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A review on microcephaly genes

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This review aims to summarize the recent findings regarding microcephaly genes. We have discussed the molecular genetics studies of microcephaly genes including a comprehensive appraisal of the seven mapped loci (MCPH1–MCPH7), their corresponding genes and protein products of the genes, their likely role in normal brain development and the details of the mutations reported in these genes.

Keywords: microcephaly, MCPH loci, MCPH gene, mutation, neurogenesis.

Introduction. Microcephaly is a neurological disorder [1] defined as a small cranium with a significantly reduced head circumference (HC) of more than two standard deviations (SD) [2, 3]. Microcephaly can occur with congenital (primary) or postnatal (secondary) onset, and is caused by genetic or non-genetic factors [4, 5]. Autosomal recessive primary microcephaly is characterized by non-progressive mild-to-moderate mental retardation and a substantial reduction in prenatal human brain growth without alteration of the cerebral architecture [6–9]. It is a model disease to study human neurogenesis [10]. Secondary, microcephaly is a disorder in which the brain is of the expected size at birth but subsequently fails to grow normally. The condition occurs due to mutations in an apparently ubiquitously expressed X-linked gene *MeCP2* which has a crucial role in maintaining the mature neuronal state [11]. The incidence is 1 in 10000 in consanguineous populations, less in non-consanguineous populations [7].

Microcephaly genes. Clinical surveys from the 1950s and earlier suggested that microcephaly was likely to be an autosomal recessive Mundelein disorder. However, molecular studies of this disorder were performed in the late 1990's [12]. Microcephaly exhibits genetic heterogeneity, having been associated with mu-

tations in seven microcephaly loci. These loci, known as «microcephaly genes», are, therefore, presumed to play important roles in size regulation during brain development [13]. So far, seven genetic loci (MCPH1-7) for microcephaly have been mapped [14]. Genetic causes of microcephaly subtypes 1–7 include mutations in genes encoding *microcephalin* (MCPH1) [15], *WDR62* (MCPH2) [8], *CDK5RAP2* (MCPH3) [16], *CEP152* (MCPH4) [39], *ASPM* (MCPH5) [17], *CENPJ* (MCPH6) [16], *STIL* (MCPH7) [18]. A detailed description of the MCPH gene mutations and their most likely functions in the development of microcephaly is as follows (Table 1).

Microcephalin (MCPH1). Microcephalin (MCPH1) is an 835 amino acid protein containing BRCA1 C-terminal (BRCT) domains. *MCPH1* gene in chromosome locus 8p23 contains 14 exons, the genomic size is 241905 bp with three isoforms reported so far and 8032 bp Open Reading Frame (ORF) [15]. The mutations identified earlier were truncating mutations and, therefore, were predicted to lead to a complete loss of the gene function [19]. Jackson and colleagues has refined the *MCPH1* region from 13cM to 2.1Mb. In two consanguineous families of northern Pakistani origin, a single homozygous 74CG (S25X) non-sense mutation was identified in the second exon of a 2.505 nucleotide, 14 exon of uncharacterized gene [15] (Figure, a) which encodes the protein microcephalin, also is referred to as

