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ORIGINAL

Characterisation of exon two of the GJB2 gene in Cubans with autosomal recessive prelingual isolated hearing loss

Caracterización del exón dos del gen GJB2 en cubanos con hipoacusia aislada prelingual autosómica recesiva

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ABSTRACT

Introduction: Hearing loss is the most common neurological disorder in humans. In its prelingual form, it occurs in one in every 1 000 live births. The most common type is isolated autosomal recessive hearing loss, caused mainly by pathogenic variants of the GJB2 gene. The most common of these in all populations is c.35delG, located in exon two, which encodes this gene. This mutation has been identified in heterozygosity in Cubans with hearing loss. Given its high allelic heterogeneity, Sanger sequencing is recommended to confirm the molecular diagnosis.
Objective: to characterise exon 2 of the GJB2 gene in a series of Cuban patients with autosomal recessive prelingual isolated hearing loss.
Method: a descriptive, cross-sectional study was conducted. From 379 cases in which molecular study was performed by allele-specific PCR of the pathogenic variant c.35delG, 13 heterozygotes were selected in which deletions D13S1830 and D13S1854 of the GJB6 gene had previously been ruled out. Sanger sequencing of exon 2 was performed, for which four specific oligonucleotides were designed to amplify two overlapping fragments to ensure complete analysis of the coding region of the GJB2 gene. Given the characteristics of the c.35delG mutation, two additional primers were included to analyse the start of exon 2. Information on the identified variants was sought on the ClinVar website. The audiometric characteristics of the patients were observed. Throughout the research, the principles of human research ethics were followed.
Results: the c.427C>T variant was identified in three individuals, while the c.94C>T mutation was found in another, and c.139G>T in a fifth. The patients presented sensorineural hearing loss with severity levels exceeding 61 dB.
Conclusion: Three pathogenic variants were identified in the coding region of the GJB2 gene, associated with severe to profound hearing loss.

Keywords: Connexin 26; Non-Syndromic; Deafness; Autosomal Recessive; Gab B 2 Binding Protein.

RESUMEN

Introducción: la hipoacusia constituye la disfunción neurológica más frecuente en el humano, en su forma prelingual aparece en uno de cada 1000 nacidos vivos; las que se presentan en mayor proporción son las aisladas autosómicas recesivas, causadas fundamentalmente por variantes patogénicas del gen GJB2; de ellas

la más común en todas las poblaciones es la c.35delG, que se localiza en el exón dos, el codificante de este gen. En cubanos hipoacúsicos se ha identificado esta mutación en heterocigosis; para concluir su diagnóstico molecular -dada su gran heterogeneidad alélica- se recomienda aplicar la secuenciación mediante el método Sanger.
Objetivo: caracterizar el exón 2 del gen GJB2 en una serie de pacientes cubanos con hipoacusia aislada prelingual autosómica recesiva.
Método: se realizó un estudio descriptivo, de corte transversal. A partir de 379 casos en que se practicó el estudio molecular por PCR alelo específico de la variante patogénica c.35delG; se seleccionaron 13 heterocigóticos, en los que previamente se habían descartado las deleciones D13S1830 y D13S1854 del gen GJB6. Se practicó la secuenciación por método de Sanger del exón 2, para la que fueron diseñados cuatro oligonucleótidos específicos a fin de amplificar dos fragmentos solapantes para asegurar el análisis completo de la región codificante del gen GJB2. Dadas las características de la mutación c.35delG, se incluyeron dos cebadores adicionales para analizar el inicio del exón 2. Se buscó la información de las variantes identificadas en la página web "ClinVar". Fueron observadas las características audiométricas de los pacientes. A lo largo de la investigación se cumplieron los principios de la ética de la investigación en humanos.
Resultados: se identificó en tres individuos la variante c.427C>T; mientras se halló en otro la mutación c.94C>T, y en un quinto la c.139G>T. Los pacientes presentaron pérdida auditiva neurosensorial con niveles de severidad que superaron los 61 dB.
Conclusión: se identificaron tres variantes patogénicas en la región codificante del gen GJB2, asociada a pérdidas auditivas de severa a profunda.

Palabras clave: Conexina 26; No Sindrómica; Sordera; Autosómica Recesiva; Proteína de Unión Gab B 2.

