

The University of Chicago Genetic Services Laboratories



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ESCO2 analysis for Roberts syndrome

Clinical Features:

Roberts syndrome (RBS) [OMIM #268300], also known as Roberts-SC phocomelia syndrome [OMIM #269000], is characterized by pre- and postnatal growth retardation, mental retardation, limb (tetraphocomelia or hypomelia) and hand malformations (oligodactyly, syndactyly, or clinodactyly), and craniofacial abnormalities (lip/palate clefting, micrognathia, hypertelorism, exophthalmos, down-slanting palpebral fissures, and ear malformations). Less common findings are cardiovascular, renal, gastro-intestinal, splenogonadal, and genital abnormalities. Neoplasms, nerve paralysis, Moya-Moya disease, and stroke are seen only rarely. Severity varies even within families, ranging from spontaneous abortions or stillbirths in severe cases to no intellectual impairment in milder ones [1].

Molecular Genetics and Cytogenetics:

At the cytogenetic level, RBS cells exhibit premature separation of centromeres (PCS) and 'puffing' of other heterochromatic regions, resulting in a railroad track appearance of most chromosomes [1]. Although its underlying etiology is still being debated [2,3], PCS has been linked to mutations in the *ESCO2* (*establishment of cohesion 1 homolog 2*) [4]. *ESCO2* is a member of the conserved Eco1/Ctf7 family of acetyltransferases involved in the establishment of cohesion between sister chromatids and in double-stranded DNA repair [2].

The *ESCO2* gene [OMIM#609353] maps to chromosome 8p21.1. Its genomic DNA is 30.3 kbps in length and includes 11 exons [4]. Out of 26 *ESCO2* mutations reported to date, 88% lead to premature stop codons within the acetyltransferase domain located in the C-terminal end of *ESCO2* [2]. About 46% of identified mutations occur in exon 3, which represents 45% of the entire coding sequence of *ESCO2* and harbors two repeat length mutational hotspots 23 and 21 nucleotides in length [2]. No clear genotype-phenotype correlations have been reported. Cellular and cytogenetic phenotypes do not appear to differ between missense and other types of mutations.

Inheritance & Epidemiology:

RBS is a rare autosomal recessive condition reported in about 100 cases worldwide [1]. With each pregnancy, parents of an affected child have a 25% chance of having another child with RBS, a 50% chance of having a carrier of one of *ESCO2* mutation, and a 25% chance of having a non-carrier. Ethnic bias has not been reported. Penetrance appears to be complete [1,2,4].

Test methods:

We offer full gene sequencing of all 10 coding exons and intron/exon boundaries.

Mutation analysis (sequencing)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1325
CPT codes:	83891, 83898 x 4, 83904 x 5, 83912
Turn-around time:	4 – 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Laboratory Faculty and Staff:

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References:

1. Van Den Berg D, and Francke U. Roberts syndrome: a review of 100 cases and a new rating system for severity (1993) Am J Med Genet 47: 1104-1123.
2. Gordillo M, et al. The molecular mechanism underlying Roberts syndrome involves loss of ESCO2 acetyltransferase activity (2008) Hum Mol Genet 17: 2172-2180.
3. Kim B, et al. EscO2 is a novel corepressor that associates with various chromatin modifying enzymes (2008) Biochem Biophys Res Commun 372: 298-304.
4. Vega H, et al. Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion (2005) Nat Genet 37: 468-470.

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