

The University of Chicago Genetic Services Laboratories



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CLIA #: 14D0917593 CAP #: 18827-49

ASPM analysis for primary microcephaly

Clinical Features:

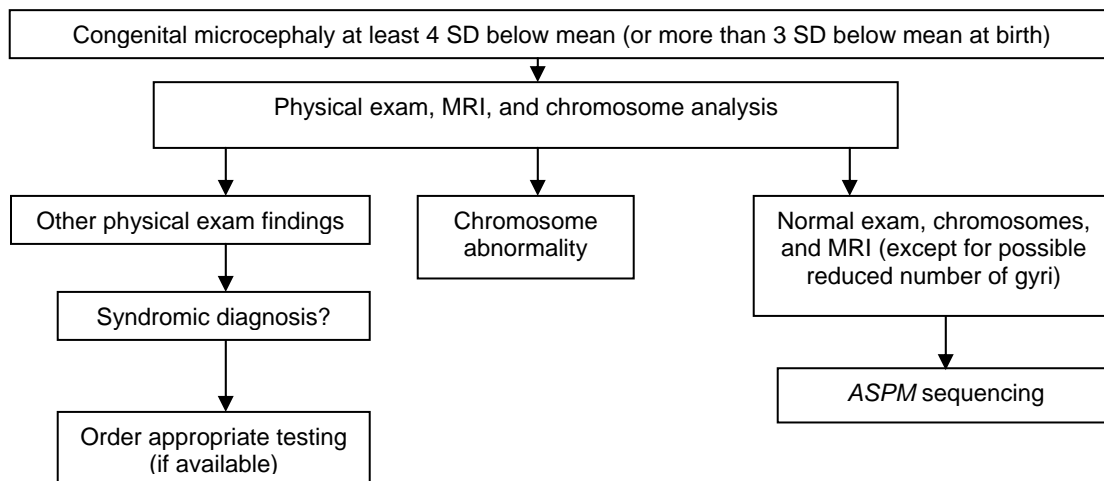
Autosomal recessive primary microcephaly (MCPH) is characterized by:

- 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 [1].

Clinical Work-up and Counseling:

Empiric studies have shown that nonconsanguineous couples having one child with MCPH and normal chromosomes and neuroimaging have a 20% risk of recurrence [2]. Recurrence risk for parents of an affected individual with *ASPM*-related MCPH is 25%.



Molecular Genetics:

Mutations in the *ASPM* [OMIM #605481] gene are the most common cause of MCPH [3]. Approximately 40% of patients (both consanguineous and non-consanguineous) with a strict diagnosis of MCPH have mutations in *ASPM*. However, very few patients (<10%) with a less restrictive phenotype have mutations in *ASPM* [4]. Thus, we expect a high detection rate for high functioning MCPH, but a lower detection rate for low functioning MCPH, especially if associated with other congenital anomalies. To date, 57 mutations have been reported in the *ASPM* gene, spanning most of the 28 coding exons. A majority of the mutations are predicted to result in a truncated protein. There is no correlation between the genotype and the degree of microcephaly or mental retardation [4].

Epidemiology:

MCPH occurs in approximately 1 in 10,000 individuals in Pakistan and an estimated 1 in 1,000,000 in the Caucasian population [1]. It is more common in consanguineous populations. *ASPM* mutations have been found in all ethnic groups studied [4].

Additional Resources:

Foundation for Children with Microcephaly

Phone: 602-487-6445

email: jenni@childrenwithmicro.org

www.childrenwithmicro.org

Test methods:

The University of Chicago Laboratory offers mutation analysis of all 28 coding exons and intron/exon boundaries of *ASPM* by direct sequencing of amplification products in both the forward and reverse directions.

Please, send a completed Microcephaly 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 microcephaly database. Patients with microcephaly, with or without *ASPM* gene mutations, can enroll in Dr. Dobyns' research study.

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

Laboratory Faculty and Staff:

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References:

1. 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.
2. Tolmie JL, McNay M, Stephenson JBP. Microcephaly: genetic counseling and antenatal diagnosis after the birth of an affected child (1987) *Am J Med Genet* 27: 583-94.
3. Bond J, et al. *ASPM* is a major determinant of cerebral cortical size (2002) *Nature Genet* 32:316-320.
4. 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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