

MICROCEPHALY– A NEURODEVELOPMENTAL HEREDITARY DISORDER WITH EMERGING DRIFTS OF ZIKV

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خلاصہ

بنیادی، مغلوب اور خود لوہیہ طور پر سر کا چھوٹا ہونا ایک کم پائی جانے والی پیدائشی اور اعصابی حالت اور ایک قدیم الایام شکل نوع ہے جو کہ عام طور پر قطر سر کے بالائی قذافی حصے میں کمی کے طور پر پیدایا جاتا ہے اور علمی صلاحیتوں میں قدرے کمی سے واضح تضایف رکھتا ہے اور اس میں کاسہ سر، کونی عمود کی مانند قشری دوارجیہ اور کھتا ہے۔ ابھی تک مختلف العناصر جینیاتی خرابی کے لحاظ سے سر کے چھوٹا رہ جانے کا ذمہ دار رسولہ خلقتوں کو کھنڈا چاچکا ہے۔ زیادہ تر خلقتے سیل سائیکل کی پیش روی میں درون خلوی فعل سر انجام دیتے ہیں۔ لہذا ان خلقتوں میں پیدا ہونے والی بے چینی نظام ہر ٹھیک مگر چھوٹے دماغ کو تشکیل دیتی ہے۔ حال ہی میں چھوٹے سر بننے کے عمل میں پیش روی کی ایک اور وجہ زید آئی کے وی دریافت ہوئی ہے۔ زید آئی کے وی میں متعدد سیل سائیکل کی جیتی، سیل کی موت، این پی سی کا تفرق اور پھیلاؤ اور چھوٹے سر کے لئے ذمہ دار خلقتوں کو پائندیوں سے آزاد کرتے ہیں جس کے نتیجے میں قشری کمزوری اور سر کے چھوٹا ہونے کا عمل وقوع پذیر ہوتا ہے۔ اس خرابی کی نشان دہی کے علاوہ اس مسئلے کی روک تھام اور علاج کی اہمیت اجاگر کرنے کی ضرورت ہے۔

Abstract

Autosomal recessive primary microcephaly (MCPH) is a rare, congenital, neurological condition with atavistic phenotype, usually distinguished by reduction in occipito-frontal head circumference strongly correlated with decreased cognitive capacity, simplified gyral cortical pattern and hypo-plastic skull vault. Being a genetically heterogeneous disorder, sixteen genes have been identified yet to be associated with MCPH. Most of the genes have intracellular function in cell cycle progression, thus perturbation in these genes leads to the formation of apparently normal but small brain. Recently, one more progressive cause of microcephaly ZIKV has been discovered. ZIKV infection pointers cell-cycle seizure, apoptosis, and inhibition of NPC differentiation and proliferation, deregulation of microcephaly causing genes, thus resulting in cortical weakening and microcephaly. Besides identification of this disorder, strong emphasis is needed in its prevention and treatment.

Introduction

Genetic studies revealed that irregularities in genetic code and main control system may lead to death dealing disorders. Millions of individuals suffering from different abnormalities authenticate the fact that, nature has already done extensive arbitrary mutagenesis on human brain resulting in rich diversity of alterations that distort cortical development in distinct and surprising manner (Walsh, 1999).

Human Brain- a Complex Brain for a Complex World

It is no exaggeration to say that humans are created as in “the best of forms” and thus have a spectacular organ, the brain. In the whole animal dominion, no other brain is gifted and efficient enough to generate higher consciousness associated with human ingenuity, increased behavioral and cognitive skills providing the solid base for our memory, attention, continual awareness, thought, language and consciousness (Sidman and Rakie, 1973; Matsuzawa, 2001).

At the time of birth the human brain is nearly three times larger and 250% heavier while the body is only 20% heavier in weight in comparison with our closest primates, chimpanzees (McHenry, 1994; Roth and Dicke, 2005). Growth occurs both in prenatal and postnatal period and skull is designed to accommodate these changes (Aicardi, 1998). The large sized brain with expanded cerebral cortex known as grey matter has made humans unusual in the animal kingdom and promoted our success and flexibility as species (Thornton and Woods, 2009). It is highly convoluted external surface about 2 mm in thickness and consists of neuronal cells and supporting glial cells that help in maintaining cognitive functions. Expansion of neural tube occur during neuronal build out that results in the cell proliferation leading to the growth of progenitor cells and finally into fully segregated neurons.

