CASE REPORT
Dermatology

JKMS

DOI: 10.3346/jkms.2010.25.10.1539 • J Korean Med Sci 2010; 25: 1539-1542

Hereditary Palmoplantar Keratoderma and Deafness Resulting from Genetic Mutation of Connexin 26

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Received: 15 June 2009
Accepted: 17 December 2009

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Gap junctions, which mediate rapid intercellular communication, consist of connexins, small transmembrane proteins that belong to a large family of proteins found throughout the species. Mutations in the *GJB2* gene, encoding Connexin 26, can cause nonsyndromic autosomal recessive or dominant hearing loss with or without skin manifestations. A 3-yr-old Korean female and her mother presented to our clinic with diffuse hyperkeratosis of the palms and soles (May 3, 2007). Skin biopsies from the soles of both patients demonstrated histopathological evidence of palmoplantar keratoderma. The patient and a number of her maternal family members also had congenital hearing loss. The combination of congenital hearing loss and palmoplantar keratoderma, inherited as an autosomal dominant trait, led us to test for a mutation in the *GJB2* gene in both patients. The results showed the R75W mutation of the *GJB2* gene in both. In conclusion, the simultaneous occurrence of a *GJB2* mutation in a mother and daughter suggests that R75W mutation cause autosomal dominant hearing loss presenting with palmoplantar keratoderma. To the best of our knowledge, this is the first report of a *GJB2* mutation associated with syndromic autosomal dominant hearing loss and palmoplantar keratoderma in a Korean family.

Key Words: Keratoderma; Palmoplantar; Hearing Loss; Connexin 26

INTRODUCTION

Congenital hearing loss is a relatively common disorder and it's prevalence is approximately 1 in every 1,000 live births and about half of these cases are hereditary (1). The pattern of inheritance can be dominant, recessive, X-linked and mitochondrial and more than one hundred genes could be involved in hearing impairment. Most cases of hereditary hearing loss are nonsyndromic sensorineural hearing loss, with autosomal recessive forms the most common (1).

Although a number of different genes have been associated with autosomal recessive nonsyndromic hearing loss (ARNHL), mutations in the *GJB2* gene (GenBank M86849, MIM 121011) encoding Connexin 26 (Cx26), with chromosomal location 13q11-12, known as DFNB1 (MIM 220290), accounts for up to half of the cases of ARNHL (2, 3). Gene analysis in Korean deafness patients also suggest that *GJB2* mutations make up a major cause of congenital hearing loss (4). However, few *GJB2* mutations have been described to be associated with syndromic autosomal dominant hearing loss (ADHL) in Korea. Herein we report a familial case of ADHL presenting with palmoplantar keratoderma (PPK) associated with a *GJB2* mutation, in a mother and daughter.

CASE REPORT

A 3-yr-old Korean female presented for evaluation of diffuse thickened scaly plaque on the palms and soles (May 3, 2007). The physical examination revealed diffuse hyperkeratosis of the palms and soles and keratotic plaques on the knuckle areas, reported to be present since 2 yr of age; there was no evidence of additional abnormalities including the teeth, hair or nails (Fig. 1). Diagnostic skin biopsies were obtained after written informed consent. A biopsy specimen from the sole showed compact hyperkeratosis, acanthosis with a well-formed granular layer, consistent with the diagnosis of PPK (Fig. 2). Her mother also had diffuse hyperkeratosis of the palms and soles, present since infancy, and biopsy from the sole of the mother's foot showed similar features (Fig. 2) (May 3, 2007). In addition, the patient was affected with bilateral severe to profound congenital sensorineural hearing loss that was diagnosed by an auditory brainstem response (ABR), and an otoacoustic emissions (OAE) test at 6 months of age. The patient showed no response in ABR and OAE. The maternal grandfather, mother, and aunt also had a history of hearing loss and hyperkeratosis of the palms and soles with the onset in infancy (Fig. 3).

The combination of hearing loss and PPK inherited as an autosomal dominant trait led us to test for a mutation in the *GJB2*

