Published in final edited form as:

Ann N Y Acad Sci. 2010 December ; 1214: 156–167. doi:10.1111/j.1749-6632.2010.05819.x.

Genetic regulation of human brain development: lessons from Mendelian diseases

Tracy J. Dixon-Salazar and Joseph G. Gleeson

Departments of Neurosciences and Pediatrics, Institute for Genomic Medicine, Howard Hughes Medical Institute, University of California, San Diego, La Jolla, California

Abstract

One of the fundamental goals in human genetics is to link gene function to phenotype, yet the function of the majority of the genes in the human body is still poorly understood. This is especially true for the developing human brain. The study of human phenotypes that result from inherited, mutated alleles is the most direct evidence for the requirement of a gene in human physiology. Thus, the study of Mendelian central nervous system(CNS) diseases can be an extremely powerful approach to elucidate such phenotypic/genotypic links and to increase our understanding of the key components required for development of the human brain. In this review, we highlight examples of how the study of inherited neurodevelopmental disorders contributes to our knowledge of both the “normal” and diseased human brain, as well as elaborate on the future of this type of research. Mendelian disease research has been, and will continue to be, key to understanding the molecular mechanisms that underlie human brain function, and will ultimately form a basis for the design of intelligent, mechanism-specific treatments for nervous system disorders.

Keywords

genetics; inherit; brain; development; CNS; disease; Mendelian

Introduction

The human cerebral cortex is made up of ~20 billion neurons, each of which makes an average of 7,000 synaptic contacts.¹ To further add to this complexity, each neuron contains 46 chromosomes, made up of ~3 billion nucleotides, and up to 25,000 individual genes are contained in one set of 23 chromosomes.² These features illustrate the potential for complex genetic regulation of the human brain and despite extensive research, much of how the brain develops and functions remains unknown. Furthermore, disorders involving the brain are among the most difficult to treat. Only with a better understanding of the nervous system will we be able to improve the quality of life of those who suffer from these disorders.

Address for correspondence: Joseph G. Gleeson, M.D., University of California, San Diego, 9500 Gilman Drive 0665, La Jolla, CA 92093-0665. jogleeson@ucsd.edu.

Conflicts of interest

The authors declare no conflicts of interest.

The identification of a disease-causing gene in families with inherited brain disorders is one of the most useful methods for gaining insight into human brain development, function, and pathology. Unlike other approaches, the identification of causative gene mutations provides three crucial capabilities: (1) the ability to explore the cause of disease directly in humans; (2) the ability to determine genetic disease risk, especially as it relates to penetrance (100% for homozygous null alleles), with a high level of certainty; and (3) the ability to create appropriate, translationally relevant cell-based and animal models for studying the mechanisms that underlie a given genetic disorder and the normal brain process it disrupts. Few other approaches allow for such direct insight into the human brain and identifying genes in families with inherited CNS disorders has led to a critical understanding of the genetic control of human brain development and function.

The last 10 years has seen the advent of better technology and better diagnostic capabilities, and subsequently the rate of identification of genes in Mendelian CNS disorders has rapidly increased.³ We know that genetic disruption of specific steps in brain development at critical time points can lead to characteristic morphological or functional anomalies, and with greater frequency brain disorders are being classified with regard to the time-dependent process they disrupt. Some developmental examples of this include disorders of cortical neurogenesis (e.g., primary microcephaly [MCPH]), disorders of neuron migration (e.g., classical lissencephaly [LIS]), disorders of axon guidance (e.g., horizontal gaze palsy with progressive scoliosis [HGPPS]), and disorders of circuit formation and function (e.g., epilepsy).^{4–7} In this review, we will discuss how Mendelian genetic studies have led to crucial insight into the pathology of these four disease examples. Further, we will explore what these findings tell us about the regulation of human brain size, cortical development, neuronal wiring, and neuronal networks, respectively. Finally, we will describe the role Mendelian genetic research is likely to play in the next 10 years, with an emphasis on whole genome sequencing and personalized medicine.

Cortical development

During development, neurons are born in distinct regions of the brain and then migrate to their specific laminar positions in a stereotyped spatiotemporal pattern. In the mammalian cerebral cortex, this process has been well characterized and the genetic mechanisms that underlie cortical development have been extensively studied.^{7–9} Using a simplified model, neuronal development can be categorized into four main processes: neurogenesis, neuron migration, axon outgrowth, and circuit formation (Fig. 1). Anatomically, neural progenitors located in the ventricular zone undergo mitosis to give rise to cortical neurons. These neurons then migrate into the cortical plate where they ultimately organize into the six-layered cortex characteristic of the mammalian brain. Newborn neurons send out axons and other neurites and these axons navigate the brain milieu until locating their appropriate synaptic targets. These processes are repeated in progression by each developing neuron and, via a series of elaborate molecular and cellular mechanisms, the neurons wire themselves together to form functional neural circuits.^{9,10}

Many causative genes have been identified in disorders of cortical development and the study of these genes in model systems has aided in our understanding of signaling pathways

that underlie these diseases. In fact, the study of human gene mutations has formed the basis for many discoveries into development of the mammalian cortex. We next discuss four disease examples that exemplify these points: (1) primary microcephaly—a disorder of neurogenesis, (2) classical lissencephaly—a disorder of neuron migration, (3) horizontal gaze palsy with progressive scoliosis—a disorder of axon outgrowth, and (4) primary epilepsy—a disorder of circuit formation and function.

