THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

TSEN54 Sequencing for Pontocerebellar Hypoplasias Type 2A and 4

Clinical Features:

Similar to other types of pontocerebellar hypoplasias (PCH), subtypes PCH2 (OMIM 277470) and PCH4 (OMIM 225753) are characterized by small cerebellum and brainstem, variable neocortical atrophy, and abnormal mental and motor development. In addition, patients with PCH2 exhibit progressive microcephaly from birth, extrapyramidal dyskinesia, chorea, and epilepsy (1). PCH4, also known as fatal infantile olivopontocerebellar hypoplasia, is associated with a more severe course and an earlier lethality than PCH2 (2).

Molecular Genetics:

Both PCH2 and PCH4 are thought to result from impaired processing of tRNA introns, caused by dysfunction in the tRNA-splicing endonuclease complex (2). Mutations in *TSEN54* [OMIM 608755], encoding one of the noncatalytic subunits of the tRNA-splicing endonuclease complex, have recently been implicated in the etiology of PCH2A and PCH4 (2).

TSEN54 maps to 17q25.1 and has 11 coding exons. The high abundance of its mRNA in the developing pons, cerebellar dentate and olivary nuclei, suggests its importance for the development of these brain areas. Budde et al (2008) sequenced the *TSEN54* gene in 58 patients from the Netherlands and other European countries, Brazil, and Israel. Four causal mutations in *TSEN54* have been linked to PCH2A and 4: two missense (p.A307S, p.S93P) and two nonsense mutations (p.Q246X, p.Q343X). 3/3 patients with PCH4 had mutations detected in *TSEN54*, and 47/52 patients with PCH2 were homozygous for the p.A307S mutation. Of these 47 patients, 31 shared European ancestry and a haplotype on which p.A307S arose as a founder mutation (2).

Inheritance and Epidemiology:

TSEN54 mutations are inherited in an autosomal recessive pattern. Parents of an affected child are likely carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *TSEN54* 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 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 20bp.

Deletion/duplication analysis is performed by oligonucleotide array-CGH. 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.

Dr. William Dobyns at the Seattle Children's Research Institute is available to review MRI scans and give recommendations regarding genetic testing. Please contact Dr. Dobyns (wbd@uw.edu) to arrange this, if desired.

TSEN54 sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1,000
CPT codes:	81406
Turn-around time:	4 weeks

TSEN54 deletion/duplication analysis

Sample specifications:	3 to 10cc 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. Barth PG. Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. Brain Dev 1993: 15: 411-422.
2. Budde BS, Namavar Y, Barth PG et al. tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia. Nat Genet 2008: 40: 1113-1118.

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