

# Autosomal Recessive Primary Microcephaly (MCPH): An Update

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## Abstract

### Keywords

- MCPH
- microcephaly
- intellectual disability

Autosomal recessive primary microcephaly (MCPH; MicroCephal 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.<sup>1–3</sup> 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.<sup>4</sup> Autosomal recessive primary microcephaly (MCPH; MicroCephal Primarily 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.<sup>5</sup> Following the discovery of the first gene linked to MCPH in 1998,<sup>6</sup> 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).<sup>7</sup> 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**).<sup>1,8–10</sup> 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.<sup>9</sup> 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.<sup>9,11–15</sup> Low set and prominent ears, high-arched palate,

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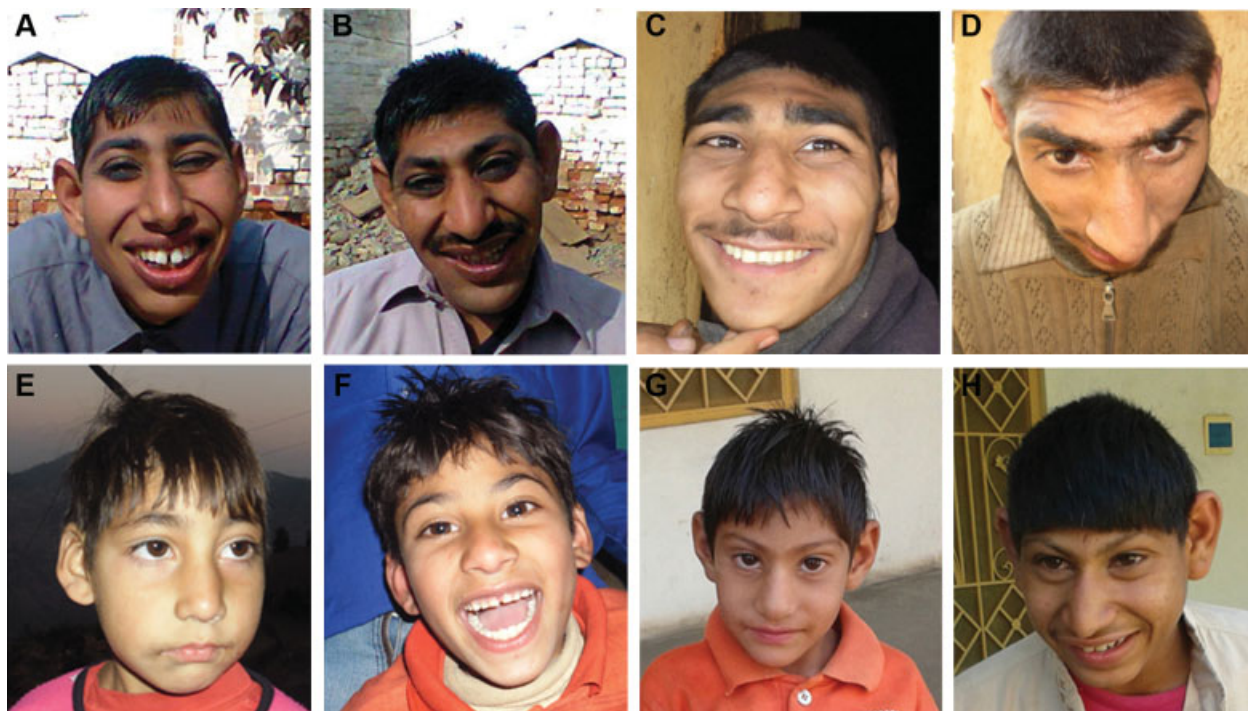
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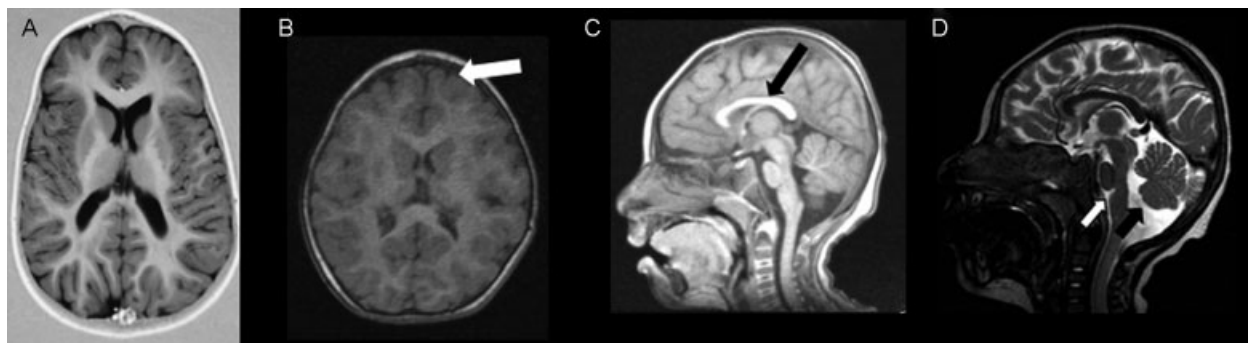
**Fig. 1** Phenotype features of patients with MCPH. Sample pictures of four affected consanguineous Pakistani family members. (A) Individual 1 at the age of 21 years and (B) his brother at the age of 28 years. (C) Individual 2 at the age of 15 years and (D) his brother at the age of 20 years. (E) Individual 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.<sup>8</sup> MCPH, microcephaly primary hereditary.

