The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu dnatesting.uchicago.edu
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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:

We offer mutation analysis of all 11 coding exons and intron/exon boundaries of *TSEN54* by direct sequencing of amplification products in both the forward and reverse directions. We also offer oligonucleotide array-CGH analysis to identify deletions/duplications involving the coding region of the *TSEN54* gene. Deletions/duplications of less than 2 kb 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.

TSEN54 sequencing may be ordered alone, or as part of our cerebellar hypoplasia panel which includes sequencing of a total of 7 genes. Please see our information sheet on our Cerebellar Hypoplasia Next Generation Sequencing Panel for more details.

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) or his coordinators, Carissa Adams(carissa.adams@seattlechildrens.org) and Brandi Bratrude (brandi.bratrude@seattlechildrens.org) 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

Cerebellar Hypoplasia Next Generation Sequencing Panel

Includes sequencing of *TSEN5*4 and 6 additional genes – see our information sheet on our Cerebellar Hypoplasia Panel for more details.

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3975
CPT codes:	81407
Turn-around time:	8 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory. Only fresh blood samples are accepted for this testing.

Note: We cannot bill insurance for the above test.

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 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 week

Deletion/duplication analysis for two or more genes (by array-CGH)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	$1545
CPT codes:	81479
Turn-around time:	4-6 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. 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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