THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

EIF2AK3 Analysis for Wolcott-Rallison syndrome

Clinical Features

Wolcott-Rallison syndrome [OMIM#226980] is characterized by permanent neonatal or early infancy insulin-dependent diabetes. Epiphyseal dysplasia, osteoporosis and growth retardation develop at a later age. Other frequent multisystem manifestations include hepatic and renal dysfunction, intellectual disability and cardiovascular anomalies (1). The majority of cases to date have originated from individuals coming from the Arabian peninsula and vicinity.

Molecular Genetics

Mutations in the *EIF2AK3* [OMIM#604032] gene cause Wolcott-Rallison syndrome (1-3). *EIF2AK3* encodes a translation-regulating kinase present in many tissues that plays an important role in trafficking of proinsulin through the secretory pathway in beta cells (1).

Inheritance

EIF2AK3 mutations follow an autosomal recessive inheritance pattern and are a rare cause of permanent neonatal diabetes mellitus. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *EIF2AK3* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp. Deletion/duplication analysis of the *EIF2AK3* gene is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. 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.

EIF2AK3 sequencing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

EIF2AK3 deletion/duplication analysis

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

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Delépine M, Nicolino M, Barrett T et al. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet 2000: 25: 406-409.
2. Durocher F, Faure R, Labrie Y et al. A novel mutation in the EIF2AK3 gene with variable expressivity in two patients with Wolcott-Rallison syndrome. Clin Genet 2006: 70: 34-38.
3. Brickwood S, Bonthron DT, Al-Gazali LI et al. Wolcott-Rallison syndrome: pathogenic insights into neonatal diabetes from new mutation and expression studies of EIF2AK3. J Med Genet 2003: 40: 685-689.

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