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Phenotypic discordance between siblings with junctional epidermolysis bullosa–pyloric atresia

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Junctional epidermolysis bullosa with pyloric atresia (JEB-PA) is an autosomal recessive disease characterized by epithelial fragility and PA. Cleavage occurs within the lamina lucida of the skin basement membrane zone. Biallelic pathogenic variants in *ITGA6* and *ITGB4* are responsible, the latter being more common.[1,2] Loss of skin and mucous membrane barrier and absorptive function results in malnutrition and risk of sepsis. Other extracutaneous manifestations include dental caries, genitourinary abnormalities and rudimentary ears[1.] Prognosis is usually poor, with reduced life expectancy predicted in most cases.[2] Two notable EB subtypes that share similarities with JEB-PA are EB simplex with PA (EBS-PA) due to *PLEC* variants, and JEB with respiratory and renal involvement (JEB-RR) caused by *ITGA3* variants.[1]

Our proband, a 36-year-old Lebanese man, had skin blistering and pyloric stenosis at birth; the stenosis was surgically corrected at 3 days of age. His parents were consanguineous. The patient's older sister had died 5 years previously at the age of 14 months, having had skin blistering, severe diarrhoea, protein-losing enteropathy (PLE), failure to thrive (FTT) and sepsis; histology of her bowel mucosa revealed epithelial clefting at the lamina propria. Postmortem examination revealed extensive de-epithelialization of the skin and small intestine, without PA.

The proband's neonatal skin biopsy revealed epidermal separation at the lamina propria. In childhood, he experienced diarrhoea, FTT and continued skin blistering. Aged 7 years, he deteriorated, developing PLE and requiring parenteral nutrition and albumin replacement. Intermittent stridor was noted. Endoscopy

was planned but the patient could not be endotracheally intubated owing to supraglottic stenosis. Subsequent colonic mucosal biopsy showed separation of the mucosa from the lamina propria; electron microscopy of repeat skin biopsies showed small numbers of poorly formed hemidesmosomes and well-formed anchoring fibrils. The diagnosis of JEB was made.

Aged 8 years, the patient developed urethral stenosis, which was treated by vesicostomy and subsequent permanent suprapubic catheter. This was complicated by hydronephrosis and chronic renal impairment. In early adulthood, he had dental veneers and crowns placed to treat severe enamel defects and caries. As an adult he performed all activities of daily living independently, as well as gym-based exercise with only minimal skin blistering. His supraglottic stenosis was asymptomatic and has been managed conservatively. His most troubling symptom was significant onychodystrophy (Fig. 1) requiring mechanical debridement. He has not had any further symptoms of PLE, but has been unable to gain weight (55 kg) despite high calorie intake.

Following informed consent from the patient, genetic testing was performed, which revealed a homozygous pathogenic frameshift variant in *ITGB4* (c.4631_4632del, p.Leu1544Glnfs*27). This variant has been reported once previously in a homozygous state, in a patient with JEB-PA (annotated as 4790delTC based on an outdated reference transcript).[3] The features of our patient, his sister and this previously reported case are compared in Table 1.

There have been several reports of *ITGB4* variant JEB-PA without PA[2,4], as in the case of our patient and his sibling; pyloric stenosis is a relatively common neonatal anomaly, but this could also represent a phenotypic extension of JEB-PA. Sibling discordance with regard to PA has been described, suggesting that the PA is due to factors other than genotype.[4] Presence of PA is not predictive of poor outcome, as mortality seems to be more dependent upon the mucosal manifestations in early life and the effect of the pathogenic variants on level of $\alpha 6\beta 4$ integrin expression[2,5]

This case demonstrates significant survival disco.rdance despite early concordance of phenotype, between siblings with JEB-PA. Although there are suggestions that patients with nonsense/frameshift mutations have more severe phenotypes than those with missense mutations, this is not an absolute demarcation.[2–5] We can reasonably expect that both siblings carried the same *ITGB4* mutation, therefore negating *ITGB4* genotype as a factor in predicting the two different outcomes. It is possible that our proband's background genetic milieu may differ from his sister's despite consanguinity, and there could be as yet unascertained environmental factors that modulate the phenotype. The proband may have simply been fortunate to survive severe illness early in life, while his sister was not as lucky, or perhaps his complications of JEB-PA were managed more effectively in light of his sister's demise. Improvement of JEB-PA manifestations with age is well-documented.[2,4] It has been postulated that severe PLE in infants with JEB-PA is due to autoimmune mucosal inflammatory responses, perhaps triggered by systemic infections. The proposed mechanism is abnormal antigen exposure secondary to the loss of epithelial barrier function.[6,7] This susceptibility may improve with age.

