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Function follows form: understanding brain function from a genetic perspective

Editorial overview

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Oscar Marín is interested in understanding the mechanisms controlling the development of the cerebral cortex, and how abnormal brain development leads to disease. The development of cortical Interneurons is an important focus of his research.

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Joseph Gleeson's goal is to identify the genetic causes and pathogenic mechanisms underlying pediatric brain disorders. In the process, his lab is uncovering new mechanisms of disease, in the context of human brain development.

The advent of modern architectural design in the 20th century brought with it the principle of ''Form Follows Function'', first coined by the American architect Louis Sullivan. The idea is simple; the organization of a structure or object should be primarily based upon its intended function or purpose. Neurobiologists have co-opted this principle in studies correlating neurological function within the confines of neuroanatomy. For instance, the analysis of the uniquely organized primary visual part of the cerebral cortex suggested unique aspects of visual processing and sensory relay, which were subsequently borne out experimentally.

This issue of *Current Opinion in Genetics and Development* focuses on new discoveries in the area of genetic regulation of neuronal development and function, where the theme is ''Function Follows Form''. Flipping the paradigm is necessary when we consider how the brain is *assembled* rather than how it *functions*, because we can begin to see common and important themes emerge in the utilization of early protomaps and conserved structures from our ancient evolutionary kindred. In other words, we can begin to understand both anatomy and disease by studying the underlying mechanism of how this most wonderful of structures is assembled in the first place. It is the field of genetics that has turned this tenant paradigm around, by ascribing specific and evolutionarily conserved genetic functions for how the brain is assembled. Understanding how the brain is wired, and the genetic underpinnings of this process, will help us to make sense of its function.

Brain assembly is under tight gene regulatory control, as evidence by the fact that most genes are expressed in developing nervous system, and half of all genetic conditions listed in the OMIM database have prominent neurological features. Thus our genes drive how our brain is assembled and how it functions to a great degree. Several articles in this issue summarize recent progress on the mechanisms controlling the development of particular neural assemblies. For instance, Reed-Geaghan and Maricich review our current understanding of the genetic pathways controlling the specification of the different classes of primary sensory neurons, their connections, as well as the molecules that mediate their role in processing specific sensory modalities such as pressure, temperature, pain, and touch. Their focus is on the transcriptional specification of individual sensory neuron classes, the role of neurotrophins on sensory neuron connectivity and survival, and the recent identification of several mechanosensitive proteins such as the Piezo channels.

The surprising discovery that the cerebral meninges can exert a powerful influence over brain development is the focus of the review by Siegenthaler and Pleasure. Despite the intricate proximity of the meninges to the

developing nervous system, it was only recently that we have begun to understand the important role that these structures play during brain development. Recent studies indicate that the meninges organize the pial basal membrane, to which the basal process of radial glial cells anchors. In addition, it has been found that the meninges release essential growth factors that control the proliferation and migration of several neuronal populations. These findings suggest that abnormal development of the meninges may lead to congenial brain disorders in humans.

Nothing is more central to the field of neurobiology than the synapse, which is considered by Melom and Littleton in their review. Genetic mapping has identified several key synaptic proteins in human disease in autism, schizophrenia and intellectual disability, now irrefutably tying these disorders to altered synaptic function. The focus in now on understanding how the synapses are altered in neurological disease, and whether these are amendable to pharmacological manipulation. In this context, the review by Rico and Marín summarizes recent progress on the identification of two schizophrenia susceptibility genes, *Neruregulin-1* and its receptor *ErbB4*, as key elements in the formation of synaptic connections in the cerebral cortex. In particular, the recent discovery that ErbB4 is exclusive to GABAergic interneurons has focused attention on specific inhibitory circuits. This has led to new models implicating pyramidal neuron desynchronization in the etiology of schizophrenia, as well as potential new avenues for treatment.

On a more conceptual level, Mitchell explores some of the least well-understood disorders in neurobiology, conditions such as dyslexia, dyscalculia, prosopagnosia, color agnosia and amusia. He summarizes evidence that suggests that these disorders may arise as a consequence of the disordered maturation of neural networks. Researchers have consistently found a steady transition from local networks to longer-range networks during at the transition from childhood to adolescence using a host of modalities. The idea is that such disorders may represent a failure to develop or refine these long-distance networks. Since most of these conditions show some form of heritability, these are now a hot topic of genetic investigation.

Recent genetic studies are beginning to shed light into the etiology of several classes of disorders for which until recently we did not even have a name. This is the case of Dystroglycanopathies, which are the focus of the article by Godfrey and colleagues. In their review, Godfrey et al. summarize the tremendous progress made in recent years in a field characterized by the problems of classifying patients with apparently dissimilar diseases. That changed with the realization that patients with disparate syndromes such as Walker-Waarburg, Muscle-Eye-Brain and Fukuyama syndromes all share a common mechanism of hypo-glycosylation of the alpha-dystroglycan molecule, key to the formation of the extracellular matrix of various organs. Along the same line, Tischfield and colleagues consider the newly emerged class of disease known as Tubulin-related disorders or Tubulinopathies in their article. Considering the unique morphology of neurons it should not be surprising that the cytoskeleton is emerging as a key element in the regulation of many aspects of neuronal development. In that context, the twenty or so copies of alpha and beta tubulin were long thought to serve basal cytoskeletal functions, but recent discoveries point to unique neurological and ophthalmological phenotypes upon mutations in several of these genes.

