-36) years, and the age at symptom onset was 18 (IQR:4-30) years.

All presented with features of early-onset parkinsonism (EOP) with dystonia, while 4 out of 7 had developmental delay, intellectual disability, and seizures.

3 out of 6 patients (50 percent) who received levodopa had good improvement and all 6 had dopa-induced dyskinesia.

Median UPDRS-III (6 cases) OFF score was 49.5 (IQR-25-54)

Median UPDRS-III ON score was 39 (IQR-20-45).

MRI brain showed GPi mineralization in 4, cerebral atrophy in 1, and cerebral and cerebellar atrophy in 1 patient.

Blood investigations and other secondary workup were negative

Table 1: Demographics, clinical and investigational features , genetic profile, treatment details and follow up profile of the cohort.

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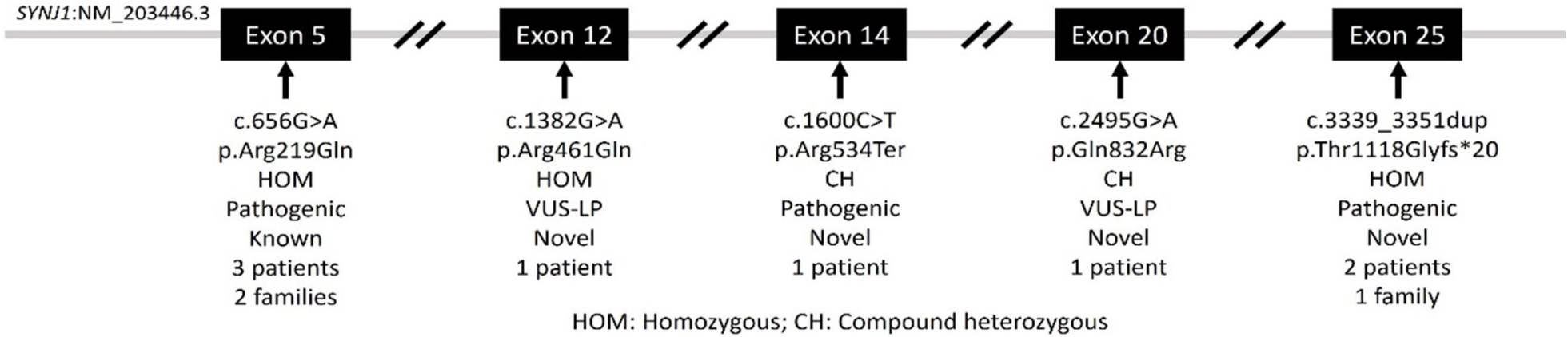

Fig 1: Diagram depicting the *SYNJ1* genetic variants identified in the cohort. Three of these variants were novel.

Results (Contd.):

Exome-sequencing revealed 5 unique variants of which 3 were novel (Fig-1).

All 3 patients with c.656G>A homozygous missense variant had atypical EOP presentation with seizures, intellectual disability, and psychosis, suggesting a possibility of clinical-genetic correlation.

In contrast, the 2 patients with homozygous frameshift duplication (c.3339_3351dup) had typical EOP presentation.

Conclusions:

PARK-*SYNJ1* is an important cause of early onset PD.

The presentation can be both typical and atypical, with additional symptoms of seizures, and cognitive and behavioral abnormality.

Despite having a suboptimal response to levodopa, they are prone to develop levodopa-induced dyskinesia.

Hence genetic correlation and appropriate pharmacotherapy helps in early detection and proper management.

References:

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