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

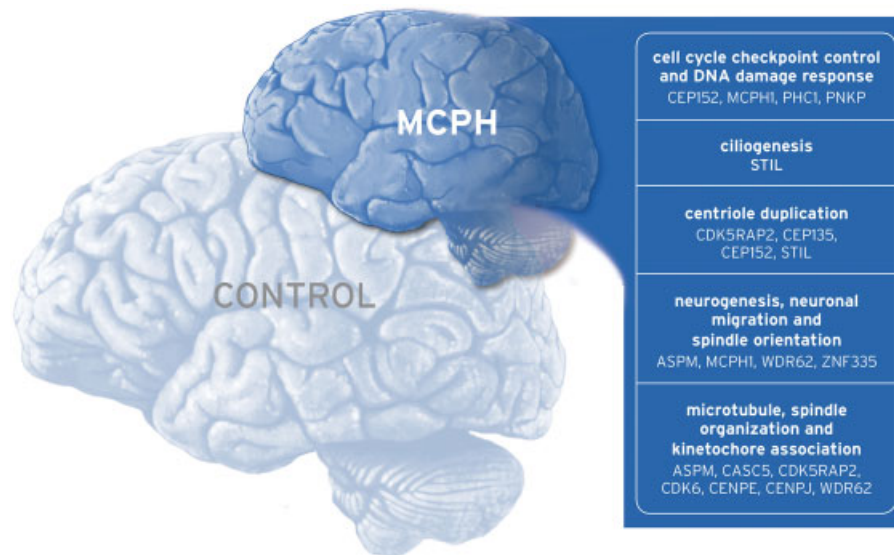
## Neuroimaging Findings

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**).<sup>3</sup> 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.<sup>9,12,16,18,19</sup> Additional abnormalities in MCPH2 include pachygyria with cortical thickening, lissencephaly, and schizencephaly.<sup>10,20</sup> 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.<sup>9,16,20</sup> 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.<sup>21</sup>

## 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.<sup>1,11,22</sup> Most reported MCPH gene mutations produce truncated nonfunctional proteins.<sup>23</sup> 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.<sup>12,24</sup>

