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CLIA #: 14D0917593 CAP #: 18827-49

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, exophtalmos, 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 (4).

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 acetyltranferase 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 mutation analysis of all 10 coding exons and intron/exon boundaries of *ESCO2* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *ESCO2* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

ESCO2 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 – 6 weeks

ESCO2 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Van Den Berg DJ, Francke U. Roberts syndrome: a review of 100 cases and a new rating system for severity. Am J Med Genet 1993: 47: 1104-1123.
2. Gordillo M, Vega H, Trainer AH et al. The molecular mechanism underlying Roberts syndrome involves loss of ESCO2 acetyltransferase activity. Hum Mol Genet 2008: 17: 2172-2180.
3. Kim BJ, Kang KM, Jung SY et al. Esco2 is a novel corepressor that associates with various chromatin modifying enzymes. Biochem Biophys Res Commun 2008: 372: 298-304.
4. Vega H, Waisfisz Q, Gordillo M 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. Nat Genet 2005: 37: 468-470.

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