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Congenital hearing loss: a literature review of the genetic etiology in a Mexican population

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Abstract

Hearing loss is the most frequent sensory disorder, with an incidence of 1:1500 live newborns. In more than 50% of patients, it is associated with a genetic cause, while in up to 30% of cases, it is related to syndromic entities. We performed a literature review of studies on congenital hearing loss of genetic origin in the Mexican population. We identified eight reports that showed that the pathogenic variants most frequently associated with hearing loss are related to the GJB2 gene, although in a low percentage (3%). Other mutations were identified in the GJB6, SLC26A4, or CHD23 genes. On this basis, a possible diagnostic strategy in Mexican patients with hearing loss is to consider an initial screening of these three genes. If these genes were negative for pathogenic variants, the following steps would be to consider second-generation sequencing analysis focused on panels of genes associated with hearing loss, isolated or syndromic, and if necessary, to perform exome or whole-genome analysis. Establishing an etiologic cause is critical in clinically evaluating patients with congenital hearing loss and their families. It can help determine rehabilitation strategies, such as hearing aids or cochlear implants and provide information on disease progression and genetic counseling in this population.

Keywords: *Congenital hearing loss. Congenital deafness. Mexican population. GJB2. GJB6.*

Pérdida auditiva congénita: revisión de la etiología genética en la población mexicana

Resumen

La pérdida auditiva es la alteración sensorial más frecuente, con una incidencia de 1:1500 recién nacidos vivos. En más del 50% de los pacientes se asocia con una causa genética, mientras que en más del 30% de los casos se asocia con entidades sindrómicas. Se llevó a cabo una revisión de la literatura de las investigaciones sobre la pérdida auditiva congénita de origen genético en la población mexicana. Se identificaron ocho reportes en los que se demostró que las variantes patogénicas más frecuentemente asociadas con pérdida auditiva se encuentran en el gen GJB2, aunque en un porcentaje bajo (3%). Se identificaron otras mutaciones en los genes GJB6, SLC26A4 o CHD23. Con base en esta información, una posible estrategia diagnóstica en pacientes mexicanos con pérdida auditiva es considerar un primer paso en el tamiz diagnóstico con los tres genes mencionados. Si estos genes fueran negativos para variantes patogénicas, el siguiente paso

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sería considerar el análisis por secuenciación de segunda generación enfocado en paneles de genes asociados con pérdida auditiva, tanto aislada como sindrómica, y en caso necesario, realizar el análisis del exoma o del genoma completo. Establecer una causa etiológica es un componente crítico en la evaluación clínica de los pacientes con pérdida auditiva congénita, ya que puede ayudar a determinar las estrategias de manejo y rehabilitación, como el uso de auxiliares auditivos o implantes cocleares, proporcionar información sobre la progresión de la enfermedad y dar asesoramiento genético en esta población.

Palabras clave: *Pérdida auditiva congénita. Sordera congénita. Población Mexicana. GJB2. GJB6.*

Introduction

Hearing loss is the most common sensory disorder, affecting more than 500 million people worldwide. Its incidence is 1:1500 live newborns (LNB); also, the hearing loss is hereditary in 1:1000 LNB and may appear as congenital sensorineural hearing loss that may affect up to 1-3% of individuals in some populations[1-4]. According to the World Health Organization (WHO)[5,6], hearing loss is classified into four groups based on its severity: mild (hearing threshold between 26-40 dB HL); moderate (hearing threshold between 41-60 dB HL); severe (hearing threshold between 61-80 dB HL); profound (hearing threshold > 80 dB HL). Since 2008, a new classification of hearing loss has been proposed by a group of experts belonging to the Global Burden Organization[7]. This proposal defines mild hearing loss in a range of 20 to 34.9 dB HL (which differs from the value of 26 dB HL considered by the WHO classification) in children and adults; it also delineates six different degrees of hearing loss, each defined by a range of 15 dB HL, depending on the better-hearing ear of the patient[8]. Although the Global Burden Organization classification does not go as far as the American Speech-Language-Hearing Association classification—which considers mild hearing loss from 16 dB HL and up to the 25 dB HL threshold, thus including a degree that precedes even the mild hearing loss regarding other classifications—if used, it would show a substantial increase in the number of people around the world who would be considered with a hearing impairment[9]. In either case, using these classifications would increase the global prevalence of mild and severe hearing loss—however, the WHO has not yet officially accepted the new Global Burden Organization classification.