However, mutations in the cytoskeletal proteins encoding genes may lead to several neurodevelopmental disorders (Thornton and Woods, 2009; Tischfield *et al.*, 2011). Due to flaws in these centrosomal proteins, preterm extension of progenitor cells occurs that may leads to defective neurogenesis resulting in severe neurodevelopmental disorders like lissencephaly, microcephaly, schizencephaly etc. (Roberts *et al.*, 2002).

Consanguineous Families and Genetic defects

One billion of the contemporary worldwide population lives in section with fondness of consanguineous marriage (Modell and Darr, 2002; Bittles and Black, 2010). According to medical genetics, a matrimony that results as a unification between two persons who are interrelated as second cousins or closer with 0.0156 or higher interbreeding coefficient (F), is called consanguineous marriage, where F represents measurement of percentage of loci at which the progeny of a consanguineous marriage is likely to receive identical gene replicas from both parentages (Bittles, 2001; Hamamy, 2012).

Consanguineous marriages are socially and culturally recommended and comprise 20-50% of all marriages in populations of North Africa, West Asia and South India and first cousin unions account for nearly one third of all unions (Tadmouri *et al.*, 2009; Bittles 2011). Generally some members of linked families get married in a reciprocal way. This outcomes in large family sizes with various rings of consanguinity. Subsequently, several children are born with genetic defects and the new born individuals have homozygous segments i.e. they receive identical ancestral genomic segments from both parents that results in an increased incidence of recessive diseases with sib ships.

Autosomal Recessive Primary Microcephaly

Microcephaly means ‘small headedness’ (Wollnik, 2010). Characterization of microcephaly can be done by the conclusion that an individual has skull circumference below the expected mean for age and sex. The measurement is made from the forehead to occipital prominence at back of the head across the brow, and is largest measurement possible. Occipitofrontal head circumference (OFC) is considered to be the most frequent method and the diagnostic tool for microcephaly (MCPH). Head circumference ranges from 2 SD to 11 SD below the mean in MCPH patients, with very mild interfamilial difference in degree of microcephaly (Mahmood *et al.*, 2011).

Clinically, it can be defined as an infrequent neurological disorder with an overall reduction of head circumference i.e., >3SD below the age and sex-related mean. Also, this reduction of head circumference is accompanying non-progressive mental retardation of intermittent degree (Woods *et al.*, 2005).

History of Microcephaly

Microcephaly has been known to man for a long time, but scientists found the full swing towards it in late 19th century. Many suppositions were made considering it as a form of atavism and some viewed it as developed due to mechanical compression of fetal brain by contraction of uterus (Fillipink and Schor, 1998).

The first classification of microcephaly was made by an Italian Scientist Carlo Giacomini (1840-1898). He classified microcephaly in three categories:

- **Microcephalia vera**
“Microcephaly vera” also has known a true microcephaly. Sloping head was the specified trait in true microcephaly but not surely perceived in all MCPH cases (Bunday, 1997; Roberts *et al.*, 2002). There is no gross pathological abnormality other than smallness of the brain in it and it was due to pure inhibition of brain.
- **Microcephalia spuria**
It also refers to “pseudo microcephaly” in which recognizable residuum or pathological state was present (Fillipink and Schor, 1998).
- **Microcephalia combinata**
It was thought to be a combination of both the developmental and pathological processes (Fillipink and Schor, 1998).

“Autosomal recessive primary microcephaly”, “True microcephaly” and “microcephaly vera” are the commonly used terminologies for the same phenotype. (Jackson *et al.*, 1998).

Genre of Microcephaly

On the basis of its age of onset, microcephaly can be categorized into Primary and Secondary microcephaly. It can be classified into Syndromic and Isolated, depending whether it is associated with other anomalies or not, respectively (Abuelo, 2007).

