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ORIGINAL ARTICLE

Mutation spectrum of non-syndromic hearing loss in the UAE, a retrospective cohort study and literature review

Omnia Elsayed[1] | **Aisha Al-Shamsi**[2]

[1]Pediatrics Department, Tawam Hospital, Al Ain, United Arab Emirates

[2]Genetic Division, Pediatrics Department, Tawam Hospital, Al Ain, United Arab Emirates

Correspondence
Aisha Al-Shamsi, Genetic Division, Pediatrics Department, Tawam Hospital, Al Ain, United Arab Emirates.
Email: aishamsi@seha.ae

Abstract

Background: Hearing loss (HL) is a heterogeneous condition that causes partial or complete hearing impairment. Hundreds of variants in >60 genes have been reported to be associated with Hereditary HL (HHL), variants of the *GJB2* gene are the most common cause of congenital SNHL, with >100 variants reported. The HHL prevalence is thought to be high in the Arab population; however, the genetic epidemiology of HHL among Emirati populations is understudied.

Aims: To shed light on the mutational spectrum of NSHL in Emirati patients seen in the genetic clinic over 10 years and to capture founder mutation(s) if any were identified.

Methods: Retrospective chart review of all Emirati patients assessed by clinical geneticists due to NSHL during the period between January 2010 to December 2020. Genetic tests were done based on clinical phenotypes of the patient and family history including targeted mutation testing, next-generation sequencing, or whole-exome sequencing (solo or trio). The authors did literature reviews using PubMed for all previously reported articles related to NSHL genes from UAE.

Results: A total of 162 patients with HL, were evaluated during the period between January 2010 to December 2020. There were 82 patients with NSHL, and only 72 patients who completed the genetic evaluations were included in this retrospective study. Among the studied group, 42 (51.2%) were males and 40 (48.78%) were females. The youngest patient was 2 years old and the oldest patient was 50 years old. Consanguinity was documented in 76 patients (92.68%). A total of 14 mutations reported here are novel (23/72 i.e., 31.9%). Twelve missense mutations, 6 nonsense mutations, 6 frameshift mutations, 2 in-frame deletion mutations, and 1 splice site mutation was found. Variants in the *GJB2* gene are the most commonly identified cause of NSHL, with c.35delG being the most followed by c.506G > A. The second commonly found variant is c.934C > G (p.Arg312Gly) in the *CDC14A* gene, found in 9 patients. This was followed by variants in *OTOF* and *SLC26A4* genes, found in 8 patients, respectively. Chromosomal microdeletions encompassing genes causing NSHL were found in 3 patients. No mitochondrial

mutations were found in this study group. A total of 11 previous reports about Emirati patients with NSHL were reviewed, with a total of 35 patients.

Conclusion: Emirati patients with NSHL have several mutations, most notably missense mutations. Novel mutations are worth further testing and represent the area for future researches.

KEYWORDS

mutations, non-syndromic hearing loss, novel, retrospective study, UAE

1 | INTRODUCTION

Emirati people (citizens of United Arab Emirates, UAE) have diverse ethnicities that include lineages from the Arabian Peninsula, Persia, Baluchistan, and East Africa. The culture is primarily tribal and encourages intra-tribal (consanguineous) marriages (Al Shamsi et al., 2014). Thus, "founder" mutations are prevalent, which markedly increase the frequency of autosomal recessive disorders (Woods et al., 2006).

Hearing loss (HL) is one of the most common sensory defects in humans and is a heterogeneous condition that results in fractional or complete hearing incompetence. According to the WHO, HL is the most prevalent sensory impairment in both childhood and adulthood, affecting approximately 360 million individuals globally, equaling 5% of the world's population (Sidenna et al., 2019). HL may occur in one (unilateral) or both ears (bilateral) and may be temporary or permanent. The types of HL include sensorineural hearing loss (SNHL), conductive hearing loss, and mixed hearing loss. SNHL is caused by intrinsic causes such as genetic variants or extrinsic causes such as noise, ototoxic drugs, bacterial, or viral infections and trauma. Conductive hearing loss develops when a defect in the conduction of sound waves occurs across the middle ear, outer ear, or eardrum. If sensorineural and conductive hearing loss occurs together, then the condition is called mixed hearing loss.