Congenital hearing loss can be classified according to its type as conductive (related to external or middle ear pathology), sensorineural (associated with internal ear and spiral ganglion pathologies), neural (associated with VIII cranial nerve alterations), and mixed (associated with pathologies including two or more of the segments). The classification of hearing impairments has important implications for their treatment. For example, the primary indication for a cochlear implant is exclusively related to the hearing thresholds indicated when congenital hearing loss is classified as severe or profound neurosensorial loss[10]. Congenital hearing loss (of any type) in patients in early childhood has different repercussions on their social and psychological development for the rest of their lives, considering that hearing is the basis of linguistic communication between individuals and their social environment. Besides the genetic assessment, detecting a genetic alteration with hereditary characteristics will allow timely intervention with patients who may require this approach for a better prognosis.

Congenital hearing loss etiology

Although there are several classifications regarding the etiology of congenital hearing loss, the most important to consider is a genetic or non-genetic cause (related to the environment)[1-4,11]. Regarding congenital presentation, more than 50% of early-onset bilateral sensorineural deafness cases have been considered to have a genetic cause[12]. The other half corresponds to non-genetic causes. Environmental factors include, for example, infections such as those associated with TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV), the diagnosis of cytomegalovirus, ototoxic drugs, prematurity, hypoxia at birth, hyperbilirubinemia, or even the permanence of the patient in neonatal intensive care units for more than five days[3,4].

Genetic factors of congenital hearing loss

When analyzing the possible genetic etiology of congenital hearing loss, one of the first aspects to consider is whether it is a syndromic presentation (a situation that represents up to 30% of cases of all types of hereditary hearing loss)[13,14] or whether it is an isolated characteristic (which corresponds up to 70% of patients).

Syndromic genetic causes of hearing loss include Usher, Pendred, Waardenburg, and Norrie syndromes. In this regard, Bahena et al. conducted an interesting study on a group of 59 patients with combined retinal and hearing impairment but no intellectual disability[15]. Most of the patients were Iranian, and seven unrelated Mexican patients were included in this study. Through exome analyses, the authors were able to elucidate all Mexican cases, as several pathogenic or probably pathogenic genetic variants were identified in the *MYO7A* (three patients), *USH1G* (one patient), and *USH2A* (two patients) genes. This study is also an example of the genetic heterogeneity observed in the Mexican population regarding the etiology of syndromic hearing loss.

When non-syndromic causes are considered, hearing loss can be classified according to the inheritance pattern; for example, 75-80% of patients have an autosomal recessive pattern, 20% are autosomal dominant, < 2% are X-linked, and < 1% are of mitochondrial origin[3,4,16]. This information is relevant because, depending on the homozygous or heterozygous condition of the patient, the genetic possibility of expression can vary from 50% risk in the case of autosomal dominant pattern (in which the presence of a single mutated allele is sufficient to cause a clinical manifestation) to 25% risk for autosomal recessive diseases, in which the presence of two mutated alleles is required to generate a clinical alteration. Also, it influences prognosis and response to treatments, including the cochlear implantation[17].

According to the information on the Hereditary Hearing Loss Homepage website, several different genes have been identified to be associated with different inheritance patterns of non-syndromic hearing loss. For example, at the DFNA1 *locus* (OMIM #124900) is the *DIAPH1* gene (OMIM *602121) on 5q31.3; at the DFNA2A *locus* (OMIM #600101) is *KCNQ4* (OMIM *603537) on 1p34.2, and at the DFNA2B *locus* (OMIM #612644) is *GJB3* (OMIM 603324) on 1p34.3; these are examples of autosomal dominant patterns. Examples of congenital hearing loss with an autosomal recessive inheritance pattern include the DFNB1A *locus* (OMIM #220290) with the *GJB2* gene (OMIM 121011) on 13q12.11; *GJB6* (OMIM 604418) on 13q12.11 and *GJB3*; DFNB1B with the mentioned *GJB6,* or *DFNB2* (OMIM #600060) with *MYO7A* (*276903) on 11q13.5[18] (Table 1)[19-25].

Also, it is essential to consider that there are heterozygous compound variants, in which patients carry different pathogenic variants at the same *locus*, or the digenic inheritance, in which pathogenic variants are present in other *loci*. Another representative example of digenic inheritance in patients with hearing loss is the presence of a pathogenic variant in each of the genes encoding connexins 26 and 30, which are doubly heterozygous[2].

The first *locus* associated with pathogenic variants with an autosomal recessive inheritance pattern was mapped in 1994 and corresponded to the *GJB2* gene[26], which encodes the connexin-26 protein. This protein is part of the structure known as connexon, which in turn forms cell-cell junction elements; pathogenic variants of these proteins can cause alterations in the cochlea[4]. Pathogenic variants are the most common cause of autosomal recessive hearing loss and are identified in up to 50% of patients with severe to profound hearing loss. The study of these pathogenic variants is complex, as more than 200 variants have been identified to date[1,4,14]. As described in studies on second-generation DNA analysis, it is still impossible to reach a molecular diagnosis in 100% of the patients[15,23].

