

Rapsyn-Related Disorders *via RAPSN* Gene Sequencing (Test #466)

Congenital Myasthenic Syndrome Fetal Akinesia Deformation Sequence

Brief Description of Clinical Features: Congenital myasthenic syndromes (CMS) are disorders of the neuromuscular junction resulting from defects in presynaptic, synaptic, or post synaptic proteins. Postsynaptic congenital myasthenic syndromes (OMIM #608931) can result from a deficiency or kinetic abnormality of the acetylcholine receptor. The protein rapsyn is encoded by *RAPSN* (OMIM #601592) and acts as a link connecting the acetylcholine receptor to the cytoskeleton-anchored dystrophin-glycoprotein complex at the neuromuscular junction, thereby stabilizing acetylcholine receptor clustering (Apel et al. *Neuron* 15:115-126, 1995). Clinical symptoms of post synaptic CMS include weakness of ocular, bulbar and limb muscles. Manifestations in the newborn period include respiratory insufficiency, poor suck and cry, feeding difficulty with choking, and facial weakness including ptosis (Abicht and Lochmüller *GeneReviews*, 2006). Patients with onset in childhood show exercise induced weakness with difficulty climbing stairs or running (Abicht and Lochmüller *GeneReviews*, 2006). Fetal akinesia deformation sequence (FADS, Pena-Shokeir syndrome, type I; OMIM #208150) is characterized by prenatal onset growth deficiency; multiple joint contractures; facial anomalies including low set and malformed ears, hypertelorism, and micrognathia; hypoplastic dermal ridges; and pulmonary hypoplasia. In some cases FADS is caused by mutations in *RAPSN* (Vogt et al. *Am J Hum Genet* 82:222-227, 2008; Michalk et al. *Am J Hum Genet* 82:464-476, 2008).

Genetics: Congenital myasthenic syndrome and fetal akinesia deformation sequence due to *RAPSN* gene mutations are inherited as autosomal recessive disorders. One mutation, p.Asn88Lys in exon 2, has been found repeatedly in CMS patients of European ancestry (Müller et al. *J Med Genet* 41:e104, 2004; Dunne and Maselli *J Hum Genet* 49:366-369, 2004). It should be noted that European CMS patients with *RAPSN* mutations other than p.Asn88Lys have also been reported (Müller et al. *Neurology* 67: 1159-1164, 2006). A milder clinical course has been seen in patients homozygous for the common mutation (Dunne and Maselli *J Hum Genet* 48:204-207, 2003). A founder mutation of the *RAPSN* promoter occurs in Near-Eastern Jews and results in prognathism, malocclusion, high arched palate, and crowded teeth (Ohno et al. *Hum Mol Genet* 12:739-748, 2003).

Description of This Particular Test: Rapsyn is encoded by the *RAPSN* gene located on chr 11p11.2. Testing is accomplished by amplifying the promoter and 8 coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Exon 2 is sequenced first. If two causative mutations are not found in exon 2, the remainder of the gene can be sequenced.

Reference Sequences: **Genomic:** NC_000011.8 **mRNA and Protein:** CCDS 7936.1

Indication for Testing: Individuals with a typical pattern of muscle weakness, decreased EMG signals with compound muscle action potential, and negative anti-acetylcholine receptor antibodies in serum. Individuals with fetal akinesia sequence and autosomal recessive inheritance.

Sensitivity of Test: *RAPSN* may account for ~20% of all CMS (Abicht and Lochmüller *GeneReviews*, 2006). FADS has multiple etiologies and *RAPSN* mutations are likely a rare cause.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *RAPSN*** **exon 2: \$ 190** **exons 1-8: \$ 590**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x9	83898 \$ 160	Sequencing x9	83904 \$ 230
Separation x1	83894 \$ 50	Interpretation/Report x1	83912 \$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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