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CLINICAL REPORT

Palmoplantar keratoderma with deafness phenotypic variability in a patient with an inherited *GJB2* frameshift variant and novel missense variant

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Abstract

Background: Variants in the *GJB2* gene encoding the gap junction protein connexin-26 (Cx26) can cause autosomal recessive nonsyndromic hearing loss or a variety of phenotypically variable autosomal dominant disorders that effect skin and hearing, such as palmoplantar keratoderma (PPK) with deafness and keratitis–ichthyosis–deafness (KID) syndrome. Here, we report a patient with chronic mucocutaneous candidiasis, hyperkeratosis with resorption of the finger tips, profound bilateral sensorineural hearing loss, and normal hair and ocular examination. Exome analysis identified a novel missense variant in *GJB2* (NM_004004.5:c.101T>A, p.Met34Lys) that was inherited from a mosaic unaffected parent in the setting of a well-reported *GJB2* loss of function variant (NM_004004.5:c.35delG, p.Gly12Valfs*2) on the other allele.

Method: Rat epidermal keratinocytes were transfected with cDNA encoding wildtype Cx26 and/or the Met34Lys mutant of Cx26. Fixed cells were immunolabeled in order to assess the subcellular location of the Cx26 mutant and cell images were captured.

Results: Expression in rat epidermal keratinocytes revealed that the Met34Lys mutant was retained in the endoplasmic reticulum, unlike wildtype Cx26, and failed to reach the plasma membrane to form gap junctions. Additionally, the Met34Lys mutant acted dominantly to wildtype Cx26, restricting its delivery to the cell surface.

Conclusion: Overall, we show the p.Met34Lys variant is a novel dominant acting variant causing PPK with deafness. The presence of a loss a function variant on the other allele creates a more severe clinical phenotype, with some features reminiscent of KID syndrome.

KEYWORDS

connexin-26, Cx26, deafness, gap junction, palmoplantar keratoderma

1 | INTRODUCTION

Biallelic pathogenic variants in the *GJB2* (MIM 220290) gene, which encodes connexin-26 (Cx26), cause autosomal recessive deafness type 1A (DFNB1A, OMIM: 220290), which is the most common cause of nonsyndromic congenital bilateral sensorineural hearing loss at any frequency and severity (mild to profound). The variant spectrum for DFNB1A includes both missense and truncating variants. Heterozygous variants in *GJB2* also cause numerous dermatologic conditions with deafness that include: palmoplantar keratoderma (PPK) with deafness (OMIM: 148350), Vohwinkel syndrome (VS) (OMIM: 124500), Bart-Pumphrey syndrome (BPS) (OMIM: 149200), hystrix-like ichthyosis with deafness (OMIM: 602540), and keratitis–ichthyosis–deafness (KID) syndrome (OMIM: 121011).

PPK with deafness, VS, and BPS represent parts of a phenotypic and genotypic spectrum with similar symptoms and localized mutations. PPK with deafness is characterized by slowly progressive, high-frequency hearing loss with palmoplantar keratodermas. Published variants that cause this syndrome include: p.Glu42del, p.Asn54His, p.Gly59Ala, p.Gly59Arg, p.His73Arg, p.Arg75Trp, p.Arg75Gln, p.Gly130Val, and p.Ser183Phe—mainly localized to the first extracellular loop of the Cx26 protein (Birkenhäger et al., 2010; Lilly et al., 2016). VS is classically defined as hearing loss (mild to moderate) and honeycomb keratoderma associated with constrictions of digits leading to autoamputation (Lilly et al., 2016). Hystrix-like ichthyosis with deafness and KID syndrome represent another spectrum characterized by more widespread keratoderma, keratitis, alopecia, dystrophic nails, photophobia, corneal vascularization, and increased susceptibility to cutaneous fungal and bacterial infections (Koppelhus et al., 2011). There are also recurrent variants that cause KID syndrome including p.Gly12Arg, p.Asn14Lys, p.Asn14Tyr, p.Ser17Phe, p.Ala40Val, p.Gly45Glu (lethal), p.Asp50Asn (accounts for about 80% of cases), p.Asp50Tyr, and p.Ala88Val (Koppelhus et al., 2011; Lilly et al., 2016). Most cases of KID syndrome are due to the presence of these *de novo* missense variants in *GJB2*, however, dominant inheritance and germline mosaicism have been reported (Koppelhus et al., 2011; Sbidian et al., 2010).