HL can also be classified as congenital or late-onset and as syndromic or non-syndromic. Syndromic hearing loss (SHL) is associated with signs and symptoms that may affect not only the ears but also other parts of the body. In contrast, non-syndromic hearing loss (NSHL) is a partial or total loss of hearing that is not associated with other signs and symptoms. Approximately 30% of all hereditary hearing loss (HHL) is syndromic. The NSHL prevalence reaches 70% worldwide (Yan et al., 2016), and more than 50% of congenital deafness has genetic causes (Brown & Rehm, 2012). NSHL can be inherited in an autosomal-dominant manner in 10% to 15% of cases, the autosomal-recessive manner in 80% of cases, with 1% to 3% exhibiting the X-linked form, and as a mitochondrial inheritance in <1% of cases (Yan et al., 2016). The recent advancement of comprehensive mutation screening by targeted next-generation sequencing or whole exome sequencing, has provided an easier and more cost-effective approach for identifying causative mutations. It provides crucial information for the diagnosis, intervention, and treatment of hearing disorders. Due to this, hundreds of variants in more than 60 genes have been reported to be involved in HHL (Brownstein et al., 2014). However, variants of the *GJB2* gene are the most common cause of congenital SNHL, with more than 100 variants reported. Several variants of *GJB2* have been found to be prevalent in some ethnic groups (Europeans, Asians, and Jewish), such as 35delG, p.Val37Ile, 235delC, and Arg143Trp (Chan & Chang, 2014; Sidenna et al., 2019). However, within the Arab population, together with the *GJB2* gene, there are several other genes also involved in HHL (Alkowari et al., 2017). It is estimated that more than 5% of individuals worldwide may suffer from HL. The prevalence of HL in the GCC countries is not well defined. In fact, all studies conducted so far include regions or specific groups but not the totality of the population. In the KSA, the prevalence of childhood sensorineural HL was estimated to range from 1 to 4/1000 live births (Al-Abduljawad & Zakzouk, 2003), while in Oman an incidence of 1.2/1000 was reported (Khandekar et al., 2006). An old retrospective study done in UAE between the period of 1994 to 1996 on 74 patients with HL showed a prevalence of 19% (syndromic) versus 81% (non-syndromic) (Al-Gazali, 1998). A recent systematic review paper about the genetic epidemiology of hearing loss in the 22 Arab countries reported that the incidence of HHL in the captured studies ranged from 1.20 to 18 per 1000 births per year, and the prevalence was the highest in Iraq (76.3%) and the lowest in Jordan (1.5%) (Sidenna et al., 2019). Due to the high consanguinity rate among the UAE population (54%) (Saleh et al., 2021), the number of novel or recurrent mutations in rare deafness genes along with variable genotype–phenotype of hearing loss severity is expected.

Therefore, the aim of this retrospective study is to shed light on the mutational spectrum of NSHL in Emirati patients seen in a genetic clinic over 10 years. At the same time, to capture the founder mutation(s) if any are identified. This cohort study can provide the prevalence/epidemiology of NSHL in the UAE.

2 | METHODS

This study was approved by Tawam Medical Human Research Ethics Committee (Ref. No.: AA/AJ/810). A retrospective chart review of all Emirati patients assessed by clinical geneticists due to NSHL during the period between January 2010 to December 2020. The genetic tests were done based on the clinical phenotypes of the patient and family history including targeted mutation testing, next-generation sequencing, or whole exome sequencing (solo or trio). All the mutations identified were confirmed by sanger sequencing. All variants are categorized into five classes (pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign) using ACMG guidelines for classification and by ClinVar, provided family history and clinical information are used to evaluate identified variants with respect to their pathogenicity.

