Molecular genetics of human microcephaly

Ganeshwaran H. Mochida[a,b,c] and Christopher A. Walsh[a]

Human microcephaly comprises a heterogeneous group of conditions that are characterized by a failure of normal brain growth. Microcephaly can be caused by many injurious or degenerative conditions, or by developmental malformations in which the growth of the brain is impaired as a result of defects in pattern formation, cell proliferation, cell survival, cell differentiation, or cell growth. These latter forms of congenital microcephaly are frequently inherited, usually as recessive traits, and are associated with mental retardation and sometimes epilepsy. Some of the genes that cause congenital microcephaly are likely to control crucial aspects of neural development, and may also be involved in the evolutionary explosion of cortical size that characterizes primates. There has recently been a rapid advance in the use of genetic mapping techniques to identify genetic loci responsible for microcephaly. Although several loci have been mapped, the condition is clearly genetically and clinically heterogeneous. Curr Opin Neurol 14:151–156.

[a]Division of Neurogenetics, Department of Neurology, and [b]Clinical Investigator Training Program, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02115, USA; [c]Pediatric Neurology Unit, Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA

Correspondence to Christopher A. Walsh, Department of Neurology, Beth Israel Deaconess Medical Center, Room 816, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, Massachusetts 02115, USA
Tel: +1 617 667 0813; fax: +1 617 667 0815;
e-mail: cwalsh@caregroup.harvard.edu

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Abbreviations

MRI	magnetic resonance imaging
OFC	occipito-frontal circumference

1350-7540

Introduction

The human cerebral cortex, the neural structure responsible for the cognitive activities that define us as human, is the product of an evolutionary history that results in progressive enlargement and specialization. The human cortex is massive compared with that of the hedgehog, a mammal with one of the simplest and smallest laminated structures classified as a cerebral cortex. Although many things distinguish the cortex of the human and the hedgehog, more cell divisions by more progenitor cells is obviously part of the difference. In recent years, we have learned a great deal about the control of neural cell proliferation and cell survival by the systematic analysis of mutants that affect the size of the nervous system of non-vertebrate species such as *Drosophila*. Most of the fundamental models of neural development are based on the homologous functions of structurally homologous genes between vertebrates and non-vertebrates.

However, although there are many shared roles for shared genes, there must also be genes that differ between flies and humans, or even between humans and hedgehogs, either in their primary structure or their expression and function. It is presumably the evolutionary alteration of these variable genes that produced the massive human cortex. The rapid advances in the analysis of the human genome now allow the direct mapping and cloning of genes that prevent the normal formation of a full-sized human cortex, resulting in an abnormally small cerebral cortex, referred to as microcephaly. Identifying these microcephaly genes promises to elucidate important causes of mental retardation, as well as the normal development and evolution of the human brain.

What is microcephaly?

Microcephaly is a condition in which the size of the head, measured by the occipito-frontal circumference (OFC), is significantly smaller than normal for the person's age and sex. Because an abnormally small head essentially invariably reflects a small cerebral cortex, head size (reflected by the OFC) is routinely recorded by pediatricians as an indicator of brain development. An OFC of greater than 2 standard deviations below the mean is often used as a definition of microcephaly in clinical practice, whereas some researchers use stricter cut-off points such as 3 standard deviations. However, microcephaly is in essence a finding on physical examination rather than a specific diagnosis or etiological condition, and is extremely heterogeneous causally,

reflecting any condition that interferes with the normal growth of the brain. This heterogeneity poses significant challenges to the clinical evaluation as well as the biological and genetic analysis of microcephaly.

The etiology of microcephaly can be broadly divided into environmental and genetic causes. Common environmental causes include congenital infections that affect the brain (such as cytomegalovirus, for example), intrauterine exposure to teratogenic agents, and hypoxic-ischemic injury prenatally or perinatally. The clinical history usually provides important diagnostic clues in these cases. On the other hand, even once environmental causes have been ruled out or a genetic cause implicated, the genetic causes of microcephaly remain quite diverse, and a search of Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/) under 'microcephaly' produced almost 300 entries. For example, a host of hereditary metabolic disorders that result in neuronal degeneration usually cause the postnatal onset of microcephaly (commonly referred to as acquired microcephaly, in which the head size is normal at birth but does not increase normally) and are not discussed here.

