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MPPH Syndrome

Synonym: Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus Syndrome

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Summary

Clinical characteristics

MPPH (*m*egalencephaly-*p*ostaxial polydactyly-*p*olymicrogyria-*h*ydrocephalus) syndrome is a developmental brain disorder characterized by megalencephaly (brain overgrowth) with the cortical malformation bilateral perisylvian polymicrogyria (BPP). At birth the occipital frontal circumference (OFC) ranges from normal to 6 standard deviations (SD) above the mean for age, sex, and gestational age; in older individuals the range is from 3 to 10 SD above the mean. A variable degree of ventriculomegaly is seen in almost all children with MPPH syndrome; nearly 50% of individuals have frank hydrocephalus. Neurologic problems associated with BPP include oromotor dysfunction (100%), epilepsy (50%), and mild-to-severe intellectual disability (100%). Postaxial hexadactyly occurs in 50% of individuals with MPPH syndrome.

Diagnosis/testing

The clinical diagnosis of MPPH syndrome can be established in individuals with the two core features: megalencephaly and polymicrogyria (PMG). The molecular diagnosis of MPPH syndrome is established in a proband with some of the suggestive clinical and imaging features by identification of a heterozygous pathogenic variant in one of three genes: *AKT3*, *CCND2*, or *PIK3R2*. While most individuals with MPPH syndrome have a germline pathogenic variant in one of these genes, some have a somatic mosaic pathogenic variant (most commonly reported in *PIK3R2* or *AKT3*).

Management

Treatment of manifestations: Hydrocephalus warrants early neurosurgical intervention. Treatment per neurooncologist for those with medulloblastoma. Oromotor difficulties, epilepsy, developmental delays, intellectual disability, polydactyly, vision issues, cardiac anomalies, thyroid abnormalities, and renal anomalies are treated as per usual clinical care standards. Social worker support and care coordination for families of affected individuals.

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Surveillance: Follow up with a pediatric neurologist regularly to monitor and treat epilepsy. Brain MRI to detect hydrocephalus and/or cerebellar tonsillar ectopia is provisionally recommended every six months from birth to age two years, and yearly from age two to six years. In older individuals, the frequency should be determined based on prior brain imaging findings as well as clinical findings. Brain imaging (with particular attention to the posterior fossa) may be considered every six months to assess for medulloblastoma. Assess growth and feeding at each visit. Routine follow up with a developmental pediatrician given the high risk of developmental delays and/or intellectual disability. Ophthalmology examination annually or as needed; endocrine follow up as recommended by endocrinologist. Assess need for social work support and care coordination at each visit.

Genetic counseling

MPPH syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Almost all individuals with MPPH syndrome have the disorder as the result of a *de novo* germline *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant; somatic mosaic pathogenic variants in *PIK3R2* and *AKT3* have been reported in a few affected individuals. Vertical transmission of a *PIK3R2* pathogenic variant from an affected heterozygous parent to several affected children has been reported in one family to date. Presumed parental germline mosaicism has been suggested in three families. Each child of an individual with a germline *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant has a 50% chance of inheriting the pathogenic variant. The risk for transmission to offspring of an individual with somatic mosaicism for an MPPH-related pathogenic variant is expected to be less than 50%. Once the MPPH syndrome-related pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MPPH syndrome are possible.

Diagnosis

Suggestive Findings

MPPH syndrome **should be suspected** in individuals with the following clinical and imaging findings [Mirzaa et al 2004, Mirzaa et al 2012]. Note: Findings shown in **bold** are core features.

Clinical findings

- **Macrocephaly** or **megalencephaly** (occipital frontal circumference ≥2 SD above the mean); onset either prenatally or postnatally
- Postaxial polydactyly of one or more extremities
- Hypotonia
- Early-onset epilepsy
- Intellectual disability
- Oromotor dysfunction (including speech/swallowing difficulties, excessive drooling, expressive speech delays)

Imaging findings

- **Cortical brain malformations** including **polymicrogyria** and **specifically, bilateral perisylvian polymicrogyria**
- Progressive ventriculomegaly leading to hydrocephalus
- Cerebellar tonsillar ectopia or Chiari malformations
- Thick corpus callosum (or mega corpus callosum)

Establishing the Diagnosis

The **clinical diagnosis** of MPPH syndrome **is established** in a proband with the two core features: megalencephaly and polymicrogyria.

