Abstract

The work focuses on molecular genetic testing of patients with Usher syndrome to confirm the diagnosis, to determine the causal cause of the disease and describe new mutations causing Usher syndrome in Czech patients. Usher syndrome is a clinically and genetically heterogeneous disease that is the most common cause of hereditary deafblindness. Based on responsible genes and disease onset is classified into three clinical subtypes. Given the fact that there is currently no specific treatment, there is a need to understand the pathophysiology of this disease and to broaden the spectrum of causal mutations.

The theoretical part of the thesis deals with the anatomy of the eye, especially the structure of the retina. Attention is also paid to retinal diseases, such as the progressive loss of vision characteristic for retinitis pigmentosa (RP). RP may occur either as an isolated disorder or also affecting other organs, so-called syndromic RP. Classic syndromic RP includes Usher's syndrome, which the work mainly deals with. The theoretical part of the thesis describes mainly the mechanism of the disease, the functions of individual Usher proteins and the genes that encode these proteins. The haplotype analysis has been previously done for the most common mutations causing Usher's syndrome in Europe Based on their results, the founder effect was confirmed.

In the practical part, Usher gene testing and haplotype analysis were performed. Using molecular genetic testing of 20 Czech probands by direct, whole exome or whole genome sequencing, new mutations likely causing Usher syndrome were found. These are mutations in *USH2A*: c.1651C>T; p.(Arg551Cys), c.485+1G>A; p.?, c.5414_5416delTTA; p.(Ile1805del) and *PCDH15:* c.2305G>A; p.(Gly769Arg). Furthermore, 167,569 bp deletion in the *USH2A* gene and 10,742 bp in *ADGRV1* were also mapped. Rare intronic variants have also been found in the *USH2A* gene, however further investigation and functional studies is needed to confirm their pathogenicity.

In addition to molecular genetic testing, the haplotype analysis was performed on 9 patients with *USH2A* mutation c.11864G>A; p.(Trp3955*), which confirmed the founder effect. In these patients, a shared area on chromosome 1 of 83,743 bp was defined.

Detailed molecular genetic testing of patients with Usher syndrome can broaden the spectrum of known disease-causing mutations and can contribute to understanding the mechanism of the disease development.

Keywords

Retina; Usher syndrome; *Retinitis pigmentosa*; congenital deafness, molecular-genetics analysis, Sanger sequencing, next-generation sequencing, mutation, haplotype analysis, haplotype, founder effect