At the same time, the authors did a literature review using PubMed for all previously reported articles related to non-syndromic hearing loss genes from UAE by using search terms “Hearing loss” OR “Deafness” AND “non-syndromic” and “UAE” and included only mutations in Emirati patients reported before here.

3 | RESULTS

A total of 162 patients with hearing loss, were seen in the genetic clinic during the period between January 2010 and December 2020. Results were divided into the following categories, (Figure 1):

1. Patients with SHL (80 patients) were excluded from this study
2. Patients with NSHL who continued and completed the genetic evaluations during the study period (72 patients) were included in this cohort study.
3. Patients with negative testing and those who were lost to follow-up and did not continue the evaluation (10 patients) were also excluded from this study.

Reviewing the previously reported patients in PubMed, there were 11 reports about Emirati patients with NSHL, with a total of 35 patients.

3.1 | Patients' demographics

Our cohort study revealed 82 patients with NSHL, 42 (51.2%) males and 40 (48.78%) females. The youngest patient was 2 years old and the oldest patient was 50 years old. Consanguinity was documented in 76 patients (92.68%), with 3 patients with no consanguinity and 3 patients with unclear information about consanguinity. Positive molecular diagnosis was found in 72 patients (87.8%), and those were of interest to this study. The remaining 10 patients with negative testing and those lost to follow-up and did

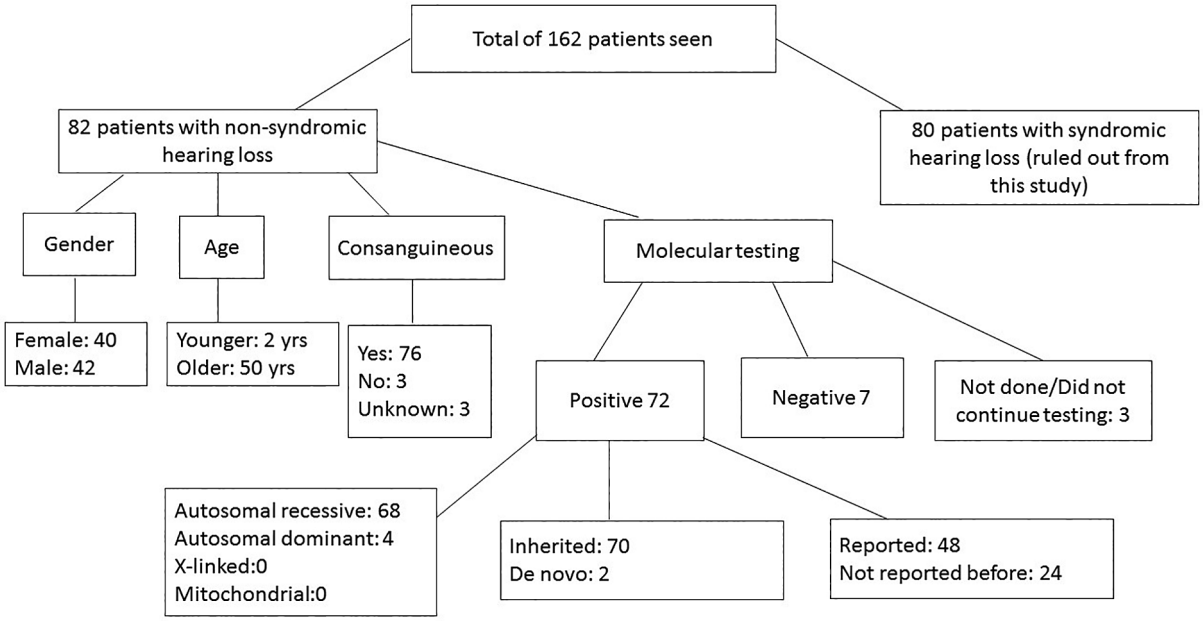

FIGURE 1 Distribution of the studied population according to their workup findings.

not continue genetic evaluation, were not included in the molecular results.