Microcephaly: an associated feature of many brain malformations

The genetic causes of microcephaly that is present at birth (congenital microcephaly) can be further subdivided into whether there is: (i) normal brain architecture versus abnormal brain architecture, as diagnosed by magnetic resonance imaging (MRI); and (ii) only nervous system findings versus associated non-central nervous system phenotypes. For example, microcephaly is a characteristic feature of brain malformations such as holoprosencephaly, schizencephaly, and Miller–Dieker lissencephaly, presumably because the abnormal brain architecture blocks the normal proliferation or maturation and the growth of neural elements (see Table 1) [1–10,11•,12,13]. Microcephaly in these cases, although it is often what prompts the radiographic evaluation of the child, is a variable associated feature of these conditions rather than an essential defining component of the condition. More recently, a newer group of microcephalic syndromes has been described, in which gyral and other architectural abnormalities are somewhat more subtle, but nonetheless allow subclassification anatomically.

Isolated microcephaly with abnormal or simplified gyral pattern

It has long been known that some patients with presumed genetic microcephaly present with severe neurological signs and symptoms, such as spasticity, severe developmental delay, and seizures. With the widespread use of brain imaging studies, particularly MRI, many patients with microcephaly and these additional neurological signs and symptoms have been found to have abnormalities in gyral formation distinct from the severe lissencephaly of the Miller–Dieker syndrome. In particular, some patients show an abnormally simplified gyral pattern, but without the complete absence of gyri and severe thickening of the cerebral cortex that characterize type I lissencephaly (Fig. 1) [14,15]. This group is collectively referred to as 'microcephaly with simplified gyral pattern'. In its extreme form, very few sulci are seen with an almost smooth brain surface, and the term 'microlissencephaly' may also be applied [16,17•]. In many cases, there are various associated findings on brain imaging, such as a thin cerebral cortex or a reduced amount of cerebral white matter [16].

Microcephaly with simplified or abnormal gyral pattern is also likely to be a diverse and genetically heterogeneous condition, and relies on the continuing clinical use of MRI for its further definition. In some cases, an autosomal recessive mode of inheritance is strongly suggested because of the presence of consanguinity in pedigrees [14,15]. No genetic loci have yet been mapped for this group of microcephaly patients, and no genes responsible for this type of malformation have been found to date. However, it is not yet certain whether some of the microcephaly loci already localized (see below) might also be associated with gyral abnormalities.

Little is known about the biological basis of microcephaly with simplified gyral pattern. Few pathological studies have been published, making it difficult even to speculate about its pathogenesis. However, it appears plausible that in many cases, abnormalities in neuronal migration coexist with a decrease in the number of

Table 1. Known genes associated with congenital microcephaly in humans, excluding metabolic or degenerative conditions

Gene	Associated condition	Gene function
LIS1	Lissencephaly	Cytoplasmic microtubule regulator [1]
DCX	Lissencephaly	Cytoplasmic microtubule regulator [2]
SHH	Holoprosencephaly	Secreted morphogen [3]
ZIC2	Holoprosencephaly	Transcription factor [4]
TGIF	Holoprosencephaly	Transcription factor [5]
SIX3	Holoprosencephaly	Transcription factor [6]
DHCR7	Smith–Lemli–Opitz syndrome	Cholesterol metabolism[7]
CREBBP	Rubinstein–Taybi syndrome	Transcriptional coactivator [8]
PAK3	X-linked mental retardation	Protein kinase [9,10]
NBS1	Nijmegen breakage syndrome	DNA repair [11•]
MECP2	Rett syndrome/X-linked mental retardation	Transcriptional repressor [12,13]

The list includes a number of conditions associated with severe architectural abnormalities of the brain (lissencephaly, holoprosencephaly), as well as a few in which the architecture is relatively normal (e.g. *PAK3*, *NBS1*). The list is quite heterogeneous in terms of the function of the genes involved.

neurons, because disorders of neuronal migration frequently accompany gyral abnormalities [18]. Some cases are associated with neuronal heterotopia, further supporting abnormal neuronal migration. The identification of genes responsible for this group of disorders will probably lead to an understanding of the pathogenesis and refinement of their classification.

Microcephaly vera

In microcephaly vera, or 'true' microcephaly, the central nervous system is typically the only affected organ system, and the brain is characteristically quite small and not grossly abnormal in its architecture. The term was coined by Giacomini in 1885 to denote a condition in which no gross pathological abnormality other than smallness of the brain was observed [19]. Clinically, this term has been used to describe a group of patients characterized by the presence of microcephaly at birth, relatively normal early motor milestones and mental retardation of variable severity. There are usually few dysmorphic features, except a narrow, sloping forehead and relative prominence of the ears. Seizures are relatively uncommon in this group of patients, unlike in patients with microcephaly with simplified gyral pattern, in which seizures appear early and are often intractable.

In patients with microcephaly vera, the gyral pattern is relatively well-preserved despite the often striking smallness of the brain (Fig. 1). Pathological study of the brain may reveal no microscopic abnormality in cortical laminar formation [20]. In some cases, however, the depletion of neurons in cortical layers II and III (which are later-born neurons) as well as the early depletion of cells in the germinative zone near the ventricles have been observed [21]. This led to a hypothesis that premature exhaustion of neuronal progenitors in the ventricular zone might be responsible for microcephaly vera [21].

