MPPH Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK396098/

SummaryClinical characteristics.MPPH (megalencephaly-postaxial polydactyly-polymicrogyria-hydrocephalus) 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.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.

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DiagnosisSuggestive FindingsMPPH 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 postnatallyPostaxial polydactyly of one or more extremitiesHypotoniaEarly-onset epilepsyIntellectual disabilityOromotor dysfunction (including speech/swallowing difficulties, excessive drooling, expressive speech delays)

Imaging findings

Cortical brain malformations including polymicrogyria and specifically, bilateral perisylvian polymicrogyriaProgressive ventriculomegaly leading to hydrocephalusCerebellar tonsillar ectopia or Chiari malformationsThick corpus callosum (or mega corpus callosum)Establishing the DiagnosisThe 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
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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].

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Establishing the DiagnosisThe 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

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Clinical CharacteristicsClinical DescriptionMPPH 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 FeaturesView in own windowFeature% of Persons w/FeatureCommentMegalencephaly100%Cortical malformations100%Typically BPP but other types of PMG have also been seenHydrocephalus~50%Ventriculomegaly seen in most individualsOromotor dysfunction~50%Specifically assoc w/BPPHypotonia~80%Epilepsy~100%Intellectual disability100%Postaxial polydactyly50%BPP = bilateral perisylvian polymicrogyria; PMG = polymicrogyriaNeurologic FindingsMegalencephaly (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

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Each seen in fewer than five individuals

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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 CorrelationsIn 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].PenetrancePenetrance is predicted to be 100% in individuals with a germline variant in AKT3, CCND2, or PIK3R2.PrevalenceMPPH syndrome has been reported to date in fewer than 100 individuals from various ethnic backgrounds. Therefore, data regarding prevalence are limited.

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Genetically Related (Allelic) DisordersTable 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 DisordersView in own windowGenePhenotype

AKT3

Gain-of-function variantsHemimegalencephaly 1Focal cortical dysplasiaMegalencephalyLoss-of-function variants 2Microcephaly & intellectual disability 3

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PIK3R2

Bilateral perisylvian polymicrogyria 51. 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 function3. Ballif et al [2012], Nagamani et al [2012], Gai et al [2015]4.

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Differential DiagnosisTable 4. Genes of Interest in the Differential Diagnosis of MPPH SyndromeView in own windowGene(s)DiffDx DisorderMOIFeatures of DiffDx DisorderOverlapping w/MPPHNot observed in MPPH

MTOR

MTOR-related disorders 2De novo / somatic mosaicMEG (congenital or postnatal); PMG (incl BPP)FCD; pigmentary mosaicism 2

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MCAP syndrome (See PIK3CA-Related Overgrowth Spectrum.)De novo / somatic mosaic 1MEG (congenital or postnatal); BPP; postaxial polydactyly; ventriculomegaly or hydrocephalusSomatic vascular malformations (capillary malformations, often multiple); somatic overgrowth (focal segmental)

PTCH1

SUFU

Nevoid basal cell carcinoma syndrome

ADMEG, polydactylyCalcine calcification, BCCs, jaw cysts, epidermal cysts, wide ribs, many other skeletal & multisystem features

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ManagementEvaluations Following Initial DiagnosisTo 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 syndromeView in own windowSystem/ConcernEvaluationComment
Constitutional
Physical exam w/particular attn to head size (OFC)
Neurologic
Assessment by pediatric neurologist w/eval of suspected seizures as indicatedTo 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 casesIn 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 & dysphagiaConsider eval for gastric tube placement as needed.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Musculoskeletal

Referral to orthopedist as needed for polydactyly

Eyes

Ophthalmologic evalTo assess for vision abnormalities

Cardiovascular

EchocardiogramTo evaluate for structural cardiac defects

Endocrine

TSH & free T4To assess for hypothyroidismMeasure glucose levels in infants.To assess for evidence of hypoglycemiaMeasurement of IGF1 & IGFBP3Indirect assessment for GHD in those w/growth restriction or poor linear growth

Genitourinary

Renal ultrasound examTo evaluate for structural renal defects

Genetic

counseling

By genetics professionals 1To 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 circumference1. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsTable 6. Treatment of Manifestations in Individuals with MPPH SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Neurosurgical

complications

(hydrocephalus &

cerebellar tonsillar

ectopia)

