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Connexin channels in congenital skin disorders

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Abstract

Gap junctions and hemichannels comprised of connexins influence epidermal proliferation and differentiation. Significant advances in our understanding of the functional role of connexins in the skin have been made by studying the diseases caused by connexin mutations. Eleven clinically defined cutaneous disorders with an overlapping spectrum of phenotypes are caused by mutations in five different connexin genes, highlighting that disease presentation must be deciphered with an understanding of how connexin functions are affected. Increasing evidence suggests that the skin diseases produced by connexin mutations result from dominant gains of function. In palmoplantar keratoderma with deafness, the connexin 26 mutations transdominantly alter the function of wild-type connexin 43 and create leaky heteromeric hemichannels. In keratitis-ichthyosis-deafness syndrome, different connexin 26 mutations can either form dominant hemichannels with altered calcium regulation or increased calcium permeability, leading to clinical subtypes of this syndrome. It is only with detailed understanding of these subtle functional differences that we can hope to create successful pathophysiology driven therapies for the connexin skin disorders.

Graphical abstract

Keywords

Connexin; Epidermis; Mutation; Genetic Disease; Hemichannel; Gap Junction

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1. Introduction

Many hereditary disorders were clinically described before the underlying genetic cause was known. Physicians grouped patients with similar disease presentation and developed diagnostic criteria based on phenotype to distinguish among different disorders. The ability to identify causative mutations increased dramatically and identified roles for many gene families in the function of different organ systems, as highlighted by the story of connexins in the skin. There are many dermatologic diseases caused by diverse connexin mutations, and confusingly, the diseases share many similarities. The present challenge for both clinicians and basic scientists is to understand how the specific pathophysiologies of the distinct mutations explain the clinical similarities and differences between diseases. While this functional level of genetic to clinical correlation is still a work in progress, we will review recent mechanistic advances in our understanding of how connexin mutations cause skin disease and summarize the known connexin diseases by pathogenic mutation. We will also describe how acquired functions of mutations in different connexin genes and disorders may provide insights into the phenotypic similarities and differences between the increasing numbers of genodermatoses linked to the connexin family.

1.1. Connexins and intercellular communication

Gap junctions allow the passage of small molecules between adjacent cells in animal tissues, coupling them electrically and metabolically [1, 2]. They contain clusters of channels made from a family of proteins called connexins (Cx). Connexins have four transmembrane domains that form the channel wall and pore, connected by two extracellular loops that facilitate compatibility, docking, and gating. On the intracellular side, connexins have N- and C-termini, and a loop connecting the second and third transmembrane domains [3, 4].

Connexins oligomerize into a hemichannel (or connexon) in the ER-Golgi pathway [5, 6]. Hemichannels are then transported to the plasma membrane, where they can become functional channels by themselves, or move to regions of cell contact and find a partner hemichannel from an adjacent cell to complete gap junction channel formation [3]. Unopposed hemichannels become active under conditions of mechanical, or ischemic stress, and allow the extracellular release of molecules like ATP, glutamate, or NAD^+, provoking different physiological responses [7, 8].

Connexins have overlapping expression patterns, and many cells express more than one. For example, Cx26, Cx30, Cx30.3, Cx31, and Cx43 are all present in keratinocytes [9, 10]. Co-expression of multiple connexins within a cell influences the composition of the hemichannels and intercellular channels formed. Hemichannels can be formed either from a single connexin, or from more than one type, leading to the formation of either homomeric or heteromeric hemichannels, respectively. The formation of heteromeric hemichannels depends on the compatibility of the connexins participating, because not all connexins can interact with each other [11, 12].

1.2. Connexins in the epidermis

Epidermal keratinocytes are subdivided into the inner most basal layer, the spinous layer, the granular layer, and the outermost cornified layer. Basal layer cells proliferate and differentiate as they move outward through the spinous, granular and cornified layers, from which they are eventually shed. Connexins are thought to play a role in maintaining epidermal integrity and homeostasis [13]. Ultrastructural analyses of human skin detected gap junctions between keratinocytes in the basal, spinous, and granular layers, but not in the cornified layers [14]. These results correlated with dye-transfer experiments showing junctional communication between keratinocytes populating the three inner layers of the epidermis [15, 16], which suggested that keratinocytes organized into "communication compartments" consisting of 20-25 cells, as dye transfer occurred between basal and supra basal keratinocytes within a compartment, but was reduced between keratinocytes in neighboring compartments. Communication compartments were postulated to correlate with epidermal proliferative units, suggesting a role for gap junctional communication in regulating keratinocyte growth [15, 17].

Cx43 is expressed throughout the interfollicular epidermis, whereas Cx26 is restricted to palmoplantar skin. Cx26 and Cx43 are also found in hair follicles and sweat glands, whereas Cx30, Cx30.3, and Cx31 are expressed in the upper, differentiated epidermal layers [18, 19]. Changes in connexin expression occur in human epidermis following pathological or experimentally induced shifts in keratinocyte proliferation. In normal skin, retinoic acid treatment resulted in thickening of the epidermis and an increased number of keratinocytes which correlated with a large induction of Cx26 expression across epidermal layers, and an increase in Cx43 levels [20]. In psoriatic lesions, an induction of Cx26 occurs in the proliferative psoriatic areas but not in the surrounding epidermis [21, 22]. In wounded skin, up regulation of Cx26 expression was also observed [23]. Taken together, these studies establish a correlation between increased connexin expression and keratinocyte proliferation and differentiation.

2. Functional consequences of connexin mutations in congenital skin disease

Mutations in five connexin genes have been linked to eleven genetic skin diseases (Table 1, discussed in section 3). Six of these clinical disorders result from mutations in Cx26, and consequently much of the mechanistic research has focused on this connexin. Cx26 mutations occur with a high frequency in humans, and most result in non-syndromic deafness without skin pathology [24, 25]. An abundance of data suggests that simple loss of function mutations in Cx26 can cause non-syndromic deafness without exhibiting epidermal pathology [26, 27]. Thus, human skin does not need functional Cx26 either during development or for normal homeostasis, yet certain mutations dramatically perturb homeostasis, possibly through dominant gain of function mechanisms. If syndromic Cx26 mutations that cause skin disease and deafness show a gain of function, then distinct skin pathologies may differentiate unique gain of function alterations in Cx26 channels.

2.1 Functional properties of Cx26 mutations linked to palmoplantar keratoderma associated with deafness (PPK)

Functional consequences of Cx26 mutations can be explored by comparing the channel activity of wild-type and mutant proteins. Using electrophysiological measurements of gap junctional coupling, it has been shown that five different mutations causing PPK, Cx26-H73R, Cx26-S183F, Cx26-R75W, Cx26-ΔE42 and Cx26-D66H, all lacked intrinsic gap junction channel activity. Four of the five showed dominant-negative inhibition of co-expressed wild-type Cx26, suggesting a mechanism for their contribution to hearing loss. When these mutations were co-expressed with Cx43, they all produced trans-dominant inhibition of Cx43 gap junction channels [28-30]. This suggested that skin disease caused by PPK mutations might be manifested through a common gain of function mechanism where the Cx26 mutations dominantly interact with other connexins, such as Cx43. This model was supported by analysis of a sixth mutation associated with PPK, Cx26-G59A. Using a dye transfer assay, it was shown that Cx26-G59A failed to form functional channels by itself, and reduced dye transfer between cells when co-expressed with either wild-type Cx26 or Cx43 [31]. Consistent with this, another dye transfer analysis of the Cx26-G59A and Cx26-R75W mutations showed that both could dominantly inhibit either wild-type Cx26 or Cx30 [32, 33].

A recent study also examined the ability of two PPK mutations to form functional hemichannels. Both Cx26-H73R and Cx26-S183F failed to form hemichannels when expressed alone in *Xenopus* oocytes. However, co-expression of the mutants with Cx43 showed significantly increased hemichannel activity in the presence of either mutant, compared to Cx43 alone. Co-immunoprecipitation experiments showed that Cx43 could be pulled down more efficiently with Cx26-H73R and Cx26-S183F than wild-type Cx26, confirming the enhanced formation of heteromeric hemichannels [30]. This result was surprising, as previous reports had shown that wild-type Cx26 was unable to co-oligomerize with Cx43 [34], and Cx43 expression failed to induce voltage-activated hemichannel currents in *Xenopus* oocytes [35].