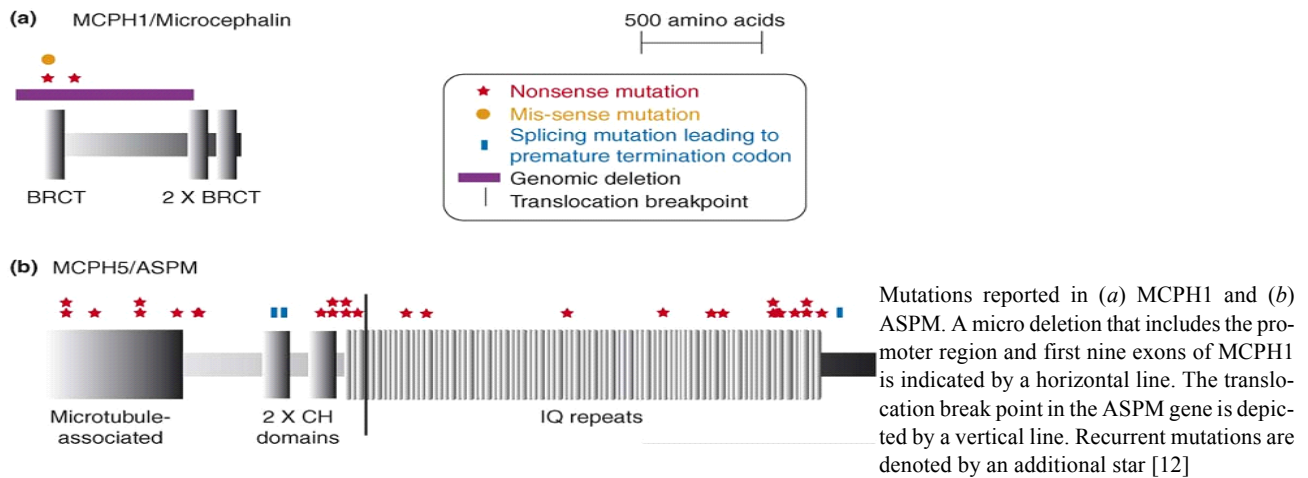
Table 1
Microcephaly genes

Locus	OMIM	Map location	Gene	Protein	Centrosome (C) or spindle pole (SP) association	DNA damage response	Function
MCPH1	251200 607117	8p.23	<i>MCPH1</i>	Microcephalin	Yes (C)	Yes	DNA damage repair; Chromosome condensation; Transcriptional regulation of DNA damage genes
MCPH2	604317 613583	19q13.12	<i>WDR62</i>	WDR62	Yes (SP)	ND	Cortical lamination, neural migration
MCPH3	604804 608201	9q33.3	<i>CDK5RAP2</i>	CDK5RAP2	Yes (C)	Yes	Predicted role in regulating; microtubule dynamics; centrosome maturation and cohesion
MCPH4	604321 613529	15q21.1	<i>CEP152</i>	CEP152	Yes (C)	Yes	Neural development
MCPH5	608716 605481	1q31	<i>ASPM</i>	ASPM	Yes (SP)	Yes	Spindle pole organization and orientation
MCPH6	608393 609279	13q12.2	<i>CENPJ</i>	CENPJ	Yes (C)	ND	Centriole biogenesis and length; microtubule dynamics
MCPH7	612703 181590	1p32	<i>STIL</i>	STIL	Yes (SP)	ND	Spindle organisation; Hh/Shh signalling

ND: not determined; OMIM: Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/omim>) number [7, 67].

BRIT1 for BRCT Repeat Inhibitor of *hTert* expression [20]. Later, the mutation in this gene was reported at disorder of microcephaly, short stature and misregulated chromosome condensation, known as Premature Chromosome Condensation Syndrome (PCC). It was therefore discovered that both MCPH1 and PCC syndrome are allelic disorders originated from mutations within the same gene [21]. A missense mutation has been reported in *MCPH1* gene demonstrating less severe cellular phenotype and mild microcephaly [22]. Also, a large deletion mutation encompassing first 6 exons of Microcephalin gene in an Iranian family, showing autosomal recessive mental retardation and mild microcephaly, has been reported [23]. Loss of function mutations in the genes associated with MCPH reduced human brain size by about two-thirds, without producing gross abnormalities in brain organization or physiology [24]. RNA interference (RNAi) of MCPH1 has implicated the corresponding protein as a DNA-damage response protein that regulates the transcription of *Chk1* and *BRCA1*, two genes involved in the

response to DNA damage. MCPH1 has a function downstream of Chk1 in the ATR-signalling pathway. MCPH1 also plays an ATR-independent role in maintaining inhibitory Chk1 phosphorylation, which prevents premature entry into mitosis [25]. Farooq et al. described the Craniosynostosis-Microcephaly with Chromosomal Breakage (CMCB) and other abnormalities that were caused by a truncating mutation (302CG) in exon 4 of the MCPH1 gene. CMCB is found to be allelic to PCC syndrome and MCPH1 [26]. Most reported mutations induce the production of non-functional, truncated proteins [2]. *Microcephalin* has a role in DNA damage response [27, 28] and regulation of cell cycle checkpoints [29]. It has been proposed that mutations in *microcephalin* are a causal link between impaired DNA damage response signaling and microcephaly and that misregulated chromosome condensation in MCPH1 is mediated by condensin II protein [30, 31]. It has been demonstrated that microcephalin protein is recruited to double-strand breaks via interaction of its C-terminal BRCT domains with phosphorylated H2AX,



