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REVIEW ARTICLE

The Effects and Treatments for Usher Syndrome: A Review

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A B S T R A C T

Usher syndrome (USH) is defined as a rare genetic disorder that affects both vision and auditory. Although the prevalence is only about 4 to 17 per 100,000 people, it covers at least half of the deaf-blindness cases around the world. After reviewing the molecular genetics basis from several papers, there were several causative genes implicated, with the most prevalent being MYO7A and USH2A, causing USH type I and II, respectively. Furthermore, other literature has found promising treatments that may help slow down or prevent further degeneration of the syndrome.

K E Y W O R D S

Deaf-blindness, Molecular genetics, Prevalence, Treatment, Usher syndrome

H I G H L I G H T S

- Usher syndrome causes 50% of deaf-blindness cases.
- Inherited by two mutated recessive genes of the parents.
- Divided into three types according to the malignancy and clinical progression.
- Encompasses the treatment, especially gene therapy.

INTRODUCTION

Usher syndrome (USH) is an autosomal genetic condition that simultaneously influences both the visual and auditory systems, with a varying manifestation of vestibular impairments in certain cases (Toms et al., 2020). USH is the most frequent cause of the deaf-blind syndrome, covering half of the deaf-blindness (18% of retinitis pigmentosa cases and 5% of congenital deafness) in people younger than 65 years old (Castiglione & Möller, 2022; Lenarduzzi et al., 2015). Patients with USH, particularly those who developed it later in life, may struggle with diagnosing and treating psychiatric problems (Rijavec & Grubic, 2009; Mathur & Yang, 2015). These cases are also often found in retinitis pigmentosa patients (Daiger et al., 2013). Retinitis pigmentosa itself is known as retinal dystrophy due to the accelerating degeneration of photoreceptors and is annotated with retinal pigment deposits of epithelial cell function (Hamel, 2006; Zhang, 2016).

USH is a hereditary condition that can occur at any time. Nine causative genes have so far been recognized: USH1C, PCDH15, MYO7A, CDH23, and SANS (Usher type I); WHRN, GPR98 and USH2A (Usher type II); USH3A (Usher type III). Mutations in these genes show clinical variability ranging from nonsyndromic HL to isolated RP (Kimberling et. al., 2010; Toms et al., 2015). The precise genes involved can change based on the person and the type of USH they have. An affected person's unique gene mutations can be identified by genetic testing, allowing for more precise diagnosis and treatment of the disease. Additionally, it might not

come straight from the parent. Moreover, it is difficult to detect and prevent USH in Indonesia since many people are unaware of their carrying the recessive gene for the condition.

USH may be detected early through sequencing techniques, such as Sanger sequencing and next-generation sequencing (NGS). These techniques help determine the molecular diagnostics of USH. Such a technique evaluates the effect of the protein from samples to the severity of hearing loss (Krawitz et al., 2014). Genetic testing is also utilized to determine who is a carrier of the mutant USH before the child is born, or when an adult is worried that they could have USH. Other than those methods, it is commonly detected when newborn babies are screened for their health, and all types of USH could be discovered using the newborn hearing screen (Toms et al., 2020). A child may be referred for additional testing to rule out USH if a hearing test indicates that they have hearing loss.

There are three different kinds of USH: type I (profound hearing loss, vestibular dysfunction vestibular from birth, and night blindness appearing earlier in life), type II (severe hearing loss and normal vestibular function at age 15-17), and type III (the most frequent one, hearing loss, progressive retinitis pigmentosa, and variable vestibular dysfunction at age 18) (Sethna et al., 2021). As of now, there is no known cure for USH. The current treatment focuses on managing hearing, vision, and balance issues. Treatment and communication services can include hearing aids, assistive listening devices, cochlear implants, auditory training, and/or learning sign language (Nagel-Wolfrum et al., 2014; Skilton et al., 2018; Wilhelm et al., 2023). As such, the goal of this review is to evaluate the existing literature regarding genetic causes of USH, its treatments, and other studies regarding USH.

