

CONCISE COMMUNICATION

Report of Chinese family with severe dermatitis, multiple allergies and metabolic wasting syndrome caused by novel homozygous desmoglein-1 gene mutation

Ruhong CHENG,* Ming YAN,* Cheng NI,* Jia ZHANG, Ming LI, Zhirong YAO

Department of Dermatology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China,

ABSTRACT

Recently, homozygous mutations in the desmoglein-1 (DSG1) gene and heterozygous mutation in the desmoplakin (DSP) gene have been demonstrated to be associated with severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome (Mendelian Inheritance in Man no. 615508). We aim to identify the molecular basis for a Chinese pedigree of SAM syndrome. A Chinese pedigree of SAM syndrome was subjected to mutation detection in the DSG1 gene. Sequence analysis of the DSG1 gene and quantitative reverse transcriptase polymerase chain reaction analysis for gene expression of DSG1 using cDNA derived from the epidermis of patients and controls were both performed. Skin biopsies were also taken from patients for pathological study and transmission electron microscopy observation. Novel homozygous splicing mutation c.1892-1delG in the exon–intron border of the DSG1 gene has been demonstrated to be associated with SAM syndrome. We report a new family of SAM syndrome of Asian decent and expand the spectrum of mutations in the DSG1 gene.

Key words: Chinese, desmoglein-1 gene, mutation.

INTRODUCTION

In 2013, a new syndrome comprising severe dermatitis, multiple allergies and metabolic wasting (SAM) was uncovered. Up to then, four families had been reported to be caused by homozygous loss-of-function mutations in the desmosomal plaque protein desmoglein-1 (DSG1) gene^{1–3} and one case was attributed to heterozygous missense mutation in the desmoplakin gene (DSP).⁴ Here, we report another family with SAM syndrome of Asian decent to further confirm that heritable skin barrier plays an important role in the pathogenesis of atopic disease.

METHODS

The probands were brother and sister born to first-degree cousins of Chinese descent. At the time of writing, the sister was 13 years old and the brother 7 years old. They shared many clinical similarities. During infancy, they displayed congenital erythroderma with flares of generalized dermatitis (Fig. 1b,f). Palmoplantar keratoderma began since an early age and aggravated with age. Yellow keratosis on the hands (Fig. 1e) and extremely thick focal keratosis on the pressure sites of the soles (Fig. 1d) had impaired manual function and walking for years. Erythematous plaques with fine scaling could spread

to all over the body during flares. At remission stage, hyperkeratotic plaques were obvious at the knees (Fig. 1g), elbows and sacrococcygeal region (Fig. 1h), with superficial erosions in the skin folds (Fig. 1c) or following slight friction. Their hair was very hard and curly (Fig. 1a) without hypotrichosis. Their teeth were normal. The nails were affected in the sister but appeared normal in the brother. It was noted that a history of recurrent severe respiratory infections accompanied by severe metabolic wasting at an early age was confirmed in the brother but denied for the sister. She had been in a good general condition since a young age, with normal physical and mental development. The boy presented with growth retardation before 5 years of age. Laboratory work-up of the boy revealed persistent and markedly elevated immunoglobulin E (IgE) levels (>25 000 IU/mL) but no other abnormalities (e.g. cardiac defect, eosinophilic esophagitis or esophageal reflux). These examinations were not available for the sister. Histopathological examination of both probands showed a psoriasiform dermatitis, with focal intracellular and intercellular edema and acantholysis within the spinous and granular layers (Fig. 2a–c). The parents had been diagnosed with palmoplantar keratoderma since an early age. However, the symptoms had improved when they grew up (Fig. 1i–l). There was no family history of respiratory allergies or atopic dermatitis. The parents also reported that they had a daughter with normal appearance

Correspondence: Zhirong Yao, M.D., Department of Dermatology, Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China. Email: dermatology.yao@sohu.com

*These authors contributed equally to the present study.

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and another two similarly affected offsprings. The affected boy had died from severe infection and metabolic wasting in infancy, while the affected girl in a good general condition was choked to death accidentally. No genetic samples were available for the three family members.