The **molecular diagnosis** of MPPH syndrome **is established** in a proband with some of the suggestive clinical and imaging findings by identification of a heterozygous pathogenic variant in one of three genes: *AKT3*, *CCND2*, or *PIK3R2* (see Table 1). While most individuals with MPPH syndrome have a germline (i.e., constitutional) pathogenic variant in one of these three genes, some individuals have been reported with a somatic mosaic pathogenic variant in one of these genes (most commonly *PIK3R2* and *AKT3*).

Note: Failure to detect either a germline or somatic mosaic pathogenic variant in one of these three genes does not exclude a clinical diagnosis of MPPH syndrome in a proband with the two core clinical and imaging features.

Molecular genetic testing approaches used to identify germline and somatic pathogenic variants can include use of a **multigene panel** or **comprehensive genomic testing** (**exome sequencing, genome sequencing**), testing for somatic mosaicism, and chromosomal microarray analysis (CMA):

- **A multigene panel** that includes *AKT3*, *CCND2*, *PIK3R2*, and other genes of interest (see Differential Diagnosis) should be considered to detect germline and somatic variants in the MPPH-related genes. 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. (5) Somatic mosaicism for variants in the three MPPH-related genes may not be detected by all commercially available multigene panels due primarily to the inability to test tissues other than blood (e.g., skin or buccal cells) and/or technical limitations in detecting low-level mosaicism; thus, clinicians considering use of a multigene panel need to select a panel specifically optimized to detect mosaicism for the three MPPH-related genes.

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

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

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

If no germline pathogenic variant is found in any of the three genes, sequence analysis for *AKT3*, *PIK3R2*, or *CCND2* with methods to detect **somatic mosaicism** and/or testing for a large **duplication of 1q43-q44** that includes *AKT3* may be warranted:

- **Testing for somatic mosaicism.** Sequence analysis of DNA derived from saliva or skin (whether visibly affected or not) may detect a pathogenic variant not detected in DNA isolated from blood.

  Note: Sensitivity to detect low-level mosaicism of a somatic pathogenic variant is greatest using massively parallel sequencing (i.e., next-generation sequencing) in tissues other than blood, and in particular will be of high yield when analyzing affected tissues.

- **CMA analysis for duplications or triplications of 1q43-q44 that includes *AKT3*.** Because not all gene-targeted deletion/duplication methods are designed to size large copy number variants, CMA is the most appropriate for detection of this duplication or triplication.

Table 1. Molecular Genetic Testing Used in MPPH Syndrome

Gene [1]	Number of Persons w/Molecularly Confirmed MPPH Syndrome Attributed to a Pathogenic Variant in Gene [2]	Number of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	CMA [5]
AKT3	~30%	50%	50% [6]
CCND2	~30%	100%	NA
PIK3R2	~40%	100% [7, 8]	NA

1. See Table A. Genes and Databases for chromosome locus and protein.
2. References for the 41 individuals with a molecularly confirmed diagnosis: Mirzaa et al [2012], Poduri et al [2012], Rivière et al [2012], Wang et al [2013], Chung et al [2014], Jamuar et al [2014], Mirzaa et al [2014], Nakamura et al [2014], Tapper et al [2014], Conti et al [2015], Harada et al [2015], Nellist et al [2015], Hemming et al [2016], Terrone et al [2016]. Note that the other 23 individuals with a clinical diagnosis of MPPH syndrome did not undergo the complete molecular and cytogenetic testing required to detect the range of causative germline and somatic pathogenic variants.
3. See Molecular Genetics for information on variants detected in this gene.
4. 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.
5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *AKT3*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 1q44 region. CMA designs in current clinical use target the 1q44 region.
6. Duplications of 1q43-q44, which include *AKT3*, are detectable by CMA and cause macrocephaly and intellectual disability [Wang et al 2013, Chung et al 2014, Hemming et al 2016]. Somatic duplication of this locus has been identified in individuals with hemimegalencephaly and focal cortical dysplasia [Poduri et al 2012, Jamuar et al 2014, Conti et al 2015]. Although these large duplications would be detected by gene-targeted deletion/duplication assays, some methods would be unable to size the duplication.
7. Mosaicism for a *PIK3R2* pathogenic variant has been reported in individuals with MPPH syndrome [Mirzaa et al 2015].
8. Most individuals with a *PIK3R2* pathogenic variant have the same recurrent p.Gly373Arg variant. Only four other *PIK3R2* pathogenic variants have been reported to date [Nakamura et al 2014, Mirzaa et al 2015, Terrone et al 2016].

