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GENETIC LANDSCAPE OF MICROCEPHALY: A COMPREHENSIVE REVIEW

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ABSTRACT

Background

Microcephaly is a neurodevelopmental disorder characterized by a small brain size at birth, which can be caused by various genetic and environmental factors. The clinical presentation of microcephaly can vary widely depending on the underlying cause, severity, and associated comorbidities. In addition to a small head circumference, individuals with microcephaly may exhibit developmental delay, intellectual disability, seizures, motor impairments, and facial dimorphisms.

Genetic Basis of Microcephaly:

Advancements in genomic technologies, particularly next-generation sequencing, have revolutionized our understanding of the genetic landscape underlying microcephaly. Numerous genes implicated in microcephaly encode proteins involved in essential cellular processes, including centrosome function, spindle assembly, DNA replication and repair, and cell cycle regulation. Mutations in these genes disrupt neuroprogenitor cell division and differentiation, ultimately leading to reduced brain size.

Diagnostic Modalities:

Diagnosing microcephaly requires a thorough clinical assessment, including measurement of head circumference, neuroimaging studies, and genetic testing. While head circumference measurements serve as a screening tool, neuroimaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) provide valuable insights into brain morphology and structural abnormalities. Genetic testing, including chromosomal microarray analysis and targeted gene sequencing, can identify causative mutations in individuals with suspected genetic forms of microcephaly.

Conclusion

Microcephaly is a complex neurodevelopmental disorder with diverse etiologies and clinical manifestations. Advances in genetics and neuroimaging have enhanced our understanding of its underlying pathogenesis and facilitated early diagnosis and intervention.

INTRODUCTION

Microcephaly is a condition characterized by a smaller-than-average head size that can be present at birth or develop after birth. It can be caused by genetic abnormalities, syndromes, metabolic disorders, infections, teratogens, and prenatal, perinatal, and postnatal injuries (1). The prevalence of microcephaly ranges between 1.5 and 8.7 per 10,000 births in the United States (2). Microcephaly can be categorized as primary/congenital or secondary/postnatal based on when it first develops (3). Primary microcephaly is

present at birth, and it can be caused by environmental and/or genetic factors(4). Various environmental factors, such as infections, toxins, radiation, or alcohol, result in primary microcephaly(5). The recent identification of epidemic infections with the Zika virus as a cause of primary microcephaly has highlighted this rare condition as a key topic in neuroscience to understand normal brain development(6)(7).

This review's main objective is to outline the various facets of MCPH that affect our capacity to identify novel genes linked to the disease and, in turn, aid in patient diagnosis. To this end, we first briefly describe the biological function of microcephaly-associated proteins and show that MCPH results from disruptions in cell cycle control. Next, as additional factors to be considered when prioritizing variants in patients, we go into the evolution and biology of these genes. Throughout, we present instances that demonstrate how a deep comprehension of the genetics and etiology of disease enables the discovery of novel disease-causing candidates. Lastly, we will address significant research queries given our understanding of the genesis and genetics of MCPH.

MCPH Incidence:

MCPH is considered a rare genetic disorder, with approximately 300 or more cases reported worldwide (8). It is more prevalent in countries where consanguineous marriages are more common, such as Pakistan, India, and Saudi Arabia, which lead to congenital genetic disorders; its incidence is about 1:10,000 per live birth (9). In contrast to the European populations, where the incidence of primary microcephaly is low about 1 in 1,000,000 in the Yorkshire region of the United Kingdom (10) where consanguineous marriages are rare almost 1.3–150 per 100,000 individuals are reported to be affected by primary microcephaly worldwide. Its incidence varies from 1:30,000 to 1:250,000 in Europeans (11).

Genetic Heterogeneity of Primary Microcephaly

Primary microcephaly is a genetically heterogeneous disorder. Worldwide mutations in 30 genes have been reported in MCPH1-MCPH30 (12). Figure 1 present the genetic versatility of microcephaly and related disorders.

Microcephalin 1 (MCPH1)

Genomic characteristics The MCPH1/microcephalin gene (MIM 607117), located on chromosome 8p23, has 14 exons and 835 amino acids. Its genomic size is 241905 bp, and it has three known isoforms in addition to an 8032 bp open reading frame (13). This gene encodes a DNA damage response protein (14).

Role in DNA assembly

MCPH1 is highly pleiotropic. It has been identified as a proximal component in the hierarchy of DNA damage response pathways and is capable of nuclear localization. By maintaining the inhibitory phosphorylation of cyclin-dependent kinase 1, the encoded protein may contribute to G2/M checkpoint arrest. Primary autosomal recessive microcephaly and premature chromosome condensation syndrome have been linked to mutations in this gene (15, 16).

BRCT domains

The protein microcephalin, which includes three BRCT domains—evolutionarily conserved amino acid tandem repeat domains that interact with phosphopeptides and are important in cell cycle control—is encoded by the MCPH1 gene (17). BRCT domains are tandem repeat amino acid domains that bind phosphopeptide and are associated to cell cycle control. These domains have been conserved throughout evolution (18).