a histone variant that marks sites of damaged DNA, further expanding the signal to Chk1 and Chk2 via subsequent phosphorylation, leading to the modulation of cell cycle, DNA repair and apoptosis [31].

WDR62 (MCPH2). *WDR62* gene was identified as the second most common cause of MCPH after finding homozygous missense and frame-shifting mutations in seven MCPH families [8]. The gene lies within the MCPH2 candidate linkage interval at chromosome 19q13.12 with 32 functional exons and genomic size of 50230 bp [21]. The gene has two predicted isoforms and the protein consisting of 1523 residues contains 15 WD repeats. In three recently published research articles, authors have found six different homozygous recessive mutations in human *WDR62* showing linkage at MCPH2 locus [8, 33, 34]. Interestingly, four of them were missense mutations. Like other MCPH proteins overexpressed *WDR62* was localized to the spindle poles during mitosis. In contrast, a mutant *WDR62* protein, carrying one of the causative missense alterations, p.Arg438His, failed to localize in the spindle poles during mitosis [8]. Bilguvar et al. have found 5 homozygous *WDR62* mutations including deletions and premature terminations in patients suffering from microcephaly and some additional phenotypes, belonging to Turkish origin [33]. *WDR62* missense mutations might impair the centrosomal function of *WDR62*, whereas, on the other hand, a complete loss of *WDR62* function might affect severely neuronal migration as well. Taken together, the current studies strongly suggested a function for *WDR62* in proliferation and spindle formation, as well as in neuronal migration, thereby showing a com-

mon mechanism underlying primary microcephaly and malformations of cortical development [5]. Yu et al. also identified six families with syndrome of congenital microcephaly and diverse defects in cerebral cortical architecture. They identified six mutations in *WDR62* gene by use of targeted high throughput sequence analysis [34]. Nuclear localization of *WDR62* in human neurons that had just migrated to the cortical plate was also observed which suggested that *WDR62* might play an important role in cortical lamination as well [8].

CDK5RAP2 (MCPH3). The cyclin dependent kinase 5 regulatory subunit-associated protein 2 is a protein that in humans is encoded by the *CDK5RAP2* gene, also referred to as the centrosome associated protein 215 (CEP215) or the CDK5 activator binding protein C48 (C48).

Four isoforms have been reported so far. The human full length, 1893 amino acid *CDK5RAP2* protein contains an N-terminal interaction site with the gamma tubulin ring complex (gTuRC), a C-terminal interaction site with CDK5 regulatory subunit1 lines and tumors, and its increased expression is positively associated with proliferation of glioblastoma cells [2, 35]. The MCPH3 locus was refined from 12 cM to 2.2 Mb by the identification from a family of northern Pakistani origin [16]. The gene contains 38 exons; genomic size is 191290 bp, with 5682 bp ORF [2, 16, 36]. Multiple transcript variants exist for this gene on chromosome 9q33.2, but the complete molecular mechanism for only two has been determined [14]. A homozygous 243T→A (S81X) nonsense mutation and an intronic mutation 15 bases prior to the normal splice acceptor sequence

IVS26-15AG (E385fsX4) were identified. Both mutations are segregated from the disease within the families and were not present in 1380 control alleles. The intronic mutation created a new, superior splice acceptor site in exon 27, leading to the addition of four new amino acids and a termination codon [16].

Hassan et al. described a previously known mutation (S81X) in MCPH family from Northern Pakistan and concluded that the exact nomenclature for this mutation was 246T → A (Y82X) [37]. Zhang et al. demonstrated that CDK5RAP2 is required for spindle checkpoint regulation. They found that loss of its function leads to chromosome mis-segregation and reduced expression of spindle checkpoint proteins, via interaction with their promoters and transcription regulation [38].

