ORIGINAL ARTICLE

Whole exome sequencing identified a novel compound heterozygous variation in *COL7A1* gene causing dystrophic epidermolysis bullosa

Li-min Cui[1] | Jian-ye Jiang[1] | Ning-ning Hu[1] | Hong-en Zou[1] | Bao-zhen Zhao[1] |
Cong-ying Han[1] | Kai Yang[2] | Yi-peng Wang[2] | Huan-xia Xing[1]

[1]Prenatal Diagnosis Center, Langfang Maternal and Child Health Care Hospital, Langfang, China

[2]Prenatal Diagnosis Center, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China

Correspondence
Huan-xia Xing, Prenatal Diagnosis Center, Langfang Maternal and Child Health Care Hospital, 168 Guangyang Road, Langfang, Hebei 065000, China.
Email: xinghx_lffy@126.com

Yi-peng Wang, Prenatal Diagnosis Center, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing 100026, China.
Email: wangyipeng@ccmu.edu.cn

Abstract

Dystrophic epidermolysis bullosa (DEB) is a series of severe genetic conditions affecting skin and nails caused by mutations in the *COL7A1* gene. DEB has a strong phenotypic variability. In the present study, we recruited a case with a boy exhibiting typical DEB indication, and performed a clinical, genetic, and experimental investigation, followed by a prenatal diagnosis on their current pregnancy. Whole exome sequencing identified a novel compound heterozygous variation in *COL7A1*, consisting of two variants, namely c.191T>C (p.Leu64Pro) and c.5124G>A (p.Leu1708=) in the proband. In vitro study by minigene system indicated that c.5124G>A would result in an increased ratio of a transcript with exon-skipping, which supported its pathogenicity. Further prenatal detection confirmed the genotype–phenotye co-separation in this family. In conclusion, the findings in our study expanded the mutation spectrum of DEB, and emphasized the importance of paying attention to specific synonymous variants in the filtering process.

KEYWORDS

COL7A1 gene, dystrophic epidermolysis bullosa, minigene system, whole exome sequencing

1 | INTRODUCTION

Dystrophic epidermolysis bullosa (DEB) represents a group of genetic disorders affecting skin and nails that usually presents at birth, which are categorized into two major types based on inheritance pattern: dominant dystrophic epidermolysis bullosa (DDEB) and recessive dystrophic epidermolysis bullosa (RDEB) (Pfendner & Lucky, 2006). Each type further consists of multiple clinical subtypes (https://www.omim.org/; updated 07 Feb 2022). Manifestations in generalized RDEB include skin fragility characterized by blistering with minimal trauma that heals with milia and scarring, tongue-mouth fusion after recurrent ruptures, esophageal webs and strictures leading to malnutrition, "mitten" hands and feet, and high risk of aggressive squamous cell carcinoma (>90%) (Fine et al., 2014; Pfendner & Lucky, 2006). In terms of DDEB, the blistering is usually mild with limited locations (hands, feet, knees, and blows); and sometimes even absent, leaving only dystrophic nails (Fine et al., 2014; Pfendner & Lucky, 2006).

COL7A1 (MIM *120120), the only known causative gene for DEB (Christiano et al., 1993), encodes the alpha-1

chain of type VII collagen, the main constituent of anchoring fibrils, which are located below the basal lamina at the dermal-epidermal basement membrane zone in the skin (Burgeson et al., 1985). Up to date, over 800 DEB-associated mutations in *COL7A1* are indexed, among which most are glycine substitutions located in the triple helix domain (THD) (http://www.col7a1-database.info) (Wertheim-Tysarowska et al., 2012). The genotype–phenotype association of various types of variations in both DEB types has been preliminarily established. That is, in RDEB, the presence or absence of residuary functional protein appears to be the most important factor in determining the disease severity (Pfendner & Lucky, 2006); while in DDEB, the dominant-negative amino acid substitutions of glycine in THD account for the most (Khan et al., 2021; Lucky et al., 2018; Varki et al., 2007; Yan et al., 2018). Specific *COL7A1* variants may confirm to both inheritance pattern, rendering it challenging in the following genetic consultation (Almaani et al., 2011).

