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REVIEW

Genomics in Neurological Disorders

Guangchun Han [1,2], Jiya Sun [1,2], Jiajia Wang [1,2], Zhouxian Bai [1,2], Fuhai Song [1,2], Hongxing Lei [1,3,*]

[1] *CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China*
[2] *University of Chinese Academy of Sciences, Beijing 100049, China*
[3] *Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing 100053, China*

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Abstract Neurological disorders comprise a variety of complex diseases in the central nervous system, which can be roughly classified as neurodegenerative diseases and psychiatric disorders. The basic and translational research of neurological disorders has been hindered by the difficulty in accessing the pathological center (*i.e.*, the brain) in live patients. The rapid advancement of sequencing and array technologies has made it possible to investigate the disease mechanism and biomarkers from a systems perspective. In this review, recent progresses in the discovery of novel risk genes, treatment targets and peripheral biomarkers employing genomic technologies will be discussed. Our major focus will be on two of the most heavily investigated neurological disorders, namely Alzheimer's disease and autism spectrum disorder.

Introduction

Neurological disorders include a wide spectrum of diseases in the central nervous system (CNS). Up till now, hundreds of neurological disorders have been classified, with symptoms varying from cognitive dysfunction to manic behavior or depression [1]. Due to the complex nature of this group of diseases, it is difficult to identify the mechanisms using conventional methodologies, where only small pathways around specific target genes are investigated. The advent of systems biology approaches has made it possible to study these complex problems from the whole-genome perspective. In the recent years, genomic technologies have been increasingly applied to the investigation of neurological disorders [2]. Exciting discoveries have thus emerged including novel risk genes, peripheral biomarkers and treatment targets. For the convenience of the limited space, we will mainly focus on two of the most studied neurological disorders, Alzheimer's disease (AD) and autism spectrum disorder (ASD).

AD is a major form of neurodegenerative diseases [3]. AD starts from memory loss and cognitive deficit in the early stage and gradually evolves into severe dementia in the late stage. The pathological hallmarks of AD include extracellular deposit of amyloid plaques and intra-neuronal neurofibrillary tangles (NFT). Although the disease-causing mutations have been identified for the familial early-onset AD (FEOAD), the genetic landscape has been perplexing

* Corresponding author.
E-mail: leihx@big.ac.cn (Lei H).

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for the late-onset AD (LOAD) that constitutes ~95% of all AD patients [4]. The prevailing hypothesis for the disease mechanism of AD has been primarily based on the studies of FEOAD, which advocates the central role of amyloid-β (Aβ) in the chain of events leading to neuronal death and cognitive and behavioral symptoms. However, Aβ-based interventions have not been successful in the clinical trials so far [5]. Due to the lack of effective treatment for curing or slowing down AD, it becomes imperative to search for novel risk genes and drug targets, as well as biomarkers for early diagnosis.

Autism spectrum disorder is a neurodevelopmental disorder characterized by social and communication deficit as well as stereotyped and repetitive behaviors [6]. According to a recent survey, 1 in 68 US children has ASD. In contrast to AD, the disease onset for ASD starts from 3 years of age to early childhood. The gender ratio is approximately 4:1 disfavoring boys. Like other psychiatric disorders, there are no clear pathological hallmarks for ASD [1]. It is believed that brain wiring is altered in ASD children, although the exact interplay between gene and environment has not been clarified. In terms of the genetic factors, some types of ASD may be caused by rare mutations, while others may be due to the combination of common variations [7]. The genetic alterations in ASD are also more complex than those in AD, which include copy number variation, insertion, deletion and single nucleotide polymorphism (SNP). In addition to the genetic and environmental factors, prenatal and perinatal factors may also contribute to the development of ASD.

Genomic studies of neurological disorders involve the investigation of the genome, transcriptome and epigenome (**Figure 1**). There are two types of technologies available for genomic studies, including sequencing and various array platforms. For the investigation of genomic variation, the samples generally come from peripheral blood, although saliva has also been used. For the investigation of transcriptome, brain tissue is the most studied since it is more relevant to the disease mechanism. The peripheral blood and cerebrospinal fluid (CSF) have also been investigated, mostly for the discovery of novel biomarkers. These three tissues have also been utilized in the investigation of epigenomic alteration. In addition, skin fibroblast has been increasingly used in induced pluripotent stem cell (iPSC) technologies. Recent advances in these fields will be summarized in the following sections.

Brain transcriptome studies

Since the disease mechanism for most of the neurological disorders is still under debate, it is necessary to conduct investigation from a systems perspective. In brain transcriptome studies, information regarding gene expression at the whole genome level can be extracted, and the dysregulation of gene expression in a disease condition can be revealed by comparing the gene expression with that from the matched healthy controls. Microarray platforms have been the main workhorse for brain transcriptome studies due to the mature technology and low cost. Sequencing technology has been increasingly used since 2008, but generally limited to small sample size due to the high cost. Although it is extremely challenging to collect relevant brain tissues for transcriptome studies considering the stringent requirement of short post mortem delay, dozens of brain transcriptome studies have already been performed and much of the original data have been released to the public [8,9].

Aberrations in the control of gene expression might contribute to the initiation and progression of AD [10] and other neurological disorders. In a recent work, Zhang et al.

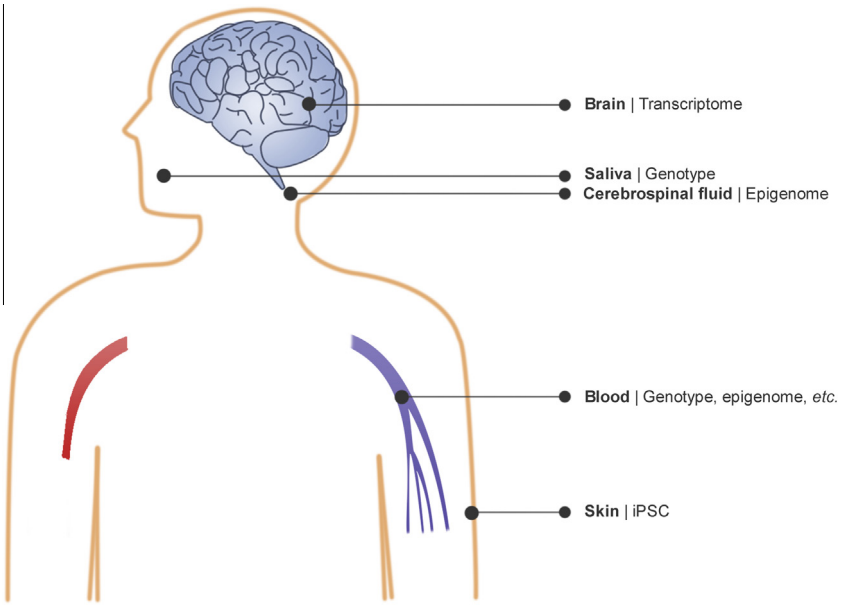

Figure 1 Application of genomic technologies to the investigation of neurological disorders
High quality brain tissues can be used in transcriptome study, in addition to the examination of pathological hallmarks. Samples for genotyping and whole exome/genome sequencing generally come from peripheral blood or saliva. Transcriptome and epigenome profiling can also be performed on peripheral blood and cerebrospinal fluid in addition to other biomarker studies. Skin fibroblasts can be reprogrammed or trans-differentiated into neurons for comprehensive analysis of the dysfunctional network in patients.