Prenatal/Congenital or Primary Microcephaly

Primary microcephaly is non syndromic in which normal brain growth failure occurs during pregnancy, resulting in unusually small brain caused by abnormal development during the first 32 weeks of gestation

(Tunca *et al.*, 2006). Primary microcephaly results due to the defective mitotic divisions and imperfect cell cycle regulation leading to reduced neuronal production (Passemar *et al.*, 2013). Primary microcephaly is non syndromic, principally autosomal recessive form defined by an absence of identifiable environmental causes and lack of associated malformations (Qazi and Reed, 1973; Ross and Frias, 1977).

Postnatal/Acquired or Secondary Microcephaly

Secondary microcephaly occurs postnatally i.e. children with secondary microcephaly had a normal developing brain size and neurological function until the onset of disease at 6-18 months (Shahbazian and Zoghbi, 2002). It is caused by decrease in synaptic connections and dendritic processes (Woods, 2004), as well as chromosomal flaws and malformations (Bhat *et al.*, 2011). As a result children usually have normal head size at birth but due to reduction in growth rate of brain, head size remains reduced in later childhood. Secondary microcephaly is characterized by convulsions, spasticity and other congenital deviations. Angel man syndrome and Rett syndrome are the most familiar examples of secondary microcephaly (Sujatha *et al.*, 1989; Opitz and Holt (1989)).

Non Genetic Causes of Microcephaly

Microcephaly can occur due to many rationale and ecological factors including cerebral anoxia, fetal infections including toxoplasmosis, cytomegalovirus, German measles and chicken pox, alcohol or poisonous chemicals in the womb, severe malnourishment, hysterical maternal phenylketonuria (PKU) and poorly controlled maternal diabetes. Insufficient gestational weight gain, deprived prenatal care, exposure to radiations and intrauterine exposure to teratogenic agents are also the non-genetic reasons resulting in microcephaly (Qazi and Reed, 1975; Ross and Frias, 1977).

Radiogenic Microcephaly

Radiogenic microcephaly is also a non-genetic type of microcephaly that results from drastic experience of mother to pelvic irradiation during the early months of pregnancy. Numbers of radiogenic microcephalic cases in utero were observed in Hiroshima after the outburst of atom bomb (Cowie, 1960). The characteristic features of radiogenic microcephaly are underdeveloped physical growth, cerebellar disorder and brachycephaly i.e. relative width and shortness of skull (Penrose, 1956).

Isolated/Non Syndromic Microcephaly

Isolated microcephaly is characterized by neurological and developmental disorders, with no other recognizable aberrations (Tang, 2006). Autosomal recessive primary microcephaly, autosomal dominant and X-linked microcephaly are the examples of isolated microcephaly. As it contains no other exceptional anomalies thus referred as non-syndromic microcephaly.

Syndromic Microcephaly

Syndromic microcephaly is the result of aggregated chromosomal anomalies including Down syndrome, Edward syndrome; single gene defects including Smith-Lemli-Opitz syndrome, Seckel syndrome etc. contiguous gene duplication or deletion including Wolf-Hirschhorn syndrome with 4p deletion, Cri-du chat syndrome with 5p deletion etc. (Abuelo, 2007; Hassan *et al.*, 2007; Singhmar and Kumar, 2011). Other syndromes having small head size with distinctive and recognizable phenotypes include Williams syndrome, Cornelia de Lange Syndrome, Feingold syndrome (Abeulo, 2007).

Zika virus associated microcephaly:

In 1940's, when Zika virus (ZIKV) was first discovered in Uganda, it was thought to be harmless. ZIKV is a mosquito borne flavivirus and has been reported to be flowing in 26 nations and regions in Latin America and the Caribbean (Tang *et al.*, 2016). Only few symptoms including slightly elevated body temperature and rashes were found to be associated with this viral disease. Later on, prenatal Zika virus infection has been associated to adversarial pregnancy and birth upshots, remarkably microcephaly and other severe brain abnormalities (Rasmussen and Jamieson, 2016). Two pregnant women with microcephaly diagnosed fetus were reported and Zika virus was detected in their amniotic fluid which shows that this virus has the ability to cross placental barrier (Calvet *et al.*, 2016). It has been observed that ZIKV induces immune responses and deregulation of MCPH related genes. Real time PCR based studies have confirmed the substantial down regulation of seven genes including ASPM, CASC5, CENPF, MCPH1, RBBP8, STIL and TBR2 (Li *et al.*, 2016).