Thus, two gain of function mechanisms have emerged for Cx26 mutations linked to PPK: i) inhibition of gap junction channels formed by other keratinocyte connexins (Cx26, Cx30 and Cx43) and ii) formation of active heteromeric hemichannels with Cx43. The trans-dominant inhibitory action of mutant proteins reduces the number of gap junction channel types available in the epidermis, and may alter both the type of molecules exchanged and the overall magnitude of gap junctional communication. Leaky hemichannels could cause uncontrolled release of cell contents like metabolites and signaling molecules into the extracellular space, affecting the behavior of surrounding cells in addition to initiating cell death. The most common mechanism thus far suggests that PPK mutations trans-dominantly alter functions of wild-type Cx43, and that novel heteromeric structures act as the pathological unit underlying inhibition of gap junction channels and the activation of hemichannels.

2.2 Functional properties of Cx26 mutations linked to keratitis ichthyosis deafness syndrome (KID)

If PPK causing mutations are characterized by trans-dominant interactions with other connexins like Cx30 and Cx43, then KID mutants might be expected to display a different alteration of Cx26 activity. This idea was supported by the first study of a KID mutation, Cx26-A40V [36]. Expression of Cx26-A40V in *Xenopus* oocytes induced large membrane currents consistent with constitutively active hemichannels. Work from several labs has established that aberrant opening of mutant Cx26 hemichannels was a common gain of function that could contribute to the skin phenotype of KID [37-43]. One exception to this rule was the KID mutation Cx26-S17F, which failed to form active hemichannels when expressed alone [39]. This enigma was resolved when a recent study demonstrated increased hemichannel activity of Cx26-S17F in the presence of wild-type Cx43 [44]. As described for heteromeric hemichannels containing PPK mutants in section 2.1, Cx26-S17F was unable to form hemichannels or gap junction channels alone, but showed significantly increased hemichannel activity when co-expressed with Cx43. Unlike the case for PPK, several of the KID mutations can also form functional gap junction channels [38, 39, 41].

More detailed studies have investigated how changes in hemichannel gating and permeation resulting from KID mutations might contribute to the loss of epidermal homeostasis. Hemichannels are large aqueous pores, allowing inorganic cations and anions, as well as larger metabolites to permeate. Cysteine scanning of three mutants, Cx26-A40V, Cx26-G45E, and Cx26-D50N revealed that two of the three residues, G45 and D50, lined the hemichannel pore. In addition, the unitary conductances of the three hemichannels were found to be markedly different. Cx26-A40V hemichannels were indistinguishable from wild-type Cx26, while Cx26-G45E and Cx26-D50N had unitary conductances that were 20% larger and 50% smaller, respectively. In addition, calcium regulation of the hemichannels differed for the three mutations; Cx26-A40V and Cx26-D50N showed significantly reduced inhibition by extracellular Ca^{2+}, whereas Cx26-G45E showed only modest impairment in Ca^{2+} regulation. However, Cx26-G45E hemichannels showed a substantially increased permeability to Ca^{2+}, whereas Cx26-D50N reduced hemichannel Ca^{2+} permeability [41, 42]. These data suggest that Cx26-A40V, Cx26-G45E and Cx26-D50N are all gain of hemichannel function mutations that produce similar epidermal pathology, but through somewhat different underlying mechanisms. Cx26-A40V and Cx26-D50N make hemichannels that lose inhibitory regulation by extracellular calcium, whereas Cx26-G45E has substantially increased Ca^{2+} permeability. Since wild-type Cx26 is known to be permeable to Ca^{2+} [45], the net results would be similar from a normally open channel with higher permeability (G45E), or a channel with normal permeability but much higher open probability (A40V). Calcium is a central regulator of keratinocyte differentiation, and the epidermis maintains an extracellular calcium gradient, with the highest concentrations in the granular layer and an abrupt reduction in the cornified layer [46]. The aberrant properties of KID hemichannels with respect to calcium would likely disrupt this gradient.