An important aspect in diagnosing, managing, and genetic counseling patients with congenital hearing loss is that its distribution is complex, as different variants predominate in different populations. For example, the c.35delG in *GJB2* is the most common variant in Europeans/Americans of European ancestry, and its carrier frequency is ~2.5% in the United States. Carrier prevalence for c. 35delG is 1.5% worldwide, ranging from 0% to 5.7% in Belarus. Another example is a carrier prevalence of 2.5% for the p.V37I variant (from 0% up to 16.7% in Thailand); the c.167delT variant has a carrier prevalence of ~4% in the Ashkenazi population, and the c.235delC variant is the most common in Japan[1-4]. As described above, considering ethnicity is critical when determining the optimal genetic analysis. When sequencing for the diagnosis of congenital hearing loss, there is a wide range of genotype frequency depending on the ethnicity of the patients[27].

Based on these considerations, the alteration's genetic etiology impacts the management and treatment of congenital hearing loss. Therefore, profile determination of the pathogenic variants in different populations allows for determining the resources and prognosis for each patient. As an example, 49 genes were identified in a study that performed genetic analysis of 1119 patients of different ethnicities[28], including 549 Caucasians, 128 Hispanics, 51 African Americans, 40 Asians, 25 Middle Easterns, 8 Ashkenazi Jews, 57 of mixed ethnicity, and seven patients described as of "other" ethnicity. In 75%, hearing loss was associated

Table 1. Comparison of information regarding the different mutations related to hearing impairment in Mexican populations

Author (year)[REF]	Arenas-Sordo et al. (2012)[19]	Mendelsberg-Fishbein et al. (2013)[20]	Hernández-Juárez et al. (2014)[21]	Loeza-Becerra et al. (2014)[22]	Martínez-Saucedo et al. (2015)[13]	Bademci et al.[a] (2016)[23]	Cengiz et al. (2017)[24]	Hernández-Nieto et al.[b] (2020)[25]
Studied population	76 individuals	11 individuals	78 individuals/ deafness	140 individuals/ deafness	Two families	Two Mexican families out of 90 families from several backgrounds	11 individuals out of seven families	805 individuals
Origen of the studied population in Mexico	Not specified	Central[c]: MEX: 6; MICH: 3; GUA: 1; CDMX:1	Northeastern[d]: NLE, SLP, and TAM	West, Northwest, East, Northeast, and Central	Not specified	Not specified	Not specified	From 25 out of 32 states. Ancestry: Latin (640), European (72), Middle East (22), other (3)
Analyzed gene/ Gene and pathogenic variant	*GJB2, GJB6,* del(GJB6-D13S1830) and del(GJB6-D13S1854), m.1555A > G in *MTRNR1*	*GJB2*: c.35delG, c.235delC and c.167delT	*GJB2* IVS1 + 1G > A and *GJB6* deletions	*GJB2, GJB6* y mt.1555A < G	*GJB2*	*CDH23*	*SLC26A4*	*GJB2*, del (GJB6-D13S1830) and del (GJB6-D13S1854).
Methods used for genetic variables identification	*a) GJB2* sequencing b) *GJB6* screening (sequencing) for two deletions: del (GJB6-D13S1830) and del (GJB6-D13S1854) c) *MTRNR1* gene (m.1555A>G in)	Three *GJB2* mutations were analyzed: a) c.35delG by direct sequencing b) c.167delT by PCR-RFLP with *Pst*I. c) C.235delC by PCR-RFLP with *Apa*I	*a) GJB2* nucleotide sequencing b) PCR-RFLP analysis to detect IVS1+1G>A c) Real-time quantitative PCR (qPCR) for deletions in *GJB6*	Direct sequencing of a) *GJB2* b) *GJB6* c)mt.1555A>G	Direct sequencing of *GJB2*	a) First *GJB2* mutations were discarded b) Whole-exome sequencing analysis	a) Pre-screening for *GJB2* variants b) Whole-exome sequencing identifying *SLC26A4* and Sanger sequencing for confirmation	Preconception expanded genetic carrier screening; panel test for 283 clinically impactful diseases. Next-generation sequencing was performed for 21 pathogenic variants and the two exons of *GJB2*, the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(GJB6-D13S1830) and del(GJB6-D13S1854)
Results	Eight previously reported pathogenic variants and two polymorphic variants in *GJB2.*		No deletions were detected in *GJB6* or *GJB2* IVS1 + 1G.	23 Hom mutations, 57 Het mutations, one double Het (*GJB2/GJB6*),	The propositus in family 1 had three mutations:			Twenty-seven cases (3.35%) were carriers of the pathogenic variant in *GJB2.*

(continues...)

