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Many roads lead to primary autosomal recessive microcephaly

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ABSTRACT

Autosomal recessive primary microcephaly (MCPH), historically referred to as *Microcephalia vera*, is a genetically and clinically heterogeneous disease. Patients with MCPH typically exhibit congenital microcephaly as well as mental retardation, but usually no further neurological findings or malformations. Their microcephaly with grossly preserved macroscopic organization of the brain is a consequence of a reduced brain volume, which is evident particularly within the cerebral cortex and thus results to a large part from a reduction of grey matter. Some patients with MCPH further provide evidence of neuronal heterotopias, polymicrogyria or cortical dysplasia suggesting an associated neuronal migration defect. Genetic causes of MCPH subtypes 1–7 include mutations in genes encoding microcephalin, cyclin-dependent kinase 5 regulatory associated protein 2 (CDK5RAP2), abnormal spindle-like, microcephaly associated protein (ASPM), centromeric protein J (CENPJ), and SCL/TAL1-interrupting locus (STIL) as well as linkage to the two loci 19q13.1–13.2 and 15q15–q21. Here, we provide a timely overview of current knowledge on mechanisms leading to microcephaly in humans with MCPH and abnormalities in cell division/cell survival in corresponding animal models. Understanding the pathomechanisms leading to MCPH is of high importance not only for our understanding of physiologic brain development (particularly of cortex formation), but also for that of trends in mammalian evolution with a massive increase in size of the cerebral cortex in primates, of microcephalies of other etiologies including environmentally induced microcephalies, and of cancer formation.

Abbreviations: 53BP1, tumor-suppressor protein p53 binding protein 1; APC, anaphase-promoting complex; ASPM, abnormal spindle-like, microcephaly associated protein; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and RAD3-related protein; BACH1, BRCA1-associated carboxyl-terminal helicase; BRCT, carboxyl-terminal domain of the breast cancer gene 1 BRCA1; BRIT1, BRCT-Repeat Inhibitor of hTert expression; BUBR1, budding uninhibited by benzimidazoles 1 homolog beta; C48, CDK5 activator binding protein C48; CASK, calcium/calmodulin-dependent serine protein kinase gene; CDC24A, cell division cycle 25A; *CDK5*, cyclin-dependent kinase 5; CDK5R1, cyclin-dependent kinase 5 regulatory subunit 1; CDK5RAP2, cyclin-dependent kinase 5 regulatory associated protein 2; CENPJ, centromeric protein J; CEP215, centrosome associated protein 215; CH, calponin homology domain; CHK1/2, checkpoint kinase 1/2; CMD, calmodulin; cnn, centrosomin; CNS, central nervous system; CPAP, centrosomal P4.1-associated protein; E, embryonal day; EB1, plus-end binding protein EB1; GLI1, glioma-associated oncogene homolog; γTuRC, gamma-tubulin ring complex; Hnf3b, hepatocyte nuclear factor 3-beta, forehead box A2; LAP, LAG-3-associated protein; Lefty2, left–right determination factor 2; LIP1, LYST-interacting protein 1; MAD2, mitotic arrest-deficient 2; MCPH, autosomal recessive primary microcephaly; MCPH1, microcephalin; MDC1, mediator of DNA damage checkpoint protein 1; MOT, microtubule-organizing center; NBS1, Nijmegen breakage syndrome protein 1; NE, neuroepithelium; OFC, occipito-frontal head circumference; PCC, premature chromosome condensation; PCM, pericentriolar matrix; PCNT, pericentrin; Pitx2, paired-like homeodomain transcription factor 2; PLK1, polo-like kinase 1; RELN, reelin; Sas-4, spindle assembly abnormal 4; SD, standard deviation; Shh, sonic hedgehog; shRNA, short hairpin RNA; STIL, SCL/TAL1-interrupting locus; SUFU, Suppressor of Fused; Tbr1, T-box brain 1; TNFalpha, tumor necrosis factor-alpha; zyg-1, ZYGote defective, embryonic lethal.

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Contents

1. *Introduction*

Microcephaly is defined as a small cranium with a significantly reduced occipito-frontal head circumference (OFC) of more than two standard deviations (SD) below the mean for age, sex, and ethnicity (severe microcephaly OFC < -3 SD). Microcephaly can be acquired (caused by environmental factors) or hereditary in origin and can become apparent congenitally (primary microcephaly) or postnatally (secondary microcephaly). The incidence of microcephaly at birth, as evaluated in birth defect registers world-wide, varies from 1.3 to 150 per 100,000 live-births, depending on the population and the applied SD threshold to define microcephaly (source: International Clearinghouse for Birth Defects Surveillance and Research, 2006 report; http://www.icbdsr.org/). Primary, non-syndromal microcephaly has an incidence of 1:30,000 to 1:250,000 live-births (Van Den Bosch, 1959).