Even in the era of molecular diagnosis, immunofluorescence (IF) is still helpful in the establishment of a broad category of DEB type (Meester et al., 2018); similarly, transmission electron microscopy (TEM) is also diagnostic and often more useful in the milder forms (Eady & Dopping-Hepenstal, 2010). But then again, the advances of next generation sequencing (NGS) has made diagnosis accurate and efficient, especially in differential diagnosis with other types of EB (Lucky et al., 2018; Yu et al., 2021).

In the present study, a family with a boy exhibiting typical EB phenotype was enrolled and underwent a clinical and genetic examination. A novel compound heterozygous variation in *COL7A1* was identified. In silico analysis was carried out to predict the pathogenicity of a novel missense variant, while in vitro minigene experiment was conduct to reveal the impact on mRNA splicing of a novel synonymous variant. Subsequently, prenatal diagnosis was performed to the fetus conceived by the proband's mother.

2 | MATERIALS AND METHODS

2.1 | Subjects

A family with a 10-year old male patient exhibiting EB phenotype was referred to our center in January, 2021. The husband was 32 and the wife was 30, and they claimed that they were non-consanguineous. They wife was pregnant at 10th gestational week. A comprehensive clinical evaluation and genetic detection were carried out to clarify the nosogenesis.

This study was approved by the Ethics Committee of Maternity and Child Care Center of Langfang. Informed consent was provided by all participants included in the study. All procedures performed in the present study were in accordance with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

2.2 | Genetic detection

Peripheral blood samples were collected from all participants. Genomic DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen GmBH), according to the manufacturer's instructions.

G-banding karyotyping was performed to identify the chromosomal abnormalities according to the AGT cytogenetics laboratory manual (Arsham et al., 2017). The standard experimental procedure involved the PHA and colchicine-stimulated lymphocyte cultures, preparation of chromosome specimens, digestion by trypsin, G-band staining, and karyotype analysis referring to the ISCN-2016 (McGowan-Jordan et al., 2016). CytoScan 750 K (Affymetrix) microarray was used to test for copy number variations (CNV), loss of homozygosity (LOH), uniparental disomy (UPD), and mosaicism, according to the manufacturer's instructions. The Affymetrix Gene Chip Command Console software (version 4.0) and Chromosome Analysis Suite (version 2.1) (Affymetrix) were used to analyze the raw data.

Whole exome sequencing (WES) was conducted on the proband to detect sequence variants. Briefly, the target-region sequences were enriched using the Agilent Sure Select Human Exon Sequence Capture Kit (Agilent). The DNA libraries were then tested for enrichment by quantitative PCR, of which the size, distribution, and concentration were determined using an Agilent Bioanalyzer 2100 (Agilent). The NovaSeq6000 platform (Illumina, Inc.), along with ~150 bp pair-end reads, was used to sequence DNA at a concentration of ~300 pM per sample using the NovaSeq Reagent kit. Sequencing raw reads (quality level Q30% >90%) were aligned to the human reference genome (accession no. hg19/GRCh37) using the Burrows-Wheeler Aligner tool (Li & Durbin, 2009), and the PCR duplicates were removed using Picard (version 1.57). Variant calling was performed with the Verita Trekker® Variants Detection system (version 2.0; Berry Genomics) and the Genome Analysis Tool Kit (https://software.broadinstitute.org/gatk/). Then, the variants were annotated and interpreted using ANNOVAR (version 2.0) (Wang & Hakonarson, 2010) and Enliven® Variants Annotation Interpretation systems (Berry Genomics), based on the common guidelines by the American College of Medical Genetics and Genomics (ACMG) (Richards et al., 2015). To assist in the interpretation of pathogenicity, we referred to three frequency databases (1000G_2015aug_eas, https://www.internationalgenome.org; ExAC_EAS, http://exac.

broadinstitute.org; gnomAD_exome_EAS, http://gnomad.broadinstitute.org) and HGMD Pro (version 2019) (Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php). Sanger sequencing using 3500DX Genetic Analyzer (Applied Biosystems) was performed to confirm the variants (Primers in Supplementary material S1).

2.3 | In silico analysis on the novel missense variant

The conservatism of amino acid (AA) affected by missense variant was analyzed using MEGA7 (http://www.megasoftware.net) with default parameters. And the pathogenicity of missense variant was predicted with Revel (an ensemble method for predicting the pathogenicity of missense variants using the following tools individually: MutPred, FATHMM, VEST, PolyPhen, SIFT, PROVEAN, Mutation Assessor, Mutation Taster, LRT, GERP, SiPhy, phyloP, and phastCons; with the cutoff value >0.7) (Hu et al., 2021).