MATERIAL AND METHODS

To find pertinent studies to include in this review, a thorough literature search was done. Searching through the PubMed database and discovering publications from 2018-2023 with the topic related to USH, USH treatment, prevalence, and molecular genetics, with the format being [(“Usher Syndrome” OR “USH”) AND (“Prevalence” OR “Treatment” OR “Diagnosis” OR “Molecular Genetics)]. To determine whether the identified papers were eligible for inclusion, three impartial reviewers looked at the titles and abstracts of each one. There are several criteria that were used to determine whether a study was included, such as relevant biological analysis, mainly focusing on USH, molecular genetics, and also its treatment (Evans, 2017). After obtaining the whole texts of the chosen articles, the final inclusion was evaluated in accordance with the established inclusion criteria. There are a total of 20 articles selected with the inclusion of 243 articles, which are not considered as a relevant biological analysis, not focused on the disorder, do not discuss enough molecular genetics, and unrelated treatments. Although every effort was made to perform a thorough search, there may have been some literature conducted in languages other than English and Indonesian that are excluded to avoid introduction to some publication bias.

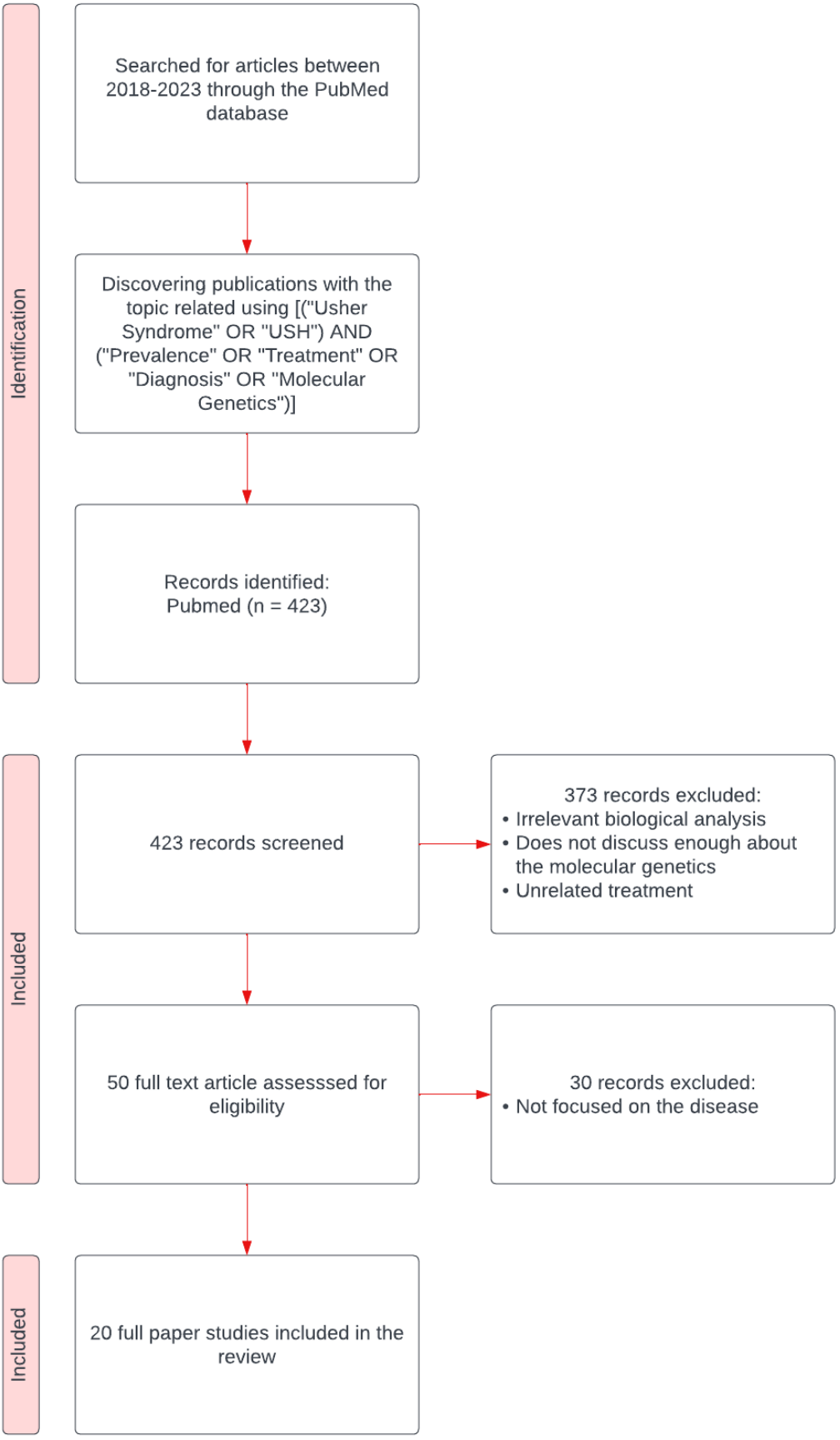

Figure 1. Framework of the review method

RESULTS

Table 1. Result of the review.

Reference	Focus of Paper	Description of Paper
Toms et al., 2020	Molecular Genetics and Treatments	Discussed about the genes that have been identified to cause USH primarily MYO7A and USH2A, and the therapeutic developments through gene replacement, editing, and small molecule drugs.
Fuster-Garcia et al., 2021	Molecular Genetics and Treatments	Mentioned the genes that affected different types of USH, where USH1C, MYO7A, PCDH15, USH1G, CDH23, and CIB2 noted to cause USH1; WHRN, ADGRV1, and USH2A related for USH2; and CLRN1 for USH3. The genes interplay and generated a dynamic protein network named usher interactome, showing a high prevalence of truncating variants. Discusses potential treatments through a gene augmentation approach, which are gene editing and antisense oligonucleotides (AONs) utilizing the CRISPR/Cas system.