Table 1. Comparison of information regarding the different mutations related to hearing impairment in Mexican populations *(continued)*

Author (year)[REF]	Arenas-Sordo et al. (2012)[19]	Mendelsberg-Fishbein et al. (2013)[20]	Hernández-Juárez et al. (2014)[21]	Loeza-Becerra et al. (2014)[22]	Martínez-Saucedo et al. (2015)[13]	Bademci et al.[a] (2016)[23]	Cengiz et al. (2017)[24]	Hernández-Nieto et al.[b] (2020)[25]
	No deletions were identified in *GJB6* or m.1555A>G. Eight cases (10.52%) with biallelic mutations. c.35delG (*GJB2*) was the most frequent pathogenic variant, with six heterozygous and two homozygous individuals. Five rare pathogenic variants were identified, including the autosomal dominant c.551G>A. c.79G>A was the most frequent benign polymorphic variant	c.35delG Hom (1); c.35insG (1); c.34G>T Het (1); c.79G>A (p.V27I) Het (2)	Mutations in *GJB2* were detected in 9.6% of the alleles; c. 35delG was the most frequent. Other six mutations were less frequently detected including (c.645_648delTAGA), (c.35G > A), and one with a possible Mexican origin (c.34G > T). There were no deletions detected in *GJB6* and *GJB2* IVS1 + 1G > A	and 59 wild-type genotypes in *GJB2.* Three Hom c.35delG and 26 Het patients. One patient with a *GJB6* deletion (including the double Het *GJB2/GJB6*). mt.1555A > G was not identified	Tp.S19R/p.R32S/p.E47*; meanwhile, the affected family members had three mutations p.F31I/p.W44*/p.V84M. The parents of both families were Het and had a normal auditive function	Het c.2959 G>A pD987N One compound Het (consanguinity)*	Hom: 3; compound Het: 4, for *SLC26A4* variants Seven families with ten different variants. in *SLC26A4.* A new recurrent variant was identified: t (c.1673A>G (p.N558S) in two families**	c.35delG (10 cases [37%]), c.101T>C (5 cases [18.5%]), c.617A>G (4 cases [14.8%]), c.109G>A (2 cases [7.4%]), other variants (deletion GJB6-D13S1830, c.416G>A, p.Leu90Pro, c.365A>T, c.169C>T, c.269T>C) (one case [3.7%] each
Conclusion	*GJB2* mutations are an important cause of prelingual deafness in the Mexican population	Two polymorphisms and three mutations were identified. The frequency of three different mutations was lower than those reported in the literature	The findings suggested that *DFNB1* mutations are a rare cause of autosomal recessive deafness in the northeastern Mexican population	The type and distribution of the mutations/alleles varied according to the specific analyzed region: 57.86% of patients had *GJB2* or *GJB6* mutated alleles, and 42.14% were wild-type	Two cases with three mutations. This situation reflects the complex patterns of mutations regarding *GJB2*	After excluding pathogenic variants in *GJB2*, a mutation was identified in 56% of the studied families. One Mexican family had a mutation in *CDH23.*	There is a spectrum of variants in *SLC26A4*. No common recurrent variation was identified. *SLC26A4* is a cause of hearing loss in Turkey, Iran, and Mexico	Sequence changes in *GJB2* had a frequency of carriers of 3.35%, and c.35delG (37%) was the most frequently identified. This result is similar to the 2.14% frequency reported in other regions of Mexico[10,13], where c.35del G was also the most commonly identified variant.

[a] Exome sequencing

[b] Preconceptional analysis with second-generation sequencing identified carriers for several diseases, including congenital hearing loss.

[c] MEX, State of Mexico; MICH, Michoacán; GUA, Guanajuato; CDMX, Mexico City.

[d] NLE, Nuevo León; SLP, San Luis Potosí; TAM, Tamaulipas.

Het, heterozygous; Hom; homozygous

*The authors identified pathogenic variants in 56% of the families, which involved 31 genes; 54% of these alterations have not been previously reported. In the remaining families of this study, mutations in the *OTOGL* and *FAM65B* genes were analyzed as new causes associated with hearing loss with autosomal recessive hearing loss.

**The authors identified 27 unique *SLC26A4* variants in 31 probands.

with 10 genes: 22% with *GJB2,* 16% with *STRC*, and 7% with *SLC26A4*. The latter gene encodes a chloride and iodide transporter and, in general, is the second most frequent autosomal recessive presentation and can also cause Pendred syndrome. Pathogenic variants of the *ECTA* genes corresponded to 5% of cases[28,29]. When these authors studied the molecular etiology in 77 patients with a cochlear implant, 13 (18%) had mutations in *GJB2,* and in eight patients, only one mutated allele was identified. Therefore, they were heterozygous for a known autosomal recessive inheritance pattern, although no other variants in other genes were identified, which was a limitation of this study.

