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Genetic Epidemiology of Hearing Loss in the 22 Arab Countries: A Systematic Review

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Background: Hearing loss (HL) is a heterogeneous condition that causes partial or complete hearing impairment. Hundreds of variants in more than 60 genes have been reported to be associated with Hereditary HL (HHL). The HHL prevalence is thought to be high in the Arab population; however, the genetic epidemiology of HHL among Arab populations is understudied. This study aimed to systematically analyze the genetic epidemiology of HHL in Arab countries.

Methods: We searched four literature databases (PubMed, Scopus, Science Direct, and Web of Science) from the time of inception until January 2019 using broad search terms to capture all the reported epidemiological and genetic data related to Arab patients with HHL.

Findings: A total of 2,600 citations were obtained; 96 studies met our inclusion criteria. Our search strategy yielded 121,276 individuals who were tested for HL over 52 years (1966–2018), of whom 8,099 were clinically diagnosed with HL and belonged to 16 Arab countries. A total of 5,394 patients and 61 families with HHL were genotyped, of whom 336 patients and 6 families carried 104 variants in 44 genes and were from 17/22 Arab countries. Of these variants, 72 (in 41 genes) were distinctive to Arab patients. Arab patients manifested distinctive clinical phenotypes. The incidence of HHL in the captured studies ranged from 1.20 to 18 per 1,000 births per year, and the prevalence was the highest in Iraq (76.3%) and the lowest in Jordan (1.5%).

Interpretation: This is the first systematic review to capture the prevalence and spectrum of variants associated with HHL in an Arab population. There appears to be a distinctive clinical picture for Arab patients with HHL, and the range and distribution of *variants among Arab patients* differ from those noted in other affected ethnic groups.

Key Words: Arab countries—Consanguinity—Diagnostic gene panel—Hearing loss—Incidence—Prevalence—Variants.

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Hearing loss (HL) is a heterogeneous condition that results in fractional or complete hearing incompetence. According to the last update of 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 (http://www.who.int/topics/deafness/en). 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, and chronic ear infections (1). 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 occur together, then the condition is called mixed hearing loss (2)

HL can also be classified as congenital or late-onset and as syndromic or nonsyndromic. 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, nonsyndromic 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 (3), and more than 50% of congenital deafness has genetic causes (4). NSHL can be inherited in an autosomal-dominant manner in 10% to 15% of cases, autosomal-recessive manner in 80% of cases, with 1% to 3% exhibiting the X-linked form, and as mitochondrial inheritance in $< 1\%$ of cases

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(3). Recessive variants are associated with prelingual nonprogressive HL, whereas dominant variants are associated with postlingual progressive HL (5).

HHL occurs together with other systemic phenotypes such as Usher syndrome, Pendred syndrome, Cockayne syndrome, and Chudley-McCullough syndrome (6). Usher syndrome is one of the most common autosomal-recessive causes of syndromic hearing loss (7). Pendred syndrome is another autosomal-recessive cause of syndromic HHL, which is characterized by mild to profound SNHL, vestibular dysfunction, and euthyroid goiter (8). In Cockayne syndrome, degeneration of the cochlear nucleus causes syndromic hearing loss, together with the gradual deterioration of cognitive and neurological functions (9). Chudley-McCullough syndrome is associated with SNHL and hydrocephalus secondary to an obstruction of the foramen of Munro (10).

Hundreds of variants of more than 60 genes have been reported to be involved in HHL (11). However, variants of the *GJB2* gene are the most common cause of congenital SNHL, with more than 100 variants reported (https://ghr.nlm.nih.gov/). The *GJB2* gene encodes connexin 26, which is the main component of gap junctions of the ear cochlea. Variants of this gene lead to the production of an altered form of connexin 26 that causes the abnormal function of gap junctions observed in HL and deafness (DFNB1), which is an autosomal-recessive condition. 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 (12). However, within the Arab population, together with the *GJB2* gene, there are several other genes also involved in HHL (13).

It is estimated that more than 5% of individuals worldwide may suffer from HL. The incidence of HL has been reported to be approximately 2–3/1,000 in the United States, 0.4/1000 in Japan, and 1.48/1000 in Denmark (14). Although the incidence of HL among the 22 Arab majority countries remains to be determined, it is thought to be higher than in other parts of the world. For example, an incidence of 18 infants among 1,000 births in Palestine has been reported (15); however, there is a dearth of studies related to the actual picture of HL in Arab patients. Therefore, the aim of this study was to shed light on the under-reporting of the condition in an Arab population and to study the spectrum of genetic variants of HL associated with HHL in the 22 Arab majority countries.

