

## Roberts Syndrome via *ESCO2* Gene Sequencing (Test #836)

**Brief Description of Clinical Features:** Roberts syndrome (RBS; OMIM#268300), also known as Roberts-SC phocomelia syndrome (OMIM#269000), is characterized by prenatal growth retardation, limb malformations including bilateral symmetric tetraphocomelia or hypomelia caused by mesomelic shortening, and craniofacial abnormalities including bilateral cleft lip and/or palate, micrognathia, hypertelorism, exophthalmos, downslanting palpebral fissures, malar hypoplasia, hypoplastic nasal alae and ear malformation. Upper limbs are more severely affected than lower limbs. Mortality is high among severely affected pregnancies and newborns. Mildly affected individuals may survive to adulthood (Gordillo et al. *GeneReviews*, 2009). The diagnosis of RBS relies on cytogenetic testing, which shows the characteristic chromosomal abnormality of premature centromere separation and separation of the heterochromatic regions in most metaphase chromosomes.

**Genetics:** RBS is inherited in an autosomal recessive manner and is caused by mutations in the *ESCO2* gene. *ESCO2* (establishment of cohesion 1 homolog 2) contains two different domains, a C-terminal portion with acetyltransferase activity and an N-terminal portion that binds to chromatin (Vega et al. *Nat Genet* 37:468-470, 2005). The acetyltransferase domain is proposed to play an important role in establishing sister chromatid cohesion during S phase after DNA replication (Williams et al. *Curr Biol* 13:2025-2036, 2003). The majority of mutations in *ESCO2* are frameshift or nonsense mutations that lead to protein truncation or nonsense-mediated decay, which suggests that the molecular mechanism underlying RBS involves loss of acetyltransferase activity. The rare missense mutations in this gene lead to highly conserved amino acid substitution in the acetyltransferase domain and cause loss of acetyltransferase activity equivalent to that produced by truncating mutations (Gordillo et al. *Hum Mol Genet* 17:2172-2180, 2008; Vega et al. *J Med Genet* 47:30-37, 2010).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of all coding exons of the *ESCO2* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

**Reference Sequences:** Genomic: NC\_000008.10  
Protein: NP\_001017420.1

mRNA: NM\_001017420.2  
mRNA and Protein: CCDS 34872.1

**Indications for Test:** Candidates for this test are patients with features consistent with Roberts syndrome, and family members of patients who have known *ESCO2* mutations.

**Sensitivity of Test:** To date, all individuals with a cytogenetic diagnosis of RBS have had mutations in *ESCO2* (Gordillo et al. 2009).

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

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

**Prices:** Sequencing of *ESCO2* gene \$ 740

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x12	83898 \$210	Sequencing x12	83904 \$320
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$100

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

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