

Hearing loss (HL) is one of the main sensory disabilities in humans, often associated with genetic defects. Thus scientists around the world are working on widening the knowledge about the genetic basis of this disorder. A number of genes related to hearing loss in humans has been identified already, which illustrates a great genetic heterogeneity of HL, nonetheless in about 35% of patients with hereditary HL, the causative mutations have not been identified yet. Therefore, basic research in this area is necessary to identify these mutations and open the way to the potential use of that knowledge in the disease detection, prevention and/or cure.

Autosomal dominant HL (ADHL) represents the second most prevalent inheritance pattern of HL. In this type of HL, disease symptoms appear when the speech abilities are developed, usually at the end of the first or in the second decade of life, sometimes even later. ADHL may lead to educational problems, difficulties in communicating or social isolation of the patients. It negatively affects emotional, psychological and physical health constituting not only a significant social but also a medical problem.

The main objective of this project is to discover a novel molecular basis of ADHL and to establish a zebrafish animal model which allows to uncover the mechanism of action and pathogenicity of the revealed genetic causes of the disorder. This goal will be achieved with the use of next generation sequencing, a breakthrough technology of DNA sequencing as well as functional studies on the zebrafish animal model.

Until today, no extensive studies on the genetic basis of ADHL in Polish patients were performed. The results of this project will be an important contribution to the development of the knowledge in the field of ADHL, not only locally but also worldwide. High-throughput DNA sequencing will be performed on the genetic material of Polish patients from the Institute of Physiology and Pathology of Hearing, a leading audiological center with a long term diagnostic, treatment and rehabilitation experience and a unique collection of 10 000 DNA samples from HL patients.

We have selected 100 samples from unrelated families with ADHL and in the first step of the project we will screen the probands for mutations in known HL genes using the innovative cochlea-specific multi gene panel. This tool combines the advantages of targeted massive parallel sequencing of genomic DNA and the knowledge gained from the recently published transcriptome of the cochlea (auditory part of the inner ear). In the second step we will use whole-genome sequencing, the most powerful sequencing method in the genetic studies. This will allow us to discover novel candidate HL genes. Next, their mode of action will be deciphered using a zebrafish animal model.

Our results will provide a comprehensive genotype-phenotype catalogue of ADHL. Combining high throughput DNA sequencing and the functional studies may be a starting point for developing new human HL models that can be used more broadly to study the resulting key pathophysiological processes, identify new connections between genes and establish new biological hypothesis. The human HL models have a potential to serve as a platform for the discovery of novel therapeutics using the high-throughput chemical screening. It is particularly intriguing as ADHL shows similarities with age-related HL.