## Pathomechanisms

MCPH genes are highly conserved among species and expected to play a role during brain evolution.<sup>3,25</sup> 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.<sup>23,26</sup> 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.<sup>1,27–29</sup> This stem cell proliferation and differentiation defect have been associated with a shift of the cleavage plane in several MCPH models.<sup>27,30,31</sup> However, the latter is not the only underlying mechanism since some MCPH mouse models—where the cleavage plane is unaffected—still display microcephaly.<sup>30,31</sup> 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<sup>32,33</sup> (►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 *Mago*<sup>+/–</sup> mutant mouse model.<sup>34</sup> 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.<sup>35</sup>

## 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.<sup>36</sup> 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.<sup>37,38</sup> Rare metabolic causes of primary microcephaly include serine biosynthesis defects, sterol biosynthesis disorders, mitochondriopathies, and congenital disorders of glycosylation.<sup>36</sup>

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.<sup>12,24</sup> 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

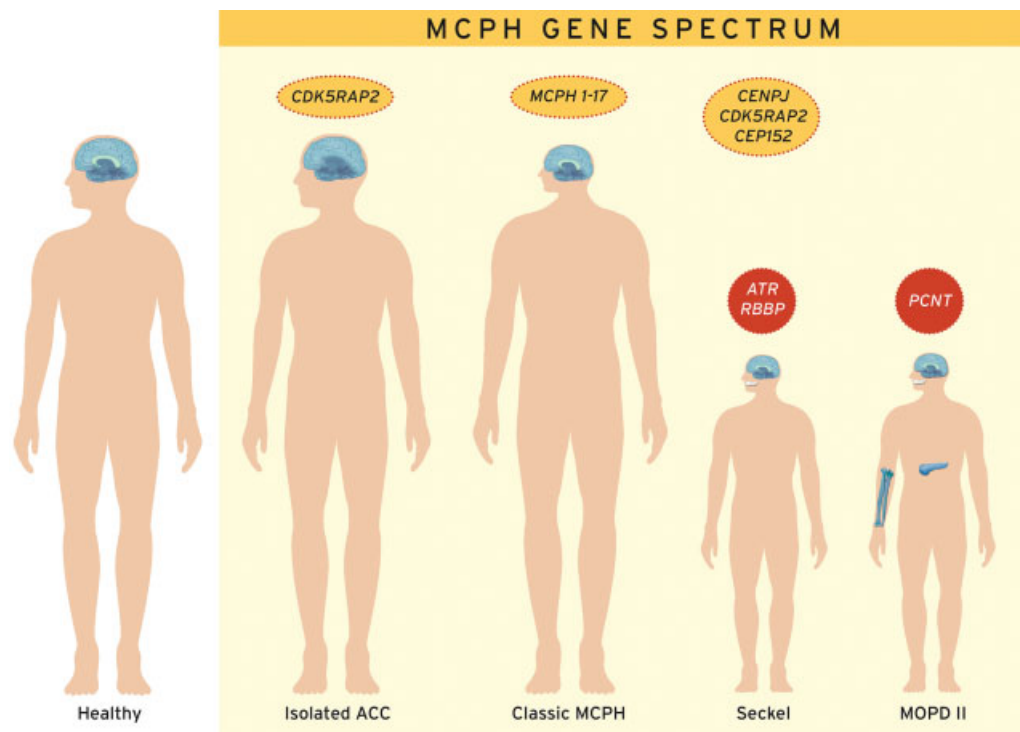
Symptomatic treatment is available for MCPH patients. Hyperactivity can be treated with, for example, methylphenidate, and epilepsies are usually controlled with single antiepileptic drug regimens. Speech therapy, if appropriate with supporting sign language, and behavioral therapy are further therapeutic 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),<sup>39</sup> Seckel's syndrome (microcephalic dwarfism type I),<sup>13,14,40</sup> and microcephalic osteoplastic dwarfism type II (MOPDII)<sup>41</sup> (►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*).<sup>39</sup> Seckel's syndrome can be caused by mutations in ataxia-telangiectasia and RAD3-related gene (*ATR*),<sup>42</sup> retinoblastoma-binding protein-8 gene (*CtIP/RBBP8*),<sup>43</sup> as well as MCPH genes: *CENPJ*,<sup>13</sup> *CDK5RAP2*,<sup>40</sup> and *CEP152*.<sup>14</sup> Characteristic findings in Seckel's syndrome include microcephaly, mental retardation, severe short stature, facial dysmorphism, and bone and teeth abnormalities.<sup>11,44</sup> MOPDII can be caused by mutations in the pericentrin gene (*PCNT*)<sup>41</sup> which encodes a protein interacting with MCPH proteins: MCPH1<sup>45</sup> and *CDK5RAP2*.<sup>28</sup> 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.<sup>41,46</sup>