INTRODUCTION

Deafness is the loss, to any degree, of the ability to perceive and discriminate sounds. In its prelingual form, it occurs in all populations with a frequency of approximately 1 in 500 newborns. It affects speech development —the usual form of communication among humans —leading to learning disorders, interpersonal relationship problems, and community identity issues.[1,2]

It is estimated that 80 % are genetic in origin, with wide heterogeneity, including isolated or undifferentiated forms—also called non-syndromic —and diseases in which hearing loss is one of the recognizable clinical signs, usually referred to as syndromic. Isolated forms appear in greater proportion and are distinguished according to the mode of inheritance into autosomal (either dominant or recessive), X-linked, maternally transmitted, or mitochondrial. In contrast, syndromic forms are classified according to the clinical manifestations that accompany hearing loss. The most common form of genetic deafness is autosomal recessive nonsyndromic (ARNS), which occurs before language acquisition and involves profound, stable hearing loss.[1,3,4]

Scientific developments in recent years have made new molecular study methods available for clinical practice, enabling the molecular basis of many hereditary forms of deafness to be identified. This has broadened our knowledge of genes linked to hearing and demonstrated that the most frequent causal pathogenic variants lie in the GJB2 gene (Gap junction protein B2), located on the long arm of chromosome 13 (locus: 13q11-12), which encodes connexin 26 (Cx26).[5,6]

The phenotype that appears most frequently, associated with mutations in the GJB2 gene, is NSAR deafness, known as DFNB1A (the first three letters of the acronym for deafness, B for recessive, and 1A for its type).[7] More than 53 pathogenic variants causing this type of deafness have been described, most of them located in exon two, which is the coding exon.[4]

The mutation causing DFNB1A-type NSAR deafness that has been observed most frequently in all populations is c.35delG;[8,9] Therefore, the first recommended procedure, as part of the diagnostic process, both in cases of sporadic occurrence (which is a form of recessive inheritance) and when there is evidence of autosomal recessive transmission, is the application of direct molecular testing, using polymerase chain reaction (PCR), to identify this pathogenic variant.[10,11]

This technique has been available through the Cuban National Medical Genetics Network since 2001. When applied to individuals who clinically present with NSAR deafness, it has been shown that the pathogenic variant c.35delG is found in a high proportion of these cases studied.[12] In those found to be homozygous, the molecular diagnosis was confirmed; however, in one group, this pathogenic variant was found in heterozygosity, in the absence of the D13S1830 and D13S1854 deletions of the GJB6 gene, which, in digenic form, can be observed in NSAR deafness, together with pathogenic variants of the GJB2 gene.[7,13,14]

Concluding an accurate diagnosis of these patients is essential for their clinical management, including informing them of their risk of transmitting hearing loss and, once duly informed, allowing them to make the

decisions they deem appropriate, supported by preventive strategies based on genetic counseling.

To this end, other procedures must be applied. As there are several variants of the GJB2 gene, most of which are found in exon 2, the coding exon,[15] it is essential to study them. The objective of this study was to characterize exon 2 of the GJB2 gene in a series of Cuban patients with autosomal recessive prelingual isolated hearing loss.

METHOD

A descriptive cross-sectional study was conducted between 2001 and 2024, based on 379 patients with congenital non-syndromic deafness. The clinical information was collected by the same group of professionals trained in the care of patients with hearing loss. Cases were selected that showed evidence of autosomal recessive inheritance or appeared in isolation in their families. The degree of hearing loss was assessed based on its magnitude, frequency, laterality, and the patients' origin.

Heterozygotes for the pathogenic variant c.35delG of the GJB2 gene were selected, which did not present any of the deletions: D13S1830 and D13S1854 of the GJB6 gene, and their DNA retained the quality specifications required for sequencing by the Sanger method. Finally, the sample consisted of 13 cases.

Oligonucleotides

To perform a complete analysis of the coding region of the GJB2 gene, the following primers were used, with the indicated hybridization temperatures:

Table 1. Primers used with their annealing temperatures for complete analysis of the coding region of the GJB2 gene

	5' sequence --> 3'	Hybridization temperature
Reverse	AGT TGG TTC TGT CTT CAC CTG	55ºC
Forward	TGG TGT TTG CTC AGG AAG AG	60ºC
Direct	TCA TCC CTC TCA TGC TGT CT	
Direct	TGA GCC TTG ACA GCT GAG CA	

The following primers were used to analyze the start of exon 2:

Table 2. Primers used with their annealing temperatures to analyze the start of exon 2

	5' to 3' sequence	Hybridization temperature
Reverse	CTA CCG GAG ACA TGA GAA GA	56ºC
Forward	TCT TCT CAT GTC TCC GGT AG	

PCR and sequencing

In a first step, all PCRs were standardized by applying a hybridization temperature gradient to ensure the correct amplification of the desired fragments. Once the specific hybridization temperatures for each primer pair were determined, the PCRs were performed. The PCR products were visualized by electrophoresis to evaluate the result. The PCR fragments were then purified and sequenced using one of the two PCR primers by the Sanger method.

