More than keratitis, ichthyosis, and deafness: Multisystem effects of lethal GJB2 mutations

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Background: Infant death in keratitis-ichthyosis-deafness (KID) syndrome is recognized; its association with specific genotypes and pathophysiology is inadequately understood.

Objective: We sought to discover characteristics that account for poor outcomes in lethal KID syndrome.

Methods: We collected 4 new cases and 9 previously reported, genotyped cases of lethal KID syndrome. We performed new molecular modeling of the lethal mutants *GJB2* p.A88V and *GJB2* p.G45E.

Results: Infant death occurred in all patients with *GJB2* p.G45E and p.A88V; it is unusual with other *GJB2* mutations. Early death with those 2 "lethal" mutations is likely multifactorial: during life all had ≥1 serious infection; most had poor weight gain and severe respiratory difficulties; many had additional anatomic abnormalities. Structural modeling of *GJB2* p.G45E identified no impact on the salt bridge previously predicted to account for abnormal central carbon dioxide sensing of *GJB2* p.A88V.

Limitations: This clinical review was retrospective.

Conclusion: *GJB2* p.G45E and p.A88V are the only KID syndrome mutations associated with uniform early lethality. Those electrophysiologically severe mutations in *GJB2* reveal abnormalities in many organs in lethal KID syndrome. All patients with KID syndrome may have subtle abnormalities beyond the eyes, ears, and skin. Early genotyping of KID syndrome births will inform prognostic discussion. (J Am Acad Dermatol 2019;80:617-25.)

Key words: connexin 26; gap junction protein, beta-2; keratitis, ichthyosis, and deafness syndrome.

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Keratitis-ichthyosis-deafness (KID) syndrome is a rare congenital disorder caused by autosomal dominant mutations in the *GJB2* gene that encodes connexin 26 (Cx26). Affected individuals typically are born with erythrokeratoderma and may develop degrees of sensorineural hearing loss and progressive vascularizing keratitis. A previous review suggested that certain patients with KID syndrome die in infancy because of sepsis, but did not evaluate their specific mutation nor abnormalities in other organ systems.[1] More recently, cases of "lethal KID syndrome" have been reported with mutations p.A88V and p.G45E in *GJB2*.[2-6] One group suggested that the p.A88V mutation depresses breathing through centrally impaired carbon dioxide (CO_2) sensing.[7]

CAPSULE SUMMARY

- Early lethality in keratitis-ichthyosis-deafness syndrome has been attributed to infection or impaired central carbon dioxide sensing.
- Uniform lethality with 2 mutations in *GJB2* had no single cause of death. Many organ systems had abnormalities.
- Clinicians should be alert to abnormalities beyond keratitis, ichthyosis, and deafness. Early genotyping will guide management.

When we became aware of 4 previously unreported infants with KID syndrome who died in infancy despite aggressive antimicrobial prophylaxis, we sought answers to the following questions: 1) Is there evidence that the *GJB2* p.A88V and p.G45E mutations are not uniformly lethal in infancy? 2) Do other *GJB2* mutations result in infant mortality? 3) Is there a single cause for the lethal outcome associated with those 2 mutations, and is abnormal CO_2 sensing sufficient to account for infant mortality in lethal KID syndrome? 4) In severe cases of KID syndrome, is there evidence for disease in organs other than skin, cornea, and inner ear?

METHODS

We reviewed new (cases 2-5) and previously published (cases 1 and 6-13) cases of lethal KID syndrome where *GJB2* mutations were identified and contacted the primary providers to obtain detailed clinical information. Primary data, including cultures, laboratory and imaging results, and pathology reports were reviewed when available. Two cases had post mortem examinations. One lethal case with a p.S17F mutation[8] was excluded because patients with this mutation usually survive into adulthood.[9]

Of the 16 cases identified, detailed clinical information was available for 13 patients. For 11 of these cases, we confirmed clinical details with the primary dermatologist. For the 2 remaining cases (6 and 13), we relied on their published case reports.[1,2] The Yale Institutional Review Board ruled this project exempt from review.

