

Pontocerebellar Hypoplasias Subtypes 2 and 4 via *TSEN54* Gene Sequencing (Test #298)

Brief Description of Clinical Features: Pontocerebellar hypoplasias subtype 2 (PCH2; OMIM 277470) and subtype 4 (PCH4; OMIM 225753) are subsets of neurodegenerative disorders, characterized by small cerebellum and brainstem, variable neocortical atrophy, and impaired cognitive and motor development (Barth, Brain Dev 15:411-422, 1993; Budde et al. Nat Genet 40:1113-1118, 2008). In addition, patients with PCH2 exhibit progressive microcephaly from birth, extrapyramidal dyskinesia, chorea, and epilepsy (Barth 1993; Budde et al. 2008). PCH4, also known as fatal infantile olivopontocerebellar hypoplasia, is associated with a more severe course, including the missing folia in the cerebellum as a neuropathological marker, and an earlier lethality than PCH2 (Budde et al. 2008).

Genetics: Both PCH2 and PCH4 are inherited as autosomal recessive disorders. PCH2 and PCH4 are caused by mutations mainly in the *TSEN54* gene, however mutations in the *TSEN2* and in the *TSEN34* genes have also been reported in few PCH2 cases (Budde et al. 2008). *TSEN54* encodes one of the two noncatalytic structural subunits of the tRNA-splicing endonuclease complex, known as TSEN54, which is involved in cytoplasmic tRNA splicing, while *TSEN2* and *TSEN15* genes encode the two catalytic subunits of the complex (Budde et al. 2008). The mRNA expression profile of the *TSEN54* gene in the developing neurons of the pons, cerebellar dentate and olivary nuclei, suggests an essential role in the morphological development of these brain structures (Budde et al. 2008). Two missense (p.Ala307Ser, p.Ser93Pro) and two nonsense (p.Gln246Stop, p.Gln343Stop) mutations in the *TSEN54* gene have been reported (Budde et al. 2008). Based on clinical and MRI findings, 52 patients were diagnosed with PCH2 and 3 patients with PCH4 (Budde et al. 2008). Forty-seven of the 52 PCH2 patients were homozygous for the p.Ala307Ser missense mutation. Of these 47 patients, 31 shared European ancestry and a haplotype consistent with a founder mutation event. Additionally, two of the PCH4 patients were compound heterozygous for the p.Ala307Ser missense mutation and one nonsense mutation (either p.Gln246Stop or p.Gln343Stop), while the third PCH4 patient was homozygous for the p.Ala307Ser missense mutation and also heterozygous for the p.Ser93Pro missense mutation (Budde et al. 2008).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 11 coding exons (exons 1-11) of the *TSEN54* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: NC_000017.10 mRNA: NM_207346.2 Protein: NP_997229.2 (CCDS 11724.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with bilateral frontoparietal polymicrogyria and family members of patients who have known *TSEN54* mutations.

Sensitivity of Test: The most common missense mutation (p.Ala307Ser) in the *TSEN54* gene accounts for 88% of the PCH2 reported cases. *TSEN2* and *TSEN34* mutations account for about 2% each (Budde et al. 2008).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of *TSEN54* gene \$ 880

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x15	83898 \$ 270	Sequencing x15	83904 \$ 400
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 80

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12).

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