CEP152 (MCPH4). Guernsey et al. have discovered both homozygous and heterozygous mutations in *CEP152* gene located within MCPH4 linkage locus at chromosome 15q21.1 in two Canadian families with MCPH using single nucleotide polymorphism (SNP)-based genome scan. However, in mice, they were able to generate a cDNA clone product of the correct size spanning exons 21–24 of the mouse *CEP152* ortholog by using RNA extracted from mouse brain tissue; cDNA could be readily detected in stage 12.5 and 14.5 embryonic brains. They have also used tools of bioinformatics to elaborate the pathogenic effect of homozygous mutation in *CEP152* gene (Q265P) in two MCPH4 linked families [39]. Blachon et al. have demonstrated that *Asl* (ortholog of *CEP152* in *Drosophila*) is a conserved gene required for ciliogenesis; which is involved in the initiation of centriole duplication and that it is dispensable for pericentriolar material (PCM) recruitment in meiosis in MC centrioles (Mother Centrioles). They were successful to show that *Asl* is essential for centriole formation in brain cells [40]. A homozygous MCPH-causing mutation was reported in human *CEP63*. CEP63 forms a complex with another MCPH protein, CEP152, a conserved centrosome duplication factor. Together, these two proteins are essential for maintaining normal centrosome numbers in cells. Using super-resolution microscopy, it was found that CEP63 and CEP152 co-localize in a discrete ring around the proximal end of the parental centriole, a pattern specifically disrupted in CEP63-deficient cells

derived from patients with MCPH. This work suggests that the CEP152-CEP63 ring-like structure ensures normal neurodevelopment and that its impairment particularly affects human cerebral cortex growth [9].

ASPM (MCPH5). The most common cause of MCPH is homozygous mutations in the MCPH5 gene [41] (Figure, b), Abnormal Spindle-like, Microcephaly associated gene (*ASPM*) [17, 42–45]. *ASPM* is a very large protein of 3477 amino acids comprising a putative microtubule-binding domain at its N-terminal [46, 47], a calponin homology domain, multiple IQ calmodulin binding domains [46, 48] and a carboxy terminal region with no identifiable domains [19, 48, 49]. *ASPM* is a large gene with 28 exons and a 10.4-kb ORF. The 24 published *ASPM* mutations comprise nonsense mutations, deletions of 1–7 base pairs, a break point translocation, and intronic splice-donor point mutations [42–45]. The mutations are distributed throughout the gene and are all predicted to produce truncated protein products ranging in size from 116 amino acids to 3,357 amino acids [42, 43]. It has been suggested that the common mechanism of action of *ASPM* mutation is nonsense-mediated mRNA decay [50]. Nonsense-mediated mRNA decay is a mechanism that selectively degrades mRNAs harboring premature termination (nonsense) codons [72]. *ASPM* hampers symmetric cell division of neural progenitors [51]. It has been suggested that a second gene causing MCPH exists at the MCPH5 locus, as mapping studies in five Jordanian and Dutch families linked the families to the MCPH5 locus but excluded the genetic region containing *ASPM* [52]. Sadi et al. identified heterozygous *ASPM* mutations in three Algerian siblings born to consanguineous parents of which two were nonsense and frameshift mutations predicting a loss of function either by nonsense-mediated mRNA decay or by synthesis of a severely truncated and presumably inactive *ASPM* protein. *ASPM*-related MCPH is associated with simplified cortical gyration [32]. The function of the *ASPM* protein in neural progenitor cell expansion, as well as its localization to the mitotic spindle and mid body, suggested that it regulates brain development by a cell division-related mechanism [49]. In some recent studies, expression of *ASPM* in cancer cells has been investigated. *ASPM* has been found down-regulated in ionizing-radiation treated cells [53] and its down-regulation has shown to decrea-

se the *Bracl* protein expression as well [54]. *ASPM* plays a role in mitotic spindle function including orientation of cleavage plane. The spindle apparatus dictates the plane of cell cleavage, which is critical in the choice between symmetric or asymmetric division [55].

