

Meeting report

Keystone Symposium 2009 The Molecular Basis of Schizophrenia and Bipolar Disorder

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강은채

*Institute of Genetic Medicine, Institute for Cell Engineering
Johns Hopkins School of Medicine*

To whom correspondence should be addressed email : ekang5@jhmi.edu

목 차

- I. Introduction
- II. The molecular basis of schizophrenia and bipolar disorder:
what do we know? What do we need?
- III. Genome-Wide studies of disease-related variation
- IV. Genes and pathways
- V. Evolution and development of the brain
- VI. Concluding remark

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The Molecular Basis of Schizophrenia and Bipolar Disorder

I. Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are severe mental illness characterized by psychosis and mood and cognitive disorder. More specifically, SCZ is characterized by deficit in the perception or expression of reality and commonly SCZ patients manifests auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with dysfunction in social and occupational skills. BP is a condition in which patient experience abnormally manic or hypo manic and abnormally depressed states for a period time in a way that interferes with normal functioning. Sometimes manic episodes lead to psychotic symptoms such as delusions and hallucinations. It is believed that both genetic and environment factors contribute to these psychiatric disease. Due to candidate gene identification by genetic studies and advance in neuroscience and developmental biology, it is likely that we are stepping more closely to elucidating the etiology of SCZ and BD. To discuss the molecular bases of SCZ and BD, this meeting brought together experts studying on different aspect of SCZ and BD, including genetics, neurobiology, cell and developmental biology, psychiatry, and chemical biology. The topics explored in the meeting was including genetics implicating new genes, loci, and genetic variation in disease; the status of epidemiology; several candidate genes and pathways, and their implication in brain development; new therapeutic approaches based on candidate pathways.

II. The molecular basis of SCZ and BD: what do we know? What do we need?

The meeting was started with keynote address by Dr. Tom Insel from National Institute of Mental Health(NIMH). Under the title of “The molecular basis of SCZ and BD: What do we know? What do we need?” Firstly, he emphasized the following several facts about the SCZ and BD;

1) Early onset and chronic course of disease

2) High disability and early mortality

Average mortal age for SCZ and BD is 56 years old, which is about 25 years shorter than the general population.

3) High heritability and complex genetics

Genome wide association studies are believed to identify common variants with low penetrance. Even though 90% of found associations are weak in non-

coding region, those are thought to do crucial role in finding pathways and effective treatment. He said that “Complex means “diverse” not “weak” .”

4) Developmental brain disorders and complex circuitry

Previously, it has been shown that the number of cortical synapse decrease as individuals is getting older. In case of psychosis patients, this number could be initially very low or, the decreasing rate is higher than normal. Since SCZ and BD are developmental brain disorder, it is believed to be predictive (68-80%) based on genetic risk, psychosis, social impairment and substance abuse.

5) Economic burden of serious mental illness

Serious mental illness is economically severe public burden. For Americans between age 15 and 44, SCZ and BD are among the top 10 sources of medical disability.

Secondly, he suggested NIMH vision for serious mental illness; early prediction, preemptive treatments, and personalized care. For biomarkers for early prediction or detection, intervention of adolescents with the prodrome and personalized treatment, he said, we need to know more about the pathophysiology of these disorders. Finally, he stressed therapeutic implication. Based on a deep understanding of the molecular basis of these disorders, molecular medicine discovery cycle begin; identification of gene, moves on the detection of cellular pathway, ending with screening of small molecules and drug development.

III. Genome-wide studies of disease-related variation

In this section, newly identified candidate genes and loci based on genome wide association studies by many groups and their biological relevance to SCZ and BD will be discussed. Also, several speakers mentioned limitation of current strategy.

