Key Challenges in Gene Therapy Development for Usher Syndrome: Insights from Machine-Assisted Rapid Scoping Review

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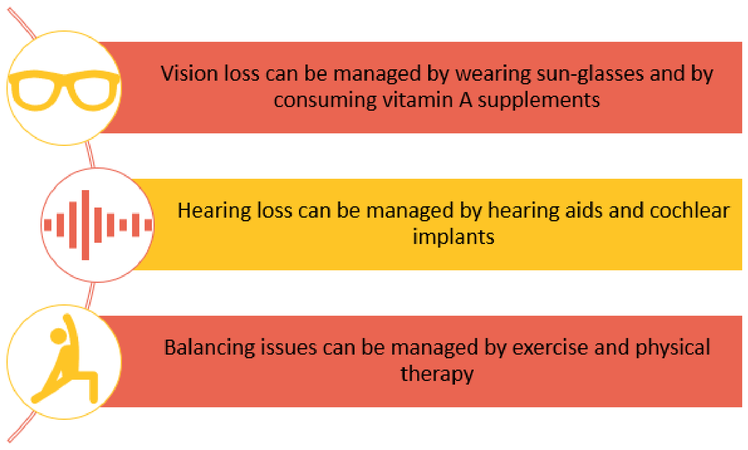
INTRODUCTION

- Usher syndrome (USH) is a rare genetic disorder that causes vision and hearing loss, and sometimes balance problems[1].
- It accounts for about 50% of all hereditary deaf-blindness cases.
- Currently there is no cure with valid evidence except symptomatic management (Figure 1).

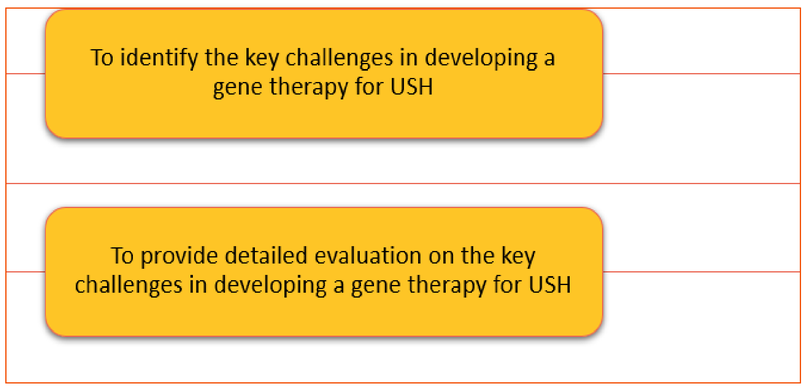
Figure. 1 Symptomatic management of USH



- The regulatory approval of Luxturna gene therapy for Leber Congenital Amaurosis (LCA2) has sparked the possibilities for the application of gene therapies in USH.
- Despite empirical evidence indicating the potential, challenges persist in the developing and approval of gene therapies for USH[2].
- Due to limited structured evidence availability on the topic, our Scoping Review (ScR) focused to uncover all potential challenges to develop a gene therapy for USH.

OBJECTIVES

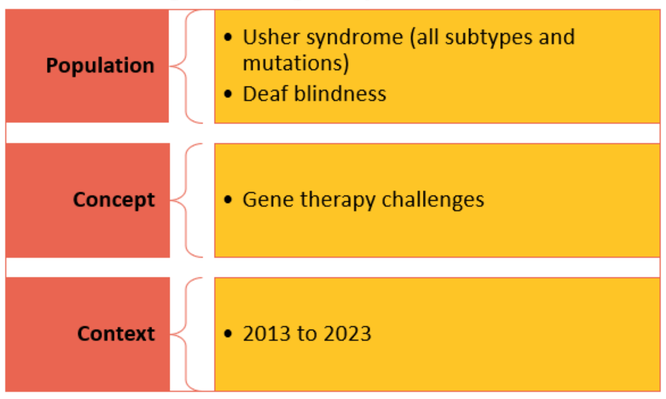
Figure. 2 Objectives of the study



METHODS

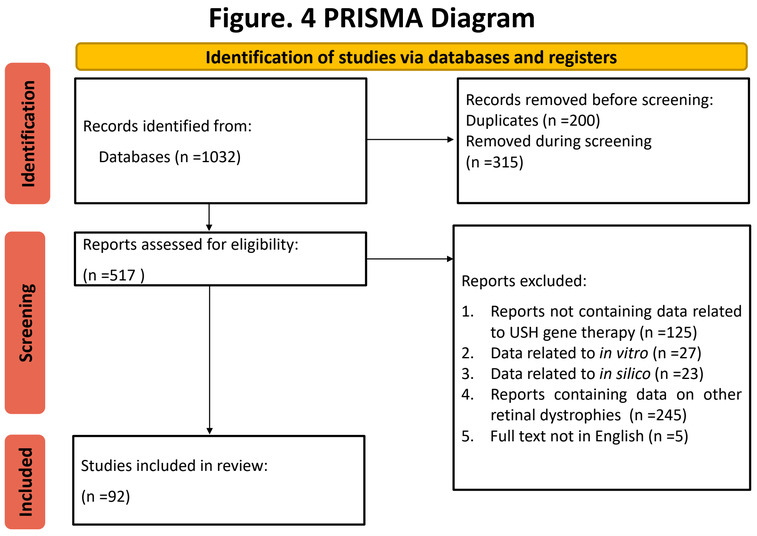
- A literature search was performed on PubMed, and Google Scholar using an artificial intelligence (AI)-powered evidence synthesis tool – MAIA
- We included clinical trials, observational studies, reviews, systematic literature reviews, meta-analyses and workshop reports related to USH.
- Data charting was done in Microsoft Excel-based data charting file using Jonna-Briggs Institute (JBI) ScR data extraction template.