METHODS

Search Strategy and Study Selection

We searched four literature databases (PubMed, Scopus, Web of Science, and Science direct) from the time of inception until February 2019. To capture as many studies as possible, we used broad search terms such as ''Hearing loss'' OR ''Deafness'' OR ''Inner ear anomalies'' OR ''Inner ear dysfunction'' AND the name of each of the 22 Arab countries (Qatar, Oman, UAE, KSA, Egypt, Somalia, Comoros, Mauritania, Morocco, Tunisia, Algeria, Libya, Lebanon, Bahrain, Palestine, Jordan, Syria, Iraq, Sudan, Yemen, Kuwait, and Djibouti). The articles were chosen for screening based on the titles and abstracts. The chosen articles were reviewed completely and screened for epidemiological parameters (Prevalence, incidence, and frequency), the number, age, and sex of the patients, consanguinity rates, and the variants reported for each of the 22 Arab countries.

Our selection criteria included the following: 1) research articles published in peer-reviewed journals, 2) Arab patients diagnosed with HHL, and 3) articles containing data about the genetic variants and/or prevalence, incidence, and frequency of HHL in Arab countries. The articles were excluded if the following criteria were met: 1) the reported variants were not clear that is associated with Arab patients with HHL, 2) it is not clear that the patients have HHL. All citations were imported into Endnote X8 and duplicate citations were removed.

Data Extraction and Quality Control

The eligible articles were fully screened and the following data were included in the study: male: female ratio, study population, study period, incidence, prevalence, frequency, consanguinity, clinical phenotypes, genes and variants, and syndromic vs nonsyndromic HHL. The data quality control was performed by two scientists (M.S. and T.F.) to ensure the data were captured correctly, and final quality control was checked by H.Z. Disagreements were resolved through discussion. To determine whether the captured variants were unique to Arab patients or shared with non-Arab patients, we rigorously checked all the variants in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), EVS (http://evs.gs.washington.edu/EVS/), LOVD (http://www.lovd.nl/), PubMed, and Google search.

RESULTS

Search Strategy

Our search technique identified 2,600 hits, of which 1,899 remained after duplicate removal; 1,750 irrelevant citations were excluded (Fig. 1). The remaining citations (n = 149) were further scrutinized for the inclusion criteria, 53 articles (unrelated n = 32, no variants could be captured n = 15, an inconclusive data n = 6) were excluded, and the remaining 96 articles were used for the systematic analysis (Fig. 1).

Epidemiology of Hearing Loss in Arab Countries

Epidemiological parameters are presented as prevalence, frequency, and incidence and were captured in 16 of the 22 Arab countries (Qatar, Oman, KSA, UAE, Egypt, Jordan, Iraq, Bahrain, Lebanon, Yemen, Kuwait, Mauritania, Morocco, Algeria, Sudan, and Palestine) (Table 1). Most of the patients captured in the majority of the Arab countries were children, with a male preponderance, diagnosed with HHL. The studies were diverse and included retrospective, cross-sectional, case-control, and prospective studies. Our search strategy captured 121,276 individuals who were tested for HL, of whom 8,099 patients were diagnosed with HL, in 16 Arab countries over 52 years (1966–2018). The reported epidemiological parameters were mostly prevalence. The HHL prevalence was highest in Iraq (76.3%) and