Primary microcephaly

MCPH is a neurodevelopmental disorder characterized by significantly reduced cranial circumference at birth and intellectual disability.^{11–13} MCPH includes a broad spectrum of phenotypes with numerous genetic and environmental causes; however, autosomal recessive MCPH (AR-MCPH) is a distinct clinical entity. AR-MCPH is associated with normal brain architecture and nonprogressive intellectual disability in an otherwise healthy person (Fig. 2).^{12,14} MRI scans of AR-MCPH patients reveal a reduced brain volume but normal brain organization, suggesting that MCPH is not a disorder of neuron migration or neuronal organization, but is rather primarily a disorder of neuronal numbers.^{12,15}

Using genetic mapping techniques in consanguineous families with AR-MCPH, at least seven MCPH-causing loci^{16–23} have been characterized and five genes have been identified thus far^{18,24–26} (Table 1). The five AR-MCPH genes, *MCPH1*, *ASPM*, *CDK5RAP2*, *CENPJ*, and *STIL*, encode proteins that are expressed in cortical neuroprogenitor cells and, interestingly, each colocalizes with the mitotic spindle apparatus at some point during cortical neurogenesis (Fig. 3). *MCPH1* encodes the microcephalin protein, which is a component of the DNA-damage response pathway²⁷ and cell lines from MCPH patient fibroblasts exhibit defective cell cycle arrest, which is predicted to reduce the total number of neural progenitors.^{26,28} The remaining MCPH genes, *ASPM*, *CDK5RAP2*, *CENPJ*, and *STIL*, encode centrosomal associated proteins that are predicted to regulate mitotic spindle function.^{24–26} The coordinated steps of cortical development rely on numerous factors including pattern formation, cell proliferation, cell survival, and cell growth,^{29,30} but studies of the MCPH genes reveal that this disorder is primarily due to a defect in one step—neuronal proliferation. Although there is currently no treatment for MCPH, the identification of a causal mutation now allows for prenatal testing for families. Importantly, the identification of MCPH-causing genes now provides a framework for us to expand our understanding of brain growth. These studies will lead to the development of a battery of diagnostic genetic tests, which can ultimately be used for prediction of clinical course and outcome, and studies of the molecular mechanisms that underlie microcephaly will ultimately form the basis for future therapies.

Although studies reveal that mitotic spindle regulation is important for understanding the pathogenic mechanisms of MCPH, they also may give us information about mammalian brain evolution. During human evolution, brain size, and specifically cortical surface area, has dramatically increased. Given that MCPH is a disorder of brain size, the study of the MCPH-causing genes across evolution may lead to insight into the genetic regulation of brain volume across species. Indeed, studies in monkeys and humans reveal that the *MCPH1* and *ASPM* genes may have experienced positive Darwinian selection over time.^{12,15,31–33}

Although much work is still needed to prove the extent of this selective pressure on the MCPH genes, these studies serve as an important example of how Mendelian disease genes allow us to explore other areas of brain development beyond pathogenic mechanisms.

Classical lissencephaly

LIS is a neurodevelopmental disorder characterized by the lack of cortical folds and an abnormally thick cortex (Fig. 4). Children born with LIS suffer from severe epilepsy, mental retardation, and often die in early life.^{34–37} Histopathology reveals a four-layer cortical structure rather than the six layers typically seen, and most of the neurons in the abnormal cortex are found in the deeper layers.³⁸ Cortical lamination is a highly orchestrated process that relies on numerous factors;⁷ however, the aggregation of neurons in the deeper layers—close to where they are born—suggests that LIS is a disorder of neuronal movement.

Genetic studies reveal that lissencephaly is a multigenic disorder that can be inherited in dominant, recessive, or X-linked patterns (Table 1). At least six genes have been implicated in causing the lissencephalic phenotype,^{39–46} three of which underlie LIS (lissencephaly without any other cerebral features). During development, committed neurons in the subventricular zone extend a leading process toward the cortical plate to which they ultimately will migrate. After this extension, a complex process of nucleus translocation occurs followed by retraction of the trailing edge of the migrating neuron.^{7,47} The three LIS genes, *PAFAH1B1* (*LIS1*), *DCX*, and *TUBA1A*, encode microtubule or microtubule associated proteins and each is localized to the leading process and cell body of migrating cortical neurons^{7,48,49} (Fig. 5). *LIS1* is a component of the cytoplasmic microtubule motor complex dynein, and studies reveal that *LIS1* may be important for translocation of the nucleus during neuron migration.^{47,50–52} *DCX* also binds to microtubules and studies show that loss of *DCX* leads to increased microtubule dynamics.^{53,54} Further, *TUBA1A* encodes a family of alpha tubulins which together with beta tubulin form the primary structure of cytoskeletal microtubules. *TUBA1A* is highly expressed during fetal brain development and disruption of this gene lead to defects in cortical lamination in animal models.^{55,56} The coordinated progression of neuron migration involves many steps, including the extension of radial glia into the cortical plate to provide a guide for neurons to migrate along, the complex organization and reorganization of the cytoskeleton as the neuron migrates, and the presence of internal and external guidance cues by which neurons navigate.^{7,9,47} The study of the LIS genes reveals that LIS is primarily a disorder of cytoskeletal reorganization during neuron migration. Future studies will provide a basis for the treatment, or even prevention, of this severe childhood disorder.

To this end, preliminary studies in animal models reveal that it might be possible to move neurons that fail to migrate properly back into place. As proof of this concept, researchers used short hairpin RNA (shRNA) technology to knockdown *DCX* expression in the developing rat cortex.^{49,57} In addition to injecting the *DCX* knockdown shRNA, a drug-inducible form of *DCX* was also injected, thereby allowing for reexpression of the *DCX* gene to occur when the drug was administered. Loss of *DCX* lead to defects in cortical neuron migration, but when *DCX* was reexpressed early postnatally, many of the delayed neurons resumed migration and ultimately reached their correct targets in the cortical plate.

