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ASPM Primary Microcephaly

Synonyms: *ASPM* Microcephalia Vera, Microcephaly Primary Hereditary 5 (MCPH5)

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Summary

Clinical characteristics

ASPM primary microcephaly (*ASPM*-MCPH) is characterized by: (1) significant microcephaly (>3 standard deviations [SD] below the mean for age) usually present at birth and always present before age one year and (2) the absence of other congenital anomalies. While developmental milestones are usually normal in young children, older children have variable levels of intellectual disability. Neurologic examination is usually normal except for mild spasticity. Seizures are not common.

Diagnosis/testing

The diagnosis of *ASPM*-MCPH is established in a proband with biallelic pathogenic variants in *ASPM* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and focused on interventions to address developmental delay / intellectual disability, speech delay, and behavior issues. The management of epilepsy and spasticity is per standard care.

Surveillance: Routine monitoring of: growth; response of seizures to treatment or new-onset seizures; management of spasticity; developmental progress, including speech and language development; educational needs; and behavior for anxiety, attention, and aggressive or self-injurious behavior. Assess family need for social work support (e.g., respite care, other local resources).

Agents/circumstances to avoid: Limit the use of methylphenidate, which exacerbates hyperactivity.

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Genetic counseling

ASPM-MCPH is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a heterozygote (carrier), and a 25% chance of being unaffected and not a carrier. Heterozygotes may have mild microcephaly (2-3 SD below the mean) but do not have other clinical findings associated with *ASPM*-MCPH. Once the *ASPM* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

ASPM primary microcephaly (*ASPM*-MCPH) **should be suspected** in individuals with the following clinical and neuroimaging findings.

Clinical findings

- Congenital microcephaly (usually identified before birth by ultrasound examination) with an occipitofrontal circumference ≥2 standard deviations (SD) below the mean at birth, and >3.5 SD below the mean before age one year
- Mild intrauterine growth restriction with postnatal catch up (Growth restriction does not persist after age two years.)
- No other congenital abnormalities
- Normal or subnormal motor development
- Usually mild intellectual disability (ID) with preserved memory but variable (range: borderline normal intellectual functioning to severe ID)
- Seizures (rare)
- Nonspecific facial features (i.e., narrow sloping forehead)

Brain MRI findings

- Reduced brain volume that affects supratentorial structures, and, to a lesser extent, the cerebellum [Passemard et al 2009] and brain stem. The mean reduction of cerebral volume is 50%, affecting both the cerebral cortex and white matter; it is more pronounced in the prefrontal and cingulate cortices than in the mesial temporal regions. The volume of the hippocampus is not affected. The cortex is thicker, especially in the prefrontal region [Passemard et al 2016].
- Commonly simplified gyral pattern with reduced gyrification index and surface of the cerebral cortex [Létard et al 2018]
- Mild lateral ventricle enlargement
- Corpus callosum dysplasia/hypoplasia [Passemard et al 2016]
- Cortical dysplasia (rare), which can be bilateral polymicrogyria [Hu et al 2014] or focal polymicrogyria [Passemard et al 2009]) and migration anomalies (heterotopias)

Establishing the Diagnosis

The diagnosis of *ASPM*-MCPH **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in *ASPM* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section

is understood to include any likely pathogenic variants. (2) Identification of biallelic *ASPM* variants of uncertain significance (or of one known *ASPM* pathogenic variant and one *ASPM* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *ASPM*-MCPH may be indistinguishable from many other primary microcephalies, recommended molecular genetic testing approaches include use of a **multigene panel** (see Option 1) or **comprehensive genomic testing** (see Option 2).

Note: Single-gene testing (sequence analysis of *ASPM*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *ASPM* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of *ASPM* microcephaly.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *ASPM* Primary Microcephaly

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ASPM	Sequence analysis [3]	~98% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

ASPM primary microcephaly (*ASPM*-MCPH) is characterized by: (1) significant microcephaly (>3 SD below the mean for age) usually present at birth and always present before age one year and (2) the absence of another congenital anomalies. While developmental motor milestones are usually normal in young children, older children have variable levels of language delay and intellectual disability. Neurologic examination is usually normal except for mild spasticity. Fewer than 15% of affected individuals have seizures.

