A novel C202F mutation in the connexin26 gene (GJB2) associated with autosomal dominant isolated hearing loss

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Abstract

Mutations in the GJB2 gene encoding connexin26 (CX26) account for up to 50% of cases of autosomal recessive hearing loss. In contrast, only one GJB2 mutation has been reported to date in an autosomal dominant form of isolated prelingual hearing loss. We report here a novel heterozygous 605G→T mutation in GJB2 in all affected members of a large family with late childhood onset of autosomal dominant isolated hearing loss. The resulting C202F substitution, which lies in the fourth (M4) transmembrane domain of CX26, may impair connexin oligomerisation. Finally, our study suggests that GJB2 should be screened for heterozygous mutations in patients with autosomal dominant isolated hearing impairment, whatever the severity of the disease.

Keywords: C202F mutation; connexin26 gene (GJB2); autosomal dominant hearing loss

Serious hearing impairment is detected in about 1/1000 children before 1 year of age. Deafness is of genetic origin in approximately 1/1000 children before 1 year of age. About 8–10% of cases are due to at least one of several X linked loci (DFN) as well as autosomal dominant and recessive loci. Two autosomal recessive loci, DFNB1-17, have been defined. Mutations in the GJB2 gene encoding connexin26 (CX26) account for up to 50% of cases of autosomal recessive hearing loss. In contrast, only one GJB2 mutation has been reported to date in an autosomal dominant form of isolated prelingual hearing loss. We report here a novel heterozygous 605G→T mutation in GJB2 in all affected members of a large family with late childhood onset of autosomal dominant isolated hearing loss. The resulting C202F substitution, which lies in the fourth (M4) transmembrane domain of CX26, may impair connexin oligomerisation. Finally, our study suggests that GJB2 should be screened for heterozygous mutations in patients with autosomal dominant isolated hearing impairment, whatever the severity of the disease.
domain of CX31, is associated with dominant, late onset hearing loss.\(^{16}\) As six CX26 molecules oligomerise to form a hemichannel or connexon,\(^{17}\) the C202F mutation might disturb the interaction between the M4 domain of a mutant CX26 and the M2 domain of the neighbouring connexin, thus resulting in the formation of a non-functional channel.

Heterozygous \(\text{GJB2}\) mutations have previously been found in families with palmoplantar keratoderma and sensorineural hearing loss,\(^{19,20}\) and in dominant non-syndromic deafness in only one instance.\(^{8}\) This latter heterozygous \(\text{GJB2}\) mutation (W44C), which is associated with profound prelingual and progressive non-syndromic deafness, lies in the E1 extracellular loop of the protein involved in interactions between connexons of adjacent cells.\(^{8}\) In contrast, the heterozygous C202F \(\text{GJB2}\) mutation reported here in late onset hearing impairment lies in the M4 transmembrane domain of the protein, thought to be important for connexin oligomerisation.

Finally, our observation suggests that screening for mutations in \(\text{GJB2}\), which account for up to 50\% of autosomal recessive hearing loss cases, should also be performed in autosomal dominant hearing loss cases, even in late onset forms of the disease.

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**Figure 1** Pedigree of the family and haplotypes for three microsatellite markers on chromosome 13. Filled symbols represent affected subjects. ns: not studied. The haplotype segregating with the disease is boxed. Insert: genetic distances between microsatellite markers.

**Figure 2** (A) DNA sequence showing the 605G→T \(\text{GJB2}\) mutation in an affected subject. (B) \(\text{SfaNI}\) restriction site analysis of PCR amplified DNA from family members. The 260 bp fragment corresponds to the mutant allele. Affected members are indicated by an asterisk.


