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ORIGINAL RESEARCH

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High prevalence of syndromic hearing loss in Mexican children undergoing cochlear implantation

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Abstract

Objective: Studies evaluating genetic sensorineural hearing loss (SNHL) in Hispanic and Latino populations using genomic technologies are lacking. Recent data has shown that Hispanic and Latino children display lower genetic diagnostic rates despite similar prevalence rates of SNHL to their Asian and White counterparts, thus negatively affecting their clinical care. Our objective was to determine the genetic contribution to SNHL in a population of Mexican children undergoing evaluation for cochlear implantation.

Methods: Pediatric patients from Mexico with severe to profound SNHL undergoing evaluation for cochlear implantation were recruited. Exome sequencing (ES) or hearing loss gene panel testing was performed. Variant pathogenicity was established in accordance to criteria established by the American College of Medical Genetics, and variants of interest were clinically confirmed via CLIA certified laboratory.

Results: Genetic evaluation was completed for 30 Mexican children with severe to profound SNHL. A genetic cause was identified for 47% (14) of probands, and 7% (2) probands had an inconclusive result. Of the diagnoses, 10 (71%) were syndromic or likely syndromic, and 4 (29%) were nonsyndromic. Eight probands (80% of all syndromic diagnoses) were diagnosed with a syndromic form of hearing loss that mimics a nonsyndromic clinical presentation at a young age and so could not be suspected based on clinical evaluation alone without genetic testing.

Monica Rodriguez-Valero and Adrian Pastolero contributed equally to this study.

Conclusion: This is the largest study to date to use comprehensive genomic testing for the evaluation of Mexican children with severe to profound SNHL. A significant proportion of children in this cohort were diagnosed with syndromic hearing loss. Future study in a larger cohort of Mexican children with varying degrees of hearing loss is required to improve the efficacy of genetic testing and timely medical intervention within these ethnically diverse populations.

Level of evidence: Level 4 (cohort study).

KEYWORDS
hearing loss, genetics, genomics, Mexico

1 | INTRODUCTION

Sensorineural hearing loss (SNHL) is the most common human sensory deficit, with an estimated prevalence of 1 out of every 500 births.[1] Pathogenic variants in known SNHL genes account for 50%–60% of pediatric SNHL cases in developed countries.[2–4] However, the genetic contribution to hearing loss in developing countries is not known, given the relatively low usage of comprehensive genetic testing strategies for hearing loss.[5]

Genetic testing for hearing loss is complex, given that there are 127 non-syndromic SNHL genes and hundreds of genetic syndromes that include SNHL as a clinical feature (http://hereditaryhearingloss.org). Identifying the genetic etiology of pediatric SNHL is an important component of understanding prognosis, guiding management, providing recurrence information for families, and, especially, identifying syndromic forms of SNHL.[2] Diagnosis of syndromic hearing loss is particularly important for patients and families, given that other organ system involvement may immediately alter clinical care. While advancements in next-generation sequencing (NGS) have led to increased diagnostic yields for pediatric SNHL, these diagnostic yields are significantly higher for White and Asian children compared to Black and, Hispanic and Latino children, who are underrepresented minorities in genetic hearing loss research.[5,6]

The estimated prevalence of congenital hearing loss within Latin American countries is similar to developed countries at 1–2/1000 newborns.[7] However, a recent study showed 10-fold less representation for evaluation of genetic hearing loss in Latino American populations compared to White populations based on the number of published studies and 37-fold less based on the number of subjects tested within these studies. Latino American subjects were also more likely to have had single-gene (*GJB2*) testing and less likely to have multi-gene testing or exome sequencing (ES) compared to their White and Asian counterparts.[5] Furthermore, Hispanic and Latino American individuals who do undergo multigene panel testing for SNHL are significantly more likely to have nondiagnostic or inconclusive results due to the higher rate of variants of uncertain significance for these populations compared to White and Asian populations.[6]

In this study, we performed comprehensive genetic testing for a cohort of 30 children with severe to profound congenital SNHL undergoing cochlear implant (CI) evaluation. We used either ES or comprehensive gene panel testing to evaluate all known non-syndromic and syndromic hearing loss genes. Our goal was to gain a better understanding of the contribution of genetics to SNHL in Mexico. We identified a genetic diagnosis in 47% of children and, unexpectedly, identified a syndromic form of SNHL in 71% of diagnoses (30% of the entire cohort). This is, to our knowledge, the only study of genetic hearing loss in the Mexican population using comprehensive genetic testing techniques.

