THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

TRMA syndrome testing: Mutation analysis of *SLC19A2*

Clinical Features

TRMA syndrome [thiamine-responsive megaloblastic anaemia syndrome, OMIM#249270] is associated with the classic clinical triad of diabetes, deafness, and megaloblastic anaemia (1). Diabetes in this condition typically occurs in infancy but has been reported in association with neonatal diabetes in rare cases (1). Other additional features which may be observed in affected individuals include congenital heart malformations, tri-lineage myelodysplasia, and visual issues such as optic atrophy or retinitis pigmentosa (1).

Molecular Genetics

Homozygous or compounded heterozygous mutations in the *SLC19A2* gene [OMIM#603941] are associated with TRMA (2). *SLC19A2* encodes a high-affinity thiamine transporter, and studies on the fibroblasts of affected individuals have shown that absence of this transporter protein results in low intracellular thiamine levels (2). The mechanism by which absence of this protein leads to the divergent symptoms associated with TRMA remains unknown (2).

Inheritance

TRMA is inherited in an autosomal recessive inheritance pattern. Therefore, 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 *SLC19A2* 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.

SLC19A2 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

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

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. Shaw-Smith C, Flanagan SE, Patch AM et al. Recessive SLC19A2 mutations are a cause of neonatal diabetes mellitus in thiamine-responsive megaloblastic anaemia. Pediatr Diabetes 2012: 13: 314-321.
2. Oishi K, Diaz G. Thiamine-Responsive Megaloblastic Anemia Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2003.

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