Abstract

Schizophrenia is a complex and debilitating psychiatric illness, of a largely unknown etiology and pathophysiology. Although we cannot see human schizophrenia-imitating phenotypes in mice, it would be possible to infer disease-associated genes using mice. This should be feasible when we target “endophenotypes”. Endophenotypes are measurable internal biological markers associated with complex diseases. Among them is prepulse inhibition (PPI). PPI is the normal suppression of a startle response when a low-intensity stimulus, eliciting little or no behavioral response, immediately precedes an unexpected stronger startling stimulus. PPI is observed in all mammals tested to date, and even in invertebrates. Importantly, measurements are possible under nearly identical conditions between humans and rodents. Biologically, PPI is a reflection of sensory motor gating mechanisms within the central nervous system, and impaired PPI is regarded as an endophenotype for schizophrenia. Endophenotypes provide simpler genetic clues to pathogenesis than the disease syndrome itself, allowing for easier analysis of disease. It is hoped that identifying genes that underpin PPI could help in deciphering the complex polygenic mechanisms that predispose to schizophrenia. To map the genetic loci determining PPI, we performed large-scale quantitative trait loci (QTL) analysis using selected inbred mouse strains. QTL analysis is a method of localizing chromosomal regions harboring genetic variants that affect a continuously distributed, polygenic phenotype. Molecular dissection of the mouse genome identified genes as promising causative candidates. We then performed the following studies regarding the genes identified using mice:

1. Functional consequences of the genes elicited by polymorphisms between different mouse strains
2. Genetic association analyses to see whether human orthologues have a role in schizophrenia
3. Genomic screening of the genes using schizophrenia samples and functional assessments of the detected variants

I will explain those results in my talk.

References: