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

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Abstract

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Background: Infant death in KID syndrome is recognized; its association with specific genotypes and pathophysiology is inadequately understood.

Objective: To discover characteristics that account for poor outcomes in lethal KID syndrome.

Methods: We collected four new cases and nine 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 two “lethal” mutations is likely multifactorial: during life all had at least one 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 CO₂ sensing of *GJB2* p.A88V.

Limitations: Clinical review was retrospective.

Conclusion: *GJB2* p.G45E and p.A88V are the only KID syndrome mutations associated with uniform early lethality. Those electro-physiologically severe mutations in *GJB2* reveal abnormalities in many organs in lethal KID syndrome. All KID syndrome patients may have subtle abnormalities beyond eyes, ears and skin. Early genotyping of KID syndrome births will inform prognostic discussion.

Keywords

keratitis; ichthyosis; and deafness syndrome (KID) syndrome; connexin 26 (Cx26); gap junction protein; beta-2 (*GJB2*)

Introduction

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/or progressive vascularizing keratitis. A previous review suggested certain patients with KID syndrome die in infancy due to sepsis, but did not evaluate their specific mutation nor abnormalities in other organ systems¹. 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 CO₂ sensing.

When we became aware of four 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 two mutations, and is abnormal CO₂ 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?

Materials and Methods

We reviewed new (cases 2–5) and previously published (cases 1, 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 of the new cases had post-mortem exams. One lethal case with a p.S17F mutation⁸ was excluded because patients with this mutation usually survive into adulthood⁹.

Of the 16 cases identified, detailed clinical information was available for 13. For 11 of these cases, we confirmed clinical details with the primary dermatologist. For the two remaining cases (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 X-ray crystal structure of Cx26 (PDB Code 2ZW3)¹⁰. Structural modeling and figure preparation were performed using Coot¹¹, UCSF Chimera (Resource for Biocomputing, Visualization, and Informatics, University of California, San Francisco), and PyMOL Molecular Graphics System (Version 1.5.0.4, Schrodinger, LLC).

Results

Thirteen patients (nine males and four females) with lethal KID syndrome, six with the *GJB2* p.A88V mutation and seven with the *GJB2* p.G45E mutation, were identified (Table 1). 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; personal communication, G. Richard). Interestingly, some Japanese individuals with *GJB2* p.G45E mutations do not have a cutaneous phenotype, due to 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 seven p.G45E patients (cases 8–11) were from a single family.

Clinical Course

All 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 due to skin changes, keratitis, and hearing loss, and was ultimately confirmed by genetic testing. Each patient was born with relatively mild skin disease (i.e., 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 two *GJB2* p.G45E patients developed increasing hyperkeratosis with fissures. Intertriginous erosions became ulcerations that waxed and waned, but on the whole, progressively worsened (Figure 1).

By 2 months of age, and often earlier, all but two 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 vast 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 six patients were investigated for and found to have central apnea. All six continued to have respiratory distress (i.e., hypoxia and increased work of breathing) beyond a corrected gestational age of 40 weeks, when apnea of prematurity should have resolved. Three of the six patients were eventually intubated, and mechanical ventilation was needed but deferred in the other three patients due to 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 the 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 (CNS) and heart (Table).

Skin Histology

Other than acanthosis and hyperkeratosis, there were no consistent findings on skin biopsy. Papillomatosis, focal parakeratosis, hyper- and hypo-granulosis and, in one 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 eight biopsies showed pale cytoplasm in the upper epidermis (Figure 2a), 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 Case 1 had few layers with poor epithelial maturation and hyperchromatic nuclei (Figure 2b, c). Case 1 had an enlarged adrenal medulla and heart, 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 CO₂ sensing¹², prompted us to model the structural consequences of mutant *GJB2*

p.A88V and p.G45E proteins. CO₂ 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 (Figure 3a) that is vital to transduction of voltage gating¹³ and confers the appropriate spacing to allow the carbamate salt bridge (Figure 3b). 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 (Figure 3b). In contrast, modeling suggests the solvent-exposed, pore-lining extracellular mutant p.G45E should not affect CO₂ sensing.

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 management of newborn KID syndrome patients. 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. KID syndrome patients with those mutations have deficits in many other organ systems as revealed by our post-mortem information on two males, and by detailed imaging and other data from 5 of the remaining eleven. Additional abnormalities likely would have identified if not for the limitations in patient data collection. This should not be surprising since connexin 26 is expressed in many tissues during development and is inducible in skin by inflammation and retinoids¹⁴. In adults, transcripts are highly expressed in the esophagus, cervix and vagina¹⁵ and protein highly expressed in esophagus, spinal cord and colon¹⁶. The striking histopathological changes in esophagus, and unanticipated pre-mortem, 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 KID syndrome patients with a variety of *GJB2* mutations¹⁷⁻²¹ yet this information has yet to appear in most reviews of KID syndrome. The current definition of KID syndrome affecting only the skin, eye, and ears is inadequate for lethal and for non-lethal variants, and handicaps evaluation of issues arising in other potentially affected organ systems.