3.2 | Molecular analysis

Seventy-two (72/82; 87.8%) patients had positive molecular testing; 68 patients (68/72; 94.4%) with autosomal recessive disorders and 4 patients (4/72; 4.8%) with autosomal dominant disorders were identified. No patients with X-linked related disorders and with mitochondrial mutations were found in this study. A total of 14 mutations reported here are novel (23/72 i.e., 31.9%) (Table 1). Twelve missense mutations, six nonsense mutations, six frameshift mutations, two in-frame deletion mutations, and one splice site mutation were found in this study.

Table 1 summarized all the mutations found in this respective study and previously reported mutations in Emirati patients with NSHL. Variants in the *GJB2* gene are the most commonly identified cause of NSHL, with c.35delG being the most followed by c.506G > A.

The second commonly found variant is c.934C > G (p.Arg312Gly) in the *CDC14A* gene, which was found in a total of 9 patients. This was followed by variants in *OTOF* and *SLC26A4* genes, found in 8 patients, respectively. The nonsense variant c.709C > T (p.Arg237Ter) in the *OTOF* gene was predominant in that group (in 5 patients), and the missense variant c.716T > A p.(Val239Asp) in the *SLC24A4* gene was the predominant in that group (in 4 patients).

On the contrary, nonsense variant c.100C > T (p.Arg34*) in the *TMC1* gene was found in a total of 5 patients, 3 of them in this study while 2 were from previous reports.

Interestingly, we did not find any mitochondrial mutation in our studied patients, but there were 5 patients reported previously with a homoplasmic mutation in the *MT-RNR1* gene.

Novel variants found in this study include the variant c.1477C > T (p.Arg493*) in the *ADGRV1* gene, in 2 siblings with healthy asymptomatic parents.

Chromosomal microdeletions encompassing genes causing NSHL were found in 3 patients; 2 patients with deletion of chromosomal region chr11:76917135–76,917,255, encompassing partially exon 40 and the entire exon 41 of *MOY7A* gene, and 1 patient with deletion of chromosomal region chr10:73337654–73,337,904 encompassing exon 9 in *CDH23* gene. Another two patients had a homozygous inversion of the chromosomal region chr3:150649557–150659952, encompassing exon 2 of the *CLRN1* gene.

Some other mutations in genes with a minor contribution to NSHL in UAE are in Table 1.

4 | DISCUSSION

Hereditary hearing loss (HHL) is one of the most common sensory disorders worldwide, with an incidence of 1–2 per 1000 newborns (Nance, 2003). To our knowledge, this is the first cohort study and literature review reporting NSHL in the Emirati population. In our retrospective cohort study, a total of 162 patients were found to have hearing loss, 82 patients had NSHL and were the group of interest in this study. Since the UAE population is known to have a high consanguineous marriage, it was not surprising that 76/82 (92%) of the studied patients here were having consanguine parents and most were first cousins. This could play a significant causal role in NSHL in our studied samples, however, to accurately estimate the significant association between consanguinity and the increased incidence of NSHL, larger patient cohorts that are homozygous for specific variants should demonstrate higher values than would normally be predicted. There was a deep literature review of genes and variants responsible for HL in the GCC region revealed 89 recessive DNA pathogenic variants reported in 138 cases/familial cases. A total of 21 genes responsible for NSHL were reported in cases from the GCC region. For individuals with NSHL, 66% of variants were detected in four genes (*GJB2, OTOF, TMC1*, and *CDH23*), with a predominance of variants located in the *GJB2* gene (37.5%) (Al Mutery et al., 2022).

In our study, we observed a male preponderance in contrast to the EU study which showed a significantly higher prevalence in females than males (Sakihara et al., 1999).