Role in fetal development

High levels of microcephalin expression are localised to the fetal brain's developing forebrain, specifically to the walls of the lateral ventricles, according to expression studies. Studies have shown that MCPH1 is essential for G2/M checkpoint arrest through the maintenance of inhibitory phosphorylation of the cyclin-dependent kinase CDK. When the cell cycle must be stopped until the damage is repaired, DNA damage response signaling pathways and cell cycle checkpoints, the regulatory mechanisms that control the sequence and timing of cell cycle transitions, are connected (15, 19).

Role in DNA repair

The finding that microcephalin localizes to DNA repair foci and that cells deprived of microcephalin by RNA interference fail at cell cycle checkpoints established microcephalin's involvement in the DNA

damage response (20). Later, people who had microcephaly disease, premature chromosome condensation syndrome (PCC) a disorder caused by an abnormal chromosomal condensation were found to have a mutation in the same gene. This discovery further highlighted the critical role that microcephalin plays in regulating DNA damage repair mechanisms and maintaining genome stability. Research states that MCPH1 primary microcephaly and PCC syndrome are allelic conditions. Both are caused by mutations in the *MCPH1* gene and have in common the cellular phenotype of aberrantly regulated chromosome condensation (8, 21).

Other specie models of MCPH1

To gain a deeper understanding of the function of MCPH1, research has employed model species such as mice, Drosophila melanogaster, and Caenorhabditis elegans. Research utilizing rodent models has demonstrated that aberrant mitotic chromosomal condensation and genomic instability can result from MCPH1 depletion(22). The function of MCPH1 in preserving genomic integrity, appropriate chromosomal alignment during mitosis, and growth during brain development has been clarified by these investigations (23). The mouse model showed decreased skull size and aberrant mitotic chromosomal condensation because of MCPH1 dysfunction(24).

MCPH2 (WDR62)

Genomic Characteristics

WDR62 gene located on MCPH2 loci on chromosome 19q13. It has been reported that this gene contributes to the formation of the cerebral cortex. Mutations in this gene have been associated with microcephaly, cortical malformations, and cognitive disability (25).

Genetic Studies

Genome-wide linkage analysis identified a 7.5 Mb locus on chromosome 19q13.12 containing 148 genes, with subsequent high-throughput sequencing revealing more than 4,000 DNA variants involving deleterious changes in a single gene, WDR62. Targeted high-throughput sequence analysis identified six mutations in the WDR62 gene in families affected by congenital microcephaly syndrome and diverse defects in cerebral cortical architecture (26).

As scaffold protein

MEKK3 controls the effect of WDR62 on neurogenesis in iFBW7 in function with FBW7, a protein comprising the F domains (27). WDR62 has been reported to be a scaffold protein for the c-Jun N-terminal kinase (JNK) signaling pathway by forming a complex with MAP kinase kinases (MKKs) 4 and 7, and JNKs. WDR62 is a 175-kDa heat-sensitive protein that is widely expressed and selectively binds with JNK but not with ERK or p38. WDR62 and JNKs associate in the absence of external stimuli and respond to either temporary or persistent ones. WDR62 increases the activity of JNK kinase, but by attracting JNK to a nonnuclear compartment, it suppresses AP-1 transcription. WDR62-transfected HEK-293T cells exhibit cytoplasmic granular localization. Stress granule (SG) resident protein overexpression attracts endogenous WDR62 and activated JNK to the SG. In addition, WDR62 is recruited to SG, and activated JNK is recruited to processing bodies (PB) when cells are treated with arsenite. Reduced SG and PB size, as well as quantity and size, are the outcomes of JNK inhibition. Together, findings suggest that JNK and WDR62 might control (5, 10, 27).

Role as a prognostic marker

According to research, WDR62 could potentially be used as a prognostic for several marker malignancies. WDR62 is noteworthy because it was found to be strongly correlated with different types of immune cell infiltration. Further, it has the potential to predict the outcome of immunotherapy, namely PD1/PD-L1 inhibitors(28).

MCPH3 (CDK5RAP2)

Genomic characteristics

MCPH3 is caused by allelic variants in the cyclin-dependent kinase 5 regulatory subunit-associated protein 2 gene CDK5RAP2. The third locus of MCPH is identified at chromosome 9q33.2 and spans about a 12cM region in a consanguineous family of northern Pakistan(29).

Role in development

CDK5RAP2 not only governs brain size but also plays a role in ocular and cochlear development and is necessary for hypothalamic nuclear separation at the midline(25, 30) . Research indicated that CDK5RAP2 should be considered as a potential gene associated with deafness and a form of holoprosencephaly. These

children should be given neurosensory follow-up to prevent additional comorbidities and allow them to reach their full educational potential (31).

Genetic Studies

There are 1,893 amino acids encoded by the 38 exons that make up this protein (69). Three mutations in CDK5RAP2 (two in families from Pakistan; one in three nonsense mutations) one in exon 4 (246T>A), one in exon 26 (4005-15A>G), which results in a new splice acceptor site, frame shift, and premature stop codon, and one in exon 8 (700G>T) have been reported about Somalian patients. Each of these mutations produces a shortened protein that lacks CDK5RAP2's functionality (32, 33).

Expression in Neural Progenitors

CDK5RAP2 is chiefly present in neural progenitors of the ventricular and sub-ventricular zones in an immature brain. It is also observed in glial cells and early born neurons but is progressively down regulated as the brain matures(34) .