Clinical and Phenotypic Manifestations of Microcephaly

Diagnosis of microcephaly is generally based on clinical features and depends upon the severity of additional syndromic features. Patients of MCPH can have mild to moderate mental retardation with non-progressive intellectual impairment, defective cognitive abilities, and facial distortions including sloping

forehead which is not always present, dwarfism or short stature, hyperactivity, seizures (10%), coordination and balance complications and other brain or neurological abnormalities. Majority of MCPH patients can be easily handled and can acquire self-help expertise (Shen *et al.*, 2005; Mahmood *et al.*, 2011). Chromosomal analysis and brain scan reports have shown great number of MCPH patients with normal height, weight and appearance. Size of head seems to be normal at birth time but as the child grows, failure of complete development of head occurs resulting in small head and retrograded forehead (Ponting and Jackson, 2005). Some patients with MCPH2 mutations have pachygyria with cortical thickening including hypoplasia of corpus callosum while in others lissencephaly, schizencephaly, polymicrogyria has been observed (Mahmood *et al.*, 2011).

Neurodevelopmental Etiology of MCPH

Microcephaly, rather than affecting growth of skull, directly affects neurogenesis that's why a preferred term 'Microencephaly' is also used (Hofman, 1984). In microcephaly weight of brain is significantly reduced, typically 430 grams as the unaffected males having 1,450 grams and disproportionately small cerebral cortex (Jackson *et al.*, 2002). As a result, hypoplasia of cerebral cortex leads to an actually 'simplified gyral pattern' as head width is preserved with no major abnormalities in cortical development (Barkovich *et al.*, 1997; Mochida and Walsh, 2001). Moreover, the only compelling neurological deficit is lessening of cognitive abilities (Bundey, 1992). Brain scan and phenotypic feature studies revealed that most of the MCPH genes are expressed in neuroepithelium and thus MCPH patients perform normal functions although they have a small brain. MCPH, according to most recent studies is considered as a main disorder of neurogenic mitosis and not of neural migration, neural apoptosis or neural function. During neurogenic mitosis, MCPH genes are likely to be responsible for modulating the expansion of neural progenitor pool and also involved in the decision to switch from symmetric to asymmetric cell division (Woods *et al.*, 2005).