Structural analyses were performed based on the crystal structure of Cx26 (Protein Data Bank code 2ZW3).[10] Structural modeling and figure preparation were performed using Coot,[11] Chimera (Resource for Biocomputing, Visualization, and Informatics, University of California, San Francisco), and PyMOL Molecular Graphics System (version 1.5.0.4; Schrödinger, LLC, New York, NY).

RESULTS

Thirteen patients (9 males and 4 females) with lethal KID syndrome, 6 with the *GJB2* p.A88V mutation and 7 with the *GJB2* p.G45E mutation, were identified (Table I). These patients were from the United States, Japan, France, and Austria. No surviving cases with *GJB2* p.A88V or p.G45E mutations were identified based on literature review and diagnostic laboratory data (ClinVar; GeneDx variant database). Interestingly, some Japanese individuals with *GJB2* p.G45E mutations do not have a cutaneous phenotype because of the presence of a second, confining mutation on the same *GJB2* allele (in cis).[3] Recently published *GJB2* p.A88V case reports provided more primary clinical information than available for *GJB2* p.G45E patients. Four of 7 p.G45E patients (cases 8-11) were from a single family.

Clinical course

All but one patients were born prematurely (average 34 weeks; range 31-37 weeks). Death occurred between 10 days and 1 year of age (average 3.5 months). Academic dermatologists cared for all patients during prolonged hospitalizations in tertiary care centers. At birth or shortly thereafter, a diagnosis of KID syndrome was suspected because of skin changes, keratitis, and hearing loss, and was ultimately confirmed by genetic testing. Each patient was born with relatively mild skin disease (ie, diffuse, thin palmoplantar keratoderma with characteristic grainy surface changes), central facial hyperkeratosis, and diffuse erythrokeratoderma. Among those who survived beyond the neonatal period, all *GJB2* p.A88V and 2 *GJB2* p.G45E patients developed increasing hyperkeratosis with fissures. Intertriginous erosions

Table I. Key clinical features of patients with keratitis-ichthyosis-deafness syndrome with *GJB2* p.A88V and p.G45E variants: Summary of cases by organ system

Case no. (citation if previously reported)	Genotype	Sex	Gestational age at birth (weeks + days)	Respiratory	Cardiovascular	Central nervous system	Gastrointestinal	Skin ulceration	Skin histology	Hematologic	Thymus	Infection onset (months)	Age at death (months)	Cause of death
1 (Meigh et al[7])	A88V	M	37	Apnea requiring intubation at birth; pneumogram demonstrating central apnea; respiratory failure; bronchopneumonia	Cardiomegaly, dilated right atrium, dysplastic tricuspid valve	No gag reflex; small interruption of the left internal capsule by gray matter; subacute to chronic germinal matrix hemorrhage	Low weight and height; zinc deficiency; thin distal esophagus; difficulty with oral feeds	Intertriginous	Baseline erythrokeratoderma: hyperkeratosis, acanthosis, mild lymphocytic infiltrate, retained granular layer, impetiginization with cocci; ulcer: upper layers of epidermis with parakeratosis and extensive ballooning degeneration and necrosis, chronic inflammatory infiltrate in the dermis	Macrocytic anemia	Hypoplastic	1	5	Respiratory failure, sepsis
2	A88V	F	34	Hypoxia; hypercapnea; pneumogram suggestive of central apnea; respiratory failure	Patent foramen ovale	Poor suck reflex; mild inferior vermian hypogenesis	Low weight; mild zinc deficiency	Inguinal creases		Normocytic anemia requiring transfusion; normal flow			1.75	Respiratory failure, sepsis
3	A88V	M	33 + 6	Increased work of breathing; acute respiratory acidosis requiring intubation at end of life	Small patent ductus arteriorsus, moderately dilated left ventricle	Normal brain ultrasound	Low weight and height; enteral and parenteral nutritional supplementation	Around gastric tube; diaper area; intertriginous	New red urticarial rash on leg: accentuated granular layer, hyperkeratosis, superficial dermal edema with perivascular mixed inflammatory infiltrate	Normocytic anemia; immunoglobulins normal		2	6	Fungemia with respiratory failure
4	A88V	F	32 + 6	Increased work of breathing; intermittent apnea	Patent foramen ovale vs small secundum atrial septal defect	No gag reflex; Dandy–Walker malformation with small germinal matrix hemorrhage and severe ventriculomegaly	Difficulty with oral feeds	Intertriginous	Baseline erythrokeratoderma: hyperkeratosis, focal parakeratosis, papillomatosis, acanthosis, horn cyst formation, thin dermis, decreased number of Langerhans cells ulcer: upper third epidermis with pale cytoplasm	Anemia requiring transfusion		0.5	2	Congenital abnormality of the brainstem

