Form 2-4-2

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Program FY2016- FY2018: Report

Field: Neurobiology of Disease

1. Principal Researcher
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Title Professor
Affiliation Graduate school for Frontier Biosciences, Osaka University

2. Project Title: Epigenetic regulation for neural network formation on psychiatric diseases

3. Japanese Group
Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
Takeshi Yagi, Professor, Graduate School for Frontier Biosciences, Osaka University
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4. U.S. Group
Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
Schahram Akbarian, Professor, Icahn School of Medicine at Mount Sinai
Hirofumi Morishita, Associate Professor, Icahn School of Medicine at Mount Sinai

5. Research Period, from/to (mm/dd/yyyy) and total number of years.
From 1 April 2016 To 31 March 2019 (3 Years)

6. Abstract, Results, and Research Significance (300 words):
Mutations associated with neurodevelopmental and psychiatric disorders include at least 50 different genes, each encoding a specific chromatin regulator, highlighting epigenetic regulation as of critical importance for orderly brain development. However, how these epigenetic modulations regulate neural circuit formation and cognitive function are poorly understood. Here we focus on clustered protocadherin (cPcdh) family as a hub linking epigenetic regulation and neural circuit formation for cognitive function through an international collaboration between a US group with an expertise on neuroepinegetics in psychiatric disorder models (Akbarian and Morishita) and a Japanese group with an expertise on cPcdh family (Yagi). US group analyzed the gene expression pattern of cPcdh family in genetically engineered mice with cognitive deficits by deletions of key histone modulating enzymes (Setdb1) in prefrontal cortex. Japanese group examine the circuit deficits and cognitive function by combining viral technology, patch-clamp techniques and behavior testing of mice showing abnormal cPcdh expression pattern. In this collaboration, we report locus-specific disintegration of megabase-scale chromosomal conformations in brain after neuronal ablation of Setdb1, including a large topologically associated 1.2-Mb domain conserved in humans and mice that encompasses >70 genes at the cPcdh locus. The cPcdh topologically associated domain (TAD^{cPcdh}) in neurons from mutant mice showed abnormal accumulation of the transcriptional regulator and three-dimensional genome organizer CTCF at cryptic binding sites, in conjunction with DNA cytosine hypomethylation, histone hyperacetylation and upregulated expression. Genes encoding stochastically expressed protocadherins were transcribed by increased numbers of cortical neurons. SETDB1-dependent loop formations bypassed 0.2-1 Mb of linear genome and radiated from the TAD^{cPcdh} fringes toward cis-regulatory sequences within the cPcdh locus, counterbalanced shorter-range facilitative promoter-enhancer contacts and carried loop-bound polymorphisms that were associated with genetic risk for schizophrenia (Jiang et al, Nature Genetics 2017).

7. Other (Research-related concerns, particular points of note):
Nothing

*Please attach any reference materials as necessary.