

Pena-Shokeir Syndrome, Type I (Fetal Akinesia Deformation Sequence) via *RAPSN* and *DOK7* Sequencing (Test #413)

Brief Description of Clinical Features: Pena-Shokeir syndrome, type I (fetal akinesia deformation sequence, FADS; OMIM #208150) is characterized by prenatal onset growth deficiency, multiple joint contractures, facial anomalies, hypoplastic dermal ridges, and pulmonary hypoplasia. Patients are often stillborn and most liveborn patients succumb to the effects of pulmonary hypoplasia in the first month of life. Head circumference is often normal. Patients have contractures of multiple joints including wrists, ankles, elbows, knees, and hips. Limbs are also affected by captodactyly, rocker bottom feet and clubfoot. Craniofacial features include an apparently short neck, simple and posteriorly rotated ears, hypertelorism, prominent eyes, epicanthal folds, micrognathia, small mouth, and high arched palate. Affected pregnancies may be complicated by polyhydramnios and some patients are born prematurely. Other findings at birth include a short umbilical cord and small placenta. Phenotypic overlap exists between Pena-Shokeir syndrome and trisomy 18.

Genetics: Abnormalities of proteins involved with neuromuscular transmission underlie Pena-Shokeir syndrome, multiple pterygium syndromes, congenital myasthenia syndrome, and limb girdle myasthenia syndrome. These disorders, which may represent a phenotypic continuum of a single entity, are most often inherited in an autosomal recessive manner. The etiology of decreased fetal movement is heterogeneous, thus identification of the underlying cause is necessary to predict recurrence risk and patient outcome. Pena-Shokeir syndrome may result from truncating mutations in *RAPSN* (Vogt et al. *Am J Hum Genet* 82:222-227, 2008) or *DOK7* (Vogt et al. *J Med Genet* 46:338-340, 2009). Other causes include primary neurogenic (Hageman et al. *Neuropediatrics* 18:45-50, 1987), prenatal exposure (Lavi et al. *Neurology* 41:1467-1468, 1991), and circulating maternal antibodies to the acetylcholine receptor (Brueton et al. *Am J Med Genet* 92:1-6, 2000). The protein encoded by *DOK7* induces autophosphorylation of the skeletal muscle receptor-like tyrosine kinase, a key protein involved in postsynaptic differentiation (Okada et al. *Science* 312:1802-1805, 2006). The protein rapsyn acts as a link connecting the acetylcholine receptor to the cytoskeleton-anchored dystrophin-glycoprotein complex at the neuromuscular junction (Apel et al. *Neuron* 15:115-126, 1995).

Description of This Particular Test: Testing of the two genes is carried out in the order specified by the client. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences:

Gene:	Genomic: NC	mRNA: NM	Protein: NP	CCDS:
<i>RAPSN</i>	000011.8	005055.3	005046.2	7936.1
<i>DOK7</i>	000004.10	173660.3	775931.3	3370.2

Indication for Testing: Stillbirths or newborns with the Pena-Shokeir phenotype and autosomal recessive inheritance.

Sensitivity of Test: Analytical sensitivity may be limited because some reported *DOK7* mutations are not expected to be detected by genomic DNA sequencing (Selcen et al. *Ann Neurol* 64:71-78, 2008). Clinical sensitivity may be low because fetal akinesia has multiple underlying causes including environmental, immunological, and genetic.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *RAPSN*, *DOK7*

Gene	CPT Codes						Total
	83890	83891	83898	83904	83894	83912	
<i>RAPSN</i>	\$ 30 x1	\$ 40 x1	\$ 160 x9	\$ 230 x9	\$ 50 x1	\$80 x1	\$ 590
<i>DOK7</i>	\$ 30 x1	\$ 40 x1	\$ 140 x8	\$ 210 x8	\$ 40 x1	\$80 x1	\$ 540
Panel	\$ 30 x1	\$ 40 x1	\$ 300 x17	\$ 440 x17	\$ 90 x1	\$ 160 x1	\$ 1,060*

*When both genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

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