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Original scientific paper

MUTATION IN SECOND EXON OF MYO15A GENE CAUSE OF NONSYNDROMIC HEARING LOSS AND ITS ASSOCIATION IN THE ARAB POPULATION IN IRAN

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Hearing loss is a genetically and clinically heterogeneous defect and more than 140 loci and 65 genes have been identified to cause autosomal recessive non-syndromic hearing loss (ARNSHL). According to the previous studies, mutations in *GJB2* are estimated to be involved in 18.17% of ARNSHL cases in the Iranian population; as a result, the remaining 81.83% of this disorder is yet ambiguous. This study aimed to determine the contribution of DFNB3 in hearing loss as well as the frequency of gene mutations in a population (Arab tribal origin) in the Southwest of Iran.

In this descriptive laboratory study, we included 25 families from the Southwest of Iran and negative *GJB2* gene. Linkage analysis was performed by DFNB3 (*MYO15A*) molecular markers (STR). The families with hearing loss linked to this locus were further analyzed for mutation detection. *MYO15A* gene exons were amplified and analyzed using direct DNA sequencing.

In studied families, one family displayed linkage to DFNB3 locus. Identified mutations include substitution and substitute C for A in 1047 location of coding region of *MYO15A* gene (c.1047 C>A) in exon 2 which cause to change Tyrosin to stop codons (P.Y349X), results in the premature truncation at amino acid position 349.

Key words: MYO15A, hearing loss, linkage analysis, Iran

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INTRODUCTION

Deafness, the inability to hear, is the most prevalent genetic sensory disorder in human populations that can significantly impact quality of life style (HILGERT *et al*., 2009). Globally it is estimated that it affects 1 in 500 child births but the prevalence of HL in Iran was 2–3 times higher than that in other parts of the world (MAHDIEH *et al*. 2010).The majority of cases are attributable to genetic factors.

There is different type of genetic transmission such as, autosomal recessive (ARNSHL) (75–85%), autosomal dominant (15–25%) (ADNSHL), Xlinked and mitochondrial inheritance (1–2%) (TABATABAIFAR *et al*., 2011; DAMAN 2012).

ARNSHL is the most common type of inherited hearing loss and it is genetically heterogeneous. To data, 65 genes and more than140 loci have been identified to cause ARNSHL (LIBURD *et al*., 2001; RICHARDSON *et al*., 2011). Recessively inherited phenotypes are common in the Iranian population as the result of a high frequency of consanguineous marriages accounts for ~38% (TABATABAIEFAR, ALASTI *et al*. 2011). Iranian families expressing such traits have cooperated with research studies to identify the critical genes for many phenotypes.

MYO15A, located on 17p11.2, has 66 exons and it is coding myosin XVa (myosin heavy-chain-15A) protein. This protein is composed of 3,530 amino acids, and has different functions such as transcription factors, cell adhesion molecules, ion channels (LIBURD *et al*., 2001; DROR 2010), and critical role for the formation of stereocilia in hair cells of the cochlea. It is localized at the tips of stereocilia that functions as a motor protein uses energy from ATP hydrolysis to move along actin filaments in the stereocilia of hair cells (BASHIR *et al.,* 2012; WOO *et al.,* 2013).

Mutations in this large gene can cause hearing loss in individuals from different populations worldwide. The aim of this project is to study the prevalence of *MYO15A* mutations in negative connexin 26 patients. Here, we report a family with five siblings affected by severe sensorineural hearing loss. As the family is consanguineous, either linkage analysis would have been informative for identifying the causative gene. This is the first study to identify *MYO15A* mutations as the ARNSHL-associated gene in population (Arab tribal origin) in the Southwest of Iran.

MATERIALS AND METHODS

Clinical evaluation

Clinical histories of patients such as age of hearing loss (pre-lingual, post-lingual), severity of hearing loss (mild, moderate or profound) and pattern of hearing loss were obtained from patient records and deafness informational questionnaires were filled out for all families and the pedigrees were drawn based on the filled-out questionnaires then written consent was obtained. Speech-reception thresholds and pure-tone audiograms were obtained from patient. Pure-tone audiometry test was performed with air conduction at 250 to 8000 Hz, and bone conduction was performed at 250 to 4000 Hz.

