

PRIMARY MICROCEPHALY

Authored by
mohammad looti

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1. Core Definition

Primary Microcephaly (MCPH), often referred to as congenital microcephaly, constitutes a severe neurological birth disorder characterized by a significantly reduced head circumference present at the time of birth. This reduction in cranial size results directly from an underlying failure of the brain, specifically the cerebral cortex, to develop adequate volume during gestation. By clinical definition, microcephaly is diagnosed when the occipitofrontal circumference (OFC) measures three or more standard deviations below the mean for age, sex, and ethnicity. This classification distinguishes MCPH as a primary disorder of neurogenesis, meaning the reduction in brain size is not typically caused by destructive processes, but rather by impaired proliferative capacity of neural stem cells early in development.

The resulting condition is not merely cosmetic; the small cranial cavity accommodates a structurally reduced brain, which fundamentally limits cognitive and motor function. Unlike other forms of microcephaly, such as those acquired later in gestation due to infection or ischemic events (secondary microcephaly), MCPH arises from intrinsic genetic defects that specifically target the mechanisms governing the rapid production of neurons. This intrinsic developmental failure sets the stage for the characteristic features of the condition: a small skull housing a brain that, while often structurally organized correctly, possesses significantly fewer neurons than a neurotypical brain.

The clinical picture defined by the source content--a small cranial cavity with specific morphological markers (low, receding forehead and a flat back of the head)--is central to the diagnosis of MCPH. Crucially, the source notes that the facial structure remains relatively normal-sized, creating a stark visual disproportion between the face (viscerocranium) and the braincase (neurocranium). This disproportion is the direct consequence of the selective impact of MCPH on brain development, sparing the growth processes of the facial skeleton. The ultimate manifestation of this developmental deficit is profound neurological impairment, including **mental lagging** (now universally referred to as intellectual disability) and **limb spasticity**, which reflect the underlying damage or insufficient development of motor control centers in the cerebral cortex.

2. Etiology and Genetic Basis

The vast majority of non-syndromic MCPH cases are inherited in an autosomal recessive manner, highlighting the powerful role of genetics in determining cortical size. The genetic landscape of

primary microcephaly is highly heterogeneous, involving mutations across numerous loci, designated MCPH1 through MCPH25 and growing. These genes encode proteins that play critical roles in regulating the cell cycle, DNA damage response, and the organization of the mitotic spindle within **neural progenitor cells** (NPCs). The recognition of this vast heterogeneity underscores the complexity of human neurogenesis and suggests multiple points at which errors can lead to a uniform developmental catastrophe: premature cessation of progenitor cell proliferation.

Two of the most intensively studied genes associated with MCPH are *ASPM* (Abnormal Spindle Microtubule Assembly) and *WDR62* (WD Repeat Domain 62). Mutations in *ASPM*, located on chromosome 1q31, are responsible for a large proportion of MCPH cases globally and are thought to control the orientation and dynamics of the mitotic spindle in NPCs, ensuring symmetric proliferative divisions that expand the progenitor pool. When *ASPM* is non-functional, progenitor cells transition too quickly from expansive, proliferative divisions to differentiative divisions, severely limiting the total number of neurons generated. This premature differentiation is the core cellular pathology driving the reduced brain size characteristic of MCPH.

Furthermore, the investigation into MCPH genes has offered significant insights into human brain evolution. Genes like *ASPM* and *Microcephalin* (MCPH1) exhibit clear evidence of positive selection along the human lineage, suggesting that slight variations in these genes were crucial for the massive evolutionary expansion of the human cerebral cortex relative to other primates. Studying pathological mutations in these genes, which reverse the expansionary process, provides a unique biological window into the molecular constraints that govern maximum brain size. Understanding these genetic drivers is paramount, as a definitive diagnosis of MCPH often relies on identifying the specific causative mutation via next-generation sequencing.

3. Pathophysiology of Cortical Development

The pathomechanism of MCPH is rooted deeply in the embryonic process of corticogenesis, particularly during the first and second trimesters of gestation when the neural stem cells, known as **radial glia**, are rapidly dividing to build the vast neuronal population of the cortex. In neurotypical development, radial glia undergo a period of sustained symmetric proliferation, where each cell division yields two new radial glia, exponentially expanding the precursor pool. This expansive phase is crucial for achieving the large number of neurons required for the complex gyrified cortex of humans.

In MCPH, the defective gene products impair the ability of the radial glia to sustain this proliferative phase. For instance, mutations in genes such as *ASPM* or *WDR62* disrupt the integrity or orientation of the mitotic machinery. This perturbation causes the progenitor cells to prematurely

switch from symmetric, proliferative divisions to asymmetric, neurogenic divisions, where one daughter cell becomes a neuron and the other remains a progenitor, or even worse, to terminal differentiation. The consequence is a catastrophic reduction in the total number of progenitor cells, leading to a diminished production of neurons.

The reduction in overall brain volume in MCPH is typically localized, primarily affecting the size of the cerebral hemispheres while structures such as the cerebellum and brainstem are often less affected, though not entirely spared. The cortex itself is generally architecturally normal; the six distinct cortical layers are present and appropriately laminated, but the cortical mantle is thinner and significantly reduced in surface area. This distinction is vital: MCPH is characterized by a failure of quantity (neuronal numbers), rather than a failure of organization (e.g., lissencephaly or polymicrogyria, which involve abnormal migration or structural organization). The resulting microcephalic phenotype is thus a direct and proportional reflection of the curtailed proliferative stage of embryonic brain development.

4. Clinical Characteristics and Associated Neurological Deficits

The core clinical characteristic of Primary Microcephaly is the pronounced reduction in head circumference evident at birth. The disproportionate growth is often dramatic, with the head appearing notably small compared to the infant's body size, which is frequently also slightly reduced (short stature). The craniofacial features described in the source are classic: a sloping or **receding forehead** (due to reduced frontal lobe development) and a flattening of the occipital region. While the face size is normal, the lack of underlying cranial support gives the appearance of micrognathia (small jaw) or prominent facial features due to the minimized neurocranium.

Neurological symptoms are universally present, correlating directly with the severity of the underlying brain volume reduction. The "mental lagging" described in early definitions is modernly defined as intellectual disability, which can range from mild learning difficulties requiring special education to severe-to-profound impairment necessitating lifelong custodial care. The degree of intellectual deficit often correlates with the extent of microcephaly, although phenotypic variability means two individuals with similar head sizes may exhibit different cognitive outcomes, likely due to differences in the specific functional regions affected.

Furthermore, the presence of **limb spasticity** is a significant motor complication derived from compromised upper motor neuron pathways, indicative of developmental abnormality in the motor cortex or associated descending tracts. Spasticity is characterized by hypertonia and exaggerated deep tendon reflexes, leading to stiffness and difficulties with coordinated movement, placing MCPH patients at risk for motor delays, gait abnormalities, and potentially requiring physical therapy and orthotic devices. Other common associated neurological issues include feeding

difficulties in infancy, delayed motor milestones, poor coordination, and, in some cases, mild to moderate seizure disorders, although seizures are generally less common in isolated MCPH than in syndromic forms of microcephaly.

5. Differential Diagnosis and Classification

The accurate diagnosis of Primary Microcephaly requires a careful differential diagnosis to distinguish it from secondary forms, which are acquired later in gestation or postnatally. Secondary microcephaly can result from environmental insults such as maternal exposure to teratogens (e.g., alcohol, leading to Fetal Alcohol Syndrome), viral infections (e.g., Cytomegalovirus, Zika virus), or perinatal asphyxia. The distinction is crucial because the management and prognosis differ, and secondary causes may require immediate intervention (e.g., antiviral treatment for infectious causes). MCPH, being congenital and genetic, typically requires extensive genetic counselling for family planning.

Clinically, MCPH is classified into two main categories: non-syndromic and syndromic. Non-syndromic MCPH (the focus of this entry) is characterized by microcephaly and associated intellectual and motor impairments, but without major congenital malformations affecting other organ systems. The genetic mutations responsible for non-syndromic MCPH specifically impair neural progenitor proliferation without broad systemic effects. In contrast, syndromic microcephaly involves microcephaly alongside other significant developmental abnormalities, such as Seckel syndrome (dwarfism, skeletal abnormalities) or Nijmegen breakage syndrome (immunodeficiency, cancer predisposition).

Diagnostic confirmation relies heavily on advanced neuroimaging and genetic analysis. Magnetic Resonance Imaging (MRI) is used to confirm the small brain volume and rule out structural abnormalities like hydrocephalus, lissencephaly, or cortical migration disorders, which are inconsistent with isolated MCPH. Definitive confirmation of non-syndromic MCPH is achieved through genetic testing, typically involving sequencing panels focused on known MCPH genes (*ASPM*, *WDR62*, *CENPJ*, etc.) to identify the underlying recessive mutation, which aids in prognosis and genetic counselling.

6. Management and Prognosis

As Primary Microcephaly is a condition resulting from an irreversible structural deficit established during early prenatal development, there is currently no cure. Management is therefore entirely supportive, focusing on maximizing the functional capacity and quality of life for the affected individual. A multidisciplinary team approach is essential, involving pediatric neurologists,

geneticists, physical therapists, occupational therapists, speech therapists, and specialized educators.

Interventions target the specific deficits outlined in the clinical profile. Physical therapy is critical for managing **limb spasticity**, aiming to maintain range of motion, prevent contractures, and improve gross motor skills. Occupational therapy focuses on fine motor skills and daily living activities. For the accompanying intellectual disability, early intervention programs and specialized educational services are essential to fostering communication skills and adaptive behavior. Medication may be required to manage associated conditions, such as anti-epileptic drugs for seizures or muscle relaxants for severe spasticity.

The prognosis for isolated, non-syndromic MCPH is varied but generally guarded regarding cognitive function. While individuals with MCPH typically have a normal life expectancy, the degree of intellectual disability often dictates the need for lifelong assistance. Individuals with milder forms of MCPH may achieve semi-independent living and vocational roles, while those with severe impairment will require comprehensive, continuous care. Genetic counselling is a critical component of prognosis, informing families about recurrence risk and the potential severity associated with specific gene mutations identified.

7. Further Reading

[Microcephaly \(Wikipedia\)](#)

[Microcephaly, Primary Hereditary, Type 1 \(OMIM\)](#)

[Primary microcephaly: a clinical, neuropathological, and molecular review](#)

[ASPM gene \(Wikipedia\)](#)