Recent genetic analysis of microcephaly

Microcephaly vera is often inherited as an autosomal recessive trait, and has recently become a subject of active linkage analysis. Like other recessive conditions, microcephaly is seen relatively more commonly in geographical areas with high consanguinity rates, such as Turkey, Pakistan, and the Arabic countries of the Middle East. Moreover, consanguineous marriages simplify genetic linkage analysis by allowing the use of homozygosity mapping [22]. Since 1998, five genetic loci for autosomal recessive microcephaly have been mapped by collaborations between molecular geneticists (principally the Woods laboratory in Leeds, United Kingdom, and the Abramowicz laboratory in Brussels, Belgium) and clinicians in areas of the world where consanguinity is common. The hope in these studies appears to be that relatively large numbers of pedigrees could be found with a uniform genetic disorder. There was also the suspicion that founder mutations might simplify gene identification. However, microcephaly has proved to be very heterogeneous so far, genetically, and there has also been no evidence of ethnically related founder mutations.

Five recessive microcephaly loci have been mapped so far. The first microcephaly locus localized, termed *MCPH1*, maps to chromosome 8p22-pter [23]. *MCPH2* was subsequently mapped to 19q13.1–13.2 [24], whereas *MCPH3* and *MCPH4* map to chromosomes 9q34 and 15q, respectively [25•,26•]. Most recently a fifth locus for primary autosomal recessive microcephaly (*MCPH5*) has been mapped to chromosome 1q31 [27•,28•]. Moreover, a recessive gene that causes microhydranencephaly (in which children showed hydranencephaly associated with microcephaly) maps to chromosome 16p13.3–12.1 [29]. Many of these loci have been mapped in only one or a few pedigrees, and the clinical presentation of the patients in pedigrees that map to *MCPH1* through *5* is generally similar, notable mainly for moderate mental retardation without other significant clinical symptoms. These factors are enough to suggest that there will be significant genetic heterogeneity in autosomal recessive microcephaly.

The extent to which 'microcephaly vera' and 'microcephaly with simplified gyral pattern' represent two distinct and non-overlapping conditions is not as clear as textbooks may make it out to be, because the widespread morphological analysis of these two conditions is only now taking place. The gyral pattern is never completely normal in any form of microcephaly because of the severely reduced brain size, and so there is some uncertainty and subjectivity as to when the gyral pattern becomes defined as abnormal. MRI analysis of the microcephalic brain has revealed an increasing richness of the variety of developmental abnormalities, and further improvements in MRI imaging promise an ever improving characterization. It is therefore ultimately possible that the several microcephaly loci may eventually be characterized by distinctive radiographic features, as has occurred for lissencephaly loci [30] and for holoprosencephaly loci [4]. However, this is at present just a speculative suggestion.

Microcephaly can be part of multiorgan genetic syndromes

Microcephaly is also frequently seen in association with a variety of chromosomal abnormalities or other well-defined genetic syndromes (see Table 1). An overview of this group of 'syndromal' microcephaly has also been provided by Opitz and Holt [31]. In these cases, the characteristic patterns of involvement of other organ systems or the presence of specific dysmorphic features

often help make the diagnosis. For example, an X-linked locus that causes mental retardation, microcephaly, and variable short stature has recently been localized to Xq12-q21.31 [32,33]. Microcephaly is also reported in relation to a variety of chromosomal rearrangements and deletions, presumably reflecting abnormalities of genes that act in a dominant fashion. The brain architecture in these conditions can vary from being severely abnormal to being basically normal, and for many of these syndromes has not been completely determined.

Recent analysis of the Nijmegen breakage syndrome may represent a model for other microcephaly syndromes. In this multiorgan disorder, affected patients present with microcephaly, growth retardation, immunodeficiency, and a predisposition to cancer [11•]. The cellular phenotypes resemble that of ataxia-telangiectasia, and show a defect in DNA repair. The protein mutated in Nijmegen breakage syndrome, nibrin (encoded by *NBS1*), together with other proteins, RAD50 and MRE11, forms a complex that is important in the repair of DNA double-strand breaks [34,35]. Although it is not well understood how the defect in this complex leads to microcephaly, the apparent importance of the repair of DNA double-strand breaks in cerebral cortical neurogenesis has been shown by a study of XRCC4 engineered mutant mice [36]. XRCC4 is another protein implicated in DNA repair, and mice that are mutant for the *Xrcc4* gene show a defect in neurogenesis and excessive apoptotic cell death of postmitotic neurons. Recently, an engineered mutation in the citron kinase, which is a target molecule for Rho GTPase, also caused defective cell division, apoptosis, and severe microcephaly in mice [37••]. These results from animal studies suggest that defects in neurogenesis and excessive apoptosis may be linked, and that both mechanisms may ultimately play a role in some forms of human microcephaly.