The study was approved by the ethics committee of Xinhua Hospital, Shanghai Jiaotong University School of Medicine. It conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo in 2004). Both parents gave their written and informed consents on behalf of themselves and as legal guardians of the probands. Peripheral blood samples of both probands and the parents were collected for DNA capture. Genomic DNA was extracted with a TIANamp Blood DNA Kit (TIANGEN Biotech, Beijing, China). Genomic DNA was polymerase chain reaction (PCR) amplified using oligonucleotide primer pairs spanning the entire coding sequence as well as intron–exon boundaries of DSG1 as previously described.¹ Purified PCR products were directly sequenced with an ABI PRISM® 3730 automated sequencer (Applied Biosystems, Foster City, CA, USA) to detect mutations in the probands and verify them in parents and 200 normal controls. In order to evaluate the consequences of the detected mutation, biopsies were obtained from both probands (hyperkeratotic plaques from the thigh and back of the sister and brother, respectively) and a healthy control. Then, RNA was extracted from skin

biopsies for cDNA synthesis and direct sequencing, as well as quantitative PCR to evaluate the expression of DSG1 at mRNA level. Quantitative real-time PCR was performed as described.¹ Skin biopsy specimens were also prepared for morphological studies, including hematoxylin–eosin staining and transmission electron microscopy.

RESULTS

In both probands, we disclosed a homozygous exon–intron boundary mutation, c.1892-1delG, an intron–exon boundary close to exon 14 of DSG1 (Fig. 3b,e). Both parents were carriers of the mutation in a heterozygote state (Fig. 3a,d). This variant has not been reported before (HGMD Professional 2014.1 professional, dbSNP, 1000 genome project, Exome Variant Server) and we excluded it from 200 control individuals. It is predicted that the splice site mutation c.1892-1delG may result in skipping of exon 14. cDNA direct sequencing of both probands confirmed the speculation that exon 14 is skipped out of frame (Fig. 3c,f). Therefore, the c.1892-1delG mutation, as a frame-shift mutation, is also named p.Gly631Glnfs*8 at protein level. At the same time, quantitative real-time PCR revealed that the homozygous mutation c.1892-1delG leads to obvious downregulation of DSG1 mRNA expression in the skin (Fig. 3h), probably reflecting mRNA decay. All of the above indicate that the homozygous



Figure 1. Clinical manifestation of probands and their parents. The sister showed (a) curly hair, (b) facial dermatitis with cheilitis, (c) superficial erosions in the skin folds and (d) extremely thick focal keratoses on the pressure sites of the soles. The brother showed (e) hyperkeratosis of palms, (f) erythematous plaques on thighs, and (g) hyperkeratotic plaques at sites of knees and (h) sacrococcygeal region. (i) Palms and (j) soles of father showed focal hyperkeratosis. (k) Palms of mother appeared normal at present and (l) hyperkeratosis is milder than father on soles with only pressure parts affected.