At the same time, our findings are consistent with a systematic review analyzing 216 peer-reviewed studies worldwide containing 43,000 HL probands, which concluded that the gene most associated with HHL was *GJB2* (Chan & Chang, 2014; Sidenna et al., 2019), which is known to be responsible for up to 50% of all prelingual NSHL cases in Caucasian populations (Gasparini et al., 2000; Al Mutery et al., 2022). Here, we found 22 patients with different mutations in the *GBJ2* gene, along with 13 patients reported previously. Until now, more than 100 mutations in the *GJB2* gene have been reported to cause NSHL. They involve a wide spectrum of missense, nonsense, frameshift, and splice site mutations. However, one truncated mutation (c.35delG) is most frequent in the majority of the Caucasian population, with the carrier frequency as high as 2–4% (Green et al., 1999). In our retrospective study, we found similar high numbers of Emirati patients with c.35delG being the most followed by c.506G > A mutations. Clinically, both are categorized as pathogenic variants with sufficient patient numbers manifesting a clear genotype–phenotype correlation.

Our study also found a mutation; c.934C > G (p.Arg312Gly) in the *CDC14A* gene in 9 patients from different

TABLE 1 Summary of mutations detected in Emirati samples

OMIM Gene	Mutation	Alleles	Variant type	Number of affected individuals	Reference/comments
ADGRV1 (OMIM 602,851)	***c.1477C>T (p.Arg493*)***	Hete	Nonsense	2	This study (Novel)
BTD (OMIM 609,019)	c.560del (p.Pro187Glnfs*77)	Homo		1	Saleh et al. (2021)
CCDC50 (OMIM 611,051)	***c.803A>G***	Hete		1	This study (Novel), Conflicting interpretations of pathogenicity: Likely benign; Uncertain significance
CDC14A (OMIM 603,504)	c.934C>G (p.Arg312Gly)	Homo	Missense	9	Imtiaz (2017)
CDH23 (OMIM 605,516)	***Deletion of chromosomal region chr10:73337654–73,337,904 encompassing exon 9***	Homo	-	1	This study (Novel)
	c.5237G>A p.(Arg1746Gln)	Homo	Missense	1	Bolz et al. (2001); Schultz et al. (2011); Zhao et al. (2015)
CLDN14 (OMIM 605,608)	***c.278 T>G p.(Ile93Arg)***	Homo	Missense	2	This study (Novel)
CLRN1 (OMIM 606,397)	***Inversion of the chromosomal region chr3:150649557–150,659,952, encompassing exon 2***	Homo	-	2	This study (Novel)
COL4A3 (OMIM 120,070)	c.2939 T>A p.Leu980*	Homo	Nonsense	3	Jin et al. (2017)
COL11A2 (OMIM 120,290)	c.966dup (p.Thr323Hisfs*19)	Homo	Frameshift	3	Vona et al. (2017)
CRYM (OMIM 123,740)	**c.108C>A, p.Ser36Arg**	Hete	Missense	1	This study (Novel), Conflicting interpretations of pathogenicity: Likely benign; Uncertain significance
EPS8L2 (OMIM 614,988)	***c.493G>T p.(Glu165*)***	Homo	Nonsense	2	This study (Novel)
ESPN (OMIM 606,351)	c.2257 T>C p.(Trp753Arg)	Homo	Missense	2 +(1)	Chouchen and Tlili (2020)
ESRRB (OMIM 602,167)	c.1058-3C>A	Homo	Splice site	*?(1*) no specific number identified*	Chouchen and Tlili (2020)

(Continues)

TABLE 1 (Continued)

