

Autosomal Recessive Primary Microcephaly (MCPH): An Update

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Abstract

Keywords

- ▶ MCPH
- ▶ microcephaly
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Autosomal recessive primary microcephaly (MCPH; MicroCephalY Primary Hereditary) is a genetically heterogeneous neurodevelopmental disorder characterized by a significantly reduced head circumference present already at birth and intellectual disability. Inconsistent features include hyperactivity, an expressive speech disorder, and epilepsy. Here, we provide a brief overview on this rare disorder pertinent for clinicians.

Introduction

Microcephaly is the clinical sign of small cranium with a significant reduction of the occipitofrontal head circumference (OFC) of more than two (microcephaly) or three (severe microcephaly) standard deviations (SDs) below the mean for age, sex, and ethnicity. According to the time of occurrence, microcephaly can be classified as primary (congenital) or secondary (postnatal). Primary microcephaly can be caused by environmental factors such as alcohol, drugs, or infections and/or by genetic defects.^{1–3} Primary microcephaly has been in the focus of neuroscience for years and even more so in the past months due to the Zika virus epidemic.⁴ Autosomal recessive primary microcephaly (MCPH; MicroCephalY Primary Hereditary) is a rare disorder characterized by severe microcephaly at birth and intellectual disability. The prevalence of MCPH ranges from 1:30,000 to 1:250,000 live births.⁵ Following the discovery of the first gene linked to MCPH in 1998,⁶ 16 genes have been reported worldwide to date and referred to as MCPH1 to MCPH17. In this review, we briefly discuss the current knowledge of this disorder relevant for clinicians.

Phenotype Features

Individuals with MCPH display nonprogressive microcephaly at birth that can already be diagnosed in utero by the 24th week of gestation using ultrasound or magnetic resonance imaging (MRI).⁷ MCPH has been reported in more than 300 families and individual patients worldwide; however, often with only sparse phenotype descriptions. Apart from intellectual disability (IQ between 30 and 70–80), hyperactivity and attention deficit, speech delay, and a narrow sloping forehead, MCPH patients usually do not have any further neurological signs (▶ **Fig. 1**).^{1,8–10} Follow-up of MCPH5 patients revealed that the OFC can diverge further from the mean following birth, to reach progressively – 4 to – 6 SD at the age of 6 months.⁹ Intellectual ability is acknowledged to be stable in patients with MCPH; however, no study highlighting the results of repetitive intelligence tests parallel to OFC measurements in patients with MCPH exists. Although short stature is a classic feature of Seckel's syndrome, it has been also reported in some individuals with *MCPH1*, *MCPH5*, *MCPH6*, *MCPH9*, and *MCPH11* gene mutations.^{9,11–15} Low set and prominent ears, high-arched palate,

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Fig. 1 Phenotype features of patients with MCPH. Sample pictures of four affected consanguineous Pakistani family members. (A) Individual 1 at the age of 21 years and (B) his brother at the age of 28 years. (C) Individual 2 at the age of 15 years and (D) his brother at the age of 20 years. (E) Individual 3 at the age of 4 years and (F) his brother at the age of 8 years. (G) Individual 4 at the age of 6 years and (H) his relative at the age of 16 years. Adapted with permission from Kraemer et al.⁸ MCPH, microcephaly primary hereditary.

unusual dermatoglyphic pattern, short stubby fingers, and inverted nipples can be also noticed in individuals with MCPH2.¹⁰ Only few patients with MCPH have been reported with seizures that are usually tonic/clonic and well treatable with antiepileptic medication.^{9,10} Additional behavioral problems described in patients with MCPH2 include impulsivity, severe tantrums, head banging, and self-biting.¹⁰ Sensorineural hearing loss is an inconsistent finding in patients with MCPH3.^{16,17}

Neuroimaging Findings

Radiological studies on individuals with MCPH reveal typically a reduction in brain volume (microencephaly) and

simplified neocortical gyration of an otherwise architecturally normal brain (—Figs. 2 and 3).³ While the classic definition of MCPH entails a lack of further severe brain malformations, it is now acknowledged that these do occur in patients with MCPH, particularly in patients with MCPH2. Such brain malformations include further abnormalities of neocortical gyration (perisylvian polymicrogyria, focal micropolygyria, and/or dysplasia), corpus callosum agenesis or hypoplasia, periventricular neuronal heterotopias, and enlarged lateral ventricles.^{9,12,16,18,19} Additional abnormalities in MCPH2 include pachygyria with cortical thickening, lissencephaly, and schizencephaly.^{10,20} Infratentorial anomalies such as cerebellar or brain stem hypoplasia with or without an increased space of the posterior fossa have