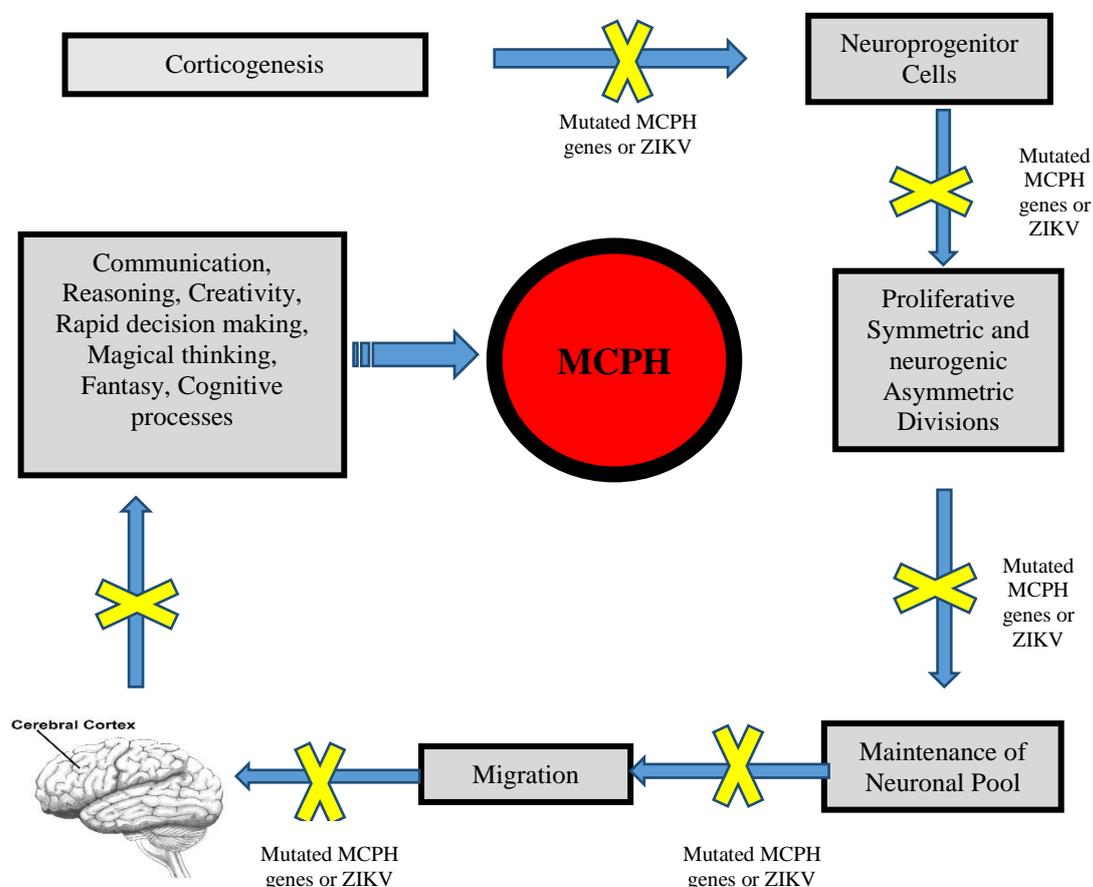


Fig.1. In brain cells, corticogenesis results in the formation of neuroprogenitor cells which later on results in symmetric and asymmetric divisions. As a result neuronal pool is generated that results in complete formation of cerebral cortex region of brain. Cerebral cortex controls all the processes including communication, reasoning, creativity, rapid decision making, magical thinking, fantasy etc. However, in microcephaly any of the involved gene or Zika virus blocks the pathway which results in poor growth of brain (Li *et al.*, 2016).

Biochemical Attributes in Microcephaly

Chromosomal analysis of patients with microcephaly revealed that there is high frequency i.e. more than 10 % of prophase like cells in lymphocytes, fibroblasts and lymphoblast cell lines and this phenomenon is due to premature condensation in the early G2 phase. This premature entrance of cells into mitosis further indicated that mutated gene is involved in cell cycle regulation (Neitzel *et al.*, 2002). In some patients a great percentage of prophase like cells was also observed in combination with normal cell cycle continuance. Highly increased frequency of chromosomal breakage has been observed in some cases (Tommerup *et al.*, 1993).

Diagnosis of Microcephaly

For the significant and increased knowledge of phenotypic diagnostics of MCPH patients, current neurodiagnostic techniques like Computed Tomography (CT) Scan and Magnetic Resonance Imaging (MRI) had provided remarkable support (Woods *et al.*, 2005). Diagnosis of microcephaly is made after the elimination of Craniosynostosis i.e. premature fusion of skull structure, microcephaly associated with multiple congenital anomalies syndromes and other chromosomal disorders e.g. Cri-Du-Chat syndrome, Microlissencephalies (Norman Roberts syndrome, Bath syndrome), Lissencephalies with cerebellar hypoplasia and also keeping out the known causes of secondary microcephaly e.g. birth asphyxia (Verloes, 2004). Microcephaly can be diagnosed before birth by prenatal ultrasound but prenatal diagnosis of fetal head by serial ultrasonographic measurement is not reliable until third trimester. Consequently, association and characterization of genes involved in microcephaly is important for proper diagnosis of microcephaly (Jackson *et al.*, 1998).

Prevalence and Incidental Statistics of Microcephaly

Predictable population of people managing microcephaly at certain time usually refers to the term 'prevalence' of microcephaly while 'incidence' refers to the annual diagnosis rate or the number of new cases of microcephaly identified each year. As compared to Asian and Arab population with high consanguineous mating rate, MCPH seems to be rare in Whites. MCPH has incidence rate of 1/10,000 in Northern Pakistani population while 1 per million in Yorkshire region of Britain (Woods *et al.*, 2005).

However, in case of ZIKV associated microcephaly, 646 cases have been reported in Pernambuco, a Brazilian state (Melo *et al.*, 2016). It has been reported that from 22nd October, 2015 till 5th March, 2016, 6158 microcephaly or Central nervous system deformities have been observed including 167 deaths. Conversely, from 2001 – 2014, averagely 163 microcephaly cases were reported per year (WHO, 2016).