2.4 | In vitro study on the novel synonymous variant

Because the novel synonymous variant (*COL7A1*: c.5124G>A) was adjacent to the splicing site, we inferred that it might affect the normal splicing of mRNA. Splice site prediction algorithms of DANN, dbscSNV, and the like also indicated it to be deleterious (Supplementary material S1). Our preliminary experimental result showed that *COL7A1* was almost absent in peripheral

blood RNA of the subjects (Supplementary material S1, Table S2), therefore, an in vitro validation experiment was conducted.

In short, the minigene plasmids containing either the *COL7A1* wild-type (WT) or the *COL7A1*:c.5124G>A mutant were constructed with an in-house designed expression backbone, pMini-CopGF (details in Supplementary material S1). Subsequently, HEK (human embryonic kidney) 293 T cells were transfected by these plasmids, respectively; and the RNA sample was extracted and reversely transcribed into cDNA. Particular impact on mRNA splicing was analyzed via PCR fragment amplification, AGE (agarose gel electrophoresis) and Sanger sequencing (details in Supplementary material S1).

2.5 | Prenatal diagnosis

Routine amniocentesis was carried out at the 20th gestational week. G-banding, SNP-array, and Sanger sequencing were performed on the fetal amniotic fluid sample as described above.

3 | RESULTS

3.1 | Clinical manifestations

The proband was diagnosed with DEB on the 10th day after birth. Our examination indicated that he presented with skin fragility, non-scarring blistering (mainly in the pretibial area), hyperkeratotic skin lesions, nail dystrophy, pruritus, and multiple hypertrophic scars (Figure 1a).
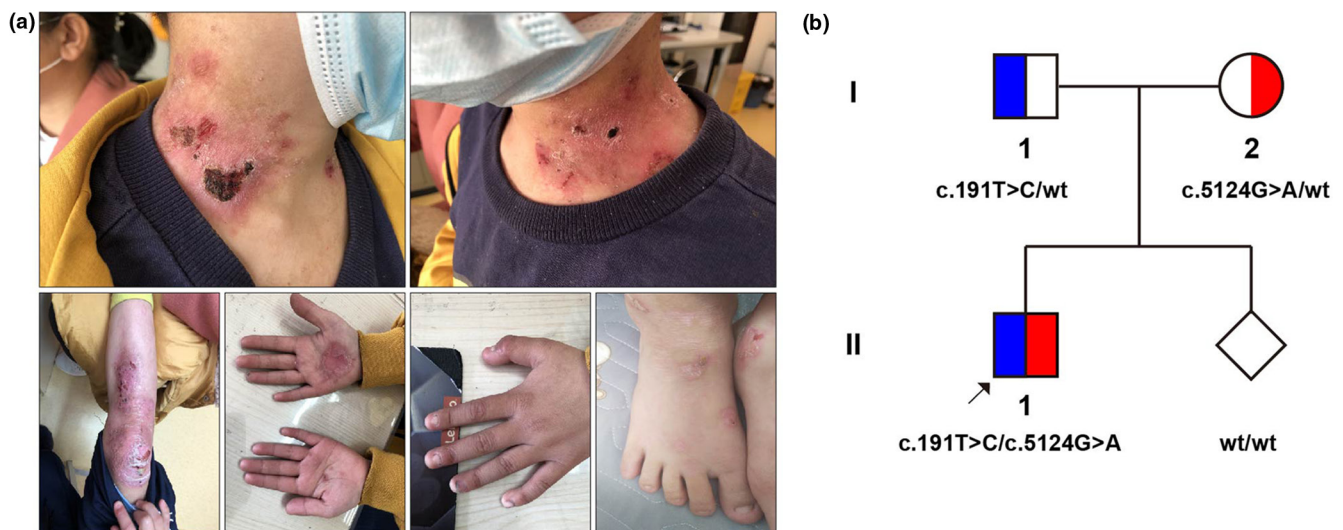

FIGURE 1 Clinical manifestations of the patient. (a) Appearance indications including non-scarring blistering (mainly in the pretibial area), hyperkeratotic skin lesions, nail dystrophy, and multiple hypertrophic scars. (b) Pedigree diagram of this family and corresponding variant carrying status

Both parents were asymptomatic, and the routine screening (ultrasonic, serological, and noninvasive prenatal testing) at early trimester of this pregnancy was normal. The pedigree diagram is shown in Figure 1b.

