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# Usher syndrome

Recent advances in our understanding of genes and therapeutics

*Usher syndrome is a rare disease that affects the sensory systems of vision, hearing, and balance. Recent advances in scientific technologies reveal the genes involved in Usher syndrome, their varying phenotypic outcomes, and avenues for therapeutic development. Dr Aziz El-Amraoui of the Pasteur Institute in Paris, France, and Dr Gwenaëlle Géléoc of Boston Children's Hospital and Harvard Medical School in the US, review these advances in our understanding of disease pathogenesis and therapeutic developments. They take stock of the current situation, discuss the need for revised diagnostic guidelines, and frame the future of research in this field.*

Approximately 400,000 people worldwide have Usher syndrome (USH), a rare genetic disease. Although classified as a rare disease, it is the most common type of hereditary deaf-blindness. Clinically, it manifests as disruption to hearing and vision with variable effect on balance. The disease can progressively worsen over time, with diminished ability to communicate, affecting mental health and impacting a person's quality of life.

There are three clinical subtypes, USH1, USH2, and USH3, each differing in disease onset, severity, and progression. Hearing aids, cochlear implants and visual aids may improve hearing and sight for patients but there is no treatment that corrects the source of the hearing and sight loss. When implanted early enough, such hearing devices can aid speech development of affected children and improve their quality of life.

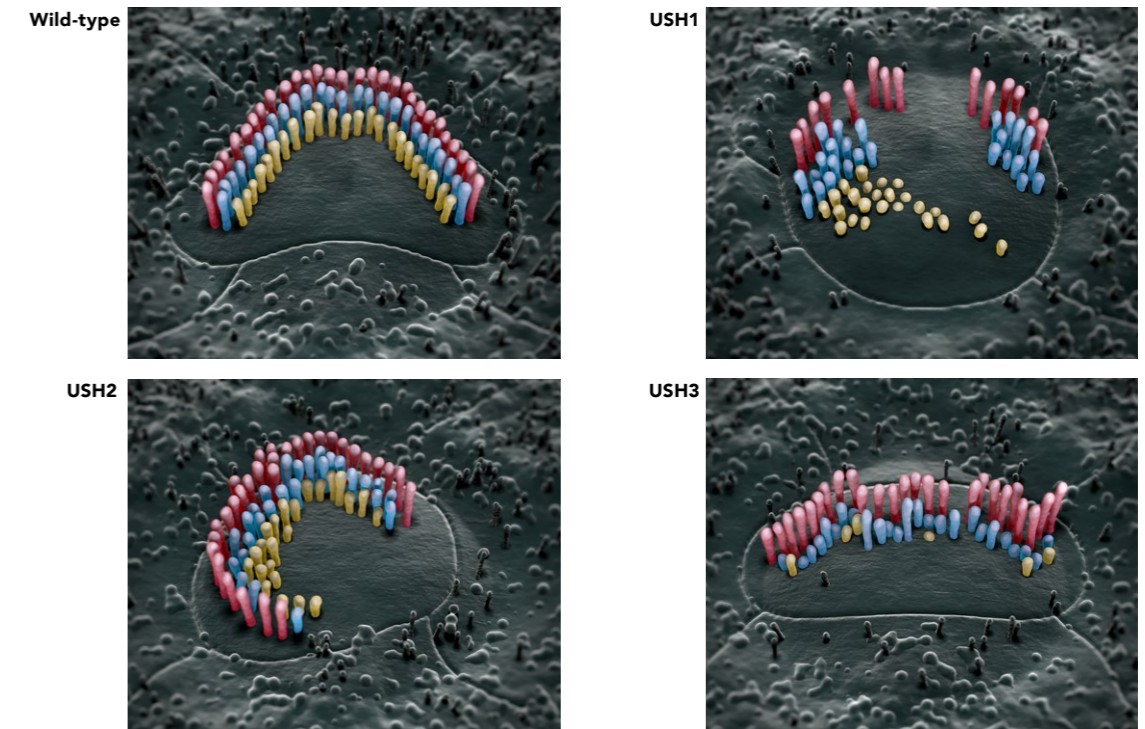
Recent advances in genetics and technologies have expanded our knowledge of USH, uncovering the disease's molecular bases, and

shedding light on phenotype-genotype associations. In recent publications, Dr Aziz El-Amraoui and Dr Gwenaëlle Géléoc review these developments, discuss innovative treatment developments, and call for revised guidelines to complement the classification of Usher Syndrome. Here, we distil some of their recent findings.

