

Clinical Exome Sequencing Identifies an *STRC* Frameshift Mutation in a UAE Family with Profound Non-syndromic Hearing Loss

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Abstract

Autosomal recessive non-syndromic hearing loss is the most common form of hereditary deafness. In this study, clinical exome sequencing followed by segregation analysis via Sanger sequencing identified an *STRC* frameshift mutation (c.4510del) as the causative mutation in a consanguineous UAE family with autosomal recessive non-syndromic hearing loss. The present study represents the first *STRC* mutation reported in the UAE population.

Introduction

Hearing loss (HL) is one of the most frequent sensory deficits, globally affecting 1 in 1000 individuals, with autosomal recessive non-syndromic hearing loss (ARNSHL) representing most of genetic deafness¹. Despite its frequency, the diagnosis of ARNSHL is often hindered by its genetic heterogeneity (69 genes and over 100 loci) as well as the variable mutational load of its genes among populations. Currently, researchers are relying on next generation sequencing (NGS) based methodologies such as targeted sequencing (TS) panels, clinical exome sequencing (CES), or whole exome sequencing (WES) as they enable the simultaneous detection of many genetic variations in a timely and cost-effective manner as opposed to traditional methods. This study aimed to use CES to identify the causative mutation in a consanguineous UAE family with ARNSHL. It also aimed to use Sanger sequencing to confirm the segregation of the identified mutation with the HL in the investigated family and screen the UAE population for this mutation.

Methods

Clinical assessment of the proband

Extraction of genomic DNA from saliva samples of the proband and his parents

Sanger sequencing of the proband's *GJB2* gene

CES and standard data analysis covering a total of 6879 genes using the proband's genomic DNA

Filtration of variants generated by CES and selection of the candidate variant

Prediction of the functional impact of the selected variant using VEP, Mutation Taster and VarSome

Sanger sequencing of the third exon of the *STRC* gene for the proband and his parents

Screening of 109 deaf individuals and 50 unrelated controls from the UAE for the c.4510del variant by Sanger sequencing

Results and Discussion

The consanguineous UAE family investigated here included one individual diagnosed with congenital bilateral profound sensorineural HL (Figures 2A and 2B). Sanger sequencing of the proband showed the absence of mutations in the *GJB2* gene, the most common ARNSHL gene in the UAE population². After prioritization of all variants generated by CES based on the shown criteria (Figure 1), only 13 variants remained (Table 1). Among them only one variant in the *STRC* gene (c.4510del, p.Glu1504Argfs*32) was categorized as "IMPACT=high", "disease causing" and "likely pathogenic" by VEP, Mutation Taster and VarSome respectively.

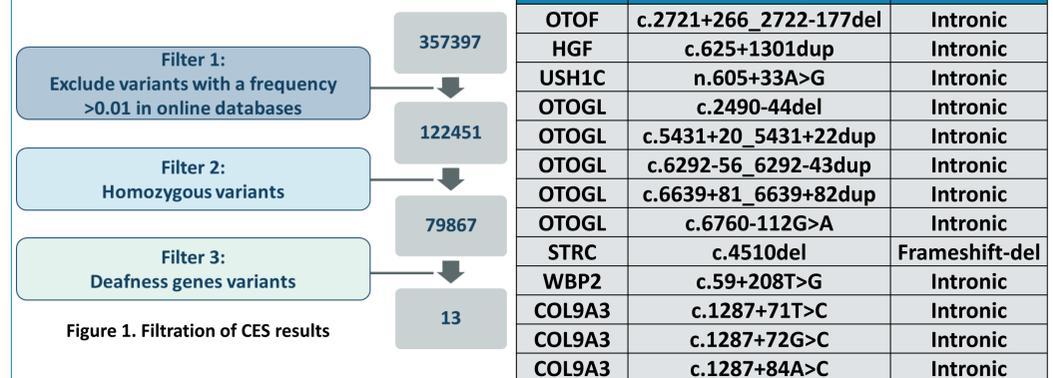


Figure 1. Filtration of CES results

Table 1. Remaining variants after filtration of CES results

Sanger sequencing confirmed the homozygous genotype of the proband and showed that both parents were heterozygous for the *STRC* variant (Figures 2C and 2D). These findings indicate that the c.4510del variant co-segregates with the HL in this family. The absence of c.4510del in 109 unrelated deaf individuals and 50 healthy controls indicated that it is rare in the UAE population (Figure 2E).

