



Glucose Transporter Type 1 Deficiency Syndrome: Mutation Analysis of *SLC2A1*

Clinical Features:

Glucose transporter type 1 (GLUT1) deficiency syndrome [OMIM # 606777] is characterized by infantile-onset epileptic encephalopathy associated with delayed development, acquired microcephaly, motor incoordination, and spasticity. Seizures typically begin within the first 4 months of life following a normal birth and gestation. Varying degrees of cognitive impairment, ranging from learning disabilities to severe mental retardation, can occur. As more affected individuals are being identified, the phenotype has expanded to include individuals with ataxia and mental retardation without seizures, individuals with dystonia and choreoathetosis, and rare individuals with absent seizures and no movement disorder (1, 2).

Clinical Workup and Treatment:

Glucose concentration in cerebrospinal fluid should be the first test considered in patients suspected of having GLUT1 deficiency syndrome. Hypoglycorrachia (low CSF glucose, less than 40mg/dl) is practically diagnostic for this disorder. Calculation of the ratio of CSF glucose concentration to blood glucose concentration is consistently about 0.33 ± 0.01 (normal ratio: 0.65 ± 0.01). Additional tests to consider include CSF lactate concentration (value is low-normal or low, often below 1.3 mmol/L) and erythrocyte glucose transporter activity (individuals with GLUT1 deficiency syndrome have a reduction of approximately 50% in glucose uptake relative to normal controls) (1).

A ketogenic diet (high-fat, adequate protein, low carbohydrate) is effective in controlling seizures in patients diagnosed with GLUT1DS. However, despite control of seizures, affected individuals continue to have varying neurobehavioral and motor deficits.

Molecular Genetics:

Mutations of the *SLC2A1* gene [OMIM #138140] have been identified in patients with GLUT1 deficiency syndrome. The *SLC2A1* gene maps to 1q35 and has 10 coding exons. The encoded protein Glut-1 (solute carrier family 2, facilitated glucose transporter member 1) is the major glucose transporter in the mammalian blood-brain barrier. Sequencing of *SLC2A1* detects mutations in approximately 91% of affected individuals. Affected individuals with whole gene deletions of *SLC2A1* have also been reported (1).

Inheritance:

The frequency of GLUT1 deficiency syndrome remains unknown. *SLC2A1* mutations are inherited in an autosomal dominant pattern and most cases are *de novo*. Germline mosaicism has not been reported but remains a possibility.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC2A1* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed 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 pathogenic and likely 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 20 bp. 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.

SLC2A1 sequencing and deletion/duplication analysis

Sample specifications:	3 to 10 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 or email.

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

References:

1. Wang D, Pascual J, De Vivo D. Glucose Transporter Type 1 Deficiency Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2002.
2. Wang D, Pascual JM, Yang H et al. Glut-1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann Neurol 2005; 57: 111-118.

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