

**Ellis–van Creveld Syndrome (EVC)  
 via *EVC* and *EVC2* Gene Sequencing (Test #783)**

**Brief Description of Clinical Features:** Ellis-van Creveld syndrome (OMIM#225500) is a chondral and ectodermal dysplasia characterized by short limbs, short ribs, postaxial polydactyly, and dysplastic nails and teeth (Ruiz-Perez et al. *Nature Genet* 24:283-286, 2000). Congenital heart defects, most commonly a defect of primary atrial septation producing a common atrium, occur in 60% of affected individuals.

**Genetics:** EVC is inherited as an autosomal recessive trait with variable expression. The *EVC* and *EVC2* genes, located in a head to head configuration on chromosome 4p16, are associated with this disorder. Heterozygous mutations in these two genes may be associated with autosomal dominant Weyers acrofacial dysostosis (OMIM#193530), which has overlapping skeletal features with EVC. EVC is a rare disorder, but with an increased frequency among the Amish population and some Arab populations. *EVC* shares a common promoter region with *EVC2*; the transcriptional start sites of the two genes are separated by only 2.6 kb. There is no significant sequence homology between *EVC* and *EVC2* at either protein or nucleic levels. The gene products of *EVC* and *EVC2* have been shown to play a role in hedgehog signaling pathway and function in bone formation and skeletal development (Valencia et al. *Hum Mutat* 30:1667-1675, 2009). The precise role of these two proteins remains to be elucidated. *EVC* and *EVC2* mutations each account for approximately half of patients with EVC. In both genes, the majority of reported mutations are nonsense, frameshift and splice site mutations.

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of all coding exons of the *EVC* and *EVC2* genes plus ~50 bp of flanking non-coding DNA on each side. Without any special request, we will sequence *EVC* first. If two likely pathogenic mutations found, testing will stop; if no mutation or only one mutation is found in *EVC*, we will proceed with sequencing *EVC2*. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340).

Reference Sequences:	Gene	Genomic	mRNA	Protein	CCDS
	<i>EVC</i>	NC_000004.11	NM_153717.2	NP_714928.1	CCDS_3383.1
	<i>EVC2</i>	NC_000004.11	NM_147127.4	NP_667338.3	CCDS_3382.2

**Indications for Test:** Candidates for this test are patients with clinical and radiographic features consistent with EVC, and family members of patients who have known *EVC* or *EVC2* mutations.

**Sensitivity of Test:** Combining *EVC* and *EVC2*, this test is predicted to detect disease mutations in at least two thirds of affected individuals with EVC (Tompson et al. *Hum Genet* 120:663-670, 2007; Valencia et al *Hum Mutat* 30:1667-1675, 2009).

**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.

**Prices:** Sequencing of *EVC* and *EVC2* gene \$ 1090 - 2060

Test	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>EVC</i>	\$30 (x1)	\$40 (x1)	\$330 (x21)	\$490 (x21)	\$70 (x1)	\$130 (x1)	\$1090
<i>EVC</i> and <i>EVC2</i> together	\$30 (x1)	\$40 (x1)	\$670(x48)	\$1010(x48)	\$140 (x1)	\$170 (x1)	\$2060

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

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