2 | MATERIALS AND METHODS

2.1 | Recruitment and participants

This research was approved by the institutional review board at Boston Children's Hospital (IRB protocol P00035179) as well as by the Research and Ethics Committees at Centro Médico ABC. Pediatric patients with severe to profound SNHL who were candidates for cochlear implantation were recruited from Centro Médico ABC in Mexico City, Mexico, and written informed consent was obtained. Eligible probands had severe to profound SNHL. No exclusions were made on the basis of age of onset, structural abnormalities of the inner ear, additional presenting features, or family history. Probands were enrolled as singletons, and parental genetic testing was not performed.

As part of the Escuchar Sin Fronteras program, which provides access to cochlear implants to families at low or no cost, a multidisciplinary clinical evaluation of all patients was performed. The team included otorhinolaryngologists, a pediatrician, a pediatric ophthalmologist, clinical geneticists, audiologists, and speech therapists. The standard clinical evaluation included preoperative EKG, renal ultrasound, TSH, and thin-cut imaging of the temporal bone with MRI and CT.

2.2 | DNA extraction, sequencing, and analysis

DNA was extracted from saliva using standard methods. Comprehensive genetic testing was completed via ES at the commercial testing laboratory GeneDx (Gaithersburg, MD) for 18 probands, commercial

gene panel testing for one proband (Invitae, San Francisco, CA), or utilizing a comprehensive hearing loss gene panel—a custom enzymatic targeted genomic enrichment and massively parallel sequencing (TGE + MPS) method for 11 probands (Twist Bioscience, San Francisco, CA). The custom gene panel was used if patient samples had a yield of less than 1000 ng of DNA, as this was not sufficient for standard commercial testing. The custom TGE + MPS gene panel was designed to include 219 established and candidate non-syndromic and syndromic SNHL genes (Table S1). Copy number variants (CNVs) were evaluated either through bioinformatic analysis (ES and commercial panel) or using a commercial multiplex ligation probe amplification (MLPA) panel for all hearing loss genes with the most previously reported CNVs: *STRC*, *OTOA*, *GJB2*, *GJB6*, *POU3F4*, *and WFS1* (MRC Holland, Amsterdam, Netherlands).

Custom variant analysis was performed using a pipeline described previously.[8] Variants were prioritized based on allele frequency, in silico predictions, published clinical data, functional studies, and other relevant data. Variant pathogenicity was established according to criteria established by the American College of Medical Genetics and the Associations for Molecular Pathology, as modified for SNHL-specific considerations.[9,10] All causative variants, as well as variants suspected to be associated with the presenting phenotypes, were clinically confirmed via Sanger sequencing in a Clinical Laboratory Improvement Amendments-certified environment (GeneDx). Clinically confirmed variants were reported to the participating families by a Medical Geneticist at Centro Médico ABC, who provided appropriate genetic counseling and follow-up recommendations. Causative variants were searched, and information was ascertained from the ClinVar variant database[11] as well as using the Genome Aggregation Database (gnomAD v3.2.1).[12]

3 | RESULTS

3.1 | Demographics and clinical characteristics

Thirty probands were included in this study (Table 1 and detailed clinical data in Table S2). All but one proband reported Mestizo Mexicano race and all probands reported Hispanic or Latino ethnicity. The median age of probands at the age of genetic testing was 3.1 years old (range from 1.2 to 6.3 years old). Twenty–seven probands (90%) have undergone bilateral cochlear implantation to date, with the other probands currently awaiting surgical date. SNHL was bilateral and affecting both ears symmetrically for all probands. A majority (27, 90%) of probands had a congenital-onset SNHL; 10% had a prelingual onset. Four (13%) probands had a positive family history of SNHL, none of whom had an affected first-degree relative (Table 1, Table S2). All probands were evaluated after 3 weeks of birth, so congenital cytomegalovirus status is unknown.

