

The 22q11.2 deletion syndrome is the most common chromosomal deletion syndrome in humans, with an incidence of 1 in 2-4000 live births. The main characteristic of 22q11 deletion syndrome is an extremely broad phenotypic spectrum, therefore the clinical recognition of the syndrome can be very difficult. More than 180 clinical features, both physical and behavioral, have been described, but no single clinical feature occurs in 100% of cases and there is no reported case of the syndrome that has all or even most of the clinical findings. The 22q11.2 deletion syndrome accounts for ~ 5% of all congenital heart disease cases among live births and is the second most common cause of intellectual disability, accounting for ~2.4% of patients with developmental delay. Other common clinical features are palate abnormalities, characteristic facial appearance, psychiatric disorders, autism spectrum disorder, microcephaly, unprovoked seizures and renal anomalies.

Most affected individuals have a loss (deletion) on chromosome 22q11.2, which includes at least 48 known genes. Hence, it remains unknown why individuals carrying identical 22q11 deletions can present with such a wide range of phenotypes. We hypothesize that the clinical variability is caused by combined occurrence of 22q11 deletion and a “second hit” somewhere in the genome. We expect to identify genes which act as modifiers in 22q11 deletion carriers, located both inside and outside of 22q11 region. Several potential genetic mechanisms underlying clinical variability will be evaluated in the proposed project: (1) coding and non-coding genetic variants within the 22q11.2 region of the non-deleted chromosome 22, (2) variation in the uncharacterized LCRs of the 22q11.2 (3) additional copy number changes elsewhere in the genome (4) coding and non-coding genetic variants in modifier genes that reside outside of the deleted region.

For investigation of genetics modifiers the state-of-art technology will be applied. At the first stage of the project detailed phenotyping of all of 170 patients with 22q11DS is a prerequisite. Next we will perform a whole genome gene-expression analysis from the blood of the recruited patients. We will identify genes with characteristic profiles in patients having a selected symptom or anomaly. Subsequently, we will perform genome sequencing to identify coding or non-coding variants in genes with altered expression. According to our hypothesis, these variants are responsible for the symptom specific expression profile and modification of the 22q11.2 deletion phenotype. Additionally, using transcriptome analysis, we will measure the impact of the length of segmental duplications, which flank the deleted region, on gene expression and its relationship to the phenotype.

Development of gene therapy for patients with diseases such as deletion 22q11 still require a major breakthrough in basic science and therefore remain futuristic at present. However, targeted symptomatic therapies are emerging that allow minimizing specific clinical features, and are emerging in many fields. These interventions require early implementation and therefore a prediction that a clinical problem will occur. Understanding the etiology of specific features will allow such a prediction and in future enable personalized treatment i.e. of seizures which may have a different genetic basis and can be treated accordingly. Schizophrenia, that occurs later in life of 22q11deletion patients has been linked in some studies with hyperprolinemia. Detection of genetic predisposition to elevated proline could lead in future to therapeutic dietary interventions as preventive measures.

Rare genomic disorders are a collectively important cause of disability in the general population, and represent a significant cost for the patients, their families, and the society. The 22q11.2 deletion syndrome is a multi-system disorder caused by a single deletion that in fact is genetically complex and can be seen as a model for gene-gene interactions and phenotype-genotype correlations. It provides a rare opportunity for studying patients with a very high probability of a given comorbidity before its onset such as with the neurodegenerative process associated with Parkinson’s disease.

The study will provide fundamental insights into the networks leading to the complex and variable developmental phenotypes associated with this genetic disorder. The results of this research will enable the prognosis and improve care of patients affected with 22q11 deletion. The data will fill key knowledge gaps about variable expression related to lifetime disabling outcomes in 22q11, thereby allowing predictive and potentially preventive strategies and targeted interventions to be developed. More importantly, these findings are of relevance to the broader group of patients with other developmental disorders, developmental anomalies of heart, facial, and organ development. Results will also have implications for understanding common psychiatric or neurological disorders like schizophrenia or Parkinson’s disease.