Mutational analysis of *GJB2*, *GJB6* and 12S rRNA genes in Vietnamese non-syndromic deaf children

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ABSTRACT :

Background: Hearing loss (HL) is one of the most common disorders worldwide. Each year in Vietnam, 15,000-20,000 babies are born with congenital HL. Deafness is influenced by both genetic and environmental factors. Alterations in prominent deafness-related genes, *GJB2*, *GJB6* and mitochondrial (mt) DNA 12S rRNA are thought to be the major causes of HL.

Objective: In our study, mutational analysis of these genes was examined to determine the prevalence of gene mutations in Vietnamese non-syndromic deaf children.

Materials and methods: Molecular analysis of these genes was investigated by PCR amplification and direct DNA sequencing. In this study, seventy six congenital deaf children and seventy eight healthy individuals with the well-characterized clinical profiles were enrolled.

Result: There were four kinds of nucleotide changes in the *GJB2* gene, including a pathogenic 235delC mutation that was identified in only patients with HL. Three known benign variants in the *GJB2* gene were found. No mutations in *GJB6* were observed. In the 12S rRNA gene, there were seven nucleotide alterations, with the m.1438A>G variant being detected in 100% of the subjects in both patient and healthy control groups.

Conclusion: Our study shows that the pathogenic 235delC mutation in GJB2 can be considered as a good candidate for further study on its functional analysis to address whether it contributes to the pathogenesis of HL in the Vietnamese population.

Keywords: Hearing loss, *GJB2*, *GJB6*, 12S rRNA, Vietnam.

INTRODUCTION:

Congenital deafness is one of the most common disorders worldwide with a prevalence of one in every 300-1000 newborns (1). In Vietnam, 15,000-20,000 babies are born with congenital hearing loss (HL) each year [unpublished data]. Gene alterations including autosomal dominant, autosomal recessive, X-linked or mitochondrial mode of inheritance contribute about 50% of children with HL (2), and 70% of which are non-syndromic HL since HL is the only symptom and no clinical signals are found. The other half is caused by non-genetic factors (3) including ototoxic drugs specifically aminoglycosides, which increase the phenotypic expression of the mutations. Alterations in *GJB2*, *GJB6* and mitochondria DNA 12S rRNA genes are thought to be the major causes of HL (4,5,6).

The *GJB2* and *GJB6* genes encoding the gap junction proteins, connexin (Cx)26 and Cx30 respectively, are located on chromosome 13q11-q12. Cx26 and Cx30 are colocalized in gap junction plaques in the cochlea, form intercellular communication channels facilitating the circulation of potassium ions and small molecules between the cytoplasm of cochlear non-sensory epithelial cells (7). Cx26 and Cx30 share 77% identity in amino acid sequence (8) and have an important role in the cochlear physiology of hearing as ablation of the Cx26 or Cx30 proteins in cochlea leads to deafness in humans (5). Mutations in the *GJB2* and *GJB6* genes have been reported to be linked predominantly to HL. Concerning *GJB2*, a total of about 100 mutated variations causing HL have been detected varying

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from mild to profound in hearing impaired individuals (6). The predominance of each mutation varies between different ethnicities or countries. Up to 85% of Caucasians carry a 35delG mutation (8), while the 235delC mutation was found to be the common pathogenic mutation among Asians including Chinese (9), Korean (10) and Japanese (11) populations with the carrier rates of 20,3%, 6,9% and 49,8%, respectively. A c.167delT mutation was present in 4,03% of Ashkenazi Jewish(12) and 2% of Argentianian (13) populations. Many amino acid substitutions in the *GJB6* gene have been identified to be responsible for HL. A 309-kb large deletion in *GJB6*, called del (*GJB6*-D13S1830), is the second most common mutation after the *GJB2* mutations. The frequencies of this deletion detected in Western populations such as Spain, France, the United Kingdom and Brazil were 25,5%, 5%, 22,2% and 6,3%, respectively (14,15). Conversely, no mutation in the *GJB6* was detected in Austrian, Chinese, Iranian and Italian populations (16,17,18).

