Expanding the spectrum of epidermolysis bullosa simplex: Syndromic epidermolysis bullosa simplex with nephropathy and epilepsy secondary to CD151 tetraspanin defect—a case report and review of the literature

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Key words: CD151 tetraspanin; epidermolysis bullosa; epilepsy; nephropathy; skin fragility.

INTRODUCTION

Heritable forms of epidermolysis bullosa (EB) are considered the prototype of genetic skin fragility disorders.[1] Classically, EB is divided into 4 types on the basis of the location of the dermoepidermal junction in relation to the basement membrane zone: EB simplex (EBS), junctional EB, dystrophic EB, and Kindler EB.[2,3] Recently, these subtypes have been further divided into "syndromic" and "nonsyndromic" variants on the basis of the presence or absence of monogenic multisystem involvement.[4]

Syndromic forms of EB are rare but carry important considerations for screening, prognosis, multidisciplinary involvement, and therapeutic targets. We present the case of a 24-year−old patient with a diagnosis of syndromic EBS with associated nephropathy, "atypical" cystic fibrosis (CF), and epilepsy secondary to a defect in CD151 tetraspanin. This is the fifth recorded case of EBS with nephropathy in relation to CD151 defects and, to our knowledge, the first case to be reported with neurologic and chloride transport complications.[2,5]

Abbreviations used:

CF: cystic fibrosis
EB: epidermolysis bullosa
EBS: epidermolysis bullosa simplex

CASE REPORT

A 24-year−old adopted woman with consanguineous parents presented to the dermatology clinic with concerns of blistering. She was reportedly born at term via uncomplicated spontaneous vaginal delivery without prenatal, perinatal, or postnatal complications. Her past medical history was notable for complex partial epilepsy refractory to multiple therapeutics requiring a vagal nerve stimulator, diplegic cerebral palsy, chronic kidney disease secondary to nephrotic syndrome from focal segmental glomerular sclerosis, and "atypical" CF diagnosed in infancy with positive sweat chloride testing and suggestive phenotype defined primarily by pancreatic insufficiency but no causative mutations identified on expanded CF genetic sequencing studies. Her epilepsy and cerebral palsy manifested in early childhood and are currently considered idiopathic by her neurology team with notably normal workup to date, including imaging evaluation and epilepsy-targeted genetic studies revealing no disease-associated mutations. She also has a history of sensorineural hearing loss and is followed by a gastrointestinal specialist for dysphagia with small esophageal strictures. Her guardians reported that,

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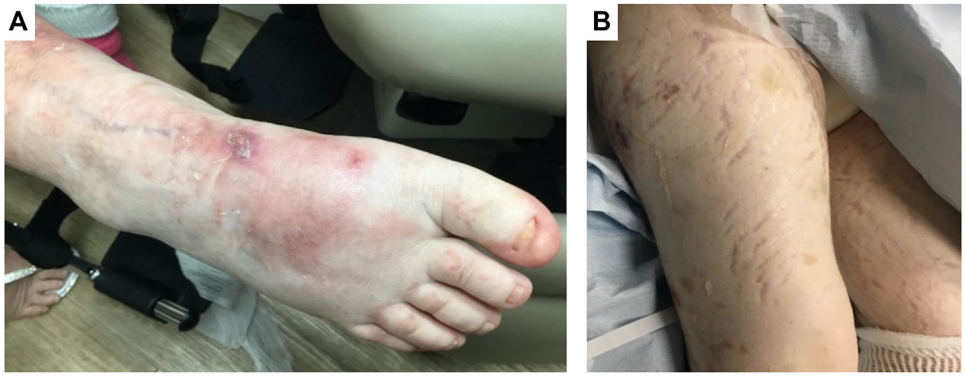

Fig 1. Case patient. **A,** The dorsum of the right foot with a single bulla as well as dystrophic nail of first digit. **B,** Right proximal lower extremity with scattered striae and 2 linear bullae on minimally erythematous bases noted along the lateral aspect of the patient's thigh.

Table I. Classification of heritable forms of epidermolysis bullosa. Recent consensus classification schemes indicate a total of 35 distinct subtypes of epidermolysis bullosa delineated by a combination of the cutaneous layer in which the separation occurs, clinical presentation, pattern of genetic inheritance, genetic abnormality, and protein involved.[2]