Continued

Table I. Cont'd

Case no. (citation if previously reported)	Genotype	Sex	Gestational age at birth (weeks + days)	Respiratory	Cardiovascular	Central nervous system	Gastrointestinal	Skin ulceration	Skin histology	Hematologic	Thymus	Infection onset (months)	Age at death (months)	Cause of death
5	A88V	M	35-36	Hypoxia; immature lungs with patchy intraalveolar hemorrhage; early bronchopulmonary dysplasia	Hypotensive requiring pressor support; echocardiogram normal	Microcephaly; acute hypoxic change in hippocampal neurons	Low weight and height; low vitamin A; abnormal maturation of nonkeratinized squamous epithelium in esophagus	Lower abdomen		Normocytic anemia; low IgG and IgA	Thymic involution	0.5	0.75	
6* (Koppelhus et al[2])	A88V	M	33 + 4	Apnea; atelectasis; cerebral irritability that required mechanical ventilation		Hydrocephalus; intraventricular and parenchymal hemorrhage		Scalp				1		Klebsiella sepsis
7 (Ogawa et al[3])	G45E	F	36	Suspected aspiration pneumonia and bronchitis	Pulmonary artery stenosis		Nasogastric tube	Perianal and genital	Baseline erythrokeratoderma: hyperkeratosis, hypergranulosis, focal vacuolar degeneration				7	
8† (Jonard et al[4] and Sbidian et al[5]) twin A	G45E	M	31				Failure to thrive despite enteral and parental alimentation	None	Orthokeratotic hyperkeratosis, acanthosis, complete absence of granular layer; keratinocytes in the upper part of the epidermis were swollen and sometimes vacuolated				1	Pseudomonas septicemia
9† (Jonard et al[4] and Sbidian et al[5]) twin B	G45E	M	31	Candida and Staphylococcus pulmonary infection; edema and dyskeratotic laryngeal mucosae	Cardiomegaly	Dilation of left ventricle	Low weight and height; enteral nutrition for difficulty feeding; dyskeratotic esophageal mucosa	None	Orthokeratotic hyperkeratosis with focal parakeratosis, focal granular layer	Anemia; immunoglobulin and lymphocyte flow normal		3	5	Candida and Staphylococcal pulmonary infection
10† (Sbidian et al[5])	G45E	M	33				Nasogastric tube	None					11	Candida and Staphylococcal septicemia
11† (Sbidian et al[5])	G45E	M	35	Respiratory failure; Candida pulmonary infection				None					0.3	Candida pulmonary infection

12 (Janecke et al[6])	G45E	F	36	Respiratory insufficiency caused by aspiration								1	12	Septicemia
13* (Gilliam and Williams[†])	G45E	M	36	Viral upper respiratory infection			Scalp		Hyper- and parakeratosis, intraepidermal neutrophils, abundant bacteria and fungi, no ballooning degeneration		Immunoglobulins and lymphocyte phenotype panel within normal limits	3.5	6	Septicemia

F, Female; *M*, male.
*Information taken from published case reports because we were not able to communicate with the primary dermatologist.
†Cases from 1 family.

became ulcerations that waxed and waned, but on the whole, progressively worsened (Fig 1).