Mutations in the mitochondrial genes including the mitochondrial (mt) DNA 12S rRNA play an important role in causing maternally inherited syndromic and aminoglycoside-induced HL (19). The most common mutation in the 12S rRNA gene is a homoplasmic m.1555A>G mutation that was detected in European children (19), Chinese (20) and Korean (21) populations at frequencies of 0,19%, 1,48% and 0,9%, respectively. The m.1555A>G mutation is located at A-site, the target for aminoglycoside antibiotics (22). Therefore, this mutation is believed to be related to aminoglycoside induced-HL (19).

In our study, mutational analysis of the deafness-related genes, *GJB2*, *GJB6* and 12S rRNA was investigated in 76 patients with congenital HL and 78 healthy individuals. All subjects were examined to determine the prevalence of these gene mutations in Vietnamese populations.

MATERIALS AND METHODS

Study subjects

The study subjects were a total of 76 non-syndromic congenital deaf children who were enrolled at Nhan Chinh School for the Deaf and the Dumb, Hanoi, Vietnam. As a control group, 78 healthy Vietnamese blood donors were analyzed. The parents or guardians of the subjects signed written informed consent forms prior to their participation in the study. The subjects were all from the Kinh ethnic background, in the age range of 2 to 15 years old and clinical data were recorded about their mother's heath during pregnancy. A detailed history of disease and use of aminoglycoside antibiotics were obtained from all subjects in patient and control groups to exclude other causes of HL. The study was approved by the Scientific Committee of Institute of Genome Research under reference number 02/QD-NCHG.

DNA sequencing

Genomic DNA was isolated from peripheral blood samples using a DNeasy blood and tissue kit (Qiagen, Hilden, Germany). To determine mutations of the

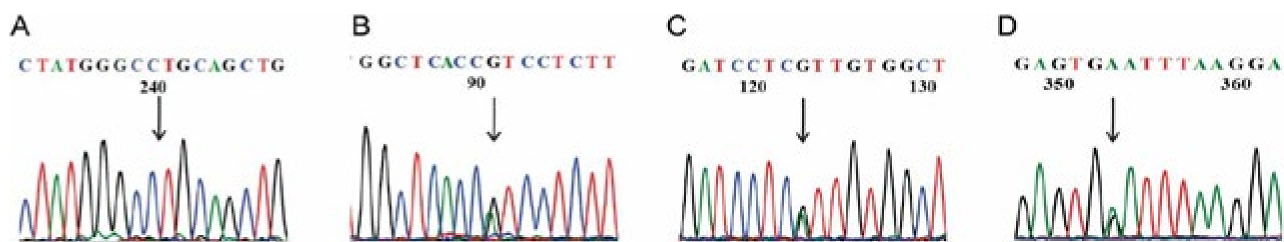

Figure 1: Partial sequence chromatograms of the GJB2 from the patients. Arrows indicate the location of the base changes. A: C deletion at position 235. B: G to A transition at position 79. C: G to A transition at position 109. D: A to G transition at position 341.

Nucleotide change	Protein change	Type of mutation	Number (%) of mutated alleles	
			Patient	Control
235delC		Frameshift	3/76 (3,95%)	0/78(0%)
79G>A	V27I	Polymorphism	4/76 (5,26%)	3/78(3,85%)
109G>A	V37I	Polymorphism	13/76 (17,1%)	8/78(10,26%)
341A>G	E114G	Polymorphism	5/76 (6,6%)	1/78(1,28%)
79G>A and 341A>G	V27I and E114G	Undefined	5/76 (6,6%)	7/78(8,97%)
79G>A,109G>A and 341A>G	V27I, V37I and E114G	Undefined	1/76 (1,32%)	1/78(1,28%)

Table 1: Frequencies of the *GJB2* mutations in patients with hearing loss and controls. No significant differences between patient and control groups (P>0.1, Fisher's exact test)

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GJB2, *GJB6* and mitochondrial 12S rRNA genes, polymerase chain reaction (The Veriti® Thermal Cycler, Applied Biosystems, USA) and DNA sequencing (ABI Prism@ 3100 and/or 3500 Genetic Analyzers, Thermo Scientific, USA) were performed as previously described (23). DNA sequence variations were identified by comparing subject DNA sequence to the *GJB2*, *GJB6* and 12S rRNA reference sequences: Genbank Accession Numbers NM_004004.5, NM_001110219.2 and NC_001807.3, respectively.

