



Keratoderma-Deafness-Mucocutaneous Syndrome Associated with Phe142Leu in the *GJB2* Gene

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Gap junctions are aggregates of intercellular channels allowing direct cell–cell transfer of ions and small molecules (1). Connexin-26 (Cx26), encoded by the *GJB2* gene, plays a role in gap junction formation in the epithelia of epidermis, skin appendages, cochlea and cornea. Its function is crucial for exchange of electrical signals and recycling of potassium ions during auditory transduction and contributes to epidermal homeostasis, barrier function and integrity (2).

Heterozygous *GJB2* mutations cause a spectrum of different, partly overlapping conditions known as palmoplantar keratoderma (PPK) with sensorineural hearing loss, Vohwinkel syndrome (VS), Bart-Pumphrey syndrome (BPS), keratitis-ichthyosis-deafness (KID) and Clouston-like syndrome (3–5).

Here, we describe a 41-year-old woman exhibiting mucocutaneous manifestations with periorificial erythematous patches, angular cheilitis and scaly erythematous psoriasiform plaques affecting different body parts. Palmoplantar keratoderma, papulopustular acne and sensorineural hearing loss manifested with age. Genetic investigations revealed a c.426C>A heterozygous variant in *GJB2* leading to p.Phe142Leu missense change localized in the 3rd transmembrane helix of Cx26. In the literature, we identified 4 subjects from 3 families with the Phe142Leu displaying similar features, supporting distinct genotype-phenotype correlation in *GJB2*-pathies (6–8).

CASE REPORT

A 41-year-old woman was seen for chronic recurrent dermatitis mainly characterized by erythema, papules and plaques that healed leaving cicatricial sequelae, associated to bilateral high-frequency sensorineural hearing loss. At age 3 days, she had been hospitalized for diffuse severe erythematous lesions over the face (cheeks), lower limbs, inguinal and intergluteal skinfolds associated to severe erythema of the oral mucosa (especially the hard palate) and perianal region. She was discharged with a diagnosis of maculopapular exanthema. Recurrent episodes of intermittent angular cheilitis were registered during childhood and adolescence together with intermittent eruptions of scaly erythematous plaques, the most affected areas being neck, trunk, pubis and the inguinal and axillary folds. Cyclosporine therapy was started after a diagnosis of psoriasis with dramatic worsening of the disease. Premature loss of permanent teeth was recorded at 25 years. At age 33 years, erythematous, scaly and oedematous lesions with clearly defined borders were noticed in the pubic area and inguinal folds, while erythematous papules and pustules involved the trunk. A skin biopsy of a plaque in the area of the mons pubis revealed

epidermal hyperplasia, hyperkeratosis with focal parakeratosis and a dermal infiltrate rich in lymphocytes and neutrophils, with numerous spores, hyphae and pseudo-hyphae in the horny layer. *Candida albicans* was cultured from this specimen and antimycotic therapy (itraconazole 100 mg/day) was started with limited improvement of lesions attributable to candidiasis. Laboratory analyses revealed lymphocytopenia with decreased T-lymphocytes CD4, CD8 and natural killer cells. At last examination, aged 41 years, she showed papulopustular acne lesions on the face (Fig. 1a,b), erythematous papules on the trunk (Fig. 1c,d), focal plantar keratoderma (Fig. 1e) that contiguously extends to the Achille tendon region (transgrediens) (Fig. 1f) and minimal hyperkeratosis on the palmar aspect of the first interdigital spaces (Fig. 1g, h). Hair, nails and sweating were not affected.

Due to the association of keratoderma and hearing loss, Sanger sequencing analysis of the *GJB2* gene was started in the proband and revealed a single heterozygous nucleotide substitution c.426C>A, absent in her parents supporting its *de novo* origin (Fig. S1¹). This variant (rs397516877 in dbSNP) was absent in gnomAD database (<http://gnomad.broadinstitute.org/>) and caused the p.Phe142Leu change scored as “pathogenic” by prediction systems such as MutationTaster, PolyPhen2 and Mutation Assessor. The clinical and genetic features of our patient, as compared to those of previously reported families mutated Phe142Leu, are shown in Table S1¹.

DISCUSSION

Here, we report a 41-year-old patient displaying the association of a distinct mucocutaneous phenotype with hearing loss, heterozygote for the Phe142Leu mutation in the *GJB2* gene. In the literature, 3 additional families with 4 patients harbouring this missense change existed: two families had a c.424T>C nucleotide substitution and one the same c.426C>A variant identified in our patient (6–8). At clinical comparison, phenotypic overlap was evident especially at neonatal age (Table S1¹). Indeed, most of the patients are described as neonates or infants, when the phenotype is particularly manifested with unusual cutaneous and mucous manifestations resembling mucocutaneous candidiasis being constantly seen. Dermatologic lesions were variably described as psoriasiform dermatitis, erythematous macules, patches and plaques. Angular cheilitis was recorded in all patients. Some individuals had inflammation of oesophageal mucosa. Squamous cell carcinoma of the hard palate was registered once. Susceptibility to