Clinical Characteristics

Clinical Description

MPPH syndrome is a developmental brain disorder characterized by megalencephaly (brain overgrowth) with the cortical malformation bilateral perisylvian polymicrogyria. To date, fewer than than 100 individuals with features of MPPH syndrome have been reported with either a clinical diagnosis (presence of the 2 core clinical and imaging findings: megalencephaly and polymicrogyria) , and/or a molecularly confirmed diagnosis [Mirzaa et al 2004, Colombani et al 2006, Garavelli et al 2007, Tohyama et al 2007, Pisano et al 2008, Tore et al 2009, Verkerk et al 2010, Osterling et al 2011, Mirzaa et al 2012, Rivière et al 2012, Kariminejad et al 2013, Zamora & Roberts 2013, Mirzaa et al 2014, Nakamura et al 2014, Tapper et al 2014, Demir et al 2015, Mirzaa et al 2015, Nellist et al 2015, Terrone et al 2016, Shi et al 2020].

Table 2. MPPH Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Megalencephaly	100%	
Cortical malformations	100%	Typically BPP but other types of PMG have also been seen

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Hydrocephalus	~50%	Ventriculomegaly seen in most individuals
Oromotor dysfunction	~50%	Specifically assoc w/BPP
Hypotonia	~80%	
Epilepsy	~100%	
Intellectual disability	100%	
Postaxial polydactyly	50%	

BPP = bilateral perisylvian polymicrogyria; PMG = polymicrogyria

Neurologic Findings

Megalencephaly (brain overgrowth). Most individuals with MPPH syndrome reported to date have congenital or early postnatal megalencephaly (i.e., rapidly progressive megalencephaly within the first year of life). Occipital frontal circumference (OFC) at birth ranges from normal to 6 SD above the mean for age, sex, and gestational age. OFCs in older individuals range from 3 to 10 SD above the mean.

In individuals with MPPH syndrome who develop hydrocephalus, brain overgrowth persists after surgical intervention (e.g., neurosurgical shunting), an observation consistent with true brain overgrowth [Mirzaa et al 2012].

Cortical malformations. To date, all individuals with MPPH syndrome have cortical brain malformations, particularly polymicrogyria (PMG). In almost all instances, the PMG is bilateral perisylvian polymicrogyria (BPP). BPP is associated with neurologic problems that can include oromotor dysfunction, epilepsy, and intellectual disability.

Ventriculomegaly and hydrocephalus. Variable degrees of ventriculomegaly are seen in almost all children with MPPH syndrome. Nearly 50% of reported individuals with MPPH syndrome have frank hydrocephalus requiring neurosurgical placement of a shunt. Based on limited retrospective data, the risk for hydrocephalus and/or cerebellar tonsillar ectopia with low brain stem or high spinal cord compression appears to be highest in the first two years of life [Mirzaa et al 2012].

Oromotor dysfunction, including expressive language or speech delay, difficulties handling oral secretions (with profuse drooling), and dysphagia is seen in most individuals with MPPH syndrome. Feeding difficulties occasionally result in gastrostomy tube placement. Oromotor dysfunction is largely attributed to (and well-known to occur with) BPP [Mirzaa et al 2015].

Tone abnormalities (including hypotonia in particular) are present at birth in most infants. Although tone may improve with age, older individuals may remain severely hypotonic.

Epilepsy. Approximately 50% of individuals with MPPH syndrome have early-onset epilepsy. Epilepsy types range from focal to generalized. Infantile spasms have been reported in some children. Epilepsy may be refractory to several anti-seizure medications. One individual with an *AKT3* pathogenic variant had severe refractory infantile spasms that responded to a ketogenic diet [Nellist et al 2015].