Connexins are integral membrane proteins that are best known for forming gap junctional intercellular channels enabling the exchange of small molecules between contacting cells, but as cell surface hemichannels, may also allow for molecular exchanges with the extracellular milieu. There are 21 human connexins which, as a group, are spatially and differentially distributed ubiquitously throughout the body. This variety in connexin makeup allows for variable timing and localization of expression, channel diversity, and selectivity in molecules that pass through the formed channels (Leybaert et al., 2017). Cx26 is highly expressed in multiple tissues including the cochlea, hair follicles, sweat glands, and epidermis of palms and soles (Koppelhus et al., 2011). Variants in *GJB2* which lead to aberrant channel activity, therefore, affect these areas specifically while other tissues where Cx26 is found remain asymptomatic (e.g., female breast) (Thiagarajan et al., 2018). Such variants can cause hearing loss possibly due to defects in metabolite and/or ion exchange through Cx26 channels, resulting in loss of hair cells during development or early in life (Mammano, 2019). They can also cause skin anomalies via formation of leaky channels that dysregulate calcium homeostasis in the epidermis (Cocozzelli & White, 2019). Specifically, *GJB2* variants known clinically to cause PPK with deafness have been shown to inhibit gap junction channel or hemichannel formation when expressed alone and to transdominantly interfere with other connexin gap junction channels (Shuja et al., 2016). Variants known to cause KID syndrome, conversely, lead to increased hemichannel opening or permeability, thus, affecting keratinocyte differentiation (Lilly et al., 2016).

2 | CASE REPORT

The patient is a 25-year-old female who presented for genetic evaluation given her history of profound congenital bilateral sensorineural deafness, PPK, chronic mucocutaneous candidiasis, and resorption of the finger tips. Her hearing loss was diagnosed in infancy and hearing aids had no benefit. She was followed with dermatology and immunology since she was about 1 year of age due to PPK and mucocutaneous candidiasis. Her dermatologic issues have involved acne vulgaris on face and neck, erythematous, flat, macular rash on bilateral legs, hyperkeratosis of the palms and soles with fissuring, and 20 nail dystrophy (Figure 1). She is treated with oral ketoconazole as prophylaxis. She has no history of vision, endocrine, autoimmune, vision, cardiac, gastrointestinal, or renal concerns. Her development and intellect were and remain normal. Family history revealed a sister with similar, though milder, symptoms and unaffected parents. Previous genetic testing was only for the *AIRE* gene (autoimmune polyendocrinopathy syndrome, OMIM: 240300) which was negative. Given multiple system involvement trio exome sequencing of the patient and her parents was performed. Sister declined testing. Results indicated two variants in *GJB2*, NM_004004.5:c.35delG, p.Gly12Valfs*2 (pathogenic, paternally inherited) and NM_004004.5:c.101T>A, p.Met34Lys (variant of uncertain significance, maternally inherited).

3 | METHODS

3.1 | Ethical compliance

Informed consent for publication of this patient was obtained. The proband is enrolled in an ongoing study, called

