

The University of Chicago Genetic Services Laboratories



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ASPM analysis for primary microcephaly

Information for Non-genetics Professionals

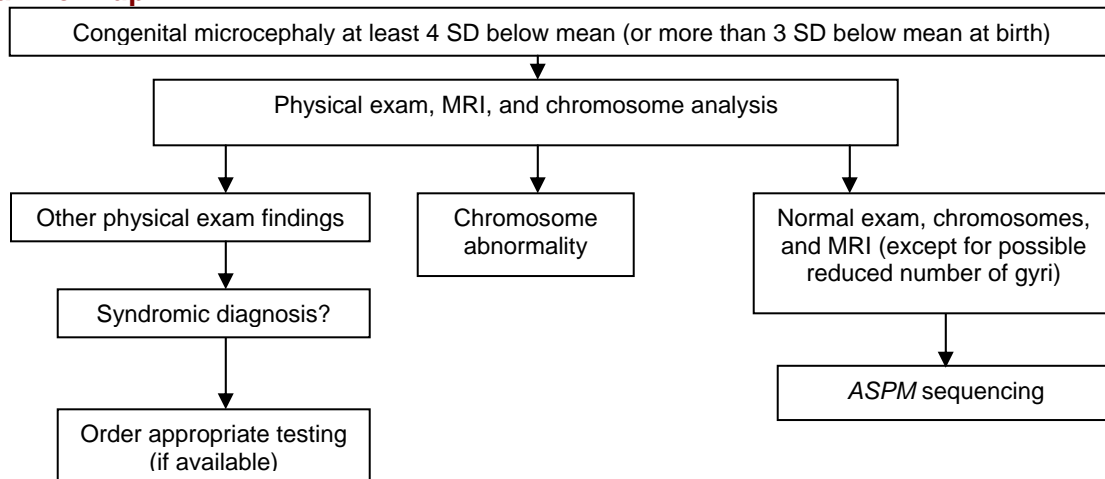
Clinical Features:

Autosomal recessive primary microcephaly (MCPH) is characterized by:

- congenital microcephaly (3 SD below the mean at birth or at least 4 SD below the mean at later ages)
- mental retardation, but no other neurological findings (febrile or other mild seizures do not exclude the diagnosis)
- normal or mildly short stature that is less severe than the markedly small head circumference
- normal weight and appearance except for the microcephaly

Brain imaging shows a mildly reduced number of gyri, and in some patients may also demonstrate agenesis of the corpus callosum or a few periventricular nodular heterotopia (numerous heterotopia suggest an alternative diagnosis). Prenatally, individuals have normal head size until approximately 20 weeks and decreased head size by 32 weeks, although this varies. The relative degree of microcephaly doesn't vary throughout life and doesn't vary within a family by more than 2 SD. Mental retardation is usually mild to moderate with no progressive decline or motor deficit.

Clinical Work-up:



Epidemiology and Etiology:

MCPH occurs in approximately 1 in 10,000 individuals in Pakistan and an estimated 1 in 1,000,000 in the Caucasian population. It is more common in consanguineous populations. *ASPM* mutations have been found in all ethnic groups studied. Mutations in the *ASPM* gene are the most common cause of MCPH. Approximately 40% of patients (both consanguineous and non-consanguineous) with a strict diagnosis of MCPH have mutations in *ASPM*.

Genetic Testing:

The first person to be tested in any family would be the individual with MCPH. Testing for mutations in *ASPM* is complicated by the fact that the gene is very large. Once a change is identified in the individual with MCPH, testing for other family members, or even prenatal testing, is relatively easy.

Reasons for genetic testing for MCPH:

- confirm the diagnosis
- offer reassurance that other family members are not affected
- provide accurate information and counseling resources for future pregnancies
- provide accurate information during a pregnancy regarding possible MCPH in the fetus

Additional Resources:

Foundation for Children with Microcephaly

Phone: 602-487-6445

email: jenni@childrenwithmicro.org

www.childrenwithmicro.org

Test ordering and Billing:

Clinical testing for MCPH is now available at The University of Chicago Genetics Services Laboratory. A test requisition form, billing form, consent form and clinical data sheet are required for testing. These forms can be found on the lab website (www.genes.uchicago.edu) or by calling the lab. If there are any questions about ordering testing, please contact the lab.

All insurance companies are different, but most of them should cover at least part of the cost of testing. We recommend that a parent or physician's office contact the patient's insurance company with the specific CPT codes (below) to learn more about the specific coverage prior to testing. With most institutions, The University of Chicago will bill the hospital or referring laboratory, which will then bill the insurance company. The patient may receive a bill for any amount not covered by the insurance company. In situations when The University of Chicago cannot bill the institution, we will require payment from the patient by check or credit card before beginning testing. The patient will need to seek reimbursement from their insurance company.

ASPM mutation analysis (sequencing)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2400
CPT codes:	83891, 83898 x 9, 83904 x 9, 83912
Turn-around time:	10 weeks

Note: We cannot bill insurance for ASPM sequencing.

Targeted analysis for a known sequence change 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:	2 - 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

Possible Results of Genetic Testing:

- **Two mutations detected:** finding two mutations will confirm a diagnosis of MCPH. Parents of a child with mutations in *ASPM* have a 25% recurrence risk with each pregnancy. Once two changes have been identified in an affected individual then it allows for easy testing of other family members or prenatal testing.
- **1 mutation detected:** finding one mutation does not confirm or rule out the possibility of MCPH. It is likely that this patient has another, unidentified mutation, in the *ASPM* gene that was not detected by our testing.
- **No mutation detected:** not finding a mutation indicates that *ASPM* is not the likely cause of this patient's microcephaly. Another gene or other factors may be the cause. Recurrence risk cannot be definitively given.
- **Variant of unknown significance:** A small number of patients will be found to have a change in the gene, but we are not sure whether that change causes MCPH or not.

Research studies:

The University of Chicago Genetic Services and Dr. William Dobyns' research laboratory will be working together to compare the mutations found by testing and the clinical features of the patients. You will be asked to fill out a clinical data form about each patient and submit it with the blood sample. This information will be used to aid in test interpretation. In addition, patients with negative or unknown results can enroll in Dr. Dobyns' research protocol for further studies.

Laboratory Faculty and Staff:

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References:

Woods GC, Bond J, Enard W. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings (2005) *Am J Hum Genet* 76: 717-728.

Bond J, et al. ASPM is a major determinant of cerebral cortical size (2002) *Nature Genet* 32:316-320.

Nicholas A, et al. The molecular landscape of *ASPM* mutations in primary microcephaly (2008) *J Med Genet* Nov 21. [Epub ahead of print].

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