All families were negative for the vestibular signs and symptoms and none of them showed any syndromic features. Besides, diabetes, cardiovascular diseases, visual problems and neurological disorders were also excluded.

We included 25 Iranian Arab families with at least four siblings affected by severe-to-profound sensorineural hearing loss from the southwest provinces of Iran with no connexin 26 mutation.

Preparation of DNA

All genomic DNA was extracted from EDTA-containing blood samples of participating all members of families using the phenol/chloroform standard procedure (WOO *et al.*, 2013).
The quality and quantity of extracted DNA were checked on agarose gel and a Nano-Drop 1000 spectrophotometer (Thermo Scientific Inc., Wilmington, DE, USA).

Slink calculation, DFNB3 STR marker genotyping

Power of the pedigrees for linkage analysis was simulated by calculating SLINK, using Fast S-Link ,version 2.51 (FISHELSON *et al.*, 2004; LINDNER and HOFFMAAN 2005). Two point and multi-point parametric logarithm of odds (LOD) scores were calculated by Superlink version 1.6 and Genehunter version 2.91. For LOD score calculations, inheritance model of autosomal recessive, complete penetrance and disease-allele frequency of 0.001 were assumed (FISHELSON and GEIGER 2004). After linkage analysis, STR markers haplotypes were reconstructed by SimWalk then visualized using Haplopainter ver. 029.5 software (THEIEHE and NURNBERG 2005). For linkage analysis of the DFNB3 locus, 5 different short tandem repeat (STR) markers were used. The criteria for selecting STR marker include greater heterozygosity values (HZ>50%), shorter amplicon and locating near the DFNB3 locus. Selection of STRs and their primers were based on their physical distance, available at NCBI Map Viewer and NCBI UniSTS.

Table1. STR markers used and their characteristics.

Marker	Physical Position (bp)	PCR product	Forward primer (5'→3')	Reverse primer (5'→3')	HZ
D17S921	14,357,388 - 14,357,565	178 (bp)	CTTGGACTCCTACAAATCCTGGCA	GGCCACCATAATCATGTCAGACAAT	0.72
D17S1843	16,161,201 - 16,161,399	199 (bp)	AATTCAAAGGCTAAAAGCAAAC	GAGAATCACCTGAACCCG	0.70
D17S953	16,199,132 - 16,199,442	123 (bp)	ACTATCCGCCCAATACA	AAGGGCTTGCTTTGAC	0.81
D17S2196	17,361,168 - 17,361,304	137 (bp)	CCAACATCTAGAATTAATCAGAATC	ATATTTCAATATTGTAACCAGTCCC	0.81
D17S620	17,676,432 - 17,676,573	142 (bp)	GAAGGTGTCTGAAACCCAAGG	CCCACCACTACCTATTGTTCTATAC	0.53

PCR and linkage analysis

The used markers are shown in table 1. Polymerase chain reaction (PCR) amplification of STR markers was performed as follow: 8 μL of Master Mix 2x (containing, $MgCl_2$, AmpliTaq^{TM} Gold DNA polymerase, and dNTPs (Applied Biosystems)), 0.45 μL of each of the primers (10 pM), 2 μL DNA (50 ng), adjusted to 18 μL using ddH2O.

For amplification, PCR program was used: an initial denaturation at 94°C for 5 minutes, and 30 cycles of 95°C for 30 seconds (denaturation), 60°C for 30 seconds (annealing), 72°C for 50 seconds (extension) and a final extension at 72°C for 5 minutes. PCR products were loaded on a 12% polyacrylamide gel electrophoresis (PAGE) and run at 35 mA for 2-6 hours, Silver staining was performed to visualize the bands on the gel following standard protocols, (In different stage , for various primers some modifications were applied).

Mutation screening of MYO15A

All 66 exons were amplified using primers designed by Oligo ver. 6.7.1.0 (National Biosciences Inc., Plymouth, MN, USA).