3.2 | Genetic findings

Results of conventional G-banding and microarray on the proband were normal. WES identified a novel compound heterozygous variation consisting of two variants, namely *COL7A1* (NM_000094): c.191T>C (p.Leu64Pro) and c.5124G>A (p.Leu1708=) in the proband. Among them, c.191T>C was inherited from his father, while c.5124G>A was from his mother (Figure 2a). Both variants were not indexed in the three frequency databases. The specific locations of both variants were depicted in Figure 2b, the *COL7A1* gene and peptide chain schematics.

3.3 | Results of the c.191T>C: P.Leu64Pro variant

It was demonstrated that the COL7A1: Leu64 residue maintained conserved among species (Figure 2c). The Revel score was 0.8539 (cutoff value for being predicted as deleterious is >0.7), and the detailed data by multiple in silico prediction tools is included in Table S1 (Supplementary material S1).

3.4 | The impact of c.5124G>A variant on mRNA splicing

Also, the residue L1708 maintained conserved among species (Figure 2c). Further in vitro study indicated that the c.5124G>A variant led to an increased ratio of the exon-skip transcript. To be specific, the amplification and
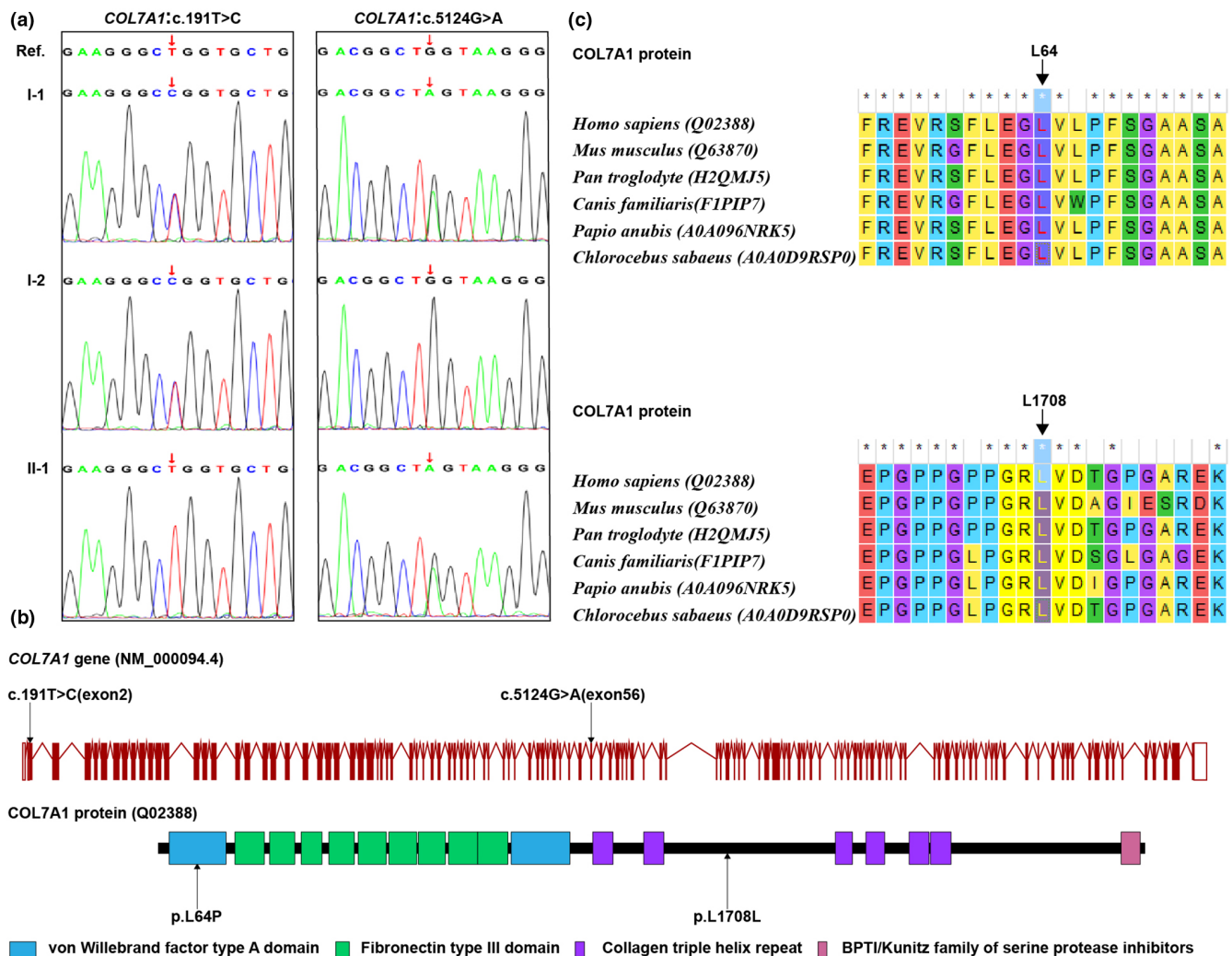

