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ORIGINAL ARTICLE

Exome sequencing analysis reveals homozygous GJB2 gene mutation in a Mexican family with profound hearing loss

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KEYWORDS
GJB2 gene;
Hypoacusia;
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Connexins;
Homozygous

Abstract
Background: Sensorineural hearing loss (SNHL) is a clinically and genetically heterogeneous disease. In some populations, c.365delG mutation in the *GJB2* gene represents the most frequent cause of hereditary SNHL. The great diversity of mutations in the *GJB2* gene worldwide highlights the participation of ethnic background in SNHL.
Objective: To describe the presence of homozygous c.del35G mutation in the *GJB2* gene in a Mexican family with SNHL.
Materials and methods: A Mexican family with SNHL was included in the study. Analysis of the *GJB2* gene was performed through whole exome sequencing (WES) and DNA direct sequencing analysis in all members of the family and in 100 normal controls
Results: Affected sibs showed the homozygous c.del35G mutation in the *GJB2* gene. Parents of the families were heterozygous for the molecular defect and had normal audition.
Conclusion: We describe a homozygous c.del35G mutation in the *GJB2* gene through WES analysis, a homozygous mutation with a very low occurrence in Mexican population.

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PALABRAS CLAVE
Gene *GJB2*;
Hipoacusia;
Mutaciones génicas;
Conexinas;
Homocigoto

El análisis de secuenciacion del exoma identifica una mutación homocigota en el gen *GJB2* en una familia mexicana con pérdida auditiva profunda

Resumen
Antecedentes: La pérdida auditiva neurosensorial (HNS) es una enfermedad clínica y genéticamente heterogénea. En algunas poblaciones, la mutación c.365delG en el gen *GJB2* representa la causa más frecuente de la HNS hereditaria. La gran diversidad de mutaciones presentes en el gen *GJB2* en todo el mundo pone de relieve la participación del genotipo étnico en HNS.
Objetivo: Describir la presencia de la mutación homocigota c.del35G en el gen *GJB2* en una familia mexicana con HNS.
Materiales y métodos: Una familia mexicana con HNS se incluyó en el estudio. EL análisis del gen *GJB2* se realizó a través de la secuenciación del exoma (WES) y el análisis de la secuenciación directa del DNA en todos los miembros de la familia y en 100 controles normales Resultados Los hermanos afectados presentaron la mutación c.del35G homocigótica en el gen *GJB2*. Los padres de los pacientes fueron heterocigotos para el defecto molecular con una audición normal.
Conclusión: Se describe la mutación homocigota c.del35G en el gen *GJB2* a través del análisis de WES, una mutación homocigota observada en una muy baja incidencia en la población mexicana.

Introduction

Non-syndromic sensorineural hearing loss (SNHL), a genetically heterogeneous affection, is a common hereditary disease that presents an occurrence of 1 in 1000 newborns. In relation to the onset, SNHL can be congenital, prelingual or postlingual. All types of inherited patterns have been observed in SNHL (autosomal dominant, autosomal recessive, mitochondrial and X-linked) being the autosomal recessive form the most frequently observed.[1] The syndromic form of sensorineural hearing loss is defined when other systemic manifestations are present; many syndromes with the presence of hearing loss are described in the OMIM (Online Mendelian Inheritance in Man). In some cases, differential diagnosis between syndromic and non-syndromic hearing loss is not easy to perform even with molecular studies because both types of hearing loss can be due to affections of the same gene.

It is considered that 200–250 genes are involved in SNHL.[2] Recently, more than 80 genes, around 1000 mutations, and 140 loci have been associated with SNHL (http://hereditaryhearingloss.org/).

Mutations in the *GJB2* gene are a frequent etiology of hereditary SNHL, they represent about 50% of such cases in several populations.[3–5] Patients that carrier homozygous mutations in the *GJB2* gene harbor a wide spectrum of hearing loss that ranges from moderate to profound NSHL; this data supports the influence of epigenetic and environmental factors in the phenotypic manifestations.[6] Previous studies show a rare presence of homozygous mutations in the *GJB2* gene in Mexican population.[7,8]

The *GJB2* gene encodes the gap junction beta-2 protein connexin 26; six connexin molecules form connexons between adjacent cells, responsible for the exchange of ions and molecules among contiguous cells.[9] Connexins are present in connective and epithelial tissues of the cochlea, which primordial function is to maintain the normal audition.[10]

Improvement of the technology plays an important role in the diagnosis of different pathologies, whole exome sequencing (WES) represents an important tool in the identification of the genetic etiology in individuals with SNHL. In the present study we describe a family with SNHL and homozygous mutation in the *GJB2* gene detected by WES.

Patient and methods

The proband was a 21-years-old man with profound congenital deafness in both ears. He was the first product of healthy and non-consanguineous parents. He has a 19-years-old sister with congenital deafness in both ears, as well (Figure 1). Family history was negative for intellectual disability or congenital malformations. No history of prenatal exposure to teratogens, maternal illness or use of aminoglycoside antibiotics was recorded. His mother had an

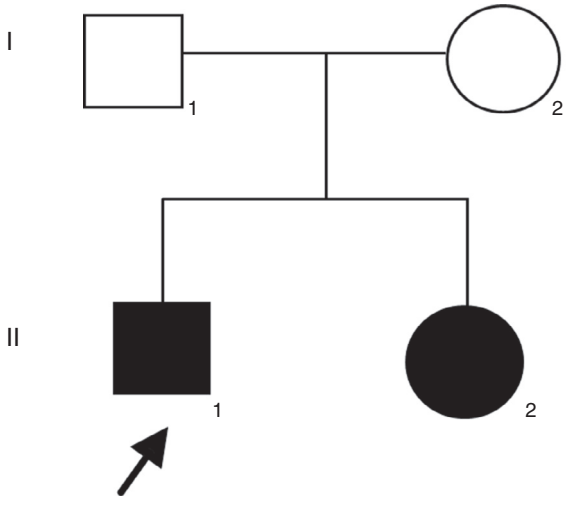

Figure 1 Pedigree of the family.