EB type	Mutated gene	Encoded protein	Inheritance pattern	Syndromic vs nonsyndromic	Syndromic associations
Simplex	KRT5, KRT14	Keratin 5, Keratin 14	AD (>AR)	NS	-
	PLEC	Plectin	AR (>AD)	S	Muscular dystrophy, pyloric atresia, dilated cardiomyopathy
	KLHL24	Kelch-like member 24	AD (>AR)	S	Dilated cardiomyopathy
	DST	Bullous pemphigoid antigen 230 (BP230/BPAg1)	AR	NS	-
	EXPH5	Exophilin 5	AR	NS	-
	CD151	CD151 tetraspanin	AR	S	Nephropathy with or without epilepsy, thalassemia, pancreatic insufficiency, KS-like cutaneous features
Junctional	LAMA3	Laminin α3	AR	NS	
	LAMB3	Laminin β3	AR	NS	
	LAMC2	Laminin γ2	AR	NS	
	COL17A1	Type XVII Collagen	AR	NS	
	ITGA6	Integrin α6	AR	S	Pyloric atresia
	ITGB4	Integrin β4	AR (>AD)	S	Pyloric atresia
	ITGA3	Integrin α3	AR	S	Interstitial lung disease and congenital nephrotic syndrome
Dystrophic	COL7A1	Type VII collagen	AD and AR	NS	-
Kindler	FERMT1	Fermitin family homolog 1	AR	NS	-

AD, Autosomal dominant; *AR,* autosomal recessive; *EB,* epidermolysis bullosa; *KS,* Kindler Syndrome; *NS,* nonsyndromic; *S,* syndromic.

3 years previously, she had developed waxing and waning blisters along the distal extensor aspects of her extremities. Biopsy results at that time were reportedly consistent with bullous pemphigoid. She had trialed topical corticosteroids, minocycline, nicotinamide, mycophenolate mofetil, methotrexate, and protracted courses of systemic corticosteroids with negligible therapeutic benefit prior to this visit. On examination, she demonstrated linear pretibial and upper extremity extensor bullae on minimally

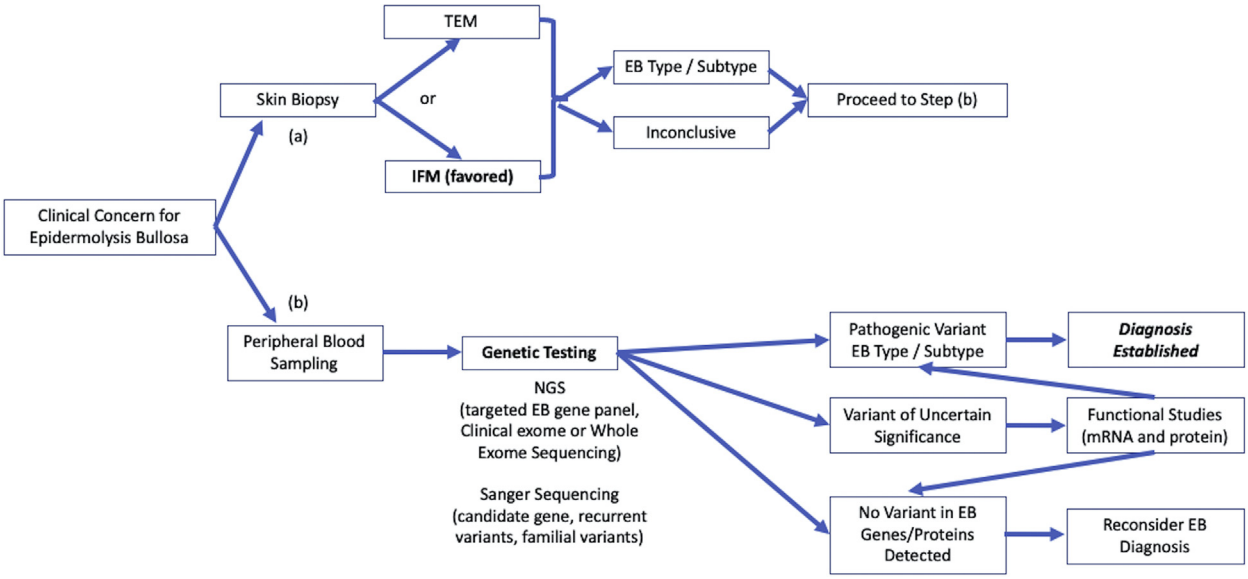

Fig 2. Recommended diagnostic evaluation of patients suspected to have a heritable form of epidermolysis bullosa (EB). As the phenotypic and genotypic understanding of EB has expanded, so has the diagnostic assessment of heritable mechanobullous diseases. In 2020, Has et al[9] outlined guidelines for the diagnostic assessment of patients with suspected EB. These guidelines solidified the clinical value of immunofluorescence mapping (IFM) or transmission electron microscopy (TEM) as well as clarified the validity of serum genetic testing by next-generation sequencing (NGS) or Sanger sequencing, especially in cases with characteristic clinical features where IFM or TEM may not be readily available. NGS, when combined with clinical phenotype, played a particularly critical role in the evaluation and ultimate diagnosis of our patient. *mRNA,* Messenger RNA.

