Research Review

Autosomal Recessive Primary Microcephaly (MCPH): A Review of ASPM Gene

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Abstract

Microcephaly is characterized by reduced skull circumference and closely correlates with reduced brain volume. Autosomal Recessive Primary Microcephaly (MCPH) is a condition in which the principal features are microcephaly and mental retardation. MCPH is a rare neuro-developmental disorder. It is the primary disorder of neurogenic mitosis, which leads to reduced neuron number. Microcephaly is defined as the Head Circumference (HC) that is four standard deviations below the mean (\(_{4SD}\)). In affected individuals, brain weight is markedly reduced and the cerebral cortex is small. Despite this marked reduction in size, no major abnormalities in cortical architecture are present. In true microcephaly, the sloping forehead was a defining feature which is not seen in all cases of MCPH. MCPH is a rare disorder; it seems rarer in whites than in Asian and Arab populations where consanguineous marriages are common. The inheritance pattern is autosomal recessive with one in four recurrence risk for autosomal recessive traits in subsequently born children. To date, seven loci (MCPH1–7) have been mapped and seven genes have been identified. These genes include Microcephalin, WD6R2, ASPM, CEP152, CDK5RAP2, CENPJ and STIL. ASPM organizes microtubules at the spindle pole during mitosis and at the central spindle during cytokinesis.

Keywords: Autosomal Recessive, Primary Microcephaly, MCPH loci, ASPM Gene

1. Introduction

Microcephaly is characterized by reduced skull circumference, measured from the forehead to the occipital prominence at the back of the head, this reduced skull circumference closely correlates with reduced brain volume (Cox et al., 2006). MCPH is one of the conditions in which the principal features are microcephaly and mental retardation (Woods et al., 2005). The greater the degree of microcephaly, the greater the risk and severity of mental retardation (Cox et al., 2006).

Autosomal recessive primary microcephaly (MCPH) is a rare neurodevelopmental disorder that results in a great reduction in brain growth. MCPH is hypothesized to be the primary disorder of neurogenic mitosis, which leads to reduced neuron number. Hence, MCPH proteins are important components of cellular pathways that regulate human brain size. Three MCPH proteins are centrosomal components but have apparently diverse roles that affect neurogenic mitosis (Cox et al., 2006).

The term microcephaly is used for the clinical finding of an HC significantly smaller than expected for a normal individual, taking into consideration age and sex (Aicardi et al., 1998). An HC of four standard deviations below the population age and sex related mean (\(_{4SD}\)) is usually the cut-off for defining microcephaly (Ross et al., 1977 and Baraitser, 1990).

The human brain is about two percent of whole body mass (Roth et al., 2005). At birth, the brain of human beings is approximately three times larger than that of our closest primate relatives (Ponting et al., 2005). Brain growth occurs both in the pre- and post-natal period (in the first three years of human life, the brain becomes four times larger than that at birth). The human skull is designed to accommodate this change (caused due to brain growth)
through growth of skull bones and delayed closure of the sutures between the skull bones. Head circumference (HC) is a useful indirect measurement of brain size. Although more accurate techniques are now available such as volumetric nuclear magnetic resonance (NMR) scanning, but HC remains the most common, simple method for evaluating gross brain size. Charts are available to plot HC against age and sex (Aicardi, 1998).

1.1. Clinical Definition of MCPH

- Microcephaly is evident at birth and is at least three standard deviations (_3SD) below the age- and sex-adjusted mean (Shen et al, 2005).
- Throughout life, the degree of microcephaly does not change. Within the same family, HC usually does not vary by more than 2SD between affected individuals.
- Microcephaly is associated with mental retardation (from mild to severe) but no other neurological findings such as spasticity or progressive cognitive decline. Fits are unusual, but do not exclude the diagnosis (Shen et al, 2005). Recently, an individual with MCPH with borderline mental retardation (intelligence quotient (IQ) = 74, with normal verbal skills) has been reported (Trimborn et al, 2005).
- Height, weight, appearance, chromosome analysis and brain scan are normal in the majority of MCPH individuals.
- Specifically for MCPH1 patients, cytogenetic analysis reveals an increased proportion of prophase-like cells. A reduction in height can occur, but the HC is always significantly more reduced than height. On MRI scan, some patients show evidence of periventricular neuronal heterotopias, which suggest neuronal migration defects (Jackson et al, 2002; Neitzel et al, 2002; Trimborn et al, 2004).

