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DFNA2/*KCNQ4* and Its Manifestations

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Over ten families have been linked to the DFNA2 locus [1–7]. This makes it one of the most frequently encountered loci implemented in autosomal dominant nonsyndromic hearing impairment. The DFNA2 region is located on chromosome 1p34 and has been shown to include *GJB3* and *KCNQ4* [1–4]. *GJB3* or *connexin 31* encodes a gap junction [3], whereas *KCNQ4* is responsible for the production of *KCNQ4* subunits, tetrameres of which constitute a voltage-gated potassium channel [4]. Both genes are believed to be involved in the K^+ recycling pathway of the inner ear [5]. Most families harbor a mutation in the *KCNQ4* gene [4–8] and, interestingly, there is still one family without any detectable mutation, suggesting a third, as yet unidentified, DFNA2-linked gene [9]. Cochlear expression studies in rat demonstrated a basal to apical increasing *kcnq4* gradient in inner hair cells and the spiral ganglion cells, whereas a reciprocal gradient was found in outer hair cells [10].

We briefly describe previously reported phenotypic data of all DFNA2 families with a known mutation [1, 3–6, 9, 11–15]. For the sake of comparison, we statistically analyzed eight of these families using similar methods and present typical audiometric curves for each of them.

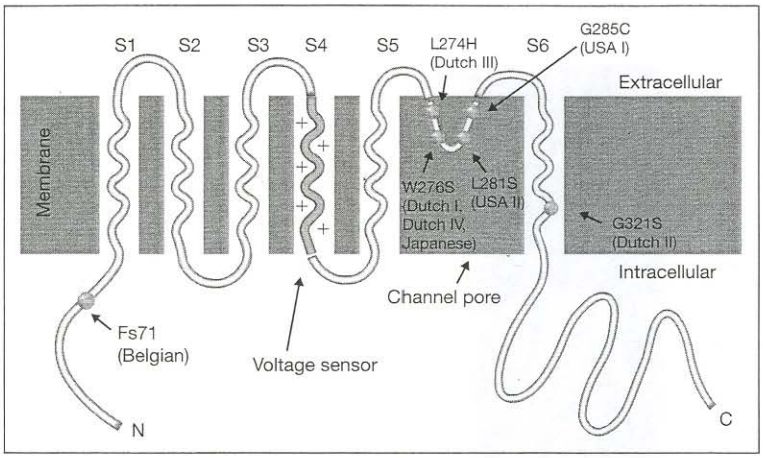

Fig. 1. Graphical representation of the *KCNQ4* voltage-gated K^+ channel. The six transmembrane domains (S1–S6) as well as the pore region are indicated. The specific mutations of all families represented in figure 2 are marked.

Patients and Methods

We collected audiograms from mutation carriers of one Belgian, one Japanese, two American and four Dutch DFNA2/*KCNQ4* families. They all carried a missense mutation, except for the Belgian subjects where an inactivating deletion in the *KCNQ4* gene was involved [6–9]. The Japanese, Dutch I and IV family harbor exactly the same mutation (W276S) and are probably unrelated [8]. W276S is therefore regarded as a potential hotspot for mutation. The specific mutations present in each family are shown in figure 1. Persons thought to have other nonhereditary causes of hearing impairment were excluded from the analyses.

Pure-tone hearing thresholds (binaural mean) were analyzed in relation to age (linear regression analysis) to construct age-related typical audiograms pertaining to age 10, 20, 30, 40, 50, 60 and 70 years for the separate families. A previous study on the Dutch IV family showed inconsistencies between the cross-sectional and the longitudinal analyses [14]. It seemed that the former one was unreliable and therefore longitudinal analysis was preferred.

Review and Results

Previously, *GJB3* mutations were detected in two small Chinese families [3]. They demonstrated progressive, high-frequency sensorineural hearing impairment and tinnitus, present from about age 30 years onwards. Later, the *KCNQ4* gene was cloned and shown to be mutated in a small French family with progressive, high-frequency hearing impairment [4].

