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Clinical Diagnostic Exome Sequencing in Patients with Neuromuscular Disorders: Genetic Testing Challenges for Complex Conditions

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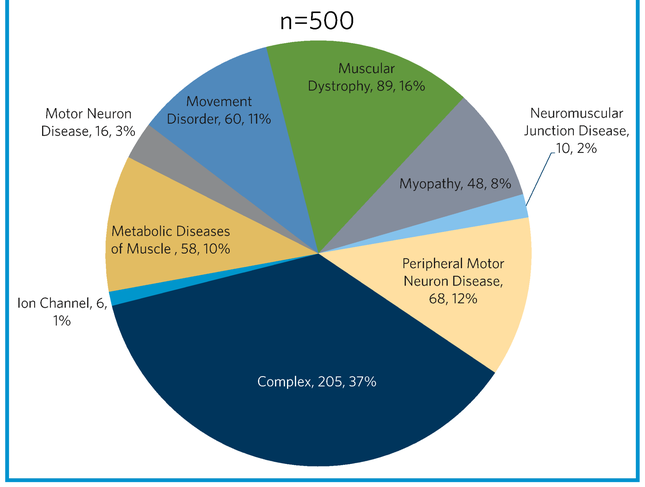
BACKGROUND

- Neuromuscular disorders (NMDs) are a group of clinically and genetically heterogeneous disorders characterized by nerve, muscle, or neuromuscular junction dysfunction presenting with a variety of features.
- Due to the diverse clinical manifestations, diagnosis can be challenging. If a genetic etiology can be determined, gene- or pathogenic alteration-specific clinical and experimental therapies could possibly be initiated.
- While the clinical utility of targeted panels has been studied, to date no studies have investigated clinical diagnostic exome sequencing (DES) in a large cohort of patients with suspected NMDs.

METHODS

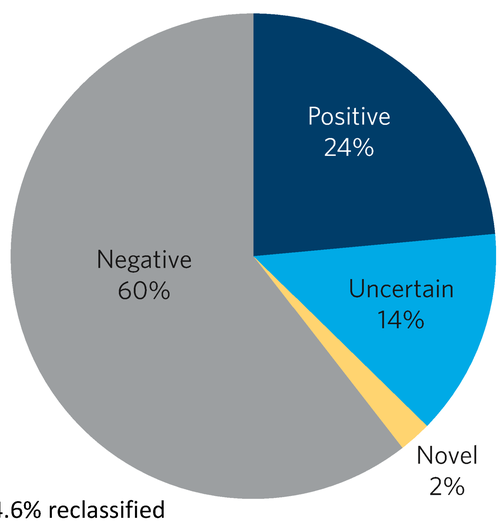
- In an unselected cohort of 560 patients with reported suspected NMDs referred for DES, the overall results categories were determined according to predefined diagnostic variant assessment criteria.
- Classification of potential NMD type was performed using previously established recommendations and provider report.
- Complex cases are defined as those having a differential diagnosis of multiple NMD categories.
- Cases with a previous diagnosis and/or uncertain neuromuscular finding were excluded from analysis.
- Cases in which a finding was reported due to clinical features of the patient beyond the NMD features (for example, cataracts) were excluded from detection rates (3 cases).
- Statistical analysis was performed using Fishers exact test.

