A novel connexin 26 gene mutation associated with features of the keratitis-ichthyosis-deafness syndrome and the follicular occlusion triad

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We report the case of a congenitally deaf white male with mild palmoplantar keratoderma, ichthyosiform scaling, follicular hyperkeratosis, and mild keratitis, features consistent with keratitis-ichthyosis-deafness syndrome. His major problem was severe, disfiguring, inflammatory dissecting folliculitis of the scalp, hidradenitis suppurativa, and cystic acne, features comprising the follicular occlusion triad. This unusual phenotype is associated with a novel heterozygous point mutation (C119T) in the gap junction β2 gene that substitutes a valine for alanine at codon 40 (A40V) in the connexin 26 protein. Through Xenopus oocyte expression studies, this mutant protein was shown to significantly disrupt the function of the specialized gap junctions connecting the cytoplasm of adjacent cells critical for tissue homeostasis. Mutations within the connexin 26 protein are associated with syndromes involving both sensorineural deafness and hyperkeratotic skin disorders. This is the first report of an association between a connexin 26 protein mutation, follicular hyperkeratosis of keratitis-ichthyosis-deafness syndrome, and severe follicular occlusion triad. (J Am Acad Dermatol 2004;51:377-82.)

Syndromes of sensorineural deafness and hyperkeratotic skin disorders result from mutations in connexin 26 (Cx26) encoded by the gap junction β2 (GJB2) gene on chromosome 13 (p 11.1).1 These mutations disturb cellular structures called gap junctions, specialized channels connecting the cytoplasms of adjacent cells. Intercellular signaling through gap junctions is essential for tissue homeostasis, tissue growth and development, and cellular response to external stimuli.2 Gap junctions are formed from 6 connexins that join to form hexameric hemicannels (connexons), which in turn abut an adjacent cell’s connexons to form the gap junction. These intercellular channels allow cells to selectively regulate the exchange of a variety of small molecules and ions and, thus, influence a wide range of cellular activity.1 Although mutations throughout GJB2 are associated with both autosomal recessive and dominant sensorineural hearing loss,3 the syndromes that involve both deafness and skin disorders, such as Vohwinkel’s syndrome4 and keratitis-ichthyosis-deafness (KID) syndrome5,6 tend to cluster within a small region of GJB2 that encodes the first extracytoplasmic domain of Cx26.

CASE REPORT
The patient, a 15-year-old white male, was one of two children of healthy, unrelated parents. He was referred for immune evaluation for extensive, recurring cysts on the scalp, face, chest, back, axillae, and groin requiring repeated courses of antibiotics, and extensive surgical debridement and grafting.

He was the product of an uneventful pregnancy and delivery, but shortly after birth, high-frequency sensorineural hearing impairment was diagnosed. At 5 years of age, chronically recurrent cystic acne appeared on his face and torso. With the onset of puberty, painful, interconnected, draining abscesses on the face, scalp, neck, chest, and axillae, inguinal, intergluteal, and perianal areas developed. He required numerous hospitalizations for surgical
debridement of these lesions with extensive grafting. Cultures from these abscesses yielded no growth or variously grew Staphylococcus aureus, S epidermidis, and Serratia marcescens. Prophylactic antibiotics were of only moderate benefit. Isotretinoin (2 mg/kg) was ineffective. He had 4 episodes of clinically suggested pneumonia as a child, but no other systemic infections. There was no family history of hyperkeratosis, deafness, or severe infections. There was a history of cystic acne on the paternal side. His sister and parents were phenotypically normal.

Examination showed a well-developed young man with sensorineural hearing impairment. Extensive scarring on his scalp (Fig 1, A), face, and neck was caused by the disease process, and by debridement and grafting procedures. He had active papulopustules and cysts on his face (Fig 1, B), torso, and suprapubic and intergluteal areas. His axillae, suprapubic, inguinal, and intergluteal areas showed interconnected draining sinuses surrounded by macerated nearly verrucous hyperkeratotic skin, reminiscent of acanthosis nigricans (Fig 1, C). He had neither oral hyperkeratosis nor abnormal dentition. Tonsils were present and there was no organomegaly. Leukonychia without nail pitting, mild palmoplantar keratoderma (Fig 1, D), and mild keratitis were also present. His body hair, including eyebrows and eyelashes, was normal except for areas of scarring alopecia.

**METHODS AND RESULTS**

Extensive evaluation for an immune-based cause of his recurrent infections was negative. Deafness was determined to be sensorineural. The presence of mild vascularizing keratitis was confirmed by slit lamp examination. Skin biopsy specimens from a scalp graft-donor site and from macerated skin in the axilla showed papillomatosis with marked hyperkeratotic skin, reminiscent of acanthosis nigricans (Fig 1, C). He had neither oral hyperkeratosis nor abnormal dentition. Tonsils were present and there was no organomegaly. Leukonychia without nail pitting, mild palmoplantar keratoderma (Fig 1, D), and mild keratitis were also present. His body hair, including eyebrows and eyelashes, was normal except for areas of scarring alopecia.