Amplification was performed, with some modifications for each amplicons, in a 50 µL volume of reaction, containing 24 µL of Master Mix 2x, 0.8 µL of each primer (10 pM), 4 µL DNA (50 ng), 20 of ddH20. PCR was done according to the following program: an initial denaturation at 95°C for 4 minutes, 30 cycles of 94°C for 30 seconds (denaturation), 61-65°C for 30 seconds (annealing), 72°C for 1 minute (extension) and a final extension at 72°C for 5 minutes. DNA sequencing of the PCR-amplified product was performed bi-directionally on an ABI 3730XL automated sequencer (Applied Biosystems, Macrogen and, Seoul, Korea) then detect any variant in the gene sequence using Seqmqn soft ward analyser.

RESULTS

In this study, most of the subjects displayed bilateral, severe to profound sensorineural HL, and most of families were consanguineous, audiological characterization of all patients is shown in figure1.

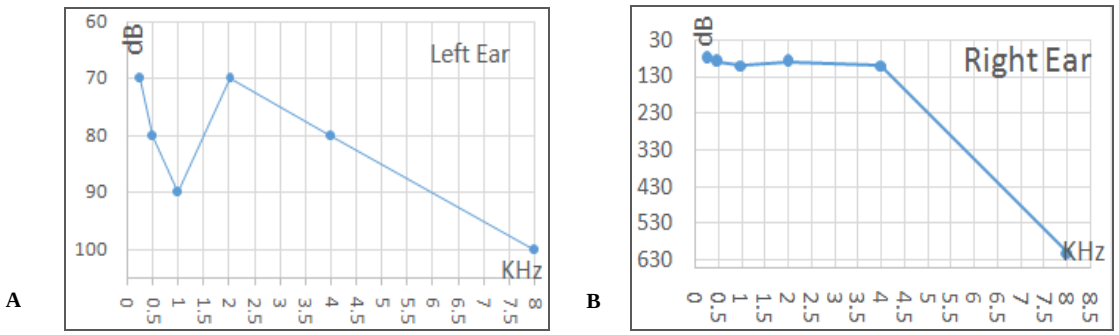

Figure 1. Audiograms of patients in family And-1. A: Audiograms of left ear, B: Audiograms of right ear.

Estimated maximum Slink for these 25 families ranged from 1.2 to 4, two point and multi point LOD and S-link scores related to this family are indicated in table 2. In haplotype analysis, one of the 25 families from khosestan province in southwest of Iran showed linkage to the DFNB3 locus (Figure. 2). Linkage to the locus was confirmed by molecular markers on electrophoresis gel (Figure.3).