Microcephalia vera ('true microcephaly') is a loosely defined, historical term referring to children with isolated, non-syndromal congenital microcephaly. This term was coined without consideration of etiology or neuropathology, and it is still applied, however, in a narrower sense, to designate patients with non-syndromal autosomal recessive microcephaly without lissencephaly or pachygyria. Syndromic microcephalies as well as secondary, often environmentally induced microcephalies which can be caused by underlying processes such as high rates of pathologic apoptosis, proliferation and patterning abnormalities, migration defects, disturbance of extracellular matrix integrity and defects of synaptogenesis will not be discussed in this review (please refer to Francis et al., 2006; Katyal and McKinnon, 2007; Abuelo, 2007; Woods, 2004).

2. *Phenotype of patients with MCPH*

Autosomal recessive primary microcephaly (MCPH, for MicroCephaly Primary Hereditary) is a rare, genetically heterogeneous disease reported in about 100 families world-wide. Historically, primary microcephaly was defined by an OFC < -3 at birth, a reduced brain volume, mental retardation (IQ between 30 and 70–80) and no further neurological findings except for mild seizures (Woods et al., 2005; Passemard, 2009) (Fig. 1). However, it is becoming clear that the true phenotype spectrum of patients with MCPH gene mutations is wider than indicated by previous publications which for the most part provide no detailed phenotype information. In individual patients, the OFC is still in the normal range (around -2 SD) at birth followed by a development of a microcephaly within the first year of life (Passemard, 2009). As recently noted, MCPH may already be evident by the 24th week of gestation through ultrasound and/or MRI analysis (Tunca et al., 2006). Also, we were able to demonstrate recently that neurological features can indeed occur in patients with MCPH due to *ASPM* gene mutations (Passemard, 2009). These include speech delay, hyperactivity and attention deficit, aggressiveness, focal or generalized seizures, delay of developmental milestones and pyramidal signs (Passemard, 2009). Hyperactivity and attention deficit appeared to be major childhood problems in all patients of our cohort and possibly caused impairments in performance. Moreover, abnormal height and weight was detected in some patients (Passemard, 2009; Trimborn et al., 2004).

Imaging studies reveal typically brains of 'normal architecture' but of reduced size (Woods et al., 2005). The latter is particularly evident in the cerebral cortex, which shows a simplified cerebral cortex structure, and there is also a slightly reduced white matter volume (Fig. 2). Individual patients with MCPH provide evidence of periventricular neuronal heterotopias (Woods et al., 2005; Trimborn et al., 2004) suggesting neuronal migration defects. Moreover, we have detected infra-tentorial anomalies (brainstem or cerebellar hypoplasia), dysmorphic and/or enlarged lateral ventricles and corpus callosum agenesia as well as focal micropolygyria and/or dysplasia (Passemard, 2009). Future studies will need to address in what way white matter disease also contributes to brain size reduction in MCPH patients. Descriptions of the histological findings in MCPH patients, indicating a significantly reduced brain volume with an almost preserved convolution pattern, are rare and were performed at a time when a genetic diagnosis was not possible (Bamatter and Rabinowicz, 1969; Robain and Lyon, 1972). An overview of MCPH features, gene mutations and the reported phenotype by MCPH gene mutation are given in Tables 1–3, respectively.

3. Genotype of patients with MCPH

Genetic causes of MCPH subtypes 1–7 include mutations in genes encoding microcephalin (MCPH1; Jackson et al., 2002, 1998; OMIM #251200), cyclin-dependent kinase 5 regulatory associated protein 2 CDK5RAP2 (MCPH3; Bond et al., 2005; Moynihan et al., 2000; OMIM #604804), abnormal spindle-like, microcephaly associated ASPM (MCPH5; Pattison et al., 2000; Shen et al., 2005; OMIM #608716), centromeric protein J CENPJ (MCPH6; Bond et al., 2005; Leal et al., 2003; OMIM #608393), SCL/TAL1-interrupting locus STIL (MCPH7; Kumar et al., 2009; OMIM #612703) as well as linkage to the two loci 19q13.1–13.2 (MCPH2; Roberts, 1999); OMIM%604317) and 15q15–q21 (MCPH4; Jamieson et al., 1999); OMIM%604321) (Kaindl, 2008); see Table 2 and