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INSIGHT

Towards the Framework of Understanding Autism Spectrum Disorders

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The prevalence of autism spectrum disorders (ASD) has been high worldwide, reaching 1/59 children in the United States as reported by the Centers of Disease Control and Prevention. Since genetic components play a major role in ASD [1], it is astonishing that the occurrence of ASD would be this high probably due to genetic causes. It is worthy to note that autistic phenotypes of ASD patients show great diversity. The severity of autistic symptoms may be correlated with whether genetic mutations affect neural development. Thus, we argue that the prevalence of severe ASD may be much lower than the common ASD usually reported. In clinic and neurobiological fields, the ASD candidate genes are usually critical genes whose loss-of-function will affect neural development dramatically. In the following sections, I will focus on the recent progress on clinical diagnosis of severe ASD, as well as genetic and neurobiological studies.

Clinical Diagnosis and Novel Technologies

Clinical diagnosis has always been a critical issue in defining the study cohorts and connecting genetic causes to clinical symptoms. However, discrepancies on the diagnosis of ASD are often reported across different clinical centers. Given the fact that clinical diagnosis of ASD still mainly relies on fulfillment of behavioral scales by clinic personnel, defining ASD from children with various of symptoms is clearly impacted by subjective views. Moreover, the standard scale for ASD diagnosis in the US may not be totally suitable for children in other countries. Thus, it is necessary to make revisions of ASD diagnosis scales to fit local culture.

During the clinical practice in China, physicians have spent tremendous efforts on revising the ASD scale and questionnaire according to Chinese culture, in order to perform more precise diagnosis. Interestingly, the accuracy of ASD diagnosis is improved with modified rating scale for social behaviors, suggesting that the naturalization work needs to be done in individual countries, in order to perform precise diagnosis for ASD [2]. Importantly, based on the modified diagnosis tools, the sex differences and clinical phenotypes of ASD in Chinese patients appear to be unique compared to Caucasian ASD patients [3].

Given the ambiguity of ASD clinical diagnosis, the search for more objective diagnostic standards is an important next step, not only for ASD, but also for other neuropsychiatric disorders such as major depression. Brain imaging techniques including magnetic resonance imaging (MRI), have become an important method for measuring structures and functions of human brain in patients with psychiatric disorders [4]. Remarkably, using brain imaging methods researchers have discovered alterations of functional connectivity in autistic children in the vasopressin-related neural circuits that are implicated in social behaviors, showing the power of brain imaging technology and further suggesting the wide application of MRI in diagnosis of ASD [5].

Furthermore, researchers using the diffusion tensor imaging (DTI) method found that the face emotional recognition is impaired in the high-functioning autism group comparing to the control group, providing novel

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insights into the brain structure abnormalities associated with high-functioning autism cohorts [6]. This finding is consistent with previous data that defects in face perception are implicated in ASD patients, and suggests the underlying neural mechanisms associated with various brain regions.

Genetic Study

The genetic study has been one of the core efforts for understanding ASD. Recently, genome-wide next-generation sequencing, including whole-exome sequencing and whole-genome sequencing, has been widely used in genetic studies of ASD. A comprehensive review has nicely summarized the latest progress [1]. However, the identifiable genetic mutations from ASD patients are still as low as 10%, which means that nearly 90% of ASD patients are still lacking affirmation of genetic mutations. The percentage of individual ASD candidate genes would only account for 0.1%–0.3% in each sequencing cohorts, suggesting that most of the ASD genetic causes are very rare mutations [1]. Therefore, in-depth genetic studies in different geographic populations are very crucial for further understanding the genetic architecture.

Besides the genetic variants, structural variants such as copy number variants are also critical components of genetic causes of ASD pathology [7]. Clinical studies using chromosome array in Chinese ASD cohorts have identified a series of structural variants associated with core autistic symptoms [8]. Moreover, researchers have identified association between polymorphism of dopamine receptor D4 gene and frontal connections in ADHD, which normally shares symptoms with ASD, suggesting the fruitful aspect of combining genetic studies with brain imaging technology [9].

Neurobiological Studies in Animal Models

Due to the complexity of genetic causes and diagnostic biomarkers, neurobiological studies of ASD candidate genes in animal models would be essential for us to understand the pathophysiology and potential therapeutic methods for ASD.

The goal of neurobiological studies of ASD is to illustrate the biological function of ASD candidate genes and identify potential molecular and cellular mechanisms, as well as neural circuits implicated in ASD. Thus, specific animal models would be central for addressing specific scientific questions. For example, although it is hard to recapitulate autistic behavioral defects in *Drosophila* models, the molecular and cellular mechanisms of ASD candidate genes are still largely conserved across species. Therefore, using *Drosophila* as the animal model has provided enormous insights into the molecular mechanisms underlying the function of neuroligin and neurexin, which are critical ASD genes, in synaptic development [10].

Importantly, in order to fully mimic core symptoms of ASD, animal models with evolutionally proximity would be more desirable for studying ASD. Thanks to the rapid progress of genome-editing technology, genetic manipulations in non-human primates have made remarkable achievements in generating transgenic, gene-edited and cloned monkeys. Although transgenic and gene-edited monkeys mimicking ASD have been established, more in-depth analyses are required for understanding the neural mechanisms of ASD or exploring potential therapeutic methods [11–16].

The main limitations of non-human primates include prolonged reproduction cycle and limited numbers of genetically-modified monkeys, which almost exclude the possibility of applying invasive experimental methods, such as electrophysiology and optic imaging. Therefore, acute genetic manipulation with viral-delivered gene editing tools may provide a more efficient way to establish genetically-engineered non-human primate models.

Perspectives

With intensive neurobiological studies in the last two decades, mounting evidence has been provided to formulate the framework of ASD. From the genetic aspect, whole-exome sequencing and whole-genome sequencing with ASD trios in different cohorts would provide important insights into the genetic architecture of ASD, which may vary geographically. Fully understanding the genetic architectures of ASD may allow more precise diagnosis. Brain imaging may provide accurate biomarkers underlying defects in specific brain regions. Combining genetic, behavioral and brain imaging approaches would make the diagnosis of ASD more comprehensive and provide insights into the therapeutic efforts.

From the neuroscience perspective, understanding the pathophysiology and abnormal neural circuits of ASD may provide ultimate insights into therapeutic approaches. Neural modulation methods, such as deep brain stimulation, transcranial magnetic stimulation and transcranial direct-current stimulation, have provided possibilities of modulating neural activity in psychiatric patients, thus sheding insights into effective intervention of ASD and major depression.

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