THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Neonatal Diabetes Mellitus with Congenital Hypothyroidism: Mutation Analysis of *GLIS3*

Clinical Features

Neonatal Diabetes Mellitus with Congenital Hypothyroidism [OMIM#610199] is characterized by neonatal diabetes mellitus, severe congenital hypothyroidism, hepatic fibrosis, polycystic kidneys and congenital glaucoma (1). Facial dysmorphism, intrauterine growth restriction and mild intellectual disability have also been reported (2).

Molecular Genetics

Mutations in the *GLIS3* [OMIM#610192] gene cause Neonatal Diabetes Mellitus with Congenital Hypothyroidism. To date frameshift mutations and gross deletions have been described (2). *GLIS3* belongs to the GLIS subfamily of Kruppel-like zinc finger proteins and functions as an activator and repressor of transcription.

Inheritance

GLIS3 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 *GLIS3* gene is performed. Targets of interests are captured and amplified using Agilent SureSelect target enrichment 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.

GLIS3 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404, 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. Taha D, Barbar M, Kanaan H et al. Neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, polycystic kidneys, and congenital glaucoma: a new autosomal recessive syndrome? Am J Med Genet A 2003: 122A: 269-273.
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.
3. 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.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS