Profound hearing loss (HL) is the most common birth defect affecting 1-6/1000 newborns and has a broad spectrum of medical and social consequences. In child development there is a critical period to acquire language skills and this process is closely related to the presence of auditory stimuli. In case of children with prelingual profound HL (occurring before the development of speech and language) the best treatment method is cochlear implantation which compensates for the malfunction of the inner ear and deliver the auditory stimuli directly to the auditory pathway. Use of this cochlea "bypass" enables the processed sound to reach the brain, where the sound information is finally interpreted. Early HL diagnosis and appropriate medical intervention is crucial for proper child development. Despite the undoubted scientific and technological progress in the field of cochlear implants (CI), there are groups of patients who benefit less or not at all from CI. Therefore, there is a need to search for factors that will allow to predict the CI outcome and enable personalization of further patient medical care and rehabilitation process. Importantly, the underlying cause of prelingual profound HL is mainly a genetic alteration that impairs the function of various elements of the auditory system. For this reason, we believe that the genetic basis of HL is an important factor affecting the CI outcome.

We suppose that not only the main pathogenic variants, but also the accumulation of other variants (mutational load) found in genes important for the auditory system are significant factors causally involved in the development of HL and associated with CI outcome. Our hypothesis assumes that the outcome of implantation depends on (1) which part of the auditory system (inner ear vs. auditory pathway) has been affected by the mutational load and (2) the number of variants that constitute the mutational load. The aim of this project is to examine the genetic background of profound HL in implanted children, characterize their mutational load and determine the prediction power of the total mutational load on CI outcome. To accomplish the presented aims we will collect DNA samples from children with profound prelingual HL treated with CI and perform high-throughput genetic analyses using multi-gene panel targeting all known genes related to HL followed by whole exome sequencing (WES). This approach will allow us to find the causative genetic variant involved in HL development and other pathogenic variants located in genes relevant for the proper functioning of the auditory system – called together as mutational load. In the next part of the study, we will divide all the detected variants into groups important for the inner ear, auditory pathway and both of these structures. In the final stage, the relationship between the total mutational load and CI outcome will be examined.

Our innovative approach takes into account not only the main genetic cause of HL, but also a total mutational load in all known genes related to HL. It will allow a comprehensive characterization of genetic background of profound HL. Analysis of the obtained results may change the current perception of HL as a monogenic disorder and help to better understand the function of the auditory system in health and disease. Knowing the genetic landscape of HL will allow a more accurate prediction of CI outcome and will be an important part of the personalized treatment and rehabilitation of patients.