Although this type of treatment is far from its translation to human patients, it does provide evidence that further study of the LIS genes may lead to new treatment and prevention strategies for this disorder.

Horizontal gaze palsy with progressive scoliosis

HGPPS is an autosomal recessive disorder characterized by absence of horizontal eye movements from birth (Fig. 6A) and progressive curvature of the spine starting in the first decade of life (Fig. 6B).^{58,59} Imaging studies in HGPPS patients reveal an absence of axons that cross the midline in the pons and medulla oblongata (Fig. 6C),^{60,61} and functional MRI studies show that activation of the primary motor cortex occurs in an atypical ipsilateral, rather than contralateral, fashion in these patients.⁶⁰ These clinical findings reveal that HGPPS results from failure of axons to decussate during brain development, and more generally suggest that HGPPS is a disorder of axon outgrowth and guidance.

Using genetic mapping techniques in consanguineous families with HGPPS, mutations in the *ROBO3* gene were identified^{61,62} (Table 1). During development, motor and sensory cortical neurons extend axons that will cross the midline in the hindbrain and travel to their ultimate destination to form synapses with their molecular targets.^{5,63} *ROBO3* is a member of the *roundabout* gene family, which is well known from animal studies to regulate neurite outgrowth, growth cone guidance, and axon fasciculation.^{64,65} Animal models reveal that *ROBO3* encodes a protein that is expressed on the surface of migrating growth cones and encodes a receptor for the chemorepellant molecule SLIT. Binding of the SLIT ligand to the *ROBO3* protein generates an axon repulsion signal and this, in turn, regulates axon growth and turning at or near the midline.^{5,66} Axon outgrowth is a highly choreographed process that involves numerous steps including growth cone formation, axon guidance and target acquisition. The combined clinical and genetic studies of HGPPS confirm that this disorder primarily results in a failure of axon guidance during hindbrain midline crossing.

In the example of HGPPS, the identification of *ROBO3* gene mutations came after extensive characterization of the *ROBO* gene family in animal models. This example confirms two critical assumptions: (1) genetic homology between species can be effectively used to identify disease-causing genes in Mendelian disorders, and (2) the study of development (i.e., midline crossing) in animal models is relevant for understanding the critical determinants of brain development in humans. Although research on how *ROBO3* mutations lead to the specific HGPPS phenotype is still in its early stages, the study of this genetic disorder, and others such as the recently identified Congenital Mirror Movement Disorder associated with *DCC* mutations,⁶⁷ will undoubtedly afford us a better understanding of axon outgrowth in human brain development.

Primary epilepsy

The epilepsies are an extremely common group of brain disorders characterized by recurrent, unprovoked seizures, which manifest phenotypically as changes in motor, sensory, or cognitive function.⁴ Primary epilepsy exists when seizures are not the result of a known insult (such as a brain malformation, neurodegeneration, or trauma), but rather seizures

themselves are the major phenotype. Our understanding of human primary epilepsy was significantly accelerated by the identification of epilepsy-causing genes in large families with autosomal dominantly inherited forms of the disorder (this review will focus only on dominant primary epilepsies). Many genes are now known to cause heritable primary epilepsy (Table 1).^{68–81} Although each of these genes causes different types of seizures that have variable ages of onset,⁸² the collective data provide compelling evidence that seizures are disorders of neural circuit formation and function.⁸³

During development, axonal projections form synapses with their appropriate targets and this ultimately leads to a series of interconnected neural networks in the brain and body.⁶³ Communication between neurons, and groups of neurons, depends primarily on the activity of transmembrane ion channels and to date mutations in over a dozen different ion channels, or their subunits, have been shown to underlie inherited primary epilepsy.^{68–81} The genes identified include eight voltage-gated ion channels which are key for action potential generation and neuronal excitability and five ligand-gated ion channels which regulate synaptic transmission (Fig. 7). The coordinated steps of circuit formation and function rely on numerous factors including synapse formation of excitatory and inhibitory neurons, early experience-independent neuronal activity and later experience-dependent neuronal activity.⁸⁴ Although the repertoire of molecules involved in circuit formation has not been fully characterized, the study of the epilepsy-causing genes reveals that ion channel dysfunction is a major cause of seizures.

Unlike MCPH, LIS, or HGPPS, the pathogenic mechanisms underlying the connection between ion channel genes and epilepsy are poorly understood. In fact, the many cellular and molecular mechanisms that underlie circuit formation are only just now being unraveled. Furthermore, given that neural circuits display both intrinsic and extrinsic activity-dependent plasticity,⁸⁵ epilepsy is not a static disorder. Each abnormal burst of electrical activity has the potential to structurally and functionally change the circuit in ways that can both help or hinder the organism.^{86,87} Therefore, the line between the causes and consequences of epilepsy are infinitely blurred. With the identification of genes that underlie Mendelian forms of epilepsy, our understanding of this disorder has been catapulted to new levels. Future studies of the role each of these genes plays in synaptic development will unquestionably advance our understanding of circuit formation in the brain and will have immediate applications towards epilepsy treatment.

Although there is no cure for epilepsy, the immediate benefits of identifying epilepsy-causing genes are many: (1) allowing for early and accurate diagnosis, (2) permitting research into which treatments improve or worsen seizures in a specific genetic epilepsy, (3) offering the possibility of genetic counseling to those who are carriers of the disease gene, (4) allowing for the creation of novel, gene-specific therapeutics, and (5) allowing for the generation of translationally relevant model systems to test potential therapies.⁸⁸ Furthermore, understanding the monogenic forms of epilepsy may ultimately help us understand the more complex forms of epilepsy that exist in the broader population.