Information processing and analysis methods

In silico analysis

To determine the characteristics of each of the identified variants, the corresponding information was searched for in the "CinVar" database.[16]

All the information generated was analyzed using descriptive statistical techniques, based on the relative frequencies found.

Ethical aspects

This research was carried out with the authorization of the Research Ethics Committee of the National Genetics Center. Throughout the study, care was taken to comply with the provisions of the World Medical Association's Declaration of Helsinki 2023, which establishes the ethical principles for medical research involving human subjects.[17]

RESULTS

The study was conducted on 13 individuals with non-syndromic deafness, all with sporadic onset in their families and no history of consanguinity. They were found to be heterozygous for the pathogenic variant c.35delG.

Mutations in exon two of the GJB2 gene were identified in five of the 13 individuals. The sequences found are illustrated in Figure 1. In three of them, c.427C>T, p.Arg143Trp, while in the remaining two, c.94C>T, p.Arg32Cys and c.139G>T, p.Glu47Ter.

In all the cases studied, audiometry results corresponded to bilateral prelingual profound sensorineural hearing loss, with hearing loss greater than 61 dB.

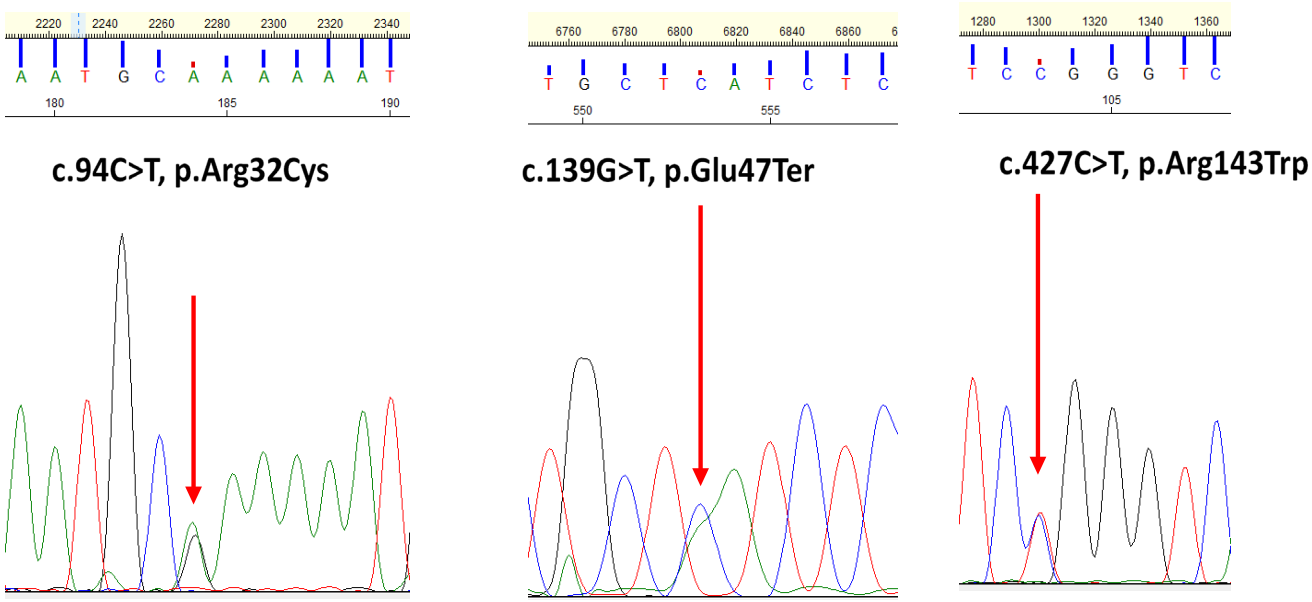

Figure 1. Sequencing of exon two of the GJB2 gene in cases where, in addition to the pathogenic variant c.35delG, the following mutations were identified: c.94C>T, c.139G>T, and c.427C>T.

