

Congenital Contractural Arachnodactyly (Beals Syndrome) via *FBN2* Gene Sequencing (Test #395)

Brief Description of Clinical Features: Congenital Contractural Arachnodactyly (CCA) (also known as Beals syndrome, OMIM 121050) is characterized by a Marfan-like appearance (tall, slender habitus in which arm span exceeds height) and long, slender fingers and toes (arachnodactyly) (Hecht and Beals. *Pediatrics* 49:574-579, 1972; Putnam et al. *Nat Genet* 11:456-458, 1995; Wang et al. *Am J Hum Genet* 59:1027-1034, 1996). However, classical CCA patients are diagnosed by a constellation of clinical findings that include the marfanoid habitus associated with CCA characteristic features such as flexion contractures of multiple joints including elbows, knees, ankles, hips, fingers and toes; kyphosis/scoliosis (sometimes severe); muscular hypoplasia and abnormal pinnae (crumpled upper helix of the external ear) (Wang et al. 1996; Snape et al. *Clin Dysmorphol* 15:95-99, 2006). It has also been reported that infants with severe/lethal CCA have cardiovascular anomalies and gastrointestinal anomalies. Cardiovascular anomalies include atrial or ventricular septal defect, interrupted aortic arch, single umbilical artery, and rarely aortic root dilatation, while gastrointestinal anomalies include duodenal or esophageal atresia and intestinal malrotation (Wang et al. 1996; Snape et al. 2006).

Genetics: CCA is inherited in an autosomal dominant manner. Mutations in the *FBN2* gene cause CCA (Putnam et al. 1995; Wang et al. 1996). *FBN2* encodes the Fibrillin-2 protein, an extracellular matrix protein that has a calcium-binding EGF-like motif and a TGF-binding protein-like motif (Putnam et al. 1995; Wang et al. 1996). It has been proposed that fibrillin-2 directs the assembly of elastic fibers during early embryogenesis (Zhang et al. *J Cell Biol* 129:1165-1176, 1995). A mix of nonsense, splicing, deletion, insertion, duplication and missense mutations has been reported in the *FBN2* gene, located mostly between exons 22 and 36 (Putnam et al. 1995; Wang et al. 1996; Park et al. *Am J Hum Genet* 78:350-355, 1998; Belleh et al. *Am J Hum Genet* 92:7-12, 2000; Gupta et al. *Hum Mutat* 19:39-48, 2002). Somatic mosaicism for an *FBN2* mutation has been reported in one case (Putnam et al. *Am J Hum Genet* 60, 818-827, 1997).

Description of this Particular Test: This test involves bidirectional DNA sequencing of all coding exons (1-65) of the *FBN2* gene along with ~50 bases of non coding flanking DNA on each side. As indicated, we will also perform sequencing of any single exon in this gene for family members of patients with known mutations and to confirm research results (\$190 charge).

Reference Sequences: Genomic: NC_000005.9 mRNA: NM_001999.3 Protein: NP_001990.2 (CCDS 34222.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with CCA and family members of patients who have known *FBN2* mutations.

Sensitivity of Test: *FBN2* mutations have been identified in up to 75% of individuals diagnosed with CCA (Gupta et al. 2002; Nishimura et al. *Am J Med Genet A*. 143:694-698, 2007).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of *FBN2* gene **\$ 2190**

CPT Codes:

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|-------------------------|--------------|--------------------------|--------------|
| Sample Ascertainment x1 | 83890 \$ 30 | DNA Isolation x1 | 83891 \$ 40 |
| Amplification x67 | 83898 \$ 730 | Sequencing x67 | 83904 \$1090 |
| Separation x1 | 83894 \$ 160 | Interpretation/Report x1 | 83912 \$ 140 |

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

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