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Neurodevelopmental disorders: hope for a new beginning

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Advances in neurobiology, brain imaging and genetics have vastly increased our understanding of the pathophysiology and causes of neurodevelopmental disorders. We can now appreciate the enormous causal diversity and multifaceted nature of neurodevelopmental conditions such as epilepsy, Tourette syndrome, obsessive compulsive disorder (OCD) and autism. Furthermore, molecular insights into both common and rare forms of neurodevelopmental disorders have revealed remarkable areas of potential overlap between disorders previously thought to be distinct, and opened a new era in the development of causative targeted molecular treatment options.

This issue of *Current Opinion in Neurology* contains six articles that cover a broad spectrum of neurodevelopmental disorders, ranging from the developmental patterning and signaling role of cilia elucidated by the study of Joubert syndrome (JBTS), tuberous sclerosis, mouse models of OCD, the relationship between epilepsy and disorders of language development, and Tourette syndrome, to neurological comorbidities in autism. These topics and authors were chosen to represent the cutting edge of neurodevelopment, either from the perspective of molecular genetics and developmental neurobiology, or to emphasize newly emerging clinical relationships and concepts.

We begin with a discussion by Lee and Gleeson (pp. 98–105) of the enigmatic JBTS, which touches on many of the shared themes highlighted in this issue. Identification of the mutational basis of this rare neurodevelopmental disorder in many cases has implicated more than 10 genes thus far, perhaps an unexpected level of genetic heterogeneity for such a rare disorder. This same theme is being echoed in common disorders such as Tourette syndrome and autism spectrum disorder (ASD), in which a wide variety of causal rare mutations in many genes may also be the rule, rather than the exception (see Bloch *et al.* also in this issue, pp. 119–125). The study of JBTS also provides a clear example of how careful study of clinical disorders can lead to significant advances in our understanding of basic neurobiological and developmental mechanisms. All known JBTS genes appear to be involved with ciliary function, emphasizing the previously unappreciated importance of cilia in a multitude of basic neurodevelopmental processes and signaling pathways. This discovery opens up new avenues of research in developmental neurobiology, similar to the discovery of genes involved in cortical neuronal migration syndromes [1,2]. At the same time, mice carrying human JBTS mutations do not necessarily recapitulate all of the pathologic features of the disorder observed in humans, challenging neurobiological investigations based solely on animal models.

Next, Tsai and Sahin (pp. 106–113) review advances in our understanding of the mechanisms of tuberous sclerosis complex (TSC). TSC mutations lead to multiple neurodevelopmental abnormalities involving neurons and glia, paralleling findings in other

neurodevelopmental syndromes, including JBTS. For example, in addition to cortical tubers and subependymal nodules, brain imaging studies in TSC demonstrate significant cerebellar abnormalities and defects in white matter tracts. Therefore it is notable that in addition to cerebellar malformations, which are observed in both conditions, patients with JBTS have significant deficits in pathway crossing that include ascending and descending cortical sensorimotor white matter tracts. Mouse models of TSC, whereas not replicating the major macroscopic abnormalities observed in humans, do show cognitive and behavioral deficits and abnormal axonal path-finding, implicating aberrant neuronal connectivity as contributing to neurobehavioral deficits in TSC, independent of tubers and subependymal nodules. Abnormal connectivity framed as a developmental dysconnection syndrome has been proposed as a potential unifying abnormality in ASD [3]. Given that both JBTS and TSC are significantly associated with ASD [4], it is interesting to speculate that the autistic symptoms in both disorders may be related to developmental abnormalities in neuronal connectivity. However, as is the case with many syndromic forms of common neurodevelopmental conditions such as autism, these disorders have multiple neuroanatomical abnormalities, ranging from microscopic changes in synapses or dendritic spines to macroscopic malformations of the cerebral cortex, cerebellum or their connecting pathways. Going forward, genetic dissection of neural circuits in animal models of these 'simple' monogenic conditions provides a great opportunity for uncovering how each of these abnormalities contributes to the cognitive and behavioral phenotypes observed. Also instructive and potentially generalizable to a variety of neurodevelopmental disorders is the demonstration that modulation of mTOR function in TSC adult animal models can reverse cognitive deficits. This indicates that despite what were considered fixed developmental or connectivity deficits, ongoing signaling abnormalities present in adults or children may contribute to the cognitive deficits and may be reversible.

As highlighted by Yang and Lu (pp. 114–118), mouse models are playing a central directive role in understanding OCD, suggesting remarkable evolutionary conservation of key striatal–cortical pathways thought to be involved in OCD and related disorders in humans. Such conservation is supported by the ability to ameliorate the core neurobehavioral phenotype in several of the mouse models of OCD with the same medications used in humans. Identification of potential OCD-related behaviors in genetically engineered mice is facilitated because excessive grooming, a repetitive behavior, can be observed under naturalistic conditions in the cage. This led to the unexpected discovery that deletion of the *Hoxb8* gene, whose expression is restricted to bone marrow-derived microglia in the CNS, leads to OCD-like behaviors [5]. The direct implication of neural-immune interactions in OCD pathogenesis is consistent with current concepts in the pathophysiology of pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS), which include OCD and tics in humans. This work resonates with the emerging theme of a pathological role of neural–immune interactions in neurodevelopmental disorders, which is also supported by data in TSC-deficient mice, when maternal immune activation in mouse models leads to increased deficits (see Tsai and Sahin, pp. 106–113).

