

The University of Chicago Genetic Services Laboratories



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CLIA #: 14D0917593 CAP #: 18827-49

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%.

Additional Resources:

The Brain Malformation Research Project at The University of Chicago

William B. Dobyns, Principal Investigator
Contact Mary King at 773-702-8247

Test methods:

The University of Chicago Laboratory offers 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.

TSEN54 sequencing:

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1500
CPT codes:	83891, 83898 x 4, 83904 x 6, 83912
Turn-around time:	4 - 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3 - 4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Molecular Diagnostics Laboratory Faculty and Staff:

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References:

1. Barth PG. Pontocerebellar hypoplasias: an overview of a group of inherited neurodegenerative disorders with fetal onset (1993) Brain Dev 15: 411-422.
2. Budde BS, et al. tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia (2008) Nature Genet 40: 1113-1118.

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