Pontocerebellar Hypoplasia

Pontocerebellar hypoplasia (PCH) is a group of rare autosomal recessive neurodegenerative disorders with a prenatal onset, characterized by cerebellar hypoplasia in addition to varying degrees of atrophy of the cerebellum and pons (1). MRI findings include a small cerebellum and brainstem, variable neocortical atrophy, severe and progressive microcephaly and variable ventriculomegaly (1). Clinically, most patients have severe intellectual disability, swallowing problems, and seizures.

Cerebellar Vermis Hypoplasia

Cerebellar Vermis Hypoplasia (CVH) consists of isolated vermis hypoplasia and may also be called “Dandy-Walker variant” due to the phenotypic overlap with Dandy-Walker malformation (DWM). DWM includes vermis hypoplasia in addition to several other features such as enlarged posterior fossa.

<table>
<thead>
<tr>
<th>Disorder and Associated Genes</th>
<th>Clinical Features / Molecular Pathology</th>
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<tbody>
<tr>
<td>PCH type 1 [OMIM#607596]</td>
<td>PCH type 1 is characterized by loss of motor neurons in the spinal cord, which is morphologically similar to the hereditary spinal muscular atrophies, in addition to the typical findings of PCH (1). Renbaum et al. (2009) identified a homozygous nonsense mutation in VRK1 in a consanguineous family with PCH type 1. VRK1 encodes a serine-threonine kinase which is thought to play a role in nervous system development and neuronal maintenance (2). Wan et al., (2012) identified homozygous and compound heterozygous mutations in EXOSC3 in affected members of nine families with PCH type 1B (3). EXOSC3 is a core component of the human RNA exosome complex.</td>
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<td>PCH type 2 [OMIM#277470]</td>
<td>PCH type 2 is characterized by dyskinesia and dystonia and is the most common subtype of PCH (4). Mutations in TSEN54, TSEN2 and TSEN34 are associated with PCH type 2. TSEN54 encodes one of the noncatalytic subunits of the tRNA splicing endonuclease complex, and TSEN2 and TSEN34 encode catalytic subunits of the tRNA splicing endonuclease. This complex has a high abundance of its mRNA in the developing pons, cerebellar dentate and olivary nuclei, suggesting it is importance for the development of these brain areas. Budde et al. (2008) sequenced the TSEN54, TSEN2 and TSEN34 genes in 52 patients with PCH type 2, and identified a common TSEN54 missense mutation (p.A307S) in the homozygous state in 47/52 patients, a homozygous missense mutation in TSEN2 one patient, and a homozygous missense mutation in TSEN34 in one other patient (5).</td>
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<td>PCH type 2D [OMIM#613811]</td>
<td>Homozygous or compound heterozygous missense mutations in the SEPSECS gene have been identified in 4 unrelated patients of Iraqi or Iraqi/Moroccon descent with cerebellocerebral atrophy, profound intellectual disability and spasticity most consistent with pontocerebellar hypoplasia type 2 (5).</td>
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<td>PCH type 4 [OMIM#225753]</td>
<td>PCH type 4, also known as fatal infantile olivopontocerebellar hypoplasia, has clinical overlap with PCH type 2, however it has a more severe course and is often associated with early postnatal death (5). The findings of polyhydramnios and contractures have been described prenatally in some cases of PCH type 4 (1). Budde et al. (2008) sequenced the TSEN54 gene in 3 patients with PCH type 4, and identified homozygous mutations in all patients (5).</td>
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<td>Inheritance:</td>
<td>VRK1, EXOSC3, TSEN54, TSEN2, TSEN34, SEPSEC5, RARS2, CHMP1A, TUBA8, RELN, VLDLR</td>
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<td>TUBA1A, TUBB2B and TUBB3 mutations are inherited in an autosomal dominant pattern.</td>
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<td>CASK mutations associated with MIC-PCH are typically de novo in females and thought to be lethal in males.</td>
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<td>Mutations in OPHN1 are inherited in an X-linked pattern and result in clinical features in affected males and females.</td>
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Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel 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 novel and/or potentially 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. Deletion/duplication analysis of the panel genes 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.

Cerebellar/Pontocerebellar Hypoplasia Sequencing Panel (16 genes sequencing)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $3975
CPT codes: 81407
Turn-around time: 8 – 10 weeks
Note: We cannot bill insurance for the above test.

Cerebellar/Pontocerebellar Hypoplasia Deletion/Duplication Panel (16 genes deletion/duplication analysis)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1545
CPT codes: 81407
Turn-around time: 4 - 6 weeks

Testing for a known mutation in additional family members by sequence analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $390
CPT codes: 81403
Turn-around time: 3-4 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: 1-2 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: