Abstract

Schizophrenia is a complex disorder affecting approximately 1% of the population worldwide. It was proposed that schizophrenia is affected by combination of multitude of genetics and environmental factors and only when the combined effect of these factors exceed the liability threshold will an individual be affected by schizophrenia. It is therefore vital to understand how certain genetic polymorphisms and environmental risk factors predispose an individual to schizophrenia. This information will be crucial for the development of treatment(s) or cure(s) for schizophrenia.

Twin studies and population studies have estimated that the genetic variations account for ~80% of the population variance in disease liability of schizophrenia. Recently Genome Wide Association Study (GWAS) has also helped to identify 108 genetic loci that might be associated with schizophrenia. This provide valuable resources for the estimation of the contribution of common genetic variants, particularly Single Nucleotide Polymorphism (SNP), to schizophrenia.

On the other hand, prenatal infection has been identified as the single largest environmental risk factor of schizophrenia. It was estimated that prenatal infection may account for 33% of the schizophrenia cases. The molecular signature induced by maternal immune activation (MIA) in the brain might help the understanding of the molecular mechanism of schizophrenia to the brain.

In this thesis, we proposed an alternative approach for estimating the contribution of SNP to schizophrenia (SNP-heritability) from GWAS summary statistics, called the SNP Heritability and Risk Estimation Kit (SHREK). Our simulation results suggest that when compared to the existing method (LD SCore regression (LDSC)), SHREK can provide a more robust estimate for oligogentic traits and in case-control designs where no confounding variables was present. Using the latest GWAS summary statistics of schizophrenia, we estimated that schizophrenia has a SNP-heritability of 0.174 (SD=0.00453), which is similar to the estimate of 0.197 (SD=0.0058) by LDSC. Our estimate suggest that common SNPs have relatively less contribution to the genetic predisposition of individuals to schizophrenia as measured by the heritability estimated and alternative method in addition to GWAS might be required to identify genetic polymorphisms contributing to variance of schizophrenia.

We also performed a hypothesis generating study for the effect of MIA on the gene expression pattern of mouse cerebellum. By using the polyriboinosinic-polyribocytidilic acid (PolyI:C) mouse model we might obtain potential candidates for effect of MIA. Additionally, recent study has shown that n-3 polyunsaturated fatty acid (PUFA) rich diet can help to reduce the schizophrenia-like phenotype in mice exposed to early MIA insults yet its mechanism remains unknown. We took the opportunity here to also study the effect of n-3 PUFA rich diet in the mouse cerebellum. In this study, we found that pathways related to neural functioning and calcium ion signally were likely to be disrupted by MIA in the cerebellum, concurring with previous genetic studies in schizophrenia. We also found that *Sgk1*, a gene that can regulate the glutamatergic system, is potentially affected by the n-3 PUFA rich diet in the PolyI:C exposed mice.

Together, our results suggested that genes related to neural function or calcium ion signaling, as well as glutamate-related genes such as *Sgk1*, might serves as potential targets for schizophrenia researches.

(516 words)