Dr. Pamela Sklar from Harvard Medical School introduced newly found candidate genes for BD by genome-wide association Studies (GWAS). CACNA1C, voltage-gated calcium channel gene, showed significant association with BD. Ankyrin G also strongly associated with BD, which is not related to sex, psychosis, age of onset , and its odd ration was ~1.45. It is known to coordinate large protein complex at specific membrane sites. She also gave newly found gene lists, which are strongly associated but genome wide p-value is not less than 10^{-5} ; SYNE 1 (odds ratio:1.22, its mutation

associated with autosomal cerebella ataxia 8), ZNF659 (odds ratio: 1.23), ARNT2 (promoter region), NPAS3(odds ratio: 1.6, translocation(t(9:14)(q34;q13), in third intron was found a SCZ patient)

Dr. Patrcik F. Sullivan from University of North Carolina at Chapel Hill described meta analysis of twelve GWAS of 14,000 cases with SCZ and 12,000 controls. GWAS finding to date for SCZ can be searched at <http://genome.gov/26525384>. According to finding so far, over 200 strongly significant associations have been yielded in human genetics However, 90% of SNPs associated are not in coding region, only 8% are non-synonymous change, and 43% are even not in a gene. That makes it harder to find their biological relevance. As a result of meta-analysis, he found some common genetic variants with low penetracne, but strongly associated; ZNF804 A, and MHC (protective for SZC). As a rare allele but strongly associated loci, 15q13 (odds ratio (OR): ~11 for autism, mental retardation, seizure0, 1q21 (OR: ~13 for autism, cephalo), 16p11(OR:~10 for autism, SZC, BD). He stressed several points that are missing in current GWAS; variable coverage of common variation, bias by European based studies, non-SNP variation(ex, indels, small repeats, etc), rare variants that are not large copy number variations(CNVs), CNV assays are imperfect in terms of size, sensitivity, and specificity limit , regions "masked-out" (retroelements) or "misses" (retroposons)

Dr. Jonathan Sebat at Cold Spring Harbor Laboratory gave a talk about analysis of genomic CNV in psychiatric disease. Sporadic case of disease occurs by spontaneous mutation, which accounts 25% of cases. Especially, CNV "hot spots" result in recurrent spontaneous mutation by non-allelic homologous recombination manner at a high rate (~1/1000), conferring high risk of disease. Example of recurrent CNV loci are 1q21, 15q11 and 15q 13. Recurrent microduplication region, 16p11.2, spanning 500kb which contains ~27 genes, has been associated with early onset of SCZ and also found de novo case of autism (AUT). OR of this CNV for SCZ, AUT and BD is 10, 15.7 and 4.5 respectively. Also, this region is significantly associated with head circumference. Individuals with duplication of this region showed reduced white matter volume. CNV in 1q21.2 also has been implicated in association with SCZ and head circumference. Microdeletion of this region is strongly associated with microcephaly. Whether the genes in 16p11.2 and 1q21.1 function in common pathway or not remains to be elucidated.

IV. Genes and pathways

In this section, speakers discussed about the candidate pathway responsible for SCZ and BD. DISC1, D2 dopamin receptor and NRG1/ErbB4

signaling were discussed. In this report, only DISC1 signaling will be covered.

Disrupted-in Schizophrenia 1(DISC1) was originally identified at the breakpoint of a balanced translocation which segregates with SCZ, BD and major depression in a large Scottish family. As supportive genetic findings have emerged and biological function has been elucidated, it has become one of the most consistent and coherent candidate genes. In this section, DISC1 function in brain development and its cellular signaling will be covered.

Dr. David J. Porteous from University of Edinburgh discussed about new findings for physical and functional interaction of DISC1 with PDE4, NDE1 and NDEL1 at synapse. He suggested the evidence for phosphorylation site of NDE1 by PKA, and this process may be modulated by PDE4B. He also provided supportive data that mouse DISC1 variants which confer specific psychiatric endophenotype showed altered binding to PDE4 and altered PDE4 activity.

Dr. Li-Huei Tsai at Massachusetts Institute of Technology discussed about DISC1 signaling in regulating neural progenitor proliferation. Her group found that DISC1 is highly expressed in neural progenitor cells and is required for their proliferation during embryonic and adult neurogenesis. She also provided the evidence indicating that DISC1 regulates the GSK3 β activity through direct physical interaction, which inhibit the phosphorylation of β -catenin by GSK3 β , and stabilize the β -catenin. This signaling leads to proliferation of neural progenitor cells. Finally, she discussed biological relevance of this signaling to psychiatric illness. Decreased in neural stem cell proliferation have been reported in SCZ patient. Genetic or pharmacological inhibition of GSK3 β in mice showed reduced mania-like behavior. Moreover, lithium chloride, a well established medication for BD inhibits GSK3 β activity like DISC1. She emphasized that these facts provide important insight into pathophysiology of psychiatric illness and potential therapeutic targets.

