

## Editorial

# Beyond the Kraepelinian Dichotomy of Schizophrenia and Bipolar Disorder

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The Kraepelinian dichotomy between schizophrenia and bipolar disorder has been a major classification for these mental disorders and is being challenged by new knowledge from the rapid progress in genomics, epigenetics and technological advances [1-3]. Indeed, pharmaceutical efforts and success using second-generation antipsychotics for either of those diseases have changed the interpretation of the biological similarity, including family histories, despite phenotypic differences between schizophrenia and bipolar disorder. Schizophrenia and bipolar disorders share genetic and environmental risk factors and comorbidity, but also medication and neurobiological mechanisms. However, in the meantime, from a clinical point of view, accurate diagnosis is often necessary to treat depressive patients for long period of their life time. Antidepressants sometimes cause unpredictable response, such as manic switch and less effective, for the patients, if they are not suffering from unipolar depression. Regardless of these clinical observations, there are some common genetic factors in schizophrenia, bipolar disorder and depression as brain disorders. Here we focus on how common disease-vulnerability genes that we analyze in our research overlap with genetic susceptibility for the development of different phenotypes and clinical progress necessary for the diagnosis of psychiatric disorders. Further, if the candidate genes were not specific to the disease, it may be difficult to detect them by gene association study using unarranged case-control subjects.

Schizophrenia has high heritability estimated at over 80% and more than 50% of recurrence risk was found in monozygotic twins [4]. Bipolar disorder, especially type I, has similar heritability to schizophrenia, and comparatively lower genetic influences have also been found in bipolar disorder type II and major depressive disorder. More than 60% of the genetic influences are from common genes among schizophrenia and bipolar disorder, which have been calculated in large family data in Sweden [5]. A number of genetic studies of bipolar disorder, schizophrenia and major depressive disorder have also accumulated shared genetic factors between these disorders [6], while relatively small amount of shared genetic influence was reported between bipolar disorder and unipolar depression [7]. Another point of view is that gene expression analysis revealed 78 candidate genes commonly altered in schizophrenia and bipolar disorder which are

functionally categorized into nervous system development, immune system development and response, and cell death [8]. This is because genetic factors alone, including shared and non-shared, are not the complete cause of these disorders, as shown in twin studies and as described above. Thus, psychological, immunological, or chemical (toxic) stressors may lead to the development of psychosis accidentally and inescapably at and before onset. Our body/brains may experience fragile periods to these stressors based on age, sex, and any other body conditions. Different stressors or even same stressors at different times could lead to the development of certain functional changes in brain to develop different psychiatric disorders. Works from another labs indicated that psychosocial risk factors such as shared environmental factors are found more between schizophrenia and psychotic major depression, than between major depression and bipolar disorder [9]. However, more research is needed including paying attention to different stressors but also to life events from prenatal to ageing throughout life span. Using the general control and case subjects might harbor genetic association in the primary and meta-analysis studies. In the future genomic, transcriptomic, and metabolomic analysis for the psychiatric disorders, we need to pay attention when collecting human subjects. Here is one example from our previous studies. In the genetic association study for alcoholism in Japan, we planned to collect the subjects with shared environmental factor (s) for both of the cases and the controls. Thus we use “super controls” that drink occasionally, no more than twice a week but also drink at least sometimes in a week or a month, because the people who never drink alcohol have no chance to feel reward from alcohol and to develop alcoholism [10]. We also collected subjects for drug abuse case-control study, in relatively distinct living area of the people in the limited periods of sample collection, because it could mimic the noise of environment from public security and culture across the area [11,12]. With regards to schizophrenia and mood disorders, it is more difficult to prepare such “super controls”, unless we can specify the disease gene and/or specific stress as life event for the psychiatric disorder. To speculate on these environmental factors that could disrupt brain function with corresponding genetic dysfunction that had been detected by human genome studies, we analyzed the behavior of genetically modified animal model treated with corresponding stressors.

Our previous genetic studies have indicated associations between cannabinoid Cb2 receptor (CNR2) gene polymorphism and all of schizophrenia, depression and alcoholism. More work is needed to reveal the neural mechanisms why the single gene dysfunction is associated with different psychiatric disorders. It is also noted that naïve Cnr2 knockout mice did not show any apparent behavioral abnormalities. Thus, difference of environmental factors at certain fragile periods of life-time seems to be associated with different phenotypes based on Cb2 receptor dysfunction, which could explain intermediate human diseases' phenotypes. Our studies have

implied a certain role of cannabinoid Cb2 receptor in anxiety and in depression induced by chronic mild stress in adult mice [13], and in hypersensitivity to methamphetamine as schizophrenic phenotype [14]. To identify roles of the receptor in schizophrenia and bipolar disorder, it is necessary to study additional stressors burdened in prenatal and adolescent periods, in addition to adult, in order to prove neurodevelopmental disorder hypothesis for those disorders. We have been attempting to reveal that certain combination of life stressors including immune response to virus, infections, undernutrition, marijuana or amphetamine use contribute differential to psychiatric disorders. Such animal models may contribute to understanding human psychiatric disorders in order to establish prophylaxis and new personalized medical therapy for the specific type of psychiatric disorders.

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