Genomic Variants and Variations in Malformations of Cortical Development

Saumya S. Jamuar, MD[a,b,c,d,e],
Christopher A. Walsh, MD, PhD[b,c,d,f,*]

KEYWORDS

• Malformations of cortical development • Genomic variants • Somatic mutation
• Microcephaly • Megalencephaly • Cortical dysplasia • Lissencephaly
• Polymicrogyria

KEY POINTS

- Development of the cerebral cortex is a tightly regulated process, and disruption in any part of this process can lead to malformations of cortical development (MCDs).
- MCD can primarily be classified into abnormalities of neurogenesis, abnormalities of neuronal migration, and abnormalities of postmigrational development.
- Recent advances in genomic technology have allowed for an unprecedented expansion in the knowledge of these disorders and have elucidated molecular pathways that can serve as targets for therapeutic interventions.

Disclosure: No conflicts of interest to declare.
C.A. Walsh is supported by grants from the National Institute of Mental Health (R01MH083565 and 1RC2MH089952), the National Institute of Neurological Disorders and Stroke (R01NS032457, R01NS079277 and R01NS035129), the Simons Foundation, the Paul G. Allen Family Foundation, and the Manton Center for Orphan Disease Research. C.A. Walsh is an Investigator of the Howard Hughes Medical Institute.
[a] Department of Paediatrics, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore; [b] Division of Genetics and Genomics, Manton Center for Orphan Disease Research, Howard Hughes Medical Institute, Boston Children's Hospital, Boston, MA 02115, USA; [c] Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA; [d] Department of Neurology, Harvard Medical School, Boston, MA 02115, USA; [e] Paediatrics Academic Programme, Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857, Singapore; [f] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02138, USA
* Corresponding author. Division of Genetics and Genomics, Boston Children's Hospital, Center for Life Sciences 15062.2, 3 Blackfan Circle, Boston, MA 02115.
E-mail address: christopher.walsh@childrens.harvard.edu

Pediatr Clin N Am 62 (2015) 571–585
http://dx.doi.org/10.1016/j.pcl.2015.03.002 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

CLINICAL BACKGROUND

The development of the human cortex is a complex and tightly regulated process. During development, distinct cell types must proliferate, differentiate, migrate, and integrate to form a highly complex structure, capable of complex cognition, language, and emotion.[1] Disruptions in any of these processes lead to malformations of cortical development (MCD), which are common causes of neurodevelopmental delay and/or epilepsy.[2] Individuals presenting early can show feeding difficulties soon after birth (in some instances, in utero swallowing difficulty may present as polyhydramnios), abnormal head size (microcephaly or macrocephaly), epileptic encephalopathies, or global developmental delay. Some patients with MCD may present early with severe neurologic impairment, whereas others present with epilepsy and mild functional impairment at a later age. Individuals who present later may exhibit focal epilepsy, learning difficulty, and behavioral issues, such as attention deficit hyperactivity disorder.[3] Occasionally, a few individuals may be diagnosed only on screening, as their deficit may not be clinically apparent.

Classification systems for MCDs, first introduced in 1996 and subsequently revised in 2001, 2005, and 2012 to incorporate the improved understanding of cortical development, divide MCDs into 3 major groups, namely, malformations secondary to abnormal neuronal and glial proliferation or apoptosis, malformations due to abnormal neuronal migration, and malformations secondary to abnormal postmigrational development. This system is based on the developmental steps at which the process is first disrupted, the underlying genes and biological pathways affected, and imaging features,[2] although there is surprising overlap in the phenotypes of many genes, reflecting involvement of some genes in more than one stage of development.

Genomic variants are changes in one allele of a gene of an individual compared with a reference genome. Variants may be small (<1 kilobasepair) and include substitutions and small insertions and deletions (indels) or may be large (>1 kilobasepair) and include copy number variants (CNVs) (larger insertions or deletions) and rearrangements, such as translocation and inversion. Lastly, genomic variants also include whole chromosome numerical alterations such as aneuploidy. Although many variants are not associated with disease (and instead are referred to as benign variants), certain deleterious variants that alter the function of a gene may cause disease, representing disease-causing mutations. Human genetic diseases have traditionally been thought to reflect either inherited or de novo (spontaneous) variants. These mutations are present in all the cells of the affected individual and can be detected in any cell of the body, including readily available peripheral blood, and are referred to as germline mutations. Somatic mutation, on the other hand, is a postzygotic mutational event that leads to an individual having 2 or more populations of cells with distinct genotypes, despite developing from a single fertilized egg[4,5]; somatic mutations thus represent a subset of the larger category of de novo mutations.

This review focuses on the recent advances in understanding the genetics of MCDs, including recent updates on the role of somatic mutations in MCDs. Large-scale sequencing projects have led to an exponential increase in the knowledge of the genes associated with MCDs, and the authors address some of these recent discoveries. Although most MCDs are caused by genomic variants, a proportion of MCDs (such as schizencephaly) are associated with nongenomic mechanisms and may be secondary to environmental causes.

EMBRYOLOGY OF CEREBRAL CORTICAL DEVELOPMENT

The normal human cortex is composed of 6 distinct histologic layers. Its development begins from neuroepithelial progenitors lining the lateral ventricles, which divide to