Intellectual disability. Almost all reported individuals with MPPH syndrome have intellectual disability that ranges from mild to severe. The degree of intellectual disability is largely determined by the following:

- Extent and severity of the cortical malformations (e.g., severity and distribution of PMG) (See Phenotype Correlations by Gene.)

- Age of onset and severity of epilepsy. Early-onset epilepsy (particularly in the newborn period), and generalized epilepsy are typically associated with more severe developmental and cognitive issues.

Other Findings

Postaxial polydactyly involving from one to all four extremities has been reported in 50% of children with MPPH syndrome.

Additional clinical features

- **Common.** Visual problems (including cortical visual impairment and blindness)
- **Each seen in fewer than five individuals**
  - Congenital cardiovascular defects (including ventricular septal defect, atrial septal defect)
  - Endocrine manifestations (including hypoglycemia, growth hormone deficiency, hypothyroidism, Hashimoto thyroiditis)
  - Renal anomalies (e.g., duplicated renal collecting system)
  - Medulloblastoma [Osterling et al 2011, Hadzipasic et al 2021]
- **Seen in one individual.** Encephalocele, cleft palate, and multiple polyps of the tongue [Demir et al 2015]

Phenotype Correlations by Gene

AKT3. Features including connective tissue laxity and cutaneous capillary malformations can overlap with megalencephaly-capillary malformation (MCAP) syndrome (see Differential Diagnosis) [Mirzaa et al 2012, Rivière et al 2012, Nakamura et al 2014, Nellist et al 2015].

CCND2

- PMG appears to be more severe and widespread, typically extending to the frontal and/or occipital lobes. These extensive cortical malformations correlate with increased severity of epilepsy and intellectual disability [Mirzaa et al 2014].
- Postaxial polydactyly is more commonly observed in individuals with *CCND2*-related MPPH syndrome than in those with a pathogenic variant in either *PIK3R2* or *AKT3* [Mirzaa et al 2014].

Genotype-Phenotype Correlations

In general, no differences in phenotype have been observed between individuals with a molecularly confirmed diagnosis and those with only a clinical diagnosis. The exceptions are several individuals with a molecularly confirmed diagnosis of MPPH syndrome who had BPP but lacked the core clinical feature of megalencephaly [Mirzaa et al 2015].

Penetrance

Penetrance is predicted to be 100% in individuals with a germline variant in *AKT3, CCND2,* or *PIK3R2.*

Prevalence

MPPH syndrome has been reported to date in fewer than 100 individuals from various ethnic backgrounds. Therefore, data regarding prevalence are limited.

Genetically Related (Allelic) Disorders

Table 3 includes other phenotypes caused by pathogenic variants in the genes associated with MPPH syndrome. Of note, the phenotypic spectrum associated with variants in the three MPPH-related genes will likely continue to expand, at least in part due to the phenotypic variability observed with somatic mosaicism.

Table 3. Allelic Disorders

Gene		Phenotype
AKT3	Gain-of-function variants	Hemimegalencephaly [1]
		Focal cortical dysplasia
		Megalencephaly
	Loss-of-function variants [2]	Microcephaly & intellectual disability [3]
CCND2	Loss-of-function variants [4]	Microcephaly & intellectual disability [4]
PIK3R2		Bilateral perisylvian polymicrogyria [5]

1. Two individuals with hemimegalencephaly with the same mosaic *AKT3* pathogenic variant (p.Glu17Lys; detectable in brain tissue only) have been reported. The paralogous *AKT1* pathogenic variant (the equivalent change in a related gene) is associated with Proteus syndrome [Lindhurst et al 2011].
2. Deletions resulting in presumed loss of function
3. Ballif et al [2012], Nagamani et al [2012], Gai et al [2015]
4. Pirozzi et al [2021]
5. Mirzaa et al [2015]