## PHENOTYPES OF USHER SYNDROME

The USH1 subtype found in up to 44% of patients has the earliest onset and is the most severe type, affecting all three sensory systems. However, USH2 is the most common form, affecting more than half of all Usher patients, with these patients having normal vestibular function (their ability to balance). Deafness is congenital in both USH1 and USH2. USH3 is the least common subtype, affecting only 2–4% of USH patients but impacting all three sensory systems.

Molecularly, each subtype is related to different genes expressed in the inner ears' sensory hair cells and the eyes' photoreceptor cells. In the simplest sense, the sensory hair cells of the inner



Hair bundles inside the cochlea.

ears detect and process sound while the photoreceptor cells in the eyes sense light. The nine different genes implicated so far (five in USH1, three in USH2 and one in USH3) associate with varying clinical features which may alter depending on the gene location. Diagnosis and classification of the disease is thus complex, and standardisation and clarity of clinical descriptions are essential for accurate diagnosis and clinical management of USH patients.

## THE ROLE OF USHER PROTEINS IN SENSORY SYSTEMS

Within the inner ear is the cochlea (the hearing organ which senses sound waves) and five vestibular organs (or balance organs), all of which contain sensory hair cells where Usher genes are expressed. The hair bundle of each hair cell contains stereocilia which are extremely sensitive in detecting and processing sound waves or head movements. In the retina of the eye, the photoreceptor cells contain an outer segment of orderly arranged disks important for detecting light.

Animal models have helped us understand how mutations in specific Usher genes alter proteins impacting the function of these three sensory systems. The USH genes encode for proteins with a variety of functions and roles. Importantly, these proteins interact and form complexes that are

essential to sensory hair-cell function in the auditory and balance organ, and photoreceptor cell maintenance in the eye. Studies in USH models confirmed an interdependence between USH proteins, showing that a defect in one protein can affect the distribution of others in hair cells or photoreceptors.

Both hearing and balance rely on a process called mechano-electrical transduction, which involves the transformation of a mechanical stimuli

channel, and the membrane to cytoskeleton cross-links, USH1 proteins are also part of the mechano-electrical transduction machinery. USH2 proteins are important for the shape of the ankle-link complex connecting the stereocilia and are vital for hair bundle development. Defective proteins affect the shape of the hair bundle leading to dysfunction and clinical hearing loss. The USH3A protein has a role in mechano-electrical transduction as well

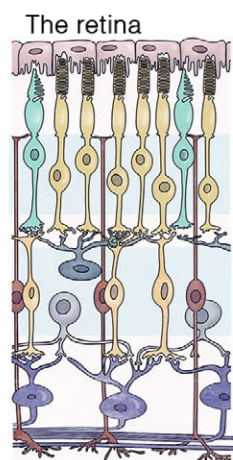
## Animal models have helped us understand how mutations in specific Usher genes alter proteins impacting the function of sensory systems.

(sound waves for hearing or head motion for balance) into electrical signals which are carried by neuronal fibres to the central nervous system. USH proteins are structurally and functionally essential in hair cells of the inner ear. USH1 protein complexes are necessary for normal stereocilia growth, and proper shaping of the interconnecting links coupling the stereocilia together.

As components of the apical tip-link, which acts as a gate to the transduction

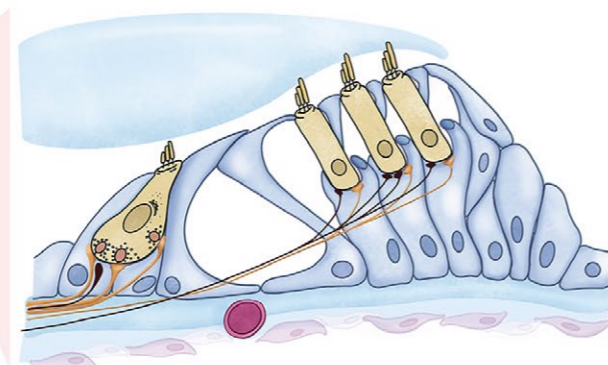
as in organisation of the synapse area of the inner hair cell. Less is understood in USH3 but lack of the protein clarin-1 has been shown to cause disorganisation of hair bundles, and inner hair cells' synaptic regions.