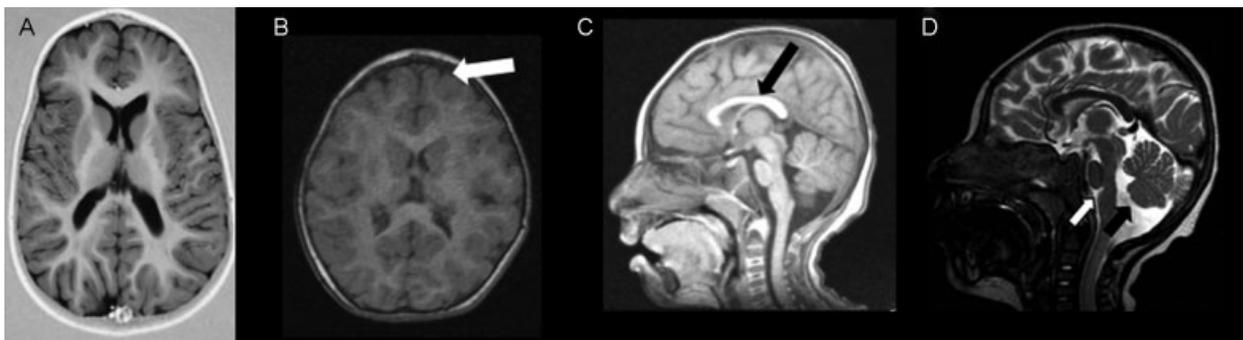


Fig. 2 (A, axial T1 image) Brain MRIs of a healthy individual and (B–D) a patient who is homozygous for a frameshift variant in the *ASPM* gene. (B, axial T1 image, white arrow) Variable degrees of simplified gyral pattern and small frontal lobe, (C, sagittal T1 image, black arrow) hypoplasia of corpus callosum, (D, sagittal T2 image, black arrow) mild cerebellar vermis hypoplasia, and (D, white arrow) a relatively small pons have all been described in patients. MRI, magnetic resonance imaging.

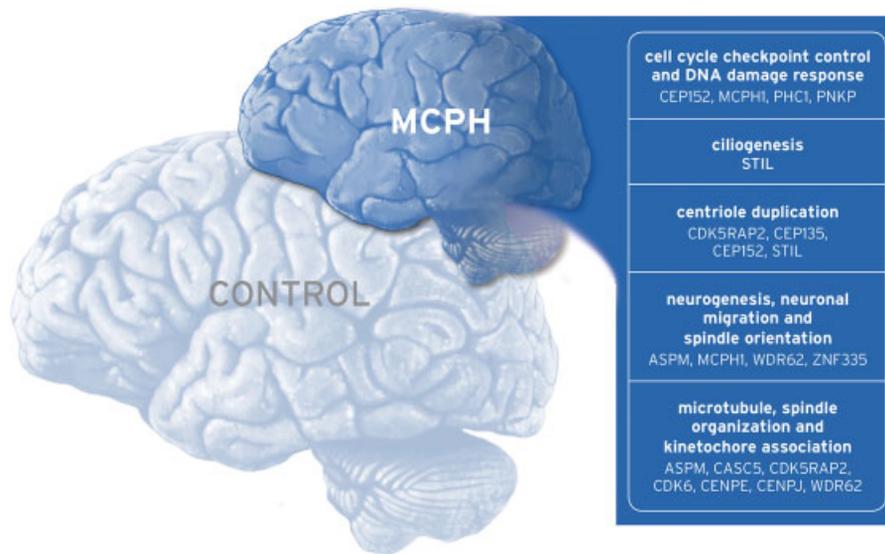


Fig. 3 Illustration of the brain phenotype in MCPH patients and the main roles of MCPH proteins. Note the typical reduction in the brain volume and the simplification in cortical gyration of an otherwise architecturally normal brain. MCPH proteins are involved in cell cycle dynamics, ciliogenesis, the centrosome, neurogenesis, and neuronal migration. MCPH, microcephaly primary hereditary.

been highlighted in individual cases.^{9,16,20} A recent quantification study of cortical regions in MCPH5 patients showed a reduction of 50% or more in the volume and surface area of all cortical regions but not of the hippocampus.²¹