The coding region of the *GJB2* was amplified by using primers: *GJB2*-F: 5'-CGTCTTTTCCAGAGG-CAAACCG-3' and *GJB2*-R: 5'-GCTAGCGACT-GAGCCTTGAC-3' attaining a-802 base pair (bp) fragment. The *GJB6* was amplified by using primers: *GJB6*-F: 5'-CACCGTGTACATTTCCCAAG-3' and *GJB6*-R: 5'-CCAGAAGGCAATCCCAACCT-3'. The amplification product length was 933-bp. The 12S rRNA was amplified by using primers: 12S rRNA-F: 5'-CCCACAGTTTATGTAGCTTAC-3' and 12S rRNA-R: 5'-CAGAACACTACGAGCCACA-3'. The amplification product length was 1100-bp.

All obtained PCR fragments were purified with a GeneJET PCR purification kit (Thermo Scientific, USA). The PCR products were sequenced on both strands with the same primers used for the PCR.

Statistical analysis

Fisher's exact test was used for group association. The level of significance in all cases was set at $p < 0.05$.

RESULTS

Mutational analysis of the *GJB2* and the *GJB6* genes

Sequencing of the *GJB2* coding region identified four nucleotide changes in this gene (Table.1 and Fig.1). These were a 235delC pathogenic mutation (Fig.1A) and three known variants including p.V27I (c.79G>A), p.V37I (c.109G>A) and p.E114G (c.341A>G) identified (Fig.1B-D). The 235delC mutation was detected in three affected subjects, accounting for 3,95% of the patient group and none of the control group carried this mutation. In the present small study, the occurrence of the 235delC mutation was not significantly different between patient and control groups (P>0.1), but this mutation has been found at higher frequencies in several Asian populations such as Chinese (20,3%) (9), Korean (6,9%) (10) and Japanese (7%) (11) populations, indicating different genetic backgrounds among Asians.

The non-pathogenic variants in the *GJB2*, considered polymorphisms (p.V27I, p.V37I and p.E114G) have been described previously (24). As shown in Table 1,

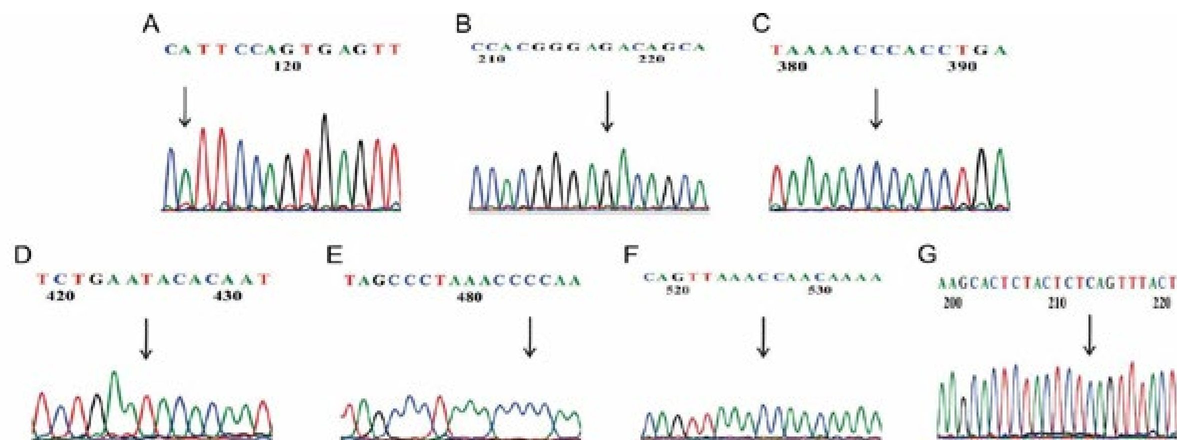

Figure 2: Partial sequence chromatograms of the mitochondrial 12S rRNA from the patients. Arrows indicate the location of the base changes. A: G to A transition at position 709. B: A to G transition at position 813. C: T to C transition at position 980. D: C to T transition at position 1048. E: T to C transition at position 1107. F: T to C transition at position 1119. G: A to G transition at position 1438.