FIGURE 2 Genetic findings. (a) The carrying status of both of the variants, *COL7A1*: C.191T>C and c.5124G>A. (b) Specific locations of the two variants in the COL7A1 gene and peptide schematics. (c) The conservatism of the two affected amino acid residues, COL7A1: P.L64 and L1708, among multiple species

subsequent electrophoresis results of WT showed that there were two bands, but there was only one band shown in the mutant lane (Figure 3a). We recycled every gel band, and collected the corresponding DNA sample from it for validation sequencing. Results demonstrated that in the WT two transcripts existed, which were the normal expected one and the 56-exon-skip one, while in the mutant only the latter one showed up (Figure 3b; detailed data in Supplementary material S1). A pattern diagram corresponding to this mechanism was shown in Figure 3c.

3.5 | Results of the prenatal diagnosis

Based on the above collective results, we conducted prenatal diagnosis of the fetus according to the demands of the couple. G-banding karyotype of the fetus' sample was normal; Sanger sequencing showed that it was wild-type at both variation sites (Figure 4a). SNP-array revealed a 378.4-kb microduplication at 2p23.3 (25,608,875-25,987,356) and a 507-kb microdeletion at 15q11.2 (22,770,422-23,277,436) (Figure 4b). Further validation demonstrated that the 2p23.3 microduplication was inherited from the father, and the 15q11.2 microdeletion was from the mother.

Fully consulted and informed, the couple decided to continue the pregnancy. A girl was eventually born at 39 weeks gestation, and all the indexes and scores of the newborn were normal.