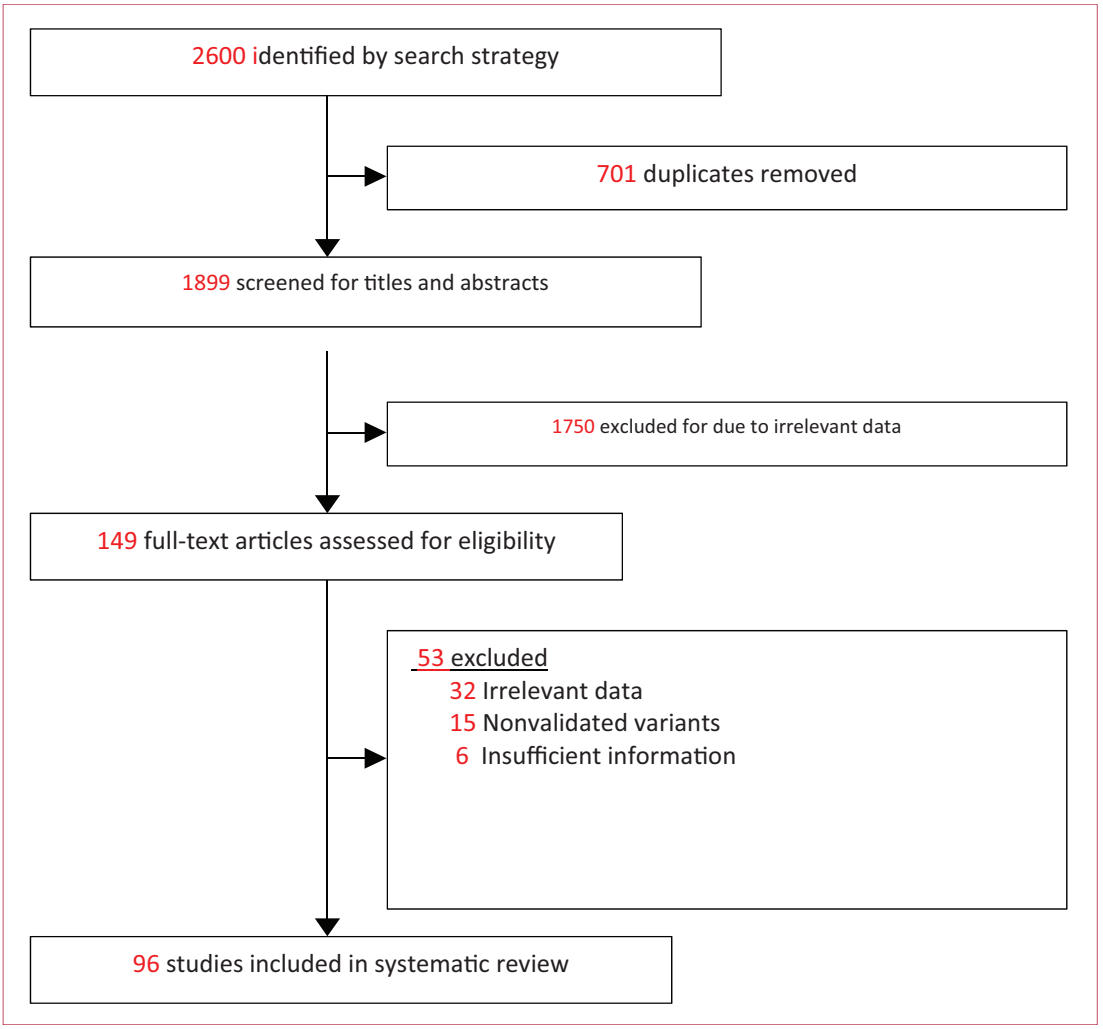

FIG. 1. Flow diagram of selected articles. n: number of selected articles.

lowest in Jordan (1.5%), The frequency ranged from 36.95% in Oman to 3.6% in Algeria, and the incidence of HL ranged from 18/1,000 births per year in Palestine to 1.2 in Oman (Table 1). Consanguinity has been widely observed among Arab patients with HHL. The reported consanguinity rates vary among different Arab countries. For instance, it is observed in 60.5% of patients with deafness in Qatar, 70% of those in Oman, 68.9% of those in KSA, 34% of those in the United Arab Emirates, 54.6% of those in Mauritania, and 56% of those in Algeria (Table 1).

Variants Reported in the Arab World and Their Associated Phenotypes

Our search strategy captured 104 variants in 44 genes that were reported in 17/22 Arab countries, with no studies related to genetic causes of HHL in five Arab countries (Syria, Comoros, Djibouti, Libya, and Bahrain). A total of 5,394 and 61 families with HHL were screened for HL using different methods of molecular diagnosis (Supplementary Tables 1, http://links.lww.com/MAO/A887, and 2, http://links.lww.com/MAO/A888), and 336 patients and 6 families were found to harbor 104 variants in 44 genes, which were distributed in 17 Arab countries. Seventy-two variants identified in 41 genes were distinctive to Arab patients (Supplementary Table 1, http://links.lww.com/MAO/A887). The variants that were shared between Arab patients and other ethnic groups are shown in Supplementary Table 2, http://links.lww.com/MAO/A888. Most of the captured variants were missense variants (29%). The distribution of variants revealed that most of the reported variants occurred in *GJB2* with 21 different variants (20%); followed by the *MYO7A* gene with 16 reported variants (15%). The *MYO15A* gene was reported with five variants (5%), *SLC26A4* with six variants (~8%), *MYO6* with four variants (~4%) (*ESP8, MT-ND5, MT-RNR1, CDH3, OTOF*, and *ATP6V1B1* with two variants (2%), and the remaining 32 genes with only one variant each (1%). The highest reported number of variants was