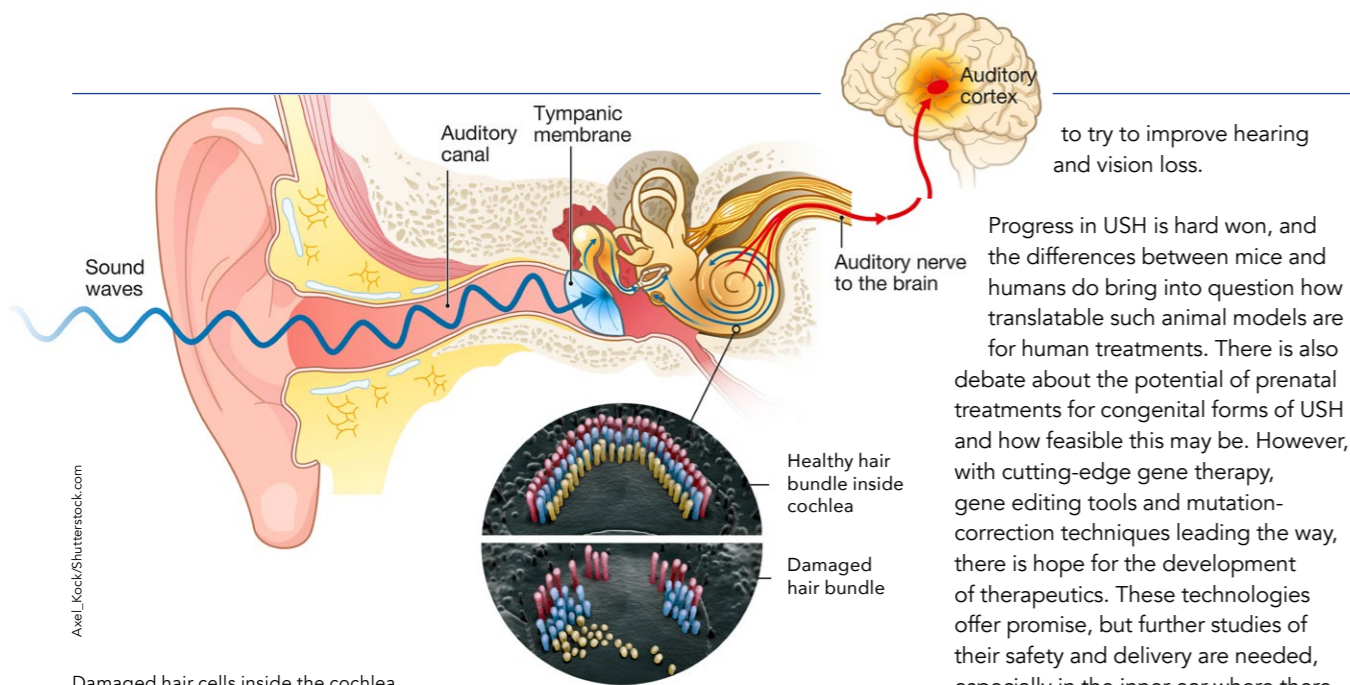
Unfortunately, patients with USH will develop retinitis pigmentosa (progressive eye diseases marked by the destruction of retinal photoreceptors) and become blind. Differences in retinal phenotypes between USH mice models and USH patients have hindered



Usher target organs

The hearing organ:





Damaged hair cells inside the cochlea.

mechanistic understanding of sight loss and limited therapeutic developments. The recent use of other animal models is poised to foster new progress. Studies in frogs and ongoing work in pig models have unveiled alterations in USH1 proteins that affect the retina photoreceptor cells causing loss of function. In mice, some mutant USH2 proteins have retinal degeneration, probably due to protein transport deficits, while the role of the USH3 protein in the retina is unknown.

#### THERAPEUTIC DEVELOPMENTS

The quest for biological therapies that treat the source of USH pathology is ongoing. Gene therapy introduces a working copy of a gene to replace or supplement the mutated one. Gene therapy and gene editing tools are being explored in preclinical models and there is a need to progress these safely into clinical trials. There are now approaches which involve targeting mutations without altering the whole gene. These include the use of 'antisense oligonucleotides' to target ribonucleic acids to prevent translation of mutated genes into dysfunctional proteins. Also, enzymes can be used to edit the mutated gene, with recent successes in mouse models of hearing loss.

There are also ongoing clinical trials aimed to address vision loss. One such trial delivers the USH1B gene to the retina using viral vector delivery systems designed to target photoreceptors, while another assesses the safety of

antisense oligonucleotide injections targeting the mutated USH2A gene. Other approaches aimed to target specific mutations include the use of translational read-through inducing drugs (or TRIDs) and gene editing tools. Success so far has been in the eye, but work is ongoing to develop new therapies for the inner ear.