4 | DISCUSSION

Epidermolysis bullosa encompasses a group of inherited blistering skin disorders, among which DEB represents a sub-group caused by *COL7A1* gene solely, yet with strong genetic complexity and phenotypic variability (Christiano et al., 1993; Fine et al., 2014; Yu et al., 2021).
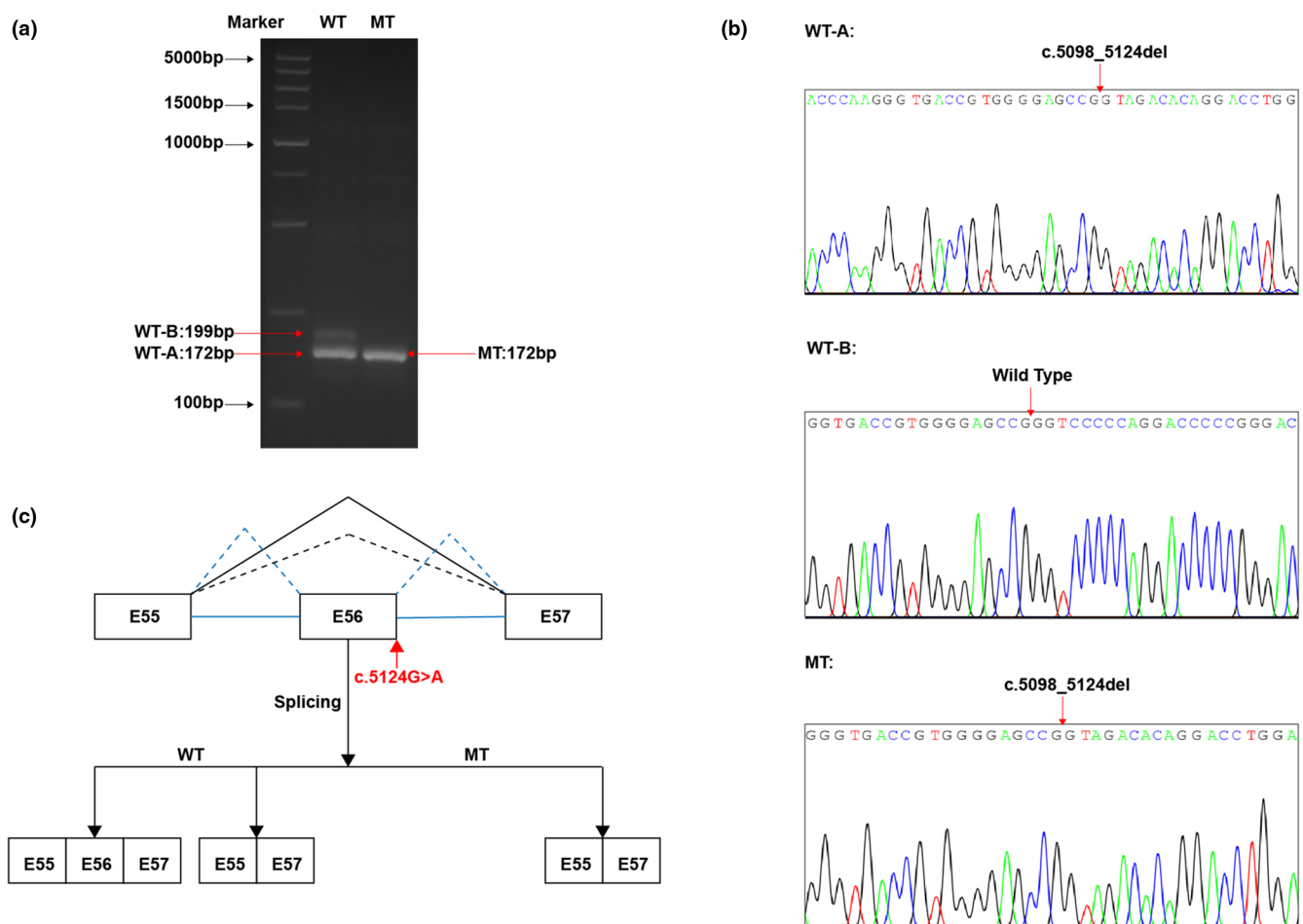

FIGURE 3 Results of the in vitro study by minigene system. (a) Electrophoresis results of PCR amplification products from the cDNA templates of wild-type (WT) and mutant (MT) transfections. (b) Sanger sequencing on the recycled gel DNA revealed two transcripts in the WT (WT-A, the 56-exon-skip one; WT-B, the normal expected one), yet one in the MT (the 56-exon-skip one). (c)The transcription schematic of this study (the dotted lines represent the splicing pattern of the WT, and the full lines represent the splicing pattern of the MT)
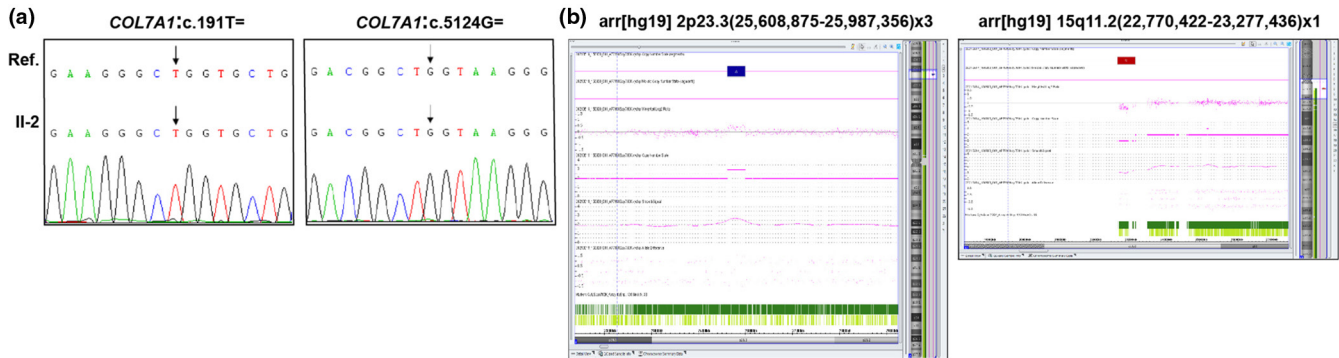
FIGURE 4 Prenatal diagnosis results. (a) Sanger sequencing demonstrates that the fetus was wild-type in both of the variants. (b) SNP-array detects two copy number variants in the fetal sample, expressed as arr [hg19] 2p23.3(25,608,875-25,987,356) × 3, 15q11.2(22,770,422-23,277,436) × 1

