Symposium 2: Molecular and Cellular Neuropsychiatry (Wed July 28, 9-11AM JST)
Chair: Akira Sawa (Johns Hopkins Univ, Baltimore, USA)

9:00-9:30 Jeong-Ho Lee (KAIST, Daejeon, Korea)
Brain somatic mutations disrupting neural circuits

9:30-10:00 Atsushi Takata (RIKEN-CBS, Wako-Saitama, Japan)The rare variant genetics of neuropsychiatric disorders; exome sequencing and beyond

10:00-10:30 Jacque Pak Kan Ip (The Chinese Univ of Hong Kong, China)
Investigating the roles of circular RNAs in synaptic plasticity

10:30-11:00 Minae Niwa (The Univ of Alabama at Birmingham, USA)
Adolescent social isolation-induced vulnerability to postpartum mental disturbance via prolonged dysregulation of the HPA axis

Symposium 2 Speaker 1:

Jeong-Ho Lee
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Brain somatic mutations disrupting neural circuits

Mutations occur during cell division in all somatic lineages due to the unavoidable DNA replication errors. Because neural stem cells continue to undergo cell division throughout human life, somatic mutations in human brain can arise from neural stem cell (NSC) niches during development and accumulate with the aging process. Although somatic diversity is an evident feature of the brain, the extent of somatic mutations affecting the neuronal structure and function and their contribution to neurological disorders remain largely unexplored. We have provided the molecular genetic evidence that brain somatic mutations arising from NSC indeed lead to the structural and functional abnormalities of brain and neural circuits observed in intractable focal epilepsies (Lee et al, Nat Genet 2012; Lim et al, Nat Med 2015; Sim et al, Neurol Genet 2018; Park et al, Neuron 2018; Sim et al, Acta Neuropathol 2019; Kim et al, JCI 2019; Kim et al, Ann Neurol 2021; Koh et al, Ann Neurol 2021), Schizophrenia (Kim et al, Biol Psychiatry 2021) and Alzheimer's disease (Park et al, Nat Commun 2019) as well as brain tumors (Koh et al, Nat Med 2018; Lee et al, Nature 2018). In this symposium, I will discuss about how we can discover brain somatic mutations in neurological disorders with disrupted neural network and understand the biological consequence of them.

Symposium 2 Speaker 2:

Atsushi Takata
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The rare variant genetics of neuropsychiatric disorders; exome sequencing and beyond

The invention of next-generation sequencing technologies has significantly contributed to a better understanding of the roles of rare variants, including newly arising (de novo) mutations, in neuropsychiatric disorders. In particular, large-scale studies focusing on protein-coding genomic regions (i.e. all exons: exome) have been conducted for autism spectrum disorders (ASD) and schizophrenia. In the first part of my presentation, I review key findings in these studies, such as newly discovered risk genes with a large effect size (e.g. odds ratio > 10) and novel knowledge on disease biology. Subsequently, I show the results of our recent family-based sequencing study of bipolar disorder, another common neuropsychiatric disorder for which large-scale analysis of de novo protein-coding mutations has not been reported despite its necessity. Our study indicates that deleterious de novo mutations confer the genetic risk of bipolar disorder, especially of bipolar I and schizoaffective disorders. We also performed a systematic survey of postzygotic (somatic) mutations by a re-analysis of the sequencing data and found that deleterious ones in known developmental disorder genes are enriched in bipolar disorder, leading to a tempting hypothesis that postzygotic mutations of developmental disorder genes may cause psychiatric disorders. Along with the importance of further analyses of postzygotic mutations, I discuss the future direction of rare variant studies of neuropsychiatric disorders in the last part of my talk.

Symposium 2 Speaker 3:

Jacque Pak Kan Ip
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Investigating the roles of circular RNAs in synaptic plasticity

Neuronal circuits in our brain are known to be plastic and are subject to experience-driven changes causing neurons to modify their structure, and functional connectivity and responses. Plasticity refers to the ability of the neuron to reorganize its synaptic connections and functions in response to alterations in sensory experience or learning. We aim to identify novel regulatory mechanisms of plasticity. Circular RNAs (circRNAs) are regulatory noncoding RNAs abundantly found in brain tissue. Their synaptically-enriched, activity-inducible, and developmentally-regulated properties suggest a role in experience-dependent synaptic plasticity. However, functional investigation of circRNAs in neurons is still in its infancy. Little is known about their role in experience-dependent plasticity. Here, we identified unique activity-dependent circRNAs upon plasticity induction. We found that circRNAs were robustly and differentially regulated. We demonstrated the changes of circRNAs in cortical and hippocampal synaptic plasticity. Our study provides evidence of an experience-dependent circRNA that is a crucial regulator of synaptic development and plasticity.

Symposium 2 Speaker 4:

Minae Niwa
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Adolescent social isolation-induced vulnerability to postpartum mental disturbance via prolonged dysregulation of the HPA axis

Pregnancy and delivery are events characterized by significant physical and psychological changes to the mother. Mood disturbances and cognitive impairments affecting mothers during the postpartum period are common and serious mental health problems, which can consequently affect the child's development and behavior. Early life stress increases the risk for postpartum depression (PPD). Lack of corresponding animal models that reflect the influence of early life stress is a knowledge gap in the field. In this presentation, I will show a novel platform to study the biological mechanisms underlying the effects of adolescent stress on postpartum behaviors in first-time mothers. Adolescent social isolation results in the aberrantly sustained elevation of glucocorticoids via hypothalamic-pituitary-adrenal (HPA) axis dysregulation and long-lasting behavioral deficits in the postpartum period. The immobility deficits were effectively ameliorated by post-delivery treatment with a glucocorticoid receptor antagonist, but not by a selective serotonin reuptake inhibitor and an allopregnanolone analog that are clinically used for PPD. I will also demonstrate the significant impact of adverse early life events on the HPA axis dysregulation and PPD in humans, supporting the validity and utility of the novel model for a subset of treatment refractory PPD.