Regulation of the Spindle Checkpoint

CDK5RAP2 is essential for regulating the spindle checkpoint. Loss of CDK5RAP2 can lead to chromosomal missegregation and decreased expression of spindle checkpoint proteins by binding to their promoters and regulating transcription (34, 35).

Microcephaly Phenotype

Mutations in *CDK5RAP2* can cause a premature transition from symmetric to asymmetric neuronal progenitor cell division, resulting in a reduction of the progenitor pool, decreased neurons, and reduced cell survival (36).

Centrosome Dysfunction

Dysfunction of *CDK5RAP2* can lead to centrosome dysfunction, known as centrosome 'rocketing'. This dysfunction was observed due to connection loss between centrosomes and the pericentriolar matrix in human *CDK5RAP2* ortholog 'centrosome'-deficient Drosophila embryos centrosome-deficient While subtle asymmetric division defects were observed in these embryos, brain sizes remained normal(37).

CASC5 (MCPH4)

Genetic Characteristics

A mutation of CASC5 in MCPH patients were initially reported the MCPH4 locus located at 15q15.1 with 27 exons(38). The mutation in CASC5 leads to skipping of exon 18, resulting in a truncated protein and impaired microtubule attachment to the chromosome centromere during mitosis. CASC5 is part of the KMN network of the kinetochore and interacts with other proteins involved in spindle assembly checkpoint activation (39).

Causative agent of microcephaly with pontine and cerebellar hypoplasia (MICPCH)

In 90.2% of the cases, causal or candidate genomic aberrations were identified, with CASK mutations being the most frequent. The study examined the genetic etiology of intellectual impairment and microcephaly with pontine and cerebellar hypoplasia (MICPCH) in 41 children(40).

Association with XLMR phenotype

The CASK gene was found to be a relatively common cause of XLMR in both males and females, according to this study, which also found multiple missense mutations in the gene in families with XLMR. Some of these individuals also showed congenital nystagmus (41).

Role in Spindle Assembly

CASC5 is part of the KMN network of the kinetochore and is required for proper microtubule attachment to the chromosome centromere and for spindle-assembly checkpoint (SAC) activation during mitosis (42). CASC5 interacts ZWINT-1, BUB1, and BUBR1. Interestingly, it also binds to MIS12 via a protein domain that is shortened due to the mutation. CASC5 localized at the equatorial plate like ZWINT-1 and BUBR1(43).

ASPM (MCPH5)

Genetic Characteristic

Abnormal spindle-like primary microcephaly (*ASPM*) is a gene crucial for the normal functioning of the mitotic spindle in embryonic neuroblasts (85). It consists of 62,567 bp with a 10,906 bp ORF, 28 exons, and 3,477 amino acids(44, 45).

Structure of *ASPM*

The ASPM protein is a 3,477 amino acid-long protein crucial for normal mitotic spindle function. The structure of the human ASPM protein includes various domains that contribute to its function in spindle organisation and cell division(45, 46). The protein contains a microtubule-binding domain at the N-terminus, a calponin homology domain, and 81 isoleucine glutamine motifs acting as a calmodulin-binding domain. The C-terminus of ASPM does not have identified domains. The major ASPM transcript consists of 81 IQ domains, most of which are organized into a higher order repeat (HOR) structure(45, 47-49) .

Role in Neurogenesis

Studies indicate that the ASPM protein helps maintain the orderly division of neural progenitor cells, which give rise to mature nerve cells (neurons). By promoting the division of these early brain cells, ASPM influences the total number of neurons and the overall size of the brain (45, 49, 50). This condition is characterized by an abnormally small head and brain, intellectual disability, and delayed development(50).

Effect of mutations in the microtubule-binding domain of the ASPM protein on spindle function

Studies have shown that *ASPM* is a microtubule minus end-associated protein crucial for spindle organisation and orientation. Mutations affecting the microtubule-binding domain can disrupt the proper localization of ASPM at spindle poles, resulting in perturbations in spindle orientation and cytokinesis (51).

CENPJ (MCPH6)

Genetic Characteristics:

Mutations in the centromere-associated protein J (*CENPJ*) gene, located in the MCPH6 locus on human chromosome 13q12.2, have been linked to primary microcephaly. This gene consists of 40,672 bp with a 5,187 bp ORF and 17 exons encoding a protein of 1,338 amino acids. It contains coiled-coil domains, protein phosphorylation sites, nonamer G-box repeats, and a leucine zipper motif (9, 19, 30).

Genetic Studies:

Four mutations have been identified in the *CENPJ* gene: one in a Brazilian family, one in two Pakistani families, a deletion mutation in a Pakistani family causing a frameshift, and a splicing mutation in Seckel syndrome patients(52). Number of mutations of all MCPH genes and mode of inheritance are enlisted in Table 1.

Role of CENPJ in the centrosomal assembly of microtubules

CENPJ, also known as centrosomal P4.1-associated protein (CPAP), plays a crucial role in the assembly of microtubules at centrosomes. This protein is involved in regulating microtubule assembly and nucleation, impacting the organisation and orientation of the mitotic spindle in neural progenitors.CENPJ, also known as centrosomal P4.1-associated protein (CPAP), plays a crucial role in the assembly of microtubules at centrosomes. This protein is involved in regulating microtubule assembly and nucleation, impacting the organisation and orientation of the mitotic spindle in neural progenitors (53, 54).

