CHARACTERIZATION OF HUMAN IPSC-DERIVED NEURONS WITH SYNGAP1 MUTATIONS

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Background: Previous studies in mice, have reported that SYNGAP1 heterozygosity results in hyperexcitability in the brain network directly affecting cognitive functions. More recently, de novo mutations in SYNGAP1 gene have been identified and implicated as a causal link to a range of neurodevelopmental disorders and epilepsy. Using in vitro human iPSCs model system, for the first time we propose that SYNGAP1 insufficiency results in neuronal hyperexcitability. We hypothesized that the loss-of-function mutations in SYNGAP1 would cause altered neuronal function as the result of disruption of ERK-AMPA receptor signaling pathway, leading to enhanced excitability. In order to test this hypothesis, we employed MEA system to record spontaneous network electrical activity from the KO vs control cell lines.

Materials/Methods: We have generated an in vitro human stem cell-derived neural model system to study the effects of LOF SYNGAP mutations. We employed Micro-electrode Array (MEA) system to perform neurophysiological characterization of neurons having SYNGAP1 mutations. Cortical neurons were differentiated from engineered iPSC lines having null SYNGAP1 mutations. Neuronal differentiation was performed in two steps: generation of NPCs from iPSC and then neuronal differentiation of NPCs directly after plating them on MEA plates. Neuronal activity was recorded continuously for 5 minutes from the multi-well MEA plate each week, for the period of 6 weeks of the neuronal maturation.

Results: Spontaneous MEA recordings from the iPSC-derived neurons from the KO lines, exhibited increased activity when compared to the WT lines. Firing rates for the KO neurons were significantly higher when compared to WT controls. Both spiking and bursting patterns were significantly higher in KO vs WT. Also, the KO neuronal cultures displayed different degrees of neural network activity, observed as “network bursts”, as early as 3 weeks of maturation.

Conclusions: This study provides an in vitro human model system to study SYNGAP1 mutational effects and as an experimental platform for developing targeted therapies. The KO neural cultures displayed coordinated neural activity at the network level, indicating early on maturation compared to the control neurons, which further supports the idea that SYNGAP dysfunction causes cognitive abnormalities in patients with SYNGAP1 insufficiency by possibly disrupting the neuronal networking. Future work is needed to delineate a causal link between SYNGAP1 insufficiency and neuronal hyperexcitability.