TABLE 1. *The epidemiological data for HLL Arab patients.*

Country	Age	M:F Ratio	Study Type	Study Period	Study Population	Number of Affected Patients	Epidemiology			Consanguinity (%)	References
							Prevalence	Frequency	Incidence/ 1000		
Qatar	0–30 y	01:01.2	Prospective	2012	126	126	–	–	–	C (56%)	(47)
	Neonates	1.08:1	Cross- sectional	2003	2,277	119	5.20%	–	–	C (60.5%)	(48)
	20–59 y	–	Cross- sectional	2013– 2014	459	134	59.70%	–	–	C (32.1%)	(49)
	1–13 y	1.07:1	prospective	2017	80	80	–	–	–	C	(13)
Oman	0–16 y	1.35:1	Retrospective	1986– 2000	1,400	1,400	3% (S) 47% (NS)	–	–	C (70%)	(16)
	0–60 y	–	Cross- sectional	1996–1997	12,400	28	–	–	–	–	(50)
	Neonates	–	–	2002–2003	2,287	262	–	–	1.2	–	(51)
	16–39	–	Prospective case-control	2010	46	17	–	36.95%	–	–	(52)
KSA	Infants and children	–	Retrospective	–	6,421	1,256	1.7%	–	–	C (44.1%)	(53)
	0.5–12	1.12:1	Retrospective case control	2010– 2016	1,600	800	16.8%	–	–	C (68.9%)	(54)
UAE	Children	–	Retrospective	1994– 1996	74	74	19% (S) 81% (NS)	–	–	C (34%)	(55)
	0–45 y	3.54:1	Prospective	2017	120	50	–	–	–	–	(56)
Egypt	6–12 y	–	Prospective	2010	555	141	20.90%	–	–	–	(57)
	7–10 y	–	Prospective	2012	453	22	2.40%	–	–	–	(58)
	neonates	1.26:1	Prospective	2017	260	78	30%	–	–	–	(59)
	–	–	Prospective	2017	2,633	585	22.20%	–	–	–	(60)
Jordan	children	–	Cross- sectional	2007– 2008	63,041	966	1.50%	–	–	–	(61)
	0–80 d	–	-	2006	8,251	745	1.37%	–	–	–	(62)
Iraq	17–50 y	–	Prospective	–	59	45	76.30%	–	–	–	(63)
Bahrain	Infants	–	Prospective	2012– 2015	1,834	5	–	–	2.72	–	(64)
Lebanon	5–15 y	–	Prospective	1966– 1967	5,020	256	5.12%	–	–	–	(65)
	Children	–	Prospective	2000	274	274	51.82% (NS)	–	–	C	(66)
Yemen	6–9 y	–	–	–	2,200	–	–	6%	–	–	(67)
Kuwait	1–5 m	–	–	2012– 2013	317	34	10.72%	–	–	–	(68)
	6–12 y	–	–	–	159	18	–	–	–	–	(69)
	6 m to 18 y	–	Cross- sectional	2013	100	100	15%	–	–	–	(70)
Mauritania	Children	1.27:1	prospective	2015	139	36	–	–	–	C (54.6%)	(71)
Morocco	–	–	prospective	2010	264	164	–	–	–	–	(72)
Algeria	–	–	prospective	2018	11 F	–	–	3.60%	1.25	C (56%)	(35)
Sudan	Children	–	prospective	2004	183	183	–	6.60%	–	–	(73)
Palestine	0–3 m	1.44:1	Prospective	2006– 2011	8,144	101	–	66.4	18	–	(74)
Total	–	–	–	–	121,276	8,099	–	–	–	–	–

F indicates family; m, months; NS, nonsyndromic; S, syndromic; y, years.

in KSA (25; 24%), followed by 17 in Morocco (16%), 16 in Tunisia (15%), 12 in Qatar (12%), 10 in Palestine (11%), 6 in UAE and Algeria (5%), 3 in Mauritania and Jordan (3%), 2 in Egypt (2%), and only 1 in Kuwait, Iraq, Yemen, Sudan, Somalia, and Oman (1%) (data not shown). Few variants were reported in more than one country. The c.35delG variant of the *GJB2* gene was reported in eight Arab countries (Qatar, KSA, Algeria, Mauritania, Egypt, Kuwait, Jordan, UAE), while the c.212 −2 A>C variant of the *GJB2* genes was reported in two Arab countries (Jordan and KSA) and the c.242G>A variant of the *LRTOMT* gene in two Arab countries (Tunisia and Morocco).

