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

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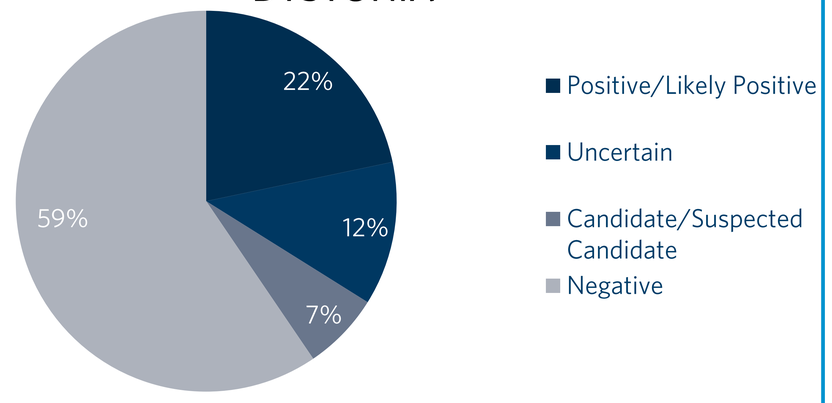
BACKGROUND

- Dystonia is a group of clinically and genetically heterogeneous disorders characterized by involuntary muscle contractions producing abnormal posturers and/or repetitive movements (1).
- Due to the diverse clinical manifestations in dystonia, diagnosis can be challenging, but if a genetic etiology can be determined, targeted therapies can be initiated and symptoms may be reduced (2).
- 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.

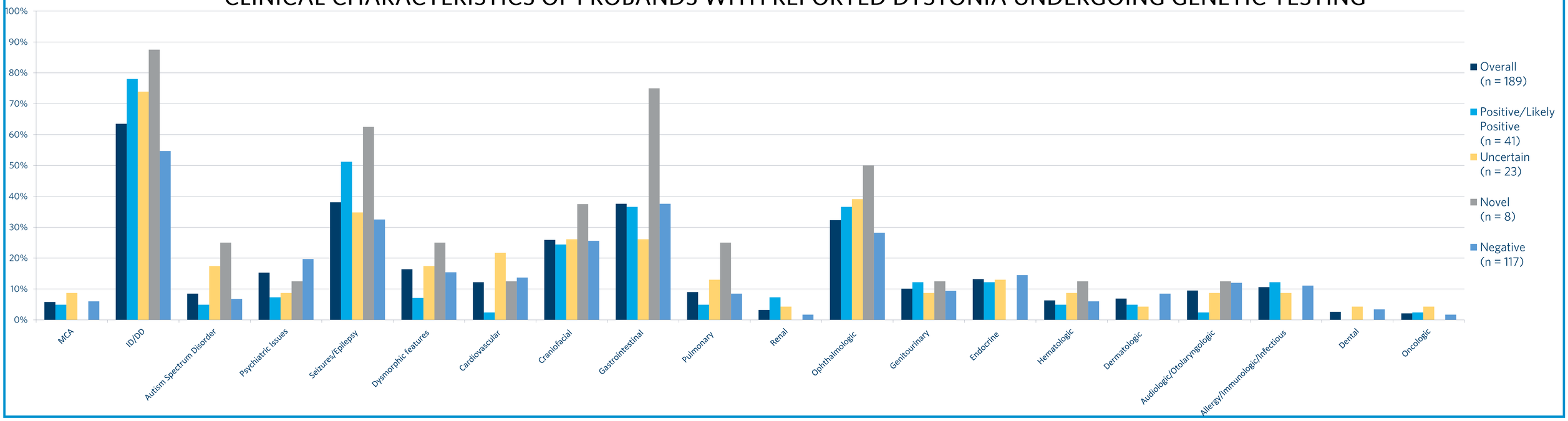
METHODS

- 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 (3).
- 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.

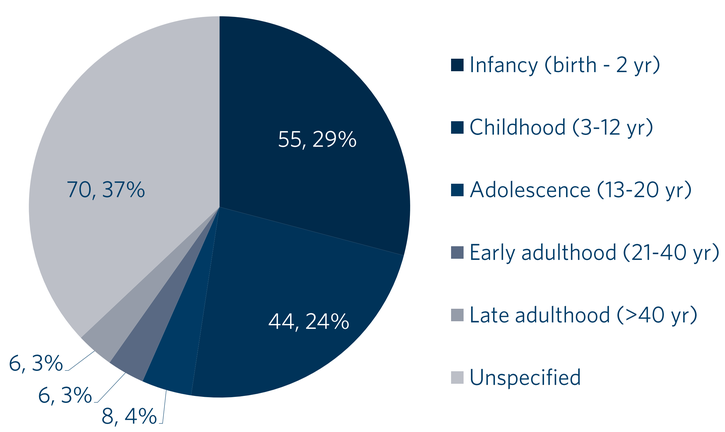
DETECTION RATES OF INDIVIDUALS WITH DYSTONIA



CLINICAL CHARACTERISTICS OF PROBANDS WITH REPORTED DYSTONIA UNDERGOING GENETIC TESTING



AGE OF ONSET OF DYSTONIA SYMPTOMS



GENE FINDINGS

ADAR	Aicardi-Goutières syndrome 6	*KCNQ2* (3 cases)	Epilepsy syndrome
ADCY5	Dyskinesia, Familial, with Facial Myokymia	*KIF1A* (2 cases)	Mental Retardation, Autosomal Dominant 9
AMPD2	*AMPD2*-related Neurodegenerative Brainstem Disorde	*KMT2B* (2 cases)	Isolated Dystonia Gene
ANO3	Isolated Dystonia Gene	*MT-ND6*	Leigh syndrome
ATP2B3	Spinocerebellar ataxia, X-linked 1	*NACC*	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination
ATRX	*ATRX* X-linked disability*	*NALCN*	Neuroaxonal neurodegeneration, infantile, with facial dysmophism
CDKN2A	Familial atypical multiple mole melanoma syndrome	*NEFL*	Charcot-Marie-Tooth disease, type 1F
COL4A1	*COL4A1*-associated disorders	*NKX2-1*	Choreoathetosis, Hypothyroidism, and Neonatal Respiratory Distress
CRYAA	Congenital cataract 9*	*PANK2*	Pantothenate Kinase-Associated Neurodegeneration
DDX3X	Intellectual disability, X-linked 102	*PIGN*	Multiple congenital anomalies-hypotonia-seizures syndrome 1
ECHS1	ECHS1-related paroxysmal exercise-induced dystonia	*PMM2*	Congenital disorder of Glycosylation
FA2H	Spastic Paraplegia 35, Autosomal Recessive (O)	*SATB2*	Glass syndrome
G6PD	G6P deficiency*	*SHOC2*	Noonan like*
GABRG2	Epilepsy syndrome	*SLC16A2*	Allan-Herndon-Dudley syndrome
GCH1	Dystonia plus Parkinsonism Gene	*SLC18A2*	*SLC18A2*-related disorder of biogenic amine neurotransmitters
GLB1	GM1-gangliosidosis	*TUBA1A*	Lissencephaly 3
GNAO1 (2 cases)	Epilepsy syndrome	*WARS2*	Mitochondrial condition
GRIA3	Epilepsy syndrome	*ZNF335*	Microcephaly 10, primary, autosomal recessive
GRIN2B	Epilepsy syndrome		

TAKE-HOME POINTS

- Genetic testing for dystonia is important as the diagnosis of genetic etiologies in several genes can lead to therapeutic decisions.
- 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. 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.

REFERENCES

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