The advent of next-generation sequencing combined with refined methods for phenotypic characterization has the potential to bring real insight to our understanding of a host of enigmatic conditions. Indeed, important progress has been made in the genetics of some of the most complex neurological and neuropsychiatric disorders. For example, Lambert and Amouyel consider the compelling evidence for the amyloid cascade hypothesis underlying Alzheimer's disease, from the perspective of a wealth of new large-scale GWAS studies. The conclusion is that many of the newly identified risk factors further strengthen the amyloid hypothesis, most importantly, for those late-onset cases for which the genetic basis was largely unknown. The great hope is that new treatments will emerge from this clarified landscape. Important progress has also been made in the genetics of Tourette disorder, with the hallmark of persistent movement or vocal tics. Extensive efforts to genetically map this condition were not very rewarding, but a shift toward a cytogenetic approach has led to the identification of several interesting candidate genes including *SLITRK1* and *CNTNAP2* genes and a gene involved in histaminergic neurotransmission, as reviewed by State. The genetics also points to some surprising clinical overlap with other neuropsychiatric conditions such as autism and obsessive compulsive disease.

Girard and colleagues discuss how the wealth of new genetic data has led to a re-thinking of underlying mechanisms of schizophrenia. Over 7800 different genes have somehow been implicated in schizophrenia. Is this too many, too few, or just right, and are these the correct genes? Even for the most statistically significant genes, the odds ratios remain very low, suggesting that variants with larger effect size are still looming. The study of copy number variants, re-sequencing candidate genes on a large scale, and whole genome sequencing remain hopes for the future. Baranzini faces a similar problem in his review on the genetic basis of multiple sclerosis. The phenotypic diversity of this condition has hindered progress in identifying causes, even for robust associations

like the connection with the HLA system. There is debate as to the degree by which multiple sclerosis is driven by numerous small genetic contributions versus a smaller number of variants of larger effect size. The GWAS and CNV studies to date have not completely clarified this point, but newer studies coming online soon should address this question.

Another area ripe for genetic study is epilepsy, in particular with the establishment of the Epilepsy Phenome/Genome Project and others. Poduri and Lowenstein address this question in their review, considering both the newly emerging class of interneuronopathies (i.e. disorders causes by abnormal interneuron function), and the unique genotype–phenotype correlations that have emerged with syndromic forms of epilepsy. Considering the contribution of GWAS, CNV and now genome sequencing, the future is bright for the identification of new causes.

In addition to the progress made on the genetic basis of neurological disease, as well as in the elucidation of the specific underlying mechanisms, there are important conceptual advances in the field. For example, work on cortical developmental disorders is shedding light into the problem of phenotypic variability, as reviewed by Manzini and Walsh in this issue. Using the developing cerebral cortex a model, they explore the causal relationships between specific gene mutations and clinical outcomes. The emerging view is that the same genes are often involved in several developmental processes, and that understanding the specific mechanisms that link disease genes with each of these developmental events will be key to decipher the heterogeneity of clinical conditions associated with abnormal brain development. Furthermore, although mouse models have not shown as dramatic phenotypes as humans, nearly always there are important lessons and mechanisms to be uncovered from their study.

Another interesting concept that is gaining experimental support is the existence of intermediate phenotypes in psychiatric disorders, which is the focus of the review by Rasetti and Weinberger. Recent evidence suggests that some relatives of those with psychiatric disease can display similar but subtler features, best appreciated at the level of altered neural circuit. It is attractive to consider this possibility as a means to better track genetic risk factors in families using a biological marker that is perhaps closer to the genetic underpinnings. Indeed, the use of fMRI to uncover the roles of selected genes in specific functional processes, such as memory, attention, verbal fluency, and emotion processing, is emerging as an important approach to unravel the basis of neuropsychiatric disorders.

The identification of genetic modifiers represents another key area for future research in the field of neurogenetics, as proposed by Kearney in her article. Although modifiers likely play enormously important roles in human disease, they are much more straightforward to study in animal models due to control over the genetic background. Although it is relatively easy to map genetic modifiers in these models, it has proven a lot more difficult to identify the variant responsible for the effect and demonstrate a clear mechanism. This suggests that identifying modifiers in humans will be that much more difficult.

Finally, Cundiff and Anderson reflect on what the future might hold in the area of induced pluripotent stem cells (IPSCs) for modeling neurological disease. IPSCs are of course taking the study of neurological disease by storm, because it has always been our dream to generate neurons from patients. The authors consider the advances in terms of what types neurons can currently be derived, which diseases have been modeled, and how the findings to date have enlighten us in terms of disease pathogenesis.

In neurogenetics, one of the most exciting transformations is the emergence of new empirical classes of disease based upon genetic classifications. We are clearly entering an age when the molecular genetics of disease is pointing to specific disrupted pathways rather than unique individual causes for a syndrome. What makes this most exciting is the research synergy that develops around these specific newly defined pathways. In much the same way that other fields of biology were able to begin to break apart diseases into unique classes based upon molecular characterization, neurobiologists, who were long dogged by the lack of access to nervous system tissue, now have at their disposal the opportunity to ask probing questions and get straightforward answers that will eventually redefine how we view neurological disease and has the potential to transform medical care.

The day is not that far off when we can reasonably expect that genetic profiling will be able uncover causes for the vast majority of neurological and psychiatric diseases, even for such conditions previously assumed intractable like epilepsy, intellectual disability, developmental brain disorders, schizophrenia, and Tourette syndrome.