In summary, the identification of genes in Mendelian brain disorders such as MCPH, LIS, HGPPS, and epilepsy has led to a greater knowledge of the genetic machinery that

underlies brain development. These studies provide direct insight into the formation and function of the human brain and are beginning to form the basis of intelligent treatment design for these devastating disorders of childhood.

Future directions

The next 10 years of Mendelian gene research look very promising. Although many genes have been identified in inherited disorders, many more remain to be discovered, as evidenced by the numerous monogenic disorders in which the causative gene remains elusive. The identification of disease-causing genes once relied solely upon the study of large, often inbred, families containing multiple affects with the disease phenotype. Linkage analysis performed on these families determined regions of the genome that were shared by the affected individuals and this, in turn, led to the direct sequencing of candidate genes in the regions of interest.⁸⁹ With the ever dropping costs of “whole exome” and “whole genome” sequencing,⁹⁰ the identification of inherited disease-causing genes will be rapidly accelerated in the coming years. Importantly, these techniques do not require the use of large families, but instead allow for disease gene identification in much smaller families and in patients with mutations that arise *de novo* in known Mendelian disease genes. Indeed, numerous gene mutations underlying Mendelian diseases have already been identified using these “next generation” sequencing techniques.^{91–98}

At some point, whole genome sequencing will ultimately translate to clinical practice, and the concept of personalized genomic medicine is on the not-so-distant horizon. Genome sequencing in patients potentially offers many benefits, including (1) the rapid diagnosis of genetic disorders, especially for those mutations that arise *de novo*; (2) the ability to determine carrier status and provide genetic counseling for Mendelian disorders of significant penetrance; and (3) the ability to determine which therapeutics are useful or harmful for a given genetic disorder, as well as allow for the design of new, gene-specific therapeutic targets. Whole genome sequencing in patients will also lead to greater scientific discovery. Specifically, we will be able to further our understanding of how genotypes regulate human phenotypes. Furthermore, we will be able to catalog human variations across many populations and begin to make sense out of the many Genome Wide Association Studies (GWAS) that targeted only a small fraction of the genome in an effort to blur the boundaries between Mendelian and complex disease.^{99,100} Moreover, we will be able to determine mutation load in a given patient and disease in an effort to understand how defects in the same gene can lead to such phenotypic diversity. And, we will be able to more accurately determine the penetrance of specific gene mutations across populations, which will lead to better genetic counseling and a better understanding of the genes involved in complex disease and complex traits.

Although no single scientific approach can answer every question about the human brain and disease, Mendelian genetics has its place in future research. The study of inherited diseases provides a relatively simple, yet profoundly powerful, method for unraveling the mysteries of human genetic diseases, and study of these disorders will continue to expand our knowledge of brain development and function. It will be important to determine which genetic characteristics are unique to the various disorders and this, in turn, will elevate our

understanding of how genetic mutations lead to a disease. Over the next several decades, the greatest challenges in genetic research will not be in the identification of disease-associated genes, but will rather be in defining the molecular mechanisms that explain how genetic mutations confer disease risk and phenotypic expression. By studying human Mendelian CNS disorders, we will be able to tackle these problems in their “simplest” form, and this will eventually lead to important discoveries into the genetic mechanisms that govern the formation and function of the complex human brain.

References

1. Drachman DA. Do we have brain to spare? *Neurology*. 2005; 64:2004–2005. [PubMed: 15985565]
2. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature*. 2004; 431:931–945. [PubMed: 15496913]
3. Peltonen L, et al. Lessons from studying monogenic disease for common disease. *Hum. Mol. Genet.* 2006; 15(Spec. No. 1):R67–R74. [PubMed: 16651371]
4. Engel, J.; Pedley, TA. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven; 1998.
5. Engle EC. Human genetic disorders of axon guidance. *Cold Spring Harb. Perspect. Biol.* 2010; 2:a001784–a001802. [PubMed: 20300212]
6. Guerrini R, Dobyns WB, Barkovich AJ. Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options. *Trends Neurosci.* 2008; 31:154–162. [PubMed: 18262290]
7. Gupta A, Tsai LH, Wynshaw-Boris A. Life is a journey: a genetic look at neocortical development. *Nat. Rev. Genet.* 2002; 3:342–355. [PubMed: 11988760]
8. Diaz AL, Gleeson JG. Themolecular and genetic mechanisms of neocortex development. *Clin. Perinatol.* 2009; 36:503–512. [PubMed: 19732610]
9. Rakic P, et al. Decision by division: making cortical maps. *Trends Neurosci.* 2009; 32:291–301. [PubMed: 19380167]
10. Borello U, Pierani A. Patterning the cerebral cortex: traveling with morphogens. *Curr. Opin. Genet. Dev.* 2010; 4:408–415. [PubMed: 20542680]
11. Aicardi, J. *Diseases of the Nervous System in Childhood*. London: Mac Keith Press; 1998.
12. Cox J, et al. What primary microcephaly can tell us about brain growth. *Trends Mol. Med.* 2006; 12:358–366. [PubMed: 16829198]
13. Woods CG. Human microcephaly. *Curr. Opin. Neurobiol.* 2004; 14:112–117. [PubMed: 15018946]
14. Kaindl AM, et al. Many roads lead to primary autosomal recessive microcephaly. *Prog. Neurobiol.* 2010; 90:363–383. [PubMed: 19931588]
15. Thornton GK, Woods CG. Primary microcephaly: do all roads lead to Rome? *Trends Genet.* 2009; 25:501–510. [PubMed: 19850369]
16. Jackson AP, et al. Primary autosomal recessive microcephaly (MCPH1) maps to chromosome 8p22-pter. *Am. J. Hum. Genet.* 1998; 63:541–546. [PubMed: 9683597]
17. Jamieson CR, Govaerts C, Abramowicz MJ. Primary autosomal recessive microcephaly: homozygosity mapping of MCPH4 to chromosome 15. *Am. J. Hum. Genet.* 1999; 65:1465–1469. [PubMed: 10521316]
18. Kumar A, et al. Mutations in STIL, encoding a pericentriolar and centrosomal protein, cause primary microcephaly. *Am. J. Hum. Genet.* 2009; 84:286–290. [PubMed: 19215732]
19. Leal GF, et al. A novel locus for autosomal recessive primary microcephaly (MCPH6) maps to 13q12.2. *J. Med. Genet.* 2003; 40:540–542. [PubMed: 12843329]
20. Moynihan L, et al. A third novel locus for primary autosomal recessive microcephaly maps to chromosome 9q34. *Am. J. Hum. Genet.* 2000; 66:724–727. [PubMed: 10677332]
21. Pattison L, et al. A fifth locus for primary autosomal recessive microcephaly maps to chromosome 1q31. *Am. J. Hum. Genet.* 2000; 67:1578–1580. [PubMed: 11078481]

