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Case Report

A rare case of COL71A1 heterozygous mutations resulting in neonatal dystrophic epidermolysis bullosa

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Summary

Epidermolysis bullosa is a group of rare hereditary vesicular skin diseases associated with mutations of COL7A1. At present, there is no effective treatment. Approximately forty percent of patients die within the first year of life, and the quality of life of survivors is seriously compromised. Pre-pregnancy genetic counseling and prenatal diagnosis is of great clinical significance for these patients and families. We describe a rare case of dystrophic epidermolysis bullosa secondary to heterozygous mutations in COL7A1.

Key words: Epidermolysis bullosa; Hereditary; No effective treatment; COL71A1.

Introduction

Epidermolysis bullosa is a rare group of hereditary blistering dermatoses with an incidence of 2/100,000. Dystrophic epidermolysis bullosa (DEB) is one of the subtypes associated with mutations in the COL7A1 gene.

Case report

A 31-year-old woman (G3P2) was admitted to our hospital in May 2018 due to "menopause for 37^{+5} week, liver dysfunction for over 40 days". The woman had been receiving regular prenatal examinations since the 8th week of pregnancy. At week 17^{+2}, screening for Trisomy 21 was performed. The results indicated that the risk was low and the AFP was normal. Oral glucose tolerance testing (OGTT) at week 25^{+3} showed that fasting blood glucose was 5.43 mmol/L, 1-hour postprandial blood glucose was 7.8 mmol/L, 2-hour postprandial blood glucose was 6.97 mmol/L. She was diagnosed with "gestational diabetes mellitus". After physical exercise and diet management, her fasting blood glucose and postprandial blood glucose were controlled within normal range. At week 32, the patient was found to have abnormal liver function: ALT (glutamic pyruvic transaminase) 66 U/L, AST (glutamic oxaloacetic transaminase) 40 U/L. At week 36^{+2}, liver function was retested, with ALT 75 U/L, AST 42 U/L, total bilirubin7.3 μmol/L. Just prior to admission, her liver function test showed ALT 291 U/L, AST 173 U/L, total bilirubin 40.4 μmol/L, without pruritis or anorexia. Results of abdominal ultrasound, hepatitis infection biomarkers, EBV (Epstein-Barr virus) and CMV (cytomegalovirus) tests were negative. Other prenatal examinations and tests showed no abnormal results.

The patient had a history of regular menstruation, with a cycle of 30-32 days. In 2011, she had delivered a fullterm stillborn infant. By report, the skin of the left hand and right foot of the female stillborn infantwas absent. No autopsy or chromosome analysis was conducted at that time. In 2013, the patient underwent cesarean delivery at week 38^{+2} due to severe intrahepatic cholestasis of pregnancy. The liveborn male infant weighed 3300 g, with a body length of 49 cm at birth, without any obvious abnormality.

The patient was examined at admission: fundal height 32 cm, abdominal circumference 101 cm, fetal position LOA, fetal heart rate 140bpm. No abdominal pressing pain at incision site of lower uterus. Ultrasound results: fetal position LOA, BPD 9.5 cm, HC 33.04 cm, FL 6.8 cm, AC 34.10 cm, fetal heart rate 146 bpm, AFI 9.6 cm, placenta at posterior wall with 3.0 cm in thickness, grade 2. During the most recent admission, the patient was diagnosed with: 1) severe intrahepatic cholestasis of pregnancy, 2) gestational diabetes mellitus (A1), 3) scarred uterus, and 4) G3P2 Singleton pregnancy, Week 37^{+5}, LOA. After admission, the patient was given hepatoprotective and bile acids lowering agents, and fetal heart rate monitoring was conducted. Three days after admission, the patient underwent cesarean delivery using combined spinal and epidural anesthesia. The liveborn male infant weighed 3800g, with a body length of 51 cm, Apgar score 10-10-10. Physical examination at birth revealed a 3.0 cm $\times$ 4.0 cm skin lesion at the dorsum of the right foot, with a bright red surface, no exudate. There were no obvious mucous membranes on the lip, right upper and lower gums, tongue tip and pharynx. The surface was bright red, without any exudate (Figure 1). There was no contracture of extremities or joints (Figure 2). No other abnormalities were found.

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Table 1. — *Genetic screening of the patient and his family*

Sequencing quality	Sequencing coverage		Average sequencing depth			Percentage of average sequencing depth > 20x			
	100%		342			99.80%			
Results of high-throughput sequencing	Clinically relevant mutated gene	Transcript Exon No.	Nucleotide change	Amino acid change	Chromosomal location	Sequencing depth	Hox/Hex	Carrier rate (ExAC East asian)	Hereditary pattern
	COL7A1	NM_000094exon11	c.1372C>T	p.Gln458Stop	Chr3-48629241	141/157 (0.53)		Hex	AD/AR
	COL7A1	NM_000094exon2	c.134G>T	p.Gly45Val	Chr3-48631933	178/152 (0.46)		Hex	AD/AR

Family validation result:

Gene	Mutation site	Infant	Father	Mother
COL7A1	c.1372C>T	Heterozygous mutation	None	Heterozygous mutation
COL7A1	c.134G>T	Heterozygous mutation	Heterozygous mutation	None

Results of sequencing:

Two heterozygous mutations at COL7A1 were identified. Results of family members revealed that both parents are heterozygous mutation carriers and the 2 mutations of the infant were inherited from them.

