THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Mitchell-Riley syndrome: Mutation Analysis of *RFX6*

Clinical Features

Neonatal Diabetes, Pancreatic Hypoplasia, Intestinal Atresia and Gallbladder Aplasia or Hypoplasia [OMIM#601346] also known as Mitchell-Riley syndrome is characterized by neonatal diabetes, hypoplastic or annular pancreas, duodenal and jejunal atresia, and absent gallbladder. Patients do not have dysmorphic features. There is overlap between Mitchell-Riley syndrome and Martinez-Frias syndrome (which shares the same OMIM#). Patients with Martinez Frias syndrome were reported to also have oesophageal atresia and hypospadias and did not have diabetes, and discussion is ongoing as to whether these are two distinct syndromes, or variable manifestations of the same syndrome (1).

Molecular Genetics

Mutations in the *RFX6* [OMIM#612659] gene have been reported in patients with Mitchell-Riley syndrome. Missense, splicing and frameshift mutations in *RFX6* have been described (2). *RFX6* is a member of the regulatory factor X family of transcription factors.

Inheritance

RFX6 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 *RFX6* 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. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

RFX6 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405, 81406
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. Smith SB, Qu HQ, Taleb N et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature 2010: 463: 775-780.
2. Senée V, Chelala C, Duchatelet S et al. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet 2006: 38: 682-687.

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