22. Roberts E, et al. Autosomal recessive primary microcephaly: an analysis of locus heterogeneity and phenotypic variation. *J. Med. Genet.* 2002; 39:718–721. [PubMed: 12362027]
23. Roberts E, et al. The second locus for autosomal recessive primary microcephaly (MCPH2) maps to chromosome 19q13.1–13.2. *Eur. J. Hum. Genet.* 1999; 7:815–820. [PubMed: 10573015]
24. Bond J, et al. ASPM is a major determinant of cerebral cortical size. *Nat. Genet.* 2002; 32:316–320. [PubMed: 12355089]
25. Bond J, et al. A centrosomal mechanism involving CDK5RAP2 and CENPJ controls brain size. *Nat. Genet.* 2005; 37:353–355. [PubMed: 15793586]
26. Jackson AP, et al. Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am. J. Hum. Genet.* 2002; 71:136–142. [PubMed: 12046007]
27. Xu X, Lee J, Stern DF. Microcephalin is a DNA damage response protein involved in regulation of CHK1 and BRCA1. *J. Biol. Chem.* 2004; 279:34091–34094. [PubMed: 15220350]
28. Alderton GK, et al. Regulation of mitotic entry by microcephalin and its overlap with ATR signalling. *Nat. Cell Biol.* 2006; 8:725–733. [PubMed: 16783362]
29. Gotz M, Huttner WB. The cell biology of neurogenesis. *Nat. Rev. Mol. Cell Biol.* 2005; 6:777–788. [PubMed: 16314867]
30. Fish JL, et al. Making bigger brains-the evolution of neural-progenitor-cell division. *J. Cell Sci.* 2008; 121:2783–2793. [PubMed: 18716282]
31. Ali F, Meier R. Positive selection in ASPM is correlated with cerebral cortex evolution across primates but not with whole-brain size. *Mol. Biol. Evol.* 2008; 25:2247–2250. [PubMed: 18718919]
32. Evans PD, Vallender EJ, Lahn BT. Molecular evolution of the brain size regulator genes CDK5RAP2 and CENPJ. *Gene.* 2006; 375:75–79. [PubMed: 16631324]
33. Woods CG, Bond J, Enard W. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings. *Am. J. Hum. Genet.* 2005; 76:717–728. [PubMed: 15806441]
34. Barkovich AJ, Koch TK, Carrol CL. The spectrum of lissencephaly: report of ten patients analyzed by magnetic resonance imaging. *Ann. Neurol.* 1991; 30:139–146. [PubMed: 1897907]
35. Dobyns WB, et al. X-linked malformations of neuronal migration. *Neurology.* 1996; 47:331–339. [PubMed: 8757001]
36. Dobyns WB, et al. Causal heterogeneity in isolated lissencephaly. *Neurology.* 1992; 42:1375–1388. [PubMed: 1620349]
37. Dobyns WB, Truwit CL. Lissencephaly and other malformations of cortical development: 1995 update. *Neuropediatrics.* 1995; 26:132–147. [PubMed: 7477752]
38. Gleeson JG, Walsh CA. Neuronal migration disorders: from genetic diseases to developmental mechanisms. *Trends Neurosci.* 2000; 23:352–359. [PubMed: 10906798]
39. Zaki M, et al. Identification of a novel recessive RELN mutation using a homozygous balanced reciprocal translocation. *Am. J. Med. Genet. A.* 2007; 143A:939–944. [PubMed: 17431900]
40. Reiner O, et al. Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. *Nature.* 1993; 364:717–721. [PubMed: 8355785]
41. Poirier K, et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). *Hum. Mutat.* 2007; 28:1055–1064. [PubMed: 17584854]
42. Pilz DT, et al. LIS1 and XLIS (DCX) mutations cause most classical lissencephaly, but different patterns of malformation. *Hum. Mol. Genet.* 1998; 7:2029–2037. [PubMed: 9817918]
43. Lo Nigro C, et al. Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. *Hum. Mol. Genet.* 1997; 6:157–164. [PubMed: 9063735]
44. Kitamura K, et al. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat. Genet.* 2002; 32:359–369. [PubMed: 12379852]

