

Hennekam Lymphangiectasia-Lymphedema Syndrome via Sequencing of the *CCBE1* Gene (Test #284)

Brief Description of Clinical Features: Primary Lymphedema is a chronic condition that arises from an abnormality of the lymphatic system. Hennekam Syndrome (OMIM 235510) is a type of primary lymphedema characterized by severe lymphedema in the limbs, genitalia and face complicated by facial dysmorphism and mental retardation (Hennekam et al. *Am. J. Med. Genet.* 34:593-600, 1989). Facial features vary, but are typically characterized by a flattened face and nasal bridge, hypertelorism, epicanthal folds, small mouth, tooth anomalies, and ear defects accompanied by hearing loss. Lymphedema is progressive, often beginning in utero with hydrops fetalis, and can be asymmetrical (Van Balkom et al. *Am. J. Med. Genet.* 112:412-421, 2002). Edema is typically accompanied by hypoproteinemia and immunologic abnormalities such as hypogammaglobulinemia and lymphocytopenia. Angiectasias of lymph vessels in the intestines and other organs (e.g. pleura pericardium, thyroid, and kidneys) are a hallmark of Hennekam Syndrome (Hennekam et al. *Am. J. Med. Genet.* 34:593-600, 1989; Alders et al. *Nat Genet.* 41:1272-1274, 2009). Additional features may include congenital heart defects, pyloric stenosis, glaucoma, hypothyroidism, camptodactyly, rectal prolapse and renal anomalies (Angle and Hersh. *Am. J. Med. Genet.* 71:211-214, 1997; Van Balkom et al. *Am. J. Med. Genet.* 112:412-421, 2002; Al-Gazali et al. *Clin. Dysmorphol.* 12:227-232, 2003; Bellini et al. *Am. J. Med. Genet.* 120A:92-96, 2003).

Genetics: Phenotypic abnormalities arise due to impaired prenatal and postnatal lymphatic flow resulting from insufficient *CCBE1* gene function during lymphangiogenesis. The *CCBE1* protein plays a direct role in lymphatic vessel formation and venous sprouting. Mutations throughout the *CCBE1* gene have been identified as causes of Hennekam Syndrome (Hennekam et al. *Am. J. Med. Genet.* 34:593-600, 1989; Hogan et al. *Nat Genet.* 41:396-398, 2009; Connell et al. *Hum. Genet.* 127:231-241, 2010). Details of the molecular mechanism of the *CCBE1* protein function remain incomplete, however it is speculated that *CCBE* may be a component of the extracellular matrix involved in guidance of migrating cells during lymphangiogenesis (Hogan et al. *Nat Genet.* 41:396-398, 2009). Mutations in the *CCBE1* gene are inherited in an autosomal recessive manner and comprise primarily missense and nonsense mutations. No predominant *CCBE1* mutations have been identified to date.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the 11 coding exons in the *CCBE1* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000018.9 mRNA: NM_133459.2 Protein: NP_597716.1 (CCDS 32838.1)

Indications for Test: Patients with clinical features of Hennekam Syndrome or a family history of lymphedema, and patients with lymphedema that test negative for mutations in the *FLT4* and *FOXC2* genes.

Sensitivity of Test: The sensitivity of this test is currently unknown.

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

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *CCBE1* Gene \$ 690

| CPT Codes | | | | | | | |
|--------------|-----------|-----------|-------------|-------------|-----------|------------|-------|
| Test | 83890 | 83891 | 83898 | 83904 | 83894 | 83912 | Total |
| <i>CCBE1</i> | \$30 (x1) | \$40 (x1) | \$180 (x11) | \$270 (x11) | \$50 (x1) | \$120 (x1) | \$690 |

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

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