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Original article

Intra-familial phenotypic variability in a Moroccan family with hearing loss and palmoplantar keratoderma (PPK)

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ABSTRACT

Mutations in the *GJB2* gene encoding connexin 26 are the main cause of hereditary hearing impairment. These mutations generate mainly autosomal recessive and rarely autosomal dominant deafness. Dominant mutations in *GJB2* can be responsible for isolated deafness as well as syndromic hearing loss associated with various skin abnormalities. Until now few papers discuss dominant mutations in the *GJB2* gene. In this work we report a rare case about a Moroccan family with a compound heterozygous mutation (the dominant p.R75Q and the recessive c.35delG alleles) in the *GJB2* gene with intra-familial phenotypic variability. This study reinforces the involvement of p.R75Q mutation of *GJB2* in syndromic deafness associated with dermatological diseases the palmoplantar keratoderma.

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1. Introduction

Deafness is widespread all over the world as the prevalence in newborns is approximately 1 to 3/1000 [1]. More than half cases of hearing loss (HL) are due to genetic factors [1]. This disorder is highly heterogeneous because many genes are concerned (http://hereditaryhearingloss.org).

Mutations in the *GJB2* gene located on chromosome 13, which encode connexin 26 are the main cause of hereditary deafness [2]. This membrane protein belongs to a large family including more than 21 connexins [3]. The Assembly of six compatible molecules of connexin creates one hemichannel called connexon that can function alone or form gap junctions with another connexon of neighboring cells. Therefore, gap junctions and connexons play an important role for intercellular communication [4]. Indeed, they permit the direct and rapid exchange of small molecules and ions such as K+, glucose, amino-acids, inositol polyphosphates (IP3), cAMP and ATP [5]. Moreover, connexin 26 is strongly expressed in the cochlea of the inner ear and in the keratinocyte of the basal layer of the skin [6] mainly in the palms and soles [3]. So, some *GJB2* mutations can affect these two organs.

On the other hand, the connexin 26 topology is an amino-terminal (NT) and carboxy-terminal (CT) domains situated on the cytoplasm, cytoplasmic loop (CL), four transmembranes domains (TM1–TM4) and two extracellular loops E1 and E2 [7]. The majority of *GJB2* mutations are nonsyndromic, have an autosomal recessive mode of inheritance (DFNB1) and are dispersed throughout all the protein. However more than 20 of the *GJB2* mutations are syndromic (associated with skin disorders), have a dominant transmission for most of them (DFNA3) and are included between the NT and E1 domains [8]. One of these dominant mutations, the p.R75Q (c.224G>A), which belongs to the group of palmoplantar keratoderma-deafness (PPK) (OMIM 148350), was described for the first time by Uyguner et al. in a Turkish family [9]. This mutation was reported as responsible for isolated deafness or with cutaneous lesions [10]. Furthermore, the association between palmoplantar keratoderma and hearing loss can also be caused by mutations in mitochondrial RNA mainly p.A7445G mutation. This substitution in the *MT-TS1* gene was initially reported in Scottish family with nonsyndromic deafness [11] and subsequently this mitochondrial mutation was documented in families with palmoplantar keratoderma in addition to hearing loss [12,13]. This mutation is characterised by progressive postlingual deafness with a late of onset [11,12,14], while in the present study all affected members exhibit a congenital profound prelingual hearing loss and their pedigree shows an autosomal dominant inheritance pattern

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more compatible with a mutation in *GJB2* gene (DFNA3). So, a compound heterozygous mutation (p.R75Q/c.35delG) was identified in the *GJB2* gene. To the best of our knowledge, this is the first time that the p.R75Q mutation was described in a Moroccan family.

2. Patients and methods

2.1. Patients

One unrelated Moroccan family took part of this study (Fig. 1A). All affected members of this family have a congenital bilateral, prelingual and profound deafness. However, the twins and their grandmother have PPK while their mother presented an isolated deafness without any skin symptoms. Written informed consent was obtained from all the family members. This work was approved by the ethics committee of the Pasteur Institute of Morocco.

2.2. Genetics analysis

DNA was extracted by using PureLink™ Genomic DNA Minikit (Invitrogen, Made in USA). The search for the most common c.35delG mutation in the *GJB2* gene and the screen of more variants in the coding region of *GJB2* gene, PCR amplification and direct sequencing were performed. PCR conditions were a mixture of 2 μl of genomic DNA (25 ng), 0.3 μl of each primer (20 μM) (forward primer: 5′AGAGTGGTGTTTGCTCAGGA3′, reverse primer: 5′GACTGAGCCTTGACAGCTGA3′) and 15 μl of Platinum PCR Super Mix (Invitrogen).

The ABI Big-Dye Terminator v1.1 sequencing reaction Kit was used and analysed on an ABI 3130 Genetic analyser. The chromatogram Sequences were analyzed by the ABI SeqScape V. 2.5 Software.

