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CASE REPORT

Novel Point Mutation of *EBSS* Gene Coexisted with 1p36 Deletion

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EBSS (epidermolysis bullosa simplex superficialis) is mainly caused by gene mutations which targeted protein as plakophilin-1, desmoplakin and keratins. 1p36 gene deleted could cause typical clinical manifestations and might also affect the expression of functional genes in other regions. Here we reported the first case of *PKP1* gene and *DSP* gene mutation coexisted with 1p36 deletion presented as serious EBSS and 1p36 deletion syndromes and identified a new homozygous mutation in the *PKP1* gene (chr1:201292246 c.1672 T>C) and in the *DSP* gene (chr6:7580346 c.3923C>T). **(Ann Dermatol 33(5) 463~466, 2021)**

-Keywords-
Chromosome 1p36 deletion syndrome, Epidermolysis bullosa simplex superficialis, Genetic variation

INTRODUCTION

EBSS (epidermolysis bullosa simplex superficialis) is mainly caused by plakophilin (*PKP*) and/or desmoplakin (*DSP*) gene mutations which targeted protein as plakophilin-1, desmoplakin and keratins[1]. Deletions of chromosome 1p36 affect approximately 1 in 5,000 newborns. The clinical features of 1p36 deletion syndrome include developmental delay, intellectual disability seizures, vision problems, hearing loss, short stature, brain anomalies, congenital heart defects, cardiomyopathy, renal anomalies, orofacial clefting, and distinctive facial features-straight eyebrows, deeply set eyes, mid-face retraction, wide and depressed nasal bridge, long philtrum, pointed chin, large, late-closing anterior fontanel, micro brachycephaly, epicanthal folds, and posteriorly rotated, low-set, abnormal ears[2]. However, except exon coding genes, some another regulatory genes in 1p36 might contribute to some new phenotypes or syndromes and need further clinical and experimental evidence. Here we reported a rare case of EBSS involved the whole-body skin in a 1p36 deletion syndrome patient and identified novel mutation points in *PKP1* and *DSP* gene.

CASE REPORT

The patient was a 16-year-old Chinese boy born to non-consanguineous healthy parents who have another healthy daughter. He was birth with a birth weight of 2.8 kg and normal-appearing skin. Straight eyebrows, deeply set eyes, wide nasal bridge, and a pointed chin was observed when he was born. When he was a 1-month baby, blisters were presented repeatedly on his armpit and inguinal skin and subsequently speeded to other body area including palms and plantar. Skin lesions could self-heal without scarring or milia. His skin problem continues to this day and without treatment. When he was 2-year old, severe growth retardation, mental retardation and slow response was found by his doctor.

At 16 years of age, his weight was 22 kg and length 105 cm (−3 cm SD). Straight eyebrows, deeply set eyes, wide nasal bridge, a pointed chin and hair loss were obvious (Fig. 1A). Erythema, blisters, erosions, scale and crust dis-

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tributed on his face, trunk, limbs, palms and plantar. Mouth chap, nail deformation, hair sparsity and cryptorchidism were observed (Fig. 1B). Mental retardation was assessed and diagnosed by neurologists. Cardiovascular examination and transthoracic echocardiography were unremarkable. Neither of the patient' parents and his sister were found to have any skin, hair, palmoplantar or cardiac abnormalities.

H&E strains showed vesicles was just beneath the level of the stratum corneum (Fig. 2A). Immunofluorescence test showed immunoglobulin (Ig) G(−), IgA(−), IgM(−), and C3 (−). Transmission electron microscopy of skin showed intracorneal cleft in stratum corneum, and desmosomes was normal (Fig. 2B). Peripheral blood sample was taken from the patient and his family members. DNA sequencing was performed using an Applied ABI 3730XL DNA Analyzer (Applied Biosystems, Warrington, UK). The primers used for PCR amplification were shown in Table 1. Gene mutation analysis in patient disclosed a homozygous T>C substitution at 1672c. in exon 10 of the *PKP1* gene (Fig. 3A), PKP1 nucleotide code is GCATCTTTCTTGCTCTTGCCCA TGAGGCA in health subject (Fig. 3C) and changes as GCATCTTTCTTGCTCTT>CGCCCATGAGGCA in this EBSS patient, amino acid code as ASFLLLPMRFR. A homozygous C>T substitution at 3923c. in exon 38 of the *DSP* gene resulting in a homozygous nonsense mutation (Fig. 3B). DSP nucleotide code is ACTGCTTGTGCCGGG in health subject (Fig. 3D) and changes as ACTGCTTGTGCC> TGGG in this EBSS patient, amino acid codes as CRCLARS. *TGM5*, *CSTA*, *SERPIN8*, *CHST8*, *FLG2*, *CDSN*, and *DSG1* genes were all without mutation. At the same time a large interstitial 1p36 deletion (chr12819330-14042104, 1222.8Kb, 31 genes) was found. Same gene test was done on his family members including his mother, father and sister and found that both his mother and his sister were heterozygous carriers of frameshift mutation in *PKP1* gene (chr1: 201292246 c.1672 T>C) but his father was without *PKP1* gene mutation.