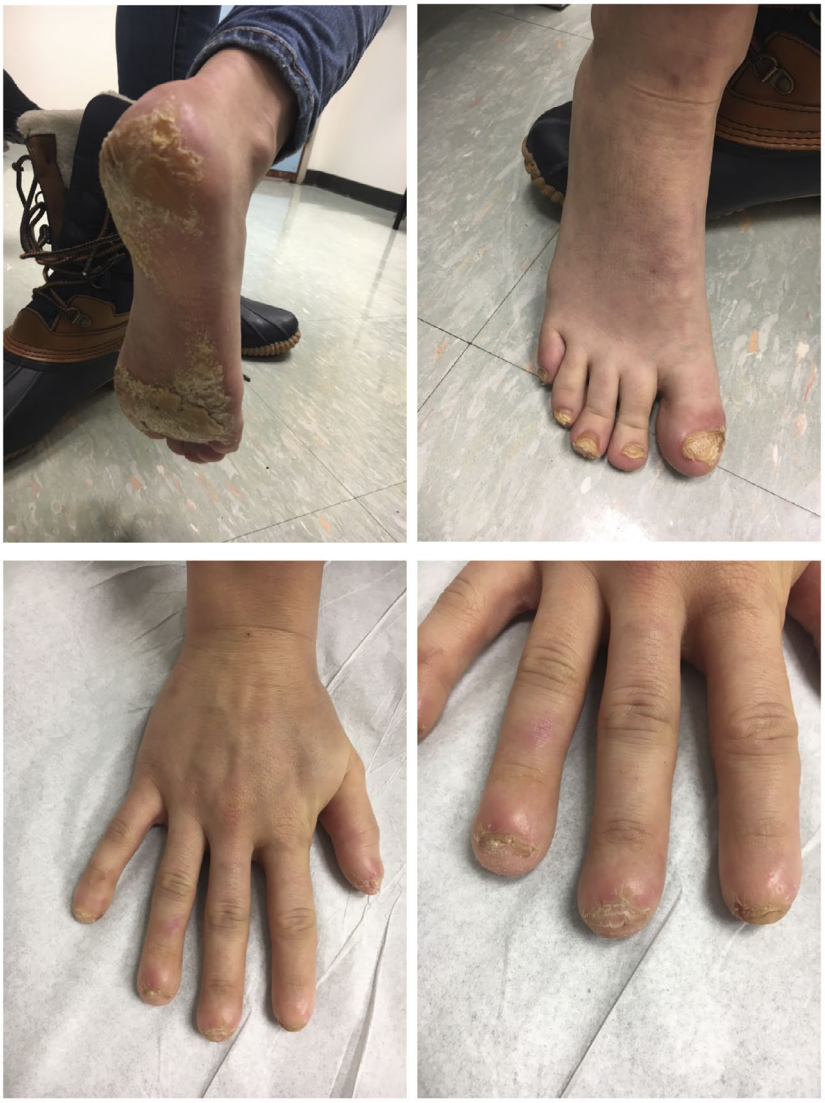

FIGURE 1 Image of the patient's hands and feet showing dermatologic findings

"T cell immunodeficiencies," examining the genetic basis of immune disorders (IRB #: 2001-4-2405, Children's Hospital of Philadelphia).

Clinical exome sequencing was performed at the Division of Genomic Diagnostics at Children's Hospital of Philadelphia using DNA extracted from patient blood specimens. Library preparation was performed using Agilent's SureSelect XT protocol and target enrichment with Agilent's Clinical Research Exome version 1. Sequencing was performed using an Illumina HiSeq 2500 and downstream processing and variant analysis using custom bioinformatics algorithms and manual interpretation (Gibson et al., 2018).

Rat epidermal keratinocytes (REKs) were grown on glass coverslips in Dulbecco's modified Eagle's medium as we previously described (Berger et al., 2014). REKs, or REKs genetically engineered to lack the expression of endogenous Cx43, were transfected with cDNA encoding wildtype Cx26 and/or the Met34Lys mutant of Cx26 (special ordered from NorClone Biotech) tagged to moxGFP (Add gene USA) or, in some cases, Cx26 was tagged to red fluorescent protein (RFP). Previously, we have demonstrated that GFP and RFP tagging has minimal effects on the localization of connexin or connexin mutants (Berger et al., 2014). Briefly, to assess the subcellular location of the Cx26 mutant, fixed cells were immunolabeled for protein disulfide isomerase (PDI) (1:500 dilution. BD Biosciences catalog # 610946) followed by goat anti-mouse 588 (1:500 dilution Invitrogen catalog # A21422) prior to Hoechst 33342 (Cat# H3570, Thermo Fisher Scientific) staining to visualize the nuclei, as we previously described (Berger et al., 2014). Finally, cell images were captured using a Zeiss LSM 800 confocal microscope equipped with airyscan and a 63x oil immersion objective.