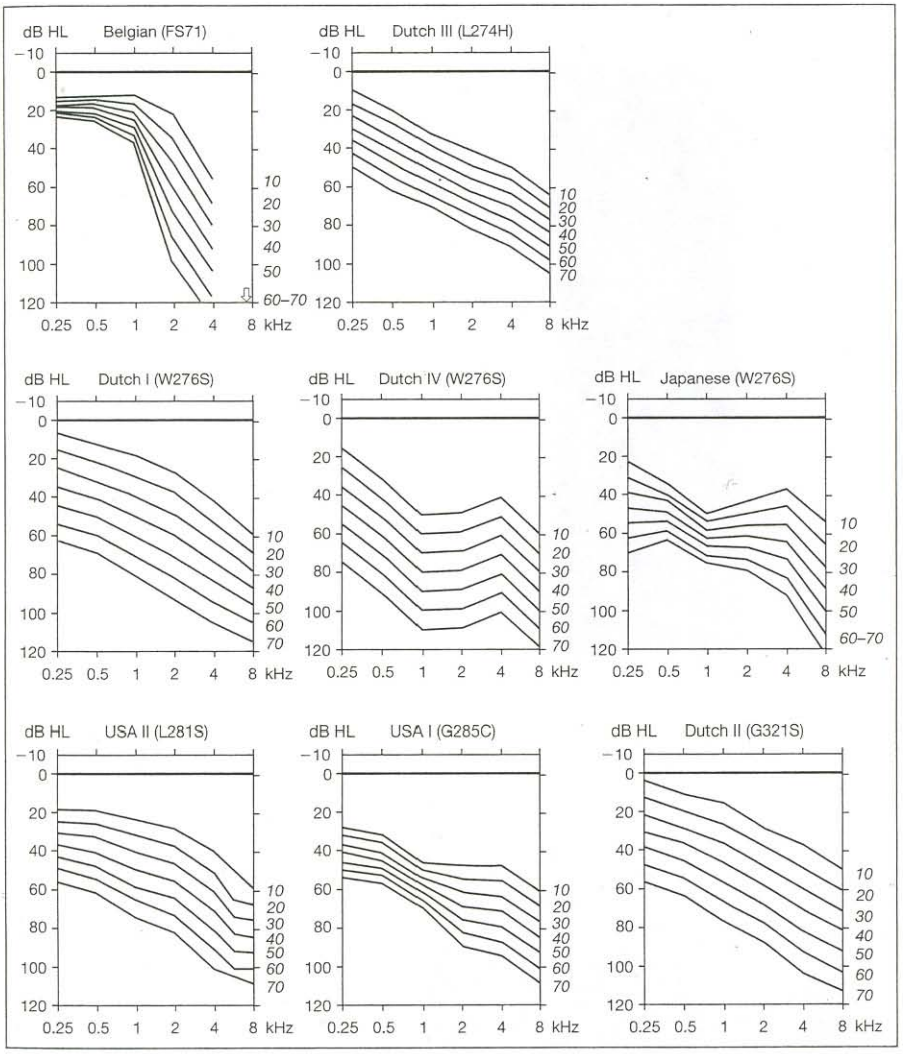

Fig. 2. Age-related typical audiograms of the DFNA2/*KCNQ4* families and the involved mutations. Italics indicate age in years.

The age-related typical audiograms of the remaining *KCNQ4* families are illustrated in figure 2. As previously described, all families have symmetrical, predominantly high-frequency sensorineural hearing impairment, progressive at all frequencies [1, 6, 9, 11–15]. The Belgian family however, has a rather atypical phenotype sparing the low frequencies, and more progressively and

severely affecting the high frequencies. Furthermore, hearing impairment in the USA I family seemed to start with higher thresholds in the lower frequencies. In contrast to the other families, some of the affected members in the Belgian and both American families reported tinnitus [1–6]. All families attained a severe to profound hearing loss by the age of 70. It is likely that hearing is congenitally impaired, especially at the high frequencies. Previous reports mentioned substantial intrafamilial variation in onset age or offset level, but annual threshold deterioration was almost uniformly calculated at approximately 1 dB/year [6, 9, 11–15]. Most *KCNQ4* mutation carriers required a hearing aid from between 10 and 40 years onwards. Vestibular testing was described in 37 members of the Dutch I family and 11 members of the Dutch IV family and revealed increased vestibulo-ocular reflex activity in approximately 30% of the cases [11, 14]. In addition, speech recognition scores had been analyzed in 45 members of the latter Dutch families [13, 14]. Given the level of pure-tone impairment, they presented with relatively good scores. Moreover, the scores did not deteriorate substantially before the third decade of life and progressed at a relatively low rate.

Discussion and Conclusions

In general, a certain genotype-phenotype correlation can be recognized in the studied DFNA2/*KCNQ4* families. The Belgian family with its purely high-frequency loss represents one exception. Their deviant phenotype could be the result of their specific type of mutation (inactivating), which is probably responsible for a reduced quantity (50%) of normal *KCNQ4* channels (haploinsufficiency). In contrast, all other known mutations lead to a (stronger) dominant negative effect with the formation of some normal (1/16) and a large majority of dysfunctional channels [9]. Further research is necessary to confirm this theory and thus confirm the existence of a true phenotype-genotype correlation.

In conclusion, DFNA2/*KCNQ4*-related hearing impairment involves symmetrical, high-frequency hearing impairment, progressive for all frequencies and probably starting from an early age onwards.

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