Delmaghani & El-Amraoui, 2022	Molecular Genetics, Prevalence, and Treatments	Recorded the pathogenic genes of USH, namely PCDH15, MYO7A, USH1C, and USH1G for USH1; USH2A, ADGRV1, and WHRN for USH2, and CLRN1 for USH3. Also discusses the rare gene, PZDZ7, which is known to be involved as the USH modifier. Addresses clinical trials, such as gene therapy using equine infectious anemia virus and equine infectious anemia virus (EIAV) lentiviral-based subretinal delivery of MYO7A and myosin VIIa in USH1B patients, subretinal capsules of human NT-501 cells transporting ciliary neurotrophic factor, and intravitreal injection of an antisense oligonucleotide and QR-421a for the USH2A model. This disease covers 1 per 10,000 people with approximately 400,000 people in total.
Stemerdink et al., 2021	Molecular Genetics and Treatments	The gene mutation of USH2A, ADGRV1, and WHRN is noted to cause USH2 with USH2A as the most common. The dynamic protein created from the genes is mainly discovered at the membrane of photoreceptor periciliary, and hair bundles of inner ear hair cells. No biological treatments are available for USH2. The current therapy focuses on the retinal degradation that occurs in USH patients, such as subretinal capsules of human NT-501 cells with a ciliary neurotrophic factor, and NPI-001 drug, gene augmentation therapy, oligonucleotide−based splice modulation therapy, translational read-through therapy, and optogenetics for advanced USH.
Jouret et al., 2019	Molecular Genetics and Treatments	Conducted research with next-generation sequencing to find the genetic and phenotypic of USH. The research reveals the target gene for patients with biallelic disease: USH2A, MYO7A, CDH23, ADGRV1, PCDH15, USH1C, CLRN1, USH1G, WHRN, and PDZD7 consecutively by frequency. 7.5% of patients with isolated sensori neural deafness had disease-mutated genes, putting them at high risk of retinitis pigmentosa. Suggests early molecular diagnosis of USH patients to avoid the development of retinitis pigmentosa.