3.2 | Diagnostic yield

The overall diagnostic yield (combining results from ES and TGE + MPS) was 14 out of 30 probands (47%) (Figure 1). Results were inconclusive for 2 of 30 probands (7%) due to the identification of variants of uncertain significance in a gene with plausible association with the proband's phenotype. Fourteen of 30 probands (47%) had negative results, with no causative variants identified.

TABLE 1 Demographic and clinical characteristics.

Demographic	*N* (%)
Sex	
Female	15 (50%)
Male	15 (50%)
Race	
Mestizo Mexicano	29 (97%)
White/Caucasian	1 (3%)
Ethnicity	
Hispanic or Latino	30 (100%)
Non Hispanic or Latino	0 (0%)
SNHL onset	
Congenital	27 (90%)
Prelingual	3 (10%)
SNHL laterality	
Bilateral	30 (100%)
Unilateral/asymmetric	0 (0%)
SNHL severity (worse ear)	
Severe to profound	30 (100%)
Other	0 (0%)
Family history	
Negative	26 (87%)
Positive	4 (13%)

Abbreviation: SNHL, sensorineural hearing loss.

3.3 | Causative genes identified

We identified causative variants for 14 probands in 10 genes (Figure 2). Three out of 30 probands (10%) were diagnosed with autosomal recessive nonsyndromic hearing loss due to pathogenic variants in the *GJB2* gene. Two probands (7%) were diagnosed with pathogenic variants in either *SLC26A4* or *CDH23*. Other causative genes included *MITF*, *PAX3*, *SPATA5L1*, *GATA2*, *MYO7A*, and *USH1C*. See Table S2 for details on all causative variants.

3.4 | Causative variants identified

A total of 19 variants were identified in 10 genes and assessed as being causative (Table S2) Of these 19 variants, 11 (57.9%) had a prior ClinVar entries suggesting they have been previously identified on clinical genetic testing, whereas 8 (42.1%) did not contain prior entries in ClinVar, indicating novelty. Of these 19 variants, 12 (63.1%) were absent from gnomAD (v3.2.1) population cohorts. Seven (36.8%) variants were reported in gnomAD at a frequency consistent with