Genetic Heterogeneity and Diversification of Microcephaly (MCPH)

Previously, Humans were thought to be troublesome concern for positional cloning but current advancements in genomics have reduced the technical limitations. Now gene identification from small pedigrees and individuals with informative chromosomal rearrangements are possible with genetic maps of ever-higher density but the richness of genetics remains premier hallmark of human brain. Human cortical malformations including microcephaly are usually "genetically heterogeneous" i.e. more than one genes are involved in causing the disease (Walsh, 1999). Disease phenotype can be a result of hereditary mutations or ZIKV in MCPH genes causing disruptions in mitotic spindle positioning, faulty chromosomal condensation mechanism during embryonic embryogenesis, DNA damage response signaling, transcriptional systemization and some other unknown centrosomal mechanisms that control neurogenesis (Mahmood *et al.*, 2011).

Microcephaly has been known to be genetically heterogeneous with thirteen causative loci mapped to date (MCPH1-MCPH13). Some other genes are recently reported to be the causative agents of microcephaly.

Future Perspective

In cerebral cortex, neurons are produced in a particular proliferative region, the ventricular zone. Then migration of post mitotic neurons on radial glia occurs to form surface of cerebral cortex. After reaching the cerebral cortex, anew arrived neurons pass the older ones to create a normal six layered cerebral cortex. In humans, this migration appears to be at peak between the 11th and 15th week of gestation with majority of neurons to reach the cortex by 24th week. Thus, the upper cerebral cortex layers are made up of later born neurons creating an inside out arrangement of cortical layering. These steps of development and proliferation, when interfered due to mutations in genes that construct our cerebral cortex or recently reported ZIKV infection, results in crippling genetic concerns related to mental health such as microcephaly, lissencephaly and other cerebral dysplasia. These developmental brain defects caused by mutations in some brain cells highlight the fact that due to spontaneous mutations during cell division, each cell has its own different genome (Mochida and Walsh, 2004).

Table 1.1: Summary of all identified MCPH loci (Thornton and Woods, 2009).

LOCUS	GENE	HUMAN PHENOTYPE	CELLULAR LOCALE	PRESUMED ACTIVITY	REFERENCES
MCPH1	<i>Microcephalin</i>	Primary Microcephaly, Short stature	Chromatin, Centrosome	DNA damage repair/ cell cycle control	Jackson <i>et al.</i> (2002)
MCPH2	WDR62 (<i>WD Repeats Containing Protein 62</i>)	Variable i.e. microcephaly, lissencephaly, Schizencephaly, polymicrogyria	Nucleus	Mitotic spindle organization	Bilguvar <i>et al.</i> (2010)
MCPH3	CDK5RAP2 (<i>Cyclin Dependent Kinase 5 Regulatory Associated Protein- 2</i>)	Primary microcephaly	Centrosome	Centrosome maturation/ spindle check point	Bond <i>et al.</i> (2005)
MCPH4	CASC5 (<i>Cancer Susceptibility Candidate 5</i>)	Primary microcephaly	Centrioles	Spindle assembly checkpoint	Jamieson <i>et al.</i> (1999)
MCPH5	ASPM (<i>Abnormal Spindle-like Microcephaly Associated</i>)	MSG, Epilepsy, cortical dysplasia	Pericentrosomal	Spindle organizer	Bond <i>et al.</i> (2005)
MCPH6	CENPJ/ CPAP (<i>Centromere Associated Protein J</i>)	Microcephaly, SCKL4, MR, Post natal dwarfism	Centrosomal	Regulation of cell cycle	Leal <i>et al.</i> (2003)
MCPH7	STIL/ SIL (<i>SCL/TALI-Interrupting Locus</i>)	Microcephaly, short stature, ataxia, seizures	Pericentrosomal	Spindle organization	Kumar <i>et al.</i> (2009)
MCPH8	CEP135 (<i>Centrosomal protein 135KD</i>)	Primary Microcephaly, Severe congenital defects and unintelligible speech	Centrosome	Centriole assembly/ DNA damage response	Hussain <i>et al.</i> (2012)
MCPH9	CEP152 (<i>Centrosome Associated Protein</i>)	Primary Microcephaly, SCKL5	Centrosome	Centriole duplication	Guernsey <i>et al.</i> (2010)
MCPH10	I.ZNF335 II. NDE1 (<i>Zinc Finger Protein 335</i>) (<i>NUDE, A.Nidulans, Homologue of I</i>)	I.Primary Microcephaly II.Primary Microcephaly Microhydrancephaly, Lissencephaly	Centrosomal	I.Chromatid remodeling II.Cytoskeletal organization	Alkuraya <i>et al.</i> (2011) & Yang <i>et al.</i> (2012)
MCPH11	PHCI / EDR1 (<i>Polyhomeotic-like 1</i>)	Primary Microcephaly	Nuclear body Nucleoplasm	DNA repair, Chromatin binding	Awad <i>et al.</i> (2013)
MCPH12	CDK6/ SCKL6 (<i>Cyclin-Dependent Kinase 6</i>)	Primary Microcephaly, SCKL6	Cytoplasm, Nucleus	Cell cycle progression.	Hussain <i>et al.</i> (2013)
MCPH13	CENPE /KIF10 (<i>Centromeric Protein E</i>)	Primary Microcephaly	Nucleus	Spindle attachment, chromosome movement	Mirzaa <i>et al.</i> (2014)
CEP63	CEP63/ SCKL6 (<i>Centrosomal Protein 63</i>)	Primary Microcephaly, SCKL6	Centrosomal	Mitotic assembly	Anderson <i>et al.</i> (2003)
HsSAS-6	SASS6/ HsSAS-6 (<i>Spindle Assembly 6 Homolog of Caenorhabditis elegans</i>)	Primary Microcephaly	Centrosomal	Centriole formation/ Cell division	Khan <i>et al.</i> (2014)
RBBP8	<i>Retinoblastoma-binding protein 8</i>	Seckel Syndrome	Nuclear	Cell proliferation	Mumtaz <i>et al.</i> (2015)
TBR2	<i>EOMES/ T Box brain 2</i>	Primary microcephaly	Neuron progenitor compartments	Neurogenesis	Arnold <i>et al.</i> (2008)

