

Unveiling gene-specific correlations and comparisons within Usher syndrome

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Historically, Usher syndrome's presentation and clinical diagnosis has been more narrowly-defined. Now with its genetic diagnoses classified into its three subtypes (USH1, USH2, and USH3), it is widely recognized for its vast degree of clinical variability. In particular, high variable expression is seen in this genetic syndrome's age of onset of retinitis pigmentosa (RP), severity of hearing loss, and deficits in the vestibular system, even within families. This study analyzes the phenotypic spectrum in probands with pathogenic variants in nine causative genes (USH1: *MYO7A*, *CDH23*, *USH1C*, *PCDH15*, *USH1G*; USH2: *USH2A*, *GPR98*, *DFNB31*; and USH3: *CLRN1*) to offer more clinical clarity among its genotype-phenotype relationships. This purpose serves to describe the phenotypic variability of each subtype beyond current classification criteria. USH1 and USH2 genotypes were focused on for comparative statistical analyses due to their relatively larger population sizes ($n > 50$ for each), while other gene level comparisons could not be made due to small cohort sizes. The study results indicated that the USH1 subtype had a more severe or profound hearing loss as compared to those with an USH2 genotype ($p = 8.54E-04^*$). Within the USH1 subtype, probands were 34 times more likely to have profound hearing loss as compared to probands with the USH2 subtype ($p < 0.0001^*$). RP onset, based on ages tested before or after the first decade of life, corroborated USH1's associated childhood onset and USH2's post-childhood onset. For those tested after age 10, the study showed that USH2 does not necessarily present as less severe, but rather has slower progression. The USH2 cohort shows greater frequency in having no vestibular issues in comparison to USH1 subtype ($p = 2.53E-10^*$). Within the USH1 subtype, probands were 15 times more likely to have vestibular issues as compared to individuals with the USH2 subtype ($p < 0.0001^*$). Overall, this study supports the *trends* seen in Usher syndrome's classically-defined subtypes. Atypical presentations, however, are noted within each clinical variable. The study does highlight the shift of Usher syndrome's rigid subtypes to broader phenotypic expressions. Widening the subtypes' spectrum facilitates the importance of genetic counselors and other healthcare providers' roles in delivering sensitive prognostic information to families. More research within USH's subtypes needs to be performed with greater population sizes to further establish stronger gene-specific correlations in variations outside of the subtypes' traditional presentations.