Induced pluripotent stem (iPS) cell technology allows studying diseases in a relevant cell type and therefore has the potential to capture pathomechanistic effects that may not be present in conventional *in vitro* model systems. iPS cells derived from patients with a pathogenic familial mutation can be used to investigate dysfunction of such mutations in a patient specific context without artificial overexpression. Gene-editing using the CRISPR/Cas9 technology is a powerful, fast and easy-to-handle tool that enables the generation of isogenic controls differing in only a single DNA base. As such, the use of isogenic lines allows investigating the dysfunction of a pathogenic familial mutation whilst retaining the same epigenetic and genetic background.

Frontotemporal dementia (FTD) is the second most common form of neurodegeneration in elderly people. It is clinically characterized by neuronal loss affecting the frontal and/or temporal lobes resulting in severe atrophy. Several genes have been identified for familial forms of FTD and one of these genes is the charged multivesicular body protein 2B (CHMP2B) located on chromosome 3 (FTD3). Pathogenic mutations within this gene lead to a dominant gain of function of CHMP2B affecting the endo-lysosomal system and therefore interfere with protein degradation and receptor recycling. However, the precise underlying patheomechanism is still poorly understood.

Here, we present the generation of a human disease model for FTD3 based on iPS cells from 3 patients with a mutation in *CHMP2B*. Using the CRISPR/Cas9 technology, we corrected the mutation of the patients and obtained isogenic, gene-corrected controls. Upon differentiation to functional forebrain cortical glutamatergic neurons, mutant neurons showed several disease related phenotypes such as enlarged endosomes, deformed and insufficiently structured mitochondria, reduced oxygen consumption and energy production, as well as increased levels of reactive oxygen species (ROS), all of which were rescued in the isogenic controls.