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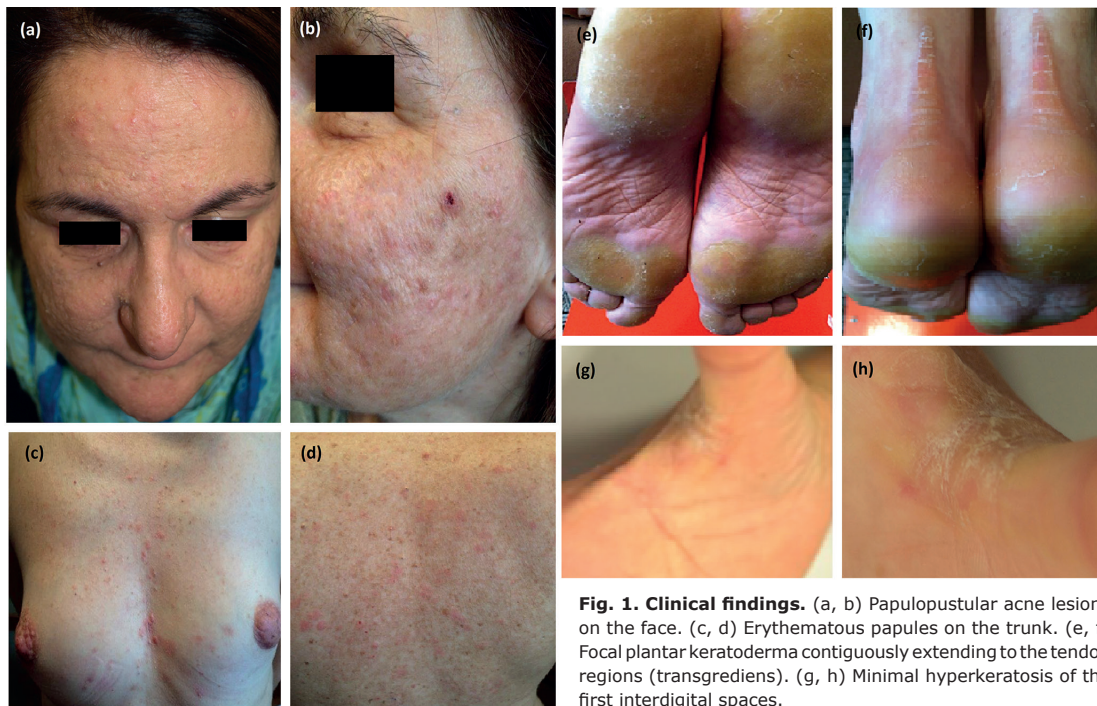


Fig. 1. Clinical findings. (a, b) Papulopustular acne lesions on the face. (c, d) Erythematous papules on the trunk. (e, f) Focal plantar keratoderma contiguous to the tendon regions (transgrediens). (g, h) Minimal hyperkeratosis of the first interdigital spaces.

infections was common although laboratory investigations, when conducted, excluded immune deficiencies. Interestingly, in our patient we recorded lymphocytopenia with decreased CD4, CD8 and natural killer cells, which can at least in part contribute to such susceptibility.

Despite a number of common features observed among Phe142Leu mutated patients, some differences exist. In fact, palmoplantar keratoderma and papulopustular acne have never been reported before. Although this may be due to very early age of previously described cases, interestingly in skin and mucosa biopsies of two other Phe142Leu patients, hyperkeratosis was recorded (6–8), while severe nodulo-cystic acne was described in KID (9).

Most *GJB2* variants causative of KID syndrome map to IC1, TM1 and EC1 domains of Cx26, involved in channel gating and regulation, and rarely to TM2 domain (1). In contrast, variants underlying VS, BPS and PPK with Deafness (Table SII¹) mostly map to EC1 and to transition zone between EC1 and TM2, with sporadic cases affecting EC2 and IC2 domains (10). The Phe142 residue lies at the beginning of TM3 (residues 129–159) with its side chain protruding into the membrane bilayers and being about 30 Å distant from the pore shrinkage (Fig. S2a¹). Notably, closely located mutations such as Thr135Ala or Val153Ile, also with side-chains buried in the membrane bilayers and far from functional sites of the hemichannel, are associated to non-syndromic hearing loss. As the Phe142Leu, these changes preserve the hydrophobic features of TM3 and are not predicted to differently affect channel architecture and stability; accordingly, more subtle conformational alterations might explain the different phenotypic consequences. We speculate that distinct mutations in TM3 helix may differentially influence the conformation of IC2,

connecting TM2 and TM3 and altering the interactions with its substrates. In particular, Phe142 is in contact with Pro87, which belongs to TM2 and disrupts its H-bond array inducing a bent of this structural element (Fig. S2b¹). Consequently, a loosen interaction due to the Phe142Leu substitution may both alter the relative orientation of TM2-TM3 and, indirectly, the IC2 conformational states. Notably, this structural feature mediates the majority of protein-protein interactions of a connexin hemichannel, including those with kinases (fundamental to regulate its open-to-close transition) and with other proteins necessary for anchoring to cytoskeleton (11).

In conclusion, we outlined the phenotype resulting from Phe142Leu in *GJB2* characterized by mucocutaneous lesions with erythematous patches, angular cheilitis, scaly erythematous psoriasiform plaques and hearing loss. The cutaneous phenotype is particularly evident and severe at birth. Palmoplantar keratoderma, papulopustular acne and teeth defects are possible additional age-related characteristics. More data are needed to confirm such genotype-phenotype correlation in *GJB2*-pathies.

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