## 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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#### References

- Kaindl AM, Passemard S, Kumar P, et al. Many roads lead to primary autosomal recessive microcephaly. *Prog Neurobiol* 2010; 90(3):363–383
- Opitz JM, Holt MC. Microcephaly: general considerations and aids to nosology. *J Craniofac Genet Dev Biol* 1990;10(2):175–204
- Woods CG, Bond J, Enard W. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings. *Am J Hum Genet* 2005;76(5):717–728
- Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WT, et al. Increase in reported prevalence of microcephaly in infants born to women living in areas with confirmed Zika virus transmission during the first trimester of pregnancy - Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65(9):242–247
- Van Den Bosch J. Microcephaly in the Netherlands: a clinical and genetical study. *Ann Hum Genet* 1959;23(2):91–116
- Jackson AP, McHale DP, Campbell DA, et al. Primary autosomal recessive microcephaly (MCPH1) maps to chromosome 8p22-pter. *Am J Hum Genet* 1998;63(2):541–546
- Tunca Y, Vurucu S, Parma J, et al. Prenatal diagnosis of primary microcephaly in two consanguineous families by confrontation of morphometry with DNA data. *Prenat Diagn* 2006;26(5):449–453
- Kraemer N, Picker-Minh S, Abbasi AA, et al. Genetic causes of MCPH in consanguineous Pakistani families. *Clin Genet* 2016; 89(6):744–745
- Passemard S, Titomanlio L, Elmaleh M, et al. Expanding the clinical and neuroradiologic phenotype of primary microcephaly due to ASPM mutations. *Neurology* 2009;73(12):962–969
- Bhat V, Girimaji SC, Mohan G, et al. Mutations in WDR62, encoding a centrosomal and nuclear protein, in Indian primary microcephaly families with cortical malformations. *Clin Genet* 2011;80(6):532–540
- Verloes A, Drunat S, Gressens P, Passemard S. Primary Autosomal Recessive Microcephalies and Seckel Syndrome Spectrum Disorders. Pagon RA, Adam MP, Ardinger HH, et al. Seattle, WA: GeneReviews(R); 1993
- Trimborn M, Bell SM, Felix C, et al. Mutations in microcephalin cause aberrant regulation of chromosome condensation. *Am J Hum Genet* 2004;75(2):261–266
- Al-Dosari MS, Shaheen R, Colak D, Alkuraya FS. Novel CENPJ mutation causes Seckel syndrome. *J Med Genet* 2010;47(6): 411–414
- Kalay E, Yigit G, Aslan Y, et al. CEP152 is a genome maintenance protein disrupted in Seckel syndrome. *Nat Genet* 2011;43(1): 23–26
- Mirzaa GM, Vitre B, Carpenter G, et al. Mutations in CENPE define a novel kinetochore-centromeric mechanism for microcephalic primordial dwarfism. *Hum Genet* 2014;133(8):1023–1039
- Issa L, Mueller K, Seufert K, et al. Clinical and cellular features in patients with primary autosomal recessive microcephaly and a novel CDK5RAP2 mutation. *Orphanet J Rare Dis* 2013;8:59–73
- Pagnamenta AT, Murray JE, Yoon G, et al. A novel nonsense CDK5RAP2 mutation in a Somali child with primary

