

Multiple Pterygium Syndromes via *CHRNA1*, *CHRND*, and *CHRNA1* Gene Sequencing (Test #415)

Brief Description of Clinical Features: Like fetal akinesia deformation sequence, the multiple pterygium syndromes may be caused by impaired intrauterine movement secondary to abnormalities in proteins at the neuromuscular junction. Lethal multiple pterygium syndrome (LMPS, OMIM # 253290) is characterized by prenatal growth deficiency, contractures, pterygia, and dysmorphic facies. Joint contractures and multiple pterygia are universal findings. Patients are stillborn or do not survive beyond the newborn period. Pulmonary hypoplasia is likely the primary cause of mortality. Contractures are found at the elbows, knees, hips, shoulders, hands, and feet. Pterygia are found between the chin and sternum as well as the popliteal, axillary, antecubital, and ankle areas. Facial features include ocular hypertelorism, epicanthal folds, small chin and mouth, and low-set ears. Patients commonly are born with hydrops, and pregnancies are affected with polyhydramnios. Escobar syndrome or Escobar variant of multiple pterygium syndrome (OMIM #265000) has clinical features that are similar to but milder than LMPS. Patients have normal intelligence and most are able to walk. Pterygia occur at the neck, axillae, popliteal, antecubital and intercrural areas. Facial features include ptosis, hypertelorism, small chin and mouth, long philtrum, and low-set ears. Patients may have difficulty opening their mouths widely and exhibit an emotionless facial appearance. Other findings include camptodactyly, syndactyly, club feet, and hypoplastic genitalia. Respiratory complications resulting from scoliosis and kyphosis may occur.

Genetics: Abnormalities of proteins involved with neuromuscular transmission underlie multiple pterygium syndromes, congenital myasthenia syndrome, limb girdle myasthenia syndrome, and Pena-Shokeir syndrome. These disorders, which may represent a phenotypic continuum of a single entity, are most often inherited in an autosomal recessive manner. Mutations in *CHRNA1* cause both LMPS and Escobar syndrome (Hoffman et al. *Am J Hum Genet* 79:303-312, 2006; Morgan et al. *Am J Hum Genet* 79:390-395, 2006). *CHRNA1* and *CHRND* mutations underlie LMPS (Michalk et al. *Am J Hum Genet* 82:464-476, 2008).

Description of This Particular Test: Testing of the three 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>CHRNA1</i>	000002.11	001039523.2	001034612.1	33331.1
<i>CHRND</i>	000002.11	000751.1	000742.1	2494.1
<i>CHRNA1</i>	000002.11	005199.4	005190.4	33400.1

Indication for Testing: Stillborn patients with features of LMPS or patients with features of Escobar syndrome.

Sensitivity of Test: Analytical sensitivity should be high because the mutations reported are readily detectable by gene sequencing. 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: *CHRNA1*, *CHRND* and *CHRNA1*

Gene	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>CHRNA1</i>	\$ 30 x1	\$ 40 x1	\$ 190 x10	\$ 290 x10	\$ 50 x1	\$ 80 x1	\$ 680
<i>CHRND</i>	\$ 30 x1	\$ 40 x1	\$ 230 x12	\$ 340 x12	\$ 50 x1	\$ 80 x1	\$ 770
<i>CHRNA1</i>	\$ 30 x1	\$ 40 x1	\$ 210 x11	\$ 320 x11	\$ 50 x1	\$ 80 x1	\$ 730
Panel	\$ 30 x1	\$ 40 x1	\$ 570 x33	\$ 860 x33	\$ 150 x1	\$ 240 x1	\$ 1890*

*When two or more of the 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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