22. Otol Neurotol. 2020 Apr;41(4):431-437. doi: 10.1097/MAO.0000000000002588.

Establishing Genotype-phenotype Correlation in USH2A-related Disorders to Personalize Audiological Surveillance and Rehabilitation.

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OBJECTIVE: USH2A-related disorders are characterised by genetic and phenotypic heterogeneity, and are associated with a spectrum of sensory deficits, ranging from deaf blindness to blindness with normal hearing. It has been previously proposed that the presence of specific USH2A alleles can be predictive of unaffected hearing. This study reports the clinical and genetic findings in a group of patients with USH2A-related disease and evaluates the validity of the allelic hierarchy model. PATIENTS AND INTERVENTION: USH2A variants from 27 adults with syndromic and nonsyndromic USH2A-related disease were analyzed according to a previously reported model of allelic hierarchy. The analysis was replicated on genotype-phenotype correlation information from 197 individuals previously reported in 2 external datasets. MAIN OUTCOME MEASURE: Genotype-phenotype correlations in USH2A-related disease. RESULTS: A valid allelic hierarchy model was observed in 93% of individuals with nonsyndromic USH2A-retinopathy (n=14/15) and in 100% of patients with classic Usher syndrome type IIa (n=8/8). Furthermore, when two large external cohorts of cases were combined, the allelic hierarchy model was valid across 85.7% (n=78/91) of individuals with nonsyndromic USH2A-retinopathy and 95% (n=123/129) of individuals with classic Usher syndrome type II ($p=0.012$, χ test). Notably, analysis of all three patient datasets revealed that USH2A protein truncating variants were reported most frequently in individuals with hearing loss. CONCLUSION: Genetic testing results in individuals suspected to have an USH2A-related disorder have the potential to facilitate personalized audiological surveillance and rehabilitation pathways.

DOI: 10.1097/MAO.0000000000002588 PMID: 32176120 [Indexed for MEDLINE]