DISCUSSION

To our knowledge, this is the first study to comprehensively and systematically analyze peer-reviewed published studies of HHL in an Arab population. Our work captured 96 studies that included 121,276 individuals who were screened clinically for HL, of whom 8,099 were diagnosed with HL (6.7%) in 16 Arab countries. The prevalence of hearing loss was high among Arab countries and reached 76.3% in Iraq (Table 1). Consanguinity among HHL Arab patients was reported in several studies (n = 11), reaching up to 70% in Oman (16). Our broad search strategy captured 5,394 individuals that were genetically analyzed for possible variants that are significantly associated with HL. The spectrum of gene variants was variable among the 5,394 where 44 nuclear and mitochondrial genes were reported to harbor 104 variants, of which 72 were unique (reported in 41 genes) to Arab patients (only found in Arab patients) (Supplementary Table 1, http://links.lww.com/MAO/A887). Genetic susceptibility to HHL shared between Arab patients and non-Arab patients was captured in nine genes, for which 32 variants were collected (Supplementary Table 2, http://links.lww.com/MAO/A888). We considered performing a meta-analysis; however, the large variation in age groups and the small number of studies permitted only a descriptive analysis.

Consanguinity, endogamy, and first cousin marriages are higher in Arab patients compared with other populations in the world (17), and they have been found to be associated with increasing genetic autosomal-recessive disorders (18). Consistent with our findings (Table 1), consanguinity was found to be associated with the reported prevalence of HHL in most of the Arab Countries. For instance, two studies in Qatar reported a hearing loss prevalence of 59.7% and 5.2% with a consanguinity rate of 32.1% and 60.5%, respectively. Another study in Oman reported a hearing loss prevalence of 47% with a consanguinity of 70%. In KSA, the prevalence of hearing loss was reported to be 1.7% and 16.8% in two studies with consanguinity rates of 68.9% and 34%, respectively. In addition, in Lebanon, consanguinity was reported to be associated with HL prevalence of 51.82%. In Mauritania, the consanguinity rate was 54.6% with 133 affected families. Finally, Morocco reported a consanguinity rate of 56% and a prevalence of 3.6%. Based on these findings, we can conclude that consanguinity may play a significant causal role in HHL in Arab populations, with the prevalence of HHL ranging from 1.5% in Jordan to the highest prevalence of 59.7% reported in Qatar. However, to accurately estimate the significant association between consanguinity and the increased incidence of HHL, larger patient cohorts that are homozygous for specific variants should demonstrate higher values than would normally be predicted by Hardy-Weinberg analysis.

The prevalence of HHL among Arab patients was reported in 16 studies (n = 16), with the highest prevalence rate in Iraq (76.3%) (Table 1), which was considerably higher than reported in the EU-Concerted Action on the genetics of hearing impairment (H.E.A.R.), among EU patients with HHL (19). In our study, we observed a male preponderance among Arab patients with HHL. In contrast, the EU study showed a significantly higher prevalence in females than males (19). The cause of the male preponderance phenomenon is still not understood; however, it has been hypothesized that the X-linked recessive mode of inheritance of some forms of HHL could play a role in the predominance of males with hearing loss (20). A few of the present studies (n = 4) reported Hearing loss incidence, for which the incidence of HHL ranged from 1.2 per 1,000 births in Oman to 18 per 1,000 births in Palestine (Table 1).

Distinctive and Shared Gene Variants

We were able to capture 72 variants (in 41 genes) that were distinctive to Arab populations (Fig. 2). The uniqueness of these variants was confirmed by searching these variants in different variant databases, including HGMD, LOVD, EVS, PubMed, and ClinVar. In addition, these variants were searched using the Google search machine to ensure their uniqueness Arab patients (Supplementary Table 1, http://links.lww.com/MAO/A887). The distinctive genetic susceptibility picture among Arab patients for HHL would suggest a diagnostic gene panel that will be useful for Hearing loss diagnosis in Arab families and allow the identification of at-high-risk families with HHL, which will aid in determining the proper treatment plans for the affected persons. It will also provide a better opportunity for genetic counseling to educate the patients' families concerning the potential risk. This would represent a classical example of using such information to develop ethnic specific customized approaches for clinical molecular diagnostics. We presume that unique Arab variants are associated with severe congenital deafness; however, further investigation is needed to determine the effects of these variants on the potential genotype-phenotype correlations in Arab patients with HHL. Because of the heterogeneity of HHL, we could not conclusively determine a distinctive genotype-phenotype correlation for unique Arab variants, in addition to the small patient groups in each of the studies reviewed.