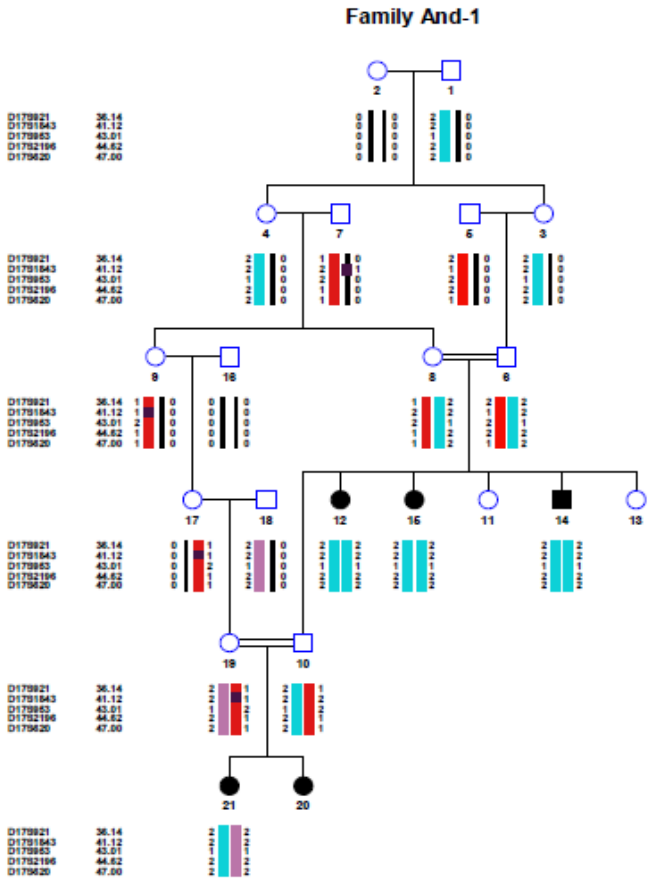

Figure 2. Pedigree and haplotype of And-1 family. The order of markers is based on the Marshfield map. This family shows linkage to the DFNB3 locus.

Table 2. S-Link and LOD scores calculated for family linked to DFNB3.

Family	S-LINK	Two point LOD score	Multipoint LOD score
Iranian Family And-1	3.75	1.75	1.9

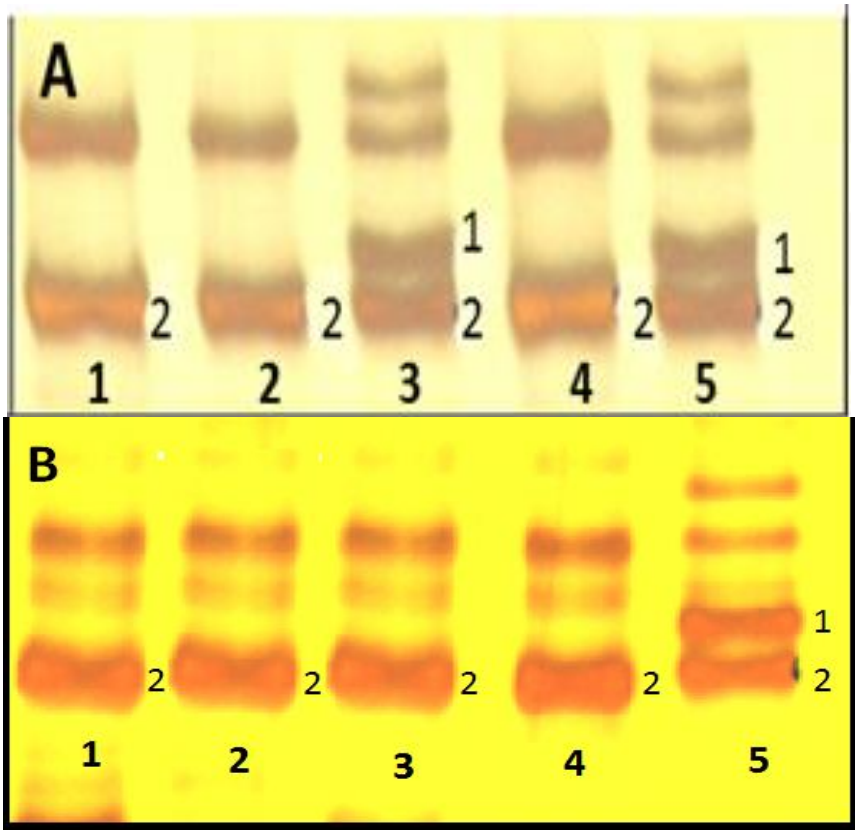

Figure 3. Results from DNA PAGE. A: STR alleles of D17S620 (lane 1, 2, 4: affected children (Homozygote), lane 3: healthy child (Heterozygote), lane 5: mother (Heterozygote)).
B: STR alleles of D17S1843 (lane1: healthy children (Homozygote), lane 2, 3, 4: 4: affected children (Homozygote) and lane 5, mother (Heterozygote)).

DNA sequencing of the *MYO15A* gene revealed a variant in exons 2 homozygous state in Family And-1 (Figure 4). This variant was nonsense substitution and substitute C for A in 1047 location of coding region of *MYO15A* gene (c.1047 C>A) which cause to change Tyrosin to stop codons (P.Y349X). The mutation segregates within the family according to a recessive pattern of inheritance in which the patient is homozygous for the mutated allele. The mother carries this mutation at the heterozygous state.