It has been reported that patients with congenital hearing loss associated with *GJB2* mutations respond adequately to cochlear implants[17]. Also, patients with cochlear implants and pathogenic variants have shown variations in the language evaluation test according to the associated genetic alteration[30]. In this regard, studies of biallelic mutations in *GJB2* or *SLC26A4* or of patients with no established genetic cause found that patients with *GJB2* mutations would have better auditive nerve functional status than those with *SLC26A4* mutations when compared to either patients with Mondini malformations and dilated vestibular ducts or patients with idiopathic hearing loss[31-33].

Regarding hearing loss with a non-syndromic autosomal dominant inheritance pattern, it has been noted that the hearing abnormality is often less severe than that present in autosomal recessive conditions and manifests between the ages of 10 and 40 years. Some presentations of hearing loss show a unique profile associated with high-frequency hearing loss, such as some pathogenic variants in *KCNQ4,* a gene encoding a potassium channel. Pathogenic variants in the *WFS1* gene cause low-frequency hearing loss (< 2 kHz), and biallelic mutations in *WFS1* cause Wolfram syndrome, with an autosomal recessive inheritance pattern. The characteristic anomalies of this syndrome are described with the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Van Beeck et al.[3] performed a study including image analysis and the clinical and genetic characteristics of 423 children with hearing loss. These authors described that the most common etiology of bilateral hearing loss in 67% of children was a genetic disorder, corresponding to 26% of the cases. In children under one year of age with severe hearing loss, 47% of the cases corresponded to a syndromic presentation, and the rest (53%) presented hearing loss as an isolated alteration.

Moreover, in patients with unilateral hearing loss, a temporal bone anomaly was identified in 27%. When considering children with hearing loss due to genetic etiology, 43% had a family history, 39% had a syndrome associated with sensorineural hearing loss, and 18% showed a known pathogenic variant or mutation; among them, a specific mutation for *SLC26A4* (with an autosomal recessive inheritance pattern) was identified. Finally, a unilateral alteration was identified in 20% of patients and a bilateral alteration in 80%.

The response to cochlear implantation is a particularly relevant aspect concerning the management and treatment of congenital hearing loss of genetic etiology. Only a few studies have been performed in pediatric populations on this feature. In a study to determine the etiological profile of 122 Lithuanian children with cochlear implants, 65 cases (53.3%) were diagnosed as non-syndromic hearing loss; in 58 of them, hearing loss was associated with *GJB2*. In contrast, syndromic alterations were identified in eight children (6.6%). Perinatal risk factors for hearing loss, such as prematurity, low birth weight, hypoxia, hyperbilirubinemia, sepsis, ototoxic agents, and meningitis, were associated with hearing loss in 16 (13.1%) and four (3.3%) patients, respectively. Importantly, cytomegalovirus was detected in 12 samples (9.8%). However, even with these results, the origin of hearing loss could not be identified in 17 children. This analysis concluded that *GJB2* alterations were the most frequent cause of hearing loss and that only 14% of patients in this cohort had hearing loss of unknown etiology[11].

In a similar analysis in Polish children, 196 patients with severe prelingual hearing loss were evaluated[29]. The study described a good response to cochlear implants in 149 children with DFNB1-related hearing loss. Furthermore, better hearing development was described in children who underwent implantation before 12 months of age. This analysis also demonstrated that cochlear implantation was the most successful treatment in patients with hearing loss associated with the DFNB1 *locus*. These findings underscore the importance of determining the molecular genetic etiology in congenital hearing loss.

Molecular profile of hearing loss in Mexico

Few studies have been conducted in Mexico to determine the etiology of congenital hearing loss in the Mexican mestizo population (Table 1). In research conducted at the Hospital Infantil de México Federico Gómez (HIMFG) in children with hearing loss (Table 1), a population of almost 100 patients was evaluated to establish the cause of the hearing loss[16]. Molecular analysis was performed in 11 patients with a c.35delG homozygous, a c.35insG heterozygous, a c.34G>T heterozygous, and heterozygous patients for the c.79G>A polymorphism, all in *GJB2*, were identified. Interestingly, several factors suggesting non-genetic causes were identified, including a positive TORCH test in 1% and infections or the use of ototoxic drugs in 3% of patients. Regarding this aspect, it is essential to mention that ototoxic drugs only cause hearing damage in patients with specific genotypes[34]. This aspect has been studied in patients requiring the use of aminoglycosides as a treatment for infectious diseases; it has been shown that some genetic alterations in mitochondrial DNA confer greater sensitivity to these drugs and, therefore, to the risk of presenting non-syndromic deafness associated with their use. Several mutations in the 12S rRNA region of mitochondrial DNA have been described in various populations[14,35], including T961insC, T961C, T961+C(n)ins, T1095C, C1494T, and A1555G. However, these pathogenic mitochondrial variants are rare, and their frequency may even vary among different ethnic groups, as has been studied in the Mexican population by Meza et al. (2011)[31]. In their study of 65 subjects, the authors did not identify any previously reported mutation related to aminoglycoside hypersensitivity, and only two of the patients treated with the aminoglycoside streptomycin had a T1189C variant of the previously mentioned 12S rRNA region, which was considered a possible mutation related to the aminoglycoside hypersensitivity.