Although Arab patients seem to have a distinctive susceptibility genetic profile, 32 variants were detected

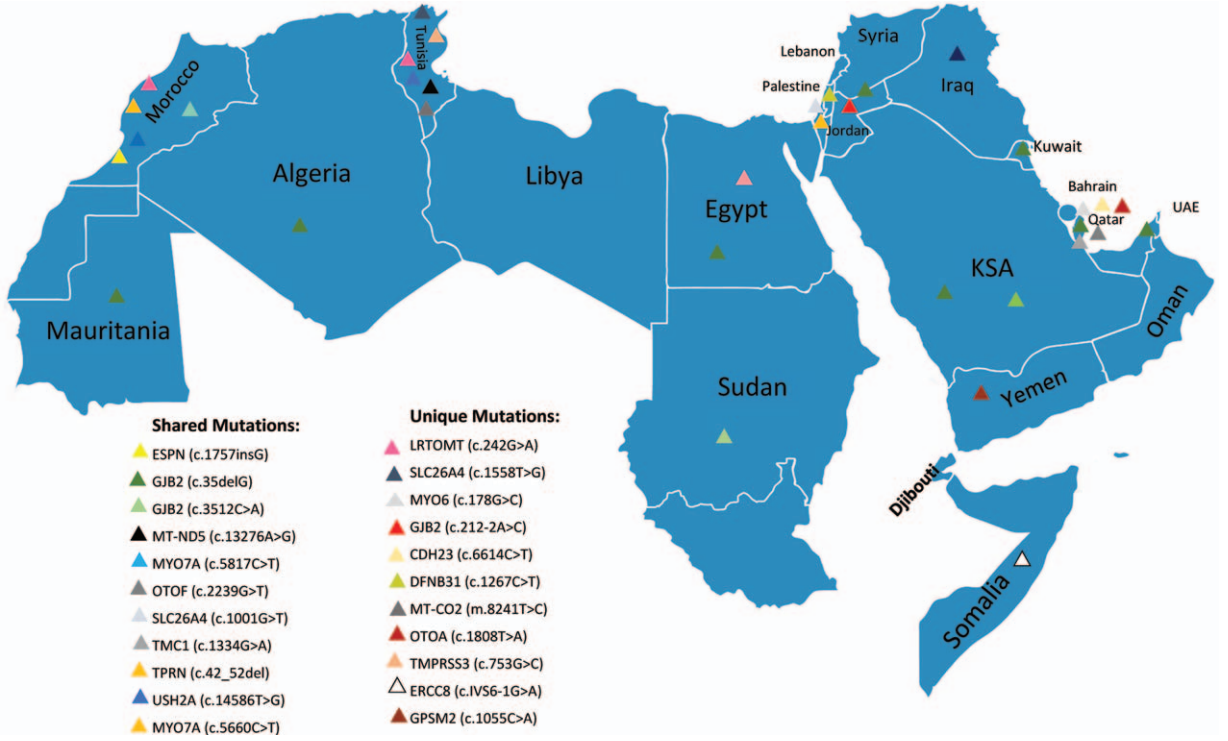

FIG. 2. Map representing the spectrum of mutated genes in Arab countries. The Blue color represents Arab countries. This work is licensed under the Creative Commons Attribution-ShareAlike 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by-sa/4.0/ or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA.

in 9 different genes (*ESPN, GJB2, MYO7A, MT-ND5, OTOF, SLC26A4, TMC1, TPRN, USH2A)* that are shared with different ethnic groups, including European, Asian, Israeli, Iranian, and Turkish people, the entire list of variants are summarized in Supplementary Table 2, http://links.lww.com/MAO/A888 (Fig. 2). The enriched variants in Arab countries whether they are distinctive or shared are listed in Table 2. The most common causative gene among our patients cohort is the *GJB2* gene, with six variants that are distinctive to Arab patients and 14 variants that are shared between Arab patients and non-Arab patients (Supplementary Table 1, http://links.lww.com/MAO/A887 and 2, http://links.lww.com/MAO/A888). 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* (12). In our study, *GJB2:* c.35delG was the most commonly reported gene among Arab patients; three studies (n = 3) identified this variant in eight Arab countries (Supplementary Table 1, http://links.lww.com/MAO/A887). This variant has been reported to be predominant among European and Mediterranean patients (12), possibly due to admixture and migration between Arab countries and Europe. The *GJB2:* c.35delG leads to a frameshift and is classified as a loss of function variant (21), Clinically, it is categorized as a pathogenic variant with sufficient patient numbers manifesting a clear genotype-phenotype correlation. Six variants of the *SLC26A4* gene were reported in 28 HHL patients and in one family (n = 4), which is known to be the second most frequent cause of autosomal-recessive NSHL (22). Three variants were unique to Arab patients and were reported in Algeria, Palestine, and Tunisia in patients with Pendred syndrome and the NSHL phenotype. However, a shared variant (p.Gly334Val) was identified between Palestinians and Iranians that manifested severe to profound HL in both ethnic groups. This finding is consistent with previous reports of the broad spectrum of phenotypes associated with *SLC26A4* gene variants (23,24).