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of MPPH Syndrome

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/MPPH	Not observed in MPPH
MTOR	*MTOR*-related disorders [2]	*De novo* / somatic mosaic	MEG (congenital or postnatal); PMG (incl BPP)	FCD; pigmentary mosaicism [2]
PIK3CA	MCAP syndrome (See *PIK3CA*-Related Overgrowth Spectrum.)	*De novo* / somatic mosaic [1]	MEG (congenital or postnatal); BPP; postaxial polydactyly; ventriculomegaly or hydrocephalus	Somatic vascular malformations (capillary malformations, often multiple); somatic overgrowth (focal segmental)
PTCH1 *SUFU*	Nevoid basal cell carcinoma syndrome	AD	MEG, polydactyly	Calcine calcification, BCCs, jaw cysts, epidermal cysts, wide ribs, many other skeletal & multisystem features
PTEN	*PTEN* hamartoma tumor syndrome	*De novo* / AD [3]	MEG (congenital or postnatal); focal segmental cortical malformations (rare)	Papillomatous papules; trichilemmomas; vascular malformations (hemangiomas, arteriovenous malformations); ↑ cancer predisposition (thyroid, breast, endometrium)
STRADA (*LYK5*)	*STRADA*-related disorders (OMIM 611087)	AR	MEG (congenital or postnatal); early-onset epilepsy	Early lethality; uniformly poor neurodevelopmental outcome

AD = autosomal dominant; AR = autosomal recessive; BCC = basal cell carcinoma; BPP = bilateral perisylvian polymicrogyria; DiffDx = differential diagnosis; FCD = focal cortical dysplasia; MCAP = megalencephaly-capillary malformation; MEG = megalencephaly; MOI = mode(s) of inheritance; PMG = polymicrogyria
1. PIK3CA-related overgrowth spectrum disorders are not known to be inherited, as most identified pathogenic variants are somatic (mosaic). No confirmed vertical transmission or sib recurrence has been reported to date.
2. Mirzaa et al [2016]
3. Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome are autosomal dominant disorders caused by either an inherited or a *de novo PTEN* pathogenic variant. *PTEN*-related Proteus syndrome and Proteus-like syndrome are also autosomal dominant disorders but are almost always caused by a *de novo* pathogenic variant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with megalencephaly-postaxial polydactyly-polymicrogyria-hydrocephalus (MPPH) syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with MPPH syndrome

System/Concern	Evaluation	Comment
Constitutional	Physical exam w/particular attn to head size (OFC)	
Neurologic	Assessment by pediatric neurologist w/eval of suspected seizures as indicated	• To incl baseline brain MRI & careful eval for medulloblastoma, incl diffusion-weighted imaging to differentiate early neoplastic transformation w/in dysplastic cerebellar tissue & early consideration of contrast-enhanced studies in suspicious cases • In the presence of hydrocephalus &/or cerebellar tonsillar ectopia, full spinal MRI to evaluate for syringomyelia or syrinx formation
Gastrointestinal/ Feeding	Feeding assessment by feeding specialist, nutritionist, & gastroenterologist for evidence of chewing & swallowing difficulties & dysphagia	Consider eval for gastric tube placement as needed.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Musculoskeletal	Referral to orthopedist as needed for polydactyly	
Eyes	Ophthalmologic eval	To assess for vision abnormalities
Cardiovascular	Echocardiogram	To evaluate for structural cardiac defects
Endocrine	TSH & free T4	To assess for hypothyroidism
	Measure glucose levels in infants.	To assess for evidence of hypoglycemia
	Measurement of IGF1 & IGFBP3	Indirect assessment for GHD in those w/growth restriction or poor linear growth
Genitourinary	Renal ultrasound exam	To evaluate for structural renal defects
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MPPH syndrome in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

GHD = growth hormone deficiency; MOI = mode of inheritance; OFC = occipital frontal circumference

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with MPPH Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Neurosurgical complications (hydrocephalus & cerebellar tonsillar ectopia)	Neurosurgical referral for those w/: • Rapidly enlarging OFC • Obstructive hydrocephalus • Symptoms of ↑ intracranial pressure • Progressive or symptomatic CBTE or Chiari malformation	Early treatment of hydrocephalus may ↓ risk for progressive CBTE, but data to determine most appropriate neurosurgical mgmt are lacking.
Feeding difficulties	• Eval w/feeding specialist &/or gastroenterologist • Dietary modification &/or placement of a gastrostomy tube as needed • Speech therapy for difficulties w/swallowing & feeding	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Polydactyly	Surgical treatment per orthopedist	
Ophthalmologic involvement	Treatment per ophthalmologist	
	Vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Central visual impairment	No specific treatment	Early intervention program to stimulate visual development
Cardiac anomalies	Treatment per cardiologist & cardiothoracic surgeon	
Thyroid abnormalities	Treatment per endocrinologist	
Renal anomalies	Treatment per nephrologist	
Medulloblastoma	Treatment per neurooncologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CBTE = cerebellar tonsillar ectopia; DD/ID = developmental delay / intellectual disability; OFC = occipital frontal circumference

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 that 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:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether 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 the 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 US 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.