NEUROMUSCULAR CATEGORY



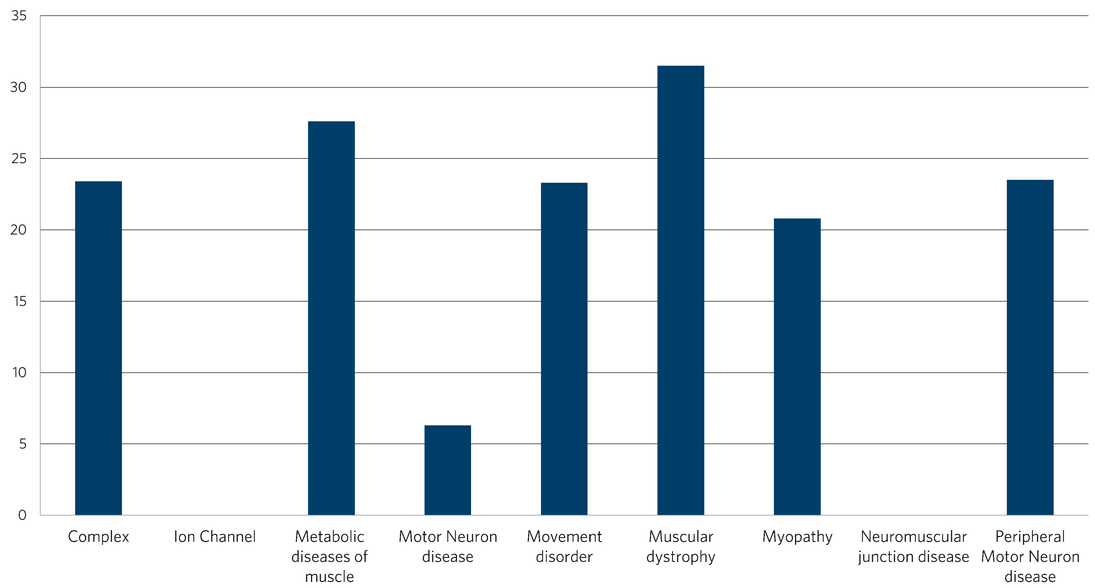
DETECTION RATES

OVERALL*



*4.6% reclassified

BY NM CATEGORY



GENE FINDINGS

CHARACTERIZED GENES

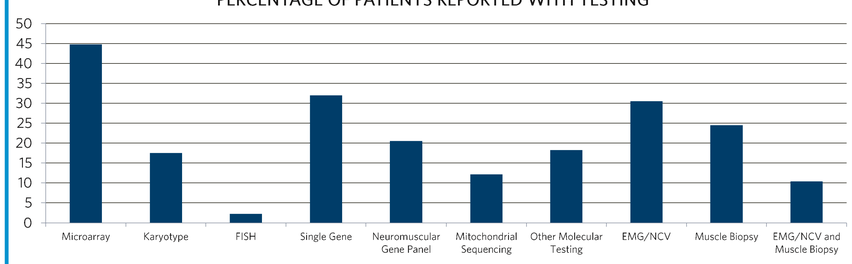
AARS	*CTNNB1*	*ITPR1*	*PDE6A*	*SLC52A2 (2)*
ABCB7	*CYP7B1*	*KCNQ2*	*PDHA1 (2)*	*SLC9A1*
ACTA1	*DMD (3)*	*KIAA2022*	*PHF8*	*SOX10*
ADCY5	*DNA2*	*KIF1A*	*PIEZO2 (2)*	*SPAST*
AGK	*DOK7 (2)*	*LAMA2 (2)*	*PLP1 (2)*	*SPG20*
ANG	*DYNC1H1*	*LINS*	*PMP22 (2)*	*SPG7 (2)*
ASXL3	*EBF3 (2)*	*LMNA (3)*	*PNPLA2*	*STAT1*
ATL1	*ECHS1*	*LRP5*	*POLG*	*TBCK*
ATP1A3	*ETFDH*	*MECP2*	*POMGNT1 (2)*	*TNNT1*
ATP8A2	*FDXR*	*MFN2 (2)*	*PRODH*	*TNNT3*
BCS1L	*FKRP*	*MORC2 (2)*	*RMND1*	*TPM2*
BICD2	*FLVCR1*	*MPZ*	*RYR1 (7)*	*TPM3*
CACNA1A (2)	*FUS*	*MPZ (3)*	*SACS (2)*	*TSEN54*
CACNA1E	*GARS*	*MT-ATP6*	*SACS*	*TUBA1A*
CAPN3	*GFER*	*MTM1*	*SCN1A*	*TUBB3*
CHRNA1	*GJB1 (2)*	*MT-ND5*	*SCN4A*	*TYMP*
CLCN1	*GNAO1 (2)*	*MT-TL1*	*SCN5A*	*VMA21*
CLCN1	*HADHA*	*NDUFAF2*	*SCN8A*	*VPS13B*
COL6A1	*HEXA*	*NEB (4)*	*SCN9A*	*VPS35*
COL6A2 (3)	*HIBCH*	*NFIA*	*SH3TC2*	*VRK1*
COL6A3	*HIVEP2*	*NKX1-2*	*SLC16A2 (2)*	*WISP3*
COQ8A	*HRAS*	*NKX2-1*	*SLC22A5*	
CREBBP	*HSPB1*	*PANK2*	*SLC26A2*	
CTBP1	*HSPB8*	*PAX9*	*SLC39A14*	