Reference	Focus of Paper	Description of Paper
Castiglione & Möller, 2022	Molecular Genetics	Looked into the known ten genes that cause USH, also the interaction between proteins and gene expression regarding those genes, and how their expression in other cells could cause comorbidities.
Jiang et al., 2015	Molecular Genetics and Diagnosis	Utilized NGS in order to identify the genes involved in USH, specifically in a Chinese cohort. From it was discovered that the genes responsible are mostly the same with the culprits being MYO7A and USH2A, with the addition of discovering new mutations in Chinese USH patients being CLRN1, DFNB31, GPR98, and PCDH15.
Mathur & Yang, 2019	Molecular Genetics and Treatments	Discussed about the mutation responsible for USH2, WHRN (previously known as DFNB31). This gene may be responsible for USH2D, also known as autosomal recessive non-syndromic deafness type 31. Animal models of WHRN orthologs encode various whirlin isoforms. The interplay between whirlin and proteins may disrupt the molecular mechanism, leading to USH. Mentions gene therapy as a treatment to aid the patients.
Colombo et al., 2021	Molecular Genetics and Diagnosis	Looked into the detection of USH through Italian patients that have retinitis pigmentosa history in their family and utilizes Sanger sequencing to validate their genetic variants of which they found 468 potential pathogenic variants.
Stabej et al., 2012	Molecular Genetics and Diagnosis	Checked through the UK population USH patients to check for responsible genes through sequencing the following genes: MYO7A, USH1C, CDH23, PCDH15, USH1G, USH2A, GPR98, WHRN, CLRN1 with the candidate gene SLC4A7 also being sequenced. They concluded that 86% of the patients had several pathogenic/likely pathogenic mutations.
de Joya et al., 2021	Diagnosis and Treatment	One of the most prevalent sensory disorders in people with USH is hearing loss. One of the current treatments is using cochlear implantation. This paper talks about the treatment of Usher-related hearing loss using gene therapy that has proven more promising results.
Gao et al., 2020	Molecular Genetics and Prevention	The 72 exon USH2A gene, which encodes usherin, is located on chromosome 1q41. It is required for the development of the retina and inner ear. Mutations in these genes have been associated with retinitis pigmentosa and USH type II. The genotype and phenotypic features of retinitis pigmentosa and USH2 in the Chinese population are the subjects of this article.
Brodie et al., 2020	Molecular Genetics and Diagnosis	The early detection of pediatric USH ocular symptoms is possible by implementing the first-line test with hearing-loss gene panel testing (HLGPT). HLGPT proven could identify early variants associated with USH.
Markova et al., 2022	Molecular Genetics and Early Diagnosis	The syndrome's diagnosis is complicated by high clinical and genetic variability. Hearing and visual issues are manifested at different ages.

Reference	Focus of Paper	Description of Paper
		Primary diagnosis begins with a clinical diagnosis of bilateral hearing loss, followed by vision impairment.
Zaw et al., 2022	Diagnosis and Treatment	Current studies with an assessment of possible treatment plans for USH that are presently undergoing medical trials.
Oishi et al., 2014	Molecular Genetics, Diagnosis, and Bioinformatics Tools	Utilized coding exons and introns for NGS with Illumina. The sequencing detected 66 novel mutations out of 104 distinct mutations, where RHO, EYS, and USH2A accounted as the causative genes of USH and retinitis pigmentosa, differing among ethnicities.
Lenarduzzi et al., 2015	Diagnosis and Bioinformatics Tools	Molecular diagnosis on 31 USH patients, detecting USH2A, MYO7A, CDH23, PCDH15, and USH1G as the causative genes. Also confirmed the genome variants with Integrative Genomic Viewer (IGV).
Major et al., 2023	Prevalence, Diagnosis, and Treatment	Noted the signs of USH patients according to their types: type I with prepubertal RP and congenital hearing impairments, type II present with mild congenital hearing impairments and retained vestibular function, and type III with early hearing impairments and variability on retinitis pigmentosa malignancy and vestibular function of which mainly in Finland. Emphasize epigenetic modification and sequence changes with new CRISPR tools for the treatment, focusing on USH2A gene mutations.
Ferla et al., 2023	Molecular Genetics and Treatment	One of the challenges for effective gene therapy treatment in USH type IB is the size of the gene. Researchers created two AAV8 vectors, which have the capacity to carry greater genes to overcome this limitation. Dual AAV8 vectors improved retinal abnormalities, according to the studies in mice and primates, which resulted in enhanced retinal function and morphogenesis after subretinal injections with dual AAV8. Thus, dual AAV8 vectors could provide a secure and productive treatment for USH type IB.
Remjasz-Jurek et al., 2023	Diagnosis and Treatment	Discussed electroretinogram as the only attested test for the diagnosis of USH. Also conducted cochlear implantation for a comparison between 35 USH children and 46 non-syndromic patients based on their vestibular assessment, imaging, genetic counseling, and ophthalmological results are evaluated with no statistical significance between the groups. The statistical analysis indicated how cochlear implant is effective in improving the auditory and speech performance of USH patients, especially those under 3 years old.