Growth. While weight and length are most often normal at birth, intrauterine growth restriction may be present in some. Growth may be delayed within the first months of life because of transient feeding difficulties. All children have normal height after age two years.

Occipitofrontal circumference (OFC). Microcephaly is often detected prior to birth, typically during the third trimester of pregnancy and rarely during the second trimester. OFC is between 2 and 8 SD below the mean at birth (32 cm and 26 cm, respectively). A clinical characteristic of *ASPM*-MCPH is a decline in brain growth with age such that OFC is between 4 and 14 SD below the mean in adulthood.

Neurologic findings – in the absence of brain malformations – are limited to a mild pyramidal syndrome (i.e., mild spasticity of the lower limbs).

Intellectual disability (ID). Early motor development is normal (in ~50%) or mildly delayed. Language is often delayed (first use of sentences after age 3 years in 80%), with poorly articulated speech or speech limited mostly to single words or short sentences.

Individuals with *ASPM*-MCPH have mild-to-severe ID. They have preserved memory despite their ID [Passemard et al 2016]. While they may have success with vocational training in crafts or services, affected individuals are likely unable to live independently.

Behavior issues. Preschool age may be very difficult because the children may become angry and hit or bite other children due to their lack of vocabulary.

Before age ten to 12 years, children are easily frustrated with learning activities and appear inattentive to others or to classroom activities. Inattentiveness (inability to listen to or carry out instructions), hyperkinesia (e.g., excessive movement, inability to sit still), and impulsiveness (no sense of danger) tend to appear at an early age and become more noticeable when children start school. Such behaviors are often considered more deleterious to functioning in a classroom than speech delay.

After age 12 years, hyperactivity and impulsiveness disappear. Teenagers are calmer and more attentive. They can appear introverted. They become cheerful, affable, and cooperative [Pattison et al 2000].

Autistic features have not been described in *ASPM*-MCPH.

Epilepsy. Fewer than 15% of individuals with *ASPM*-MCPH have epilepsy. Epilepsy is more likely to occur when brain MRI shows cortical anomalies (polymicrogyria, cortical dysplasia). Seizures that often begin after age two years are variable: focal or tonic and tonic-clonic generalized seizures have been reported. Focal seizures should prompt the clinician to search for a focal dysplasia or unilateral polymicrogyria [Passemard et al 2009]. West syndrome has not been reported.

EEG may be normal or show focal spikes.

Other findings. Some individuals with *ASPM*-MCPH have hypo- and/or hyperpigmented macules [Létard et al 2018].

Findings that are rare, without a recurrent pattern, and are likely coincidental include: scoliosis (2 families [Létard et al 2018]), middle ear hypoplasia [Létard et al 2018], deafness [Darvish et al 2010], preaxial polydactyly [Ahmad et al 2017], unilateral cystic kidney [Passemard et al 2009], and tricuspid insufficiency [Ariani et al 2013].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

Age of onset is used to distinguish primary from secondary microcephaly. Primary microcephaly (PM) is congenital (present at birth) while secondary microcephaly refers to a normal OFC at birth followed by postnatal microcephaly.

Microcephalia vera is a general term used to describe congenital microcephaly associated with neurologic features.

ASPM-MCPH is also designated as MCPH5 (i.e., the 5th primary microcephaly [MCPH] locus to be identified).

Prevalence

A review of the literature in 2019 identified 685 individuals with *ASPM*-MCPH belonging to 321 families. Most families come from the Asian subcontinent and Middle East (Pakistan, Saudi Arabia, Egypt, and Iran). A few families are from Europe and the Americas [Létard et al 2018].

ASPM-MCPH is the most common form of primary microcephaly. To date, biallelic *ASPM* pathogenic variants explain 30%-50% of MCPH depending on the geographic origin of the individual and the rate of consanguinity in the population.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ASPM*.

Differential Diagnosis

Monogenic disorders in the differential diagnosis of *ASPM*-MCPH include the primary microcephalies (PMs), a group of rare, phenotypically and etiologically heterogeneous disorders of brain growth characterized by (1) a head circumference close to or greater than 2 SD below the mean at birth and greater than 3 SD below the mean by age one year; (2) absence of extracephalic anomalies; and (3) mild-to-severe intellectual disability. Additional clinical or neuroimaging features can be associated. Most PMs are inherited in an autosomal recessive manner. To date, pathogenic variants in more than 100 genes are responsible for PM (for review, see Jayaraman et al [2018]).

