Congenital Myasthenia Syndromes Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing of 19 Genes

Panel Gene List

AGRN, ALG2, ALG14, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, COLQ, DOK7, DPAGT1, GFPT1, GMPPB, LRP4, MUSK, RAPSN, SCN4A, SYT2

Clinical Features

Congenital myasthenia (CM) describes a heterogeneous group of disorders that result from the disruption of the structure and function of the neuromuscular junction, and are characterized by fatigable weakness of skeletal muscle[1, 3]. Age-of-onset, pattern of weakness and disease severity are variable, but affected muscles groups may include limb, trunk, bulbar, respiratory, facial, and extra-ocular[2]. Features of CM typically present shortly after birth or early childhood, although rare cases have been reported with late childhood or early adulthood onset[3]. In neonates with CM, major findings include feeding difficulties, poor suck and cry, choking spells, and ptosis. Additionally, arthrogryposis multiplex congenital, respiratory insufficiency, sudden apnea, and cyanosis may be observed in severe cases[3]. Individuals with later onset CM may present with muscle fatigability and difficulty running or climbing stairs, delayed motor milestones, and extraocular muscle weakness. Minor symptoms may be exacerbated by fever, infections, or excitement. Diagnosis of CM is based on clinical findings, a decremental EMG response, positive family history, genetic testing, and absence of anti-acetylcholine receptor and anti-muscle-specific tyrosine kinase (MuSK) antibodies[3]. This is in contrast to the more common myasthenia gravis, which manifests as a result of an autoimmune disease and will be positive for MuSK antibodies[4]. This test is not diagnostic of myasthenia gravis[3].

Genetics

CM is typically inherited in an autosomal recessive pattern; however four genes included on this panel (*CHRNA1, CHRNB1, CHRND, CHRNE*) have been associated with both autosomal recessive and autosomal dominant inheritance. Congenital myasthenic syndromes (CMS) have been classified into three subtypes based on the location of the affected protein within the neuromuscular junction: presynaptic, synaptic basal lamina-associated, and postsynaptic.[5] Presynaptic myasthenic syndromes are due to pathogenic variants in the *CHAT* and *SYT2* genes, which catalyzes acetylcholine production and acts as a calcium sensor in the neuromuscular junction,respectiviely.[5, 20] Synaptic basal lamina-associated myasthenia can be due to pathogenic variants in the *COLQ* gene, which anchors acetylcholinesterase to the synaptic basal lamina, or the *AGRN* gene which is critical for the formation of the neuromuscular junction.5 Most forms of CMS (85%) are classified as post-synaptic.[5] Genes associated with these syndromes include *CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, RAPSN, DOK7, MUSK, LRP4*, and *SCN4A*. Five of these genes, *CHRNA1, CHRND, CHRNE*, and *CHRNG* encode the transmembrane subunits of the adult nicotinic acetylcholine receptor (AChR).1 Pathogenic variants in any of the subunits can alter ion function. Gain of function variants are dominantly inherited and lead to prolonged channel openings (slow channel syndrome). Loss of function variants are recessively inherited and lead to shortened channel openings (fast channel syndrome).[1, 3] The most common cause of postsynaptic CMS are pathogenic variants in CHRNE that lead to AChR deficiency syndrome1. The *LRP4, MUSK, DOK7*, and *RAPSN* genes are components of a signaling pathway necessary for neuromuscular endplate development and maintenance.4, 18 SCN4A encodes a sodium ion channel that plays a role in action potential propagation.[3] Additionally, genes involved in Nglycosylation (*GFPT1, DAPGT1, ALG2, ALG14, GMPPB*) have also been associated with CMS.[4]

Test Methods

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Clinical Sensitivity

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Congenital Myasthenia Panel depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below.

Diagnostic Yield of Congenital Myasthenia Panel Genes in Selected Populations

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selcted Population(s)[a]
AGRN	AR	Agrin deficiency	Rare[1,2]
ALG2	AR	ALG2- related CMS	Rare[3,4]
ALG14	AR	ALG14-related CMS	Rare[16]
CHAT	AR	Choline acetyltransferase deficiency	5%[5]
CHRNA1	AD/AR	Acetlycholine receptor deficiency Slow channel congenital myasthenia Fast channel congenital myasthenia	<1%[6]
CHRNA1	AD/AR		<1%[6]
CHRND	AD/AR		<1%[6]
CHRNE	AD/AR		49%[6]; Founder mutations in European, Brazilian, and African populations [6,7, 8, 15]
CHRNG	AR	LMPS; Escobar syndrome (EVMPS)	~27% of EVMPS;[23] 5-8% patients with LMPS/FADS;[22-23] 7-10% for AMC[21,24]
COLQ	AR	End plate acetylcholinesterase deficiency	13%[5]

DOK7	AR	DOK7-related CMS	10^{5} - 21%[11] ; Founder mutation in European, Canadian, and Brazilian populations [6,9, 10]
DPAGT1	AR	DPAGT1-related CMS	<1% [12]
GFPT1	AR	GFPT1- related CMS	4% [6]
GMPPB	AR	GMPPB-related CMS	Rare [17]
LRP4	AR	LRP4-related CMS	Rare [18]
MUSK	AR	MuSK deficiency	Rare[5,6]
RAPSN	AR	Rapsyn deficiency	15^{5} -20%[11]; Founder mutation in European, and Indian populations 6,13, 14
SCN4A	AR	Sodium channel myasthenia	Rare [5,6]
SYT2	AD	SYT2-related CMS	Rare [19,20]

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