Rare diseases are a diverse group of mostly inherited diseases with a very low prevalence of less than 1/2000 in the population. Identification of new genetic variants associated with these specific diseases is important for accurate and effective diagnosis and therapy. A variety of laboratory methods is used to identify genetic variants, including non-targeted methods such as aCGH and massive parallel sequencing of gene panels, exome or whole genome. The data obtained contains a number of benign findings and distinguishing them is not easy. In order to refine the filtering of variants according to the clinical features of the patient, the terminology of Human Phenotype Ontology was created. It is a structured ontology of individual phenotypic traits, its use increases the detection rate of genetic methods. This extensive terminology has been translated into Czech language and is ready for use. Furthermore, we present five cases in which the Human Phenotype Ontology terms were used to successfully find a causative variant.

The first patients are monozygotic twins with Zimmermann-Laband syndrome and a heterozygous pathogenic variant c.1606G>A p.(Ala536Thr) in the *KCNN3* gene. Their phenotype is unusually mild, the absence of gingival fibromatosis is a surprising finding. The second case report is a patient with localized mosaic neurofibromatosis on the arm, in whom a heterozygous pathogenic variant c.7549C>T, p.(Arg2517*) of the *NF1* gene was found in the neurofibroma in 13% of NGS reads. We also detected a reduction in peak heights corresponding to exons 3, 5, 6, 7, 9, 11, 15, 16, 21, 23, 24, 25 and 56 of the *NF1* gene using MLPA. These variants were not found in buccal swabs or peripheral blood. Following case series describe a group of patients with ectodermal dysplasia in whom pathogenic variants were detected in the *EDA, EDAR, EDARADD, TP63* and *WNT10A* genes. This report highlights the importance of interdisciplinary collaboration with stomatologists. The fourth case is a heterozygous variant c.448G>A p.Glu150Lys of the *TBC1D24* gene in a father and son with autosomal dominant hearing loss. Interesting coincidental finding occurred in the younger patient, who is also a compound heterozygote for two *STRC* gene variants. We can speculate one of the variants is a second hit variant. The last case is a young patient with Crohn's disease in whom two variants c.3646C>T; p.Arg1216Trp, and c.3391G>A; p.Ala1131Thr of the *DUOX2* gene were found, their pathogenicity was elucidated by functional studies. These case reports confirm the irreplaceable role of non-targeted laboratory diagnostics in modern genetics.

Keywords: rare diseases, next generation sequencing, Zimmermann-Laband syndrome, neurofibromatosis, ectodermal dysplasia, hereditary deafness, Crohn's disease