pISSN 1011-8934
eISSN 1598-6357

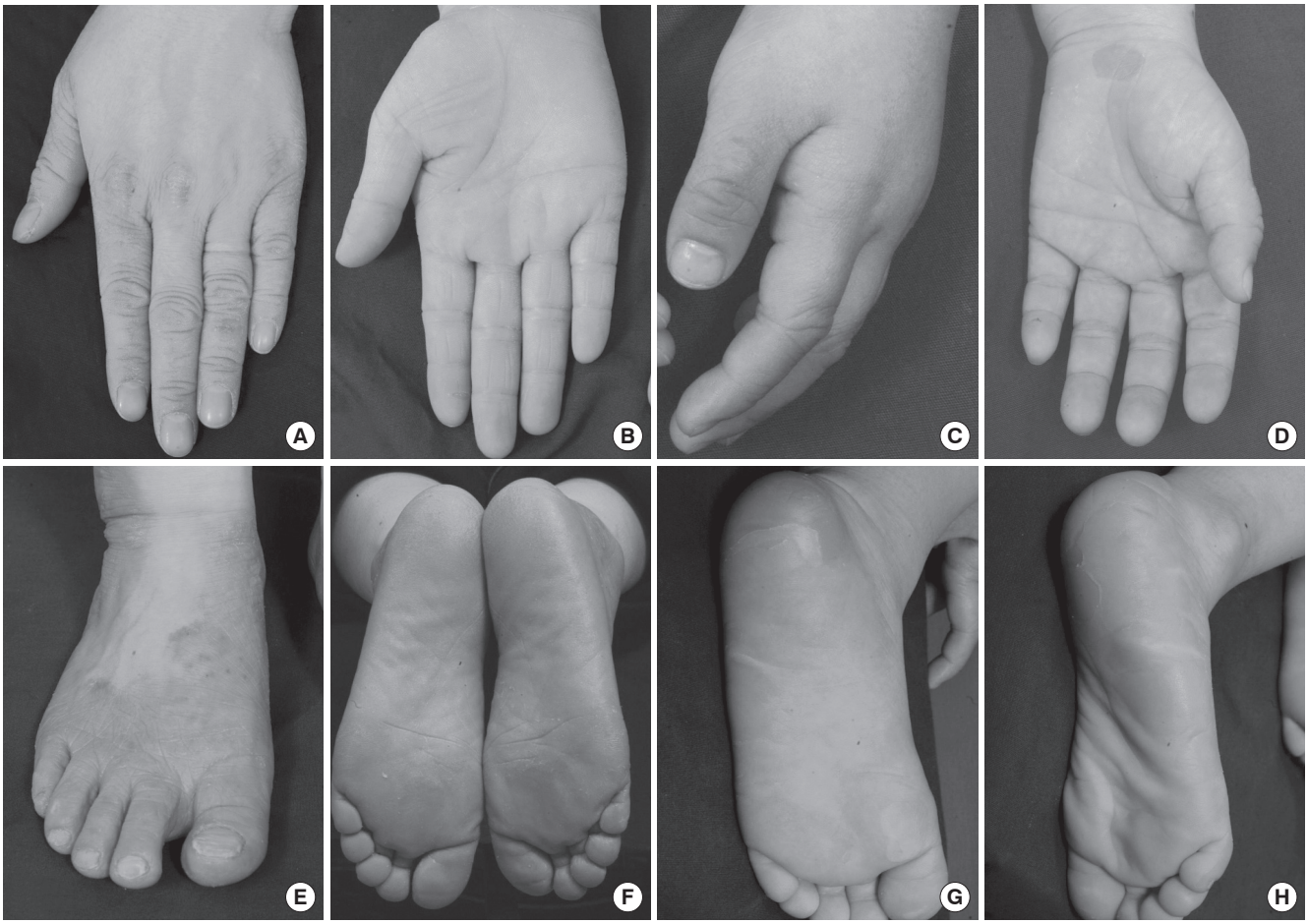

Fig. 1. Clinical features of the mother and her daughter. Keratotic plaques on the knuckle area (**A**, **C**) and diffuse hyperkeratosis of the hands (**B**, **D**) and feet (**E**-**H**); mother (**A**, **B**, **E**, **F**) and daughter (**C**, **D**, **G**, **H**).