Neurosurgical referral for those w/:

Rapidly enlarging OFCObstructive hydrocephalusSymptoms of ↑ intracranial pressureProgressive 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 gastroenterologistDietary modification &/or placement of a gastrostomy tube as neededSpeech therapy for difficulties w/swallowing & feeding

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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 ophthalmologistVision servicesChildren: through early intervention programs &/or school districtAdults: referral to low vision clinic &/or community vision services

Central visual

impairment

No specific treatmentEarly 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 nursingConsider

involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CBTE = cerebellar tonsillar ectopia; DD/ID = developmental delay / intellectual disability; OFC = occipital frontal circumference1. 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 IssuesThe 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.SurveillanceGiven the limited number of individuals reported with MPPH syndrome, formal surveillance guidelines do not exist.Table 7. Recommended

Surveillance for Individuals with MPPH SyndromeView in own

windowSystem/ConcernEvaluationFrequency

Neurologic

Eval w/pediatric neurologistBrain MRI for hydrocephalus &/or cerebellar tonsillar ectopia

Birth ‒ 2 yrs: every 6 mosAge 2-6 yrs: annuallyAge >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 medulloblastomaConsider 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 pediatricianAnnually &/or as needed

Eyes

Ophthalmology eval

Endocrine

Endocrine eval for hypoglycemia, GHD &/or thyroid issuesAs 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 visitGHD = growth hormone deficiencyEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 syndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Physical exam w/particular attn to head size (OFC)

Neurologic

Assessment by pediatric neurologist w/eval of suspected seizures as indicatedTo 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 casesIn 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 & dysphagiaConsider eval for gastric tube placement as needed.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Musculoskeletal

Referral to orthopedist as needed for polydactyly

Eyes

Ophthalmologic evalTo assess for vision abnormalities

Cardiovascular

EchocardiogramTo evaluate for structural cardiac defects

Endocrine

TSH & free T4To assess for hypothyroidismMeasure glucose levels in infants.To assess for evidence of hypoglycemiaMeasurement of IGF1 & IGFBP3Indirect assessment for GHD in those w/growth restriction or poor linear growth

Genitourinary

Renal ultrasound examTo evaluate for structural renal defects

Genetic

counseling

By genetics professionals 1To 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 circumference1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with MPPH syndromeView in own windowSystem/ConcernEvaluationComment

Constitutional

Physical exam w/particular attn to head size (OFC)

Neurologic

Assessment by pediatric neurologist w/eval of suspected seizures as indicatedTo 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 casesIn 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 & dysphagiaConsider eval for gastric tube placement as needed.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Musculoskeletal

Referral to orthopedist as needed for polydactyly

Eyes

Ophthalmologic evalTo assess for vision abnormalities

Cardiovascular

EchocardiogramTo evaluate for structural cardiac defects

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Renal ultrasound examTo evaluate for structural renal defects

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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 circumference1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Recommended Evaluations Following Initial Diagnosis in Individuals with MPPH syndrome

System/ConcernEvaluationComment

Constitutional

Physical exam w/particular attn to head size (OFC)

Neurologic

Assessment by pediatric neurologist w/eval of suspected seizures as indicatedTo 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 casesIn 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 & dysphagiaConsider eval for gastric tube placement as needed.

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Musculoskeletal

Referral to orthopedist as needed for polydactyly

Eyes

Ophthalmologic evalTo assess for vision abnormalities

Cardiovascular

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Endocrine

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Renal ultrasound examTo evaluate for structural renal defects

Genetic

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By genetics professionals 1To 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.

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

To incl motor, adaptive, cognitive, & speech/language eval

Eval for early intervention / special education

Community or online resources such as Parent to Parent;

Social work involvement for parental support;

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GHD = growth hormone deficiency; MOI = mode of inheritance; OFC = occipital frontal circumference1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of ManifestationsTable 6. Treatment of Manifestations in Individuals with MPPH SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Neurosurgical

complications

(hydrocephalus &

cerebellar tonsillar

ectopia)

Neurosurgical referral for those w/:

Rapidly enlarging OFCObstructive hydrocephalusSymptoms of ↑ intracranial pressureProgressive 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 gastroenterologistDietary modification &/or placement of a gastrostomy tube as neededSpeech therapy for difficulties w/swallowing & feeding

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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 ophthalmologistVision servicesChildren: through early intervention programs &/or school districtAdults: referral to low vision clinic &/or community vision services

Central visual

impairment

No specific treatmentEarly 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 nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CBTE = cerebellar tonsillar ectopia; DD/ID = developmental delay / intellectual disability; OFC = occipital frontal circumference1. 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 IssuesThe 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

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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.