Repeated infections are a serious problem for these KID syndrome patients. The 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 Cx26²² explains some, but not all, of the clinical observations in this group of patients. Loss of function mutations in *GJB2* cause non-syndromic deafness, while gain of function mutations in *GJB2* are responsible for several skin diseases including KID syndrome²². At least 11 *GJB2* mutations are associated with KID syndrome, and all tested show leakiness of connexin hemichannels. In electrophysiological or biochemical testing, p.A88V and p.G45E proteins show distinct abnormalities potentially more severe than other Cx26 mutants^{23, 24}. Thus, the progressively increasing hyperkeratosis, late onset of erosions, and upper-epidermal pallor in the histopathology of these KID syndrome patients suggest that irritation or infection upregulates suprabasal expression of mutant Cx26, resulting in hemichannels that leak ATP and calcium, leading to abnormal differentiation, barrier dysfunction, and cell death^{24, 25}.

Understanding of the effect of dominant *GJB2* mutations on organs other than skin is even more limited. The frequency of respiratory difficulties in this group of patients is striking. Anatomic abnormalities in lungs of KID syndrome patients have not been demonstrated. Dale and colleagues have shown that connexin 26 is expressed in the central respiratory control center of the medulla oblongata, and that cells sense intracellular CO₂ by forming a carbamate bridge that regulates hemichannel opening¹². *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 CO₂ 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. Thus, as attractive as the central CO₂ 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 demonstrates that the current definition of KID syndrome obscures the effect of *GJB2* mutations on other organ systems. This is likely true for non-lethal 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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Capsule Summary

What is already known?

Early lethality in KID syndrome has been attributed to infection or impaired central CO₂ sensing.

What this article adds to our knowledge?

Uniform lethality with two mutations in *GJB2* had no single cause of death. Many organ systems had abnormalities.

How this information impacts clinical practice and/or changes patient care?

Clinicians should be alert to abnormalities beyond keratitis, ichthyosis and deafness. Early genotyping will guide management.



Figure 1. Late skin findings in lethal KID syndrome. Intertriginous hyperkeratosis and denudation in a patient with *GJB2* p.A88V mutation (case 1).