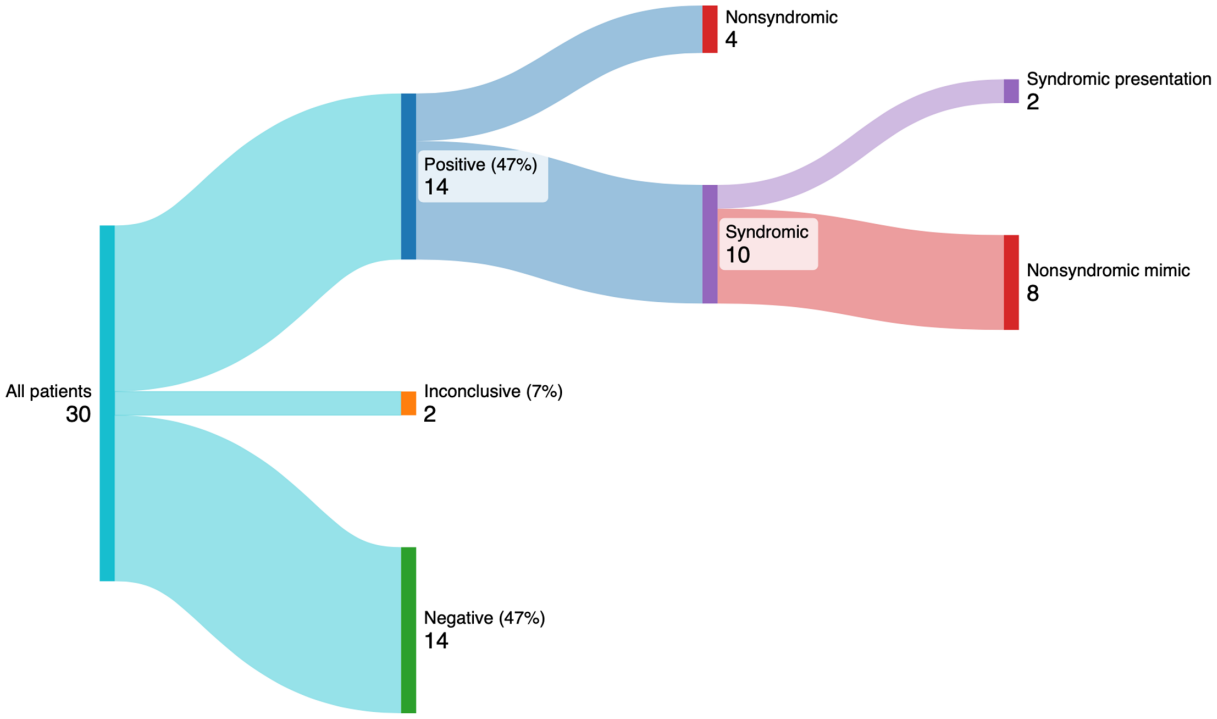

FIGURE 1 Diagnostic yield and categories of clinical presentation. Nonsyndromic refers to a genetic condition associated only with sensorineural hearing loss (SNHL). Syndromic refers to a condition that is resented as multisystemic and includes SNHL. Nonsyndromic mimic refers to a condition that presents as isolated SNHL, but additional syndromic features manifest with age.

autosomal recessive SNHL with the highest allele frequency in African or African Americans for three variants, Europeans (non-Finnish) for two variants, Admixed Americans for one variant, and "Other" for one variant. The common c.35del (p.Gly12fs) variant in *GJB2* was the only causative variant identified in multiple probands.

3.5 | Nonsyndromic diagnoses

Three probands with *GJB2* pathogenic variants were identified and had no syndromic features or malformations on the MRI and CT scans. All clinical tests (renal ultrasound, EKG, thyroid test, and ophthalmology review) were normal for these probands, and two underwent CI surgery prior to the time of publication. One proband (115-01) was found to have causative mutations in the gene *TBC1D24*. That proband has normal inner ear CT and MRI results. He is 3 years old with no history of seizures and has bilateral CI.

3.6 | Syndromic diagnoses

We identified a substantial number of syndromic diagnoses (Figures 1 and 2). Of all 14 diagnoses made, 10 (71%) were syndromic or likely syndromic. Eight probands (80% of all syndromic diagnoses) were diagnosed with a potentially syndromic form a hearing loss that mimics a nonsyndromic clinical presentation at young ages. Variants were identified in the *MYO7A*, *CDH23* (x2), and *USH1G* genes, suggestive of either Usher syndrome of nonsyndromic hearing loss (*MYO7A* and *CDH23*) for four probands. Two diagnoses were made due to the identification of variants in the *SLC26A4* gene in probands with EVA based on imaging studies, resulting in a diagnosis of either nonsyndromic EVA and hearing loss (DFNB4) or Pendred syndrome. One proband was found to have a pathogenic variant in the *MITF* gene consistent with a diagnosis of Waardenburg syndrome type 2A; no clinical features apart from SNHL were appreciated on physical exam by a clinical geneticist prior to or following genetic testing. One diagnosis of *GATA2*-related SNHL and myelodysplasia (Embarger syndrome) was made for a young proband presenting only with SNHL. Two probands presented with syndromic features appreciated prior to CI surgery were identified to have diagnoses in two genes: *SPATA5L1* and *PAX3* (Waardenburg syndrome type I).

Usher syndrome, or possible Usher syndrome, was identified in four cases. One proband (89-01) harbored two rare heterozygous variants in the gene *MYO7A*, which may cause either nonsyndromic SNHL or Usher syndrome type IB. Preoperative Ophthalmology assessment was normal, but electroretinography and vestibular evaluation have not been performed. Subject 122-01 presented with bilateral, congenital severe SNHL, mild motor delay, and abnormal preoperative vestibular testing (decreased function of the saccule and lateral semicircular canal bilaterally). This subject was identified to harbor a homozygous pathogenic variant in *USH1C*, causative of Usher syndrome type IC. Ophthalmology assessment has been normal from birth to 3 years old, with retinography planned for the future. One female proband, 83-01, was found to have a homozygous pathogenic