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).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

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.

Surveillance

Given the limited number of individuals reported with MPPH syndrome, formal surveillance guidelines do not exist.

Table 7. Recommended Surveillance for Individuals with MPPH Syndrome

System/Concern	Evaluation	Frequency
Neurologic	• Eval w/pediatric neurologist • Brain MRI for hydrocephalus &/or cerebellar tonsillar ectopia	• Birth – 2 yrs: every 6 mos • Age 2-6 yrs: annually • Age >6 yrs: frequency of brain MRI based on prior results & clinical findings, w/ particular attn to apnea or other abnormal patterns of respiration, headaches, changes in gait, or other neurologic problems. Note: Recommended frequency of brain MRI is provisional.
	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	At each visit
Risk of medulloblastoma	Careful eval of serial brain imaging w/particular attn to posterior fossa for medulloblastoma	Consider brain imaging every 6 mos for medulloblastoma risk.
Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	At each visit
Development	Monitor developmental progress & educational needs.	
	Eval w/developmental pediatrician	Annually &/or as needed
Eyes	Ophthalmology eval	
Endocrine	Endocrine eval for hypoglycemia, GHD &/or thyroid issues	As recommended by endocrinologist
Family/ Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources), care coordination or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

GHD = growth hormone deficiency

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

MPPH syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all individuals with MPPH syndrome have the disorder as the result of a *de novo* germline *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant. Somatic mosaic pathogenic variants in *PIK3R2* and *AKT3* have been reported in a few individuals with MPPH syndrome [Mirzaa et al 2015, Alcantara et al 2017].
- Vertical transmission of a *PIK3R2* pathogenic variant from an affected heterozygous parent to several affected children has been reported in one family to date [Mirzaa et al 2015].
- Parental germline mosaicism was suggested in three families by recurrence of MPPH syndrome in sibs and failure to detect the pathogenic variant in DNA isolated from parental blood samples [Rivière et al 2012, Mirzaa et al 2015, Szalai et al 2020].
- Recommendations for the evaluation of parents of a proband include molecular genetic testing for the pathogenic variant identified in the proband and a baseline neurologic assessment including measurement of head size.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the proband most likely has a *de novo* pathogenic variant.
- Another possible explanation is parental germline (or somatic and germline) mosaicism [Rivière et al 2012, Mirzaa et al 2015, Szalai et al 2020]. A parent with somatic and germline mosaicism for an MPPH syndrome-related pathogenic variant may be mildly/minimally affected.
- Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. While there may be phenotypic variability within the same family, all sibs who inherit a pathogenic variant will have features of MPPH syndrome.
- If the *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (but as-yet unknown) because of the possibility of parental germline mosaicism; further data are needed to establish the recurrence risk for sibs [Rivière et al 2012, Mirzaa et al 2015, Szalai et al 2020].

Offspring of a proband

- Each child of an individual with a germline *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant has a 50% chance of inheriting the pathogenic variant.

- The risk for transmission to offspring of an individual with somatic mosaicism for an MPPH-related pathogenic variant (i.e., the pathogenic variant is thought to have occurred post-fertilization in one cell of the multicellular embryo) is expected to be less than 50%.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a germline *AKT3*, *CCND2*, or *PIK3R2* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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 parents of affected individuals.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the MPPH syndrome-related pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MPPH syndrome 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**
  Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome

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. MPPH Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
AKT3	1q43-q44	RAC-gamma serine/threonine-protein kinase	AKT3	AKT3
CCND2	12p13.32	G1/S-specific cyclin-D2	CCND2	CCND2

Table A. continued from previous page.