45. Gleeson JG, et al. Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. *Cell*. 1998; 92:63–72. [PubMed: 9489700]
46. Boycott KM, et al. Homozygous deletion of the very low density lipoprotein receptor gene causes autosomal recessive cerebellar hypoplasia with cerebral gyral simplification. *Am. J. Hum. Genet.* 2005; 77:477–483. [PubMed: 16080122]
47. Bielas SL, Gleeson JG. Cytoskeletal-associated proteins in the migration of cortical neurons. *J. Neurobiol.* 2004; 58:149–159. [PubMed: 14598377]
48. Gleeson JG. Neuronal migration disorders. *Ment. Retard. Dev. Disabil. Res. Rev.* 2001; 7:167–171. [PubMed: 11553932]
49. Kerjan G, Gleeson JG. Moving neurons back into place. *Nat. Med.* 2009; 15:17–18. [PubMed: 19129774]
50. Hatten, ME. LIS-less neurons don't even make it to the starting gate. *J. Cell Biol.* 2005; 170:867–871. [PubMed: 16157697]
51. Kerjan G, Gleeson JG. Genetic mechanisms underlying abnormal neuronal migration in classical lissencephaly. *Trends Genet.* 2007; 23:623–630. [PubMed: 17997185]
52. Tsai JW, et al. LIS1 RNA interference blocks neural stem cell division, morphogenesis, and motility at multiple stages. *J. Cell Biol.* 2005; 170:935–945. [PubMed: 16144905]
53. Koizumi H, et al. Doublecortin maintains bipolar shape and nuclear translocation during migration in the adult forebrain. *Nat. Neurosci.* 2006; 9:779–786. [PubMed: 16699506]
54. Tanaka T, et al. Lis1 and doublecortin function with dynein to mediate coupling of the nucleus to the centrosome in neuronal migration. *J. Cell Biol.* 2004; 165:709–721. [PubMed: 15173193]
55. Jaglin XH, Chelly J. Tubulin-related cortical dysgeneses: microtubule dysfunction underlying neuronal migration defects. *Trends Genet.* 2009; 25:555–566. [PubMed: 19864038]
56. Kumar RA, et al. TUBA1A mutations cause wide spectrum lissencephaly (smooth brain) and suggest that multiple neuronal migration pathways converge on alpha tubulins. *Hum. Mol. Genet.* 2010; 19:2817–2827. [PubMed: 20466733]
57. Manent JB, et al. Dcx reexpression reduces subcortical band heterotopia and seizure threshold in an animal model of neuronal migration disorder. *Nat. Med.* 2009; 15:84–90. [PubMed: 19098909]
58. Dretakis EK, Kondoyannis PN. Congenital scoliosis associated with encephalopathy in five children of two families. *J. Bone Joint Surg. Am.* 1974; 56:1747–1750. [PubMed: 4434049]
59. Sharpe JA, Silversides JL, Blair RD. Familial paralysis of horizontal gaze. Associated with pendular nystagmus, progressive scoliosis, and facial contraction with myokymia. *Neurology.* 1975; 25:1035–1040. [PubMed: 1237821]
60. Haller S, Wetzel SG, Lutschg J. Functional MRI, DTI and neurophysiology in horizontal gaze palsy with progressive scoliosis. *Neuroradiology.* 2008; 50:453–459. [PubMed: 18214457]
61. Jen JC, et al. Mutations in a human ROBO gene disrupt hindbrain axon pathway crossing and morphogenesis. *Science.* 2004; 304:1509–1513. [PubMed: 15105459]
62. Chan WM, et al. Horizontal gaze palsy with progressive scoliosis can result from compound heterozygous mutations in ROBO3. *J. Med. Genet.* 2006; 43:e11–e14. [PubMed: 16525029]
63. Sanes JR, Yamagata M. Many paths to synaptic specificity. *Annu. Rev. Cell Dev. Biol.* 2009; 25:161–195. [PubMed: 19575668]
64. Marillat V, et al. The slit receptor Rig-1/Robo3 controls midline crossing by hindbrain precerebellar neurons and axons. *Neuron.* 2004; 43:69–79. [PubMed: 15233918]
65. Sabatier C, et al. The divergent Robo family protein rig-1/Robo3 is a negative regulator of slit responsiveness required for midline crossing by commissural axons. *Cell.* 2004; 117:157–169. [PubMed: 15084255]
66. Chen Z, et al. Alternative splicing of the Robo3 axon guidance receptor governs the midline switch from attraction to repulsion. *Neuron.* 2008; 58:325–332. [PubMed: 18466743]
67. Srour M, et al. Mutations in DCC cause congenital mirror movements. *Science.* 2010; 328:592. [PubMed: 20431009]