A diagnosis of EBSS combined with 1p36 deletion syndrome was made basing on his clinical features, skin pathological founds and genetic results.

Approval for this study was obtained from the Clinical Research Ethics Committee at the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China. Experiments on human tissue were performed in compliance with the Declaration of Helsinki Principles. The patient and his fam-

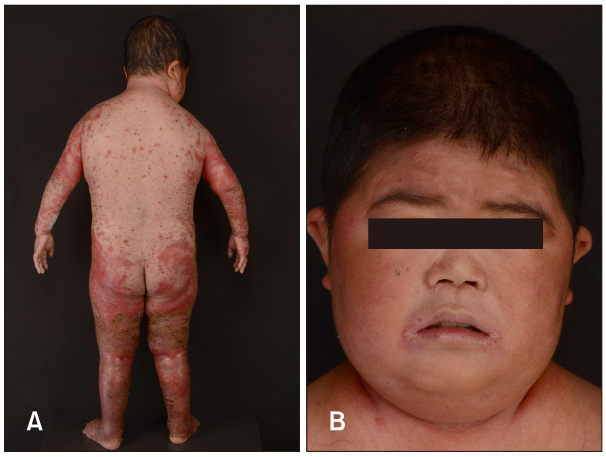

Fig. 1. Clinical images of patient. (A) Wide spread skin lesions of scattered erosions, crusts, and postinflammatory and hypopigmentation. (B) 1p36 deletion syndrome characteristic facial features include straight eyebrows, deeply set eyes, wide nasal bridge, and a pointed chin.

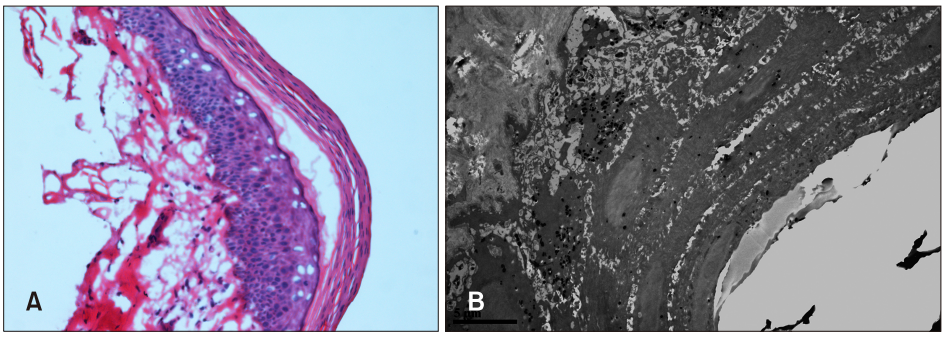

Fig. 2. Skin pathology and electron microscopy. Biology was done on forearm lesions. (A) H&E strain showed vesicles was just beneath the level of the stratum corneum (×100). (B) Transmission electron microscopy of skin showed intracorneal cleavage presented above the level of keratohyalin granule within the stratum granulosum, and desmosomes was normal (×400).

Table 1. PCR primers

Primer name	Sequence (5′–3′)	Sequence (3′–5′)	Size (bp)
PKP1	TATCTGGAACCACGACCCT	CCTTCTCCGCCGCATT	604
DSP	GAAATTGTCAGGCTCAA	TCTGTGGTCTGGGTTAG	509