Table 6. Treatment of Manifestations in Individuals with MPPH SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other
Neurosurgical

complications

(hydrocephalus &

cerebellar tonsillar

ectopia)
Neurosurgical referral for those w/:
Rapidly enlarging OFCObstructive hydrocephalusSymptoms of ↑ intracranial pressureProgressive or symptomatic CBTE or Chiari malformation
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Feeding difficulties

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Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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 ophthalmologistVision servicesChildren: through early intervention programs &/or school districtAdults: referral to low vision clinic &/or community vision services

Central visual

impairment

No specific treatmentEarly 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 nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CBTE = cerebellar tonsillar ectopia; DD/ID = developmental delay / intellectual disability; OFC = occipital frontal circumference1. 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.

Treatment of Manifestations in Individuals with MPPH Syndrome

Manifestation/ConcernTreatmentConsiderations/Other

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Rapidly enlarging OFC

Obstructive hydrocephalus

Symptoms of ↑ intracranial pressure

Progressive or symptomatic CBTE or Chiari malformation

Eval w/feeding specialist &/or gastroenterologist

Dietary modification &/or placement of a gastrostomy tube as needed

Speech therapy for difficulties w/swallowing & feeding

Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.

Education of parents/caregivers 1

Children: through early intervention programs &/or school district

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Motor Dysfunction

Gross motor dysfunction

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SurveillanceGiven the limited number of individuals reported with MPPH syndrome, formal surveillance guidelines do not exist.Table 7. Recommended Surveillance for Individuals with MPPH SyndromeView in own windowSystem/ConcernEvaluationFrequency

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Eval w/pediatric neurologistBrain MRI for hydrocephalus &/or cerebellar tonsillar ectopia

Birth ‒ 2 yrs: every 6 mosAge 2-6 yrs: annuallyAge >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 medulloblastomaConsider 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 pediatricianAnnually &/or as needed

Eyes

Ophthalmology eval

Endocrine

Endocrine eval for hypoglycemia, GHD &/or thyroid issuesAs 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 visitGHD = growth hormone deficiency

Table 7. Recommended Surveillance for Individuals with MPPH SyndromeView in own windowSystem/ConcernEvaluationFrequency

Neurologic

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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 medulloblastomaConsider brain imaging every 6 mos for medulloblastoma risk.

Feeding

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At each visit

Development

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Eyes

Ophthalmology eval

Endocrine

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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 visitGHD = growth hormone deficiency

Recommended Surveillance for Individuals with MPPH Syndrome

System/ConcernEvaluationFrequency

Neurologic

Eval w/pediatric neurologistBrain MRI for hydrocephalus &/or cerebellar tonsillar ectopia

Birth ‒ 2 yrs: every 6 mosAge 2-6 yrs: annuallyAge >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 medulloblastomaConsider 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 pediatricianAnnually &/or as needed

Eyes

Ophthalmology eval

Endocrine

Endocrine eval for hypoglycemia, GHD &/or thyroid issuesAs 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

Eval w/pediatric neurologist

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Monitor those w/seizures as clinically indicated.

Assess for new manifestations incl seizures, changes in tone, mvmt disorders.

Measure growth parameters.

Evaluate nutritional status & safety of oral intake.

GHD = growth hormone deficiency

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

Therapies Under InvestigationSearch 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 InheritanceMPPH 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 TestingOnce 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.

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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.

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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

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinHGMDClinVar

AKT3

1q43-q44

RAC-gamma serine/threonine-protein kinase

AKT3

AKT3

CCND2

12p13.32

G1/S-specific cyclin-D2

CCND2

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PIK3R2

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615938MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 3; MPPH3Molecular PathogenesisAKT3, 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 functionTable 8. MPPH Syndrome: Gene-Specific Laboratory ConsiderationsView in own windowGene 1Special Consideration

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31 March 2016 (gm) Original submission

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