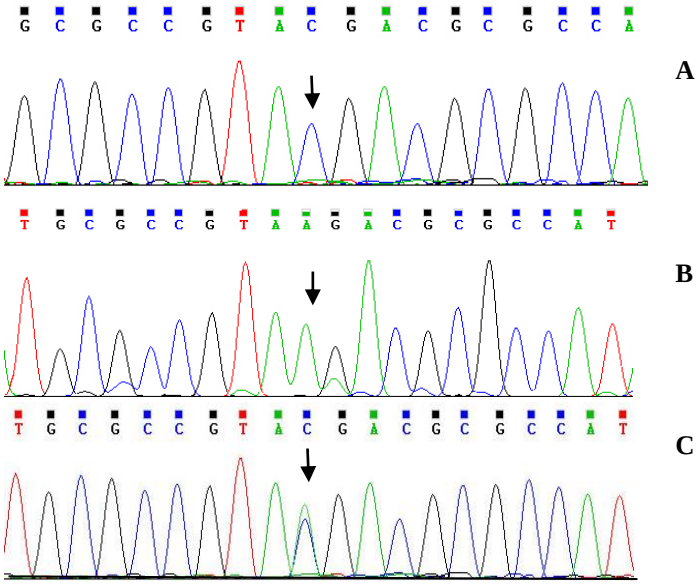

Figure 4. Sequencing chromatograms of *MYO15A* variants (c.1047C>A). Wild type, heterozygous and mutant alleles of respective deafness genes for a normal control (A), an affected (B) and carrier (C) member of family And-1.

DISCUSSION

GJB2 mutations are responsible for 50% of HL in Caucasian populations, whereas the mean frequency of *GJB2* mutations among the Iranian deaf groups is > 18.17% (MAHDIEH *et al.*, 2004). The frequency of *GJB2* mutations the Iranian deaf groups decreases gradually both west to east and north to south (ROBBANI *et al.*, 2010) and the frequency of this gene in Khuzestan provenance is 13% (HOSSEINIPOUR *et al.*, 2005). The specific position of Iran and the existence of various ethnic groups (such as, Persian, Azeri, Kurd, Lur, Arab, balooch, Gilaki, Mazandarani and, Turkmen) suggest the high heterogeneity throughout Iran, that intra group marriages may give rise to a high homogeneity in some mutations and loci within groups (BAGHERIAN *et al.*, 2010). On the basis of this point, it can be concluded that other genes and mutations involved in causing deafness. However, ethnic and geographical variations should be an important factor for determining the most appropriate type of assay.

The nonsense mutation (c.1047C>A (p.Y349X)) detected in *MYO15A* in family And-1, results in the premature truncation at amino acid position 349 located in the first domain (N-terminal extension) of the myosin XVa protein, which is normally comprised of 3530 amino acids.

Myosin XVa is present at the very tip of each stereocilium in the developing and mature hair bundles of the cochlear and vestibular system. Mutant this gene produces defective protein, resulting in abnormally short stereocilia in hair bundles (MICHEL *et al.*, 2005).

In this investigation, one of the 25 families was link to DFNB3 (*MYO15A* gene) ~ 4% of Arab population in Southwest Iran.

In Iran, FATTAHI, *et al.* in 2011 performed linkage analysis of DFNB3 in 140 families with ARNHL, 8 families showed linkage to the DFNB3 locus, suggesting a *MYO15A* mutation frequency of 5.71% in this cohort of Iranian population (Fars, Azeri, kord, Sistani) (FATTAHI *et al.*, 2012).

In 2002, FRIEDMAN *et al*. reported that 5% responsible of hearing loss in Pakistan was associated with *MYO15A* (HINNANT *et al.*, 2002) and, the frequency of *MYO15A* related deafness in Turkey has been reported about 9.9% (HINNANT *et al.*, 2002, SIRMACI *et al.*, 2011). Considering the relatively high frequency of *MYO15A* related deafness in countries neighboring Iran (Pakistan and Turkey), the frequency of 5.71% was reasonable (FATTAHI *et al.*, 2012). *MYO15A* mutation frequency of in our cohort (Arab population) was near to frequent reported by Fattahi. In present investigation, we find a mutant allele of *MYO15A* had five deaf individuals in two consanguineous marriage loops and was linked to this region with a simulated Lod score of 1.7. Patients and parents were homozygote and heterozygote, respectively, for this mutation.