PIK3R2	19p13.11	Phosphatidylinositol 3-kinase regulatory subunit beta	PIK3R2	PIK3R2

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 MPPH Syndrome (View All in OMIM)

123833	CYCLIN D2; CCND2
603157	PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 2; PIK3R2
603387	MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 1; MPPH1
611223	AKT SERINE/THREONINE KINASE 3; AKT3
615937	MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 2; MPPH2
615938	MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 3; MPPH3

Molecular Pathogenesis

AKT3, *CCND2*, and *PIK3R2* encode key proteins within the phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway, a major signaling pathway involved with key cellular functions including protein synthesis, metabolism, cell cycle, survival, growth, and proliferation [Engelman et al 2006, Vanhaesebroeck et al 2012].

Pathogenic gain-of-function variants in these and other genes within the pathway (including *PIK3CA* and *MTOR*) are associated with a spectrum of diffuse and segmental developmental brain disorders including megalencephaly, hemimegalencephaly, polymicrogyria, and focal cortical dysplasia [Mirzaa & Poduri 2014].

AKT3 is a serine/threonine kinase and the principal target of phosphatidylinositol 3,4,5-trisphosphate (PIP3). *PIK3R2* encodes the beta regulatory subunit of the PI3K enzymatic complex, a kinase complex that phosphorylates phosphatidylinositol 4,5-bisphosphate, to generate PIP3. Binding of PIP3 to the AKT complex leads to phosphorylation of multiple downstream PI3K-AKT-MTOR targets, including MTOR (mammalian target of rapamycin) itself.

CCND2, a protein that mediates the G1-S transition of the cell cycle, is among the downstream targets of the PI3K-AKT-MTOR pathway [Engelman et al 2006, Mirzaa et al 2014].

Mechanism of disease causation. Gain of function

Table 8. MPPH Syndrome: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
AKT3	Mosaic genetic variants (incl copy number abnormalities of the AKT3 locus) may occur.
PIK3R2	Mosaic genetic variants may occur.

1. Genes from Table 1 in alphabetic order.

Table 9. MPPH Syndrome: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
AKT3	NM_005465.7 NP_005456.1	c.1393C>T	p.Arg465Trp	Most common MPPH-assoc pathogenic variant [Alcantara et al 2017]

Table 9. continued from previous page.

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
PIK3R2	NM_005027.4 NP_005018.2	c.1117G>A	p.Gly373Arg	Most common *PIK3R2* pathogenic variant [Rivière et al 2012, Nakamura et al 2014, Mirzaa et al 2015, Terrone et al 2016].

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.

Cancer and Benign Tumors

AKT3 is a key modulator of several sporadic tumors (including melanoma, glioma, and ovarian cancer) that occur in the absence of any other findings of MPPH syndrome. Somatic pathogenic gain-of-function missense variants across all functional domains of *AKT3* are seen in a variety of tumors in the Catalogue of Somatic Mutations in Cancer (COSMIC). These somatic variants in *AKT3* are **not** present in the germline; thus, predisposition to these tumors is not heritable.

CCND2. Sporadic tumors (including ovarian and testicular tumors) occurring in the absence of any other findings of MPPH syndrome have shown high-level expression of CCND2. CCND2 is also overexpressed in astrocytomas and glioblastomas [Parry & Engh 2012, Koyama-Nasu et al 2013]. Importantly, three individuals with an *MPPH* or *CCND2* pathogenic variant have developed medulloblastoma [Osterling et al 2011; Hadzipasic et al 2021; Author, unpublished data] suggesting a causal link.

PIK3R2. Somatic pathogenic gain-of-function variants in *PIK3R2* occur in sporadic tumors, particularly endometrial cancer in the absence of any other findings of MPPH syndrome. These somatic *PIK3R2* variants are not present in the germline; thus, predisposition to these tumors is not heritable.

Chapter Notes

Author Notes

Dr Ghayda Mirzaa is a clinical and molecular geneticist at the Seattle Children's Research Institute and the University of Washington School of Medicine. Her research is focused on understanding the developmental basis and genetic causes of developmental brain disorders, including brain growth abnormalities, cortical malformations, and epilepsy. Dr Mirzaa's research team studies the natural history of MPPH syndrome.

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