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Two novel compound heterozygous families with a trimutation in the *GJB2* gene causing sensorineural hearing loss

M. Martínez-Saucedo [a,1], M.R. Rivera-Vega [a,1], L. Gonzalez-Huerta [a], H. Urueta-Cuellar [a], J. Toral-López [b], P. Berruecos-Villalobos [c,2], S. Cuevas-Covarrubias [a,*]

[a] Servicio de Genética, Facultad de Medicina, Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Edo. México, Mexico
[b] Departamento de Genética Médica, Centro Médico Ecatepec, ISSEMYM, Edo. México, Mexico
[c] Servicio de Audiología, Hospital General de México, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico

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ABSTRACT

Background: Sensorineural hearing loss (SNHL) is a genetically heterogeneous disease. *GJB2* gene mutations seem to be the most frequent cause of hereditary hearing impairment in several populations. There is variability in the mutations in the *GJB2* gene worldwide; this remarks the influence of ethnic background in SNHL.
Objective: To describe the presence of two trimutations in the *GJB2* gene in two Mexican families with hereditary SNHL.
Materials and methods: Two unrelated Mexican families with prelingual SNHL were included in the study. Analysis of the *GJB2* gene through PCR and DNA direct sequencing analysis was performed in all members of the families and in 100 normal controls.
Results: Affected member of the family 1 showed the trimutation p.S19R/p.R32S/p.E47*, whereas affected members of the family 2 showed the trimutation p.F31I/p.W44*/p.V84M. Parents of both families were heterozygous with normal audition.
Conclusion: We found a novel mutation in the *GJB2* gene and two trimutations with SNHL not previously reported. This remarks the complexity in the pattern of mutations in the *GJB2* gene in SNHL and enriches the spectrum of the type of molecular defects in the *GJB2* gene.

1. Introduction

Sensorineural hearing loss (SNHL) is a common hereditary sensory disorder with a prevalence of 1 in 1000 newborns. More than half of congenital SNHL cases have a genetic component with all types of inheritance, predominantly the autosomal recessive (http://hereditaryhearingloss.org/main.aspx?c). SNHL represents a genetically heterogeneous disorder that is present worldwide. In some cases, a more complex pattern of inheritance is observed that includes digenic inheritance, gene-environment interactions, and the presence of modifier genes [1–4]. Non-syndromic deafness represents 60–70% of all inherited hearing impairments; a great diversity of mutations in several loci have been associated with recessive SNHL (http://hereditaryhearingloss.org/main.aspx?c). *GJB2* gene (MIM 121011) mutations represent a significant cause of SNHL; they are responsible for as much as 50% of such cases in several populations [5–8]. GJB2 gene encodes the gap junction subunit – connexin 26 (Cx26), that forms a molecular complex located in the cell membranes of neighboring cells called gap junction. The gap junctions allow the exchange of metabolites and potassium that are essential for maintaining the electrical potential in the cochlea [9]. Gap junctions made of connexin 26 are localized in the epithelial and connective tissues of the cochlea; their proper function is fundamental to adequate audition [10]. About 150 mutations, including polymorphisms, have been described in the *GJB2* gene (http://davinci.crg.es/deafness). Some *GJB2* mutations are present in particular frequencies depending on the population; the c.35delG mutation is frequent in Caucasians, and the c.235delC and c.167delT mutations seem to be the most

* Corresponding author at: Dr. Balmis 148 Col. Doctores, C.P. 06726 México, DF, Mexico.
E-mail addresses: sergiocuevasunam@gmail.com, sercuevas@yahoo.com (S. Cuevas-Covarrubias).
[1] These authors contribute equally to this work.
[2] Deceased.

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frequent causes of recessive hearing impairment in Asian and Jewish people, respectively [11–15]. This diversity in the type of mutations in the *GJB2* gene in various populations highlights the influence of ethnic background.

In the present study, we describe two novel compound heterozygotes with three mutations in the *GJB2* gene causing SNHL.