Distinctive Genotype-Phenotype Correlation

We captured 32 variants in 153 Arab patients who were shared with other ethnic groups (Supplementary Table 2, http://links.lww.com/MAO/A888). Some of these shared variants seemed to have a distinctive clinical phenotype in (26) Arab patients compared with the other ethnic groups. For example, the *MYO7A*: c.5660C>T variant was reported to be associated with severe to profound HL in eight Palestinian patients (n = 1) (27), while in Canada, Germany, and Denmark, it was reported to be associated with Usher syndrome Type I among Caucasian patients (28). Another example was demonstrated with the variant *USH2A*: c.14586T>G, which was associated with mild HL in Tunisia (3), while among European patients, it was associated with Usher syndrome type II (29). The *OTOF*: c.2239G>T variant was

TABLE 2. *Summary table that shows genetic variants that are specifically enriched in the Arab countries.*

Gene	Nt Change	AA Change	Number of Screened Patients	Number of Affected Patients	Method of Detection	ClinVar Classifcation	Clinical Phenotype	Arab Country	References
BDP1	**c.7873T>G**	**p.Ter2625Gluext11[d]**	8	5	WES	P[a]	NS, early onset, progressive HL	Qatar	(75)
CDH23	**c.6614C > T**	**p.Pro2205Leu**	80	5	NGS	P	NS, severe to profound sensorineural HL	Qatar	(13)
DFNB31	**c.1267C>T**	**p.Arg423[a]**	39	8	Sanger	P[a]	Usher S, severe to profound congenital HL	Palestine	(27)
ESPN	c.1757insG	p.C585fs71[a]	8	6	NGS	P	NS, severe to profound HL	Morocco	(76)
GJB2	c.35delG	p.Gly12Valfs[a]2	698	62	NGS Sanger	P	NS Profound HL	Algeria Mauritania KSA Egypt Jordan Kuwait Qatar	(77) (71) (78) (79) (70) (47) (56)
GJB2	c.389G>T	p.Gly130Val	1111	16	Sanger	LP [a]	NS, bilateral severe sensorineural HL	Egypt	(21)
LOXHD1	**c.1588G>T**	**p.Glu530[a]**	7 F	1 F	Sanger	–	NS Early-onset sensorineural bilateral HL	Qatar	(80)
LRTOMT	**c.242G>A**	**p.Arg81Gln**	35	16	NGS Sanger	LP	NS, moderate to profound congenital prelingual and bilateral	Tunisia Morocco	(3,81)
MYO15A	**c.453_455delCGAins TGGACGCCTGGT CGGGCAGTGG**	**p.Glu152Glyfs[a]81**	7 F	2 F	Seq	-	NS, early-onset sensorineural bilateral HL	Qatar	(80)
MYO6	**c.2507G> A**	**p.Arg836His**	33	11	NGS	LP	NS, Pre-lingual HL	KSA	(38)
MYO7A	**c.3500T>A**	**p.Leu1167His**	23	8	WES	P	NS, HL	Morocco	(82)
MYO7A	c.470+1G>A	-	13	6	NGS	P[a]	NS, profound HL	KSA	(83)
OTOF	**c.1469 C>G**	**p.Pro490Arg**	10	7	Sanger	P[a]	NS, Profound- Severe HL	Oman	(46)
SLC26A4	**c.1558 T>G**	**p.Leu445Trp**	39	23	Sanger	–	Pendred S, profound to severe congenital deafness, thyroid goiter	Tunisia	(34)
SLC26A4	**c.410C > T**	**p.Ser137Leu,**	11 F	2F	NGS	P	NS, profound HL	Algeria	(35)
TBC1D24	**c.641G>A**	**p.Arg214His**	7	5	WES	Common polymorphism	NS, profound congenital bilateral sensorineural HL	Morocco	(84)
TMPRSS3	**c.753 G>C**	**p.Trp251Cys**	42	13	Sanger	P	NS, severe to profound, congenital sensorineural deafness	Tunisia	(34)
TPRN	c.42_52del	p.Gly15Alafs[a]150	17	7	NGS	P	NS, profound HL	Morocco	(85)
			2163 patients 18 F	198 patients 5F					