Molecular genetics research has been conducted on hearing loss etiology in Mexican mestizo populations (Table 1). For example, in a study conducted in northeastern Mexico, a pathogenic variant of *GJB2* was identified in 78 patients. A mutation in *GJB2* was identified in 9.6% of the alleles; c.35delG was the most frequently identified, and six other mutations were also detected. Interestingly, the IVS1+1G>A *GJB2* variant was not detected. This study determined that mutations in the *DFNB1 locus* are a rare cause of autosomal recessive non-syndromic sensorineural hearing loss in this population[21].

In a cohort of patients attending the Hospital General de México Dr. Eduardo Liceaga, mutations in *GJB2*, *GJB6,* and mt.1555A<G were studied, and a double heterozygous (*GJB2*/*GJB6*) was detected in this group, as well as three patients homozygous for c.del35 in *GJB2*, while 26 patients were heterozygous for this gene. Conversely, the mt.1555A<G mutation was not detected. In this cohort, 57.86% of patients showed one or two affected alleles of *GJB2* or *GJB6*[22].

As described in the previously mentioned studies performed in Mexico in specific populations with hearing loss, the most frequent pathogenic variants have been identified in well-known genes such as *GJB2* and *GJB6*. However, it was impossible to identify a genetic alteration in a significant percentage of patients. Therefore, genomic analyses should be performed using next-generation sequencing (NGS) techniques, including gene panels or whole exome, or genome studies[30]. Implementing this technology will allow efficient simultaneous screening of multiple genes[25].

An example of the scope of NGS is that with exome sequence analysis was possible to establish the etiology in 27% of patients in a group of children with development anomalies with no previous diagnosis. Also, genomic studies can provide a timely diagnosis in managing infants in neonatal intensive care units[36]. This situation underlines the importance of using these molecular techniques in diagnosing diseases such as congenital hearing loss in patients without a definitive etiology.

Several populations with congenital hearing loss in different parts of the world have been studied by NGS, including a small group of Mexican patients with congenital hearing loss in whom an alteration in *GJB2* was excluded before NGS. Bademci G et al. studied 160 families (including two of Mexican origin) by exome analysis for all known genes associated with non-syndromic congenital hearing loss[23]. In this research, the authors identified a novel variant c.2959G>A, p.D987N in the *CDH23* gene in one of the Mexican families. Cengiz et al. identified mutations in *SLC26A4* in Mexican patients (Table 1), corresponding to three homozygous and four compound-heterozygous patients[24].

Hernández-Nieto et al.[25] conducted an interesting analysis in which they analyzed data from 805 individuals with NGS (Table 1). The population examined differed from those described in other hearing loss studies since the patients requested a preconception NGS analysis due to genetic counseling. The population analyzed included patients born in Mexico. Different population origins were identified by ancestry analysis, most of them corresponding to the Latino population, and several carriers of other diseases were identified. Among these abnormalities, congenital hearing loss genes were found in 27 cases (3.35%), corresponding to carriers of *GJB2* gene pathogenic variants. This frequency is similar to those reported by other authors in northeastern Mexico[19,22]. Although it came from a population that consulted for a situation unrelated to congenital hearing loss (among other characteristics that may contribute to some bias of this study), this information is interesting as a reference to the frequency of carriers in the general Mexican population for pathogenic variants of *GJB2*.

Congenital hearing loss is a public health problem in Mexico. As in other populations, its etiology is diverse. Although few studies have been conducted in Mexico, they have shown *GJB2* pathogenic variants, compound heterozygous, and the presence of pathogenic variants in other genes such as *GJB6* or *SLC26A4* in this population; there are also some families with particular characteristics due to the genes involved. Interestingly, the frequency (3.35%) of the c.35delG variant in *GJB2* was found in a population analyzed by exome who consulted for preconception genetic diagnosis[25]. The studies reviewed here indicate the genetic heterogeneity of congenital hearing loss in the Mexican population and the importance of establishing the diagnosis, etiology, and genetic counseling when the most frequent causes have been excluded. Also, the studies showed the implications of genetic diagnosis for patient management, such as that related to cochlear implants. As discussed in this review and summarized in Table 1, the most frequent pathogenic variants associated with hearing loss in the Mexican population are related to the *GJB2* gene, although in a low percentage, followed in frequency by pathogenic mutations in *SLC26A4* and mutations in *CHD23* in third place. Based on these data, a possible diagnostic strategy would be screening for these three genes in Mexican patients. If the result is negative for pathogenic variants at these *loci*, the following step would be a second-generation sequencing analysis focused on panels of genes already associated with isolated and syndromic hearing loss. If these analyses are not informative, second-generation sequencing should be considered, first by whole-exome analysis, and, in the case of negative results, whole-genome sequencing should be performed.