2. Materials and methods

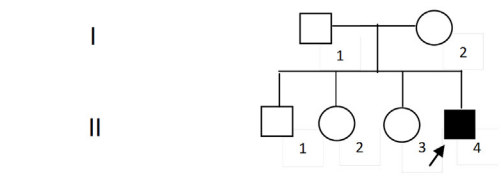
2.1. Patients

Patient 1 is a 40-year-old male with congenital sensorineural deafness in both ears. He is the only affected member of four siblings of healthy and non-consanguineous parents. 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 psychomotor development was normal. Medical examination revealed profound SNHL with no other clinical data or evidence of syndromic deafness. Radiological examination with CT and MRI scans of the skull showed normal structures. Thyroid parameters were normal. Informed consent was obtained from the patient prior to his participation in the study.

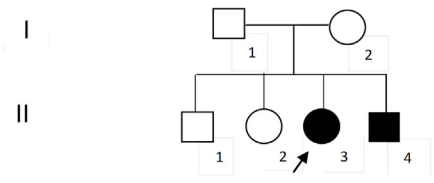
Patient 2 is a 24-year-old girl with profound congenital deafness in both ears. She is the third child of healthy and non-consanguineous parents. She has a 16-year-old sibling with congenital deafness in both ears. Family history was negative for intellectual disability or congenital malformations. No history of prenatal exposure to teratogens, maternal illness, or use of aminoglycoside antibiotics was recorded. Her mother had an uneventful pregnancy with a vaginal delivery at 38 weeks of gestation. Her psychomotor development was normal. Medical examination revealed profound SNHL with no evidence of syndromic deafness. Radiological examination with CT and MRI scans of the skull showed normal structures. Thyroid parameters were normal. Informed consent was obtained from the patient prior to her participation in the study.

3. Mutation analysis

Analysis of the *GJB2* gene was conducted as described previously [11,12]. The coding exon and flanking intronic regions of the *GJB2* gene were amplified by PCR. All of the PCR products were directly sequenced. DNA was analyzed on an ABI 3730XL automated sequencer (Applied Biosystems, Inc., Foster City, CA, USA). The *GJB2* gene was sequenced in both families and in 100 normal controls to detect common polymorphisms. DNA sequence variations were identified through comparison of subject DNA sequences to the *GJB2* reference sequence (Genbank accession numbers M86849, U43932, and/or XM_007169).



Pedigree of the family 1.



Pedigree of the family 2.

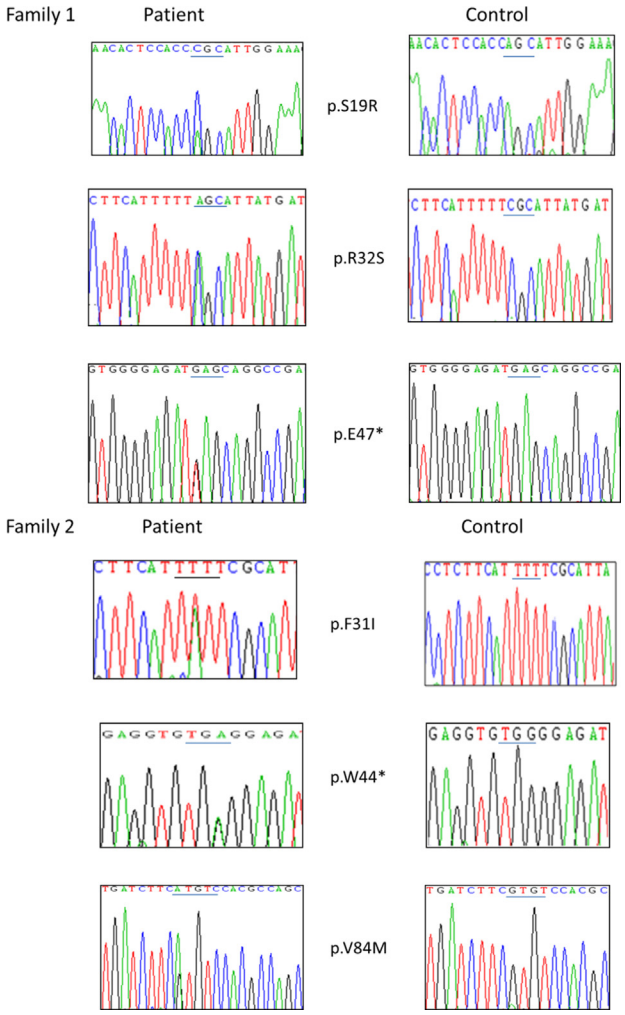


Fig. 1. Pedigrees of the families and their respective electropherograms.