Title:

Clinical Diagnostic Exome Sequencing in Dystonia: the Challenges of Genetic Testing for Complex Conditions

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Description:

Introduction: Dystonia is a group of clinically and genetically heterogeneous disorders characterized by involuntary muscle contractions producing abnormal posturers and/or repetitive movements. Due to the diverse clinical manifestations, diagnosis can be challenging. If a genetic etiology can be determined, targeted therapies can be initiated and symptoms may be reduced. The continual discovery of new genetic etiologies for dystonia can aid in treatment but also underscores the complexity of genetic testing. With the ability to re-analyze and test for newly reported or novel genetic etiologies, Diagnostic exome sequencing (DES) may have clinical utility in the treatment of dystonia.

Methods: In an unselected cohort of 189 patients with reported dystonia referred for DES who then underwent characterized and/or novel candidate gene analysis (probands with informative family members in which novel genetic analysis was requested), the overall results categories were determined according to predefined diagnostic variant assessment criteria. Available clinical information was reviewed, due to the clinical complexity of distinguishing between dystonia and pseudo dystonia with record review,

cases with dystonic posturing or dystonia like symptoms were also included in analysis.

Results: Of the1 189 cases referred for genetic testing, all cases had additional findings beyond dystonia. 100 (52.9%) had intellectual disability/ developmental delay, 72 (38.1%) had seizures/epilepsy, 31 (16.4%) had dysmorphic features, 29 (15.3%) had psychiatric issues, 16 (8.5%) had autism spectrum disorder and 1 (5.8%) had multiple congenital anomalies reported. In addition, 71 (37.6%) had gastrointestinal, 61 (32.3%) ophthalmologic, 49 (25.9%) craniofacial, 25 (13.2%) endocrine, 23 (12.1%) cardiovascular, 20 (10.6%) allergy/immunologic/ infectious, 19 (10.0%) genitourinary, 18 (9.5%) audiologic/ otolaryngologic, 17 (9.0%) pulmonary, 13 (6.9%) dermatologic, 12 (6.3%) hematologic, 6 (3.2%) renal, 5 (2.6%) dental, and 4 (2.1%) oncologic findings.

Of 189 probands, 41 (21.7%) had Positive/Likely Positive results and 23 (12.2%) had uncertain findings in characterized genes. Out of 122 cases in which uncharacterized or novel gene analysis was performed 8 (6.6%) had novel candidate findings. 177 (61.9%) of cases were negative results.

Of the positive/likely cases, 2 cases were initially reported as negative, 1 as a finding novel gene and 2 uncertain in a different gene and later re-classified as positive due to prospective, proactive re-analysis, thus increasing the diagnostic rate 2.6%. 151 (79.9%) of cases had previous genetic testing. Three cases were found to have findings in two genes (*GNAO1* and *ATP2B3, ANO3* and *NALCN,* and *ATRX* and *G6PD*).

Conclusion: Genetic testing for dystonia is important as the diagnosis of genetic etiologies in several genes can lead to therapeutic decisions. The absence of genetic findings in these genes also demonstrates that medications such as Levodopa may not be helpful. While panel specific testing may be helpful in certain cases, DES has the advantage of re-classification for new genes in this rapidly changing field. There are also advantages as many cases are not straightforward. Many individuals have complex clinical presentations along with the confusion of potential psychogenic dystonia. While it is best for individuals with dystonia or dystonia-like symptoms to be evaluated by experts in this field, any individuals are being tested before these additional conditions are ruled out.

Detection rates of individuals that present with dystonia or potential dystonia are similar to individuals with other genetic conditions undergoing DES; many having previous genetic testing. While some of these conditions expand upon the known phenotypes of conditions (as is common in dystonias), other may be explained by complex patients with multiple findings may potentially have a psychogenic dystonia.

Genetic testing for dystonia continues to be challenging, but DES has unique advantages that align well with the ever expanding list of genes underlying this disorder, the complexity of clinical diagnosis and precision medicine obtained by these test results.

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Brain/Nervous System
Genetic Testing
Neuroscience
Whole exome sequencing

Primary Topic Focus:
Clinical Cytogenetics and -Genomics

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Learning Objective 1:	Describe the characteristics and detection rates of patients with dystonia undergoing clinical exome sequencing