erythematous bases (Fig 1). Onychodystrophy and dental enamel hypoplasia as well as scattered poikiloderma and patchy alopecia were also diagnosed. No mucosal ulcerations or erosions were noted. Further examination of her medical history revealed that the patient had developed small transient blisters along her extremities with minimal trauma when she was a toddler. It was not until these blisters became persistent and severe that requests for medical evaluation were prompted. Biopsies specimens were collected, which showed a subepidermal separation with negative direct immunofluorescence staining. Neither immunofluorescence mapping nor transmission electron microscopy were readily available. Suspicion of a heritable form of skin fragility prompted an EB-specific next-generation sequencing—based serum DNA evaluation, which revealed that the patient was homozygous for an autosomal recessive c.406 C>T mutation in exon 6 of the *CD151* gene, resulting in the replacement of the glutamine at codon 136 with a premature stop codon, synonymous with 2 reported cases in the literature[6] and identified as a disease-associated variant. This finding, combined with her clinical presentation, supported a diagnosis of *CD151*-associated syndromic EBS with nephropathy. She was tapered off of all forms of immunosuppressants, with a care plan that was shifted to careful skin care, nutrition, and ocular health. The blisters substantially improved with this regimen, and she was referred to a multidisciplinary EB clinic for further evaluation and treatment.

DISCUSSION

EB is a complex condition defined by skin fragility with a significant degree of phenotypic heterogeneity and variable severity. Approximately 21 genes with more than 1000 separate mutations have been identified in the 35 known subtypes of heritable EB (Table I).[2,7,8] Diagnosis has traditionally relied on the ultrastructural evaluation of tissue with immunofluorescence mapping or transmission electron microscopy. The development of EB-specific genetic sequencing studies has substantially improved this diagnostic evaluation—especially in cases with characteristic clinical features where immunofluorescence mapping or transmission electron microscopy may not be readily available (Fig 2).[9]

Once a diagnosis is made, the subclassification of EB into "syndromic" and "non-syndromic" forms has expanded diagnostic, therapeutic, and prognostic implications. One of the most recently described

