THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

STXBP1 Analysis for Early Infantile Epileptic Encephalopathy

Clinical Features:

Early infantile epileptic encephalopathy (EIEE) [MIM #308350], also known as Ohtahara syndrome, is a severe form of epilepsy characterized by frequent tonic spasms with onset in the first months of life. EEG reveals suppression-burst patterns, characterized by high-voltage bursts alternating with almost flat suppression phases. Seizures are medically intractable with evolution to West syndrome at 3-6 months of age and then Lennox-Gastaut syndrome at 1-3 years of age. EIEE represents less than 1% of all epilepsies occurring in children less than 15 years of age (1). Patients have severe developmental delay and poor prognosis.

Molecular Genetics:

Mutations of the Syntaxin binding protein 1 *(STXBP1)* [OMIM #602926] have been identified in patients with early infantile epileptic encephalopathy 4 (EIEE4) [MIM #612164]. The *STXBP1* gene maps to 9q34.1 and has 19 coding exons. Syntaxin binding protein 1, more commonly referred to as MUNC18-1, is a neuron specific protein of the SEC1 family of membrane-trafficking proteins. MUNC18-1 is expressed throughout the brain and is a key component for calcium-dependent neurotransmitter release. Sequencing of *STXBP1* detected mutations in 4 out of 106 patients with EIEE [2]. Earlier reports identified 4 heterozygous missense mutation in 13 patients with EIEE (2). Affected individuals with microdeletions involving *STXBP1* have also been reported (3).

Inheritance:

STXBP1 mutations are inherited in an autosomal dominant pattern. Most cases are *de novo* and there has been one family reported with paternal mosaicism of a *STXBP1* mutation (4).

Resources:

Aaron's Ohtahara Foundation
www.ohtahara.org

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *STXBP1* 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. We also offer deletion/duplication analysis of the *STXBP1* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. 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. *STXBP1* sequence analysis is also offered as part of our Early Infantile Epileptic Encephalopathy Panel (see website for more details).

STXBP1 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

STXBP1 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	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. Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. Neurology 2009: 72: 273-281.
2. Saitsu H, Kato M, Mizuguchi T et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet 2008: 40: 782-788.
3. Deprez L, Weckhuysen S, Holmgren P et al. Clinical spectrum of early-onset epileptic encephalopathies associated with STXBP1 mutations. Neurology 2010: 75: 1159-1165.
4. Saitsu H, Hoshino H, Kato M et al. Paternal mosaicism of an STXBP1 mutation in OS. Clin Genet 2011: 80: 484-488.

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