4 | RESULTS

Trio exome sequencing results indicated two variants in *GJB2*: NM_004004.5:c.35delG, p.Gly12Valfs*2 (pathogenic, paternally inherited) and NM_004004.5:c.101T>A, p.Met34Lys (variant of uncertain significance, maternally inherited). The p.Met34Lys variant was found at an allele fraction of 0.17 in the proband's mother with follow-up Sanger sequencing further confirming the likelihood of mosaicism in the parent (Figure 2). The p.Met34Lys variant is novel and has not been reported in the literature or the genome aggregation database (gnomAD). The variant occurs at a position known to harbor pathogenic variants causing nonsyndromic hearing loss (e.g., p.Met34Thr and p.Met34Ile) (Snoeckx et al., 2005) and is predicted to be pathogenic by multiple computational tools (MutationTaster, REVEL, and SIFT).

Laboratory results showed that when the Met34Lys mutant protein was expressed in rat epidermal keratinocytes it localized extensively to the endoplasmic reticulum as denoted by the localization of PDI while wildtype Cx26 formed clearly identifiable gap junctions at sites of cell-cell apposition (Figure 3a). Attempts to rescue the delivery of the Met34Lys mutant by the co-expression of wildtype Cx26 typically revealed that the Met34Lys mutant retained Cx26 within intracellular compartments suggesting a potential intermixing of mutant and wildtype Cx26 (Figure 3b). However, in REKs lacking Cx43 we could find a few cases where the Met34Lys mutant and wildtype Cx26 were assembled into gap junction plaques at the cell surface (Figure 3c). Collectively, these localization studies suggest that not only is the Met34Lys mutant trafficking defective, but it also has the capacity to impede normal delivery of co-expressed wildtype Cx26 to the cell surface.

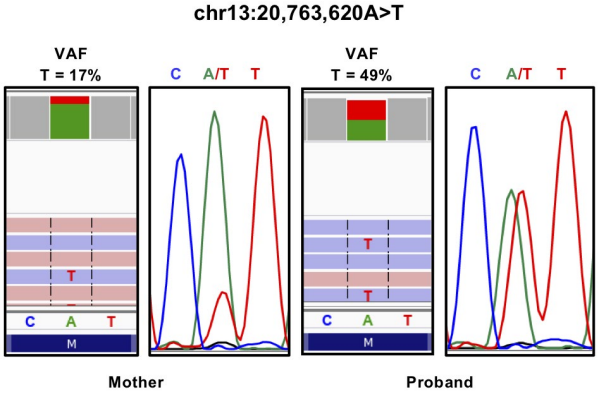

FIGURE 2 Exome and Sanger sequencing data showing maternal mosaicism (17%) and heterozygosity (~50%) in the proband at position chr13:20,763,620A>T, resulting in p.Met34Lys

5 | DISCUSSION

Our patient has profound congenital sensorineural hearing loss and skin findings including acne vulgaris on her face and neck, erythematous, flat, macular rash on bilateral legs, palmoplantar keratoderma, dystrophic nails, and persistent fungal infections. Her trio exome sequencing revealed two variants in *GJB2*. The paternally inherited variant c.35delG, p.Gly12Valfs*2 is the most commonly reported variant in the *GJB2* gene to result in DFNB1A in Caucasians (Putcha et al., 2007). This frameshift predicts premature polypeptide chain termination (if the resulting mRNA is translated at all) or early degradation of the extremely short Cx26 fragment. The maternally inherited p.Met34Lys variant in exon 2 of the *GJB2* gene is novel. Mosaicism for this variant in the proband's mother (approximately 34% of cells in blood) is predicted to be sufficiently low enough to not cause disease in her auditory and skin tissues. Likelihood of germline transmission of this variant is amplified by the presence of our patient's similarly affected sister. Different variants affecting the p.Met34 residue, specifically p.Met34Thr, have been published as disease-causing variants for a hearing loss phenotype alone (with variable expressivity and reduced penetrance) (Putcha et al., 2007; Shen et al., 2019). Given our patient's obvious skin anomalies and truncating second allele, due to the p.Gly12Valfs*2 variant, we propose that the p.Met34Lys variant is pathogenic and causes her phenotype, which is clinically most reminiscent of PPK with deafness. We suspect the truncating variant on the other allele is also the reason why this patient is presenting with a more severe and expanded phenotype than what is typically seen in PPK. Specifically, the resorption of the finger tips mimics VS, whereas the mucocutaneous candidiasis is a feature primarily described in KID syndrome.