Nucleotide change	Type of mutation	Number (%) of mutated alleles	
		Patient	Control
709G>A	Undefined	16/76 (21%)	10/78(12,82%)
1119T>C	Polymorphism	3/76 (3,95%)	10/78(12,82%)
1438A>G	Polymorphism	76/76(100%)	78/78 (100%)
1541T>C	Polymorphism	1/76 (1,32%)	0/78 (0%)
709G>A and 980T>C	Undefined	1/76 (1,32%)	1/78(1,28%)
1048C>T and 1107T>C	Undefined	1/76 (1,32%)	0/78(0%)
709G>A, 813A>G and 1119T>C	Undefined	1/76 (1,32%)	1/78(1,28%)

Table 2: Frequencies of the mtDNA 12S rRNA variants in patients with hearing loss and controls. No significant difference between patient and control groups (P>0.07, Fisher's exact test)

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the p.V27I, p.V37I and p.E114G variants were identified in all patient and healthy control groups with the carrier frequencies ranging from 1,28% to 17,1%. The frequencies of the p.V27I, p.V37I and p.E114G variants all found in French population were less than 2% (25). We additionally found both a two nucleotide change containing p.V27I and p.E114G and a variant with a three nucleotide change containing p.V27I, p.V37I and p.E114G which were carried by both patient and healthy control groups. The variant with a two nucleotide change has been reported to occur at a frequency of 0,78% in an Iranian population (26).

The *GJB6* gene has been shown to cause deafness mainly through the large deletion called del(D13S1830). The frequencies of the deletion detected in Spain, France, the United Kingdom and Brazil were 25,5%, 5%, 22,2% and 6,3%, respectively (14,15). In our study, none of the patient or control group subjects carried mutations or deletions in the *GJB6* gene.

Mutational analysis of the mitochondrial 12S rRNA gene

In the current study, a total of seven nucleotide changes in the 12S rRNA gene were identified (Table 2). Of these nucleotide changes, a m.1438A>G variant (Fig. 2G) was present at a frequency of 100% in our population. This frequency was comparable to that reported in Chinese, Korean and Tunisian populations (27,21,20). In contrast, this variant was found in less than 2% of Iranian subjects (28).

The remainder were six known variants including m.709G>A, m.813A>G, m.980T>C, m.1048C>T, m.1107T>C nd m.1119T>C (Fig. 2A-G and Table. 2). The m.709G>A and m.1119T>C variants were identified in both patient and control groups with the carrier frequencies of (21% versus 12,82%) and (3,95% versus 12,82%), respectively. Similarly, the m.709G>A variant ocurred in both patient and control groups at frequencies of 21,1% and 19,7% in Korean, of 2,2% and 1,23% in Chinese and of 14,9% and 15% in Iranian populations, respectively (21,20,28). The m.1119T>C variant was found in both patients and control subjects in Korean and Iranian populations at a rate ranging from 1,4 to 4,4% (21,28), whereas 2,2% of affected subjects and none of a control group carried this variant in a Chinese population (20).

In addition, we observed a two nucleotide change containing m.709G>A and m.980T>C and also a variant with a three nucleotide change containing m.709G>A, m.813A>G and m.1119T>C which were identified in both patient and healthy control groups. In other studies, the m.980T>C variant detected in both patient and control groups in an Iranian population were 2,8% and 2%, respectively (28) and the m.813A>G variant was carried by 1% of hearing impaired subjects in a Tunisian population (27). We additionally found a variant with a two nucleotide change containing m.1048C>T and m.1107T>C which was carried by 1,32% of the patient group but not by the control group. Other studies indicated that the m.1048C>T variant found in the Tunisian population was present in 2% of control subjects (27) and also in 1,48% of Chinese (20) and 0,9% of Iranian (28) populations with HL. Therefore, different variants of this gene occur in different ethnic backgrounds.