STIL (MCPH7)

Genomic Characteristics

The STIL (MCPH7) gene, located on chromosomes 1p33–p32.3, plays a crucial role in various cellular processes. It encodes a cytosolic protein essential for mitotic entry, apoptosis regulation, and centrosome function(55).

Genetic Studies

Studies in zebra fish and mice have shown that mutations in STIL lead to severe developmental abnormalities and embryonic lethality(56). It is involved in neural development, cell mitosis, centriole replication, and the Sonic Hedgehog (Shh) pathway. STIL is expressed in all cell types and fluctuates throughout the cell cycle, making it challenging to detect in unsynchronized cells. In cancer, STIL overexpression is linked to an increased mitotic index and cancer development(57).

Function in DNA repair

Studies have shown that STIL is involved in DNA damage response and interacts with proteins like BRCA1, which are crucial for DNA repair pathways(58). Depletion of STIL has been associated with enhanced DNA double-strand breaks caused by DNA-damaging agents, ongoing genomic instability, and the increased formation of micronuclei (59).

CEP135(MCPH8)

Genomic Characteristics

The CEP135 gene encodes centrosomal protein (CEP135) and is composed of 26 exons and 1,140 amino acids. It is a conserved helical protein observed throughout the cell cycle at the centrosome. A truncated mutation in CEP135 was identified in a Pakistani family, causing microcephaly by changing glutamine to serine at position 324 and leading to the premature termination of a codon(9, 30, 60).

Genetic Studies

Studies have shown that CEP135 is associated with pericentriolar material and is essential for maintaining the organisation and structure of centrosomes and microtubules(61) . Mutations in CEP135 have been linked to autosomal-recessive primary microcephaly, affecting centriole biogenesis and microtubule organisation, ultimately impacting mitotic progression and neural progenitor cell development(15, 61) .

Function in the cell cycle:

CEP135 is crucial for anchoring molecules necessary for establishing the centrosome structure and organisation, potentially acting as a scaffolding protein important for centrosome function (62). Studies have shown that CEP135 is involved in regulating spindle orientation, cell proliferation, migration, and angiogenesis by mediating microtubule dynamics and stabilization(63).

CEP152(MCPH9)

Genomic Characteristics:

The CEP152 gene is located at the MCPH4 locus on chromosome 15q21.1 and has been associated with microcephaly, designated as MCPH9 . Mutations in the CEP152 gene can lead to microcephaly, affecting brain development(64).

Genetic Studies

Studies have shown that these mutations can impact cell division and lead to a reduction in head size. Functional assays have revealed that mutant CEP152 fails to localize with g-tubulin, confirming the pathogenicity of these mutations (5, 64).

Role in neurodevelopment:

CEP152 is considered a strong candidate for causing microcephaly, particularly MCPH4, and may play a crucial role in human brain size evolution(63). Studies have shown that CEP152 is expressed in the embryonic mouse brain and is involved in centrosome function, like other MCPH genes. Positive selection has influenced the evolution of the *CEP152* gene in humans, indicating its importance in brain development and size regulation (63, 65).

ZNF335(MCPH10)

Genomic Characteristics

MCPH10 is caused by a mutation in the ZNF335 gene on 20q13. Zinc finger protein 335 (ZNF335) is a crucial component involved in brain development and neurogenesis, particularly associated with primary microcephaly(66). Variants in the ZNF335 gene have been identified as risk factors for microcephaly in various populations worldwide. ZNF335 is part of a trithorax H3K4-methylation chromatin remodeling complex that regulates neuronal gene expression and cell fate (67).

Genetic Studies

A variation in the ZNF335 gene caused Arg1111 to be replaced with His (R1111H) in the 13th zinc finger domain in an Israeli family. This substitution resulted in the formation of larger transcripts and premature termination, leading to reduced levels of the ZNF335 protein. Studies have shown that ZNF335 binds with the chromatin remodeling complex and regulates gene expression levels critical for brain development Knockout studies in mouse models have demonstrated that the absence of ZNF335 results in a severe reduction in brain size, highlighting its essential role in brain growth and development(68, 69).

Role in neurogenesis:

The trithorax H3K4-methylation chromatin remodeling complex plays a crucial role in regulating neuronal gene expression and cell fate determination. This complex, which includes ZNF335 as a component, is involved in modulating the expression levels of genes critical for brain development and neurogenesis (70).

PHC1(MCPH11)

Genetic Characteristics

Polyhomeotic like 1 (PHC1), which codes for a polycomb group protein, has been discovered as a new

cause of MCPH. This gene, which is found on chromosome 12p13, is essential for controlling the cell cycle and remodeling chromatin (71).

Genetic Studies

Research has demonstrated that mutations in PHC1 cause abnormalities in chromatin control, cell cycle progression, and DNA repair pathways. In patient cells, overexpression of wild-type PHC1 can cure cellular deficiencies linked to DNA damage repair and aberrant cell cycle, highlighting the pivotal function of PHC1 in these processes(71, 72).