By 2 months of age, and often earlier, all but 2 patients experienced serious infection, with the skin and respiratory tract being the usual sites. Many of these patients were eventually diagnosed with septicemia. *Candida* species and *Staphylococcus aureus* were the most common organisms cultured. Several patients were evaluated for immunodeficiency, but no consistent immunodeficiency was found.

The majority of patients suffered from significant functional abnormalities related to nutrition and breathing, with respiratory difficulties being the single most significant issue. Infection or aspiration pneumonia contributed to these difficulties in some, but not all, patients. All *GJB2* p.A88V patients had respiratory problems. Two of these 6 patients were investigated for and found to have central apnea. All 6 continued to have respiratory distress (ie, hypoxia and increased work of breathing) beyond a corrected gestational age of 40 weeks, when apnea of prematurity should have resolved. Three of the 6 patients were eventually intubated, and mechanical ventilation was needed but deferred in the other 3 patients because of parent preference for supportive care. Caffeine, which is used to treat apnea of prematurity, was used in cases 1 and 2 with no appreciable improvement.

Seven of 13 patients were diagnosed with failure to thrive and required nutritional supplementation. Two were found to have mild zinc deficiency, and oral zinc supplementation was thought to temporarily improve the skin in one of them. Half of the patients had mild to moderate anemia.

In addition to the expected changes in skin, eyes, and ears, many patients had additional anatomic abnormalities, most commonly in the central nervous system and heart (Table I).

Skin histology

Other than acanthosis and hyperkeratosis, there were no consistent findings from the obtained skin biopsy specimens. Papillomatosis, focal parakeratosis, hyper- and hypogranulosis and, in 1 case, horn cyst formation were reported. This variability may be related to biopsy site location and its time point in the clinical course. Four of 8 biopsy specimens showed pale cytoplasm in the upper epidermis (Fig 2, *A*), suggestive of nutritional deficiency.

Post mortem examination

Two patients underwent post mortem examination. Both had hypoplastic thymi for their age and abnormal maturation of the squamous epithelium in the esophagus. The distal esophageal epithelium in

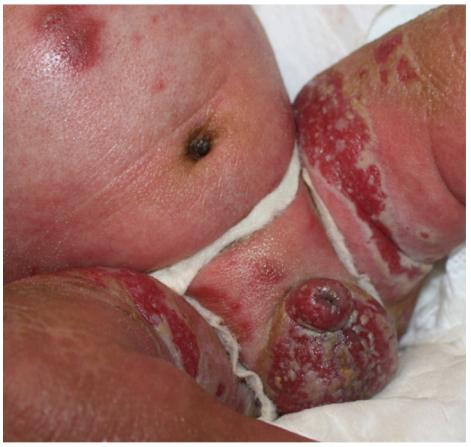

Fig 1. Late skin findings in lethal keratitis-ichthyosis-deafness syndrome. Intertriginous hyperkeratosis and denudation in a patient with *GJB2* p.A88V mutation (case 1).

case 1 had few layers with poor epithelial maturation and hyperchromatic nuclei (Fig 2, *B* and *C*). Case 1 had cardiomegaly and adrenal medullary hyperplasia, and case 5 also had early bronchopulmonary dysplasia, pan lobular hepatic microsteatosis, natal teeth, cleft of the secondary palate, a duplicated left renal collecting system, undescended testes, camptodactyly of all digits, and mild microcephaly (5th percentile).