DISCUSSION

The present study is the first report of the association between congenital deafness and mutations in the *GJB2*, *GJB6* and 12S rRNA genes in the Vietnamese Kinh population. In this study, we observed that the pathogenic 235delC mutation in *GJB2* occurred with a frequency of 3,95% in the affected subjects and mutation in *GJB6* were absent in all subjects in patient and control groups. Previous reports showed that the frequencies of the 235delC mutation were higher in several populations, such as Chinese (20,3%) (9), Korean (10) and Japanese (7%) (11) populations (Table.3). Therefore, the 235delC mutation needs further analysis to determine whether it is a predominant mutation causing HL in the Vietnamese population.

The *GJB2* mutations have been proposed as the ma-

	Patient's	Percent of pathogenic mutations			
Countries	number	GJB2 -235delC	GJB6 -D13S1830	mtDNA- 1555A>G	References
Vietnam	76	3,95%			This study
Japan	1343	7%			Tsukada K et al. [11]
Korean	22	6,9%			Lee KY et al. [10]
Korean	227			0,9%	Bae JW et al. [21]
Nanjing, China	135	27,41%		1,48%	Lu Y et al. [20]
Mexico	140		0,71%		Loeza-Becerra F *et al.* [30]
Argentina	476		3%		Dalamon V *et al.* [13]
France	256		5%		Marlin S *et al.* [15]

Table 3: Frequencies of *GJB2, GJB6* and mtDNA 12S rRNA mutations in different countries

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jor causes of congenital deafness. In this study we observed three nucleotide changes in the *GJB2* which were non-pathogenic polymorphisms. Among these, the p.V37I variant has been considered as both pathogenic and non-pathogenic and occurred with the high relative carrier frequency of 17,1% and 10,26% in the patient and control groups, respectively (Table. 1). The results were comparable to those reported in other investigations in Japanese (11) and Chinese (9) hearing impaired subjects. Whereas, the variant was detected at lower frequencies in a French population in less than 2% of patients with HL (25). A very common mutation in the *GJB2* gene causing HL, a 35delG mutation, was found in most hearing impaired individuals. In a Caucasian population, the 35delG accounted for up to 85% of all the *GJB2* mutations in deaf children (8). However, the patient group in our observation did not carry this mutation, which was similarly to previous studies in Korean and Japanese populations (10,11,24). Therefore, this observation suggested that there was a different geographic distribution of the *GJB2* mutations causing HL.

Concerning *GJB6*, the present study was in agreement with previous reports in Austrian, Chinese, Iranian and Italian populations (16,17,18) showing that no mutation in the *GJB6* was detected in the Vietnamese population, so indicating that the common cause of HL in our cohort was not due to alterations in the *GJB6* gene.

Mutations in the 12S rRNA gene has been indicated to be responsible for both non-syndromic and aminoglycoside-induced pediatric HL (29). In the current study, there were seven kinds of nucleotide changes in the 12S rRNA identified. Among the variants in the 12S rRNA gene found, the m.1438A>G variant was present in 100% of all subjects, indicating that this variant might be one of the most common polymorphisms in the Vietnamese population. In addition, the mutation m.1555A>G is thought to be the most common mitochondrial mutation associated with HL found in many populations such as European children (19), Chinese (20) and Korean (21) populations (Table.3). However, this mutations was not identified in our population as well as several populations including Mexican (30). In this study, no difference in seven nucleotide alterations in the 12S rRNA between patient and control groups was found, suggesting that these variants were not related to HL in Vietnamese population.

Our data is an initial investigation of genetic causes of non-syndromic deafness in the Vietnamese population. However, further investigation with a larger sample size is necessary to determine the significance of these gene mutations in Vietnamese deafness.

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