Expression of a gene

Significant changes in gene expression are caused by the mutation in the PHC1 gene, especially in global gene expression patterns. The PHC1 mutation affects the DNA repair response after DNA damage by impairing PHC1 recruitment to damaged DNA locations (73). This mutation causes histone H2A to be ubiquitinated, which essentially hinders DNA repair. It has been demonstrated that overexpressing wild-type PHC1 in patient cells may cure cellular deficiencies linked to DNA damage repair and aberrant cell cycle patterns, underscoring the vital role PHC1 plays in preserving appropriate gene expression and cellular activities(74).

CDK6(MCPH12)

Genetic Characteristics

The long arm of chromosome 7 contains the CDK6 gene, which is essential for controlling the cell cycle process and distinct cell type differentiation at the MCPH 12 locus. The CDK6 gene is responsible for cell cycle progression, and its mutation causes an imbalance between symmetrical and asymmetrical cell division, ultimately leading to primary microcephaly (10, 75).

Genetic studies

According to research, CDK6 mutations impact every phase of the cell cycle and cause abnormalities such as deformed nuclei, centrosomes, and impaired cell proliferation. These mutations are linked to primary microcephaly. Interestingly, deletion of Cdk6 does not result in microcephaly in mice, despite the fact that CDK6 mutations are linked to microcephaly in humans. This highlights the species-specific variations in the phenotypic impact of these mutations(3, 76).

Role in Apical Neuronal Precursor Cell Proliferation

Research has demonstrated that CDK6 is produced at the crucial embryonic phases E11.5 and E15.5 in the developing neuroepithelium of the cerebral cortex, which are essential for cortical establishment and neuronal production. It has been noted that CDK6 has a role in neocortical development and ORG (outer radial glia) enlargement. A kinase-independent role of CDK6 in regulating oRGs is shown by the disruption of ORG expansion, a process essential for neocortical folding, caused by CDK6 deletion. The mutation in CDK6 that causes primary microcephaly operates through an unknown mechanism, emphasizing the intricate role of CDK6 in regulating brain development and size(77, 78).

CENPE(MCPH13)

Genetic Characteristics

Microcephalic primordial dwarfism is largely caused by mutations in the Centromere Protein E (CENPE) gene, which have profound effects on development. Whole exome sequencing of a non-consanguineous European family revealed a heterozygous mutation in CENPE, underscoring the genetic origin of this disorder (79).

Mutations

Research has indicated that mutations in CENPE may result in oblique cell divisions and abnormal phosphorylation of the proteins that make up pericentriolar material (PCM). Although these mutations are found in the protein's coiled-coil domain, they do not affect CENPE expression. Crucially, CENPE-mutant patient-derived cells do not show signs of cell cycle exit, indicating that mutant CENPE proteins maintain the partial activity required for cell cycle advancement (60, 80) .

SASS6 (MCPH14)

Genetic Characteristics

The centriolar assembly protein, or SAS-6, is thought to be the cause of MCPH. A protein that interacts with the CEP152, CEP135, and CEP63 proteins is encoded by this gene(81). A missense mutation in SASS6 that interferes with cell division processes and contributes to the development of MCPH has been found by whole exome sequencing. The centriole is hampered by the discovered missense mutation in SASS6, which

results in improper cell division and impacts centriole formation(82).

Mutations

According to research, SAS-6 self-associates into assemblies that resemble cartwheel centres and is essential for the multiplication of centrosomes (83). Aberrant phosphorylation of pericentriolar material proteins and oblique cell divisions has been associated with mutations in SASS6. The identification of compound heterozygous mutations in SASS6 in a Chinese fetus with MCPH14 further emphasizes the genetic complexity underlying this condition. These mutations were classified as pathogenic and highlight the critical role of SASS6 in centrosome dynamics and spindle orientation during mitosis, shedding light on its involvement in MCPH14(84).

MFSD2A (MCPH15)

Genetic Characteristics

Belonging to the Major Facilitator Superfamily (MFS), MFSD2A functions as a trans membrane transporter that facilitates the absorption of certain important fatty acids via the blood-brain barrier, specifically docosahexaenoic acid (DHA). Human chromosome 1p33 has the MFSD2A gene, which codes for 530 amino acids. Positions 217 and 227 of the gene include two N-conjugated glycosylation sites. Twelve α-helix fragments make up the protein, and mice and humans have a very similar sequence (85, 86).

Mutations

Microcephaly can result from mutations in MFSD2A, which dysregulate the transporter's activity in brain endothelial cell. Because this gene causes changes in how neurons function, it has been demonstrated that knocking it out is fatal in models of both zebra fish and mice(87).These mutations affect the protein's transport function, which results in a fatal microcephaly condition linked to insufficient absorption of LPC lipids(88).

ANKLE2 (MCPH16)

Genetic Characteristics

The ANKLE2 (Ankyrin Repeat and LEM Domain Containing 2) gene is located at the 12q24.33 cytogenetic band and encodes a 938 amino acid protein with a molecular mass of approximately 10,000 Da. Mutations in *ANKLE2* have been linked to MCPH16, highlighting its critical role in brain development and size regulation (49, 89).