Genetic Causes and Findings

Seventeen MCPH loci have been identified in patients with MCPH worldwide (→Table 1). Biallelic mutations in *ASPM* are the most common cause of MCPH (68.6%), followed by those in the *WDR62* gene (14.1%) and *MCPH1* gene (8%). More genetic loci are still expected to exist given the lack of mutations in known loci in approximately 50 to 75% of western Europeans or North Americans with MCPH and approximately 20 to 30% of Indians or Pakistanis with MCPH.^{1,11,22} Most reported MCPH gene mutations produce truncated nonfunctional proteins.²³ A premature chromosome condensation and high frequency of prophase-like cells (detected through karyotyping) can be present in lymphocytes, fibroblasts, and lymphoblast cell lines of patients with *MCPH1*.^{12,24}

Pathomechanisms

MCPH genes are highly conserved among species and expected to play a role during brain evolution.^{3,25} The discovery of MCPH animal models opened the door for understanding the possible roles of MCPH proteins during brain development. MCPH proteins are ubiquitously expressed and many of them are associated with the centrosome or the mitotic spindles.^{23,26} The microcephaly phenotype has been linked to a periventricular neural stem cell defect in the area with a premature shift from symmetric, “self-renewing” to asymmetric progenitor cell divisions

leading to premature neurogenesis, a depletion of the progenitor pool, and thus a reduction of the final number of cells in the brain.^{1,27–29} This stem cell proliferation and differentiation defect have been associated with a shift of the cleavage plane in several MCPH models.^{27,30,31} However, the latter is not the only underlying mechanism since some MCPH mouse models—where the cleavage plane is unaffected—still display microcephaly.^{30,31} Additional studies in MCPH models have also identified defects in chromosome condensation, microtubule dynamics, cell cycle checkpoint control, and/or DNA damage-response signaling during embryonic neurogenesis^{32,33} (→Fig. 3). Recently, it has been shown that mitotic delay in the neuronal progeny that leads to increased apoptosis is the major cause of microcephaly phenotype in *Magoh*^{+/-} mutant mouse model.³⁴ This could also play a role in MCPH. Intriguingly, infection of human neural progenitor cells with Zika virus dysregulates cell cycle progression in these cells and increases apoptosis.³⁵

Diagnosis

Detailed clinical history should be obtained from the family about the pregnancy timeline and possible environmental causes of microcephaly such as infections or drug abuse during pregnancy. Family history about parental consanguinity and other affected siblings is also a key element for patients with putative MCPH. Except for prominent microcephaly, results of physical examination are usually normal in MCPH patients. Height, weight, and OFC have to be measured and plotted into developmental charts. Postnatally, TORCH [(T)oxoplasmosis, (O)ther Agents, (R)ubella, (C)ytomegalovirus, and (H)erpes Simple] (especially cytomegalovirus; CMV) and metabolic causes of primary