Microcephaly is one of the most debilitating genetic syndromes, generally triggered by aberrant neuronal proliferation and survival. Autosomal recessive primary microcephaly (MCPH) is a congenitally rare heterogeneous disease categorized by reduced occipitofrontal head circumference (OFC) at birth, at least 2-3 standard deviations below the mean for age, ethnicity and sex. In MCPH patients, variable degree of intellectual disability is present due to small brain with simplified gyral pattern, corpus callosum agenesis and pituitary anomalies; though no gross effect on the architecture of brain has been observed (Woods and Parker, 2013). Microcephaly can be classified into Primary microcephaly if it is present at birth and is non-progressive while Secondary, if involves genetic and other non-genetic factors resulting in slow growth of head after birth. Recent reports have demonstrated a clear view that Zika virus infection causes aberrant Neuroprogenitor cell differentiation resulting in the development of immature neurons with final deregulated cell cycle consequences. These effects later on become a progressive cause of microcephaly in human fetus or new born babies (Li *et al.*, 2016).

Till date no possible cure of microcephaly has been discovered. As, its quiet impossible to return a child's head circumference to normal shape and size. A lot of research and work is in progress to decrease the effect of other related deformations and neurological disabilities. However, in utero gene therapy can be considered for normalizing brain cells. By targeting the causative genes, in utero method can be considered as a potential technique for the treatment of microcephaly and associated disorders. Upcoming advances in hereditary diagnosis will help exceptionally early start of gene therapy specifically in the pregnancy of high-risk mothers already having patients in the family.

As, ZIKV is an emerging cause of microcephaly, so future research and investigation must focus at thoughtful understanding of the causes that are promoting vertical transmission of this virus and at pinpointing probable therapeutic schemes for decreasing vertical transmission, specifically, antiviral causes with explicit activity against Zika virus, and discovering the part of adjunctive intermediations (e.g., intravenous immunoglobulins or pooled Zika virus-specific immunoglobulins). It is expected that this prompt spread of ZIKV around the globe will be a strong push for collective exploration on the basic biologic assets of the virus, mainly since the threat of neurotropic and teratogenic virus toxicities are placing an emotional and economic load on society.

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