Structural analysis of p.A88V and p.G45E mutant Cx26

The frequency of serious respiratory difficulties, along with evidence that Cx26 is important for CO_2 sensing,[12] prompted us to model the structural consequences of mutant *GJB2* p.A88V and p.G45E proteins. CO_2 modulation of Cx26 channel function results from formation of a carbamate bridge on the intracellular surface between Arg104 on one Cx26 molecule, and Lys125 on an adjacent Cx26 molecule, in the hexameric hemichannel.[7,12] Pro87 introduces a kink in Cx26 (Fig 3, *A*) that is vital to transduction of voltage gating[13] and confers the appropriate spacing to allow the carbamate salt bridge (Fig 3, *B*). Mutant p.A88V protein necessitates a packing rearrangement of the transmembrane helix to avoid unfavorable stereochemical clashes between the new valine and the adjacent proline. The required repacking of Cx26 p.A88V plausibly leads to repositioning of the intracellular end of the transmembrane helix and its proximity to Lys125 on the neighboring Cx26 protomer (Fig 3, *B*). In contrast, modeling suggests the solvent-exposed, pore-lining extracellular mutant p.G45E should not affect CO_2 sensing.

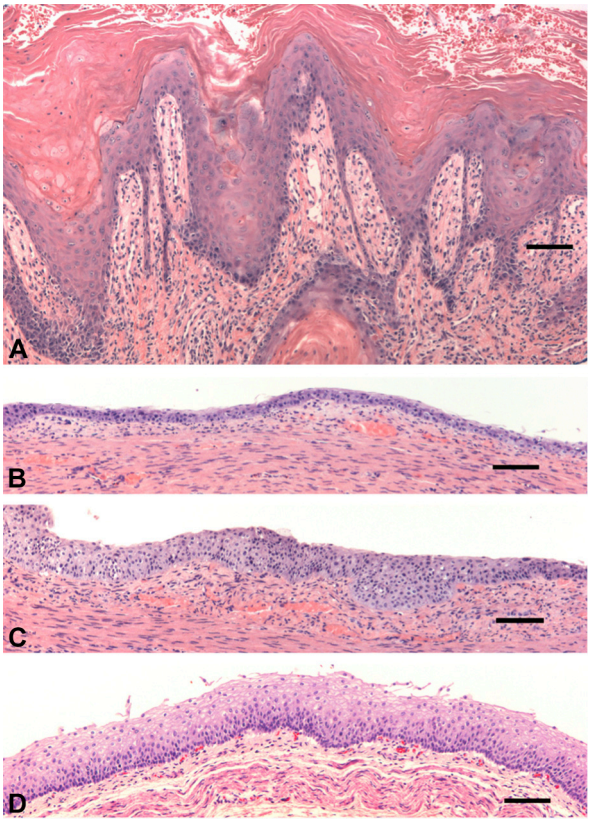

Fig 2. Histopathology of skin and esophagus in lethal keratitis-ichthyosis-deafness syndrome. **A**, Skin from the thigh of the patient shown in Fig 1 reveals hyperkeratosis, papillomatosis, and focal ballooning degeneration, with pale cytoplasm in keratinocytes of the upper epidermis. **B**, Distal esophagus from case 1 shows thin mucosa limited to basal layer with no maturation and hyperchromatic nuclei. **C**, Disordered maturation in the few areas where the mucosa is not thin. **D**, Matched normal control of distal esophagus from a 2-month-old infant. Hematoxylin–eosin stain; bar = 100 μm.

DISCUSSION

Infant mortality in KID syndrome with *GJB2* p.A88V or p.G45E mutations appears to be unavoidable despite intensive medical interventions; all succumb to the disease despite modern intensive neonatal care in tertiary academic centers and prophylactic antimicrobials. This information should encourage early genotyping in order to guide the management of newborns with KID syndrome. No abnormalities in a single organ system can account for the early lethality of these Cx26 mutations. Infant death in KID syndrome caused by other *GJB2* mutations is rare.