- microcephaly and sensorineural hearing loss. *Am J Med Genet A* 2012;158A(10):2577–2582
- 18 Yu TW, Mochida GH, Tischfield DJ, et al. Mutations in WDR62, encoding a centrosome-associated protein, cause microcephaly with simplified gyri and abnormal cortical architecture. *Nat Genet* 2010;42(11):1015–1020
  - 19 Desir J, Cassart M, David P, Van Bogaert P, Abramowicz M. Primary microcephaly with ASPM mutation shows simplified cortical gyration with antero-posterior gradient pre- and post-natally. *Am J Med Genet A* 2008;146A(11):1439–1443
  - 20 Bilgüvar K, Öztürk AK, Louvi A, et al. Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations. *Nature* 2010;467(7312):207–210
  - 21 Passemard S, Verloes A, Billette de Villemeur T, et al. Abnormal spindle-like microcephaly-associated (ASPM) mutations strongly disrupt neocortical structure but spare the hippocampus and long-term memory. *Cortex* 2016;74:158–176
  - 22 Sajid Hussain M, Marriam Bakhtiar S, Farooq M, et al. Genetic heterogeneity in Pakistani microcephaly families. *Clin Genet* 2013;83(5):446–451
  - 23 Barbelanne M, Tsang WY. Molecular and cellular basis of autosomal recessive primary microcephaly. *BioMed Res Int* 2014;2014:547986
  - 24 Neitzel H, Neumann LM, Schindler D, et al. Premature chromosome condensation in humans associated with microcephaly and mental retardation: a novel autosomal recessive condition. *Am J Hum Genet* 2002;70(4):1015–1022
  - 25 Gilbert SL, Dobyns WB, Lahn BT. Genetic links between brain development and brain evolution. *Nat Rev Genet* 2005;6(7):581–590
  - 26 Hussain MS, Baig SM, Neumann S, et al. CDK6 associates with the centrosome during mitosis and is mutated in a large Pakistani family with primary microcephaly. *Hum Mol Genet* 2013;22(25):5199–5214
  - 27 Lizarraga SB, Margossian SP, Harris MH, et al. Cdk5rap2 regulates centrosome function and chromosome segregation in neuronal progenitors. *Development* 2010;137(11):1907–1917
  - 28 Buchman JJ, Tseng HC, Zhou Y, Frank CL, Xie Z, Tsai LH. Cdk5rap2 interacts with pericentrin to maintain the neural progenitor pool in the developing neocortex. *Neuron* 2010;66(3):386–402
  - 29 Fish JL, Kosodo Y, Enard W, Pääbo S, Huttner WB. Aspm specifically maintains symmetric proliferative divisions of neuroepithelial cells. *Proc Natl Acad Sci U S A* 2006;103(27):10438–10443
  - 30 Pulvers JN, Bryk J, Fish JL, et al. Mutations in mouse Aspm (abnormal spindle-like microcephaly associated) cause not only microcephaly but also major defects in the germline. *Proc Natl Acad Sci U S A* 2010;107(38):16595–16600
  - 31 Fietz SA, Huttner WB. Cortical progenitor expansion, self-renewal and neurogenesis—a polarized perspective. *Curr Opin Neurobiol* 2011;21(1):23–35
  - 32 Kraemer N, Ravindran E, Zaqout S, et al. Loss of CDK5RAP2 affects neural but not non-neural mESC differentiation into cardiomyocytes. *Cell Cycle* 2015;14(13):2044–2057
  - 33 Mahmood S, Ahmad W, Hassan MJ. Autosomal recessive primary microcephaly (MCPH): clinical manifestations, genetic heterogeneity and mutation continuum. *Orphanet J Rare Dis* 2011;6:39–54
  - 34 Pilaz LJ, McMahon JJ, Miller EE, et al. Prolonged mitosis of neural progenitors alters cell fate in the developing brain. *Neuron* 2016;89(1):83–99
  - 35 Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. *Cell Stem Cell* 2016;18(5):587–590