DISCUSSION

Cx26—encoded by the GJB2 gene—is expressed in the cytoplasmic membranes of the hair cells of the cochlea, associated in hexamers, which constitute the connexons; two of which, originating from adjacent cells, join through their extracellular regions to form a functional channel through which potassium recycling occurs, necessary to maintain the high endolymphatic concentration of this ion, required to preserve the function of the inner ear.[15,18,19]

Pathogenic variants in the GJB2 gene, which encodes CX26, are the most common cause of NSAR deafness. Its diagnosis is complicated by the fact that a group of those with GJB2 mutations has been found to carry only one mutant allele and, in addition, to have deletions of the GJB6 gene (which encodes connexin-30), specifically D13S1830 and D13S1854. (double heterozygosity) in the form of prelingual deafness with digenic inheritance due to mutations involving the GJB2 and GJB6 genes.[7,14,20]

Therefore, in selecting the sample for this research, it was essential to start with individuals who, in the absence of GJB6 gene deletions, carried the pathogenic variant c. 35delG of the GJB2 gene in heterozygosity. Additionally, expert DNA analysis ensured that the samples were in optimal condition and therefore met the quality specifications required for sequencing.

The primers were designed to characterize exon 2 of the GJB2 gene. Although two overlapping fragments were amplified to ensure complete analysis of the sequence under study, given the characteristics of the c.35delG mutation, additional primers were designed to analyze the exon two start. The latter served as verification that all patients in the series studied were heterozygous for the pathogenic variant c.35delG.[16]

Exon 2 sequencing, which encodes the GJB2 gene, confirmed heterozygosity in 13 cases. Three genetic changes affecting the nucleotide sequence of connexin 26 (c.94C>T, c.139G>T, and c.427C>T) were identified. By consulting the ClinVar database, which collects all mutations described in the context of genetic diseases to date, these were identified as pathogenic variants.[21]

The point mutation c.94C>T leads to a change at position 32 of CX26 from a positively charged amino acid (arginine) to cysteine, which contains a thiol group (p.Arg32Cys). This affects the structure and function of this protein.[22,23,24,25,26,27,28,29,30]

In the c.139G>T variant, guanine (G) is replaced by thymine (T) at nucleotide 139 of the GJB2 gene; this

introduces a premature stop codon in the GJB2 gene sequence and, therefore, the production of a truncated, non-functional Cx26 (p.Glu47Ter, referred to in some texts as E47X), which causes the production of a truncated, non-functional protein, which interrupts the synthesis of CX26 and therefore the formation of gap junctions and affects hearing.[31,32,33,34,35]

The change at position 427 from cytosine (C) to thymine (T) (c.427C>T) produces a change from arginine to tryptophan at position 143 of CX26 (p.Arg143Trp), has been described in other regions of Latin America and Europe;[36,37,38] among the variants found in this study, it was the one that appeared most frequently (3/5).

The last two variants (c.139G>T, c.427C>T) were previously described in another series of reported Cuban cases, while c. 94C>T is described for the first time in a sample from this country. Similarly, other mutations not found in this study were found in the study mentioned earlier.[39] Those described, in addition to c.35delG, vary in frequency with respect to the findings in this study. This reflects the high allelic genetic heterogeneity of the GJB2 gene.

The three variants identified in this study are recognized as pathogenic in the databases consulted [16,17,18,19] and have been reported to cause sensorineural hearing loss ranging from mild to profound. The patients included presented with bilateral prelingual profound sensorineural deafness with hearing loss ranging from severe to profound. However, cases with these variables and mild hearing loss have been described; this may reflect the fact that the instances originated at the National Center for Medical Genetics of Cuba, a national reference institution.

The results obtained confirmed the diagnosis of the patients studied. Based on this, a cascade screening program can be designed for their families, using allele-specific PCR molecular studies to identify carriers. This is important for developing preventive strategies based on genetic counseling. Additionally, these findings suggest that pathogenic variants can be found in the Cuban population and should be considered in the country's diagnostic algorithm.

CONCLUSION

Three pathogenic variants were identified in the coding region of the GJB2 gene, associated with severe to profound hearing loss.

Limitations of this research

Only cases with evidence of the presence of the pathogenic variant c35delG in heterozygosity of the GJB2 gene were studied; an extension of this study may provide new results.

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