Obsessive compulsive disorder is highly comorbid with Tourette syndrome, so it is not surprising that imaging, pharmacology and pathological investigations in humans have also implicated striatal–cortical circuits in Tourette syndrome pathophysiology, as reviewed by Bloch *et al.* (pp. 119–125) in this issue. From a pharmacological standpoint, the most effective drugs in suppressing tics in Tourette syndrome have been dopamine antagonists, which unfortunately have significant side effects. Thus, the discovery of rare mutations in histidine decarboxylase, the rate-limiting enzyme in histamine synthesis neurotransmitter dopamine, provides the potential for a new era in therapy development for Tourette syndrome [6]. This finding of a rare mutation in a family with apparent autosomal dominant Tourette syndrome emphasizes how genetics can significantly advance clinical therapeutics.

In reviewing other genetic developments in Tourette syndrome, Bloch *et al.* also emphasize that the genetic overlap between Tourette syndrome and other neurodevelopmental conditions such as ASD and schizophrenia suggests shared causes and neural circuitries between disorders that had previously been considered distinct. Here again, finding causal genes, even in rare forms of common developmental disorders, opens new directions in our understanding of disease pathogenesis and development of therapeutics.

Epilepsy is one of the most common neurodevelopmental syndromes and perhaps is prototypical in its wide variety of genetic and environmental causes. This heterogeneity and its comorbidity with many other neurodevelopmental disorders suggest that in many cases epilepsy may reflect the limited response of the brain to diverse forms of injury. So, unraveling epilepsy's causal relationship with a variety of speech and language disorders represents a significant clinical and research challenge, as reviewed here by Pal (pp. 126–131). As Pal discusses, new-onset epilepsy puts children at risk for significant problems in language in general, but specific forms of epilepsy may actually share the same neurobiological or genetic cause with heritable language disorders. For example, study of rolandic epilepsy, which was previously considered benign, has demonstrated that it is influenced by the same genetic locus on chromosome 11 that is related to comorbid speech sound disorder. Here, the study of the classic EEG signature of centrottemporal spikes as an endophenotype, rather than the broad clinical syndrome of rolandic epilepsy itself, was an important step taken to shed light on this relationship. Pal also highlights how recent genetic studies have bolstered the notion that some forms of epilepsy and language dysfunction share a common cause. The relationship between alterations in language circuits and epileptogenesis is an exciting area that warrants further study and will be greatly facilitated by finding new causal mutations.

Autism is perhaps one of the most broad of the neurodevelopmental disorders, as it appears to be comorbid with intellectual disability, OCD, Tourette syndrome, epilepsy, developmental language disorders and attention deficit hyperactivity disorder, hence the term ASD. Many of its neurological comorbidities have historically not been well appreciated [7], especially sleep, epilepsy and motor dysfunction, which are covered in detail by Jeste (pp. 132–139). The comorbidity of ASD with epilepsy has been appreciated for more than a decade, but still there remain many unanswered questions, including optimal treatment and the relationship of EEG abnormalities with cognition and behavior in ASD. Sleep problems are observed in a majority of children with autism, a fact well appreciated by parents, but poorly assessed by most clinicians. Since poor sleep can impact on so many other factors, including cognition, behavior and the risk for seizures, recognition and proper treatment of sleep problems is critical. The same is true of motor dysfunction, which, as Jeste discusses, could also serve as an early diagnostic or prognostic biomarker, since certain aspects of motor function clearly precede development of language and complex social interactions in infants. How simple motor coordination or even tone relates to deficits in higher order motor programming, such as praxis, and how these relate to prognosis and treatment remain to be determined. Further, as Jeste emphasizes, these aspects of the ASD phenotype also provide endophenotypes or biomarkers potentially related to shared neurobiological mechanisms, that may be more tractable to measure in animal models than complex behavioral phenomena.

Several major themes emerge from this collection: how the study of rare syndromes informs our understanding of common disorders; how the study of disease leads to breakthroughs in the understanding of basic biological mechanisms; the enormous utility of mouse models in understanding disease mechanisms, notwithstanding the challenges of modeling human disease phenotypes in an evolutionarily distant organism such as mice; the potential for common mechanisms in causative distinct disorders; the intersection of immune and developmental pathways in neurodevelopmental disorders; and the possibility of treating or

even reversing severe neurodevelopmental disabilities in adulthood despite the presence of what are considered fixed anatomical deficits. In this manner, the advances highlighted in these six articles truly provide real hope for significant improvements in our understanding and treatment of neurodevelopmental disorders.

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