In attempt to prove pathogenicity, the Met34Lys mutant was expressed in rat epidermal keratinocytes. Results revealed that the p.Met34Lys mutant was retained in the endoplasmic reticulum, therefore, failing to reach the plasma membrane to function as a gap junction channel. The Met34Lys mutant was shown to be most often dominant to wildtype Cx26, preventing its delivery from the endoplasmic reticulum to the cell surface. These findings mirror that found for the Cx32 (encoded by *GJB1*) p.Met34Lys mutant, further suggesting that amino acid substitution at this particular residue renders connexin trafficking defective (Yum et al., 2002). Early experiments also suggest that the p.Met34Lys mutation is transdominant to a second skin connexin, Cx30 (data not shown). Clinically, we propose that the Met34Lys mutant is a transdominant negative inhibitor on other keratinocyte connexins and that this contributes to the skin disease in the patient, but this requires further testing. Failure to form functioning gap junction channels and suggestion of transdominant

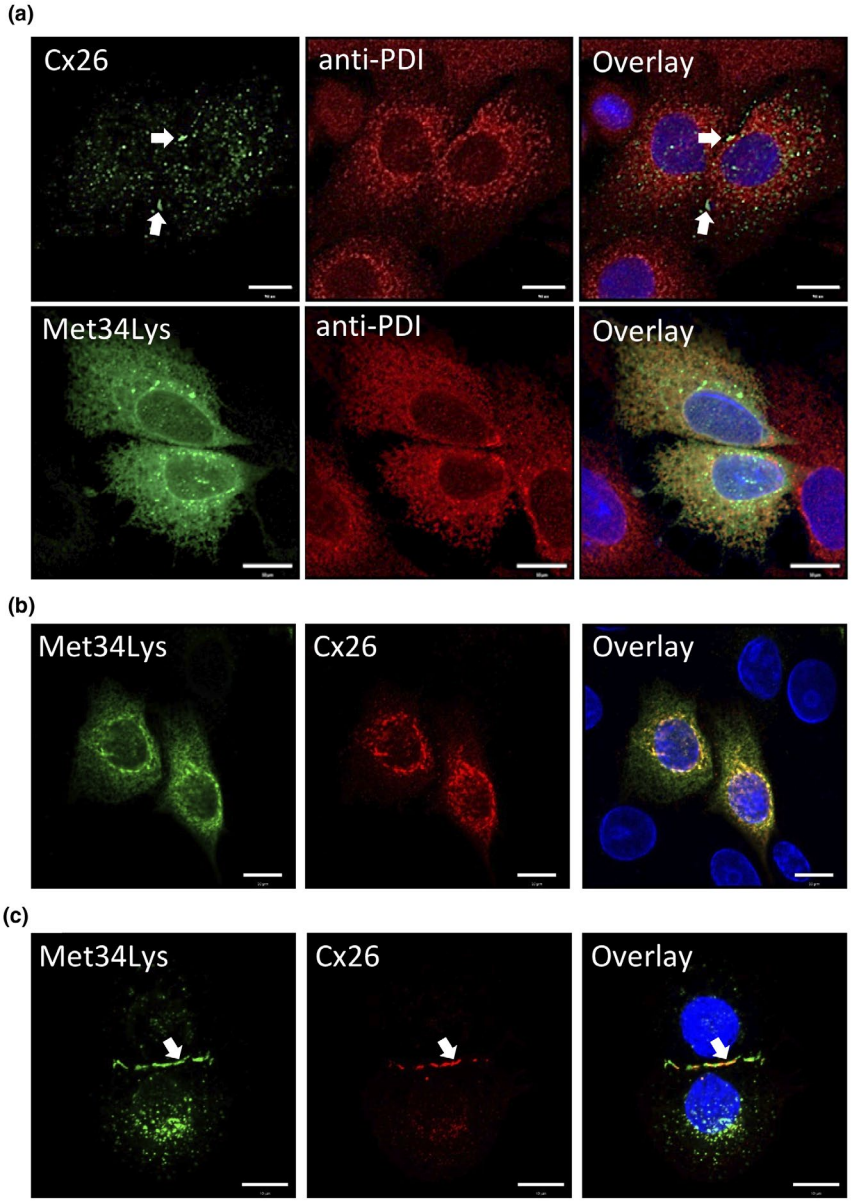

FIGURE 3 The Cx26 M34K mutant is retained within the endoplasmic reticulum. (a) REKs were engineered to express GFP-tagged wildtype Cx26 (Cx26-GFP) or the Met34Lys mutant (Met34Lys) prior to labeling for the endoplasmic reticulum resident protein disulfide isomerase (PDI). Note that wildtype Cx26 assembled into structures in keeping with gap junctions (arrows) while the mutant extensively colocalized with PDI. (b) When the Met34Lys mutant was co-expressed with Cx26 tagged to RFP, the mutant typically retained the wildtype Cx26 counterpart within intracellular compartments. (c) In some occasions, particularly in REKs lacking endogenous Cx43, co-expressed Cx26 tagged to RFP rescued the delivery of the Met34Lys mutant to sites of gap junction formation (arrows). Blue denotes Hoechst stained nuclei. Bars = 10 μm

interference with other connexins are findings consistent with the mechanism previously reported for PPK with deafness mutations (Lilly et al., 2016; Shuja et al., 2016).

It is notable that PPK with deafness is a dominantly inherited condition. The diagnosis of our patient who has PPK with deafness as a result of the novel p.Met34Lys variant in the setting of a truncating second allele is quite unique and has implications for recurrence risk counseling. PPK with deafness due to the known variant p.Arg75Gln has been reported in trans to the p.Gly12Valfs*2 