DISCUSSION

The absence of vision as well as hearing is the main symptom of Usher syndrome (USH). Retinitis pigmentosa (RP), an eye condition, could result in regard to vision. Complete blindness and deafness may result from the condition's worsening (Tsang et al., 2020). There are three separate categories of USH: type I, type II, and type III. Patients of type I are born with sensorineural hearing loss that ranges from mild to severe and affects both ears bilaterally. The deteriorating condition is prominent in childhood. It disrupted the vestibular system, responsible for managing the body's stability and direction in space. The patients usually require a cochlear implant to be able to learn to speak (Koenekoop et al., 2020a).

Type II is designated at the baby stage and persistent visual loss begins in adolescence with moderate to acute hearing loss that mainly affects the capacity to hear high-frequency noises. Unlike other types, this type does not involve vestibular abnormalities that hinder balance. Night blindness and reduced peripheral vision are further characteristics of a condition of this type. Reduced central visual acuity results from variations in the incidence and severity of loss of vision among and between families. Type III, on the other hand, has a late beginning and frequently coexists with normal hearing at birth. Most often in middle age, hearing loss starts in late childhood or adolescence and becomes acute over time. With RP, vision loss may also appear during that period. As a result, the patients experience vestibular irregularities and balance problems (MedlinePlus, 2020).

Molecular genetics

As discussed in the table, there are several genes that are noted to cause USH. While the patient frequently fails to replicate the retinal phenotype in the retina, USH genes appear in the sensorial hair cells of the cochlea and the five vestibules in the inner ear. These genes are detected through next-generation sequencing (NGS) or Sanger sequencing. Previously, 80% of causative gene exons were identified with Sanger sequencing. However, due to the price and time efficiency, NGS is preferred for a higher diagnostic rate in large patients' as it is able to provide the detection of novel and known mutations, especially as well as DNA rearrangement (Toms et al., 2020; Géléoc & El-Amraoui, 2020).

MYO7A and USH2A are the most prevalent causative genes among others. MYO7A covers at least 50% of USH type I, whilst USH2A reports roughly 80% of type II (Toms et al., 2020). There are several genes that have been discovered to cause USH1, which are USH1C, MYO7A, CDH23, CIB, USH1G, and PCDH15. In USH2, if clinical characteristics are unclear, the diagnosis is established by the discovery of biallelic pathogenic mutations in one of three genes, which are ADGRV1, USH2A, or WHRN (Koenekoop et al., 2020a). The gene responsible that is causative of USH3 is CLRN1.

All of these mutated genes altered the functionality of their inner ear hair cells and retina. A rare gene, PDZD7, is known to imply the USH2 modifier for retinal disease in USHIIA. For USHIIC, this gene is homozygous dominant, where it causes autosomal recessive 57 (DFNB57) (O'Neill, 2018). PDZD7 favors attaching with GPR98, whilst WHRN with USH2A. If WHRN and PDZD7 interacted in the cochlear hair cells, it may connect USH2A with GPR98. These genes interplay with a dynamic multiprotein, which is related to the formation of the USH2 complexes (Chen et al., 2014). Other new genes, such as USH1E, USH1H, and USH1K are reported in the linkage to chromosomes 21, 15, and 10. However, the relation has not yet been evaluated. These genes encode for different locations in their expression, mainly from photoreceptors and hair cells for structural proteins, also calyceal processes for USH1 and periciliary complex for USH2 (Castiglione & Möller, 2022).