68. Aridon P, et al. Increased sensitivity of the neuronal nicotinic receptor alpha 2 subunit causes familial epilepsy with nocturnal wandering and ictal fear. *Am. J. Hum. Genet.* 2006; 79:342–350. [PubMed: 16826524]
69. Baulac S, et al. First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. *Nat. Genet.* 2001; 28:46–48. [PubMed: 11326274]
70. Biervert C, et al. A potassium channel mutation in neonatal human epilepsy. *Science.* 1998; 279:403–406. [PubMed: 9430594]
71. Charlier C, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat. Genet.* 1998; 18:53–55. [PubMed: 9425900]
72. Cossette P, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat. Genet.* 2002; 31:184–189. [PubMed: 11992121]
73. De Fusco M, et al. The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. *Nat. Genet.* 2000; 26:275–276. [PubMed: 11062464]
74. Du W, et al. Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. *Nat. Genet.* 2005; 37:733–738. [PubMed: 15937479]
75. Escayg A, et al. Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2. *Nat. Genet.* 2000; 24:343–345. [PubMed: 10742094]
76. Heron SE, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. *Lancet.* 2002; 360:851–852. [PubMed: 12243921]
77. Jouvenceau A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet.* 2001; 358:801–807. [PubMed: 11564488]
78. Singh NA, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat. Genet.* 1998; 18:25–29. [PubMed: 9425895]
79. Steinlein OK, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.* 1995; 11:201–203. [PubMed: 7550350]
80. Wallace RH, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na⁺-channel beta1 subunit gene SCN1B. *Nat. Genet.* 1998; 19:366–370. [PubMed: 9697698]
81. Zuberi SM, et al. A novel mutation in the human voltage-gated potassium channel gene (Kv1.1) associates with episodic ataxia type 1 and sometimes with partial epilepsy. *Brain.* 1999; 122(Pt. 5): 817–825. [PubMed: 10355668]
82. Ottman R, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. *Epilepsia.* 2010; 51:655–670. [PubMed: 20100225]
83. Steinlein OK. Genetic mechanisms that underlie epilepsy. *Nat. Rev. Neurosci.* 2004; 5:400–408. [PubMed: 15100722]
84. Kullmann DM. Neurological channelopathies. *Annu. Rev. Neurosci.* 2010; 33:151–172. [PubMed: 20331364]
85. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron.* 2004; 44:5–21. [PubMed: 15450156]
86. Sayin U, Sutula TP, Stafstrom CE. Seizures in the developing brain cause adverse long-term effects on spatial learning and anxiety. *Epilepsia.* 2004; 45:1539–1548. [PubMed: 15571512]
87. Sutula TP, Hagen J, Pitkanen A. Do epileptic seizures damage the brain? *Curr. Opin. Neurol.* 2003; 16:189–195. [PubMed: 12644748]
88. Mullen SA, Scheffer IE. Translational research in epilepsy genetics: sodium channels in man to interneuronopathy in mouse. *Arch. Neurol.* 2009; 66:21–26. [PubMed: 19139296]
89. Dawn Teare M, Barrett JH. Genetic linkage studies. *Lancet.* 2005; 366:1036–1044. [PubMed: 16168786]
90. Bonetta L. Whole-genome sequencing breaks the cost barrier. *Cell.* 2010; 141:917–919. [PubMed: 20550926]
91. Choi M, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc. Natl. Acad. Sci. USA.* 2009; 106:19096–19101. [PubMed: 19861545]
92. Hoischen A, et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. *Nat. Genet.* 2010; 42:483–485. [PubMed: 20436468]

93. Lupski JR, et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. *N. Engl. J. Med.* 2010; 362:1181–1191. [PubMed: 20220177]
94. Ng SB, et al. Exome sequencing identifies the cause of a Mendelian disorder. *Nat. Genet.* 2010; 42:30–35. [PubMed: 19915526]
95. Nikopoulos K, et al. Next-generation sequencing of a 40 Mb linkage interval reveals TSPAN12 mutations in patients with familial exudative vitreoretinopathy. *Am. J. Hum. Genet.* 2010; 86:240–247. [PubMed: 20159111]
96. Reversade B, et al. Mutations in PYCR1 cause cutis laxa with progeroid features. *Nat. Genet.* 2009; 41:1016–1021. [PubMed: 19648921]
97. Roach JC, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science.* 2010; 328:636–639. [PubMed: 20220176]
98. Volpi L, et al. Targeted next-generation sequencing appoints c16orf57 as clericuzio-type poikiloderma with neutropenia gene. *Am. J. Hum. Genet.* 2010; 86:72–76. [PubMed: 20004881]
99. Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. *Nat. Rev. Genet.* 2010; 11:415–425. [PubMed: 20479773]
100. Manolio TA, et al. Finding the missing heritability of complex diseases. *Nature.* 2009; 461:747–753. [PubMed: 19812666]
101. ADAMI. Medline Plus Microcephaly (image), NIH. 2009
102. Caviness VS Jr, Takahashi T, Nowakowski RS. Numbers, time and neocortical neuronogenesis: a general developmental and evolutionary model. *Trends Neurosci.* 1995; 18:379–383. [PubMed: 7482802]
103. Noctor SC, et al. Neurons derived from radial glial cells establish radial units in neocortex. *Nature.* 2001; 409:714–720. [PubMed: 11217860]
104. Reid CB, Tavazoie SF, Walsh CA. Clonal dispersion and evidence for asymmetric cell division in ferret cortex. *Development.* 1997; 124:2441–2450. [PubMed: 9199370]
105. Buchman JJ, Tsai LH. Spindle regulation in neural precursors of flies and mammals. *Nat. Rev. Neurosci.* 2007; 8:89–100. [PubMed: 17228329]
106. Takahashi T, Nowakowski RS, Caviness VS Jr. The cell cycle of the pseudostratified ventricular epithelium of the embryonic murine cerebral wall. *J. Neurosci.* 1995; 15:6046–6057. [PubMed: 7666188]

Figure 1.

Overview of early cortical neuron development. Cortical neurons are born and undergo fate determination in the ventricular zone (VZ) and subventricular zone of the developing cortex. These neurons then migrate through the intermediate zone (IZ) and into the cortical plate (CP), where they come to reside in their specific cortical layer. Maturing neurons then send out axons, which grow outward until they reach their designated target. This process is repeated with each newly born neuron. Ultimately, neurons form many synaptic connections to create functional neural circuits. Mendelian disorders can occur at any of these developmental stages, and specific examples include primary microcephaly (MCPH), classical lissencephaly (LIS), horizontal gaze palsy with progressive scoliosis (HGPPS), and primary epilepsy.