Additional support for KID hemichannels disrupting the calcium homeostasis has come from studies of mouse models of KID syndrome (Figure 1). Transgenic mice expressing the Cx26-G45E and Cx26-S17F mutations have been generated, and both models develop

features of KID syndrome [47, 48]. Cx26-G45E mice develop a severe lethal form of the disease, and significantly increased hemichannel activity was found to be present in primary keratinocytes derived from KID lesions [47]. In Cx26-S17F animals, the epidermal calcium gradient was altered, with elevated Ca^{2+} found in both the intra- and extracellular compartments of the cornified layer, which was correlated with defects in the epidermal water barrier and altered lipid secretion [49].

2.3 A generalized role for hemichannels in connexin skin disorders

Increased hemichannel activity has now been linked to Cx26 mutations underlying both KID and PPK. While not as thoroughly studied, there is evidence that altered hemichannel function may also play a role in other connexin genodermatoses. For example, the Cx30 mutants, Cx30-G11R and Cx30-A88V, associated with hidrotic ectodermal displaysia (HED) caused cell death *in vitro*, which could have resulted from the presence of functional hemichannels, an idea supported by the detection of large voltage-activated currents in cells expressing mutant proteins. Analysis of HeLa cells transfected with Cx30-G11R and Cx30-A88V showed that cells expressing the mutant connexins had an ATP leakage 2-3 fold higher than control cells, suggesting that ATP release through hemichannels may play a role in the HED syndrome phenotype [50]. Additional support for active hemichannels contributing to skin disease came from analysis of the Cx43-G8V mutation causing keratoderma-hypotrichosis-leukonychia totalis syndrome (KHLT). Expression of the Cx43-G8V mutation in HEK293 cells resulted in the formation of functional gap junction channels and increased hemichannel activity [51]. The Cx43-G8V hemichannels increased membrane current, Ca^{2+} influx, and cell death compared to wild-type Cx43. Some Cx43 mutations causing Oculodentodigital dysplasia (ODDD) have also been shown to exhibit increased hemichannel activity [52], although it remains to be seen if there is any clear correlation with skin pathology. ODDD mutations linked to skin disease have also been shown to display dominant negative inhibition of wild-type Cx43 [53, 54].

3. Human epidermal disorders caused by connexin mutations

3.1 Syndromic diseases caused by mutations in *GJB2* (Cx26)

Currently, five syndromic diseases are attributed to mutations in Cx26 (Table 1). Common to all are sensorineural deafness and palmoplantar keratoderma (thickening of the skin on the palms and soles). Cx26 is expressed at low levels in palmoplantar skin [55], whereas hyperproliferative epidermis demonstrates upregulated Cx26 [20]. Syndromic diseases due to Cx26 can be broadly divided into two groups. In the first group, PPK with deafness [28], Vohwinkel syndrome (VS) [56], and Bart-Pumphrey syndrome (BP) [57] are thought to represent phenotypic subtypes within a spectrum, and the pathogenic mutations among the three diseases overlap and mainly affect the first extracellular loop (Figure 2). Clinically, they are similar as well, with palmoplantar keratoderma and deafness, but without the widespread keratoderma seen in keratitis-ichthyosis-deafness syndrome or hystrix-like ichthyosis deafness syndrome [58].

PPK, VS and BP have a few distinguishing characteristics, which led to their different categorization, but it is unclear how important these characteristics are. Palmoplantar

keratoderma develops in infancy in VS, in childhood in BP. VS has starfished-shaped keratoses over the knuckles, BP has knuckle pads [59, 60]. Finally, VS patients, but not BP patients, have been described to have constrictive bands on their fingers and toes leading to pseudoainhum (auto-amputation) [59]. BP patients on the other hand have been found to have leukonychia (white nails) that improves over time [60].

KID syndrome [61, 62] and hystrix-like ichthyosis deafness syndrome (HID) [63] form the second group and have deafness and palmoplantar keratoderma, like the other syndromic Cx26 diseases. However, in KID/HID the skin involvement is more extensive. The thickening, or hyperkeratosis, of the palm and soles also involve other areas of the body, initially described as ichthyosis [64], but keratoderma is used here to more accurately describe the clinical presentation seen in KID syndrome [65].