Remarks:

This sequencing methods involved a comprehensive screening of exons related to hereditary skin diseases, type of mutations analyzed include point mutation, insertion mutation and deletion mutation.

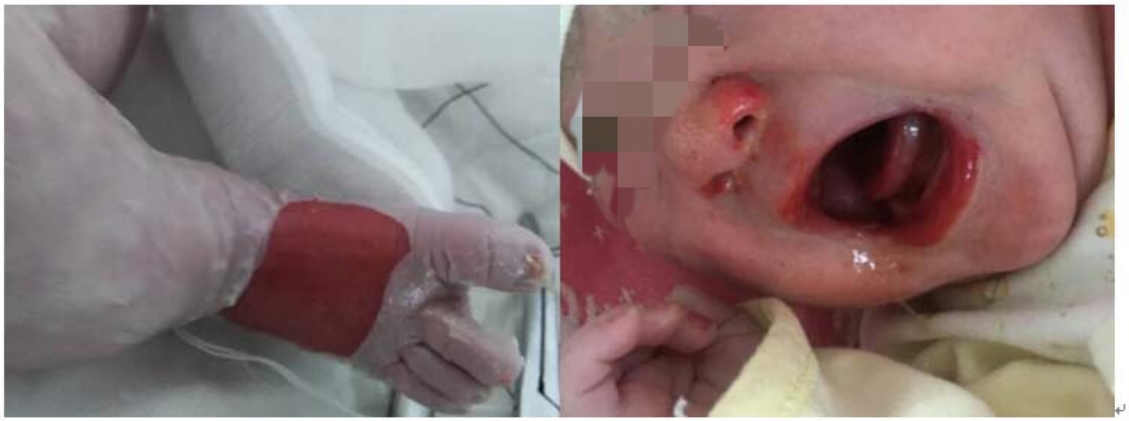

Figure 1. — There is a 3.0 cm × 4.0 cm skin lesion at the dorsum of the right foot, with a bright red surface, no exudate. No obvious mucous membrane on the lip, right upper and lower gums, tongue tip and pharynx, the surface was bright red, without any exudate.

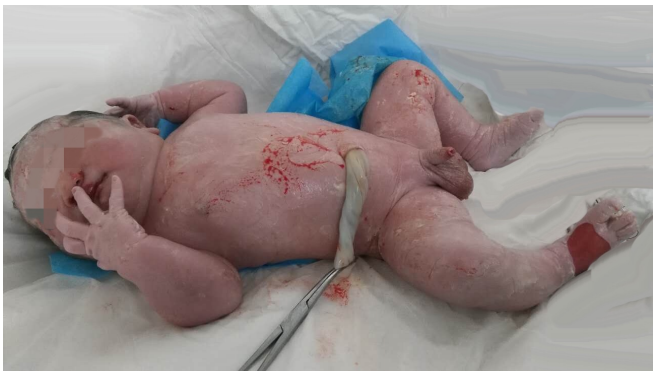

Figure 2. — There was no contracture of extremities or joints.

No family history of skin diseases was confirmed. The infant was treated with antibiotics, hemorrhage prevention, recombinant bovine basic fibroblast growth factor, and intravenous nutrition. Despite treatment, widespread blistering started to present over the whole body, and the mucous membrane lesions at the oropharynx were aggravated. Because of malnutrition, sepsis, and gastrointestinal hemorrhage, the family elected to withdraw treatment and the infant died two days after birth. After getting informed consent from the parents of the infant, a comprehensive genetic screening of hereditary skin diseases was conducted using Agilent exon chip capture and high-throughput sequencing (Table 1). Results of sequencing revealed two distinct heterozygous mutations at COL7A1. Results of family members revealed that both parents are heterozygous mutation carriers and the two mutations of the infant were inherited from them. No other additional mutations were found.