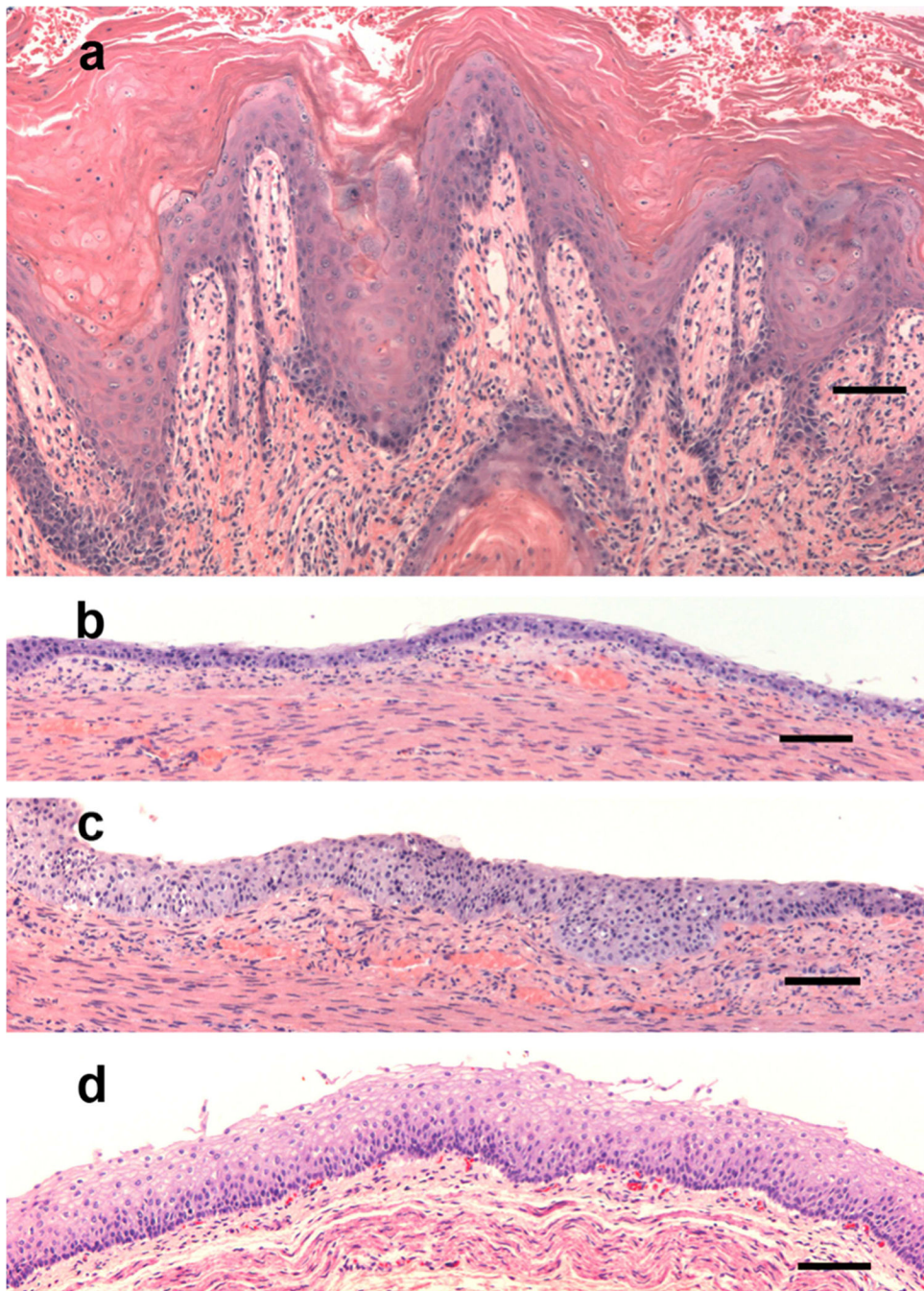


Figure 2. Histopathology of skin and esophagus in lethal KID syndrome. (a) Skin from thigh in Figure 1 shows hyperkeratosis, papillomatosis and focal ballooning degeneration, with pale cytoplasm in keratinocytes of the upper epidermis. (b). Distal esophagus from case 1 shows thin mucosa limited to basal 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 2-month infant. Hematoxylin and Eosin. Bar = 100um.