As proposed for other populations[37], these data reflect the importance of genetic evaluation with molecular studies to establish the genetic etiology of congenital hearing loss in Mexican patients.

In conclusion, establishing an etiological cause is critical in the clinical evaluation of infants and children with congenital hearing loss and their families, as has been emphasized by many authors[38]. Identifying underlying causes could help choose rehabilitation strategies, such as hearing aids or cochlear implants. This will provide insights into disease progression, facilitate monitoring of clinical manifestations and associated complications, and provide parents information on the risk of recurrence. Finally, this review is critical because it summarizes all the research conducted in Mexico on the genetic etiology of hearing loss.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Chang KW. Genetics of hearing loss—nonsyndromic. Otolaryngol Clin North Am. 2015;48:1063-72.
2. Sommen M, Schrauwen I, Vandeweyer G, Boeckx N, Corneveaux JJ, van den Ende J, et al. DNA diagnostics of hereditary hearing loss: a targeted resequencing approach combined with a mutation classification system. Hum Mutat. 2016;37:812-9.
3. van Beeck Calkoen EA, Engel MSD, van de Kamp JM, Yntema HG, Goverts ST, Mulder MF, et al. The etiological evaluation of sensorineural hearing loss in children. Eur J Pediatr. 2019;178:1195-205.
4. Sheffield AM, Smith RJH. The epidemiology of deafness. Cold Spring Harb Perspect Med. 2019;9:a033258.
5. World Health Organization. Report of the Informal Working Group on Prevention of Deafness and Hearing Impairment Programme Planning. Geneva, 18-21 June 1991. Geneva: World Health Organization; 1991. Available from: http://www.who. int/iris/handle/10665/58839
6. Pascolini D, Smith A. Hearing impairment in 2008: a compilation of available epidemiological studies. Int J Audiol. 2009;48:473-85.
7. Global Burden of Disease (GBD). Seattle: Institute for Health Metrics and Evaluation; 2019. Available from: https://www.healthdata.org/gbd/2019
8. Olusanya BO, Davis AC, Hoffman HJ. Hearing loss grades and the *International classification of functioning, disability and health*. Bull World Health Organ. 2019;97:725-8.
9. Clark JG. Uses and abuses of hearing loss classification. ASHA. 1981;23:493-500.
10. Teagle HFB, Park LR, Brown KD, Zdanski C, Pillsbury HC. Pediatric cochlear implantation: a quarter century in review. Cochlear Implants Int. 2019;20:288-98.
11. Byckova J, Mikstiene V, Kiveryte S, Mickeviciene V, Gromova M, Cernyte G, et al. Etiological profile of hearing loss amongst Lithuanian pediatric cochlear implant users. Int J Pediatr Otorhinolaryngol. 2020;134:110043.
12. Van Heurck R, Carminho-Rodrigues MT, Ranza E, Stafuzza C, Quteineh L, Gehrig C, et al. Benefits of exome sequencing in children with suspected isolated hearing loss. Genes (Basel). 2021;12:1277.
13. Martínez-Saucedo M, Rivera-Vega MR, Gonzalez-Huerta Luz M, Urueta-Cuellar H, Toral-López J, Berruecos-Villalobos P, et al. Two novel compound heterozygous families with a trimutation in the *GJB2* gene causing sensorineural hearing loss. Int J Pediatr Otorhinolaryngol. 2015;79:2295-9.