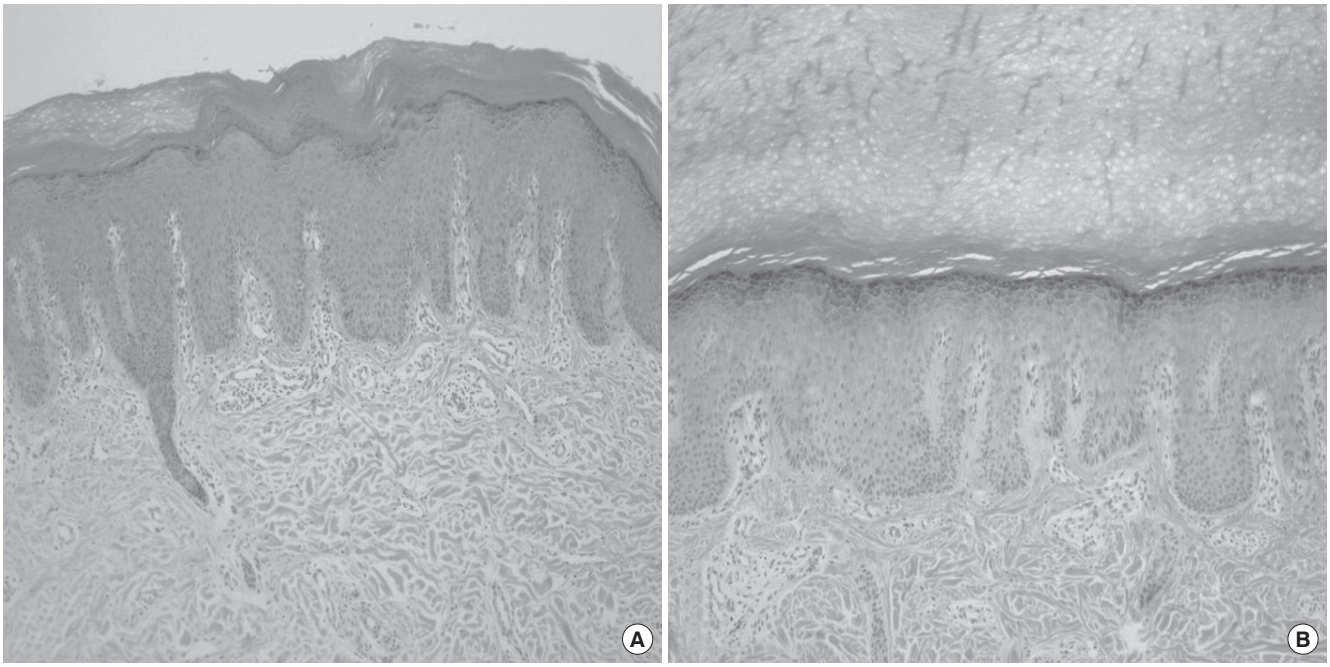

Fig. 2. Histopathological features of the mother and her daughter. Biopsy specimens from the soles showed compact hyperkeratosis, acanthosis with a well-formed granular layer, consistent with the diagnosis of palmoplantar keratosis. (**A**) mother, (**B**) daughter (H&E stain, ×100).

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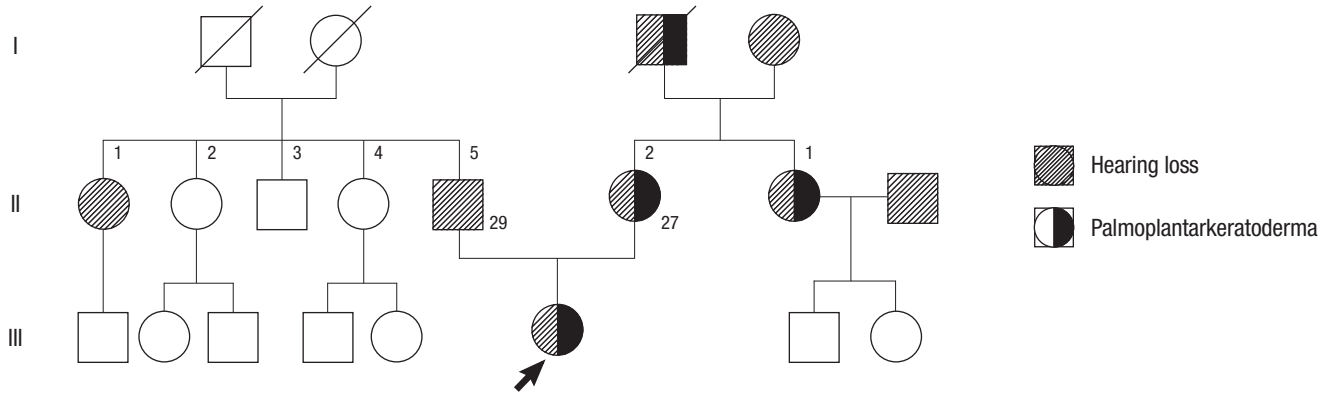

Fig. 3. Pedigree chart. The maternal grandfather, mother, and aunt also had a history of hearing loss and hyperkeratosis of the palms and soles with the onset in infancy; the arrow denotes the proband.