  - 36 von der Hagen M, Pivarsci M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. *Dev Med Child Neurol* 2014;56(8):732–741
  - 37 Kelley RI, Robinson D, Puffenberger EG, Strauss KA, Morton DH. Amish lethal microcephaly: a new metabolic disorder with severe congenital microcephaly and 2-ketoglutaric aciduria. *Am J Med Genet* 2002;112(4):318–326
  - 38 Ashwal S, Michelson D, Plawner L, Dobyns WB; Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2009;73(11):887–897
  - 39 Jouan L, Ouled Amar Bencheikh B, Daoud H, et al. Exome sequencing identifies recessive CDK5RAP2 variants in patients with isolated agenesis of corpus callosum. *Eur J Hum Genet* 2016;24(4):607–610
  - 40 Yigit G, Brown KE, Kayserili H, et al. Mutations in CDK5RAP2 cause Seckel syndrome. *Mol Genet Genomic Med* 2015;3(5):467–480
  - 41 Rauch A, Thiel CT, Schindler D, et al. Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. *Science* 2008;319(5864):816–819
  - 42 O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat Genet* 2003;33(4):497–501
  - 43 Qvist P, Huertas P, Jimeno S, et al. CtIP mutations cause Seckel and Jawad Syndromes. *PLoS Genet* 2011;7(10):e1002310
  - 44 Faivre L, Le Merrer M, Lyonnet S, et al. Clinical and genetic heterogeneity of Seckel syndrome. *Am J Med Genet* 2002;112(4):379–383
  - 45 Tibelius A, Marhold J, Zentgraf H, et al. Microcephalin and pericentrin regulate mitotic entry via centrosome-associated Chk1. *J Cell Biol* 2009;185(7):1149–1157
  - 46 Majewski F, Goecke TO. Microcephalic osteodysplastic primordial dwarfism type II: report of three cases and review. *Am J Med Genet* 1998;80(1):25–31
  - 47 Jackson AP, Eastwood H, Bell SM, et al. Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am J Hum Genet* 2002;71(1):136–142
  - 48 Roberts E, Jackson AP, Carradice AC, et al. The second locus for autosomal recessive primary microcephaly (MCPH2) maps to chromosome 19q13.1–13.2. *Eur J Hum Genet* 1999;7(7):815–820
  - 49 Nicholas AK, Khurshid M, Désir J, et al. WDR62 is associated with the spindle pole and is mutated in human microcephaly. *Nat Genet* 2010;42(11):1010–1014
  - 50 Bond J, Roberts E, Springell K, et al. A centrosomal mechanism involving CDK5RAP2 and CENPJ controls brain size. *Nat Genet* 2005;37(4):353–355
  - 51 Moynihan L, Jackson AP, Roberts E, et al. A third novel locus for primary autosomal recessive microcephaly maps to chromosome 9q34. *Am J Hum Genet* 2000;66(2):724–727
  - 52 Genin A, Desir J, Lambert N, et al. Kinetochore KMN network gene CASC5 mutated in primary microcephaly. *Hum Mol Genet* 2012;21(24):5306–5317
  - 53 Jamieson CR, Govaerts C, Abramowicz MJ. Primary autosomal recessive microcephaly: homozygosity mapping of MCPH4 to chromosome 15. *Am J Hum Genet* 1999;65(5):1465–1469
  - 54 Bond J, Roberts E, Mochida GH, et al. ASPM is a major determinant of cerebral cortical size. *Nat Genet* 2002;32(2):316–320
  - 55 Pattison L, Crow YJ, Deeble VJ, et al. A fifth locus for primary autosomal recessive microcephaly maps to chromosome 1q31. *Am J Hum Genet* 2000;67(6):1578–1580
  - 56 Jamieson CR, Fryns JP, Jacobs J, Matthijs G, Abramowicz MJ. Primary autosomal recessive microcephaly: MCPH5 maps to 1q25–q32. *Am J Hum Genet* 2000;67(6):1575–1577
  - 57 Gul A, Hassan MJ, Hussain S, Raza SI, Chishti MS, Ahmad W. A novel deletion mutation in CENPJ gene in a Pakistani family with autosomal recessive primary microcephaly. *J Hum Genet* 2006;51(9):760–764

