Functional significance of *NRGN*, a schizophrenia risk gene, in regulating synaptic plasticity and calcium channel activity

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Schizophrenia is one of the leading causes of disability worldwide, and its highly heritable nature implies genetic underpinnings. Genome-wide association studies identified *NRGN* as a risk gene associated with schizophrenia in multiple populations, and individuals carrying the *NRGN* risk variant exhibit decreased hippocampal activation during contextual learning. Neurogranin, encoded by the schizophrenia risk gene *NRGN*, is a neuron-specific, calmodulin-binding protein abundant in the postsynaptic compartments. The expression of neurogranin is reduced in the postmortem brains of patients with schizophrenia, implicating the hypofunction of neurogranin in schizophrenia. Interestingly, the expression levels of neurogranin are rapidly increased in response to elevated neuronal activity in the hippocampus, and the activity-dependent translation of neurogranin is required for contextual memory formation. However, the overall impact of neurogranin levels on the induction of synaptic plasticity remain elusive. Through an integrative approach using whole-cell patch clamp and quantitative phosphoproteomic analysis, we found that neurogranin bidirectionally modulate long-term potentiation (LTP) in the hippocampus by shifting the phosphorylation pattern of postsynaptic density proteins, including glutamate receptors and selective ion channels. In particular, synaptic PP2B activity was required for mediating the deficit in LTP caused by reduced neurogranin levels, thus revealing a novel mechanistic link of a schizophrenia risk gene to cognitive deficits. Lastly, currently ongoing studies highlighting the significance of neurogranin levels in controlling the activity of L-type calcium channels will be discussed.