The interesting point of our result was ethnic of our population (Arab), sequence analysis of *MYO15A* gene in 130 families showed this novel variant (c.1047 C>A) (P.Y349X) in exon 2, in Saudi Arabian tribal origin for first time, then reported present study in Iranian Arabian tribal origin. Brownstein al. in 2011, employing targeted DNA capture and massively parallel sequencing (MPS), screened 246 genes known to be responsible for human deafness in 11 probands of Israeli Jewish and Palestinian Arab origin , they reported 6 novel mutations, three of which related to MYO15A gene that they detected a deletion (c.373delCG (p.R125VfsX101)) mutations in exon 2 of MYO15A gene in Palestinian Arab origin from middle eastern families (TABIBAH *et al.*, 2011), base of this report, its look, exon 2 may be hotspot region for Arab ethnic. Although, studies with more patients origin Arab in different country is needed.

VOZZI *et al.* used Ion Torrent DNA sequencing technology to analyze 96 genes related to HL in 12 families coming from Qatar and reported 1 novels mutations in second exon of MYO15A gene ((c.453_455delCGAinsTGGACGCCTGGTCGGGCAGTGG) (p.E152GfsX81)) (Vozzi, Morgan et al. 2014).

In Iran, also FATTAHI,*et al*. in 2011 reported 7 novel mutations, including 4 missense mutations (c. 1387A>G; c.8467G>A; c.5810G>A), 1 nonsense mutation (c.5925G>A), and 2 deletions (c.4904-4907delGAG, c.5419-21delT) in different regions of the myosin-XV protein (FATTAHI, SHEARER *et al*. 2012).

In 104 unrelated multiplex and consanguineous Turkish families population, Basak Cengiz reported missense mutation (c.867C>G (p.Y289X)) in second exon using autozygosity mapping (DUMAN *et al.*, 2010).

There are several reports of second exon mutation in *MYO15A* gene in different populations of the Middle East, base of this reports, it appears that this exon can be considered as a hotspot exon, and considering that this gene is very large size (66 exon), exon 2 can be used as first-line candidate for screening *MYO15A* mutation in the populations of the Middle East countries.

Our present investigation illustrates that in 4% of studied families, HL was associated with *MYO15A* gene. However, the cause of HL in the remaining 96% families is still unknown and more extensive studies may be necessary. Correspondingly, in order to gain more information on the exact molecular bases of HL, further studies on the different populations and other loci for the same populations have to be performed.

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MUTACIJA U DRUGOM EGZONU MYO15A GENA IZAZIVA NESINDROSKI GUBITAK SLUHA I NJEGOVA ASOCIJACIJA U ARAPSKOJ POPULACIJI U IRANU

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Izvod

Gubitak sluha je genetički gubitak i klinčki heterogen efekat. Utvrđeno je više od 150 lokusa i 65 gena koji izazivaju autosomalne recesivne nesindromske gubitke sluh. (ARNSHL). Prema prethodnim studijama, mutacije u *GJB2* su utvrđene da su uključene u 18.17% of ARNSHL slučajeva u Iranskoj populaciji; kao rezultat preostalih 81.83% tog poremećaja je još uvek dvosmislen. Cilj ovih ispitivanja je određivanje doprinosa DFNB3 kako gubitku sluha tako učestalosti mutacija gena u Jugozapadnom delu Irana arapskog porekla. Identifikovane mutacije uključuju substituciju C sa A u 1047 lokacija kodirajućeg regiona .*MYO15A* gena (c.1047 C>A) u egzonu 2, koji izaziva promenu tirozina u stop koodonu (P.Y349X), što kao rezultat ima prevremenu skraćivanje u 349-oj poziciji aminokiselina.

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