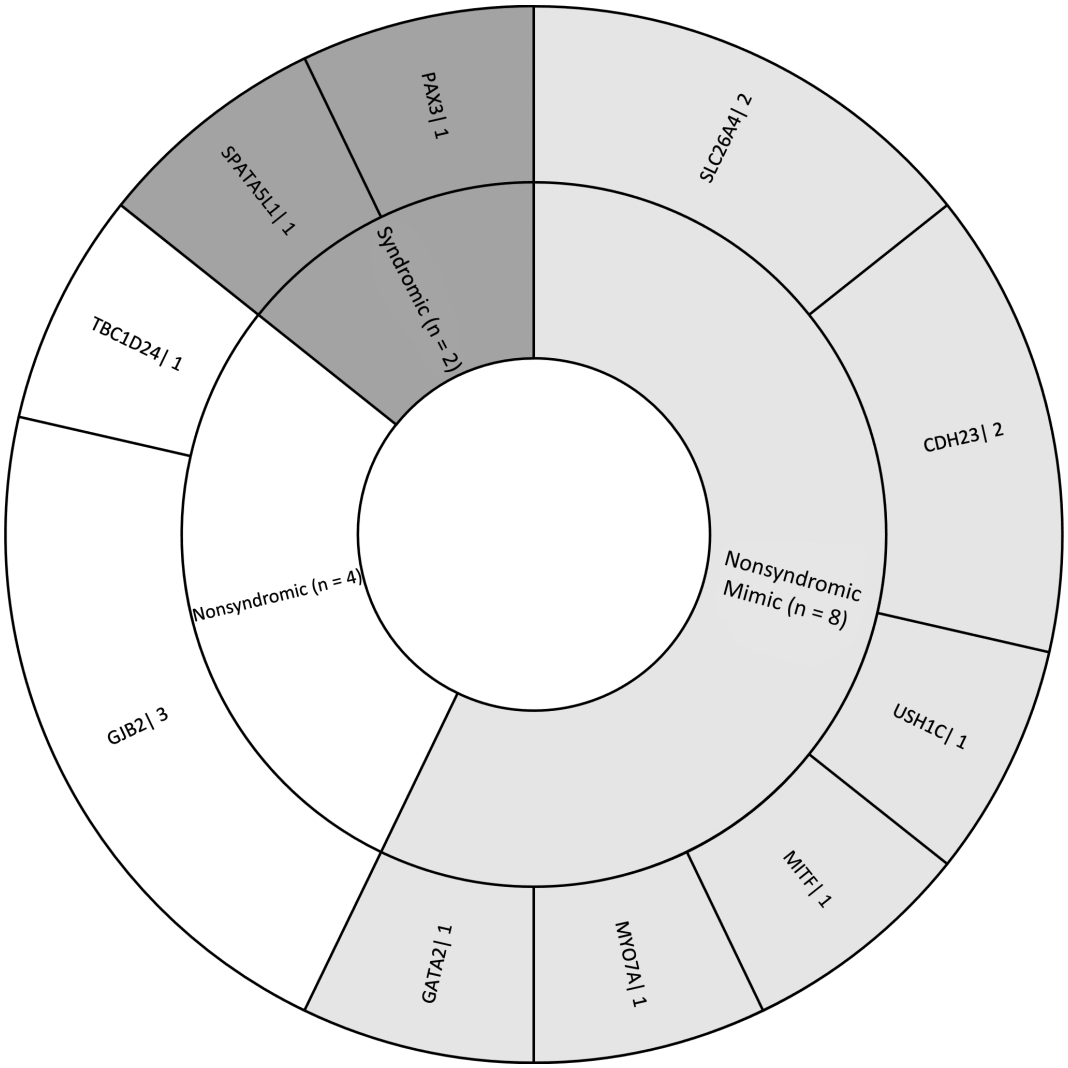

FIGURE 2 Causative genes identified. Nonsyndromic refers to a genetic condition associated only with sensorineural hearing loss (SNHL). Syndromic refers to a condition that is resented as multisystemic and includes SNHL. Nonsyndromic mimic refers to a condition that presents as isolated SNHL, but additional syndromic features manifest with age.

variant in *CDH23*, causative Usher Syndrome type ID or nonsyndromic SNHL. Vestibular testing was not done prior to surgery, but her developmental milestones were within range. This proband also had an incidental finding of a heterozygous pathogenic variant in *KCNQ1*, causative of Long QT syndrome 1. The preoperative EKG had no arrhythmia, and the QT interval was within range. An ophthalmology exam revealed astigmatism, retinography has not been completed. A second proband, 123-01, had two variants in *CDH23*, one pathogenic and one variant of uncertain significance (VUS), but based on criteria, we determined this to be a likely positive genetic result. Preoperative vestibular testing was normal, as was an MRI, CT, and EKG. The ophthalmology exam, which did not include retinography, was normal.

