



The Era of Precision Medicine: Reshaping Usher Syndrome

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Usher syndrome (USH) is an inherited syndromic disorder that is characterized by retinitis pigmentosa (RP) and sensorineural hearing loss with or without vestibular dysfunction. There are three types of USH, with distinct phenotypes [1,2]. Type I (USH1) is the most severe form of USH, characterized by severe congenital deafness, vestibular dysfunction, and prepubertal RP onset. In type II (USH2), hearing loss is less severe, vestibular symptoms are not present, and the onset of RP occurs around puberty. Type III (USH3) shows postlingual progressive hearing loss with or without vestibular symptoms, and the onset of RP is quite variable, as it occurs in people in their 20s to 40s. Currently, 400,000 people worldwide are estimated to be affected by USH. However, only 1% of these cases have been officially identified (<https://www.ushersyndromesociety.org/who-we-are/usher-syndrome-facts.html>). USH is responsible for 3% to 6% of cases of early childhood deafness. Therefore, early diagnosis, counseling, intervention, and auditory rehabilitation are important to treat USH.

To date, USH has been traced to 16 causative genes and three unidentified loci (<https://sph.uth.edu/retnet/sum-dis.htm#A-genes>), implying wide genetic heterogeneity of this syndrome. In addition, mutations in these genes have shown a broad degree of clinical variability, ranging from nonsyndromic hearing loss to isolated RP. Given the clinical and genetic heterogeneity of this condition, patients with a milder phenotype tend to be underdiagnosed [3]. Therefore, confirming a genetic diagnosis for patients with USH remains a challenge, even if we identify underlying variants in the potentially causative genes of USH.

To make an accurate genetic diagnosis of USH with an indefinite phenotype, it is crucial to be familiar with the precise correlations between genotypes and phenotypes. Recently, Lee et al. [4] reported two probands with USH2, who manifested postlingual deafness and late-onset RP. In their study, compound heterozygous mutations in *USH2A* were identified in each family, and two novel variants (c.1823G>A:p.C608Y and c.14835delT:p.G4371fs) were found. Notably, that the proband carrying two

nonsense variants (p.S4945fs and p.G4371fs) showed more severe hearing loss than the other proband, who carried a nonsense (p.R2723X) and a missense (p.C608Y) variant. This is also consistent with previous studies reporting that patients with truncating variants of *USH2A* showed more severe and earlier-onset hearing loss than those with missense variants [5,6]. Based on this evidence, we know that nonsense variants tend to be more functionally deleterious and lead to more severe phenotypes in terms of hearing loss. However, further studies are needed to confirm age-matched genotype-phenotype correlations and discrepancies in RP phenotypes.

In recent years, USH has emerged as a target for gene and molecular therapy. Several studies have shown that the *Ush1c* gene (encoding harmonin) in Anc80L65 adeno-associated virus (AAV) or *Whrn* (encoding whirlin) in AAV8 was successfully delivered into the inner ear of USH mice to restore their auditory and vestibular function [7,8]. It was also reported that antisense oligonucleotide injection to correct a splicing error in the *Ush1c* gene improved hearing function in USH type IC mice [9]. To prepare for the upcoming era of precision medicine for hearing loss, we need to make genetic diagnoses more reliable and evidence-based. To achieve this, the genotype-audiotype correlation should be further investigated, and a consortium-based evaluation should be performed in the near future.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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