

MYH3-Related Distal Arthrogyryposis Syndromes via MYH3 Gene Sequencing

Distal Arthrogyryposis 2A (Freeman-Sheldon Syndrome)

Distal Arthrogyryposis 2B (Sheldon-Hall Syndrome)

(Test #337)

Brief Description of Clinical Features: Distal arthrogyryposis (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 arthrogyryposis 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 arthrogyryposis 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: *MYH3*-associated distal arthrogyryposis syndromes are inherited as autosomal dominant disorders. Missense mutations affecting catalytic activity of the embryonic skeletal muscle myosin heavy chain 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). In contrast, mutations in *MHY3* which alter residues that interact with other proteins of the contractile apparatus, such as actin and troponin, have been shown to cause SHS (Toydemir et al. 2006). Thus far, with one exception, amino acid substitutions are the only form of *MYH3* mutations identified in patients. A single amino acid deletion represents the one exception, and this change was found in two unrelated SHS patients (Toydemir et al. 2006). SHS is also caused by mutations in the *TNNT3* and *TNNI2* genes (Sung et al. *Am J Hum Genet* 73:212-4, 2003).

Description of This Particular Test: The isoform of myosin heavy chain that is expressed prenatally in skeletal muscle is coded by the *MYH3* gene (OMIM #160720) located on chr 17p13.1. Testing is accomplished by amplifying the 39 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: **Genomic: NC_000017.9 mRNA and Protein: CCDS 11157.1**

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

Sensitivity of Test: *MYH3* mutations appear to be a common cause of Freeman-Sheldon syndrome. Mutations were found in 26 of 28 cases, 75% of which were sporadic (Toydemir et al. 2006). Among 38 Sheldon-Hall syndrome patients who tested negative for mutations in *TNNI2* or *TNNT3*, twelve were found to have *MYH3* mutations.

Turn Around Time: Maximum of 40 days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of MYH3	Exons 3-41	\$ 1990
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x39	83898 \$650	Sequencing x39	83904 \$ 970
Separation x1	83894 \$160	Interpretation/Report x1	83912 \$ 140

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

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