3. Results

Genetic analysis of exon 2 of *GJB2* gene for two eleven years old twins (IV.1, IV.2) from a non-consanguineous Moroccan family (Fig. 1A) reveals that they are compound heterozygous for the dominant p.R75Q and the recessive c.35delG *GJB2* mutations (Fig. 1B). Clinical examination showed that both twins exhibit skin lesions on the hands and soles of feet (Fig. 1C). The familial segregation was confirmed, their father (III.1) is homozygous for c.35delG the most common mutation in *GJB2* gene, while the analysis of sequences of the *GJB2* gene coding region from their mother (III.2) and maternal grandmother (II.1) reveals the presence of the dominant mutation p.R75Q in the heterozygous state (Fig. 1B) proving that deafness and skin lesions may be originally inherited from their maternal grandmother. Their mother, despite her congenital hearing loss, she has no dermatological disorders (Fig. 1C). The sequence analysis of their unaffected maternal uncle (III.3) showed the absence of p.R75Q mutation (Fig. 1B).

4. Discussion

Mutations in *GJB2* generate mainly autosomal recessive hearing loss DFNB1, rarely autosomal dominant deafness DFNA3. Dominant mutations in *GJB2* are both nonsyndromic (delE42, W44S, W44C, R75Q, R143Q, M163L, D179N, R184Q and C202F) (conne-

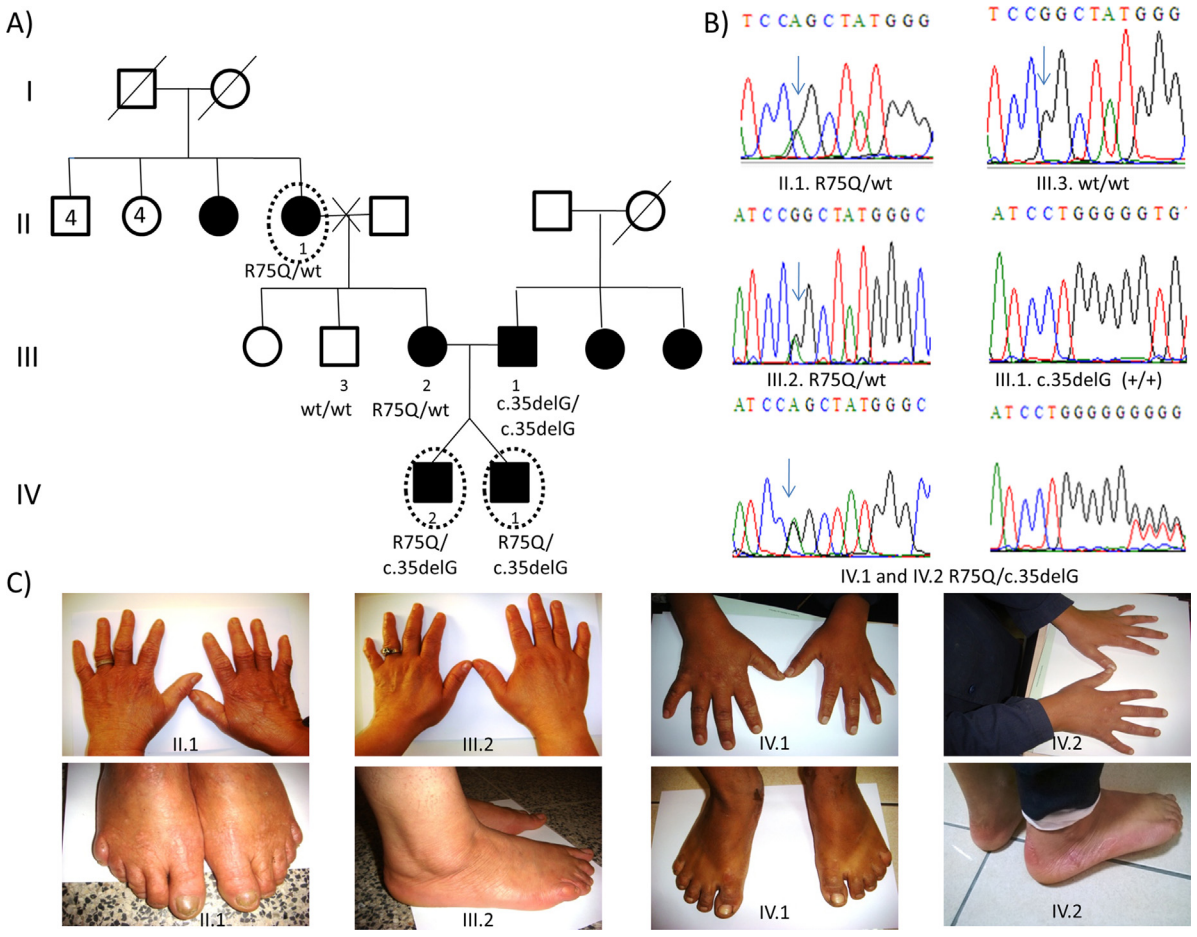

Fig. 1. Phenotype and genotype finding. A. Pedigree of the family with the dominant p.R75Q (c.224G>A) and recessive c.35delG GJB2 mutations. I, II, III, and IV indicate generation numbers. Affected members with dominant p.R75Q presenting palmoplantar keratoderma in addition of deafness are circled (II.1, IV.1 and IV.2). B. Sequence analysis of the dominant p.R75Q mutation (II.1, III.2), normal sequence (III.3), homozygous c.35delG (III.1) and compound heterozygous (p.R75Q/c.35delG) (IV.1 and IV.2). Arrow indicates the presence or absence of p.R75Q mutation. C. Cutaneous lesions proving palmoplantar keratoderma in palms and soles of affected members (II.1, IV.1 and IV.2) while no palmoplantar keratoderma of twin deaf mother's (III.2).

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