Mutations

Mutations that exhibit typical traits such as a sloping forehead, macules on the body, and anomalies in the face have been identified as the causal agents of primary microcephaly, specifically in two siblings. One of the affected female siblings tragically died not long after birth. Research on the ortholog of the human ANKLE2 gene, Drosophila dANKLE2, has shown that downregulating this gene changes cell proliferation, increases cell death, and decreases the number of neuroblasts, all of which are factors in microcephaly(90).

CITK (MCPH17)

Genetic Characteristics

Citron kinase, encoded by the *CIT* gene, has been identified as a causative agent of primary microcephaly in multiple studies. The CIT gene has been linked to MCPH (with homozygous or compound heterozygous mutations identified in affected individuals(76).

Mutations

During cytokinesis, the last stage of the cell cycle, the CRIK protein, which is generated by the CIT gene, interacts with the microtubule motor protein KIF14 to form a contractile ring that results in the production of two daughter cells. Failure to complete cytokinesis and apoptosis may ensue from this process's disruption. Studies have shown that knockout of the CRIK protein interrupts the localization of KIF14, leading to cytokinesis failure and increased apoptosis. This disruption in cell division processes contributes to reduced cerebral volume and genome instability(91).

WDFY3/ALF (MCPH18)

Genetic Characteristics

ALF (autophagy-linked FYVE protein), also known as WD repeat and FYVE domain-containing protein 3 (WDFY3), has been found to be the causal gene for MCPH18 in a multiplex Israeli Arabic family. By encouraging the aggregation of Disheveled Segment Polarity Protein 3, this gene acts as a scaffold and is essential for controlling the Wnt signaling pathway

(DVL3). The WDFY3 gene encodes an autophagy scaffold protein that is essential for various cellular processes, including autophagy and neurodevelopment (92).

Mutations

Pathogenic mutations in WDFY3 have been associated with neurodevelopmental delay, intellectual disability, macrocephaly, and psychiatric disorders such as autism spectrum disorders and attention deficit hyperactivity disorders. Studies have shown that WDFY3 interacts with DVL3 to regulate Wnt signaling, which is crucial for brain development and size regulation (93,94).

COPB2(MCPH19)

Genetic Characteristics

A gene called COPB2 (Coatomer Protein Complex Subunit Beta 2) is linked to MCPH19, located on chromosome 3q23 (95). The COPB2 gene is involved in the trafficking of vesicles from the Golgi apparatus to the endoplasmic reticulum. The identified mutation disrupts the localization of KIF14, leading to cytokinesis failure and apoptosis (96).

Mutations

The WD40 protein-binding domain of COPB2 contains a homozygous missense mutation that has been found in a non-consanguineous family with primary microcephaly. The identified mutation disrupts the localization of KIF14, leading to cytokinesis failure and apoptosis. This disruption in cell division processes contributes to reduced cerebral volume and genome instability. Hypomorph mutations in COPB2, even though mice homozygous with patient variations are normal, are most likely a result of species differences (96, 97). All MCPH genes and their loci involved in autosomal recessive primary microcephaly were arranged in table 2.

KIF14 (MCPH20)

Genetic Characteristics

KIF14 is a member of the kinesin-3 motor family that is localized at the mitotic spindle, at the spindle midzone, and at the midbody, where it acts together with CIT-K to promote cytokinesis.KIF14 is a multi-domain protein with four interacting regions (98).The first region, encoded by the first two exons, interacts with the protein regulator of cytokinesis 1 (PRC1) and is crucial for its enrichment of the central spindle and mid-body during mitosis. The second region is the kinesin motor region, responsible for the association of spindle microtubules and ATPase activity. The third region is the fork head associated domain (FHA), or phosphopeptide recognition domain, which has greater binding affinities for proteins with phosphor-threonine-containing epitopes. The last part of this protein is the tail region, which interacts with the contractile ring component, citron Rho-interacting kinase (CRIK) (99,100).

Mutations

In mitotic cells derived from MCPH20 patients, neither KIF14 nor CIT-K were detected at the midbody, resulting in cytokinesis failure. *KIF14* is involved in diverse cellular mechanisms, including cell division, microtubule dynamics, intracellular transportation, and transduction signaling. It is also known as an oncogenic kinesin, with elevated levels found in various cancers such as prostate, hepatocellular, breast, lung, cervical, ovarian, and glioma (101)

NCAPD2 (MCPH21)

Genetic Characteristics

Non-SMC Condensin I Complex Subunit D2 is linked to MCPH21 chromosome 12p13.31. The non-SMC condensin I complex's member D2, which is encoded by this gene, is essential for transforming chromatin into chromosomes. Primary microcephaly, a disorder characterised by a smaller head size and intellectual incapacity, has been connected to mutations in NCAPD2 (102).

Mutations

The NCAPD2 gene of a three-year-old Indian kid with primary microcephaly and intellectual impairment has a unique homozygous splice-site mutation (c.3477+2T>C), according to research research (103). This variation was pathogenic and caused the afflicted person to have primary microcephaly. This mutation was discovered using whole exome sequencing, underscoring the importance of NCAPD2 in neurodevelopment and its connection to microcephaly. NCAPD2 has been associated with various neurodevelopmental disorders, including Alzheimer's disease, autism, and Parkinson's disease (104).