The term primary is potentially confusing because it corresponds to additional meanings, such as (i) time of onset: microcephaly is present since the 7th month of gestation (Aicardi, 1998) and (ii) aetiological: microcephaly is without an identifiable syndromic, environmental or cytogenetic diagnosis (Woods, 2004; Roberts et al, 2002; Trimborn et al, 2005). In affected individuals, brain weight is markedly reduced and the cerebral cortex is small. Despite this marked reduction in size, no major abnormalities in cortical architecture are present (Mochida et al, 2001).

Microcephaly is divided into two categories, primary microcephaly, which is present at birth and secondary microcephaly, which develops postnatally (Woods, 2004). The basic difference between these two groupings is that primary microcephaly is usually a static developmental anomaly, whereas secondary microcephaly refers to a progressive neurodegenerative condition (Qazi et al, 1973; Opitz et al, 1992; Dobyns, 2002 and Rosenberg et al, 2002).

2. Causes

Many nongenetic and genetic causes of primary microcephaly with mental retardation are known, such as congenital infection with toxoplasma, maternal alcohol overconsumption during pregnancy, and Rubenstein Taybi syndrome, all of which must be excluded before the diagnosis of MCPH is considered (Cowie, 1960; Winter et al, 2003).

Brain size of individuals affected with microcephaly is similar to that of early homonids, indicating that these genes might have had a role in evolutionary expansion of the primate brain. There have been many recent advances in the understanding of the molecular basis of MCPH, which has proved of greater complexity and interest than initially thought (Cox et al, 2006).

Clinical surveys have suggested that MCPH was likely to be an autosomal recessive Mendelian disorder. However, molecular studies of this disorder were not instigated until the late 1990s. (Cox et al, 2006). Microcephaly is a feature of many different clinical disorders and can have environmental, maternal or genetic etiologies (Firth et al, 2005). It can occur as a discrete entity in conjunction with learning difficulties but without other developmental malformations or major neurological deficits (Bundy, 1992). If environmental, metabolic or cytogenetic
etioologies are absent, it is known as true microcephaly, microcephaly Vera, recessive microcephaly or primary microcephaly. It is likely to be genetic in etiology, with many cases having an autosomal recessive mode of inheritance (Aicardi, 1998). In true microcephaly, the sloping forehead was a defining feature as shown in figure 1; however, it is not seen in all cases of MCPH (Bundey, 1997; Roberts et al, 2002).

Over time, microcephaly Vera has referred to the condition of any child with congenital microcephaly (microcephaly present at birth) accompanied by a range of neurological features, and hence it has lost specificity as a diagnosis. This led to the introduction of a new diagnostic label, autosomal recessive primary microcephaly, shortened to “MCPH” (Jackson et al, 1998).

MCPH is primarily a disorder of foetal brain growth. The timing of the reduction in growth has been elucidated by ultrasound of affected pregnancies. Up to 20 weeks of gestation, normal head measurements are found. Whereas, a decreased HC is seen by 32 weeks (Woods, 2004). After birth, HC lies between _4 and _12 SD (Roberts et al, 2002). Relative degree of microcephaly does not vary throughout life, and within the same family HC usually does not vary by more than _2 SD between affected individuals (Roberts et al, 2002).

Before the discovery of MCPH genes, autosomal recessive microcephaly was reported to have an incidence of 1/30,000 in Japan, 1/250,000 in Holland, and 1/2,000,000 in Scotland (Komai et al, 1955; Bosch, 1959; Tolmie et al, 1987). MCPH is a rare disorder; it seems rarer in whites than in Asian and Arab populations where consanguineous marriages are commonly practiced. The incidence of MCPH estimates between one in 30,000 and one in 250,000 in European Caucasians, but much higher in some consanguineous populations (one in 10,000 in Northern Pakistanis). The inheritance pattern is autosomal recessive with one in four recurrence risk for autosomal recessive traits in subsequently born children (Bundey, 1992). Empirc recurrence risk for a nonconsanguineous couple having one child with a diagnosis of MCPH has been calculated as 1 in 5 if detailed chromosome studies and neuroimaging yield normal results (Tolmie et al, 1987).