OMIM Gene	Mutation	Alleles	Variant type	Number of affected individuals	Reference/comments
GJB2 (OMIM 121,011)	c.35del (p.Gly12Valfs*2)	Homo	Frameshift	15+(6)	Tlili, Mutery, et al. (2017); Wilcox et al. (2000); D'Andrea et al. (2002); Al-Qahtani et al. (2009)
	c.-23+1G>A (c.-3170G>A or IVS1+1G>A)	Homo	Splice site	2+(1)	Denoyelle et al. (1999), Barashkov et al. (2011, 2014)
	c.506G>A (p.Cys169Tyr)	Homo	Missense	5+(6)	Mahfood et al. (2021)
ILDR1 (OMIM 609,739)	c.804delG (p.Glu269ArgfsTer4)	Homo	Frameshift	(5)	Tlili, Fahd, et al. (2017)
MT-RNR1 (OMIM 561,000)	m.827A>G (n.180A>G)	Homoplasmic	Non-coding	(1)	Mohamed et al. (2020)
	m.669T>C (n.22T>C)			(4)	
MYO6 (OMIM 600,970)	c.2751dup (p.Gln918Thrfs*24)	Homo	Frameshift	2	Kwon et al. (2014)
MYO7A (OMIM 276,903)	***c.223G>T (p.Asp75Tyr)***	Homo	Missense	3	This study (Novel)
MYO7A (OMIM 276,903)	***Deletion of chromosomal region chr11:76917135–76,917,255, encompassing partially exon 40 and the entire exon 41***	Homo	-	2	This study (Novel)
MYO15A (OMIM 602,666)	***c.3791C>A p.(Pro1264Gln)***	Homo	Missense	1	This study (Novel)
OTOF (OMIM 603,681)	c.5566C>T (p.Arg1856Trp)	Homo	Missense	3	Sloan-Heggen et al. (2016); Chang et al. (2015)
	c.709C>T (p.Arg237Ter)	Homo	Nonsense	(5)	Houseman et al. (2001)
PCDH15 (OMIM 605,514)	c.2382_2384del p.(Val795del)	Homo	In-frame deletion	1	Zhan et al. (2015)
SLC26A4 (OMIM 605,646)	c.1211C>T p.(Thr404Ile)	Het (with below)	Missense	1	Landa et al. (2013)
	c.2174_2177dup p.(Leu727Tyrfs*28)	Het (with above)	Frameshift	1	Houseman et al. (2001); Zhan et al. (2015); Landa et al. (2013); Courtmans et al. (2007)
	c.716T>A p.(Val239Asp)	Homo	Missense	3 + *(1)*	Tlili, Fahd, et al. (2017); Park et al. (2003); Soh et al. (2014)
	c.1150G>C (p.Glu384Gln)	Homo	Missense	1 + *(1)*	Ben-Salem et al. (2014)
STRC (OMIM 606,440)	c.4510del (p.Glu1504Argfs*32)	Homo	Frameshift	(1)	Mahfood et al. (2019)
SYNE4 (OMIM 615,535)	***c.752C>T p.(Pro251Leu***	Homo	Missense	1	This study (Novel)

families. Interestingly, the same mutation was reported before to be associated with deafness and male infertility (Imtiaz, 2017), none of our patients had fertility issues reported. A previous report about mutations in *CDC14A*, done by Delmaghani et al. (2016), caused autosomal-recessive severe to profound congenital deafness and suggested that the hearing impairment arises from abnormally short kinocilia in the differentiating hair bundles of cochlear sensory cells.

On the other hand, mutations in the *OTOF* gene are frequently associated with the clinical phenotype of non-syndromic auditory neuropathy (Varga et al., 2003) or more specifically auditory synaptopathy (Roux et al., 2006). O*TOF* gene is frequently implicated in autosomal recessive NSHL and many of its pathogenic alleles include stop-codon changes and deletions or duplications that result in premature truncation of the protein. Mutation in the *OTOF* gene was studied in many deaf cohorts from Spain, Turkey, the USA, Colombia, Argentina, Pakistan, Brazil, China, Taiwan, Iran, Japan, and Korea (Pandey et al., 2017). However, a load of hereditary hearing loss as a result of *OTOF* mutations in the UAE remains largely unexplored, but among our studied patients here we found the following mutations c.709C>T (p.Arg237Ter) and c.5566C>T (p.Arg1856Trp).