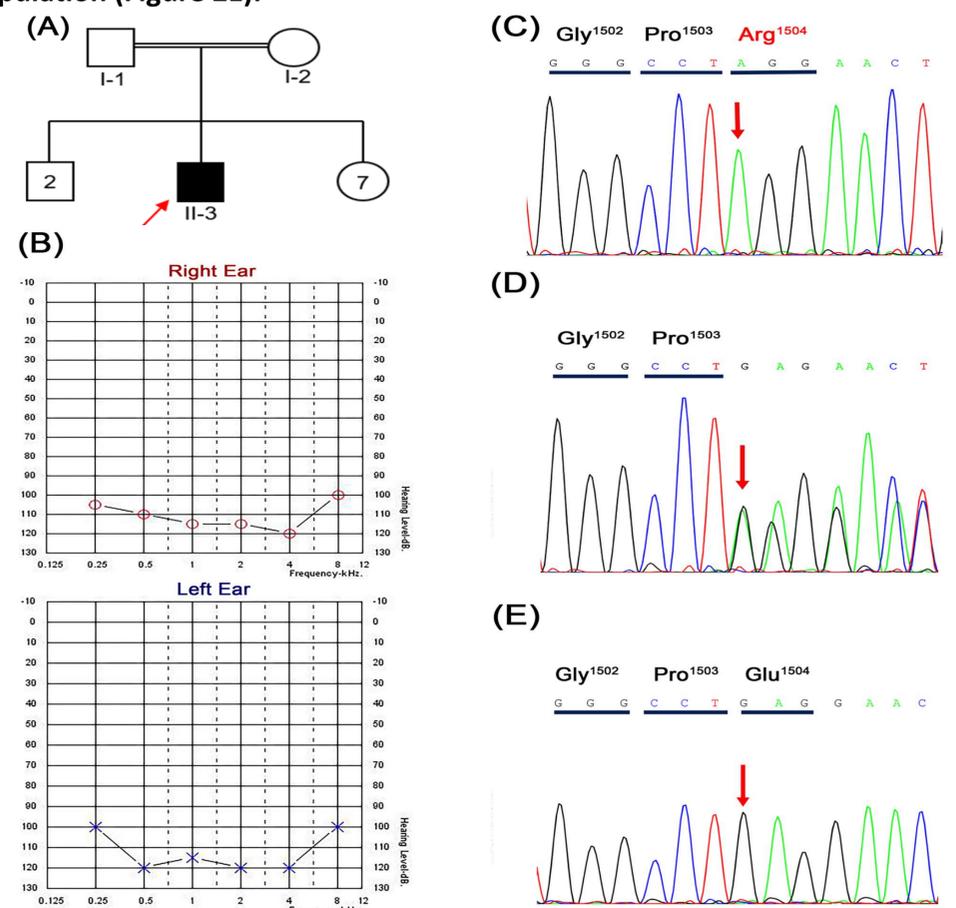


Figure 2: Pedigree, Audiograms and Electropherograms. (A) Pedigree of the affected family. Arrow denotes the proband. (B) Audiograms of individual II-3 (C) Electropherogram of a homozygous mutant individual with the c.4510del frameshift mutation. (D) Electropherogram of a heterozygous individual. (E) Electropherogram of a homozygous wild type individual.

Conclusion and Recommendations

In conclusion, CES allowed the efficient identification of the homozygous NM_153700.2:c.4510del frameshift mutation as the causative mutation in a consanguineous UAE family with ARNSHL. These results add the *STRC* gene to the spectrum of non-syndromic hearing loss genes in the UAE population. They also emphasize the importance of using NGS-based techniques in genetic testing, especially in populations with high consanguinity rates. Further studies are needed to better understand the epidemiology of genetic deafness in the UAE to improve diagnosis and hopefully lead to the development of treatments in the future.

Acknowledgments

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References

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