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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CASK Sequencing

Clinical Features and Inheritance:

Severe, *de novo* phenotype in females: X-linked mental retardation and microcephaly with pontine and cerebellar hypoplasia (MIC-PHC) [OMIM #300749] is characterized by severe or profound mental retardation (MR), microcephaly, and disproportionate pontine and cerebellar hypoplasia in females. Seizures, sensorineural hearing loss and retinal anomalies (optic disk pallor/optic nerve hypoplasia) may also be present. These mutations are typically *de novo* and thought to be lethal in males (1).

Mild, familial phenotype in males: Affected males have mild to moderate MR, and carrier females seem to be unaffected. In 2 families, MR was accompanied by nystagmus in multiple affected individuals (2).

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.

Molecular and Biochemical Genetics:

Mutations of the *CASK* [OMIM #300172] gene, or calcium/calmodulin-dependent serine protein kinase, have been identified in females with MIC-PCH and in males with X-linked MR (1, 2). *CASK* has 27 coding exons and belongs to the membrane-associated guanylate kinase (MAGUK) family. CASK interacts with brain-specific T-box family member TBR1. CASK also functions in both pre- and post-synaptic sites as part of large signaling complexes. *CASK* mutations were detected in 4/46 individuals with MIC-PCH including 3/13 females and 1/33 males (1). A resequencing screen of X-chromosome coding exons in individuals from approximately 350 families with X-linked MR revealed *CASK* mutations in 4 families (2). Nonsense, splicing, missense and deletions have been described. Some genotype-phenotype correlations have been suggested. Loss-of-function mutations of *CASK* may be associated with the severe phenotype in girls (MIC-PCH) and reduced viability or even *in utero* lethality in males, while missense (hypomorphic) mutations may be associated with a mild-moderate MR phenotype in males and no phenotype or very mild MR in female carriers. This correlation is simply speculative, though, based on very small numbers to date.

Additional Resources:

Foundation for Children with Microcephaly
Phone: 602-487-6445
email: jenni@childrenwithmicro.org
www.childrenwithmicro.org

The Brain Malformation Research Project at Seattle Children's Research Institute
William B. Dobyns, Principal Investigator
Phone: 206-884-1025
Email: wbd@uw.edu

Test methods:

We offer mutation analysis of all 27 coding exons and intron/exon boundaries of *CASK* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *CASK* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp 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.

Please, send a completed CASK Clinical Checklist and patient consent form with each sample.

This information will be used to aid in interpretation of the test result. The clinical data form, along with the test result, will be shared with Dr. Dobyns and stored anonymously in a *CASK* database. Patients with MIC-PHC, with or without *CASK* gene mutations, can enroll in Dr. Dobyns' research study.

CASK 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.

CASK sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$2040
CPT codes:	81407
Turn-around time:	4 weeks

CASK deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

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:

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 to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Najm J, Horn D, Wimplinger I et al. Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum. Nat Genet 2008: 40: 1065-1067.
2. Tarpey PS, Smith R, Pleasance E et al. A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. Nat Genet 2009: 41: 535-543.

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