Editorial

Systems Genetics of Alzheimer’s Disease: From GWAS to Disease Pathways

The increasing availability of high-dimensional omic data, such as Genome-wide Association Studies (GWAS), transcriptomic, and metabolomic data, makes it possible to identify molecular characteristics potentially associated with Alzheimer’s Disease (AD) pathology. The present contributions in this Thematic Issue reflect the efforts of the most relevant research groups in the scientific field of omics research and the challenge the use of “Big Data” in AD.

Although GWAS have identified novel associations underlying susceptibility to AD, most of these genetic variants explained only modest fractions of disease heritability. Thus, it is crucial to shift from the view of single gene to a pathway perspective, in which system-wide interactions in multiple biological levels together define the disease state. Pathway- and network-driven models provide ideal vehicles for integrating relevant findings from GWAS and other modalities to enhance understanding of disease mechanism. The paper contributed by Shen and Liang et al. applied Dense Module Search algorithm, which proposed a “dual-evaluation” strategy to investigate collective effects of multiple genetic association signals for Alzheimer’s disease on an AV-45 PET measurement [1]. Their investigation of co-operating groups of genes, not only confirmed previously reported AD genes, but also highlighted several new candidate genes, their genetic functional relationship and molecular pathways underlying AD, and other types of neurodegenerative diseases.

Whole transcriptome analyses may offer new insights into the pathophysiology of AD from a systems perspective [2]. By using a qualitative methodology based on within-sample relative expression orderings of genes, Hong et al. examined the gene expression patterns in four brain regions of AD and proposed that two main distinct expression patterns existed in AD. Therefore, it was concluded that that aging might be one of the reasons for the heterogeneous expression of AD [3].

Metabolomics, which measures the biochemical products of cell processes downstream of genomic, transcriptomic, and proteomic systems, has generated significant research interest because of its potential to capture early AD-related changes of metabolites. An increasing evidence has shown that the gut microbiota plays a potential role in the pathogenesis of AD, therefore, it is essential to examine alterations in metabolites of Outer Membrane Vesicles (OMVs) secreted by gut microbiota. In this issue, Liu and colleagues made an effort to provide an insight into this matter. They identified 18 specific metabolites altered remarkably in the OMVs of AD patients. The pathway and function analysis identified that several of the most commonly altered metabolic pathways are associated with AD, including the cholinergic synapse, tryptophan metabolism, phenylalanine, tyrosine, and tryptophan biosynthesis pathways [4]. The metabolic signatures identified might provide insights into further understanding of alterations in complex biological networks involved in AD.

Genome-wide association studies have identified variants of the gene that encode Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) - an endocytic-related protein - as risk factors for Late-onset AD (LOAD). However, subsequent replication studies on the association between PICALM gene variants and AD have revealed inconsistent results. The paper by Zeng et al. conducted an updated meta-analysis to highlight the current evidence on the roles of three polymorphisms (rs3851179, rs541458, and rs592297) of PICALM gene in susceptibility to AD. Through a more comprehensive searching approach, their results provided evidence of a significantly decreased risk of AD for rs3851179 and rs541458 polymorphisms under all genetic models, but no association between rs592297 and AD risk [5]. SNP rs3851179 may confer reduced AD risk by increasing PICALM expression in the microvasculature [6].

The role of Cyclin-dependent kinase 5 (Cdk5) in the pathology of AD has been of great significance in the last decades. An abnormal elevation of Cdk5 activity is associated with Aβ generation, and synaptic abnormality observed in the AD brain. Recently, an integrative computational evaluation (by integrating large scale literature knowledge data, independent gene expression data and related pathway/network information) confirmed CDK5 as an AD candidate gene [7]. The review by Cai’s group provided a review of the current literature on how Cdk5-related microglial dysregulation is associated with AD, with special attention to its impact on β-amyloid plaques and tau pathology [10].
SUMMARY AND OUTLOOK

Advances in high-throughput technological tools such as genomics, transcriptomics, proteomics, and metabolomics, together with the development of novel computational and statistical tools have improved the approach to the study of complex diseases such as AD. It is anticipated that this Special Issue of Current Alzheimer Research will be of great value to many investigators and it will inspire new and transformative multi-omics research in the realm of AD pathology.

REFERENCES


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