During gene therapy, the 'correct' copy of a gene may be delivered using various vector systems. Adeno-associated viruses (AAVs) have been used in the replacement of four USH genes, namely USH1C, USH1G, USH2D, and USH3A, with successes noted for delivery of correct USH1C genes to the inner ear in mouse models, restoring normal hair-bundle shape and function.

There is immense potential for gene therapy in USH, but it is not without challenges. For example, AAV gene delivery systems have limited capacity and several USH genes exceed this. This is overcome by using dual AAV vectors where the separate gene codes are reformed once in the cell. There is now an ongoing clinical trial using dual AAV vectors to supplement USH1B

to try to improve hearing and vision loss. Progress in USH is hard won, and the differences between mice and humans do bring into question how translatable such animal models are for human treatments. There is also debate about the potential of prenatal treatments for congenital forms of USH and how feasible this may be. However, with cutting-edge gene therapy, gene editing tools and mutation-correction techniques leading the way, there is hope for the development of therapeutics. These technologies offer promise, but further studies of their safety and delivery are needed, especially in the inner ear where there are additional complexities.

El-Amraoui and Géléoc recommend that new guidelines are developed to redefine the current Usher syndrome classification which is based on clinical phenotypes. They suggest genotypes and available data on disease pathogenic mechanisms from animal models should also be taken into account to differentiate causal USH genes from other genes that form part of a separate category of deaf-blindness syndrome. By understanding phenotype-genotype correlations, it is hoped predictive models could indicate severity and progression of symptoms. There is a need for early precise diagnosis so adapted hearing prosthetic devices can be fitted and regular eye checks can begin.

Collectively, it is hoped that better diagnosis, better understanding of the disease by clinicians and researchers, and the advent of therapeutics will bring much needed help to Usher syndrome patients. The reviews by the researchers' help us take stock of where we are in our knowledge and where we are heading, bringing this rare disease to the forefront of our minds.

**With cutting-edge gene therapy, gene editing tools and mutation-correction techniques leading the way, there is hope for the development of sense-dedicated therapeutics.**

# Behind the Research



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## Research Objectives

Dr Aziz El-Amraoui and Dr Gwenaelle Geleoc research Usher syndrome.

## Detail

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### Bio

After a PhD in neuroscience obtained in Lyon-I, **Dr Aziz El-Amraoui** joined the Paris Pasteur Institute, where he now leads a research unit working on fundamental and medical aspects of hearing and vision in health and disease. His team is focused on late-onset, progressive hearing and vision impairments, building on accurate disease pathogenic mechanisms to develop adapted treatment solutions.

**Dr Gwenaelle Géléoc** received a PhD in sensory neuroscience from the University of Montpellier, France, and is now Associate Professor at Boston Children's Hospital and Harvard Medical School. As Director of the Harvard Speech, Hearing and Bioscience Graduate program, she aims to train the next generation of scientists in her field of studies. Her research focuses on the physiology of the sensory hair cells of the auditory and balance organs of the inner ear, in health and disease.

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- The Usher Syndrome Society; The Barber Gene Therapy Fund



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## Personal Response

### What are some of the challenges with studying a rare disease such as Usher syndrome?

**Aziz:** A prerequisite for any disease study is a precise and complete clinical description of the associated symptoms. These clinical data set the stage for better diagnosis and prognosis, and call for the establishment of appropriate model systems that better reflect actual human phenotypic features. Considering the clinical and genetic extreme heterogeneity of deafness and blindness disorders, it's unlikely that one therapeutic strategy could apply to all. The discovery of the precise pathogenic mechanisms and production of the right disease model(s) will thus be key to design the most adapted and efficient therapeutic option (viral or non-viral gene therapy, RNA therapy, or gene editing).

**Gwenaelle:** Moving forward, similarly to other rare diseases, one major challenge will be to bring new therapies to the clinic for a limited number of patients. Much research is now directed towards personalised medicine with development of mutation-specific therapies that restrict the number of patient candidates for such treatment. These restrictions impact the development of such therapies and their path to clinical trials. Furthermore, since USH is a rare degenerative disease that affects cells that cannot be replaced (hair cells and photoreceptor cells do not regenerate), benefit of such therapy will depend on disease progression and timing of the treatment. In some cases, foetal gene therapy will have to be considered, rendering medical and ethical concerns even more critical in the path towards development of novel therapies for USH patients.