Table 1 List of MCPH genes

Locus	Protein	Gene	Location	OMIM	Putative clinical/neuroimaging features	Ref.
MCPH1	Microcephalin 1	<i>MCPH1</i>	8p23.1	607117	Short stature, premature chromosome condensation, increased frequency of prophase-like cells.	6,12,24,47
MCPH2	WD-repeat-containing protein 62	<i>WDR62</i>	19q13.12	613583	Low set and prominent ears, high-arched palate, unusual dermatoglyphic pattern, short stubby fingers, inverted nipples, seizures, impulsivity, severe tantrums, head banging, self-biting. Perisylvian polymicrogyria, focal micropolygyria, periventricular neuronal heterotopias, pachygyria with cortical thickening, lissencephaly, schizencephaly, cerebellar hypoplasia.	10,18,20,48,49
MCPH3	Cyclin-dependent kinase 5 regulatory subunit-associated protein 2	<i>CDK5RAP2</i>	9q33.2	608201	Sensorineural hearing loss Cerebellar hypoplasia.	16,17,27,50,51
MCPH4	Kinetochores scaffold 1	<i>KNL1</i>	15q15.1	609173	Enlarged ventricles.	52,53
MCPH5	Abnormal spindle-like, microcephaly-associated protein	<i>ASPM</i>	1q31.3	605481	Short stature, seizures, hyperactivity and attention deficit, speech delay Cerebellar hypoplasia, perisylvian polymicrogyria.	9,19,30,54–56
MCPH6	Centromeric protein J	<i>CENPJ</i>	13q12.2	609279	Short stature, joint stiffness, small ears, notched nasal tip, hypertelorism, strabismus, seizures.	50,57,58
MCPH7	SCL/TAL1-interrupting locus protein	<i>STIL</i>	1p33	181590	Short stature, strabismus, ataxia, seizures. Lobar holoprosencephaly.	59–61
MCPH8	Centrosomal protein 135 kD	<i>CEP135</i>	4q12	611423		62
MCPH9	Centrosomal protein 152 kD	<i>CEP152</i>	15q21.1	613529	Short stature, impulsivity, aggression, tantrums.	63
MCPH10	Zinc finger protein 335	<i>ZNF335</i>	20q13.12	610827	Cataracts, arthrogryposis, death in infancy.	64
MCPH11	Polyhomeotic-like 1 protein	<i>PHC1</i>	12p13.31	602978	Short stature.	65
MCPH12	Cyclin-dependent kinase 6	<i>CDK6</i>	7q21.2	603368		26
MCPH13	Centromeric protein E	<i>CENPE</i>	4q24	117143	Small hands and feet, mild spasticity, absent speech, poor gross, and fine motor skills. Cerebellar hypoplasia.	15
MCPH14	SAS-6 centriolar assembly protein	<i>SASS6</i>	1p21.2	609321	Behavioral, psychiatric manifestations. Cerebellar hypoplasia.	66
MCPH15	Major facilitator superfamily domain-containing protein 2A	<i>MFSD2A</i>	1p34.2	614397	Spastic gait, progressive disease course, increased plasma lysophosphatidylcholines containing mono- and polyunsaturated fatty acyl chains. Paucity of cerebral white matter volume, cerebellar hypoplasia, brain stem hypoplasia.	67,68

Table 1 (Continued)

Locus	Protein	Gene	Location	OMIM	Putative clinical/neuroimaging features	Ref.
MCPH16	Ankyrin repeat- and LEM domain-containing protein 2	<i>ANKLE2</i>	12q24.33	616062	Short stature, ptosis, glaucoma, knee contractures, adducted thumbs, abnormally pigmented macules, spastic quadriplegia. Enlarged posterior horns of the lateral ventricles.	69
MCPH17	Citron rho-interacting serine/threonine kinase	<i>CIT</i>	12q24.23	605629	Short stature, bulbous nose, renal aplasia, spasticity. Microlissencephaly, brain stem hypoplasia, cerebellar hypoplasia, abnormal lamination.	70–73

microcephaly should be ruled out. Metabolic disorders often cause secondary rather than primary microcephaly and are often associated with additional symptoms and clinical signs.³⁶ Metabolic screening investigations, if necessary, should mainly focus on maternal phenylketonuria, phosphoglycerate dehydrogenase deficiency, and Amish lethal microcephaly (2-ketoglutaric aciduria) as secondary causes of microcephaly.^{37,38} Rare metabolic causes of primary microcephaly include serine biosynthesis defects, sterol biosynthesis disorders, mitochondriopathies, and congenital disorders of glycosylation.³⁶

Neuroimaging of the brain with ultrasound and/or MRI are useful for the differential diagnosis in patients with primary microcephaly. Cognitive abilities can be later quantified using standard, often nonverbal cognitive tests. Cytogenetic analysis of peripheral blood is useful to detect an increased frequency of prophase-like cells characteristic for MCPH1. In patients with MCPH1, a premature chromosome condensation and high frequency of prophase-like cells in lymphocytes, fibroblasts, and lymphoblast cell lines can be diagnosed through karyotyping.^{12,24} The clinical diagnosis of MCPH can be confirmed through Sanger sequencing of the two most frequently affected genes *ASPM* and *WDR62* and/or through next-generation sequencing technologies including MCPH gene panel sequencing or whole exome sequencing. Molecular genetic tests for some MCPH genes are currently available for research basis only.

Therapy

Symptomatic treatment is available for MCPH patients. Hyperactivity can be treated with, for example, methylphenidate, and epilepsies are usually controlled with single antiepileptic drug regimens. Speech therapy, if appropriate with supporting sign language, and behavioral therapy are further therapeutic approaches that should be considered. Promotion and support of the patient and his family as well as (genetic) counseling of family members are highly important.