GJB2 mutations encoding p.A88V and p.G45E have far-reaching clinical consequences beyond keratitis, ichthyosis, and deafness. Patients with KID syndrome and these mutations have deficits in

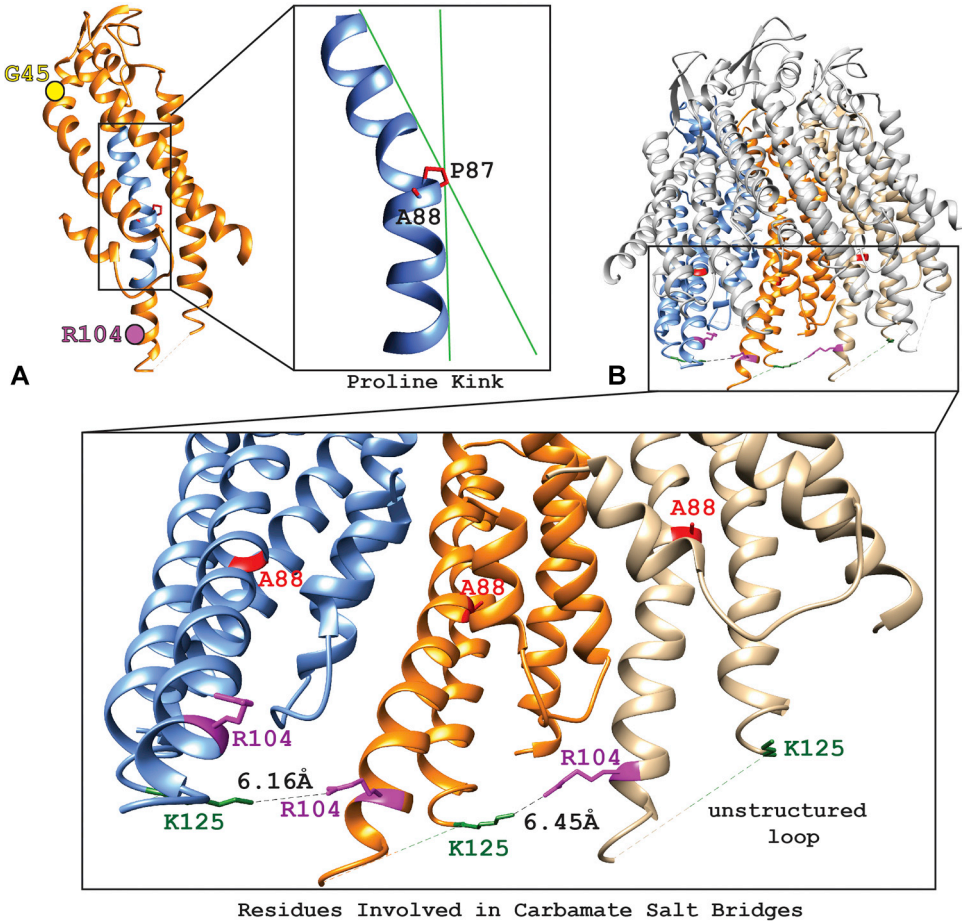

Fig 3. Structural analysis of connexin 26 (Cx26) containing the p.A88V mutation. **A**, A single Cx26 protomer (orange) with the transmembrane region of the second transmembrane helix (TM2) highlighted in blue. The critical P87 adjacent to A88 is shown in a zoomed-in image of the TM2 helix and illustrates helical kinking induced by P87 (green lines aid visualization of the altered helical angle). Also shown are the positions of external G45 (yellow sphere) far from the carbamate binding region, and internal R104 on TM2 (purple sphere) involved in carbamate binding. **B**, Cx26 hemichannel (top) with zoomed-in image (bottom) of 3 neighboring Cx26 protomers (colored blue, orange, and tan) showing the R104 (purple) and K125 (green) residues critical to carbon dioxide binding. The distance between these residues ranges from ~ 6.1 to 6.5 Å.