NCAPD3 (MCPH22)

Genetic Characteristics

Non-SMC Condensin II Complex Subunit D2 is linked to the MCPH22 chromosome 11q25. It is part of the non-SMC condensin II complex and plays a significant role in chromosome condensation during neurogenesis, impacting the pool of neurons and cortex size (105) .

Mutations

Mutations in NCAPD3 have been linked to autosomal recessive primary microcephaly, a condition characterised by reduced brain size and intellectual disability. Studies have shown that disruptions in condensin-dependent mitotic chromosome integrity due to mutations in NCAPD3 can lead to microcephaly by affecting neuronal cell proliferation, viability, and survival (106). Research has highlighted the importance of NCAPD3 for proper chromatin organisation and chromosome condensation. Mice with mutations in genes encoding condensin complex proteins, including NCAPD3, exhibited microcephaly with decreased brain weight and reduced cortical surface compared to controls (107).

NCAPH3 (MCPH23)

Genetic Characteristics

Non-SMC Condensin I Complex Subunit H at MCPH23 chromosome 2q11.2. This gene encodes a regulatory subunit of the condensin complex I, which plays a crucial role in chromosome condensation. The condensin complex I is essential for proper nuclear organisation and localization (108).

Mutations

Mutations in NCAPH have been linked to autosomal recessive primary microcephaly, a condition characterised by reduced head size and intellectual disability. The condensin complex I, including NCAPH, is vital for mitotic chromosome assembly and proper chromatin organisation during cell division (109).

NUP37 (MCPH24)

Gene Location

NUP37 is mapped to chromosome 12q23.2 and comprises 10 exons that encode a protein with 326 amino acids (110).

Role in cancer

Studies have shown that NUP37 acts as an oncogene, promoting the growth, motility, and invasion of cancer cells. Up-regulation of NUP37 has been observed in hepatocellular carcinoma, where it enhances metastasis and invasion. NUP37 has been identified as a prognostic biomarker in various cancers, including glioma and pan-cancer studies (111,112)

MAP11 (Microtubule-associated protein 11) at MCPH25

Gene Location

MAP11 mutations are responsible for MCPH25, a form of autosomal recessive primary microcephaly. MAP11 is mapped to chromosome 7q22.1, previously known as C7orf43 (113).

Protein Characteristics

Encodes a protein of 580 amino acids that interacts with alpha-tubulin in mitosis and co-localises with Plk1, a key regulator, during mitosis (114).

Association with Microcephaly

A homozygous nonsense mutation in MAP11 has been linked to primary microcephaly in consanguineous Bedouin parents and their three siblings. Highly expressed in the brain and cerebellum. Interacts with mitotic spindles and gamma-tubulin during mitosis in SH-SY5Y cells (115).

LMNB1 (MCPH26) and LMNB2 (MCPH27)

Nuclear lamina proteins

LMNB1 and *LMNB2* encode two associated constituents of the nuclear lamina, which interact with various proteins (116).

Mitotic Spindle Interaction

These genes produce dominant-negative mutant proteins that disrupt the organisation of filaments and damage the formation of the mitotic spindle (117).

Primary Microcephaly

LMNB1 and *LMNB2* mutations have been connected to primary microcephaly. In HeLa cells, defective nuclear envelopes are formed with these mutations (118).

RRP7A(MCPH28)

Genetic Characteristics and Microcephaly

Autosomal recessive primary microcephaly-28 (MCPH28) is caused by a homozygous mutation in the RRP7A gene on chromosome 22q13. Ribosomal RNA-processing protein 7 homolog A, or RRP7A, is a gene that codes for a protein involved in neurogenesis, neocortex development, resorption of primary cilia, and ribosome biogenesis (119) Autosomal primary microcephaly-28 (MCPH28), a condition marked by considerably decreased head size (down to -8 SD) and variable impaired cerebral development seen from early life, has been linked to mutations in the RRP7A gene (120).

PDCD6IP(MCPH29)

Genetic Characteristics and Microcephaly

Autosomal recessive primary microcephaly-29 (MCPH29) is caused by a homozygous mutation in the PDCD6IP gene on chromosome 3p22 (121). A homozygous frameshift mutation in the PDCD6IP gene has been identified in two brothers from a consanguineous Saudi family with MCPH29. This mutation segregates with the disorder in the family and was not present in multiple public databases, including gnomAD (121,122).

BUBI (MCPH30)

Genetic Characteristics and Microcephaly

Autosomal recessive primary microcephaly is caused by homozygous or compound heterozygous mutation in then the BUB1 gene on chromosome 2q14 (123). Unrelated individuals with microcephaly and delayed intellectual development 3-year-old boy (P1) and a 16-year-old girl (P2)—were reported. The kids were found using the GeneMatcher programme after genetic testing revealed allelic mutations in the BUB1 gene. P1, who was born into an apparently unrelated Austrian family, displayed intrauterine growth retardation, increased nuchal translucency, and the Pierre-Robin sequence. He was identified as having many congenital anomalies at birth, such as a lengthy tracheal stenosis that required a tracheotomy and later surgery, hypospadias, a minor atrial septal defect, choanal stenosis, and clefting of the soft palate (124).