A candidate gene, SLC4A7 is found on the human chromosome of 3p22, which is also proposed to be causative for USHIIB (Choi et al., 2021). SLC4A7, also known as sodium bicarbonate cotransporter NBCn1, is involved in regulating pH balance and ion transport across cell membranes. It exhibits a broad expression

pattern within the central nervous system, suggesting its potential role in various neurological processes. However, when tested with mice, the gene did not bring the required stimuli potential and the mutation sequence was not detected. This indicates that the gene may not be a potential causative gene candidate for USH (Choi et al., 2021).

Prevalence

USH affects between 4 and 17 persons per 100,000 people worldwide. In the United States, USH has been diagnosed in more than 16,000 people. It is one of the most prevalent genetic forms of deaf-blindness. Although it was anticipated that the prevalence may be as high as 1:6,000, an examination of Oregon's youth who have hearing loss also discovered such 11% contained pathogenic mutations in genes linked to USH syndrome (Koenekoop et. al., 2020b). Therefore, it accounts for 50-60% of all inherited blind and deaf cases and has a rate of causing 3-6% of all childhood hearing loss incidences (Delmaghani & El-Amraoui, 2022).

In Indonesia itself, according to Evans et al. in 2017, roughly 1 in 15,000 Indonesians are thought to have USH type I. Uncertainty surrounds the cause of Indonesia’s greater prevalence of USH type I. However, a number of factors, particularly the high percentage of consanguinity in Indonesia, are likely to be responsible. There are several difficulties that Indonesians with USH must overcome. Some of them are a shortage of ability to obtain early diagnosis and treatment, the ignorance of USH, and the stigma attached to deaf-blindness. However, a number of groups in Indonesia are attempting to enhance the lives of persons with USH. These groups include the Indonesian National Association of the Deafblind (INABD) and the Indonesian Usher Syndrome Foundation (IUSF).

In most nations, type I and type II USH are the most prevalent types. Heritage of eastern and central Europeans and French Acadians are more likely than the general population to have certain genetic mutations that cause type I USH. Only about 2% of all patients with USH are type III. However, type III is more common among Finland's population, which represents about 40% of cases, particularly in those with an ethnic background from Eastern and Central Europe (Major et al., 2023; Mathur & Yang, 2015).

The clinical manifestations of USH, which has an autosomal recessive inheritance pattern, include rod-cone dystrophy or RP, varied vestibular dysfunction, and sensorineural hearing loss (SNHL). When a gene has an autosomal recessive pattern, both copies of the gene in each cell are mutated. One copy of the mutant gene is present in each parent of a child with USH, although the parents themselves are not affected. Currently, there are a number of clinical trials underway to develop new treatments for USH. Some of these trials are investigating gene therapy, which could potentially cure the diseases, and the syndrome's signs and symptoms (Azaies et. al., 2018). A more thorough analysis of 189 USH patients revealed a disproportionate number of men, some variation in audiograms, and a wide range of ophthalmologic variation. One hundred and thirteen (113) sibships were subjected to genetic analysis, which revealed a segregation ratio compatible with recessive inheritance (Verbakel et al., 2018).

Treatment

It appears that there is no viable treatment for USH yet. Although, various approaches could be done to manage the symptoms and improve the quality of life for patients and individuals that live with USH. The different kinds of USH would then require a more diverse treatment plan for each type. It should be stated that the best treatments are available when diagnosis could be confirmed as soon as possible, through the genes mentioned in the molecular genetics section, for example, if USH gets diagnosed in young patients that already have congenital hearing loss before RP could have developed further, the photoreceptors potentially could be saved by early neuroprotective interventions (Zaw et al., 2022). Furthermore, the treatment for hearing loss could be done through the application of hearing aids and cochlear implants have been proven to be effective (de Joya et al., 2021; Stemerdink et al., 2021). Other promising treatments are also undergoing

clinical trials, such as gene replacements, small molecule drugs, gene editing therapies, and spice-altering antisense oligonucleotides (Mathur & Yang, 2019; Toms et al., 2020; Zaw et al., 2022).