frameshift variant in a Moroccan family. In this family, deafness and dermatologic findings were most severe in members with both variants, while maternal relatives without the p.Gly12Valfs*2 fared better, with either nonsyndromic hearing loss or hearing loss with milder PPK (Bousfiha et al., 2016). Similarly, two Chinese families presenting with PPK with deafness have been reported with known variants (p.Arg75Gln and p.Arg75Trp, respectively) in *trans* to a known recessive hearing loss *GJB2* variant (p.Val37Ile). Intrafamilial variability was consistent with the more severely affected individuals having

both the dominant and recessive variants (Pang et al., 2014). Based on these examples and the experiments described above, it can be hypothesized that our patient's naturally conceived pregnancies could be at risk for PPK with deafness from the p.Met34Lys variant alone. The severity of the skin findings would be predicted to be less in a child with a normally functioning second allele. Pregnancies would not be at risk for autosomal recessive nonsyndromic hearing loss (DFNB1A), unless her partner/sperm donor were to be a *GJB2* pathogenic variant carrier or affected with DFNB1A themselves.

In summary, we report a case of PPK with deafness due to a novel variant in *trans* to a truncating variant. The pathogenicity of the p.Met34Lys variant was studied beyond correspondence to the patient phenotype by expressing it in rat epidermal keratinocytes and uncovering its failure to form a gap junction channel in the plasma membrane. Our findings also provide evidence that variants causing PPK, when paired with a truncating variant on the other allele, may result in an expanded and more severe phenotypic presentation.

6 | DATA AVAILABILTY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTION

All authors have reviewed, discussed, and agreed to their individual contributions to this work as described below. Emma C. Bedoukian: conceptualization, writing—original draft, reviewing, and editing, submission. Stefan Rentas: conceptualization, writing—reviewing and editing, laboratory work, and interpretation. Cara Skraban: writing—reviewing and editing. Qing Shao: laboratory studies, writing—reviewing and editing. James Treat: writing—reviewing and editing. Dale W. Laird: conceptualization, methodology, writing—reviewing and editing. Kathleen E. Sullivan: conceptualization, writing—reviewing and editing, resources.

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