### 2.1. MCPH Proteins

All the MCPH proteins that have been identified till date seem to be important part of the mitotic apparatus. Because of their expression in neuronal progenitors, it is possible that understanding their function might benefit other clinical spheres such as stem-cell therapy of neurological disorders (Cox et al, 2006). The cellular localization of three of the MCPH proteins C2K5RAP2, ASPM and CENPJ is known to be centrosomal during mitosis. This suggests that the centrosome is an important organelle during neurogenic mitosis (Jerison, 1973). A novel locus, MCPH7, has been mapped to chromosome 1p32.3–p33, which also encodes a gene (STIL) producing a centrosomal protein (Kumar et al, 2009).

### 2.2. Genes and Loci

In the past decade, there has been great progress in identification and mapping of primary microcephaly genes. To date, seven autosomal recessive loci (MCPH1–7) have been mapped and five genes have been identified. The description is given in Table 1.

MCPH is expected to exhibit genetic heterogeneity due to

### Table 1. MCPH Loci

<table>
<thead>
<tr>
<th>Loci</th>
<th>Autosomal Localization</th>
<th>Linkage Reference</th>
<th>Genes</th>
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<tbody>
<tr>
<td>MCPH1</td>
<td>8p23.1</td>
<td>Jackson et al, 2002</td>
<td>Microcephalin</td>
</tr>
<tr>
<td>MCPH2</td>
<td>19q13.1-13.2</td>
<td>Roberts et al, 1999; Nicholas et al 2010</td>
<td>WDR62</td>
</tr>
<tr>
<td>MCPH3</td>
<td>9q33.2</td>
<td>Bond et al, 2005; Guernsey et al 2010</td>
<td>C2K5RAP2</td>
</tr>
<tr>
<td>MCPH4</td>
<td>15q15-q21</td>
<td>Jamieson et al, 1999</td>
<td>CEP152</td>
</tr>
<tr>
<td>MCPH5</td>
<td>1q31.3</td>
<td>Bond et al, 2002</td>
<td>ASPM</td>
</tr>
<tr>
<td>MCPH6</td>
<td>13q12.12</td>
<td>Bond et al, 2005</td>
<td>CENPJ</td>
</tr>
<tr>
<td>MCPH7</td>
<td>1p33</td>
<td>Kumar et al, 2009</td>
<td>STIL</td>
</tr>
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its broad clinical phenotype (Jackson et al, 1998; Leal et al, 2003). Here the genes are given in chronological order of discovery: MCPH1, MCPH5, MCPH3, MCPH6 and MCPH7 (Bond et al, 2002; Jackson et al, 2002 and Bond et al, 2005). All seven genes participate in one important non-redundant function i.e. to allow enhanced foetal brain growth compared with that of other mammals (Cox et al, 2006).

2.3. MCPH5 / ASPM Gene

Homozygous mutations of the MCPH5 gene, also known as abnormal spindle-like microcephaly-associated gene (ASPM), are the most common cause of the MCPH phenotype (Roberts et al, 2002; Kumar et al, 2004). The orthologue of the Drosophila gene (ASP) abnormal spindle, is a 28-exon gene spanning 63 kb of genomic DNA and contains ten, 434-base-pair open reading frames (Bond et al, 2002) and codes for 3477 amino acids. The pathogenic nature of mutations in the ASPM gene is a truncation that does not result in nonsense-mediated decay, but in the production of a truncated ASPM protein (Cartegni et al, 2002; Kourprina et al, 2005). In many populations, ASPM (abnormal spindle-like, microcephaly associated) appears to be the major MCPH gene and more than 30 distinct ASPM mutations have been reported, including nonsense, frameshift and splice-site mutations (Bond et al, 2002, 2003) as well as a single missense mutation (Gul et al, 2006) and a translocation breakpoint disrupting the gene (Pichon et al, 2004) and are predicted to result in truncated products ranging in size from 116 (R116X) to 3357 amino acids (K3328fsX29) (Bond et al, 2002; Kumar et al, 2004; Bond et al, 2003; Shen et al, 2005). Investigation of the expression pattern of ASPM mRNA in mouse foetal brain revealed expression at sites of active neurogenesis in the neuroepithelium (Bond et al, 2002).