***CENPJ* (MCPH6).** The human centromeric protein J encoded by gene *CENPJ*, also referred to as centrosomal P4.1-associated protein (CPAP), LAG-3-associated protein (LAP) or *LYST*-interacting protein1 (LIP1). The human full length *CENPJ* protein of 1338 amino acid contains a 112-amino acid long microtubule destabilizing motif PN2-3 [56] and two C-terminal 14-3-3 binding sites [57]. The *CENPJ* gene (MIM 609279) spans 40672 bp with 5187 bp ORF. Four mutations have been reported in this gene so far. Initially two mutations were reported in three families [16] including two families from Northern Pakistan having one mutation and other from Brazil with second mutation within a previously identified locus on human chromosome 13q12.2 [58]. The 6-Mb MCPH6 region was refined by the use of novel polymorphic microsatellite markers that were genotyped in the original Brazilian family used to map the locus and in two additional northern Pakistani affected consanguineous families [16]. This facilitated the reduction of the locus to 3.1 Mb and enabled the selection of *CENPJ* gene in which two homozygous mutations were identified: the frameshift mutation 17 del C in exon 2 (T6fsX3), in two pedigrees, and the missense mutation 3704A → T in exon 16 (E1235V), in one pedigree. 3704A → T is the only MCPH mutation described that is not predicted to result in a protein truncation. The E1235V mutation occurs in a highly conserved Tcpl0 binding domain, which is involved in binding to the protein 4.1R-135 [4]. Later, in a Pakistani family, a deletion of four consecutive nucleotides (TCAG) was identified in exon 11 of *CENPJ* gene, leading to frameshift and premature termination by a codon 19 bp downstream in the same exon, predicted to add six amino acids downstream of the mutation [59]. More recently, a novel splicing mutation in *CENPJ* gene [60] has been observed in Seckel syndrome patients. *CENPJ* is localized at the centrosome during mitosis and it is concentrated at the mitotic spindle poles during pro-metaphase and metaphase [16, 56]. Cho et al. have observed that depletion of *CENPJ* disrupts centrosome integrity, and cells lacking CPAP are arrested in mitosis

with multipolar spindles. It has been found that *CENPJ* depletion by the use of siRNA lead to an increase of multiple spindle poles, mitosis arrest and apoptosis [61]. *CENPJ* interacts with the N-terminal domain of the p65 subunit (RelA) of NF-kappa B, a transcription factor important for various cellular events such as inflammation, immune response, proliferation and apoptosis [62].

***SIL/STIL* (MCPH7).** The human *SCL/TAL1*-interrupting locus gene encodes *STIL*, also referred to as *SCL*-interrupting locus (*SIL*). *STIL* is an immediate early gene that encodes a cytosolic protein of 150 kDa. It contains 20 exons and 1287 residues in full-length protein [2, 18, 63]. Two isoforms have been reported. The *STIL* gene spans 63018 bp with 5225 bp ORF. Sequence analysis of *STIL* revealed 3 different homozygous protein truncating mutations in affected members of 5 Indian families linked to MCPH7. Heterogeneity analysis of 24 families previously excluded from linkage to the six known MCPH loci suggested linkage of five families (20.83 %) to the MCPH7 locus. Further, another ascertained family was homozygous for the same mutation as one of the original families [18]. It is also reported that the two MCPH-associated proteins *STIL* and CPAP interact with each other and are required for procentriole formation, implying a central role of centriole biogenesis in MCPH [64]. Karkera et al. found that the human *STIL* protein contains a putative nuclear localization signal and a cysteine-terminal domain similar to the C-terminal domain of TGF-beta [63]. *STIL* is an early response gene that is ubiquitously expressed in proliferating cells and during early embryonic development [65, 66]. *STIL* is expressed throughout the cytosol with increased expression in the perinuclear region that likely plays a role in mitotic entry (cell cycle progression G2-M), apoptosis control and centrosome function [18].