Two probands (125-01 and 87-01) were identified to have pathogenic variants in *SLC26A4*, providing a diagnosis of Pendred syndrome or enlarged vestibular aqueduct (EVA) and nonsyndromic hearing loss (DFNB4). CT and MRI revealed a bilateral incomplete partition of the cochlea and enlarged vestibular aqueducts. One of the probands had vestibular testing (head impulse test, rotary chair, and cVEMPs) prior to CI surgery with normal results. The two probands have bilateral cochlear implants. No cerebrospinal fluid gusher was observed in their surgeries and both have good CI performance.

Proband 120-01 had a heterozygous likely pathogenic variant *GATA2*, associated with Embarger syndrome, or primary lymphedema with myelodysplasia and SNHL. He is 3 years old with no known lymphedema or myeloid neoplasms, but he will be follow-up regularly in Hematology and Immunology given this syndromic SNHL diagnosis.

Proband 116-01 was found to have two pathogenic variants in the *SPATA5L1* gene, constituting a unifying diagnosis for her intellectual disability, spastic-dystonic cerebral palsy, gross developmental delay, and severe SNHL. One proband (90-01) was identified to have Waardenburg syndrome type 1 with a heterozygous pathogenic variant in *PAX3* (blue eyes, white forelock, dystopia canthorum, and altered skin pigmentation was appreciated preoperatively), and one

proband (113-01) was found to have a heterozygous pathogenic variant in *MITF* (no syndromic features appreciated).

3.7 | Inconclusive results

One female proband (93-01) was found to harbor one VUS in *PCDH15* and one VUS in *CDH23*. There is limited evidence that digenic inheritance of pathogenic variants in these genes cause Usher syndrome type I. Parenteral testing was not performed, so it is unknown where the variants are located (*in cis* or *in trans*). Her imaging studies and ophthalmology evaluation were normal (with no retinography performed). Vestibular testing was not performed prior to CI surgery. This genetic diagnosis was determined to be inconclusive.

The other inconclusive result was in another female proband (112-01) that has two rare heterozygous VUS in *CDH23*, with phase unknown. She had normal labyrinthine anatomy by CT and MRI. Vestibular testing was not performed prior to CI surgery. Ophthalmology assessment was normal, again, with no retinography studies yet performed.

4 | DISCUSSION

Pediatric SNHL is a major public health issue, and establishing the etiologic cause is critical to providing the best care for patients and families. Given that the majority of pediatric hearing loss is due to a genetic cause, genetic testing is critical in the medical evaluation of children with SNHL. However, genetic testing for hearing loss is difficult due to the extreme genetic heterogeneity of hearing loss and the associated costs required for testing and analysis.

Although comprehensive genetic testing for pediatric hearing loss using gene panels or ES is the standard of care, even in developed countries, the use of genetic testing for hearing loss is variable across centers due to cost and access issues. In developing countries like Mexico, genetic testing for children with SNHL is rarely performed. This has important implications not only for direct clinical care for children with SNHL but is also reflected in the disparities in diagnostic rates for children who are Hispanic or Latino. Further research to understand the genetics of hearing loss in Hispanic and Latino children is therefore critical.