Hongjun Song at Johns Hopkins Univ. School of Medicine discussed the role of DISC1 in Neuronal development. DISC1 is highly expressed in dentate gyrus of hippocampus of developing and adult mouse brain. His group used retrovirus mediated birth dating and genetic manipulation of dentate granule cells during developing and adult dentate gyrus, and examined the function of DISC1 in regulating neuronal development and integration in vivo. New neurons with DISC1 knockdown showed irregular morphology with enhanced dendritic outgrowth and bigger soma size, accelerated migration and axon mistargeting. These cells develop more spines, but fail to maintain the mature forms. To explore the functional interaction of DISC1

in vivo, his groups examined the new neurons with double knockdown of DISC1 and its interacting partners; FEZ1 and NDEL1, and provide the evidence for their interactions in vivo. Finally, he introduced interesting techniques that the induced pluripotent stem cell from fibroblast of psychiatric disorder patient can be differentiated into neuronal cells and these cells can be transplanted into mouse brain and integrated as functional neurons. That will provide new insight to understand the etiology of psychiatric disease by using human neuronal cells.

V. Evolution and development of the brain

To understand the human brain development compared to other species, some groups focused to investigate the evolution of human genome. In this section, studies on human specific genomic function on brain development will be discussed.

Dr. Fred H. Gage from the Salk Institute for Biological Studies suggested the new role of L1 retrotransposon elements in neuronal diversification as a new mechanism. His group added reversed sequence of EGFP gene containing intron into 3' UTR of L1 gene, which made it possible to label with GFP only the cells with active L1 transcription. As an example of potential role of L1 in neuronal diversification, he suggested that L1 insertion in the promoter region of psd-93 increases its expression and results in more neuron cell differentiation rather than astrocytes or glia cells. He showed that L1 promoter region has Sox2 binding site and CpG islands, and provided evidence that L1 expression is regulated by Sox2 and MeCP2. For supportive data, he demonstrated that MeCP2 knockout mouse showed increased L1 insertion. In conclusion, he provided the model that L1 expression is repressed in neural stem cell by MeCP2 and SOX2, but in neuronal progenitor cell active L1 changes Psd-93 expression, causes neuronal cell differentiation. The somatic neuronal diversification implicates not only the relevance for the understanding of brain complexity and neuronal organization in mammals, but also shed light on the differences in cognitive abilities, personality traits and psychiatric conditions.

Dr. Bruce T. Lahn at University of Chicago, talked about the fast-evolving genes of the human brain. His group surveyed 214 brain genes and 95 non-brain genes, then compared how many nonsynonymous changes occurred during unit biological clock in primates (Human and Chimpanzee) and rodents (mouse and rat). While there is no difference in change rate of brain physiology genes, brain development genes and unclassified genes evolved faster in primate than in rodents. To explore the relevance of microcephaly to brain

evolution, he investigated microcephaly gene evolution rat, as a result, in primate microcephaly gene evolve 3 times faster than rodents, while total genes average was very similar. When he looked at the Microcephalin gene, a specific regulator of brain size, excess of amino acid change was found in that gene. Similar result was observed with ASPM gene, another microcephaly gene. Those excess nonsynonymous changes are thought to be accumulation of positive selection on polymorphism profile, since advantageous mutation hit build haplotype very quickly as seen in his data (30% of population have same haplotype). His research gave a new insight on the genetic basis of human evolution.

VI. Concluding Remark

Neuropsychiatric disorders like SCZ and BD are very challenging to elucidate its etiology and pathophysiology and develop therapeutic drugs; lack of understanding of neurobiology of higher cognition, emotion regulation and executive function, limited access to human experimental neurobiology, lack of useful animal model for cognition, emotion and other brain function, and its complexity based on the genetic interaction as well as genetic and environmental interaction. In spite of its daunting challenge, this meeting brought promising insight based on recent advance in neuropsychiatric genetics and neuroscience. It was good opportunity to integrate molecular studies across basic and clinical disciplines and facilitate building new approaches.

Keywords: schizophrenia, bipolar disorder, neurodevelopmental disorder, genome-wide association studies, DISC1, β -catenin, adult neurogenesis, transposable elements, L1, brain development

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