The three broad phenotypic categories of monogenic primary microcephaly include the following:

- Isolated PM in which the primary microcephaly is not associated with extracerebral malformations (e.g., *ASPM*-MCPH, most tubulinopathies). Many PMs are also known as *m*icro*c*ephaly *p*rimary *h*ereditary or MCPH) * although some may have different names for historical reasons;
- PM with short stature (i.e., Seckel syndrome *);

- Syndromic PM, a heterogeneous group in which PM is associated with extracerebral anomalies and growth impairment (e.g., Rubinstein-Taybi syndrome, Cornelia de Lange syndrome, Meier-Gorlin syndrome, *DYRK1A* intellectual disability syndrome)

* MCPH and Seckel syndrome may be further subdivided by the presence of cortical malformations and/or chorioretinopathy.

Genes associated with the three broad phenotypic categories of PM (excluding those with a true clinically recognizable "syndromic gestalt" such as Rubinstein-Taybi syndrome and Cornelia de Lange syndrome) are listed in Table 2. OMIM phenotypic series referenced in Table 2 (see OMIM entries designated with the prefix "PS") are based on the presence of microcephaly and associated features. Due to the intrinsic phenotypic variability associated with pathogenic variants in each gene, the clinical overlap across these phenotypic series is considerable.

Although the three broad phenotypic categories have been valuable for clinical management and for differential diagnosis, this simple classification does not reflect underlying pathophysiologic mechanisms.

Table 2. Monogenic Disorders with Congenital Microcephaly and Intellectual Disability to Consider in the Differential Diagnosis of *ASPM* Primary Microcephaly

Disorder/Phenotype [1]	Gene(s)	MOI	Clinical Features Distinguishing the Disorder from *ASPM*-MCPH
MCPH (OMIM PS251200)	*ANKLE2* *CDK5RAP2* *CDK6* *CENPE* *CENPJ* *CEP135* *CEP152* *CIT* *COPB2* *KIF14* *KNL1* *MAP11* *MCPH1* *MFSD2A* *NCAPD2* *NCAPD3* *NCAPH* *NUP37* *PHC1* *SASS6* *STIL* *WDFY3* *WDR62* *ZNF335*	AR (AD) [2]	• *ANKLE2-*, *CENPJ-*, *CEP152-*, *KIF14-*, *NCAPD2-*, *PHC-*, & *ZNF335*-MCPH: may have IUGR w/subsequent short stature • *MFSD2A*-MCPH: may have hydrocephalus • *STIL*-MCPH: may have holoprosencephaly • *WDR62*-MCPH: often severe cortical dysplasia (DD w/the cortical malformation, complex phenotypic series) • *ZNF335*-MCPH: early lethality
Microcephaly-micromelia syndrome (OMIM 251230)	*DONSON*	AR	• Short stature • Inconstant anomalies of forearm
Meier-Gorlin syndrome (OMIM PS224690)	*CDC45* *CDC6* *CDT1* *GMNN* *MCM5* *ORC1* *ORC4* *ORC6*	AR (AD) [3]	• *ORC1* Meier-Gorlin syndrome: short stature • Mammary hypoplasia in females • Bilateral microtia & aplasia or hypoplasia of the patellae are characteristic but inconstant. • ID uncommon

Table 2. continued from previous page.