Within published literature addressing hearing loss in Hispanic and Latino American countries, there is an uneven distribution of geographic representation; over 50% of subjects are either from Brazil or Argentina[5,13] with limited representation of North, Central, or other South American Countries. Individuals from Mexico, in particular, where there is an estimated prevalence of prelingual SNHL of 2.2 per 1000 infants, are underrepresented in hearing loss genetics research.[7] Likely due to the use of single-gene testing, there is an overall genetic diagnostic yield of 10.9% for SNHL in Mexico compared to the 50%–60% diagnostic yield for individuals in the United States.[6] Whereas some founder mutations in *GJB2* have been identified in the Mexican SNHL population, including c.365A>T, p.(Lys122Ile), there is a notable lack of knowledge regarding a wider genetic etiological spectrum of SNHL in Mexico.[14,15]

Most of the multidisciplinary cochlear implant centers in Mexico and Latin America are formed by otorhinolaryngologists, audiologists and speech therapists, and occasionally include a geneticist in the initial evaluation. Typically, genetic evaluation only occurs for patients with evident syndromic features, so nonsyndromic mimics are only diagnosed later in life once they present other symptoms, and true nonsyndromic hearing loss may never be evaluated for a genetic etiology. Mexico has a fragmented health system, so it is common for patients with CI to get follow-up care in a smaller institution that does not have a clinical genetics program. In addition, the lack of a national database or united health care system may contribute negatively to accessing genetic diagnosis. A multidisciplinary team-based approach to the evaluation of children with SNHL used in this study may assist with guiding clinicians toward genetic evaluation, which clearly has major clinical implications for the care of children with SNHL.

Prior studies of genetic hearing loss in Mexican children with SNHL have been small and focused on single-gene testing. The diagnostic strategy recommended in some CI centers in Mexico is to screen *GJB2*, *SLC26A4*, and *CHD23* genes; additional genetic analyses are explored only if initial screening is nondiagnostic.[16] There remains a lack of access to genetic testing even when the patient has a clearly syndromic clinical presentation and when genetic diagnosis may directly inform care. These patients may have tested through a private lab for a fee or through a research study.

Mexican children with SNHL are usually diagnosed and implanted at CI centers in the main cities of the country. However, after initial implantation and habilitation, many families transfer their health and audiologic care to smaller clinics near their homes due to geographical boundaries and economic burden. If diagnostic assessment for the etiology of hearing loss does not occur pre- or perioperatively at a central medical center, the subsequent change of location is likely to interrupt the diagnostic process due to a lack of resources, such as Medical Genetics services, at these smaller centers. Early and comprehensive genetic testing for hereditary hearing loss is needed to ensure proper access to tailored management.

Prior studies have shown a reduced diagnostic yield for children with hearing loss who are Hispanic or Latino, with an increased number of inconclusive cases compared to other groups. This study did not replicate that finding, with a diagnostic yield (48%) that is very close to prior large studies in the U.S.[2] We did replicate the finding that *GJB2 is* the most common cause of genetic hearing loss in Mexico but did not identify patients with the previously identified founder mutation (c.365A>T, p.(Lys122Ile)).[14] We also identified several novel variants that have not been described in the published literature in relation to SNHL or cataloged in ClinVar and gnomAD databases, underscoring the potential value of comprehensive genetic testing for groups underrepresented in genetic research.

It is unclear why we identified so many children with syndromic hearing loss in this cohort. One hypothesis is that these parents were more likely to seek medical attention for their children; however, the majority of these diagnoses were children who did not yet display

other clinical features aside from hearing loss. Syndromic hearing loss is more commonly identified in children with severe to profound hearing loss, but the rate identified here is still high. Further research in larger cohorts will be needed to replicate this finding.

There were some limitations to this study, including selection bias. The probands included in this study were recruited from a single site in Mexico City. Though cochlear implantation through the Escuchar Sin Fronteras program is offered at no cost to families in need, submission of an application through an online portal is necessary to participate. The resulting cohort is not representative of the whole country, as parents who apply to this program need to have access to the internet, which is less commonly available in rural areas of Mexico. We believe this to be a major contributing factor to why we do not have indigenous children in our cohort. A major limiting factor to this study is that genetic testing for parents could not be performed. In addition, although this group represents the largest cohort of its kind, it is still relatively small and limited in this way.

5 | CONCLUSION

In conclusion, we performed a relatively large study of children in Mexico with hearing loss using comprehensive genetic testing. We identified a high rate of syndromic hearing loss. This study raises several important questions and supports the need for further comprehensive genetic testing for hearing loss in Hispanic and Latino populations.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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