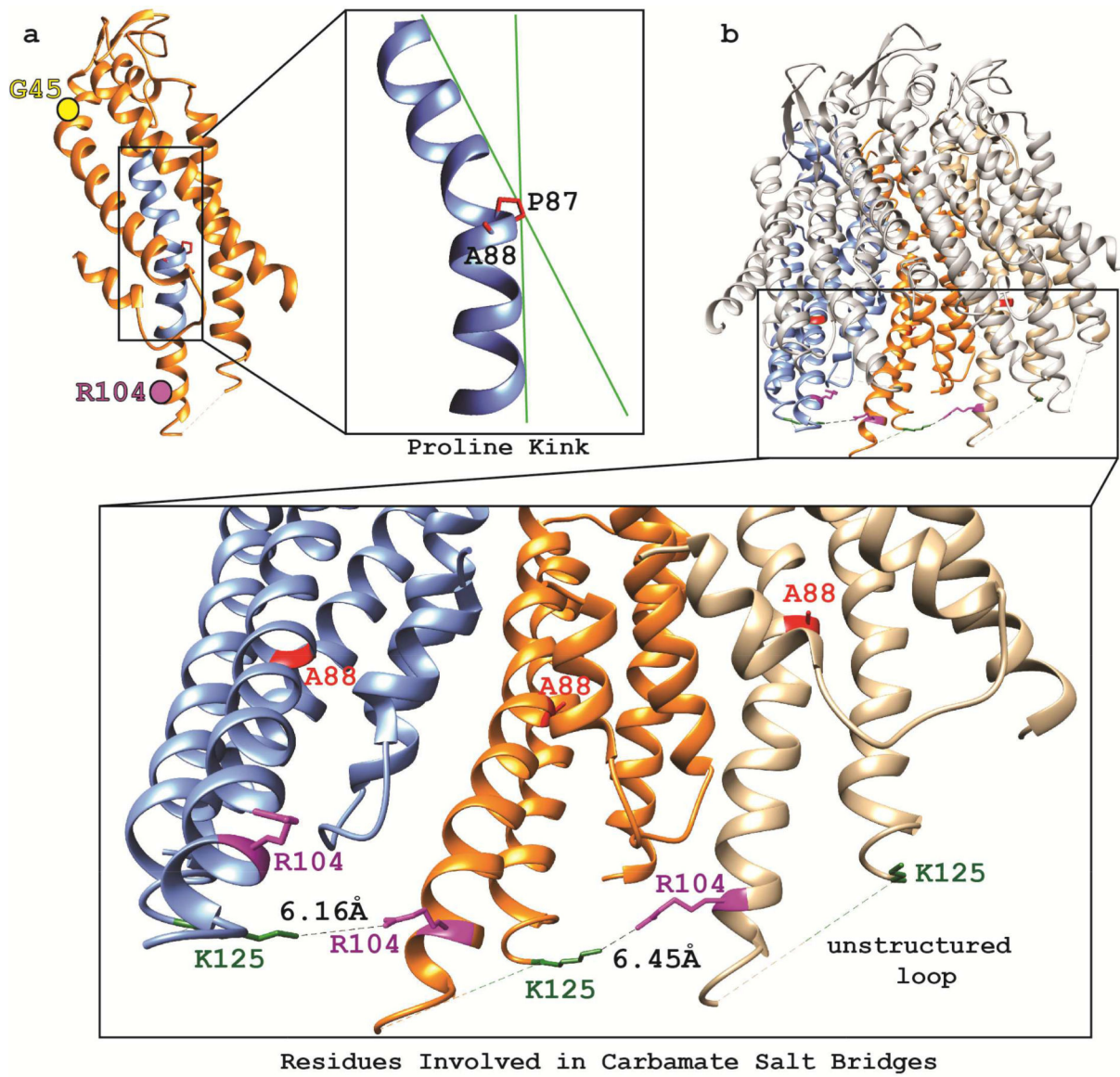


Figure 3. Structural analysis of Cx26 containing the p.A88V mutation

(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 three neighboring Cx26 protomers (colored blue, orange, and tan) showing the R104 (purple) and K125 (green) residues critical to CO₂ binding. The distance between these residues ranges from ~ 6.1 to 6.5 Å.

Table 1.

Key clinical features of KID patients with *GJB2* p.A88V and p.G45E variants. Summary of cases by organ system. For the two cases in grey, we relied on the published case reports, as we were not able to communicate with the primary dermatologist. Asterisked cases are from one family.

Case (citation if previously reported)	Genotype	Gender	Gestational age at birth (weeks + days)	Respiratory	Cardiovascular	Central Nervous System	Gastrointestinal	Skin Ulcerations	Skin Histology	Hematologic	Thymus	Infection Onset (months)	Age at death (months)	Cause of death
1 (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 erythroderma; 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; hypercapnia; pneumogram suggestive of central apnea	patent foramen ovale	poor suck reflex; mild inferior vermian hypogensis	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 arteriosus; moderately dilated left ventricle	normal brain ultrasound	low weight and height; emeral and pariental nutritional supplementation	around gastric tube; diaper area; intertriginous	new red urticarial rash on legs; 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 v. small secundum atrial septal defect	no gag reflex; Dandy-Walker malformation with small germinal matrix hemorrhage and severe ventriculomegaly	difficulty with oral feeds	intertriginous	ulcer: upper third epidermis with pale cytoplasm	anemia requiring transfusion		0.5	2	congenital abnormality of the brainstem
5	A88V	M	35-36	hypoxia; immature lungs with patchy intralveolar hemorrhage	hypotensive requiring pressors echocardiogram normal	microcephaly; acute hypoxic change in hippocampal neurons	low weight and height; low vitamin A; abnormal maturation of non-keratinized squamous epithelium in esophagus	lower abdomen		normocytic anemia; low IgG and IgA	thymic involution	0.5	0.75	
6 (2)	A88V	M	33 + 4	apnea; atelectasis; cerebral irritability that required		hydrocephalus; intraventricular and parenchymal hemorrhage		scalp				1		Klebsiella sepsis

Case (citation if previously reported)	Genotype	Gender	Gestational age at birth (weeks + days)	Respiratory	Cardiovascular	Central Nervous System	Gastrointestinal	Skin Ulcerations	Skin Histology	Hematologic	Thymus	Infection Onset (months)	Age at death (months)	Cause of death
7 (3)	G45E	F	36	mechanical ventilation suspected aspiration pneumonia and bronchitis	pulmonary artery stenosis		nasogastric tube	perianal and genital	baseline erythroderma: hyperkeratosis, hypergranulosis, focal vacuolar degeneration			7		
* (4,5) 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
* (4,5) twin	B G45E	M	31	candida and staph pulmonary infection; edema and dyskeratotic laryngeal mucosae	cardiomegaly	dilation of left ventricle	low weight ana 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* (5)	G45E	M	33				nasogastric tube	none				1		candida and staphylococcal septicemia
11* (5)	G45E	M	35	respiratory failure; candida pulmonary infection				none				0.3		candida pulmonary infection
12 (6)	G45E	F	36	respiratory insufficiency due to aspiration		psychomotor delay	low weight and height	none	hyper- and parakeratosis, intraepidermal neutrophils, abundant bacteria and fungi, no ballooning degeneration	no immunologic incompetence		1	12	septicemia
13 (1)	G45E	M	36	viral upper respiratory infection				scalp		immunoglobulins and lymphocyte phenotype panel wnl		3.5	6	septicemia

* same family