

Rare disease is defined as a condition occurring in fewer than 1 in 2,000 people. However, taken together, rare diseases affect numerous patients, the current estimates from the National Institutes of Health (NIH) is that there are more than 7,000 rare diseases which altogether affect 8%-10% of the general population. Neurological rare diseases are the largest group representing ~50% of all rare disease cases. According to Rare Genomics Institute (RGI) only ~400 rare diseases have therapies, and about 80% have a strong genetic component. Neurological rare diseases often appear early in life, and about 30% of children with rare diseases will die before reaching the age of five. Early diagnosis of rare disorders is the key to halting disease progression. However, diagnosis of rare diseases can be challenging and is often delayed owing to limited knowledge about these conditions among clinicians, as well as difficulties in accessing specialized services. Because of the unmet medical need caused by rare diseases, these disorders deserve attention in their own right. However, learning more about rare diseases could also provide insights or lead to new treatments for common disorders with more complex etiology. The advent of Next-Generation Sequencing (NGS) has changed the landscape of rare genetic disease research, with causative genes being identified at an accelerating rate. NGS is a powerful, unbiased approach for detecting genetic variation and is currently the popular platform for the discovery of rare-disease-causing genes. This technology has quickly become the method of choice for discovering pathogenic mutations in rare uncharacterized monogenic diseases. Reports demonstrated mutations detection in over 70% of neurological rare diseases by NGS but the subsequent validation of a variant as disease causing is frequently the rate-limiting step and most challenging one. For a well-defined rare disease, the detection of mutations in the same gene in unrelated individuals or families results in a comparatively straightforward genetic validation. However, typically only one family is available for genetic analysis, hence pathogenicity should be supported by functional studies, but in most cases the diagnosis is based on exome sequencing results alone given the laborious work and complexity in establishing causality between the detected variant and the presented phenotype.

Human induced Pluripotent Stem Cells (hiPSCs) obtained by reprogramming technology are a source of great hope for modeling human diseases in vitro, allowing to noninvasive look insight into the cellular processes occurring in the patient organism and also for new drugs testing and development. Thanks to the present revolution in hiPSC technology, cells differentiated in-vitro from hiPSCs can be used instead of human brain tissues for studying disease progression, including disease onset and the time-course of disease advance. hiPSC derived neurons mimic patient specific neural development in-vitro and allow for the generation of specific neuronal subtypes, thus are of major interest to the stem-cell and biomedical community. These cells demonstrate similar features to fetal neurons, enabling the research of congenital neurological diseases. We anticipate that by genome engineering of candidate-genes identified by NGS in hiPS cell lines, differentiation of hiPSCs into neurons, and time-course characteristics of patient specific neurons using, dramatic progress in the elucidation of underlining mechanisms of the investigated rare neurodevelopmental diseases is expected. In this proposal, we outline a pipeline for whole genome scanning, validation of findings in vitro and in depth translational investigation of genes predicted to harbor deleterious effect in rare neurodevelopmental disorders. We reason that this approach can lead to a better understanding of the pathogenesis of these neurological disorders, and for tailored patient based treatment. This study will include 8 cases with rare neurological phenotypes.