Distinctive variants to Arab countries are labeled in **Bold**.
[a]Reported in Clinvar.
[b]Reported in EVS.
[c]Reported in HGMD.
[d]Nomenclature revised by ENSEMBEL.
[e]Nomenclature revised by HGVS.
B indicates benign; F, families; Fs, frameshift variant; LP, likely pathogenic; M, missense variant; N, nonsense variant; NC, noncoding; NGS, next-generation sequencing; NS, nonsyndromic; P, pathogenic; PCR, polymerase chain reaction; S, syndromic; Seq, sequencing; SS, splice site variant; VUS, variant of unknown significant; WES, whole exome sequencing; WMGS, whole mitochondrial genome sequencing.

detected in two Qatari patients who presented with early-onset prelingual profound sensorineural HL (13); however, among Spanish patients, the *OTOF* gene is a major cause of profound HL (30). Additionally, the c.470+1G>A variant in the *MYO7A* gene was associated with profound HL with reduced night vision in HHL patient from KSA, whereas in Israel, it was reported to be associated with severe HL and retinal degeneration. These examples suggest that the genome of the Arab ethnicity is distinct and might have a unique susceptibility profile to HHL (31). Therefore, the Arab genome revolution, which is currently aimed to map the ethnic variants responsible for the susceptibility of Arab patients to genetic diseases (31,32), will be extremely informative in disease diagnosis, prognosis, and management, and it will provide a platform for the development of customized clinical molecular diagnostic tools (31,33).

Syndromic and Nonsyndromic HHL

Among our patient cohort, the majority of the captured variants were associated with NSHL (82 variants, 79%), while only 22 variants (21%) were associated with SHL (Supplementary Tables 1, http://links.lww.com/MAO/A887 and 2, http://links.lww.com/MAO/A888). This result is consistent with global findings that approximately 70% of HHL patients are nonsyndromic and approximately 30% are syndromic. Usher, Pendred, Chudley-McCullough, and Cockayne are autosomal-recessive syndromic forms of HHL. Three genes (*GPR98, GPR99,* and *DFNB31)* were captured that were associated with Usher syndrome in Arab patients from Morocco and Palestine and contained variants unique to Arab patients (Supplementary Table 1, http://links.lww.com/MAO/A887); however, two genes, *USH2A* and *MYO7A,* contained shared variants between Arab patients from Palestine, Tunisia, and Caucasians (Supplementary Table 2, http://links.lww.com/MAO/A888). Pendred syndrome was reported in 23 patients from Tunisia with a distinctive variant c.1558 T>G; p.Leu445Trp of the *SLC26A4* gene presenting with profound to severe congenital deafness and thyroid goiter (34), and two Algerian families presented with profound HL due to variant *SLC26A4:* c.410C > T p.Ser137Leu (35), which was also unique to Algeria (Supplementary Table 2, http://links.lww.com/MAO/A888). Overall, approximately 9% of our affected HHL had variants in the *SLC26A4* gene, compared to 5% of all prelingual deafness in East Asia due to variants of the same gene (36). Variants of this gene were associated with broad phenotypic heterogeneity in France (37). Chudley-McCullough syndrome was captured in one study from Yemen in two patients from consanguineous families who were affected by hearing impairment, which was assumed to be associated with the *GPSM2* gene variant (c.1055C>A; p.Ser352*). Cockayne syndrome-associated hearing loss was captured from a study reporting two Somali siblings carrying a variant of the *ERCC8* gene (c. IVS6-1G>A) caused by a splice site change leading to a frameshift mutation. Overall, phenotypic data from the reported syndromes were consistent with the reported phenotypes of syndromes associated with HHL worldwide.

LIMITATIONS AND CONCLUSION

We encountered a few limitations in our study. First, a dearth of studies were related to the genomic epidemiology among Arab populations. Second, the large age variation and small number of studies did not allow us to perform a meta-analysis. Third, it was difficult to follow a general trend of the incidence or prevalence due to the scattered reports on the epidemiology of HHL among Arab patients (16 of the 22 Arab countries). Finally, the captured studies often contained incomplete data.

This is the first systematic review to capture the prevalence and spectrum of HHL variants in an Arab population. There appears to be a distinctive genetic susceptibility profile to HHL among Arab patients in addition to a distinctive clinical profile even with the shared variants. However, epidemiological data were lacking in some of the Arab countries. Further research is required to accurately estimate the prevalence and incidence of HHL to provide and plan better healthcare for HHL patients. In addition, there is a need to implement newborn screening programs for HHL in Arab countries. The collection of variants in this study is important in diagnosis, disease management, and genetic counseling for Arab patients with HHL; however, there is a need for further well-controlled studies to identify more variants and standardize clinical measures across majority Arab countries.

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