This case adds to the current literature by demonstrating phenotypic variability in JEB-PA (including the absence of PA) even in patients with ostensibly the same pathogenic genotype.

References

1 Fine JD, Bruckner-Tuderman L, Eady RA *et al*. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol* 2014; **70:** 1103–26.

2 Schumann H, Kiritsi D, Pigors M *et al*. Phenotypic spectrum of epidermolysis bullosa associated with α6β4 integrin mutations. *Br J Dermatol* 2013; **169:** 115–24.
3 Nakano A, Pulkkinen L, Murrell D. Epidermolysis bullosa with congenital pyloric atresia: novel mutations in the beta 4 integrin gene (ITGB4) and genotype/phenotype correlations. *Pediatr Res* 2001; **49:** 618–26.
4 Dang N, Klingberg S, Rubin AI *et al*. Differential expression of pyloric atresia in junctional epidermolysis bullosa with ITGB4 mutations suggests that pyloric atresia is due to factors other than the mutations and not predictive of a poor outcome: three novel mutations and a review of the literature. *Acta Derm Venereol* 2008; **88:** 438–48.
5 Ashton GH, Sorelli P, Mellerio JE *et al*. Alpha 6 beta 4 integrin abnormalities in junctional epidermolysis bullosa with pyloric atresia. *Br J Dermatol* 2001; **144:** 408–14.
6 Salvestrini C, McGrath JA, Ozoemena L *et al*. Desquamative enteropathy and pyloric atresia without skin disease caused by a novel intracellular β4 integrin mutation. *J Pediatr Gastroenterol Nutr* 2008; **47:** 585–91.
7 Freeman EB, Koglmeier J, Martinez AE *et al*. Gastrointestinal complications of epidermolysis bullosa in children. *Pediatr Dermatol* 2008. **158:** 1308–14.

Figure 1 (a) Fingernail and (b,c) toenail onychodystrophy in the proband with junctional epidermolysis bullosa–pyloric atresia/.

Table 1 Comparison of the phenotypic features of junctional epidermolysis bullosa–pyloric atresia caused by the same pathogenic variant (ITGB4 c.4631_4632del).

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Patient	Sex	Age	Cutaneous features	Pyloric features	Other extracutaneous features
1 (our proband)	M	Alive at 36 years	Severe skin blistering at birth, which significantly improved over time; minimal skin blistering as adult	Pyloric stenosis	PLE and FTT in childhood; supraglottic stenosis causing stridor; dental enamel hypoplasia and caries; urethral stenosis with hydronephrosis and renal impairment
2 (our proband's sister)	F	Died at 14 months	Severe skin blistering at birth	Nil	PLE and severe FTT in early childhood; sepsis
3 (Nakano et al., 2001[4])[a]	F	Alive at 13 years	Mild skin blistering	Pyloric stenosis	Severe corneal erosions

FTT, failure to thrive; PLE, protein-losing enteropathy. [a]Information on the clinical state of this individual is limited to the reference.

CPD questions

Learning objective

To demonstrate an understanding of the clinical and genetic features of junctional epidermolysis bullosa–

pyloric atresia.

Question 1

Which of the following extracutaneous features occur in junctional epidermolysis bullosa–pyloric atresia (JEB-PA) apart from pyloric atresia?

(a) Tracheo-oesophageal fistula.

(b) Pseudosyndactyly and rudimentary ears.

(c) Genitourinary abnormalities and dental caries.

(d) Genitourinary abnormalities and keratoconus.

(e) Jejunal atresia and muscular dystrophy.

Question 2

Genes coding for which of following proteins are implicated in the pathogenesis of junctional epidermolysis bullosa–pyloric atresia (JEB-PA)?

(a) Integrin α6.

(b) Integrin α3 subunit.

(c) Plectin.

(d) Integrin β4.

(e) Laminin-332.

