

Hearing loss (HL) is one of the most common and heterogenous sensory disorder in humans. According to the World Health Organization, it is estimated that as many as 466 million people worldwide suffer from disabling HL and its prevalence will continue to increase in the coming years. Currently used therapeutic methods such as hearing aids and cochlear implants are very effective, but there is still a group of patients that do not fully benefit from the treatment. This group of patients includes individuals with congenital inner ear malformations (IEMs), in whom anomalies of the ear anatomical structures are observed, i.e., malformations involving the cochlea, vestibule, semicircular canals or the vestibulocochlear nerves.

Genetic factors are considered to be an important cause of IEMs. However, despite a continuous and dynamic development of the field as well as molecular techniques, genetic background of IEMs is still poorly understood. A very interesting research and diagnostic puzzle is a group of patients with the most common defect of the inner ear that is enlarged vestibular aqueduct (EVA) or cochlea incomplete partition type 2 (IP2). Even with the use of advanced genetic testing, the causative variants of the *SCL26A4* gene are identified only in about 25% of patients, while in another 25% a characteristic set of genetic variants called the CEVA haplotype is observed. The putative molecular mechanism by which the CEVA haplotype affects the *SLC26A4* function remains unknown.

The main goal of our project is to discover new molecular causes of IEMs and to develop an animal model (zebrafish) that will allow us to understand the molecular basis of ear development and the formation of IEMs. This goal will be achieved by our comprehensive approach in which we will perform a family sequencing studies using revolutionary next-generation sequencing technology as well as functional studies in the zebrafish animal model. Based on the surprising similarity of the zebrafish and human genomes, this model will be used to validate the pathogenic potential of genetic variants detected in IEMs patients. For the first time, we will also integrate the results of comprehensive studies on *SLC26A4* regulatory background to identify hidden heredity. In addition to using a zebrafish model, we plan to induce patient-derived cochlea specific cells that will be used to explore a cell-specific architecture of the *SCL26A4* locus with high throughput methods.

The results of the proposed project will make an important contribution to the development of IEMs field, not only locally but also globally. We have a unique opportunity to conduct such advanced research by having access to a large collection containing over 13 000 DNA samples from clinically well-characterized group of patients of the Institute of Physiology and Pathology of Hearing. The results will form the basis for the creation of an atlas of genetic causes of IEMs, that will combine the genetic results with detailed imaging data and clinical features. From the medical point of view, our discoveries will expand diagnostic and clinical knowledge, becoming an important element of personalized patient care. In the context of basic research, the results of this project will expand the knowledge on the genetics of ear development and formation of IEMs. The data will be used to establish models for verifying the pathogenicity of the identified variants, that in the future may become a testing platform for new therapeutic approaches.