“SNCA gene mutations’ (G209A and G188A) mediated aberrant histone modifications and chromatin remodeling in DA neurons derived from hESCs (A53T- and E46K-induced) and Parkinson’s disease patient-derived A53T-hiPSCs”

Parkinson's disease (PD) is a neurodegenerative disease that affects approximately 1% of the population over 60 years of age and is characterized by the progressive degeneration of midbrain A9-type dopaminergic (DA) neurons in the substantia nigra pars compacta. This degeneration observed in PD can occur either sporadically or due to genetic mutations. Among the genetic mutations, G209A and G188A mutations on the SNCA gene can individually cause early-onset autosomal-dominant PD and lead to A53T and E46K amino acid changes respectively, in α-synuclein, a protein commonly implicated in PD. Histone modifications have also been implicated in PD as past research has reported histone modifications in cellular and animal models of PD. However, human cellular models are required to get a better understanding of changes occurring in PD. Human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) that harbor a PD-causing mutation and their isogenic matched control can be used to study PD. A proteomic study conducted by our lab identified α-synuclein interactions in A53T-induced and wild-type (WT) hESCs and showed that most of the genes coding for the proteins interacting with α-synuclein belong to H4 family. Thus, in the current study, I will focus on identifying histone modifications that occur on H4 in DA neurons derived from SNCA A53T- and E46K-induced and wild-type hESCs and PD patient-derived hiPSCs (A53T-mutated and A53T-corrected). Common histone modifications identified between mutated cell lines will elucidate their potential role in changes in gene expression and chromatin remodeling that can further lead to PD pathogenesis.