Answer 1

Which of the following extracutaneous features occur in junctional epidermolysis bullosa–pyloric atresia (JEB-PA) apart from pyloric atresia?

(a) Incorrect. Tracheo-oesophageal fistula is not an extracutaneous manifestation of JEB-PA.

(b) Incorrect. Pseudosyndactyly is not an extracutaneous manifestation of JEB-PA.

(c) Correct. Genitourinary abnormalities and dental caries commonly occur in JEB-PA.

(d) Incorrect. Keratoconus is not an extracutaneous manifestation of JEB-PA.

(e) Incorrect. Neither of these are extracutaneous manifestations of JEB-PA.

Answer 2

Genes coding for which of following proteins are implicated in the pathogenesis of junctional epidermolysis bullosa–pyloric atresia (JEB-PA)?

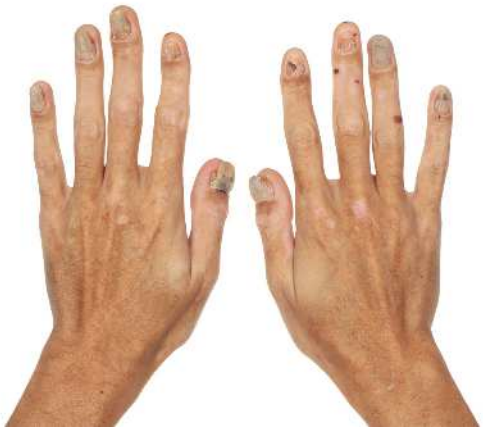
(a) Correct. Integrin α6 is encoded by *ITGA6* and is implicated in JEB-PA.

(b) Incorrect. *ITGA3* encodes Integrin α3 is encoded by and is implicated in JEB with respiratory and renal involvement .

(c) Incorrect. *PLEC* encodes plectin is encoded by, and is implicated in EB simplex (EBS) with PA, as well as EBS with muscular dystrophy (EBS-MD) and EBS-Ogna.

(d) Correct. *ITGB4* encodesIntegrin β4 is encoded by and is implicated in JEB-PA.

(e) Incorrect. *LAMA3, LAMB3 and LAMC2* encode laminin-332 is encoded by, which is implicated in other forms of JEB without PA, namely: JEB generalized-severe, JEB generalized-intermediate, JEB localized, JEB inversa and JEB laryngo-onycho-cutaneous syndrome..



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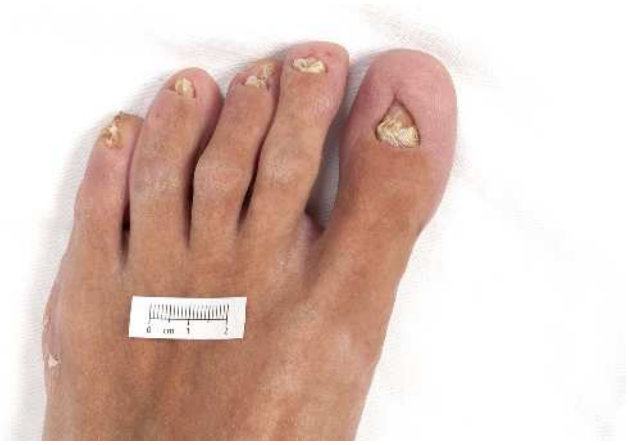

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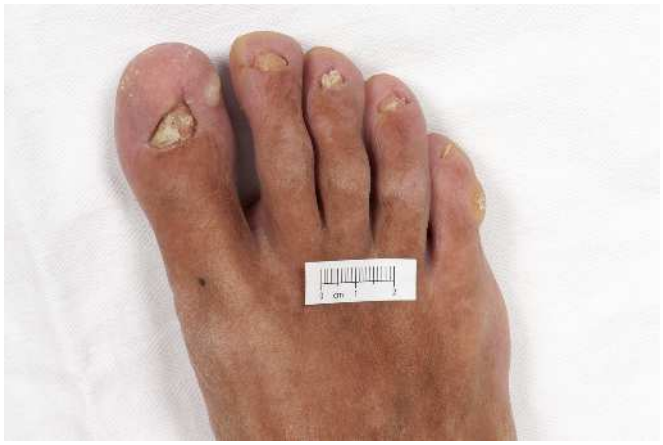

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