Pitt Hopkins syndrome (PTHS) is a genetic developmental disorder that severely affects cognitive, motor and social development. PTHS is characterized by distinct facial features, absent speech, absent or delayed walking, low muscle tone, gastrointestinal problems and autistic-like behaviour. The patients may develop breathing problems and/or epilepsy. PTHS has been diagnosed in less than 1,000 people in the world. It is caused by mutations in one of the two alleles of a gene called TCF4. Most of the mutations found in PTHS patients are of de novo origin meaning that the mutation is not present in the parents. TCF4 gene has attracted wider interest mainly due to the fact that polymorphisms (genetic variations that may create predisposition to a disease) in this gene have been linked to schizophrenia.

TCF4 gene encodes a protein named Transcription Factor 4 (alias ITF2, SEF2 or E2-2). Transcription factors are proteins that regulate expression of genes. There are about 2,000 different transcription factors encoded by the human genome. TCF4 is broadly expressed and involved in the development and functioning of many different tissues and cell types. Evidence is accumulating that in the nervous system TCF4 plays an important role in proliferation, differentiation and migration of neurons, as well as brain plasticity – a process that enables the brain to rewire itself in response to the stimuli from learning and experience.

The goal of the current project is to identify genes that are regulated by TCF4 in the brain neurons. We will generate adeno-associated virus based vectors for overexpression and knockdown of TCF4 protein, identify TCF4-regulated genes and determine the binding sites of TCF4 in its target genes. The knowledge of TCF4 target genes is instrumental in deciphering the role of TCF4 in biological processes that contribute to the pathology of Pitt Hopkins syndrome. It also allows us to test whether increasing the activity of the remaining TCF4 protein (produced from the intact allele in PTHS patients) by pharmacological modulation is feasible for PTHS treatment. Focusing on target genes that are related to brain plasticity, a process that is ongoing lifelong, enables us to obtain insights into adult functions of TCF4 that in turn may represent suitable targets for therapeutic intervention of Pitt-Hopkins syndrome.