Whole-Exome Sequencing in a Movement Disorders Clinic

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Objective

- To evaluate the diagnostic utility of whole exome sequencing (WES) in patients from a movement disorder clinic.

Background

- Many patients with suspected genetic movement disorders do not have a known molecular diagnosis.
- Molecular diagnosis can significantly impact patients and their families by guiding treatment, providing prognostic information and informing genetic counseling for at-risk family members.

Methods

- We performed a retrospective chart review of movement disorder patients evaluated in our clinic with WES analyzed between January 2013 and December 2020.
- Cases were ascertained through a search of the electronic medical records for presence of multiple movement disorder phenotypes, early age at onset, or positive family history.

Results

- WES was requested for 41 patients and 28 (68.3%) received WES results; the other 13 (31.7%) were denied approval by their insurance company.
- The median age at symptom onset was 20.5 years (range: birth-63 years).
- The median age at testing was 45.5 years (range: 4-69 years).
- A positive family history of a movement disorder in a 1st or 2nd degree relative was present in 57.1% of patients.
- 46% of the patients had undergone targeted genetic testing prior to WES.
- The molecular diagnostic yield in our WES cohort was 17.9% (5/28 patients).

Figure 1: Predominant movement disorder phenomenology for which WES was completed

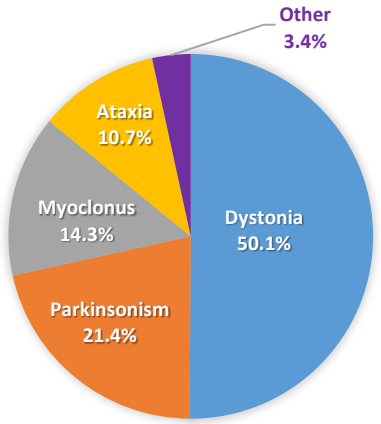

Table 1: Genes with pathogenic variants detected in our WES cohort

Gene	Variant	Movement Disorder	Diagnosis	Zygosity	Inheritance
PANK2	p.K478E: c.1432A>G	Dystonia	Neurodegeneration with brain iron accumulation (NBIA)	Het	AR
SPG11	p.E1630X: c.4888G>T	Spasticity	Hereditary spastic paraplegia (HSP)	Het	AR
PSEN1	p.E120G: c.359A>G	Myoclonus	Early-onset dementia	Het	AD
TOR1A	p.E303del: c.907_909delGAG	Dystonia	Torsion dystonia	Het	AD
GLRA1	p.E403del: c.1207_1209delGAG	Dystonia	Hereditary hyperkplexia	Het	AD

Conclusions

- WES has an important diagnostic value in movement disorder patients, particularly in those with atypical presentation and high index of suspicion for genetic etiology.