Disorder/Phenotype [1]	Gene(s)	MOI	Clinical Features Distinguishing the Disorder from *ASPM*-MCPH
Cortical dysplasia, complex, w/other brain malformations (OMIM PS614039, Congenital Fibrosis of the Extraocular Muscles, Tubulinopathies Overview)	*CTNNA2* *KIF2A* *KIF5C* *TUBA8* *TUBB* *TUBB2A* *TUBB2B* *TUBB3* *TUBG1*	AD (AR) [4]	• Brain dysplasia of variable severity • Fusion between caudate & putamen nuclei w/indistinct anterior arm of the internal capsule • Neonatal seizures
Seckel syndrome (OMIM PS210600)	*ATR* *CENPJ* *CEP152* *CEP63* *DNA2* *NIN* *NSMCE2* *RBBP8* *TRAIP*	AR	• IUGR • Severe short stature (>3 SD below the mean) • Microcephaly may be disproportionate (in SD) compared to height. • Beaked nose • Sloping forehead
Microcephalic osteodysplastic dwarfism (MOPD) type II	*PCNT*	AR	• IUGR w/subsequent very short stature • Mild skeletal dysplasia • Risk of brain hemorrhages
RNU4ATAC disorders	*RNU4ATAC*	AR	• IUGR w/subsequent short stature • Brain malformations • Ocular & auditory sensory deficit • Encompass a spectrum of 3 phenotypes: primary MOPD type I, Roifman syndrome, & Lowry Wood syndrome
Microcephaly & chorioretinopathy (MCCRP) (OMIM PS251270)	*PLK4* *TUBGCP4* *TUBGCP6*	AR	• Chorioretinopathy (inconstant) • *PLK4*-MCCRP: IUGR w/subsequent short stature
Microcephaly w/or w/o chorioretinopathy, lymphedema, or ID (OMIM 152950)	*KIF11*	AD	• Chorioretinopathy & lymphedema (inconstant) • ID uncommon
Asparagine synthetase deficiency	*ASNS*	AR	• Low CSF asparagine level • Progressive encephalopathy w/cortical atrophy & seizures
Serine biosynthesis defects	*PHGDH* *PSPH* *PSAT1*	AR	• Low CSF serine level • Neonatal seizures
DYRK1A ID syndrome	*DYRK1A*	AD	• Distinctive facies: bitemporal narrowing, deep-set eyes, large simple ears, pointed nasal tip

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; IUGR = intrauterine growth restriction; MCPH = primary hereditary microcephaly; MOI = mode of inheritance; SD = standard deviation(s)

1. Disorders are associated with intellectual disability unless otherwise noted.

2. MCPH is inherited in an autosomal recessive manner with the exception of *WDFY3*-MCPH, which is inherited in an autosomal dominant manner.

3. Meier-Gorlin syndrome is inherited in an autosomal recessive manner with the exception of *GMNN* Meier-Gorlin syndrome, which is inherited in an autosomal dominant manner.

4. Cortical dysplasia, complex, with other brain malformations (CDCBM) is inherited in an autosomal dominant manner with the exception of *CTNNA2*- and *TUBA8*-CDCBM, which are inherited in an autosomal recessive manner.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ASPM* primary microcephaly (*ASPM*-MCPH), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *ASPM* Primary Microcephaly

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, OFC.	During 1st 2 yrs of life transient FTT is common & typically resolves spontaneously.
Feeding	Nutrition / feeding team eval	Low threshold for clinical feeding eval if signs of FTT
Neurologic	Neurologic eval	If seizures are a concern: • Consider an EEG. • Review brain MRI for evidence of polymicrogyria, cortical dysplasia.
Development	Developmental assessment	• To incl motor, adaptive, cognitive & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen for behavior issues incl sleep disturbances, ADHD, & anxiety.
Mild spasticity	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support & resources	Assess need for: • Community or online resources such as Parent To Parent; • Social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; FTT=failure to thrive; OFC = occipitofrontal circumference; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *ASPM* Primary Microcephaly

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Speech delay	Speech therapy	Augmentative & alternative communication in case of severe oral communication disorder
Behavior issues	Cognitive behavioral therapy	Methylphenidate seldom effective in ADHD [Author, personal observation]
Epilepsy	Treatment by experienced neurologist w/ASM according to type of seizures	• Usually responsive to mono or bi-therapy • Education of parents/caregivers [1]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	Feeding therapy &/or dietary supplements to ↑ caloric intake	
Spasticity	Physical medicine & rehab / PT & OT	Stretching to ↑ mobility
Family/Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states and provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies, and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication Issues

Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation) in individuals with pyramidal tract involvement.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *ASPM* Primary Microcephaly

System/Concern	Evaluation [1]
Feeding	• Measurement of growth parameters (weight, height, OFC) • Eval of nutritional status
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl new-onset seizures, spasticity, contractures (rare).
Development	Monitor developmental progress & educational needs.
Speech delay	Monitor speech development.
Psychiatric/ Behavioral	Ancillary behavior assessment for anxiety, attention, & aggressive or self-injurious behavior; referral for formal eval if concerns
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills
Miscellaneous/ Other	Assess family need for social work support (e.g., respite care, other local resources).