Figure. 3 Eligibility criteria



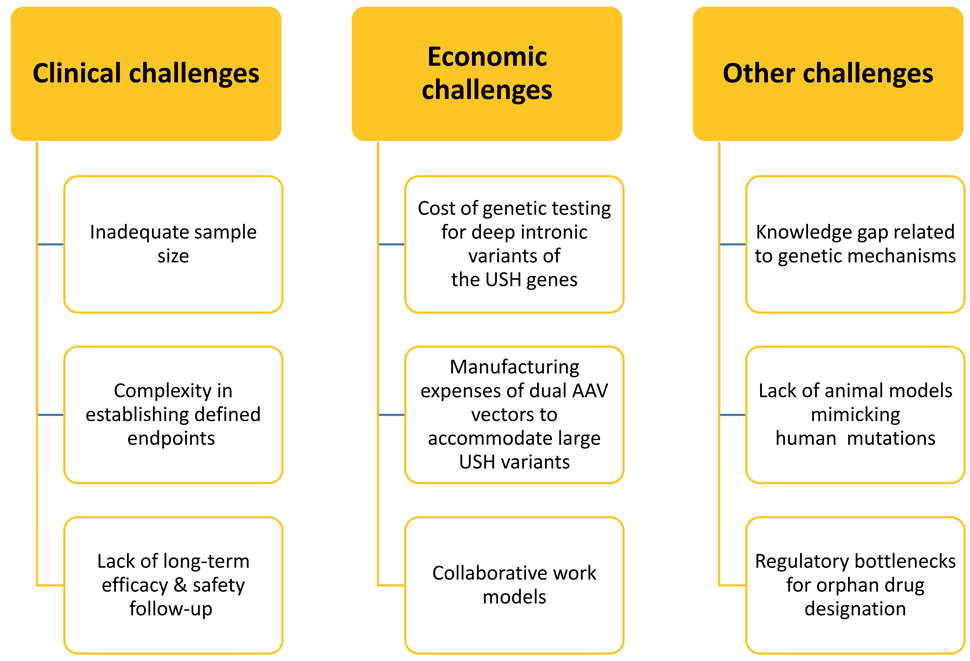
RESULTS

Figure. 4 PRISMA Diagram



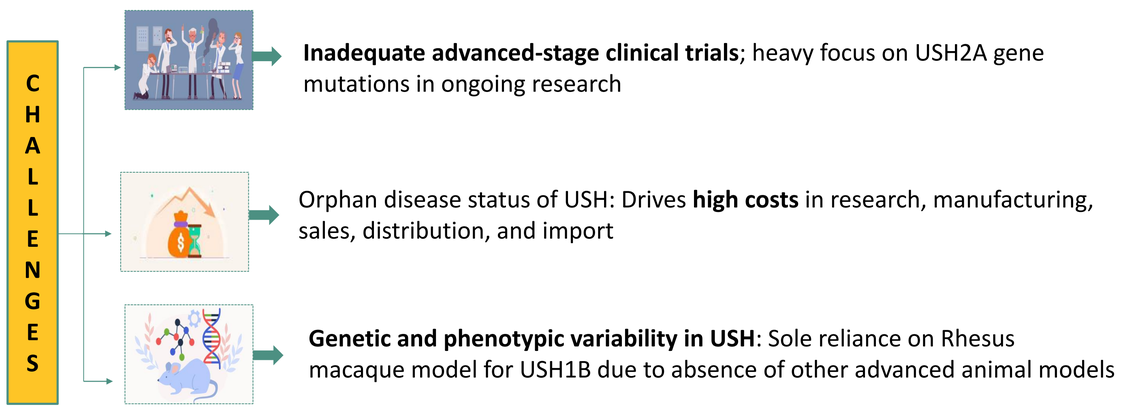
RESULTS CONTD..

Figure. 5 Types of challenges for USH gene therapy



Abbreviations: AAV: Adeno-associated viral vector, USH: Usher syndrome

Factors influencing USH gene therapy development



Abbreviations: USH: Usher syndrome, USH1B: Usher syndrome type IB, USH2A: Usher syndrome type IIA

DISCUSSION

- This ScR summarises the current landscape of ongoing research and clinical trials in developing a gene therapy for USH through a machine assisted **(MiaA)** fast and robust evidence synthesis.
- Developing a clinical translation of a gene therapy for USH has a series of multifaceted challenges spanning from **pre-clinical to regulatory domain**.
- The **limited availability of non-human primate models** that mimic the genetic diversity and mutations seen in USH patients hampers the translation of preclinical findings[3].
- On the clinical front, the rarity of USH poses a significant challenge, leading to trials with very **few participants** and necessitating the optimization of data collection for robust results.
- The constrained capacity of good manufacturing practice-grade commercial production of adeno-associated vectors (AAV) and lentiviral vectors has resulted in **elevated costs**.

USE OF TECHNOLOGY IN EVIDENCE SYNTHESIS

- MAIA use helped us to quickly gather evidence for this ScR and could finish the work in <4 weeks.
- The integrated system may help stay focused on evidence screening and quality reducing cognitive overload for analysts.

CONCLUSION & NEXT-STEPS

- Researchers are using innovative delivery methods like minigenes and nanoparticles, along with genetic counselling and advanced sequencing techniques to mitigate these challenges.
- Clinical trial designs, harmonized regulations, market assessment strategies, and research collaborations have the potential to drive disease-modifying interventions and enhance the quality of life for USH patients.

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