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SLC2A1 Analysis for Glucose Transporter Type 1 Deficiency Syndrome

Clinical Features:

Glucose transporter type 1 deficiency syndrome (GLUT1DS) [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 GLUT1DS. Hypoglycorrhachia (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 erthyrocyte glucose transporter activity (individuals with GLUT1DS 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 Solute Carrier Family 2, Member 1 *(SLC2A1)* [OMIM #138140] have been identified in patients with GLUT1DS. 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 GLUT1DS 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:

We offer full gene sequencing of all 10 coding exons and intron/exon boundaries of *SLC2A1* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *SLC2A1* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. 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.

SLC2A1 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4-6 weeks

SLC2A1 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000

CPT codes:	81404
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 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.

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.