OFC = occipitofrontal circumference; OT = occupational therapy; PT = physical therapy
1. To be performed at each visit

Agents/Circumstances to Avoid

Use of methylphenidate should be limited, as it exacerbates hyperactivity [Author, personal data].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ASPM primary microcephaly (*ASPM*-MCPH) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ASPM* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ASPM* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) may have mild microcephaly (2-3 SD below the mean) but do not have other clinical findings associated with *ASPM*-MCPH.

Sibs of a proband

- If both parents are known to be heterozygous for an *ASPM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) may have mild microcephaly (2-3 SD below the mean) but do not have other clinical findings associated with *ASPM*-MCPH.

Offspring of a proband. To date, individuals with *ASPM*-MCPH are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ASPM* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ASPM* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASPM* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Autosomal recessive primary microcephaly

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ASPM Primary Microcephaly: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ASPM	1q31.3	Abnormal spindle-like microcephaly-associated protein	ASPM @ LOVD	ASPM	ASPM

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ASPM Primary Microcephaly (View All in OMIM)

605481	ABNORMAL SPINDLE-LIKE, MICROCEPHALY-ASSOCIATED; ASPM
608716	MICROCEPHALY 5, PRIMARY, AUTOSOMAL RECESSIVE; MCPH5

Molecular Pathogenesis

The *a*bnormal *sp*indle-like *m*icrocephaly gene (*ASPM*; for review, see Létard et al [2018]) is the human ortholog of the *D melanogaster* "abnormal spindle" gene (*asp*) [Jamieson et al 2000, Pattison et al 2000, Bond et al 2002]. Four *ASPM* isoforms have been described [Kouprina et al 2005]. The human full-length, 3,477-amino acid ASPM protein contains two actin-binding calponin homology (CH) domains and an amino-terminal ASH

microtubule-binding domain, and displays 81 calmodulin-binding IQ repeats [Bond et al 2002, Kouprina et al 2004, Kouprina et al 2005].

ASPM localizes to the centrosome in interphase, the spindle pole during metaphase, and the midbody during cytokinesis [Kouprina et al 2005, Paramasivam et al 2007, Higgins et al 2010], and plays a role in mitotic spindle function including orientation of the cleavage plane. ASPM maintains symmetric cell divisions and is downregulated with the switch from proliferative to neurogenic divisions [Fish et al 2006]. ASPM plays a crucial role in the division of neural progenitor cells by keeping them cycling and promoting symmetric proliferative divisions at the expense of asymmetric neurogenic divisions [Fish et al 2006], thus expanding the pool of neural progenitors in the ventricular zone. ASPM-induced microcephaly is thought to result from reduced numbers of neural progenitors undergoing proliferation during early neurogenesis, possibly associated with increased apoptosis among these progenitors. This depletion of the neural stem cell pool results in a smaller brain.

Recently, it has been shown that ASPM plays a role in centriole biogenesis and duplication during interphase, maintaining the number of centrioles and centrosomes over the course of several rapid cell cycles in neural progenitors.

Mechanism of disease causation. The majority of *ASPM* pathogenic variants are predicted to result in a loss of protein function. Frameshift or nonsense variants are the most frequent (~90%); splice (~8%) and missense (< 2%) variants have been reported [Jayaraman et al 2016].

Table 6. Notable *ASPM* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_018136.4 NP_060606.3	c.3978G>A	p.Trp1326Ter	Founder variant in Turkish & Pakistani families [Létard et al 2018]
	c.9557C>G	p.Ser3186Ter	Founder variant in Pakistan [Létard et al 2018]
	c.7782_7783del	p.Lys2595SerfsTer6	Common pathogenic variant in Europe, Africa, & Asia; may be recurrent due to a hot spot [Létard et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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