From a clinical presentation point of view, the patient in this study fitted well with the pretibial subtype (MIM #131850), mainly due to his blistering being more located in pretibial area (Lee et al., 1993). However, his onset occurred after birth, which is not consistent with most cases of this subtype (Fine, 2016; Naeyaert et al., 1995; Yenamandra et al., 2017). So, this could not rule out other subtypes like the general RDEB (MIM #226600), epidermolysis bullosa pruriginosa (MIM #604129), etc. This again demonstrated the phenotypic overlap between DEB's clinical subtypes.

Sequencing identified two novel variants in *COL7A1*, which presented an autosomal recessive pattern in this family. In the absence of in vitro evidence, both variants were uncertain of significance according to the ACMGG general interpretation guidelines (Richards et al., 2015). To be specific, the c.191T>C (p.Leu64Pro) variant met with PM1 + PM2 + PP3 evidence levels, while c.5124G>A met with PM2 + PP3. Yet, the following experimental results by minigene system confirmed that the synonymous variant, c.5124G>A, would affect the normal mRNA splicing, resulting in an increased exon-skip transcript ratio, thus promoting its pathogenicity grade to "likely pathogenic". The conservatism of the Leu64 residue affected by c.191T>C in various species can support the pathogenicity to a certain extent, but it is not enough to raise the level. Collectively, this variation measured up to be diagnostic. Further prenatal diagnosis confirmed that the couple's fetus was wild-type and the neonate was born without any skin phenotype, which was in-line with the co-separation principle and supported the above assessment. To the best of our knowledge, only one case of DEB associated with a *COL7A1* synonymous mutation has been reported (Covaciu et al., 2011). This rare condition reminds us to be careful when filtering the variants.

Although the two copy number variants harbored by the fetus were parentally inherited, there may still be risk of intrafamilial phenotypic heterogeneity and incomplete penetrance to them, which cannot completely exclude their pathogenicity. Especially for the 507 kb microdeletion at 15q11.2, it covers four OMIM genes, of which the *NIPA1* (MIM *608145) gene is associated with the autosomal dominant spastic paraplegia type 6 (MIM #600363) characterized by limbs spasm and pes cavus (Rainier et al., 2003). The ClinGen database showed that the evidence for haplodose sensitivity of genes contained in this segment was not clear (https://www.clinicalgenome.org/). Rosenfeld et al. (2013) reported that the microdeletion this segment had a penetrance of about 10.8%, emphasizing the necessity to pay attention to the future development of the newborn. In addition, the couple still has a 25% risk of DEB in their future pregnancy, so supporting diagnostic methods such as prenatal diagnosis are still recommended.

In conclusion, we enrolled a family with proband exhibiting DEB presentations, performed WES to identify causative variation. A compound heterozygous variation with two novel variants were detected; following in silico analysis and in vitro study supported its pathogenicity. Our findings expanded the mutation spectrum of *COL7A1* gene, and provided solid evidence for the genetic counseling to the affected family.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

HX and YW designed this study. LC wrote this manuscript, and KY reviewed and corrected it. HZ and BZ recruited the case and did the clinical examination. NH and CH performed the genetic experimental study. LC, KY,

and JJ conducted in vitro study, analyzed experimental data, and composed all figures and tables.

DATA AVAILABILITY STATEMENT

The underlying data supporting the results of this study can be required to the corresponding author based on reasonable demand.

ORCID

Kai Yang ![ORCID] https://orcid.org/0000-0002-7457-3106
Huan-xia Xing ![ORCID] https://orcid.org/0000-0002-7175-5019

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Cui, L-m, Jiang, J-y, Hu, N-n, Zou, H-e, Zhao, B-z, Han, C-y, Yang, K., Wang, Y-p & Xing, H-x (2022). Whole exome sequencing identified a novel compound heterozygous variation in *COL7A1* gene causing dystrophic epidermolysis bullosa. *Molecular Genetics & Genomic Medicine*, 10, e1907. https://doi.org/10.1002/mgg3.1907