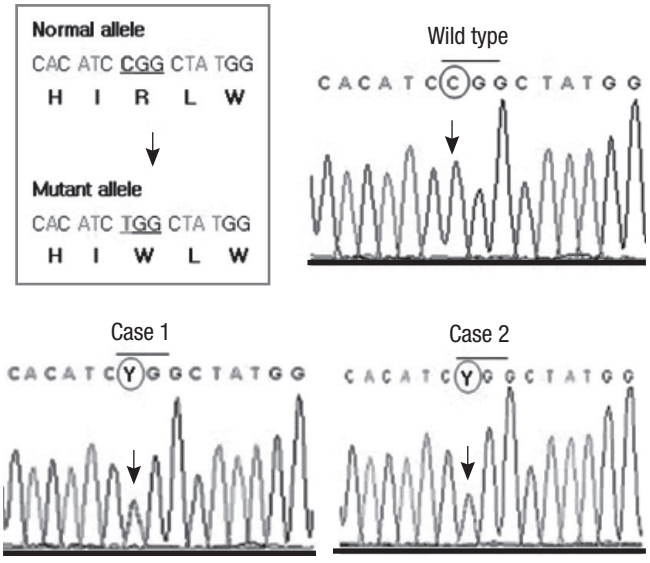

Fig. 4. Mutation analysis in the mother and her daughter. Sequence analysis of the GJB2 gene shows a heterozygous c.223C>T mutation (R75W), which alters the arginine codon and tryptophan replacement (arrows). Y means C and T.

gene in this patient and her mother. As shown in Fig. 4, mutation analysis of the entire *GJB2* gene in the mother identified a heterozygous R75W mutation and V27I mutation. In addition, the mutation analysis of the entire *GJB2* gene in the patient identified a heterozygous R75W mutation that caused an arginine to tryptophan substitution (R75W) at position 75.

Cochlear implantation was done to modify hearing loss of the patient and further hearing rehabilitation had been provided by the hearing support service team in hospital. Her functional auditory skills were slightly improved and attended to special school for the children who had hearing impairment.

DISCUSSION

Six *GJB2* mutations have been found in association with syndromic PPK and ADHL (delE42, G59A, R75Q, H73R, G130V and including R75W) (5-10). The R75W mutation was previously reported in association with hearing loss and keratoderma in familial and sporadic cases (9, 11, 12).

In both the mother and the affected daughter, we found a heterozygous R75W mutation of the *GJB2* gene. Therefore, this specific mutation must be the cause of hereditary hearing loss and PPK in her mother and the patient. Similar to the present patient, R75W mutation in previous report (9, 11, 12) also has shown ADHL associated with PPK. While, the V27I type of mutation, observed only in the mother, is relatively common in Koreans with ARNHL (13), and this specific mutation may lead to the hereditary hearing loss in maternal family members including grandparents. Thus, in this case, defect of Cx26, resulting from R75W mutation of *GJB2* gene, was thought to be the cause of hereditary hearing loss and PPK in her mother and the patient.

Gap junctions are ensembles of gap junction channels formed by integral membrane proteins called connexins. Cx26, one of the human connexins, is found in a variety of cells and tissues, including the cochlea, epidermis of the palms and soles, hair follicles, and sweat glands (14). Cx26 contains four transmembrane domains with a cytoplasmic N-terminus, two extracellular loops, a single intracellular loop, and a cytoplasmic C-terminus. The extracellular loops, especially the first extracellular domain, are of critical importance for voltage gating, channel permeability, connexon-connexon interactions, and formation of gap junctions (15, 16); mutations of this domain lead to interference with the activity of Cx26 channels and consequently functional defects in gap junctions of the auditory organs. In addition to hearing loss, mutations in the first extracellular domain of Cx26 are known to be associated with skin disease, which suggests that the first extracellular domain of Cx26 is also essential for the correct formation and/or function of gap junctions in the epidermis of the palms and soles. Likewise, it is well known that most pathogenic *GJB2* mutations, including R75W mutation, causing both hereditary hearing loss and skin manifestations cluster in the first extracellular domain of the Cx26 peptide (17).

This present case showed familial occurrence and a relatively

early age of onset of PPK. In addition to hearing loss, a number of inherited PPKs are also associated with a genetic predisposition to other conditions, including cancer and heart failure (18). As a result, clinicians should be aware that infancy with inherited PPK may have additional medical problems. The genetic mapping and identification of genes may help with the diagnosis and prevention of other possible medical problems in such cases.

In conclusion, the simultaneous occurrence of a *GJB2* mutation in a mother and daughter suggests that R75W mutation cause ADHL presenting with PPK. To the best of our knowledge, this is the first report of a *GJB2* mutation associated with syndromic autosomal dominant hearing loss and PPK in a Korean family.

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 DOI: 10.3346/jkms.2010.25.10.1539