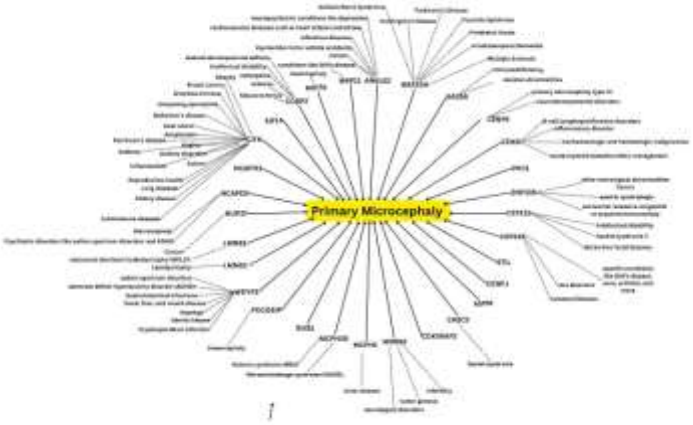
Table 1: Genes and loci are involved in autosomal recessive primary microcephaly.

Locus	Genes	Location	Subcellular Location	Pathways	Ethnicity	Reference
MCPH1	*Microcephalin*	8p23.1	Nucleus	DNA damage response, regulation of chromosome condensation	Pakistani	Jackson et al. 2002
MCPH2	*WDR62*	19q13.12	Centrosome	Centriole biogenesis	Northern Pakistani & Indian	Bilguvar et al. 2010
MCPH3	*CDKRAP2*	9q33.2	Kinetochore	Centriole biogenesis	Northern Pakistani	Bond et al. 2005
MCPH4	*CASC5*	15q15.1	Centrosome	Attachment of microtubule to the centromere, a checkpoint of spindle assembly, mitosis activation	Moroccan	Jamieson et al. 1999

MCPH5	*ASPM*	1q31.3	Centrosome	Centriole biogenesis	Pakistani, Turkish	Bond et al. 2005
MCPH6	*CENPJ*	13q12.12-q12.13	Centrosome	Centriole biogenesis	Brazilian	Leal et al. 2003
MCPH7	*STIL*	1p33	Centrosome	Formation of pro-centriole and biogenesis of centrioles	Indian	Kumar et al. 2009
MCPH8	*CEP135*	4q12	Centrosome	Centriole biogenesis	Northern Pakistani	Hussain et al. 2012
MCPH9	*CEP152*	15q21.1	Centrosome	Centriole biogenesis	Eastern Canadian	Kodani et al. 2015
MCPH10	*ZNF335*	20q13.12	Nucleus	Transcriptional regulation of brain-specific genes	Arab Israeli	Yang et al. 2012
MCPH11	*PHC1*	12p13.31	Nucleus	GMNN negative regulation	Saudi	Awad et al. 2013
MCPH12	*CDK6*	7q21.2	Centrosome	Unknown	Pakistani	Hussain et al. 2013
MCPH13	*CENPE*	4q24	Kinetochore	Unknown	European	Mirzaa et al. 2014
MCPH14	*SASS6*	1p21.2	Centrosome	Centriole assembly	Pakistani	Khan et al. 2014
MCPH15	*MFSD2A*	1p34.2	Plasma Membrane	Transport of omega 3 fatty acid across BBB (blood-brain barrier)	Northern Africa	Alakbarzad et al. 2015
MCPH16	*ANKLE2*	12q24.33	Not well characterized	diminished proliferation and enhanced apoptosis	Mexican	Yamamot et al. 2014
MCPH17	*CIT*	12q24.23	Midbody	Cytokinesis	Egyptian Turkish, Saudi	Li et al. 2016
MCPH18	*WDFY3 /ALF*	4q21.23	Nucleus and Cytoplasm	Involvement in autophagy and regulating Wnt signaling	Arab Israel	Li et al. 2016
MCPH19	*COPB2*	3q23	Cytosolic	Regulator of intracellular trafficking		Distasio et al. 2017

MCPH20	*KIF14*	1q32.1	Midbody	Cytokinesis	Pakistani, German, Saudi	Moawia et al. 2017
MCPH21	*NCAPD2*	12p13.31	Condensin I	Mitotic chromosome condensation, impaired DNA decantation	Indian	Martin et al. 2016
MCPH22	*NCAPD3*	11q25	Nucleus and Condensin II	Condensation of Mitotic chromosome, impaired DNA decantation	USA UK	Martin et al. 2016
MCPH23	*NCAPH*	2q11.2	Condensin I	Impaired DNA Decantation	Portuguese	Martin et al. 2016
MCPH24	*NUP37*	12q23.2	Nuclear pore complex		Pakistani	Braun et al. 2018
MCPH25	*MAP11*	7q22.1	Microtubules associated protein	Roll in spindle dynamics and cell division	Bedouin	Perez et al. 2019
MCPH26	*LMNB1*	5q23.2	Nuclear lamina spindle	Nuclear envelope assembly of the mitotic spindle	Scottish	Cristofoli et al. 2020; Parry et al. 2021
MCPH27	*LMNB2*	19p13.3	Nuclear lamina spindle	Nuclear envelope assembly of the mitotic spindle	England	Parry et al. 2021

Figure1: Primry Microcephaly associated genes and their associated disorders causing by mutations of genes.



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