Studies of the ASPM gene in mice have shown that its expression is maximal in the regions of active neurogenesis and is down-regulated when neurogenesis is completed, this indicates that ASPM is involved in neuron production (Bond et al, 2002). Using reverse-transcription polymerase chain reaction (RT-PCR), MCPH5/ASPM expression was localized to various embryonic and adult tissues, with the exception of post-mitotic tissues of adult brain and skeletal muscle.

2.4. Structure of ASPM Protein

The 3477 amino acid ASPM protein has been predicted to contain one N-terminal microtubule-binding domain, two calponin homology (CH) domains (common in actin-binding proteins), 81 Ile–Gln repeat motifs, which are predicted to experience a conformational change when bound to calmodulin, and a C-terminal region of unknown function (Bond et al, 2002; Kourprina et al, 2005; Rhoads et al, 2005; Saunders et al, 1997) (Figure, 2). Structural projections suggest that ASPM directly interacts with the intracellular cytoskeleton and assumes a semi-rigid rod conformation upon interactions with multiple calmodulin molecules. The N-terminal microtubule binding domain is homologous to that of cilia proteins. This finding has led to a prediction of ciliary function for ASPM (Ponting, 2006), though, this model of ciliary function does not explain the mitotic distribution of ASPM. Collectively, exon 3 (1,486 bp) and exon 18 (4,755 bp) contain most of the coding region of the gene (Saunders et al, 1997). ASPM mutations in humans produce a mitotic defect specific to the brain. In Drosophila, ASP recessive mutants are infertile with dividing neuron progenitors unable to conclude asymmetric cell division (Gonzalez et al, 1990). Drosophila ASP gene product is associated with the minus ends of microtubules at spindle poles in mitosis and meiosis (Ripoll et al, 1985; Gonzalez et al, 1990). ASP is required in microtubule organization of the mitotic spindle poles and the central spindle in meiosis and mitosis (Gonzalez et al, 1990; Avides et al, 2001).

It can be hypothesized that, during neurogenesis, ASPM organizes microtubules at the spindle pole during mitosis and at the central spindle during cytokinesis. Unlike Drosophila ASP cytoplasmic dispersal during interphase, the intracellular distribution of ASPM protein was determined as nuclear or centrosomal during interphase. Both ASP and ASPM are redistributed to the poles of the bipolar mitotic spindle, early in the mitosis, in a dynactin-dependent manner (Kouprina et al, 2005; Saunders et al, 1997; Wakefield et al, 2001; Riparbelli et al, 2002). This suggests a role of ASPM protein in mitotic spindle function during mitosis, possibly through regulation of BRCA1 (Zhong et al, 2005; Bae et al, 2005).
3. Conclusion and Future Prospects

As there are many possible causes of microcephaly, the diagnosis of MCPH should only be made after differential diagnoses have been sought and eliminated. With identification of MCPH genes, the following are becoming increasingly available for MCPH patients: Prenatal diagnosis (to detect a recurrence of the disorder), postnatal diagnosis (to distinguish the disorder from the many differential diagnoses), and carrier testing (in consanguineous families in which the disease is known to occur). There are five genes, known to date, that can cause this neurodevelopmental disorder. Current evidence suggests that MCPH is a primary disorder of neurogenic mitosis.

As such, MCPH may have much to teach us about the control of neuron production by neural stem cells and about how this has been modulated by evolution to control the brain sizes of different species. The present data will be helpful in better diagnosis and management of MCPH in the future. As MCPH is a genetic disorder, gene therapy is a promising hope for its treatment. Stem cell therapy offers particular potential in areas of poorly met, medical need. Diseases of the brain, such as stroke, microcephaly and Parkinson's disease, can dramatically reduce quality of life. They consequently represent major healthcare costs, particularly in terms of long-term care. Fetal Stem cell transplantation therapy offers the potential to alleviate the symptoms of, or cure MCPH and many other genetic disorders. Genetic counseling is also effective. The genetic counselor can help a person or family understand their risk for the MCPH, educate the person or family about that disease, and assess the risk of passing the diseases on to children.

References


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organization in Drosophila S2 cells by dynein, abnormal spindle protein (Asp), and KLP10A. Mol. Biol. Cell, 16, pp. 3176-3186.


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