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PROGRAMMA

GENERATION OF NOVEL INDUCED PLURIPOTENT STEM CELL MODELS FOR THE STUDY OF SPINOCEREBELLAR ATAXIA TYPE 17

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Spinocerebellar Ataxia (SCA) type 17 is a rare dominant neurodegenerative disease characterized by severe motor and psychiatric symptoms. SCA17 is caused by an expansion of CAG repeats in the TATA-Binding Protein (*TBP*) gene, which becomes longer than 49 repetition and is translated into an elongated polyQ tract in the coded protein. Mutant TBP tends to misfold forming intranuclear insoluble aggregates both in glial and neuronal cell in the cerebellum (mainly in Purkinje cells). TBP forms containing an intermediate polyQ tract (41-47/49 Qs) show incomplete penetrance. Recently, a concomitant heterozygous mutation in *STUB1* gene has been identified to exacerbate the pathogenicity of intermediate TBP alleles, triggering a SCA17 digenic variant (SCA17-DI). STUB1 encodes for the C terminus of HSC70-Interacting Protein (CHIP), an E3 ubiquitin ligase serving as HSP70 co-chaperone involved in protein degradative pathways, probably modulating TBP levels. To identify molecular mechanisms responsible for SCA17-DI, we developed patient derived iPSC models carrying: i) fully expanded TBP (SCA17), ii) intermediate TBP (healthy), and iii) intermediate TBP/STUB1^{mut} alleles (SCA17-DI). Fibroblasts were successfully reprogrammed obtaining 14, 9, and 2 iPSCs clones respectively. Notably, the reprogramming efficiency of SCA17-DI fibroblasts was lower than expected, possibly due to the role CHIP on Yamanaka factors clearance, already described in literature. Selected clones have been characterized for pluripotency markers expression (NANOG, OCT3/4, SOX2) through RT-qPCR, and IF (OCT4, C-MYC, TRA-1-60), as well as for their ability to originate germinative layers. Karyotype evaluation revealed no alterations in chromosomes numbers and morphology. In conclusion, we generated new SCA17 iPSC models useful to study the role of STUB1 in differentiated Purkinje cells involved in SCA17 degeneration.