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Genes and the long and winding road to cortical construction and cognition

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Over the last half century an enormous synergy has emerged between the direct genetic study of disordered human brain development and basic developmental neurobiology. Nowhere is this more true than in conditions that involve abnormalities in cognition and behavior, where a knowledge of molecular etiology provides a concrete starting point for the complex journey from stem or progenitor cell to cortical circuit to cognition (Rakic and Goldman 1982; Caviness and Rakic 1995). In this issue of NBD, we attempt to highlight this synergy by providing a collection of 5 reviews focusing on different areas at the intersection between developmental neurobiology and disease.

Since the earliest days of experimental embryology, investigators have been fascinated by the problem of how a structure as complicated as brain can construct itself (Schaper, 1897; Louis and Stapf, 2001; Spemann and Mangold, 2001), especially the human cerebral cortex (Rakic 2009). Starting from a single cell, then advancing to a cluster of amorphous cells, the vertebrate embryo begins to specify neural tissue as a sheet of specialized ectoderm whose edges rise up and roll into a tube in a process called neurulation. As the neural tube closes, pseudo-stratified neural epithelial cells comprising the wall of the tube move their nuclei basally (outward) to synthesize new DNA and translocate apically (to the center) to split into daughter cells in M-phase at the surface of what will become either the central aqueduct that closes off in the mature spinal cord or the ventricular system that remains open in the forebrain and brainstem (Sauer and Chittenden, 1959). In the process, cell proliferation, strategic apoptosis and cell shape changes enabled by manipulation of the cytoskeleton accomplish the morphogenesis that maps out the rudimentary forebrain, hindbrain, brainstem and spinal cord. In the midst of all this cellular pushing and shoving, the cerebral cortex begins to emerge as the earliest neurons free themselves from the neural epithelium. Rebelling against the constraints of interkinetic nuclear migration, progenitor cells in the forebrain break away from the pseudo-stratified epithelium to form a secondary proliferative zone of cells that undergo less regimented divisions that

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amplify neural numbers (1970; Bystron et al., 2008). In higher vertebrates, expansion of these subventricular, transit amplifying divisions will force young neurons and glia as they migrate away from their place of origin to create folds and undulations of the overlying cortex (Martinez-Cerdeno et al., 2006). And all the while, even as they move out to take up positions in the forming cortex, migrating neurons leave behind and send out axons and growth cones that seek other neuronal targets they have yet to know, but are already programmed to find or die (Hamburger, 1992). Then as neurons take their rightful place, they elaborate dendritic tree-like arbors in recognizable configurations sufficiently stereotyped to enable the synthesis of neuronal classifications, of which many forms have been appreciated since the turn of the last century (Ramon y Cajal, 1911; Ascoli et al., 2008).

We now enjoy a growing mechanistic understanding of the cellular framework of cortical construction, the hardware of cognition and behavior. However, it is only in the last twenty years or so that the molecular elements that underlie the processes involved in brain formation have been coming to light. And this story, often driven by study of clinical disorders, is more fascinating than ever imagined. The five articles in this special issue are not intended to provide a comprehensive overview of these advances. Rather, they discuss selected examples of some intriguing insights that take us from brain construction to higher cortical function. These have been chosen from the perspective of molecular insights that have been gained from the study of clinically recognized disorders of brain, and in particular cerebral cortex, formation.

This issue starts with a consideration of the complexities of progenitor proliferation and patterning of gene expression in developing brain, exemplified by the Wnt signaling pathways (Freese et al.). The versatility and complexity of Wnt signaling is remarkable, ranging from regional patterning of many key neural structures including the hippocampus, to axon pathfinding, synapse formation and adult neurogenesis. Here, very basic molecular and cell biology, rather than study of human disorders, has been at the root of much progress in decoding this extremely complex set of interconnected pathways. It is remarkable that despite having a central role in many fundamental neurodevelopmental pathways, clinical evidence for direct involvement of Wnt pathway component mutations in disordered human neurodevelopment, as opposed to dementia or cancer (Logan and Nusse 2004), remains relatively sparse. Nevertheless, animal models suggest that Wnt pathway gene malfunction may be at the core of human cases of neural tube defects (Carter et al., 2005; Wang et al., 2006a; Wang et al., 2006b) and cortical malformations associated with mental retardation (Xu et al., 2004; Zhou et al., 2006; Hildebrandt and Zhou, 2007). Mouse models demonstrate a significant role for Wnt signaling in formation of the corpus callosum, suggesting that screening Wnt pathway genes in human patients with various forms of callosal agenesis may prove fruitful as well. The challenge of such an approach is that the diversity and complexity of Wnt signaling requires screening large numbers of genes.

Next, a discussion of the neuronal migration syndromes in human subjects highlights the identification, through clinical genetic investigation, of critical genes whose impact span proliferation, migration, axon extension and connectivity (Guerrini and Parrini). Here, study of several rare human disorders has greatly illuminated our understanding of basic processes of cortical development. In parallel with the early role of mouse mutants toward understanding neuronal migration and cortical histogenesis (Caviness and Rakic 1982; Sidman, 1983), the ability to categorize and study migration disorders in human clinical populations, made possible by advances in neuroimaging, has led to a revolution in our understanding of the molecules involved in neuronal proliferation and migration (Ross and Walsh, 2001; Gupta et al., 2002; Barkovich et al., 2005; Ross, in press). One example among many described by Guerrini and Parrini is the discovery of LIS1 and DCX as causes of lissencephaly and subcortical band heterotopia, which revealed a signaling pathway highlighting the central role of cytoskeletal dynamics in neuronal migration. Another theme here is pleiotropy, in which a

variety of human syndromes can be caused by mutations in the same gene. In this way, detailed clinical observations and phenotyping followed by translational genetic work have greatly informed basic cell biology. One observation whose molecular basis is not well understood is the relative focality of certain neuronal migration disorders, such as forms of polymicrogyria (PMG) associated with language dysfunction, or relative a-p gradients of migratory defects associated with DCX and LIS1 mutations. In some cases, what appear to be relatively focal events actually disrupt more broadly distributed circuits, leading to more widespread cortical dysfunction. Such developmental disconnection has been posited to underlie autism (Geschwind and Levitt, 2007) and may also contribute to deficits in language and other aspects of higher cognition in patients with these known migration syndromes.