Mutation Continuum of Microcephaly Genes in Pakistan population. Due to high rate of consanguinity (~61 %) and large family size, Pakistani population has proved to be rich for genetic linkage studies. A total of about 95 families have been reported with mutations in any of microcephaly genes from Pakistan (Table 2). Except one recently discovered locus from India (MCPH7), all other MCPH loci have been reported in Pakistani families. *ASPM* gene mutations have been found in 83 families with 2 families having compound

Table 2
Mutations in microcephaly genes (*MCPH1*, *WDR62*, *CDK5RAP2*, and *CENPJ*) from Pakistani families

Gene	Mutation	State of mutation	Present in N of families from Pakistan	Reference
<i>MCPH1</i>	74C-G	Homozygous	Two	[15]
<i>WDR62</i>	3232G-A	Homozygous	One	[8]
	246T-A	Homozygous	Two	[16, 37]
<i>CDK5RAP2</i>	IVS26-15A-G	Homozygous	One	[16]
	17delC	Homozygous	Two	[16]
<i>CENPJ</i>	3243del	Homozygous	One	[59]

heterozygous mutations. Two mutations 3978G → A and 8508delGA were most common, segregating in 18 and 4 families, respectively. *CDK5RAP2* gene mutations have been found in three Pakistani families so far, and they are exclusive to Pakistan. One mutation (IVS26-15A → G) was observed in one family while other mutation (Y82X) was present in two families. Two mutations (17delC and 3243delTCAGa) have been found in *CENPJ* gene segregating in three Pakistani families [14]. In one Pakistani family, linked to *MCPH2* locus, a missense mutation 3232G → A (Ala1078Thr) in exon 27 of the *WDR62* gene has been detected [8]. Previously the locus was reported in Pakistani families only but the mutations in *WDR62* gene have been found in microcephaly patients from other countries as well [8, 33, 34].

Mutations in genes encoding not only mitotic and apoptotic proteins but also transcription factors may be responsible for malformative microcephaly syndromes [68]. *CASK* is a multidomain scaffolding protein that interacts with the transcription factor TBR1 and regulates expression of genes involved in cortical development. It has been reported that all affected individuals with *CASK* mutations had congenital or postnatal microcephaly [69]. The common variations in the microcephaly genes do not affect the risk of Alzheimer Disease or that their effect size is small [70]. It was suggested that *ASPM* and microcephalin have the potential to be biomarkers in ovarian cancer [71].

Conclusion. The proteins encoded by the microcephaly genes are involved in various molecular mechanisms including cell division, cell cycle regulation, appropriate spindle orientation, DNA damage response

signaling, microtubule dynamics, etc. Recent functional studies have confirmed the presence of microcephaly proteins at centrosome for at least part of the cell cycle. Therefore, it may be concluded that centrosome is the final integration point for many regulatory pathways affecting prenatal neurogenesis in mammals. Better genotyping, neuro-imaging and neuro-physiological testing, along with constitution of genetically homogeneous groups of patients, would help in establishing exact genotype-phenotype correlation. Mutation screening in microcephaly families is need of the time. It will help in genetic counselling and prenatal diagnosis for microcephaly, and thus in turn may help reducing the incidence of microcephaly from highly consanguineous population.

C. Шахид, С. Иршад

Гени мікроцефалії (огляд)

Резюме

В огляді узагальнено дані останніх років з вивчення генів мікроцефалії. Обговорюються результати молекулярно-генетичного дослідження цих генів, зроблено оцінку семи визначених локусів (MCPH1–MCPH7), описано відповідні їм гени і білкові продукти генів, їхня можлива роль у нормальному розвитку мозку, а також мутації у цих генах.

Ключові слова: мікроцефалія, локус MCPH, ген MCPH, мутація, нейрогенез.

C. Шахид, С. Иршад

Гены микроцефалии (обзор)

Резюме

В обзоре обобщены данные последних лет по изучению генов микроцефалии. Обсуждаются результаты молекулярно-генетического исследования этих генов, сделана оценка семи определенных локусов (MCPH1–MCPH7), описаны соответствующие им гены и

белковые продукты генов, их вероятная роль в нормальном развитии мозга, а также мутации в этих генах.

Ключевые слова: микроцефалия, MCPH локус, MCPH ген, мутация, нейрогенез.

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