In 2023, the clinical trials conducted are more focused on looking at gene therapy, which may be able to treat the illnesses. It is a newer form of treatment, which tries to compensate for or fix the genetic flaws that lead to conditions like USH (Ivanchenko et al., 2023). Gene therapy entails the introduction of functional copies of the damaged genes into the intended cell types in an effort to reinstate the synthesis of the faulty or absent protein. It has been established that anomalies in specific genes necessary for the development and function of the retina and inner ear are the main cause of USH (Amariutei et al., 2023). These mutations cause the loss or malfunctioning of sensory perception-related proteins, which cause the symptoms of the disease.

Gene therapy is mainly addressed for the current treatment. Gene replacement therapy, that attempts to correct genetic faults by introducing functional copies of the faulty genes onto the target cells, serves as one of the most promising approaches in gene therapy. Gene replacement treatment for USH focuses on giving the damaged inner ear or retinal cells the right form of the mutant genes linked to the disorder. This includes viral vectors like adeno-associated viruses (AAVs) to deliver the therapeutic genes (Lahlou et al., 2023). The viral vectors will deliver healthy genes upon reaching the cells, which subsequently create the protein that is either lacking or defective. This therapy mainly aims to delay or stop the progression of vision and hearing loss in persons with USH by recovering the production of significant protein. Currently, this type of therapy is constantly being researched and improved, including the proper viral vectors and delivery techniques. Gene replacement therapy needs to be ensured of its security, efficiency, and benefits in the long run. Although animal studies have shown encouraging outcomes, mainly in USH type IB and IF, more investigations and clinical trials are required before it can be extensively utilized in USH patients (Ferla et al., 2023).

Another genome editing technology that is currently being studied, in particular CRISPR-Cas9, which has become an effective instrument in the field of genetic research, can be used to correct certain mutations in genes linked to USH. With the use of the CRISPR-CaS9, which is the newest gene editing technique, researchers can precisely choose and change DNA sequences, creating previously unimaginable prospects for reversing disease-causing mutations. For directly treating the underlying genetic flaws, CRISPR-Cas9 shows promise. In order to direct the Cas9 enzyme to the precise position of the mutation in the target genes linked to USH, researchers are developing particular guide RNA molecules. The Cas9 enzyme causes double-stranded breaks in the DNA once it reaches the target location. The cell's built-in repair mechanisms then take over, and researchers can offer a template with the proper DNA sequence to direct the repair procedure. This makes it possible to fix the disease-causing mutations, resulting in the creation of useful proteins (Major et al., 2023; Vartanian et al., 2023).

Clinical trials are being carried out to evaluate the safety and efficacy of the CRISPR-Cas9 technique for treating USH, which is currently being enhanced. Primates, such as monkeys, are useful study subjects for gene therapy research before going on to human trials since they and humans have similar genetic and physiological make-ups. There are several promising results regarding the clinical trials in the mice, up to the primates for treating the USH, mainly type IB (Renner et al., 2023). These researchers seek to assess the potential of CRISPR-Cas9 as a therapeutic approach for treating the USH gene mutations that result in the disorder and correcting aberrant protein function.

Bioinformatics tools

Bioinformatics tools have been highly regarded in detecting the presence of USH and visualizing its genomic data. Thus, it is highly used in the diagnosis, management, and further research of this particular disease. For instance, one of the detection tools, NGS, is applied with a bioinformatics pipeline to process the

raw sequencing data. The pipeline helps to reckon the genome alterations by validating and monitoring the molecular genetics of the clinical results (Roy et al., 2018). The genes known to be linked to (USH) can be sequenced to identify and predict the genetic mutations causing the disease. When compared to other conventional approaches, NGS has been shown to improve the identification of USH by 25–55% (Oishi et al., 2014). The genetic profile then could be analyzed to see if a person's a carrier of the mutation or not. Further treatment such as the target gene would be identified for new treatment. One of the advantages of using NGS rather than other tools is it is relatively inexpensive and quickly performed.