Discussion

Epidermolysis bullosa is a group of rare hereditary vesicular skin diseases with an incidence of 2/100000 live births. Currently, epidermolysis bullosa is categorized into three clinical types: epidermolysis bullosa simplex, junctional epidermolysis bullosa, and dystrophic epidermolysis bullosa. Dystrophic epidermolysis bullosa (DEB) is a group of monogenetic hereditary skin diseases characterized by increased skin or mucosal fragility. In response to minor injury, blisters form at the level of the anchoring fibrils in the sublamina densa in the uppermost dermis, with severe pruritus. In adult patients, skin lesions are characterized by pruritic papules or nodules with varying levels of damage on the extensor surfaces of extremities that heal with atrophic scars. DEB is categorized into two types: autosomal dominant DEB (DDB) and recessive DEB (RDEB) [1], RDEB is further classified into severe generalized types (Hallopeau-Siemens, RDEB-HS) and minor (non Hallopeau-Siemens, RDEB-nHS) [2]. Studies have confirmed that DEB is associated with mutations of COL7A1 [3], the gene that encodes type VII collagen in the epidermal basement membrane zone. The COL7A1 gene is located on the chromosomal region denoted 3p21.3. The gene is 23kb in length and has 118 exons, more than any previously described gene [4]. More than 500 COL7A1 mutations have been identified in DEB with different phenotypes [5]. Eight mutations have been identified in China and the biological consequences of such diverse mutations are extremely variable.

The skin and mucosal presentations in our case are typical of DEB. Genetic analysis revealed two heterozygous mutations in the exon region of COL7A1: c.1372C>T (cytosine>thymidine), c.134G>T (guanine>thymidine), resulting in amino acid changes: p. Gln458Stop (glutamine> termination mutation), p. Gly45Val (glycine > proline). These mutations have not yet been reported according to HGMDpro. We referred to the ACMG guidelines and found: c.1372C>T, is a nonsense mutation (PVS1), carrier frequency absent (PM2), phenotype matches (PP4). The variant is graded as pathogenic according to ACMG guidelines; c.134G>T, carrier frequency absent (PM2), phenotype matches (PP4), SIFL and Polyphen software supported that the variant would have a deleterious effect on the gene or gene product (PP3), and variant is considered "uncertain significance". The infant was compound heterozygous and the two COL7A1 heterozygous mutations were confirmed to be inherited from his parents. The parents were asymptomatic. Therefore the hereditary pattern in this case was autosomal recessive.

In 2003, Sato-Matsumura el al. reported 1 case of neonatal autosomal RDEB-HS [6]. The patient was born with bullae and erosions predominantly on the trunk, limbs, and the mucous membranes of the mouth, nose, and conjunctiva. The fingernails and toenails dropped off three months after birth. Genetic analysis revealed compound heterozygous mutation with 434insGCAT and R2261X, which were inherited from his father and mother respectively. The 434insGCAT mutation resulted in a frame shift and led to premature termination codon (PCT) in exon 5, and the R2261X mutation led to PCT in exon 86. Both mutations led to premature termination of type VII collagen synthesis, causing a shortened protein product and absence of normal type VII collagen.

Autosomal recessive hereditary DEB is the most severe subtype of DEB, namely Hallopeau Siemens disease (TTS-

RDEB). It is characterized by systemic skin mucosal blistering and scarring, accompanied by severe deformities, andmulti-organ involvement. The most severe complication of TTS-RDEB is the development of squamous cell carcinoma (SCC) in chronic erosive areas [7]. Over 50% of TTS-RDEB patients experience SCC around the age of 30 and eventually die from metastasis.

Generally, DEB can be diagnosed based on symptoms, signs and medical history. Prenatalultrasound may show polyhydroamnios, large stomach, pyloric atresia or stenosis. Local edematous lesions in extremities or the snow flake sign of fetal skin denudation may also be present. Postnatal findings can include contracture of extremities or joints or stricture of the gastrointestinal tract [8, 9]. In our case, there was no obvious abnormality in ultrasound examination during pregnancy and no contracture of extremities or joints after birth.

Continuous ultrasound monitoring during pregnancy can play a great role in early detection of DEB. Immunofluorescence and electron microscope are valuable to the classification of DEB. Fetoscopy allows direct visual examination of skin lesions and is valuable to prenatal diagnosis in combination with fetal collagenase expression assessment. In high-risk women, prenatal genetic diagnosis can be performed by chorionic sampling, amniocentesis, or amniotic fluid cell DNA extraction [10]. Some studies have found that the AFP level in amniotic fluidis elevated, when the fetus has DEB [11]. Our patient had normal Trisomy 21 screening during pregnancy, no obvious abnormality in ultrasound during pregnancy, and no prenatal diagnostic indicators. Therefore, no amniocentesis was performed. Currently, the second-generation high-throughput sequencing is a novel tool for DEB detection, which can also help elucidate the associated pathogenic genetic mutation and functional changes at mRNA and protein levels [12]. The in-depth understanding of genotype and phenotypic correlation is necessary for the development of future genetherapy.

At present, there is no effective treatment for autosomal recessive DEB. Supportive care interventionsinclude nutritional support, avoidance of collision and friction, care at blistering areas, and prevention of secondary infection. In published studies, die within the first year of life and the quality of life of survivors is severely compromised. omised. Pre-pregnancy genetic counseling and prenatal diagnosis can be of great clinical significance to these patients and families.

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Conflict of Interest

The authors declare no competing interests.

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