HID syndrome was historically described for patients with widespread severe keratoderma, mild PPK, and no vascularizing keratitis (although punctate keratitis had been reported as well) [66, 67]. However, the only known causative mutation for HID syndrome is Cx26-D50N [63], which is also the most common mutation seen in KID syndrome [68], and increasingly HID is thought to be a variant of KID syndrome.

Even among patients with KID syndrome, there is a strongly dichotomous genotype-phenotype correlation [40]. Patients with Cx26-D50N, the most common mutation, live into adulthood, and clinical concerns include vascularizing keratitis causing blindness, and development of squamous cell carcinomas in chronically inflamed skin [68, 69]. However, for patients who carry Cx26-G45E or Cx26-A88V [70-75], the prognosis is grim, as every patient has died in early childhood from sepsis, possibly augmented by an uncharacterized immune dysfunction [76]. One patient with Cx26-S17F has also presented with the lethal form of the disease [77].

One recent lethal case of KID syndrome in a patient with Cx26-G45E demonstrated a novel genetic pathogenesis, and resolved a mystery in the genetics of syndromic deafness [74]. Initial reports had identified Cx26-G45E as a recessive allele causing nonsyndromic deafness in the Japanese population [78, 79], a role incompatible with its dominant linkage to lethal KID syndrome. In a larger follow-up study of 1343 Japanese patients with sensorineural hearing loss, 33 patients were identified who carried the Cx26-G45E mutation, but lacked any dermatological problems [80]. These patients were also found to have Cx26-Y136X mutations in cis.

Subsequent screening of 920 healthy Japanese controls showed that none carried either Cx26-G45E or Cx26-Y136X alone, suggesting the two mutations were in complete linkage disequilibrium in the Japanese population, and it was hypothesized that Cx26-Y136X in cis protected patients from their otherwise lethal Cx26-G45E mutation [74].

It had been theorized, but never documented in any human disease, that a revertant mutation could release the disease state caused by a lethal mutation previously confined by a co-existing nonsense mutation. The first case of KID syndrome due to Cx26-G45E presented in Japan as a result of this revertant mechanism [74]. The patient’s healthy mother was heterozygous for Cx26-G45E/Cx26-Y136X mutation in cis, which confined the diseased

Cx26 product and protected her from KID syndrome. A prezygotic recombination event in the patient's mother removed the Cx26-Y136X mutation in cis, leaving only Cx26-G45E in the patient, who developed typical manifestations of lethal KID syndrome. In vitro assays confirmed that the Cx26-G45E mutant, but not the Cx26-G45E/Y136X mutant induced abnormally high hemichannel activity in neurobiotin uptake assays [74].

3.2 Non-syndromic skin-limited diseases caused by mutations in *GJB2* (Cx26)

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) [81, 82] manifests as an epidermal nevus in a linear Blaschkoid pattern [83]. Lines of Blaschko represent the developmental path of ectodermal precursor cells, and post-zygotic somatic mutations in one of these precursors lead to a disease state in the resulting linear band of keratinocytes [84]. Mutations in Cx26 were first hypothesized to be the cause of PEODDN because several patients with KID syndrome were found to additionally have porokeratotic eccrine ostial and dermal duct nevi [81, 82]. Cx26 mutations in the affected skin, but not peripheral blood or unaffected skin, were found, confirming this hypothesis [81]. Finally, whole exome sequencing of paired blood and affected skin also identified Cx26 mutations only in the affected epidermis [85]. All of the somatic mutations identified to date were single amino acid changes linked to KID syndrome. Thus, PEODDN is a mosaic form of KID syndrome resulting from a post-zygotic somatic mutation affecting only a small portion of keratinocytes. This is clinically significant when patients with porokeratotic eccrine ostial and dermal duct nevi are of childbearing age, as they need to be counseled that there is a risk their sperm or ova also carry the mutation [85].

3.3 Syndromic diseases caused by mutations in *GJA1* (Cx43)

Oculodentodigital dysplasia (ODDD) [86] is unlike any of the other syndromic connexin diseases in that the hearing loss is conductive, not sensorineural [87, 88]. Skin findings are not common and when present are generally mild with variable hair loss, nail brittleness, and rare cases with palmoplantar keratoderma [89]. It would be reasonable to hypothesize then that either Cx43 is not critical for skin function, or other connexins provide redundancy. More striking in ODDD are the characteristic facial and digital structural anomalies, including microcephaly, microphthalmia, thin noses, and syndactaly [87].