many other organ systems as revealed by our post mortem information on 2 males and by detailed imaging and other data from 5 of the remaining 11 patients. Additional abnormalities likely would have been identified if not for the limitations in patient data collection. This should not be surprising because Cx26 is expressed in many tissues during development and is inducible in skin by inflammation and retinoids.[14] In adults, transcripts are highly expressed in the esophagus, cervix, and vagina,[15] and the protein is highly expressed in esophagus, spinal cord, and colon.[16] The unanticipated striking histopathologic changes in the esophagus found on postmortem examination should alert us to potential barrier and other functional abnormalities in stratified squamous epithelia in all KID syndrome patients. Dandy–Walker malformations (identified in case 4 here) were previously noted in a large fraction of patients with KID syndrome with a variety of *GJB2* mutations,[17-21] yet this information has yet to appear in most reviews of KID syndrome. The current definition of KID syndrome affecting only the skin, eyes, and ears is inadequate for lethal and for nonlethal variants and handicaps the evaluation of issues arising in other potentially affected organ systems.

Repeated infections are a serious problem for patients with KID syndrome. Patients with A88V and G45E mutations in *GJB2* are profoundly susceptible to and poorly able to respond to infections despite

vigorous interventions. To date, no intrinsic adaptive or innate immune abnormalities have been identified in KID syndrome. We question whether the physically diminished epithelial barriers shown in skin and esophagus in our patients (and unexplored in vagina and cervix) are the source of these repeated infections and perhaps account for the frequency of fungemia.

Our current understanding of the expression and physiologic function of normal and mutant Cx26[22] explains some, but not all, of the clinical observations in this group of patients. Loss of function mutations in *GJB2* cause nonsyndromic deafness, while gain of function mutations in *GJB2* are responsible for several skin diseases, including KID syndrome.[22] At least 11 *GJB2* mutations are associated with KID syndrome, and all tested show leakiness of connexin hemichannels. In electrophysiologic or biochemical testing, p.A88V and p.G45E proteins show distinct abnormalities potentially more severe than other Cx26 mutants.[23,24] Therefore, the progressively increasing hyperkeratosis, late onset of erosions, and upper epidermal pallor in the histopathology of these patients with KID syndrome suggest that irritation or infection upregulates suprabasal expression of mutant Cx26, resulting in hemichannels that leak adenosine triphosphate and calcium, leading to abnormal differentiation, barrier dysfunction, and cell death.[23,24,25]

Understanding the effects of dominant *GJB2* mutations on organs other than the skin is even more limited. The frequency of respiratory difficulties in this group of patients is striking. Anatomic abnormalities in lungs of patients with KID syndrome have not been demonstrated. Meigh et al[12] have shown that Cx26 is expressed in the central respiratory control center of the medulla oblongata, and that cells sense intracellular CO_2 by forming a carbamate bridge that regulates hemichannel opening. *GJB2* p.A88V fails to form the carbamate bridge and the hemichannel malfunctions. In silico structural analysis of p.A88V indicated substitution of valine for alanine at position 88 can alter the intracellular carbamate salt bridge required for CO_2 sensing. By contrast, our structural analysis places the p.G45E mutation on the extracellular portion of the molecule, where it would be unlikely to impact the carbamate salt bridge. Therefore, as attractive as the central CO_2 sensing defect is to explain pulmonary problems in patients with A88V mutations, it does not explain pulmonary problems in patients with G45E mutations.

Our analysis highlights the clinical heterogeneity of KID syndrome, underscores the complex expression and combinatorial cell biology of connexins, and shows that the current definition of KID syndrome obscures the effect of *GJB2* mutations on other organ systems. This is likely true for nonlethal as well as lethal variants. We set out to determine whether these severe mutations had a uniformly lethal outcome and if there was a unifying explanation for that outcome. We found that no single problem accounted for the poor outcome, but rather that these individuals had a surprisingly large number of organ systems with developmental and acquired disease, emphasizing the old adage that the severest examples of disease may not be typical, but they can serve to reveal subtle and previously unappreciated abnormalities.

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