Figure 2. Anatomical features of primary microcephaly (MCPH). (A) Children with MCPH have a reduced head circumference beginning at birth and a small, but architecturally normal, brain as compared to a healthy control. Figure reprinted with permission.¹⁰¹ (B) MRI scans of a healthy child and a child with microcephaly. The microcephalic brain shows reduced brain volume, with the largest volume loss seen in the cortical areas.

Figure 3.

Genes that cause MCPH localize to the centrosome during the cell cycle and play a role in neurogenesis. During neurogenic proliferation, progenitors first undergo symmetric cell division where two daughter cells of progenitor fate are produced. This is followed by asymmetric cell division in which one daughter cell follows a progenitor cell fate and the other follows a neural fate.^{29,102–104} Committed neurons then migrate to the cortical plate (CP). The cell cycle is critically regulated by the mitotic machinery,^{29,105,106} and each of the five MCPH genes (*MCPH1*, *APSM*, *STIL*, *CENPJ*, and *CKD5RAP2*) colocalize with the mitotic apparatus during at least some part of the cell cycle. Genetic studies reveal that MCPH is primarily a disorder of cortical neurogenesis and not a disorder of migration, cell death, or cell growth and provide insight into the genes that regulate brain size in humans.

Figure 4. Anatomical features of classical lissencephaly (LIS). Children with LIS, also known as smooth brain syndrome, lack folds and ridges in the outer cortical layers and typically have a smaller head size as compared to healthy controls (wm, white matter). Figure reprinted with permission.⁴²

Figure 5.

Genes that cause LIS localize to the leading edge of cortical neurons and play a role in neuron migration. Committed neurons migrate along radial glia to reach their specified layer in the developing cortical plate. Neuron migration involves a strictly regulated process of cytoskeletal rearrangements. Each of the LIS-causing genes (*DCX*, *LIS1*, *TUBA1A*) act as key regulators of microtubules. Genetic studies reveal that LIS is primarily a disorder of neuron migration and provide mechanistic information about the genetic regulation of cortical development in humans.

Figure 6.

Anatomical features of horizontal gaze palsy with progressive scoliosis (HGPPS). (A) Photo of a patient with HGPPS showing lack of horizontal eye movements when attempting to look to either side. Upward and downward eye movements are normal. (B) MRI of the spine of a patient with HGPPS shows profound scoliosis. (C) MRI scans from a normal brain (a,b) and a patient with HGPPS (c,d). Patients with HGPPS display pons hypoplasia (boxed region in a,b); absent protrusions of the abducens nuclei (arrowheads in a,b); and flat,

butterfly-like appearance of the medulla (open arrow in c,d). Figures reprinted with permission.⁶¹

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 7.

Many of the genes that cause primary epilepsy are cell surface receptors that act to regulate neural circuit formation and network signaling. During circuit formation, neurons from different brain areas form stereotypic synaptic connections. Circuit formation is initially neuronal activity independent, but as signaling receptors are expressed at the cell surface, neuronal activity begins to shape circuit structure and function. Thirteen of the identified genes that cause primary epilepsy fall into the voltage-gated or ligand-gated ion channel class and are expressed in the axon or at the synapse in various neuronal types. Studies reveal that epilepsy can result from a primary defect in ion channel function and also provide evidence that certain types of epilepsy result from defects in circuit formation and function in the developing neocortex.

Table 1

Genes involved in Mendelian disorders of cortical development and function

Disorder	Gene name	Localization	Cellular function
Neurogenesis primary microcephaly (MCPH)	<i>MCPH1</i>	Centrosome	Coordinates entry into mitosis
	<i>ASPM</i>	Pericentrosome	Regulates mitotic spindles
	<i>CDK5RAP2</i>	Centrosome	Coordinates centrosome during mitosis
	<i>CENPJ</i>	Centrosome	Coordinates centrosome during mitosis
	<i>STIL</i>	Pericentrosome	Regulates mitotic spindles
Neuron migration isolated lissencephaly sequence (ILS)	<i>DCX</i>	Microtubules	Bundles microtubules during migration
	<i>LIS1</i>	Microtubules	Component of dynein motor complex
	<i>TUBA1A</i>	Microtubules	Major constituent of microtubules
Axon outgrowth horizontal gaze palsy with progressive scoliosis (HSPPS)	<i>ROBO3</i>	Growth cone receptor	Guidance of projection axons
Congenital mirror movements (CMM)	<i>DCC</i>	Growth cone receptor	Guidance of projection axons
Circuit formation primary epilepsy	<i>SCN1A</i>	Axonal receptor	Action potential initiation
	<i>SCN1B</i>	Axonal receptor	Action potential initiation
	<i>SCN2A</i>	Axonal receptor	Action potential initiation
	<i>GABRA1</i>	Postsynaptic receptor	Synaptic inhibition
	<i>GABRG2</i>	Postsynaptic receptor	Synaptic inhibition
	<i>CHRNA2</i>	Presynaptic receptor	Synaptic transmission
	<i>CHRNA2</i>	Presynaptic receptor	Synaptic transmission
	<i>CHRNA4</i>	Presynaptic receptor	Synaptic transmission
	<i>CACNA1A</i>	Presynaptic receptor	Synaptic transmission
	<i>KCNQ2</i>	Axonal receptor	Axon potential propagation
	<i>KCNQ3</i>	Axonal receptor	Axon potential propagation
	<i>KCNA1</i>	Presynaptic receptor	Synaptic transmission
	<i>KCNMA1</i>	Presynaptic receptor	Synaptic function