

# The University of Chicago Genetic Services Laboratories



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## Genetic Testing for Primary Microcephaly

### Autosomal recessive primary microcephaly (MCPH):

Characterized by:

- congenital microcephaly (3 SD below the mean at birth or at least 4 SD below the mean at later ages)
- mental retardation (MR), 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. MR is usually mild to moderate with no progressive decline or motor deficit [1].

Mutations in the *ASPM* [OMIM #605481] gene are the most common cause of MCPH [2]. 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* [3]. 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 anomalies. To date, over 85 mutations have been reported in the *ASPM* gene, spanning most of the 28 coding exons. Most *ASPM* mutations are predicted to result in a truncated protein. There is no correlation between the genotype and the degree of microcephaly or MR [3]. *Asp*, the *Drosophila* ortholog of *ASPM*, is necessary for the formation of the mitotic spindle in mitosis and meiosis [1].

Several other genes, including *CDK5RAP2*, *CENPJ*, *MCPH1*, and *STIL*, have been reported to cause MCPH in a small number of families.

- Homozygous mutations in *CDK5RAP2* [OMIM #608201] have been identified in three Pakistani families with MCPH [4,5]. *CDK5RAP2* is a centrosomal protein and may be involved in microtubule production during mitosis [1].
- Four Pakistani families with MCPH have been reported with homozygous mutations in *CENPJ* [OMIM #609279] [4,6]. *CENPJ* is a centrosomal protein and likely shares a very similar role with *CDK5RAP2* [1].
- Homozygous mutations in *MCPH1* [OMIM #607117] have been reported in multiple populations, including at least one Pakistani family and at least one Caucasian family [7-9]. *MCPH1* encodes the Microcephalin protein, which is believed to play a role in cell-cycle timing [1].
- Kumar, et al (2009) reported three Indian families with MCPH that were homozygous for mutations in *STIL* [OMIM #181590]. *STIL* is necessary for proper mitotic spindle organization [10].

### Other Microcephaly Disorders:

Autosomal recessive microcephaly, infantile-onset seizures, and developmental delay (MCSZ) [OMIM #613402] and microcephaly, cortical malformations, and MR [OMIM #600176] are more severe disorders.

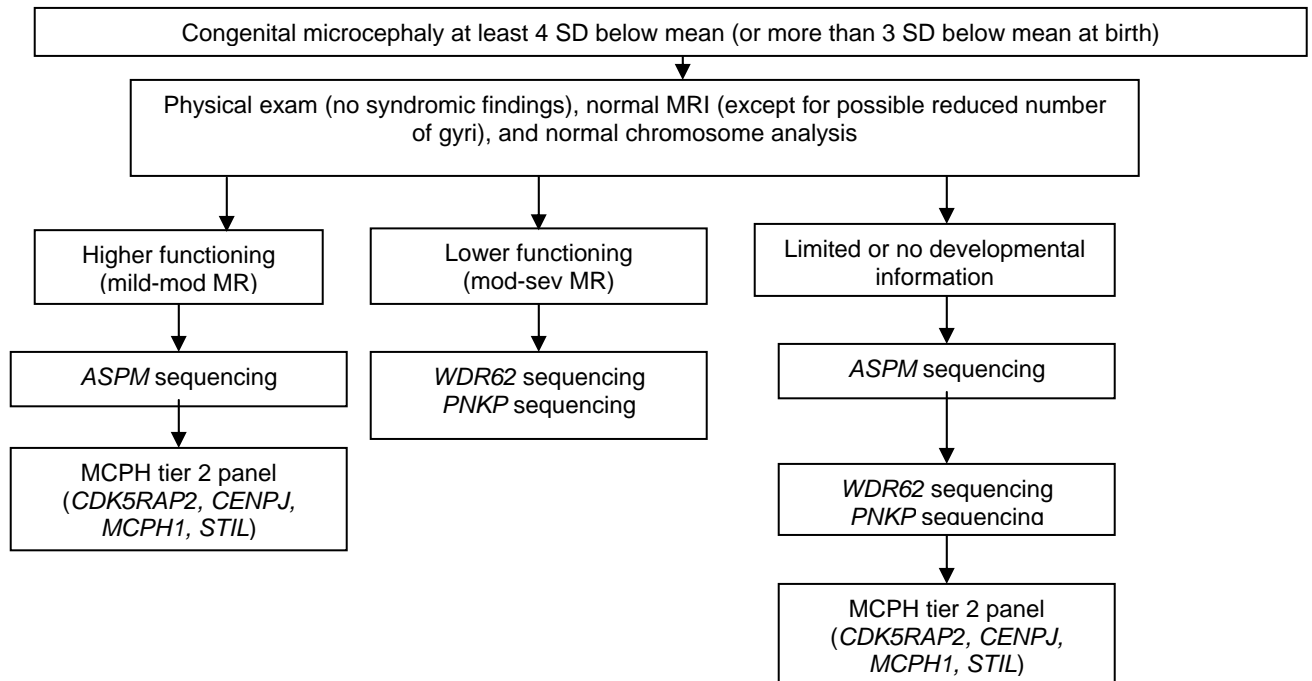
In patients with MCSZ, MR is usually severe to profound with variable behavioral problems and seizures are severe and intractable. Mutations in the *PNKP* [OMIM #605610] gene have been described in seven families with MCSZ. Both homozygous, consanguineous patients and compound heterozygotes were reported. The *PNKP* protein is involved in DNA repair of both double and single-stranded breaks. Of the 14 patients described, none have reported a higher frequency of infections and no cancers have been reported by the age of 21 [11].

