

## Congenital Fiber Type Disproportion Panel - Test #329

**Brief Description of Clinical Features:** Congenital fiber type disproportion (CFTD; OMIM #255310) is a genetically and clinically heterogeneous congenital myopathy usually presenting as hypotonia and delayed motor milestones before 1 year of age. Clinical findings among CFTD patients include proximal limb-girdle weakness, weakness of neck flexion and ankle dorsiflexion, facial weakness, and absent or decreased deep tendon reflexes (Clarke et al. *Ann Neurol* 63:329-337, 2008; Lawlor et al. *Hum Mutat* 31:176-183, 2010). Patients sometimes exhibit ophthalmoplegia and ptosis, the former being a common finding in *RYR1*-related CFTD (Clarke et al. *Hum Mutat* 31:E1544-1550, 2010). Dependence on nocturnal ventilation support is a common finding (Clarke et al. 2008, 2010). Most patients remained ambulatory and greater than 90% of cases demonstrate static or improving weakness (Clark and North *J Neuropathol Exp Neurol* 62:977-989, 2003). Type 1 muscle fibers were smaller than type 2 fibers by 50% - 77% in one study (Clarke et al. 2008) and 47% in another (Lawlor et al. 2010). Marked fiber size disproportion was due to hypotrophy of type 1 fibers and hypertrophy of type 2 fibers. Overall type 1 fiber predominance, absence of type 2B fibers, and absence of other histopathology was commonly observed in patient biopsies (Clarke et al. 2008).

**Genetics:** Mutations in the gene encoding the muscle form of tropomyosin 3 (*TPM3*; OMIM #191030) are the most common identified cause of CFTD. CFTD due to *TPM3* mutations may be inherited in a dominant or recessive manner (Lawlor et al. 2010; Clarke et al. 2008; Ryan et al. 2001). Recessive mutations in *RYR1* (OMIM #180901) is the second most common identified cause of CFTD. In all reported *RYR1* cases, each patient was compound heterozygous for one null mutation and one missense mutation (Clarke et al. 2010). Mutations in *SEPN1*, *ACTA1*, and *TPM2* are each a rare cause of CFTD. *SEPN1*-related myopathy is inherited as a recessive disorder, and the reported cases of *ACTA1*- and *TPM2*-related CFTD were inherited as dominant conditions (Laing et al. *Ann Neurol* 56:689-694, 2004; Brandis et al. *Neurmuscul Disord* 18:1005, 2008).

**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:	Genomic: NC_	mRNA: NM_	Protein: NP_	CCDS:
<i>TPM3</i>	000001.9	152263.2	689476.2	41403.1
<i>RYR1</i>	000019.8	000540.2	000531.2	33011.1
<i>SEPN1</i>	000001.9	020451.2	065184.2	41282.1
<i>ACTA1</i>	000001.9	001100.3	001091.1	1578.1
<i>TPM2</i>	000009.10	003289.3	003280.2	6587.7

**Indication for Testing:** Individuals with symptoms consistent with congenital myopathy and muscle biopsy studies showing fiber type disproportion in the absence of nemaline bodies and other histological findings suggestive of another diagnosis.

**Sensitivity of test:** Lawlor et al. (2010) found 6 of 13 patients with type 1 fiber hypotrophy to have mutations in *TPM3*. In another cohort of 23 CFTD families, six were found to have *TPM3* mutations (Clarke et al. 2008). Clarke et al. (2010) found heterozygous *RYR1* mutations in 4 of 7 families in which mutations in the other CFTD genes were ruled-out.

**Turn Around Time:** Approximately 2 to 3 weeks per gene or maximum of 80 days for the panel.

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

**Price: Sequencing of *TPM3*, *RYR1*, *SEPN1*, *ACTA1*, *TPM2* Genes:**

CPT Codes	<i>TPM3</i>	<i>RYR1</i>	<i>SEPN1</i>	<i>ACTA1</i>	<i>TPM2</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 160 (x8)	\$ 1420 (x90)	\$ 200 (x16)	\$ 140 (x11)	\$ 160 (x9)	\$ 1870 (x124)
83904	\$ 240 (x8)	\$ 2140 (x90)	\$ 290 (x16)	\$ 210 (x11)	\$ 230 (x9)	\$ 2810 (x124)
83894	\$ 40 (x1)	\$ 190 (x1)	\$ 50 (x1)	\$ 40 (x1)	\$ 50 (x1)	\$ 370 (x1)
83912	\$ 60 (x1)	\$ 170 (x1)	\$ 80 (x1)	\$ 70 (x1)	\$ 80 (x1)	\$ 290 (x1)
<b>Totals:</b>	<b>\$ 570</b>	<b>\$ 3990</b>	<b>\$ 740</b>	<b>\$ 590</b>	<b>\$ 590</b>	<b>\$ 5,508*</b>

\*When 3 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#: 7185561, AU ID: 1407125 expires 12/20/12)

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