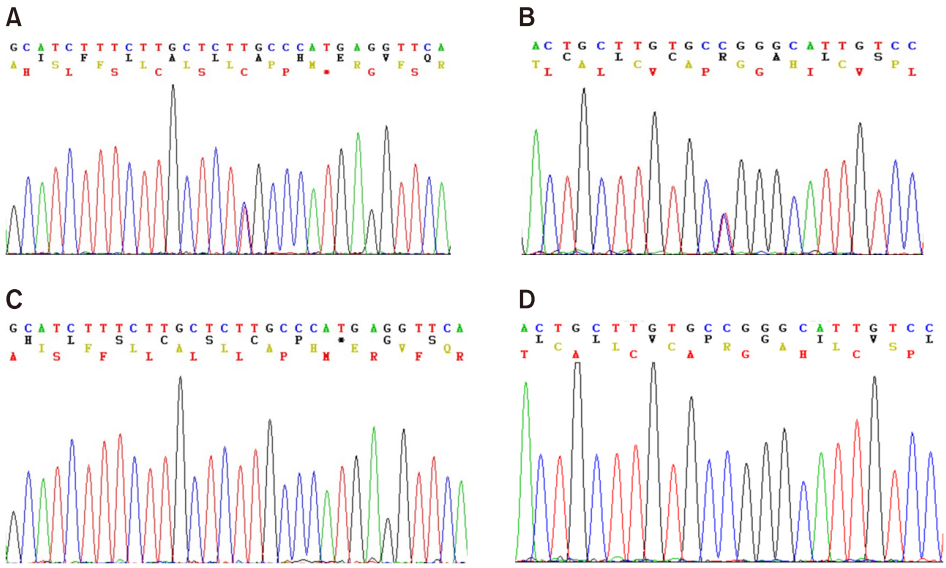

Fig. 3. Array-based copy number variant analysis of the peripheral blood. DNA assay showed that PKP1 nucleotide codes is GCATCTTTCTTGCTCTTGCCCATGAGGCA in health subjects and changes as GCATCTTTCTTGCTCTT>CGCCCATGAGGCA in this EBSS (epidermolysis bullosa simplex superficialis) patient, amino acid codes as ASFLLLPMRFR. DSP nucleotide codes is ACTGCTTGTG CCGGG in health subjects and changes as ACTGCTTGTGCC>TGGG in this EBSS patient, amino acid codes as CRCLARS. (A) Patient's gene mutation on exon 10 of *PKP1* (chr1:201292246 c.1672 T>C); (B) patient's gene mutation in exon 23 of *DSP* gene (chr6:7580346 c.3923C>T). (C) Healthy subjects without DNA mutation at the same gene locus of *PKP1*; (D) healthy subjects without DNA mutation at the same gene locus of *DSP*.

ily members have signed the study informed consent and the consent form about publishing all photographic materials.

DISCUSSION

Tanaka et al.[3] have reported that *PKP1* and *DSP* mutations could cause similar skin phenotypes. The first mutation in the *DSP* gene was reported in 1999. p.Gln1124 and p.Arg1249 pathogenic homozygous nonsense mutations in *DSP* gene have been identified until now[4,5]. *DSP* gene mutation was associated with several abnormal keratosis skin diseases such as PPK (palmoplantar keratoderma)[6] and SAM (severe dermatitis, multiple allergies and metabolic wasting syndrome)[7]. Favre et al.[8] reported that recessive mutation in the *DSP* gene was related with cardiomyopathy, skin fragility and hair defects. In this case we identified a new homozygous mutation in the *DSP* gene (chr6:7580346 c.3923C>T) which might induce the amino acid changes of DSP functional proteins.

The carboxyl terminus of PKP1, reelevated to calcium stability of desmosomes, is localized in the plasma membrane and the amino terminus. PKP1 plays an important part in the recruitment of desmoplakin to the cell membrane and desmosome assembly. *PKP1* gene mutation could induced dysplasia-skin fragility syndrome (ED-SFS) of which the clinical features involved skin fragility and erosions, patches of scale crust on the trunk and limbs, peri-oral cracking and inflammation, hypotrichosis, palmoplantar keratoderma with painful fissuring and other somewhat variable ectodermal anomalies[9]. In this case we identified a new homozygous nonsense mutation in the *PKP1* gene (chr1:201292246 c.1672 T>C) in this patient and his family members. For the family members carried *PKP1* gene mutation but were all without clinical perennation, we speculated that *PKP1* mutation was not the individual pathogenic genes in this patient. This patient presented EBSS clinical and pathological features, and *DSP* and *PKP1* mutation was previously reported as the pathogenic genes of EBSS. Further investigation of the functional consequence of this new mutation could help deeper understanding the pathogenesis of EBSS.

ED-SFS was also caused by *PKP1* gene mutations. However, widening of the intercellular spaces between adjacent keratinocytes and small desmosomes could be observed via transmission electron microscopy in ED-SFS patients. In this case we found that the desmosomes were normal which was not supported the ED-SFS diagnosis. Skin fragility-woolly hair syndrome is a rare autosomal recessive disorder involving the desmosomes and is caused by mutation in the *DSP* gene. In this case the patient was without cardiac symptoms and the desmosomes was normal

via transmission electron microscopy. Acantholytic epidermolysis bullosa is characterized by acral bullae, and histologically demonstrates suprabasal clefting with acantholysis. In this case H&E strains and transmission electron microscopy showed vesicles were just beneath the level of the stratum corneum and without suprabasal cleft or acantholysis.

1p36 deletion syndrome is a common clinical recognizable malformation syndrome. Genes are deleted in patients with 1p36 deletion syndrome, for example the neuroblastoma suppressor gene, *KCNAB2*, *PAX7*, *DVL1*, *MMP23B*, *GABRD*, *PRDM1RERE*, *UBE4B*, *CASZ1*, *PDPN*, *SPEN*, *ECE1*, *HSPG2*, and *LUZP1*[2]. Collectively, this case represents the first desmosomal genodermatoses coexisted with 1p36 deletion to be reported from China and add to genotype-phenotype correlation in this group of inherited disorders. This 1p36 deletion patient presented as more serious skin symptoms compared with other EBSS patients who reported to be with *PKP1* or *DSP* gene mutation. We prompted that the 1p36 gene deletion might interact with other genes functions, such as changing the gene promoter activations especially on the adjacent genes which induced other genetic diseases, but the interaction of 1p36 genes and functional genes in other regions needed more genetic evidences in future.

In summary, we have reported the first case of *PKP1* gene and *DSP* gene mutation coexisted with 1p36 deletion presented as serious EBSS and 1p36 deletion syndromes and identified a new homozygous mutation in the *PKP1* gene (chr1:201292246 c.1672T>C) and in the *DSP* gene (chr6:7580346 c.3923 C>T).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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