**DISCUSSION**

Genetic studies have linked mutations in connexin genes with a spectrum of disorders including hearing loss, neuropathy, cataract formation, and a variety of dermatologic syndromes. GJB2 was selected for analysis in this case because defects in Cx26 are the most common single cause of genetic hearing loss in Caucasian people of European descent and are associated with hyperkeratotic skin disorders.

As the patient’s parents were both homozygous normal at 119, this case appears to represent a spontaneous missense point mutation. GJB2 C119T leading to A40V has not been found in any cases of syndromic, nonsyndromic, dominant, or recessive deafness, or in 132 control chromosomes.

Our patient’s mutation is within the first extracellular domain at the junction of the first membrane-spanning domain of the Cx26 protein. Significantly, its location is consistent with other GJB2 mutations previously associated with clinical syndromes that include both deafness and skin disease (Fig 2, B). This region is highly conserved across those β-gap junctions involved in skin disorders and/or deafness in both human beings and mice and is crucial for voltage gating and connexon-connexon interactions. Gap junctions control and coordinate the rapid, but regulated, exchange of small ions, metabolites, and signaling molecules in part through their ability to open and close. As shown by our oocyte functional data, A40V appears to compromise this function.

The principle connexins in human skin are Cx26 and connexin 43. Cx26 is normally restricted to hair follicles and eccrine sweat glands. Although Cx26 is not expressed on normal mature keratinocytes, it has been found in the hyperplastic epidermis of lesions of psoriasis, basal cell carcinoma, chronic wounds, viral warts, and in the physiologic hyperproliferation of both vaginal and buccal epithelium. Cx26 mutations associated with palmoplantar keratoderma disrupt intercellular conductance of coexpressed connexin 43 and, therefore, may exert their cutaneous phenotype in part through their negative effect on connexin 43.
The follicular occlusion triad, consisting of hidradenitis suppurativa, severe cystic acne, and dissecting cellulitis of the scalp, is a conspicuous feature of this case. In its early stages, keratin plugs or comedones are prominent characteristics of this syndrome. Although not reported in others with KID syndrome, it is possible that features of the follicular occlusion triad result from the

Fig 1. Phenotype of patient. Scarring alopecia of scalp from combination of disease process and surgical debridement (A), papulopustules and cysts over face (B), erosion and maceration of axillary vault with acanthosis nigricans-like changes (C), and mild plantar keratoderma (D).
hyperproliferative tendency of this patient’s epidermis leading to plugging of the follicular orifices, cyst formation, and rupture and spillage of keratin and glandular secretions into the subcutaneous tissue. This extruded keratin and secretions are known to cause an inflammatory response. However, the exact mechanism for the extensive inflammation, tissue destruction, sinus formation, and scarring that is seen in this patient remains to be elucidated.

Much remains to be learned about the interplay of gap junctions and inflammatory processes. Studies have suggested that loss of gap junction cellular communication in murine models results from the down-regulation of connexons by such pro-inflammatory mediators as tumor necrosis factor-\(\alpha\) and IL-1\(\beta\).\textsuperscript{19,20} This loss of connexon function is hypothesized by DeMaio et al.\textsuperscript{20} to contribute to disordered tissue function during inflammation. As gap junctions may be affected by inflammatory cytokines, so disordered gap junctions may play a role in an aberrant inflammatory process. In support of this, deficiency of a pancreatic connexon significantly worsened an otherwise mild reversible form of acute pancreatitis.\textsuperscript{21}

**Fig 2.** Connexin 26 polypeptide. \textbf{A,} Sequence chromogram of portion of parents’ and patient’s gap junction \(\beta 2\) gene. Nucleotide substitution is at position 119 in proband only (arrow). \textbf{B,} Proband’s point mutation results in substitution of valine for alanine at codon 40. Nearly all mutations resulting in syndromes of hearing loss and skin disorders are clustered within first extracytoplasmic domain.
CONCLUSION

We have identified a patient with features of both KID syndrome and follicular occlusion triad, who has a novel mutation in Cx26.

We believe this novel heterozygous missense A40V mutation in GJB2 underlies our patient’s congenital sensorineural deafness and unique keratinizing disorder. The genetics of the follicular occlusion triad have yet to be discerned. The association of our patient’s follicular occlusion triad with KID syndrome may be purely coincidental. However, given the wide variation in the expression of skin disorders associated with Cx26 mutations and the significant impact on cellular viability that A40V demonstrated in the oocyte assay, it is intriguing to speculate that this novel mutation might lead to such disruption of function as to be a key factor in our patient’s unique phenotype. Whether mutations in Cx26 may underlie other unusual cutaneous inflammatory syndromes with hyperkeratosis merits further study.

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REFERENCES


Fig 3. Xenopus oocyte functional assay. A, Oocytes injected with wildtype connexin 26 (Cx26) appeared normal. B, Oocytes injected with valine for alanine at codon 40 (A40V) exhibited disorganized pigmentation. During hyperpolarizing and depolarizing voltage steps (C), negligible whole cell membrane currents were recorded from wildtype Cx26 cells (D), in contrast to large membrane currents displayed by A40V-injected cells (E).


