

## Distal Arthrogyrosis Syndrome Panel (Test #335)

**Brief Description of Clinical Features:** Distal arthrogyrosis (DA) syndromes are a group of multiple congenital contracture disorders with distal joint involvement, variable clinical expression, and autosomal dominant inheritance (Bamshad et al. *Am J Med Genet* 65:277-281, 1996). Distal arthrogyrosis 2A (DA2A, OMIM #193700), or Freeman-Sheldon syndrome (FSS), is the most severe DA syndrome. Patients with FSS have, in addition to distal joint contractures, facial findings secondary to contractures of facial muscles. A small mouth with a whistling-like appearance is a universal finding. The eyes are often deep-set and the nasal bridge wide. Other findings include epicanthal folds, strabismus, bilateral ptosis and reduced eyelid size. FSS patients also often have H-shaped dimpling of the chin, small nose, long philtrum, high palate, small tongue, and nasal speech. Skeletal findings include ulnar deviation of the hands, camptodactyly, kyphoscoliosis, clubfoot, and contractures of the knees or hips. Distal arthrogyrosis 2B (DA2B, OMIM #601680), or Sheldon-Hall syndrome (SHS) is the most common DA syndrome. Clinically, SHS is less severe than FSS, but more severe than *TPM2*-related DA (DA1). Facial features reminiscent of FSS are present, but are less pronounced.

**Genetics:** Distal arthrogyrosis syndromes are inherited as autosomal dominant disorders. Missense mutations affecting catalytic activity of the MYH3 protein are a known cause of FSS (Toydemir et al. *Nat Genet* 38:561-565, 2006; Tajsharghi et al. *Arch Neurol* 65:1083-1090, 2008). Deletions involving one amino acid, nonsense mutations, and missense mutations in the carboxyl terminus are reported for *TNNI2*, and one *TNNT3* missense mutation (p.Arg63His) has been identified in a family with SHS.

**Description of This Particular Test:** The following genes are tested 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:	Subtype:	Genomic: NC	mRNA: NM	Protein: NP	CCDS:
<i>MYH3</i>	DA2A (Freeman-Sheldon)	000017.9	002470.2	002461.2	11157.1
<i>TPM2</i>	DA1	000009.10	003289.3	003280.2	6587.7
<i>TNNI2</i>	DA2B (Sheldon-Hall)	000011.9	003282.3	003273.1	31333.1
<i>TNNT3</i>	DA2B (Sheldon-Hall)	000011.9	006757.3	006748.1	7727.1

**Indication for Testing:** Individuals with clinical symptoms consistent with distal arthrogyrosis syndromes and facial features consistent with Freeman-Sheldon or Sheldon-Hall syndromes.

**Sensitivity of Test:** *MYH3* mutations appear to be a common cause of FSS. Mutations were found in 26 of 28 cases, 75% of which were sporadic (Toydemir et al. *Nat Genet* 38:561-565, 2006). *TNNI2* appears to be a less common cause of SHS than *MYH3* (Toydemir et al. 2006). Among fourteen individuals with FSS, none were found to have *TNNI2* mutations (Sung et al. *Am J Hum Genet* 72:681-690, 2003). Among 47 DA families, one was found to have a *TNNT3* mutation (Sung et al. 2003). *TPM2* mutations are a rare cause of DA (Sung et al. 2003).

**Turn Around Time:** Approximately 2 to 3 weeks per gene or maximum of 40 days for the panel.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price: Sequential Sequencing of MYH3, TPM2, TNNI2, TNNT3 Genes:**

CPT Codes	<i>MYH3</i>	<i>TPM2</i>	<i>TNNI2</i>	<i>TNNT3</i>	Panel
83890	\$30 (x1)	\$30 (x1)	\$30 (x1)	\$30 (x1)	\$30 (x1)
83891	\$40 (x1)	\$40 (x1)	\$40 (x1)	\$40 (x1)	\$40 (x1)
83898	\$650 (x39)	\$160 (x9)	\$130 (x7)	\$230 (x14)	\$1,120 (x69)
83904	\$970 (x39)	\$230 (x9)	\$190 (x7)	\$340 (x14)	\$1,690 (x69)
83894	\$160 (x1)	\$50 (x1)	\$60 (x1)	\$80 (x1)	\$ 270 (x1)
83912	\$140 (x1)	\$80(x1)	\$80 (x1)	\$100 (x1)	\$ 190 (x1)
	<b>\$1,990</b>	<b>\$590</b>	<b>\$530</b>	<b>\$820</b>	<b>\$3,340*</b>

\*When 2 or more genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

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