Patients with microcephaly, cortical malformations, and MR have moderate to severe MR and brain malformations including: callosal abnormalities, polymicrogyria, schizencephaly and subcortical heterotopia.

Some of these patients have also been described with seizures [12]. This form of MCPH is caused by mutations in the *WDR62* [OMIM#613583] gene. Homozygous missense and frameshift mutations were first reported in seven consanguineous families with primary microcephaly and simplified gyri. Like other MCPH genes, *WDR62* encodes a spindle pole protein that is expressed in neuronal precursor cells undergoing mitosis in the proliferative phase of neurogenesis [13].

### 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 [14]. Recurrence risk for parents of an affected individual with a confirmed mutation causing MCPH is 25%.



### 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 [3]. *PNKP* and *WDR62* mutations have been found in several ethnicities, including Palestinian, Turkish, and Mixed European [11-13].

### Additional Resources:

#### Foundation for Children with Microcephaly

Phone: 602-487-6445

email: [jenni@childrenwithmicro.org](mailto:jenni@childrenwithmicro.org)

[www.childrenwithmicro.org](http://www.childrenwithmicro.org)

### Test methods:

The University of Chicago Laboratory offers mutation analysis of all 28 coding exons and intron/exon boundaries of *ASPM*, all 16 coding exons and intron/exon boundaries of *PNKP*, and all 30 coding exons and intron/exon boundaries of *WDR62* by direct sequencing of amplification products in both the forward and reverse directions. Physicians may also choose to order our MCPH Tier 2 Panel. This panel includes full gene sequencing for the *CDK5RAP2*, *CENPJ*, *MCPH1*, and *STIL* genes. Sequencing for these genes cannot be ordered individually.

*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 gene mutations, can enroll in Dr. Dobyns' research study. Please contact him at [wbd@u.washington.edu](mailto:wbd@u.washington.edu) for more information.

#### ASPM sequence analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube  
Cost: \$2400  
CPT codes: 83891, 83898 x 9, 83904 x 9, 83912  
Turn-around time: 6 - 8 weeks

**Note: We cannot bill insurance for ASPM sequencing.**

#### PNKP sequence analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube  
Cost: \$1675  
CPT codes: 83891, 83898 x 4, 83904 x 7, 83912  
Turn-around time: 4 - 6 weeks

#### WDR62 sequence analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube  
Cost: \$2400  
CPT codes: 83891, 83898 x 9, 83904 x 9, 83912  
Turn-around time: 4 - 6 weeks

#### MCPH Tier 2 Panel (CDK5RAP2, CENPJ, MCPH1, and STIL sequence analysis)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube  
Cost: \$3150  
CPT codes: 83891, 83898 x 12, 83904 x 12, 83912  
Turn-around time: 8 - 10 weeks

**Note: We cannot bill insurance for MCPH Tier 2 Panel.**

#### Targeted analysis for a known sequence change in additional family members

Sample specifications: 3 to10 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(s)

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

#### **References:**

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