3.4 Non-syndromic skin-limited diseases caused by mutations in *GJB6* (Cx30)

Ectodermal dysplasias are a group of diseases in which structures derived from the ectoderm (e.g. hair, teeth, nails, sweat glands, mucous glands, and sebaceous glands) are abnormal [90]. HED (also known as Clouston syndrome) is the only one caused by connexin mutations [91, 92]. Patients have thickened dystrophic nails, and often have short wiry hair or no hair [93]. Other ectodermally derived structures are unaffected. Like many of the other connexin disorders, these patients also have diffuse palmoplantar keratoderma [94]

In HED, the dorsal aspects of the hands and feet can have pebbly pink lesions corresponding to enlarged eccrine acrosyringia, which can transform with growth into syringofibroadenomas, a benign eccrine tumor [95]. Rarely, cases of HED with longstanding syringofibroadenomas have been found to develop squamous cell carcinomas [96], although it is unclear if these tumors are a direct result of aberrant connexin function.

3.5 Non-syndromic skin-limited diseases caused by mutations in *GJA1* (Cx43)

Keratoderma-hypotrichosis-leukonychia totalis syndrome (KHLT) has recently been found by exome sequencing to be caused by the mutation Cx43-G8V [51]. Unlike ODDD, KHLT has severe skin dysfunction with hyperkeratosis of areas of the body prone to friction (e.g., ankles, elbows, and knuckles), congenital alopecia, and white discoloration of all twenty nails [97]. In vitro experiments showed that the mutation increased hemichannel activity [51]. If indeed the cutaneous disease phenotype of KHLT is from Cx43-G8V's gain of function, it reinforces that like KID syndrome among others, one must not only know the affected gene, but also how the protein activity is functionally altered.

3.6 Non-syndromic skin-limited diseases by mutations in *GJB3*, *GJB4*, and *GJA1* (Cx31, Cx30.3, and Cx43, respectively)

Erythrokeratodermia variabilis et progressiva (EKVP) can result from mutations in one of three different connexin genes [89, 98, 99]. Historically, erythrokeratoderma variabilis and progressive symmetric erythrokeratoderma were considered separate entities even though both had sharply demarcated hyperkeratotic plaques, because erythrokeratoderma variabilis would present with the additional component of transient pink patches. Furthermore, the distribution of progressive symmetric erythrokeratoderma was thought to be more predictable, i.e. symmetric, and favoring extensor surfaces such as arms and legs. Approximately half the patients with either disease would have palmoplantar keratoderma as well [100]. Erythrokeratoderma variabilis was first linked to mutations in Cx31, and subsequently Cx30.3 [98, 100].

However, some patients with erythrokeratoderma variabilis never had many transient pink patches, and most patients' skin lesions over time would stabilize [101]. Thus, it was not surprising that mutations in Cx30.3 were found in patients with both erythrokeratoderma variabilis and progressive symmetric erythrokeratoderma [102]. One family had two daughters, one of whom clinically had erythrokeratoderma variabilis and the other daughter progressive symmetric erythrokeratoderma, and the pathology of their skin lesions were identical [101]. Thus, the term erythrokeratodermia variabilis et progressiva was proposed to encompass both.

Terminology aside, there were still patients with EKVP with unknown mutations [103]. Recently, a group of these patients were found to carry Cx43 mutations [89]. These patients with EKVP shared striking features such as thick white lunulae without nail dystrophy and periorificial darkening, which had not been previously reported in the other connexin-associated cases. As we learn more about genotype-phenotype correlations, a more logical nomenclature for these diseases would include both the identified mutation in a patient and their manifestation of the disease, such as for these patients Cx43-associated EKVP.