14. Arenas-Sordo ML, Linares-Mendoza EP, Peñuelas-Romero KJ, Castro-Peña S, Agís-Ocaña JG. Non-syndromic hearing loss of genetic origin. Current concepts. Otorrinolaringología. 2020;65:43-58.
15. Bahena P, Daftarian N, Maroofian R, Linares P, Villalobos D, Mirrahimi M, et al. Unraveling the genetic complexities of combined retinal dystrophy and hearing impairment. Hum Genet. 2022;141:785-803.
16. Lucotte G, Diéterlen F. The 35delG mutation in the connexin 26 gene (GJB2) associated with congenital deafness: European carrier frequencies and evidence for its origin in ancient Greece. Genet Test. 2005;9:20-5.
17. Lustig LR, Lin D, Venick H, Larky J, Yeagle J, Chinnici J, et al. *GJB2* gene mutations in cochlear implant recipients: prevalence and impact on outcome. Arch Otolaryngol Head Neck Surg. 2004;130:541-6.
18. Online Mendelian Inheritance in Man, OMIM®. An online catalog of human genes and genetic disorders. Baltimore: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University; 2021. Available from: https://omim.org
19. Arenas-Sordo ML, Menendez I, Hernández-Zamora E, Sirmaci A, Gutiérrez-Tinajero D, McGetrick M, et al. Unique spectrum of *GJB2* mutations in Mexico. Int J Pediatr Otorhinolaryngol. 2012;76:1678-80.
20. Mendelsberg-Fishbein P, Márquez-Ávila CS, García-Delgado C, Sánchez-Boiso A, Rodríguez-Espino BA, Vázquez-Martínez ER, et al. Importance of the diagnosis of connexin 26 gene mutations in the integral management of non-syndromic congenital deafness. Bol Med Hosp Infant Mex. 2013;70:89-97.
21. Hernández-Juárez AA, Lugo-Trampe JJ, Campos-Acevedo LD, Lugo-Trampe A, Treviño-González JL, de la Cruz-Ávila I, et al. *GJB2* and *GJB6* mutations are an infrequent cause of autosomal-recessive nonsyndromic hearing loss in residents of Mexico. Int J Pediatr Otorhinolaryngol. 2014;78:2107-12.
22. Loeza-Becerra F, Rivera-Vega MR, Martínez-Saucedo M, Gonzalez-Huerta LM, Urueta-Cuellar H, Berruecos-Villalobos P, et al. Particular distribution of the *GJB2*/*GJB6* gene mutations in Mexican population with hearing impairment. Int J Pediatr Otorhinolaryngol. 2014;78:1057-60.
23. Bademci G, Foster J 2nd, Mahdieh N, Bonyadi M, Duman D, Cengiz FB, et al. Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. Genet Med. 2016;18:364-71.
24. Cengiz FB, Yilmazer R, Olgun L, Sennaroglu L, Kirazli T, Alper H, et al. Novel pathogenic variants underlie SLC26A4-related hearing loss in a multiethnic cohort. Int J Pediatr Otorhinolaryngol. 2017;101:167-71.
25. Hernandez-Nieto C, Alkon-Meadows T, Lee J, Cacchione T, Iyune-Cojab E, Garza-Galvan M, et al. Expanded carrier screening for preconception reproductive risk assessment: Prevalence of carrier status in a Mexican population. Prenat Diagn. 2020;40:635-43.
26. Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. Nature. 1997;387:80-3.
27. Chan DK, Schrijver I, Chang KW. Diagnostic yield in the workup of congenital sensorineural hearing loss is dependent on patient ethnicity. Otol Neurotol. 2011;32:81-7.
28. Sloan-Heggen CM, Bierer AO, Shearer AE, Kolbe DL, Nishimura CJ, Frees KL, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016; 135:441-50.
29. Sloan-Heggen CM, Smith RJ. Navigating genetic diagnostics in patients with hearing loss. Curr Opin Pediatr. 2016;28:705-12.
30. Shearer AE, Eppsteiner RW, Frees K, Tejani V, Sloan-Heggen CM, Brown C, et al. Genetic variants in the peripheral auditory system significantly affect adult cochlear implant performance. Hear Res. 2017;348:138-42.
31. Luo J, Xu L, Chao X, Wang R, Pellittieri A, Bai X, et al. The effects of *GJB2* or *SLC26A4* gene mutations on neural response of the electrically stimulated auditory nerve in children. Ear Hear. 2020; 41:194-207.
32. Chen PY, Lin YH, Liu TC, Lin YH, Tseng LH, Yang TH, et al. Prediction model for audiological outcomes in patients with GJB2 mutations. Ear Hear. 2020;41:143-9.
33. Oziębło D, Obrycka A, Lorens A, Skarżyński H, Ołdak M. Cochlear implantation outcome in children with DFNB1 *locus* pathogenic variants. J Clin Med. 2020;9:228.
34. Ou YH, Chen AW, Fan JY, Cheng WL, Lin TT, Chen MK, et al. Aminoglycoside-associated nonsyndromic deafness and speech disorder in mitochondrial A1555G mutation in a family: A case report. Medicine (Baltimore). 2018;97:e12878.
35. Meza G, Torres-Ruíz NM, Tirado-Gutiérrez C, Aguilera P. mtDNA mutations, hearing loss and aminoglycoside treatment in Mexicans. Braz J Otorhinolaryngol. 2011;77:573-6.
36. Raza S, Hall A. Genomic medicine and data sharing. Br Med Bull. 2017;123:35-45.
37. Adadey SM, Wonkam-Tingang E, Twumasi Aboagye E, Nayo-Gyan DW, Boatemaa Ansong M, Quaye O, et al. Connexin genes variants associated with non-syndromic hearing impairment: A systematic review of the global burden. Life (Basel). 2020;10:258.
38. Boudewyns A. Etiological work-up for congenital hearing loss: When? Why and How? Toulouse, France: 12th European Symposium on Pediatric Cochlear Implants (ESPCI): 2015.