Novel Point Mutation of EBSS Gene Coexisted with 1p36 Deletion

Yue Zheng, Qingfang Xu, Wei Lai

Department of Dermato-Venereology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, P. R. China

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 co-existed 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 keratins1. 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 ears2. 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-
distributed 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’s 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 GCATCCTTTGCTCTTGCCCA TGAGGCA in health subject (Fig. 3C) and changes as GCATCCTTTGCTCTTT>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 ACTGCTTTGCAGGCG in health subject (Fig. 3D) and changes as ACTGCTTTGCAGGC>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 (chr1:20129330-14042104, 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-

| Primer name | Sequence (5’→3’) | Sequence (3’→5’) | Size (bp) |
|-------------|-----------------|-----------------|-----------|
| PKP1        | TATCTGGAACCCACGACCT | CCGTGCTTGCCGCATT | 660 |
| DSP         | GAAATTGTACGACGCTAA | TCTGCTGGTCTGGGTAG | 509 |
EBSS Coexisted with 1p36 Deletion Symptom

Vol. 33, No. 5, 2021

465

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 GCATCTTTCTTGCTCTTGCCCATGAGGCA in this EBSS (epidermolysis bullosa simplex superficialis) patient, amino acid codes as ASFLLLPMRFR. DSP nucleotide codes is ACTGCTTGTGCCG in health subjects and changes as ACTGCTTGTGCCC 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.

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 now4,5. 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 anomalies9. 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. 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.

FUNDING SOURCE

This research was supported by Guangdong Basic and Apply Basic Research Foundation (2020A1515010305) and Meizhou science and technology program (191224092055033).

ORCID

Yue Zheng, https://orcid.org/0000-0003-1847-2375
Qingfang Xu, https://orcid.org/0000-0002-6460-8723
Wei Lai, https://orcid.org/0000-0002-2784-492X

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