Another emerging theme in the study of complex neuropsychiatric disorders has been the unexpected contribution of genes that were first recognized in association with rare brain malformations. Jouberts syndrome, which involves severe cerebellar-brainstem malformations, is also among one of several syndromic disorders strongly associated with autism (Abrahams and Geschwind, 2008; Alvarez Ruetero et al. 2008) and schizophrenia (Amann-Zalcenstein et al., 2006). The neural mechanism of this Jouberts-ASD association is unknown, but new data highlights the disruption of primary cilia function in Joubert Syndrome pathophysiology. This has illuminated new features of extracellular signaling events that support cross-talk among critical developmental signaling pathways, such as Wnt and SHH, and that promote neurogenesis, cell polarity, and axonal guidance (Lee and Gleeson). The presence of severe defects in decussation of major long tracts in patients with Jouberts is also intriguing, especially considering the known role of cilia in midline signals that underlie the generation of lateralized structures in vertebrates (Basu and Bruekner, 2008; Hirokawa et al. 2006). Study of this Mendelian disorder promises to help elucidate how these processes relate to complex features of human brain development and cognition.

One of the most complex functions supported by a cerebral cortex is human language. Basic human genetic studies of reading, as well as spoken language have yielded diverse functional categories of implicated genes, ranging from transcription factors to cell-adhesion molecules (Newbury et al. 2010, Alarcon et al. 2008, Vernes et al. 2008). In this issue, Gabel et al. introduce the surprisingly prevalent disorders affecting reading ability (Gabel et al.). The recent evidence suggests that reading disability (RD) is associated with neuronal migration impairments that are akin, though in much milder form, to the brain malformations discussed in several of the accompanying articles. This work reveals a remarkable convergence of the neuropathology observed of RD in small cohorts of human subjects, and the deficits in neuronal migration observed in mouse models when genes recently associated with RD are perturbed. Both ectopia and periventricular nodular heterotopias are observed in human pathological material from patients with a history of RD, and in RNAi mediated knockdown of DYXC1C1 in mice. Related, but not identical neuronal migration deficits are observed with knockdown of DCDC2 and KIAA0319 in mice, two other genes associated with RD in humans. Here again, is an example of how clinical, pathological and genetic studies in humans have led to a new cadre of genes with apparently important roles in cortical development, specifically neuronal migration. How such events lead to relatively focal disruption of reading and language, sparing most other cognitive functions remains an important challenge to the field. Perhaps observations in allied, but more severe disorders of human neuronal migration, such as PMG, can work synergistically to inform a broader understanding of language circuit development.

Finally, recent advances in genomics have made it possible to approach the multi-factorial, complex genetic interactions that influence higher integrative functioning and are discussed in the context of autism spectrum disorders (ASD) (Hogart et al.). Many of the issues faced in identifying the genetic factors predisposing to ASD are exemplified in the genomic disorders of chromosome 15q11-q13, in which gene duplications, deletions and imprinted alleles have

been associated with autistic features and indicated regional genes that may contribute to autism susceptibility. Here again, new findings emphasize the important contribution of chromosomal structural variation to ASD (Sebat et al., 2007; Abrahams and Geschwind, 2008; Bucan et al., 2009). The majority of patients with maternally inherited duplications of the 15q11-13 region have autistic symptoms, making it among the most commonly recognized genetic causes of ASD (Hogart et al.; Abrahams and Geschwind, 2008). In addition to genes that are in the duplication or deletion, one has to consider nearby genes, as the effects of a structural chromosomal abnormality may typically dysregulate genes a half a million base pairs distant. Here, the connection between specific genes and cognition is complicated by the involvement of several genes, including GABAR3 and UBE3A, the latter implicated in the pathophysiology of Angelman syndrome (discussed in Hogart et al.). Since the duplication varies in size, Hogart et al. emphasize that careful and detailed phenotyping that permits sophisticated genotype-phenotype correlation is necessary to elucidate the gene-brain-cognition relationships that lead to ASD.

These articles highlight the capacity for investigation of morphological disruptions of human brain, genetics and genomics to identify genes and genetic interactions that can impact cortical function in subtle ways. Basic neuro-developmental processes, such as regionalization and neuronal migration are implicated in several clinically distinct disorders. How such diverse clinical phenotypes relate to these basic mechanisms remains an exciting frontier of this research. In the future, as pathogenic mechanisms are better understood, one can imagine cognitive disease classifications based on etiology (“cause”), such as distinct disorders of neural migration, or cell fate, which could presumably share molecularly guided therapies more successfully than therapies targeting current disease classifications based on observed neurobehavioral phenotypes (“outcome”). Furthermore, development does not end in childhood or puberty. Many developmental pathways are also implicated in later onset disorders involving neurodegeneration (e.g. Wexler and Geschwind, 2006; Rogers and Schor, in press). Thus early developmental events might lead to changes in circuit patterning or resilience that leaves certain cell types or regions vulnerable to later neurodegeneration (Wexler and Geschwind, 2006). We hope that these discussions will heighten interest in examinations of the ways in which genes that are involved in constructing cortex impact its later function as well.

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