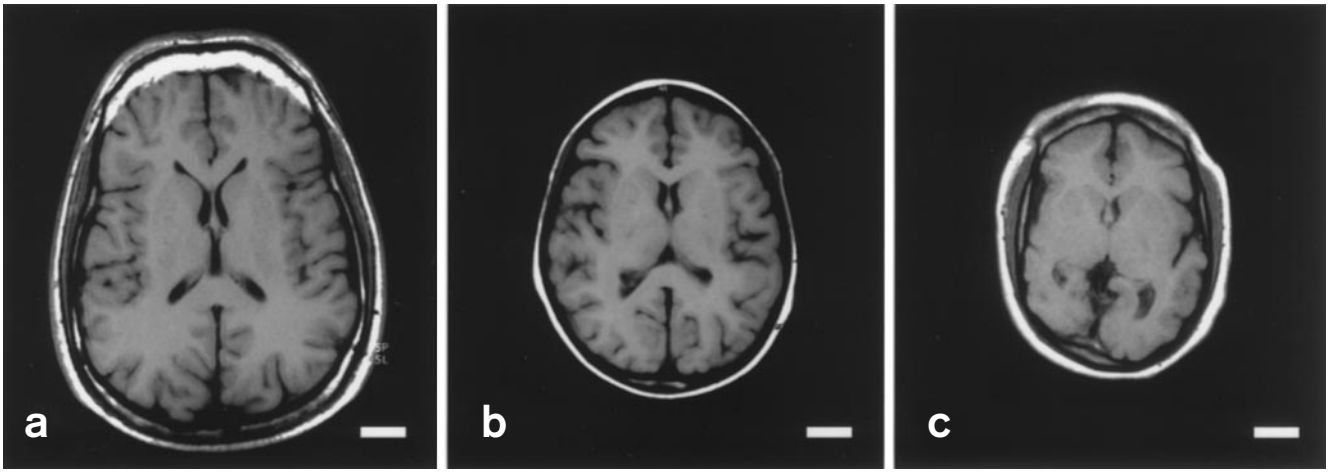
Other candidate genes for microcephaly based upon animal studies

Although no primary microcephaly genes have yet been identified in humans, a few engineered mutations in mice produce notable microcephaly, suggesting that mutations in the homologous genes in humans might cause a similar phenotype. Among these are the trisomy 16 mouse (a murine model of Down's syndrome), in which defects in cortical progenitor cells seem to be important [38•]. Also, engineered mutations in BF-1 cause a profoundly decreased size of the cortical hemispheres with severe architectural abnormalities [39]. Engineered mutations in the mouse *Tlx* gene (a homologue of the *Drosophila* gene, *tailless*) also show profound defects in rhinencephalic and limbic structures, and increased aggressiveness [40]. None of these genes maps near the known human microcephaly loci, and these engineered mutants certainly confirm the impression that the decreased size of the cerebral cortex can have many different genetic and pathogenic mechanisms.

Conclusion

On the basis of the scattered information from mouse and human studies, a few suggestions may be possible about the potential genetic causes of microcephaly. As

Figure 1. Magnetic resonance image of a normal cerebral cortex, microcephaly vera, and microcephaly with simplified gyral pattern



(a) An axial magnetic resonance imaging (MRI) scan of a normal individual, showing the normal size and architecture of the cerebral cortex. (b) An axial MRI scan (reproduced at the same relative size) of an individual with microcephaly vera. The brain is greatly reduced in size. The cerebral cortex is smaller in surface area, but shows relatively normal gyri and sulci. (c) An axial MRI (at the same relative size) from an individual with microcephaly and simplified gyral pattern. The cortex is not greatly thickened, as is characteristic of classic or type I lissencephaly, but there are relatively few preserved gyri. Scale bar = 2 cm.

no genes responsible for this condition have yet been found, the exact pathogenesis remains unclear. Although a decreased number of neurons in the cerebral cortex is considered to be primarily responsible for the smallness of the brain in many forms of genetic microcephaly, there are many potential ways in which the number of cortical neurons could be subnormal. For example, the decreased proliferation of neuronal progenitors, the decreased production of mature neurons by each neuronal progenitor, or excessive cell death of neuronal progenitors or of mature neurons may all lead to an eventual decrease in the number of neurons. One or more of these mechanisms may be involved in the pathogenesis of human genetic microcephaly, but these mechanisms will not be clear until more genes are identified.

Acknowledgements

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