4. Conclusions

Accumulating evidence suggests that diverse connexin mutations associated with distinct epidermal phenotypes consistently give rise to novel gain of function activities. It is likely that numerous disease mechanisms, including changes in hemichannel activity, may be

involved for the hereditary skin diseases involving connexins. Indeed, mechanisms may even vary within individual clinical classifications, as appears to be the case for the KID causing mutation Cx26-S17F. There may also be common pathological mechanisms across the diverse disorders. Thus far, the leading mechanism appears to the formation of dysregulated hemichannels that perturb calcium homeostasis both within keratinocytes, and in the extracellular epidermal calcium gradient. Additional characterization of disease causing mutations and the further study of transgenic animals expressing them in the skin will improve our understanding of the pathophysiology of the connexin skin diseases. Experimental approaaches combining specific connexin inhibitors with the existing animal models will be a powerful next step toward confirming, or eliminating, any proposed role of hemichannel activity in skin disease.

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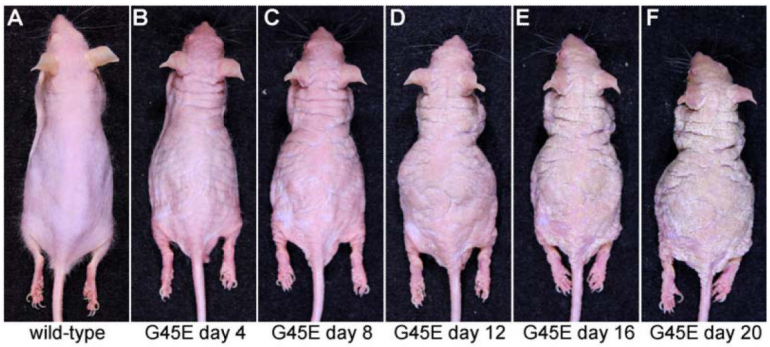

Figure 1.

A mouse model of KID syndrome. Eight-week-old control or transgenic mice were induced with doxycycline chow. Expression of human Cx26-G45E in basal keratinocytes produced a progressive pathology over 3 weeks that replicated the epidermal features of KID syndrome. (A). A control mouse has normal skin. (B-F) A transgenic mouse imaged on days 4-20 after induction at 4 day intervals. Changes are evident at day 4 and pathology is severe by day 20.

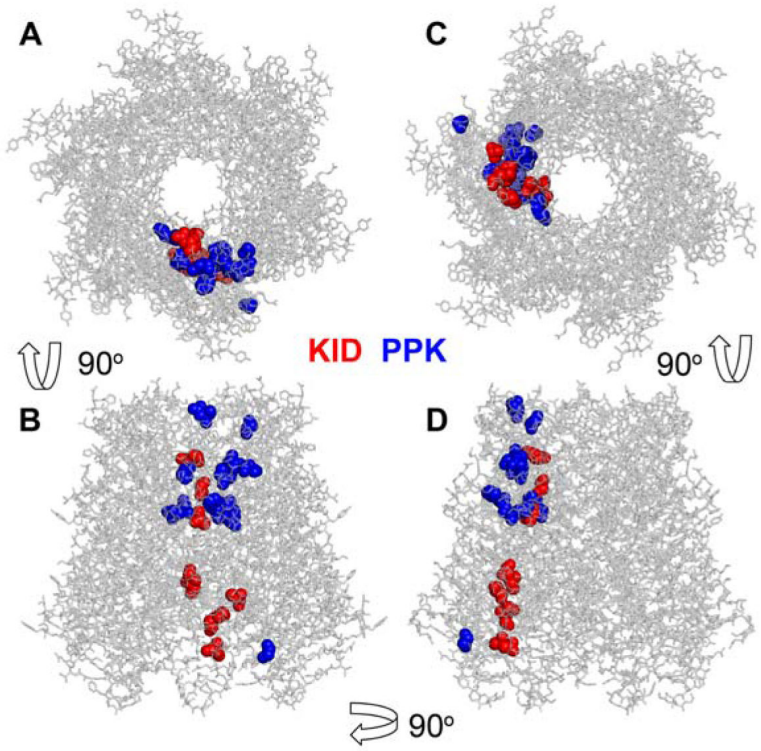

Figure 2.