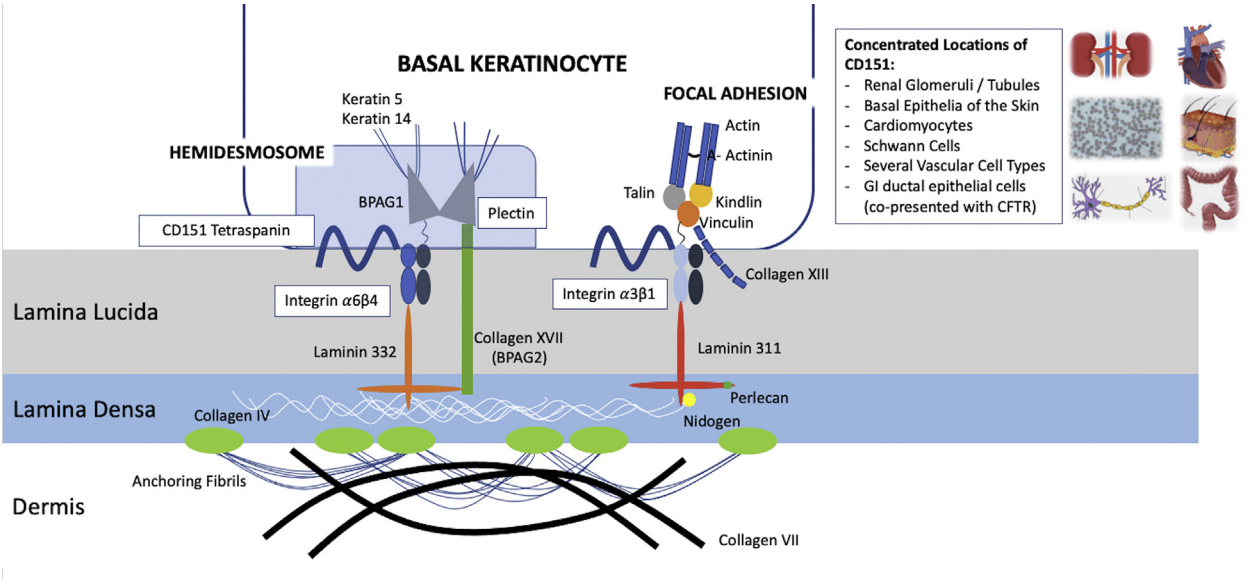

Fig 3. Representation of basal keratinocyte attachment with emphasis on CD151 location and function. CD151 has been shown to have high concentrations in the glomeruli and tubules of the kidney, basal epithelia of the skin, cardiomyocytes, Schwann cells, ductal epithelial cells of the colon and prostate, as well as several vascular cell types (including endothelial cells, megakaryocytes, and platelets). Of note, knockout mice missing the integrin $\alpha 3$ subunit display focal and segmental glomerular sclerosis with tubular dilation, similar to patients with CD151 defects, further clarifying the role of CD151 in mediating laminin-integrin interaction.[6] In humans, integrin $\alpha 3$ genetic defects have been shown to produce a syndromic junctional epidermolysis bullosa phenotype with interstitial lung disease and nephrotic syndrome.[4] Proteins within boxes represent known syndromic forms of epidermolysis bullosa. *CFTR,* cystic fibrosis transmembrane conductance regulator; *GI,* gastrointestinal.

syndromic EBS subtypes involves an autosomal recessive mutation in tetraspanin CD151, which, in a single proband, resulted in a Kindler-like EB presentation with pretibial blistering and multisystemic manifestations, including nephropathy, poikiloderma, nail dystrophy, loss of teeth, alopecia, and esophageal strictures.[5] Ultrastructural evaluation of this patient's skin revealed the absence of *CD151* within the basement membrane and similarities to patients with *EXPH5* gene mutations (a nonsyndromic form of EBS), prompting its classification as an EBS subtype. This presentation aligned with 3 similar cases from 2 families discovered to have homozygous frame-shift mutations in *CD151* and a similar pretibial blistering pattern with nephritis, sensorineural deafness, and anemia secondary to β-thalassemia.[6]

Tetraspanin CD151 is a transmembrane protein, now known to be essential to the development of hemidesmosomes through stabilization of laminin-integrin binding (Fig 3). It is highly expressed in the cells of the vascular, renal, and nervous systems as well as the basal epithelia of the skin.[10] Some studies have also shown high levels of tetraspanin CD151 expression in normal human bronchial epithelial cells, where the CF transmembrane conductance regulator plays a critical role in chloride transport.[11] In the cutaneous basement membrane, CD151 tetraspanin binds with $\alpha 6\beta 4$ integrin and stabilizes its interaction with laminin-332, playing a critical role in the formation of the hemidesmosomal complex. A similar stabilization effect occurs within both the renal tubules and keratinocyte focal adhesion units when CD151 binds to $\alpha 3\beta 1$ integrin. In mice, CD151 deficiency has been shown to result in kidney failure secondary to focal and segmental glomerular sclerosis with tubular dilation.[5] The presence of tetraspanin CD151 in the central/peripheral nervous system as well as in epithelial cells containing high concentrations of CF transmembrane conductance regulator proteins suggests that *CD151* dysfunction could lead to abnormalities in chloride transport and nerve conduction. This, along with the notable absence of historical, structural, imaging-based, and laboratory-based evidence suggesting alternative etiologies underlying our patient's epilepsy and CF, supports the notion of a unified pathologic process.

Treatment recommendations for all forms of EB are largely supportive and hinged upon careful

Table II. Recommended diagnostic evaluation of patients discovered to have defects in CD151 tetraspanin

Organ system	Associated abnormalities	Suggested workup
Renal	Nephrotic syndrome (focal segmental glomerular sclerosis)	Urinalysis Renal ultrasound Referral to nephrologist
Hematologic	β-thalassemia	Complete blood cell count Referral to hematologist
Gastrointestinal	Pancreatic insufficiency (secondary to cystic fibrosis)	Nutrition assessment Referral to gastrointestinal specialist
Neurologic	Sensorineural hearing loss Epilepsy	Neurologic examination Electroencephalogram Hearing screen
Other	Cystic fibrosis	Sweat chloride testing

attention to wound care, blister prevention, nutrition, ocular health, and oral hygiene. In syndromic EB, screening for multisystem involvement may be prudent with the appropriate genetic findings. In the case of *CD151* defects, urinalysis, renal ultrasound, and complete blood count should be considered, as well as referrals to nephrology, hematology, and audiology specialists. On the basis of our case, a reasonable argument could be made to include electroencephalography, sweat chloride testing, and detailed neurologic assessment in the screening of patients discovered to have this defect (Table II). This case also outlines the importance of considering *CD151*-associated EBS in patients with pediatric nephropathy and concomitant or subsequent blistering, even if the blistering is mild or delayed.

CONCLUSION

To our knowledge, this case represents the fifth report of a CD151 tetraspanin mutation resulting in EBS with nephropathy[2,5] and adds to the literature by being the first reported case associated with epilepsy and CF. More reports are needed to further elucidate the full phenotypic spectrum of this rare clinical entity.

Conflicts of interest

None disclosed.

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