NOVEL CANDIDATE

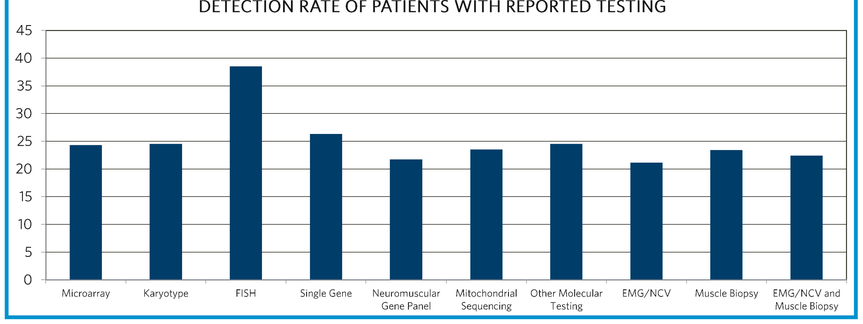
ADCY5
KLF7
LAS1L
MADD
MSTO1
POU3F3
SLC12A6

PREVIOUS REPORTED TESTING

PERCENTAGE OF PATIENTS REPORTED WITH TESTING



DETECTION RATE OF PATIENTS WITH REPORTED TESTING



ADDITIONAL DATA

- 16 cases with findings in 2 genes
- Positive rates:
  - Trios-25.4%
  - Duos-21.4%
  - Proband-19.7%

Additional features	n	% with involvement	Detection rate
Multiple Congenital Anomalies	41	7.3%	34.1%
ID/DD	282	50.4%	29.4%
Autism Spectrum	34	6.1%	20.6%
Psychiatric	54	9.6%	14.8%
Seizures/Epilepsy	67	12.0%	29.9%
Movement Disorder	192	34.3%	21.4%
Abnormal Brain MRI	139	24.8%	25.9%
Phenotype is Progressive	184	32.9%	21.7%
Dysmorphic Features	108	19.3%	25.0%
Failure to thrive/ Undergrowth	113	20.2%	35.4%
Overgrowth	20	3.6%	15.0%
Hypotonia	210	37.5%	31.9%

Organ System Involvement	n	% with involvement	Detection rate
Allergy/ Immunologic/ Infectious	42	7.5%	16.7%
Audiologic/Otolaryngologic	70	12.5%	21.4%
Cardiovascular	93	16.6%	21.5%
Craniofacial	101	18.0%	25.7%
Dental	21	3.8%	28.6%
Hematologic	29	5.2%	17.2%
Dermatologic	65	11.6%	15.4%
Endocrine	65	11.6%	12.3%
Gastrointestinal	183	32.7%	20.2%
Genitourinary	60	10.7%	23.3%
Metabolic/ Biochemical	93	16.6%	24.7%
Musculoskeletal/ Structural	457	81.6%	23.9%
Neurologic	536	95.7%	24.3%
Obstetric	4	0.7%	25.0%
Oncologic	7	1.3%	0.0%
Ophthalmologic	137	24.5%	23.4%
Pulmonary	85	15.2%	27.1%
Renal	20	3.6%	30.0%

CONCLUSION

- Genetic testing for NMDs is important as diagnosis of genetic etiologies can lead to therapeutic decisions.
- While panel-specific testing may be helpful in certain cases (such as suspected trinucleotide repeat disorders), DES has the advantage of reclassification for new genes and correct diagnosis for individuals with complex clinical presentations.
- While not significant, the detection rate for trio cases was highest; suggesting family centered exome as most beneficial.
- Genetic testing for NMDs continues to be challenging, but DES has unique advantages of testing for multiple classifications of NMDs at the same time due to the complexity of clinical diagnosis, and is uniquely positioned to identify dual diagnoses, novel candidate gene findings, and findings in newly characterized genes.