STRESZCZENIE W JĘZYKU ANGIELSKIM

Osteogenesis imperfecta is a genetic disorder of connective tissue, caused by factors associated with collagen type I molecules disruption. The disease is characterised by a wide spectrum of clinical features and variable severity of symptoms, ranging from mild to lethal. The genetic background is correlated with presence of numerous pathogenic variants located in several genes that directly or indirectly affect type I collagen molecules. Despite many years of research, important issues such as the pathogenesis of the disease, the genotype-phenotype correlation, and the development of an effective treatment require further research. Taking into account the growing importance of molecular research in the above-mentioned aspects, the chance for a full understanding of osteogenesis imperfecta is to be found in modern, high-throughput genomic DNA analysis.

The aim of the study was to determine the genetic background in a group of Polish patients with osteogenesis imperfecta and to search for genetic variability in genes with a confirmed involvement in the pathogenesis of the disease. Additionally, it was planned to establish the relationship between the genotype and the observed phenotypic effect and to determine the effectiveness of the next-generation sequencing method in the diagnostics of osteogenesis imperfecta.

The next generation sequencing analysis, using custom designed gene panel, was performed in a group of 197 Polish patients suspected with osteogenesis imperfecta. The study group included both prenatal and postnatal cases, ranging from 3 months to 46 years. Patients presented variable degree of clinical features. Based on the analysis of bioinformatics data, the presence of selected pathogenic variants was confirmed by Sanger sequencing. The genomic DNA of patients who tested negative was analyzed using the MLPA method to identify deletions or duplications within the type I collagen genes. The study also included a comparison of the prevalence of particular clinical features using statistical tools. Additionally, an analysis of the data retrieved from the OIVD database to assess the lethality of variants recorded in the "lethal regions" and an analysis of all variants associated with type 2 osteogenesis imperfecta in the type I collagen genes were performed.

The distinct aspects of obtained results were reported in three separate publications. The first publication presents the results of the first study on the genetic basis of osteogenesis imperfecta in a group of Polish patients. The obtained results were described in three main sections: characteristics of the studied population, analysis of the genetic background and phenotypic characteristics of patients with a confirmed cause of the disease. The most important results include the identification of 97 variants located in the type I collagen genes, among them 38 were novel. The genotype-phenotype correlation and the statistical significance of the occurrence of particular clinical features between patients with types 1, 3 and 4 were also determined. The second publication reports seven patients with pathogenic variants located in the "lethal regions" of type I collagen genes. Contrary to the original assumptions, the detected variants were associated with the occurrence of non-lethal forms of the disease. The review of all glycine substitutions annotated in the OIVD database showed that 71% and 40% of changes located in the "lethal regions" of *COL1A1* and *COL1A2* genes are responsible for the occurrence of OI type 2. In turn, the analysis of all missense variants leading to fatal outcome showed that 17% of changes reported in the *COL1A1* gene and 64% in the COL1A2 gene correspond to the

location of "lethal regions". The last publication describes the first glycine-to-tryptophan substitution located in the *COL1A1* gene, identified in a patient with a progressive-deforming form of osteogenesis imperfecta.

The presented results may contribute to broadening knowledge about this rare disease. Previously undescribed variants detected in the studied group expand the spectrum of changes related to the pathogenesis of the disease. Dissemination of results regarding known variants, combined with clinical data, may also contribute towards creating a predictive model determining the genotype-phenotype correlation. Perhaps in the long term, the results obtained will help in developing an effective treatment dedicated to patients with osteogenesis imperfecta.