Differential Diagnosis

All diseases associated with primary (congenital) microcephaly without further extracranial malformations and without facial dysmorphism are included in the differential diagnosis of MCPH. Phenotyping and genotyping of patients with overlapping but seemingly distinct phenotypes has revealed a phenotype and genotype overlap with isolated agenesis of the corpus callosum (ACC),³⁹ Seckel's syndrome (microcephalic dwarfism type I),^{13,14,40} and microcephalic osteoplastic dwarfism type II (MOPDII)⁴¹ (→ Fig. 4). No specific causative gene has been linked to isolated ACC; however, it has been reported in individuals with heterozygous mutation in *MCPH3* gene (*CDK5RAP2*).³⁹ Seckel's syndrome can be caused by mutations in ataxia-telangiectasia and *RAD3*-related gene (*ATR*),⁴² retinoblastoma-binding protein-8 gene (*CtIP/RBBP8*),⁴³ as well as MCPH genes: *CENPJ*,¹³ *CDK5RAP2*,⁴⁰ and *CEP152*.¹⁴ Characteristic findings in Seckel's syndrome include microcephaly, mental retardation, severe short stature, facial dysmorphism, and bone and teeth abnormalities.^{11,44} MOPDII can be caused by mutations in the pericentrin gene (*PCNT*)⁴¹ which encodes a protein interacting with MCPH proteins: *MCPH1*⁴⁵ and *CDK5RAP2*.²⁸ MOPDII patients have been reported to have microcephaly, mental and motor retardation, short stature with disproportionately short limbs, clinodactyly and/or brachydactyly, epiphyseolysis, dental anomalies, and insulin resistance.^{41,46}

Conclusion

The ongoing discovery and research on MCPH genes and their animal models will increase our knowledge in this rare nonprogressive neuropediatric disorder. Moreover, MCPH genes might play a role during evolution, and therefore, they are suitable candidates for studying normal brain development.

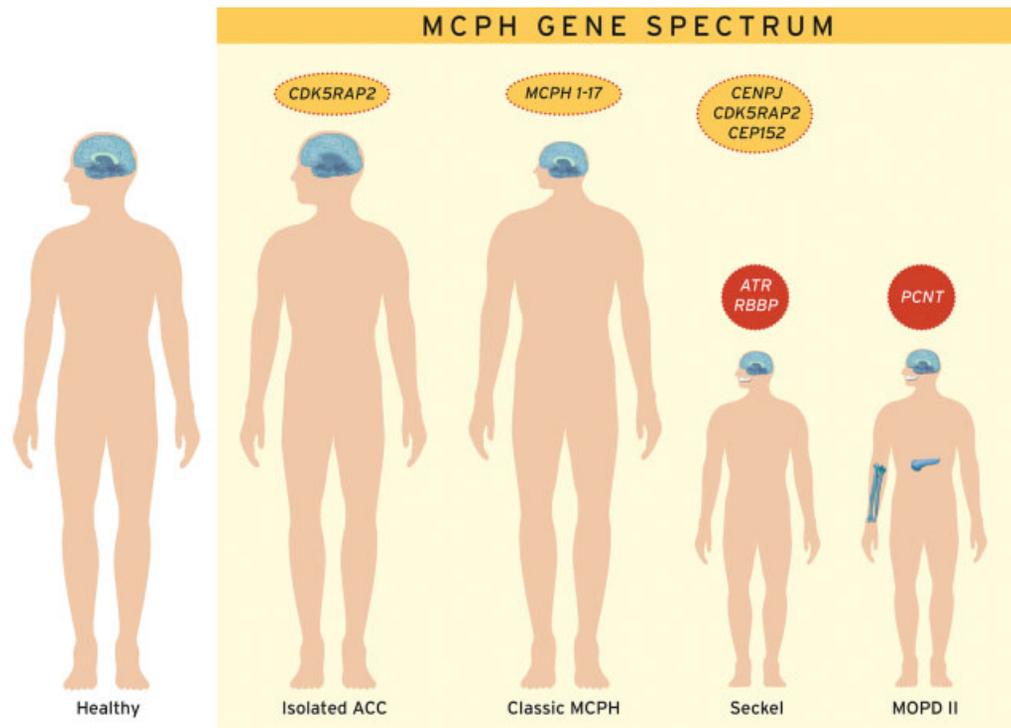


Fig. 4 MCPH gene spectrum. MCPH gene mutations can cause overlapping phenotypes ranging in severity from almost asymptomatic isolated ACC to very severe form of MOPDII. ACC, agenesis of the corpus callosum; MCPH, microcephaly primary hereditary; MOPDII, microcephalic osteoplastic dwarfism type II.

Competing Interest

The authors declare that they have no competing interest.

Authors' Contributions

All authors wrote and approved the final article.

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