Generation of human induced pluripotent stem cell lines from two Italian siblings affected by Unverricht-Lundborg disease

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Unverricht-Lundborg disease (ULD) is an autosomal recessive disorder characterized by tonic-clonic seizures, myoclonus, ataxia, and dementia. The main mutation described in ULD patients is an unstable expansion (>30 times) of a dodecamer sequence (CCCCGCCCCGCG) in the promoter of the gene encoding Cystatin B (CSTB), a protease inhibitor. The expansion mutation downregulates CSTB expression and this, in turn, leads to enhanced activity of lysosomal cathepsins with consequent activation of apoptotic events mainly involving cerebellar and cortical neurons. The reported loss of GABAergic hippocampal neurons, and consequent increment of neuronal excitability, may be responsible of seizures and myoclonic episodes. The main objective of this work is the establishment of an *in vitro* model of ULD using ULD patient-derived induced pluripotent stem cells (iPSCs), with the aim of unravelling the molecular mechanisms underlying the disease. ULD patients of this study are two Italian siblings affected by a severe and a mild form of the disease, respectively. Fragment length analysis on CSTB amplified promoter showed that both patients bear the same number of dodecamer repeats on CSTB gene. This is in line with the notion that disease severity does not always correlate with the number of repeats and suggests that other, yet unknown, molecular events may be involved in ULD pathophysiology. Somatic cells from our patients and from a healthy subject have been reprogrammed to iPSCs. Preliminary data performed on iPSCs and on iPSC-derived neural stem cells and neurons show a reduction of CSTB gene and protein expression and, contextually, increased expression levels of cathepsins in ULD cells. Further studies on ULD iPSC-derived neurons undergoing in our laboratory will hopefully shed light on the potential mechanisms responsible for the disease.

Reference:

Lucchino V, Scaramuzzino L, Scalise S, Grillone K, Lo Conte M, Esposito C, Aguglia U, Ferlazzo E, Perrotti N, Malatesta P, Parrotta EI, Cuda G. Generation of human induced pluripotent stem cell lines (UNIMGi003-A and UNIMGi004-A) from two Italian siblings affected by Unverricht-Lundborg disease. Stem Cell Res. 2021 May;53:102329. doi: 10.1016/j.scr.2021.102329. Epub 2021 Apr 9. PMID: 33865103.