A Moroccan family with autosomal recessive sensorineural hearing loss caused by a mutation in the gap junction protein gene connexin 26 (GJB2)

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Abstract
We report a mutation in the connexin 26 gene (Cx26) in a consanguineous Moroccan family linked to the DFNA3/DFNB1 locus on human chromosome 13q11-q12. Affected subjects display congenital, bilateral, sensorineural hearing loss. We have previously identified Cx26 mutations in consanguineous Pakistani families. This current finding indicates that Cx26 mutations are not restricted to ethnically and geographically distinct populations. This is an important observation since it will help to determine the overall contribution of connexin 26 mutations to autosomal deafness in different populations.

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Keywords: DFNB1/DFNA3; connexin 26 (GJB2); sensorineural hearing loss

We have reported recently that both autosomal dominant (DFNA3) and autosomal recessive (DFNB1) forms of non-syndromal, sensorineural deafness are caused by mutations in the connexin 26 gene (Cx26).\(^1\) Immunohistochemical analysis of human connexin 26 expression in the stria vascularis, basement membrane, limbus, and the spiral prominence of the cochlea is consistent with the hypothesis that Cx26 mutations can be involved in the molecular pathology of these forms of hereditary deafness. The connexins are a family of intercellular gap junction proteins sharing similar topology and with a high degree of conservation that facilitate the diffusion of small molecules between adjacent cells.\(^2\) Connexins oligomerise within the plasma membrane of one cell to form "hemi-channels" or "connexons"; extracellular connexon domains from adjacent cells interact to complete intercellular junctions.

We identified a North African family originating from Morocco with two children of a first cousin marriage presenting with genital, symmetrical, bilateral, sensorineural hearing loss and a third newborn child of undetermined diagnosis. Clinical and ophthalmological examinations were normal, excluding syndromal deafness, as were routine tests for acquired hearing loss caused by infection or ototoxic drugs. Subject II.1 is an 8 year old girl with congenital, symmetrical, bilateral, perceptive hearing loss (Fletcher index 115 dB). II.2 is a 5 year old boy with congenital, symmetrical, bilateral, perceptive hearing loss. At low frequencies there is a threshold of 95 dB. At or above 1000 Hz (left ear) and 2000 Hz (right ear) no threshold could be determined. II.3 is a 1 year old boy who at the time of BERA examination (~2 months old) showed normal curves for the left ear and pathological curves for the right ear.

Genetic linkage analysis was performed on this family using microsatellite markers for known dominant (DFNA1-11) and recessive (DFNB1-8) non-syndromal deafness loci.\(^3\) Only the markers D13S175 and D13S292, for...
locus DFNB1/DFNA3 at chromosome 13q11-q12, were homozygous in the affected subjects. The family was genotyped for a further five markers from the locus to determine whether or not this was a region of autozygos or chance homozygosy (fig 1). Haplotype analysis was concordant with linkage to DFNA3/DFNB1 even though a statistically significant lod score could not be generated with this family. Therefore, affected subjects were screened for mutations in Cx26. The entire Cx26 coding sequence was amplified as a single 790 bp fragment and sequenced using internal primers with an automated ABI 377 DNA sequencer. 

Direct DNA sequencing showed a single guanosine deletion that was homozygous in affected subjects II.1 and II.2, and heterozygous in subjects I.1, I.2, and II.3 (fig 2). This deletion occurs in a stretch of six guanosine residues at positions 30-35nt in the Cx26 coding sequence. It is not possible to identify at which of these positions the residue is deleted; however, in all cases the deletion results in premature truncation of the Cx26 protein by introducing a stop codon at amino acid 13.

We have previously identified two homozygous Cx26 mutations in three consanguineous families from the Mirpur region of Pakistan. 

In these pedigrees, premature termination codons were found at amino acids 24 and 77. The identification of a novel mutation in this Moroccan family indicates that Cx26 mutations causing non-syndromal, sensorineural deafness have arisen independently in geographically and ethnically distinct populations. Therefore, it is probable that Cx26 mutations will contribute to autosomal recessive, non-syndromal, sensorineural hearing loss in other populations. A study of markers linked to DFNA3/DFNB1 in 19 consanguineous New Zealand families of western European origin has shown cosegregation of the same alleles in affected subjects consistent with approximately 50% of the families segregating DFNA3/DFNB1. Consequently, more extensive Cx26 mutation analysis is required in families displaying autosomal recessive, non-syndromal, sensorineural deafness to establish the overall contribution of the DFNA3/DFNB1 locus to inherited hearing loss. Given the functional and structural similarities of the connexin proteins, any human connexin genes mapping to regions of the genome containing known deafness loci will merit further investigation as candidate genes for non-syndromal, sensorineural hearing loss.

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