Drosophila Models of Complex Neurological Disorders in Humans

Young Ho Koh
Laboratory of Molecular Neurogenetics, ILSONG Institute of Life Science, Hallym University, Korea, 413-060

The fruit fly *Drosophila* has been utilized as a powerful biological system to address fundamental questions concerning neurological disorders in humans, since the basic molecular components and important signal transduction pathways in humans are evolutionaryconserved in *Drosophila*. The clinical symptoms and patho-physiology underlying monogenic neurological disorders including familial forms of Parkinson's disease, Alzheimer diseases, Huntington's disease, and Ataxia have been proven to be faithfully replicated in *Drosophila*, when causative mutant proteins were transgenically expressed in *Drosophila* neurons or cells. Previously unknown molecular and cellular etiologies underlying several neurological disorders were revealed by investigating *Drosophila* models of them. However, more than 90% of reported cases of neurological disorders are complex forms. Inheritance patterns of complex neurological disorders do not follow the law of Mendel's segregation. Nevertheless, complex disorders are more often observed among the families or relatives of affected patients, strongly suggested that theyare most likely to be caused by interaction of multiple genetic mutations or combinations of genetic and environmental risk factors. Predisposing genetic mutations may induce abnormal brain wirings, altered synaptic architectures and functions, imbalances in neurotransmitters, defective neuronal activities, or death of selected types of neurons that are increasing the person's susceptibilities to the onset and progression of complex disorders that are triggered by other genetic mutations or environmental risk factors. Complex neurological disorders are including sporadic forms of Parkinson's disease, Alzheimer diseases, Amyotrophic lateral sclerosis, Dystonia, etc. Our understanding of genetic and environmental risk factors involved with the onset and progression of complex neurological disorders are, however, still rudimentary.Therefore,

identifying unknown factors involved with the onset and progression of complex neurological disorders in humans is one of the major challenges in modern medical sciences and my major research goal as well.

Early onset torsion dystonia observed from teenagers and children all over the world is one of the most severe neurological disorders. Molecular genetic studies identified a glutamic acid deletion mutation in TorsinA protein (DE HtorA) as a causative mutation of this disorder. 30% penetrancy among DE HtorA carriers suggested that early onset torsion dystonia is one of many complex neurological disorder that are required other genetic mutations or environmental risk factors for onset and progression of symptoms. I have generated a *Drosophila* model of early onset torsion dystonia by expressing DE HtorA in neurons. DE HtorA flies showed severe behavioral abnormalities resemble those observed from human patients. Further genetics, biochemical, cell and molecular studies revealed that altered synaptic architectures caused by DE HtorA clusters at synapses, endosomes, or nuclear membrane increased flies susceptibilities to other risk factors that trigger severe behavioral abnormalities. Those behavioral and structural defects were rescued when human or *Drosophila* smad2 were overexpressed. Those evidences suggested that early-onset torsion dystonia is caused by abnormal trafficking of Smad2 between synapses and endosomes or nuclei, resulted in abnormal development of synaptic architectures. Because a *Drosophila* model of early onset torsion dystonia is the first animal model for complex neurological disorders in humans, I am now utilizing early onset torsion dystonia flies to identify and investigate genetic factors that may enhance or suppress behavioral symptoms of this disorder.

Another major interest in my research program is identifying and investigating important molecular components that localize at synapses and regulate proper development of brain wirings and synaptic architectures at the molecular levels. Previous studies in many complex neurological disorders in humans suggested that one or many genetic mutations or variations inducing abnormalities at formation, development, plasticity, and transmission at neuronal circuits or synapses responsible for increased susceptibilities to other genetics or environmental risk factors. I have identified several mutations that increased flies' susceptibilities to high temperatures that are triggered abnormal

behaviors, such as paralysis or uncontrollable seizures. Intensive studies in one of those temperature-sensitive (TS) mutant flies revealed that mutations in an SH3 domain and FCH domain protein, *Nervous Wreck* (*Nwk*) induced abnormal development of dendrites of motor neurons and their synaptic architectures. Localization patterns, genetic interactions, and biochemical data suggested that *Nwk* may regulate homeostatic regulatory mechanisms that prevent synapses and brain circuits from being run away excitation or quiescence state. This is the first report to showing existence of synaptic molecular components mainly involved with homeostatic regulatory mechanisms. Recently I have also identified molecular defects in other TS mutant flies including *Makorin 1* (a ring and zink-finger domain protein;*Mkrn1*), *Heat Shock Protein Cognate 70-3* (*HSC70-3*), *RhoGAP19D*, and *CdGAPr*. Those TS mutant flies will be used to study how geneticdefects in those genes contribute increased flies' susceptibilities to other risk factors.

In summary, my research program would make significant contributions to (I) understanding molecular and cellular etiologies of complex neurological diseases in humans, (II) providing new targets for pharmaco-genetic research aimed at accelerating the development of drugs that might modulate disease progression during the preclinical or clinical periods, and (III) identifying at-risk groups both for disease onset and progress during the preclinical period by enhanced diagnosis.