Syndromic Cx26 mutations mapped onto the crystal structure of Cx26. Amino acids mutated in KID disorders are colored red, and those mutated in PPK disorders are colored blue. Only one of the six subunits present in the hemichannel has been labeled. (A). View from the extracellular surface of the hemichannel looking into the cell through the pore. (B). Side view of a hemichannel with the extracellular surface pointed up. (C). View from the intracellular hemichannel surface looking out through the pore. (D). Side view of a hemichannel with labeled residues rotated 90 degrees. KID mutations tend to line the channel pore, whereas PPK mutations cluster near the extracellular end of the channel and are distributed across the channel wall.

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Table 1

Clinical phenotypes of connexin skin diseases.

	gene	protein (mutation)	mode	palmoplantar keratoderma	other keratoderma	deafness	leukonychia	nail dystrophy	hypotrichosis	other skin findings	other findings
syndromic											
palmoplantar keratoderma with deafness (OMIM 148350)	*GJB2*	Cx26 (Del42E, N54H, G59A, G59R, H73R, R75Q, R75W, G130V, S183F)	AD	diffuse> focal		sensori-neural					
Vohwinkel syndrome (OMIM 124500)	*GJB2*	Cx26 (D66H, G59S, G130V)	AD	diffuse	rarely	sensori-neural			rarely	pseudoainhum, starfish keratosis on knuckles	
Bart-Pumphrey syndrome (OMIM 149200)	*GJB2*	Cx26 (N54K, G59S)	AD	diffuse		sensori-neural	variable improves with age			knuckle pads	
keratitis ichthyosis* deafness syndrome (OMIM 148210)	*GJB2*> *GJB6*	Cx26 (G12R, N14K, N14Y , S17F, A40V, G45E, D50N, D50Y, A88V) > Cx30 (V37E)	AD	diffuse	areas of friction sometimes ulcerated	sensori-neural		variable	variable		vascular keratitis
hystrix-like ichthyosis deafness syndrome (OMIM 602540)	*GJB2*	Cx26 (D50N)	AD	Diffuse, milder than KID	more severe & extensive than KID	sensori-neural		variable	variable		absent to punctate keratitis
oculodentodigital dysplasia (OMIM 164200)	*GJA1*	Cx43 (Y17S, S18P, G21R, G22E, V96M, F52dup, R76S, L90V, Y98C, K102N, I130T, K134E, G138R, R202H, V216L, fs260)	AD	mild in rare cases		conductive		mild, some brittleness	variable		many, see [82]
non-syndromic											
porokeratotic eccrine ostial and dermal duct nevus	*GJB2*	Cx26 (N14Y, G12R, G45E, M93I)			Blaschkoid plaques						
erythrokeratodermia variabilis et progressiva (OMIM 133200)											
erythrokeratodermia variabilis	*GJB3*, *GJB4*> *GJA1*	Cx31 (G12R, G12D, L34P, R42P, C86S, L135V, F137L, L209F), Cx30.3 (R98C, T130M, F137L,	AD> AR	variable	geographic plaques		prominent lunulae with GJA1 mutations			transient geographic pink patches (in childhood)	

	gene	protein (mutation)	mode	palmoplantar keratoderma	other keratoderma	deafness	leukonychia	nail dystrophy	hypotrichosis	other skin findings	other findings
		M190L) > Cx43 (E227D, A44V) M190L) > Cx43 (E227D, A44V)									
progressive symmetric erythrokeratodermia	*GJB4*	Cx30.3 (G12D)	AD	variable	progressive symmetric plaques on extensors > trunk						
hidrotic ectodermal dysplasia (Clouston) (OMIM 129500)	*GJB6*	Cx30 (G11R, V37E, D50N, A88V)	AD	focal in areas of friction					total body worsens with age	pebbly plaques on dorsal fingers and toes	
keratoderma-hypotrichosis-leukonychia totalis syndrome (OMIM 104100)	*GJA1*	Cx43 (G8V)	AD	focal in areas of friction	plaques in areas of friction		all 20 nails		total body	keratosis pilaris	

Disease names are those that have been used in the literature. The colors group diseases whose cutaneous clinical features make them difficult to distinguish. This applies both to diseases of similar phenotype but different genotype (EKV and PSEK) as well as disease of similar genotypes exhibiting a spectrum of closely related phenotypes (VS, PPK, BP).

*As explained in section 3.1, ichthyosis is not used. The “>” sign denotes relative frequency, AD = autosomal dominant, AR = autosomal recessive.