Here, we also found four variants in the *SLC26A4* gene reported in 5 patients previously (Courtmans et al., 2007; Houseman et al., 2001; Landa et al., 2013; Park et al., 2003; Soh et al., 2014; Tlili, Fahd, et al., 2017). Mutations in *SLC26A4* are a frequent cause of hearing loss and are causally linked to a syndromic form of hearing impairment, Pendred syndrome (MIM 274600), and NSHL with enlarged vestibular aqueduct (MIM 600791) (Chouchen et al., 2020).

It is well known that variants in the head and tail domains of the *MYO7A* gene, encoding myosin VIIA, cause Usher syndrome type 1B and non-syndromic deafness (Ben-Salem et al., 2014). Here, we found 2 novel variants in the *MYO7A* gene, given the absence of retinal disease in all affected patients examined, this finding further supports the premise that the *MYO7A* gene is responsible for two distinct diseases and gives evidence that the c.223G>T (p.Asp75Tyr) mutation in a homozygous state may be responsible for NSHL.

Mutations in the *ILDR1* gene with phenotype-genotype correlation alongside the molecular diagnosis of a consanguineous UAE family with five deaf individuals found to be homozygous for a novel frameshift mutation c.804delG were reported previously (Tlili, Fahd, et al., 2017) included in Table 1.

Other pathogenic variants in a total of 22 additional NSHL genes have been reported here with the majority being missense, nonsense, and frameshift variants (Table 1). Among these genes, *COL11A2, MYO6, TMC1, TRIOBP*, and *TMPRSS3* are the most frequent in our region.

TABLE 1 (Continued)

OMIM Gene	Mutation	Alleles	Variant type	Number of affected individuals	Reference/comments
TMC1 (OMIM 606,706)	c.100C>T (p.Arg34*)	Homo	Nonsense	3 + (2)	Tlili, Fahd, et al. (2017); Kurima et al. (2002); Shafique et al. (2014); Dallol et al. (2016)
TMIE (OMIM 607,237)	***c.391_393delAAG (p.L131del)***	Homo	In-frame deletions	1	This study (Novel)
TRIOBP (OMIM 609,761)	***c.3232del p.(Arg1078Alafs*135)***	Homo	Frameshift	1	This study (Novel)
	c.2758C>T (p.Arg920*)	Homo	Nonsense	2	Gu et al. (2015)
TMPRSS3 (OMIM 605,511)	***c.800C>A (p.Ser267*)***	Homo	Nonsense	2	This study (Novel)
USH2A (OMIM 608,400)	c.9860_9873del (p.His3287Profs*54)	Homo	Frameshift	2	Carss et al. (2017)

Note: Mutation in Italics and bold font is novel. The number in italics is of previous reported affected individuals.

In conclusion, we showed that patients with NSHL from UAE have several mutations, most notably missense mutations. Novel mutations were found in our study worth further testing and represent areas for future research. Further research is also required to accurately estimate the prevalence and incidence of HHL to provide and plan better healthcare for HHL patients. The collection of variants in this study is important in diagnosis, disease management, and genetic counseling; however, there is a need for further well-controlled studies to identify more variants and standardize clinical measures across the UAE population.

AUTHOR CONTRIBUTIONS

OS and AA-S contributed to conception and design. AA-S drafted the manuscript. All authors contributed to the acquisition, revised manuscript, and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors. This study is approved by Tawam Human Research Ethics Committee (Ref. No.: AA/AJ/810).

INFORMED CONSENT

Not required in this study.

ORCID

Aisha Al-Shamsi https://orcid.org/0000-0001-8757-7782

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