Integrative Genomics Viewer (IGV) is a bioinformatics tool that can help to visualize multiple genomic data from the sequence alignment, validating the variant assessed. The source patient dataset themselves could vary from genomics, DNA sequencing data, microarray data, and also RNA-seq data. The tools may detect the exact genomic position of the variations, evaluate how well the disease phenotype co-segregates with them in families, and look into any potential functional repercussions. Additionally, IGV can show other genomic characteristics linked with USH, such as regulatory components, known disease-associated variations, or gene expression profiles across multiple tissues or developmental stages. With the help of this thorough visualization and integration of various genomic data, it will be easier to evaluate genetic variants and gain important new knowledge about the underlying molecular causes of USH (Lenarduzzi et al., 2015; Robinson et al., 2023).

Future prospect

The insight between the patient's genotype and the clinical progression remains a huge gap in the current literature. Therefore, future studies may explore the genetic part of USH with the case-controlled condition of the association, which helps in the identification of genotypes and optimal timing for cochlear implantation (Davies et al., 2021). Despite the mutations' variability, there hasn't been much commercial attention to the treatment due to the small sample sizes. CRISPR may be one such alternative option to correct the base transitions within USH2A gene mutations but limited to in vivo deliverance (Major et al., 2023). Therefore, an in-silico study can also be referred to as an additional alternative to support the result. Protein structure prediction may be undermined to understand the homologous structure, where it may help to determine the missense variants of USH as well for protein domain alignment as the mutations and splicing may cause alterations in the overall structure (Zhang et al., 2020; García-García et al., 2013).

Further molecular interaction simulations may also assist in finding treatments by evaluating the binding ability of the causative gene mutations. As such, the binding ability domains may be revealed through cryo-EM and molecular dynamics simulations, comparing the wild-type and the gene mutation domains (Ivanchenko et al., 2023). These methods have been advanced with deep learning integration which provided higher structure determination of the 3D model prediction along with the motion for the interaction occurring at the atomic resolution in a set time (Zhang et al., 2022; Long et al., 2021). Furthermore, this advancement may also support better protein maps to differentiate the genetic linkage between the gene mutations.

For further assessment, clinical data of the patients' samples may be evaluated to refer to the protein domains. This may reveal the correlation between the genotype and phenotype of the causative genes. Although it may not have succeeded, the following studies may assess the clinical significance thoroughly. It may look through the severity and cause of the disease as well as the patients' demographic to undermine the clinical-based classification data (Galbis-Martínez et al., 2021). Some genes are also known to overlap with other deaf-blindness syndromes where the genotype and phenotype correlation is critical for treatment development, especially for gene therapy and precision medicine. Hence, this may be helpful to reveal the pathogenic variants of the genes, related genes to USH-like phenotypes, and even algorithm development for the determination of the phenotypic effects to the allelic variants (Nisenbaum et al., 2022). In addition,

NGS is also expanding to more countries where it may cover more countries for yielding a better sequencing result, which may discover novel gene variants that tackle hearing impairment (Souissi et al., 2022).

CONCLUSION

Usher syndrome is known to cover at least 50% of deaf-blindness cases, regardless of its low prevalence. This disorder is divided into three categories: USH1, USH2, and USH3. There are many causative genes of USH. However, the most common ones are MYO7A and USH2A which cause USH1 and USH2 respectively. The treatments may be determined after knowing the genes accounted for by each type. Photoreceptors, gene therapy, and small molecule drugs have been discovered to be promising therapies with further clinical trials required. Despite that, the majority of the treatment can only slow down the disease's progress, and help alleviate those affected, but does not cure the disease. As such, the review of the literature included in this paper has analyzed what USH is, its prevalence, the molecular genetics involved, and the possible treatments for USH.

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