- 58 Leal GF, Roberts E, Silva EO, Costa SM, Hampshire DJ, Woods CG. A novel locus for autosomal recessive primary microcephaly (MCPH6) maps to 13q12.2. *J Med Genet* 2003;40(7):540–542
- 59 Kakar N, Ahmad J, Morris-Rosendahl DJ, et al. STIL mutation causes autosomal recessive microcephalic lobar holoprosencephaly. *Hum Genet* 2015;134(1):45–51
- 60 Kumar A, Girimaji SC, Duvvari MR, Blanton SH. Mutations in STIL, encoding a pericentriolar and centrosomal protein, cause primary microcephaly. *Am J Hum Genet* 2009;84(2):286–290
- 61 Darvish H, Esmaeeli-Nieh S, Monajemi GB, et al. A clinical and molecular genetic study of 112 Iranian families with primary microcephaly. *J Med Genet* 2010;47(12):823–828
- 62 Hussain MS, Baig SM, Neumann S, et al. A truncating mutation of CEP135 causes primary microcephaly and disturbed centrosomal function. *Am J Hum Genet* 2012;90(5):871–878
- 63 Guernsey DL, Jiang H, Hussin J, et al. Mutations in centrosomal protein CEP152 in primary microcephaly families linked to MCPH4. *Am J Hum Genet* 2010;87(1):40–51
- 64 Yang YJ, Baltus AE, Mathew RS, et al. Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation. *Cell* 2012;151(5):1097–1112
- 65 Awad S, Al-Dosari MS, Al-Yacoub N, et al. Mutation in PHC1 implicates chromatin remodeling in primary microcephaly pathogenesis. *Hum Mol Genet* 2013;22(11):2200–2213
- 66 Khan MA, Rupp VM, Orpinell M, et al. A missense mutation in the PISA domain of HsSAS-6 causes autosomal recessive primary microcephaly in a large consanguineous Pakistani family. *Hum Mol Genet* 2014;23(22):5940–5949
- 67 Alakbarzade V, Hameed A, Quek DQ, et al. A partially inactivating mutation in the sodium-dependent lysophosphatidylcholine transporter MFSD2A causes a non-lethal microcephaly syndrome. *Nat Genet* 2015;47(7):814–817
- 68 Guemez-Gamboa A, Nguyen LN, Yang H, et al. Inactivating mutations in MFSD2A, required for omega-3 fatty acid transport in brain, cause a lethal microcephaly syndrome. *Nat Genet* 2015;47(7):809–813
- 69 Yamamoto S, Jaiswal M, Charng WL, et al. A drosophila genetic resource of mutants to study mechanisms underlying human genetic diseases. *Cell* 2014;159(1):200–214
- 70 Harding BN, Moccia A, Drunat S, et al. Mutations in citron kinase cause recessive microlissencephaly with multinucleated neurons. *Am J Hum Genet* 2016;99(2):511–520
- 71 Basit S, Al-Harbi KM, Alhijji SA, et al. CIT, a gene involved in neurogenic cytokinesis, is mutated in human primary microcephaly. *Hum Genet* 2016;135(10):1199–1207
- 72 Li H, Bielas SL, Zaki MS, et al. Biallelic mutations in citron kinase link mitotic cytokinesis to human primary microcephaly. *Am J Hum Genet* 2016;99(2):501–510
- 73 Shaheen R, Hashem A, Abdel-Salam GM, Al-Fadhli F, Ewida N, Alkuraya FS. Mutations in CIT, encoding citron rho-interacting serine/threonine kinase, cause severe primary microcephaly in humans. *Hum Genet* 2016;135(10):1191–1197