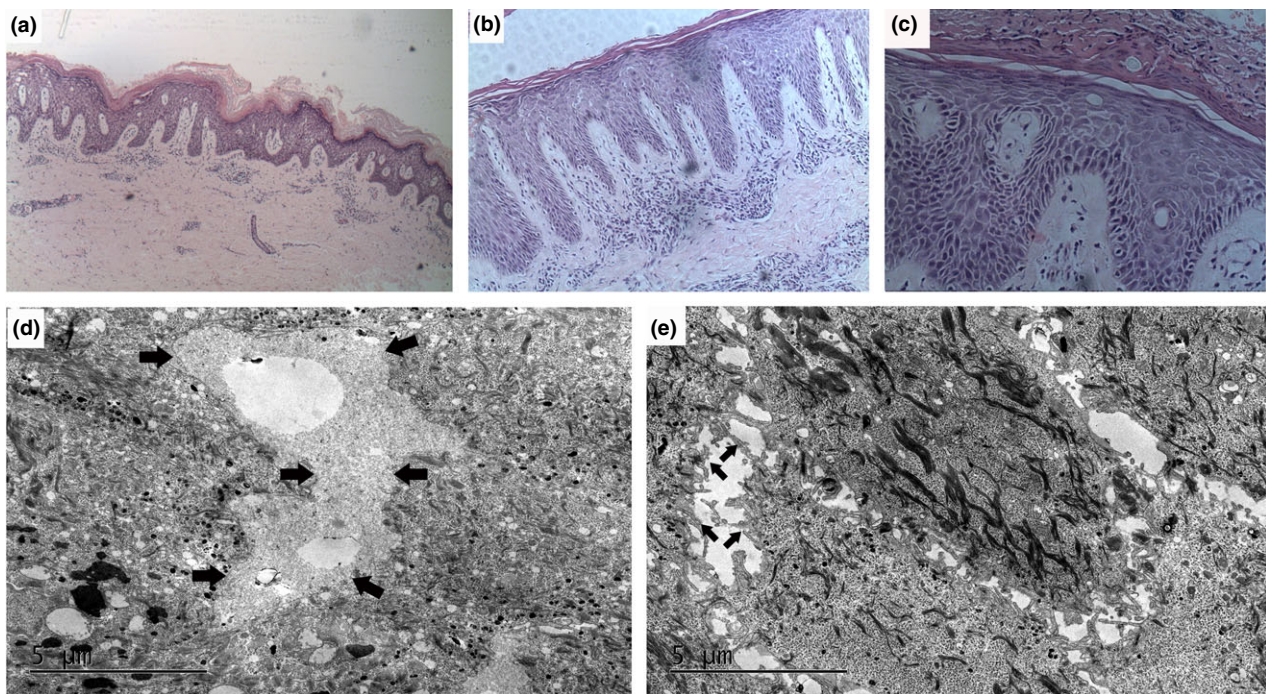


Figure 2. Hematoxylin–eosin staining and transmission electron microscopy. (a,b) A psoriasiform dermatitis, with (b) focal intracellular and intercellular edema and (c) acantholysis within the spinous and granular layers (original magnifications: [a] $\times 40$; [b] $\times 100$; [c] $\times 200$). (d) Deficiency of desmosomes in some areas resulting in broadening of intercellular space (arrows). (e) Reduced desmosomes in some areas with microvilli-like processes (arrows).

mutation c.1892-1delG can affect the function of DSG1 at protein level. In the sections submitted to electron microscopy, the density of the desmosomes appeared reduced or deficient in some areas, resulting in microvilli-like processes (Fig. 2e) or the broadening of intercellular space (Fig. 2d) observed. The keratinocytes, desmosomes, hemidesmosomes, basement membrane and tonofilaments were otherwise ultrastructurally normal (data not shown).

DISCUSSION

The current study reports the fifth family with a new biallelic mutation in the exon–intron border of the DSG1 gene associated with SAM syndrome. In the family, both patients shared features of SAM syndrome, including severe palmoplantar keratoderma, erythroderma, severe dermatitis, skin erosions and scaling, multiple allergies and elevated IgE. They also presented with hard curly hair but without manifestations of microcephaly, cardiac defects and hypotrichosis presented in previous cases caused by DSG1 mutations or macrocephaly, a widespread superficial pustulosis presented in the case resulted from heterozygous missense mutation in the desmoplakin gene (DSP).⁴ It is noted that a definite history of recurrent severe pulmonary infections with metabolic wasting and growth retardation was recorded at an early age for the boy, which was absent in his older sister with the same genotype of the DSG1 gene. Our cases of SAM syndrome with the

homozygous mutation c.1892-1delG showed a relatively milder phenotype, when compared with cases (c.49-1G>A, homozygous, exon 2; c.1861delG, homozygous, exon 13) reported by Samuelov *et al.*,¹ but relatively more complicated than cases (p.R887*, homozygous, exon 15; p.Ile872Serfs*10, homozygous, exon 15) reported by Has *et al.*² and Schlipf *et al.*³ The severity of individual cases affected by SAM syndrome is generally determined by the position of mutation loci. Also, genetic heterogeneity could be observed in our SAM family between the sister and brother in the history of recurrent infections, which further indicated that environmental factors or genetic modifiers may account for the phenotypic variability.²

Because homozygous loss-of-function mutation in the DSG1 gene was demonstrated to be the cause of SAM syndrome, DSG1, as a member of the cadherin family of calcium-dependent cell adhesion molecules expressed in the epidermis, has been recognized as a key member both in maintaining epidermal integrity in the superficial layers and supporting keratinocyte differentiation. But how heritable skin barrier defect leads to atopic disease and affects keratinocyte differentiation requires further study.

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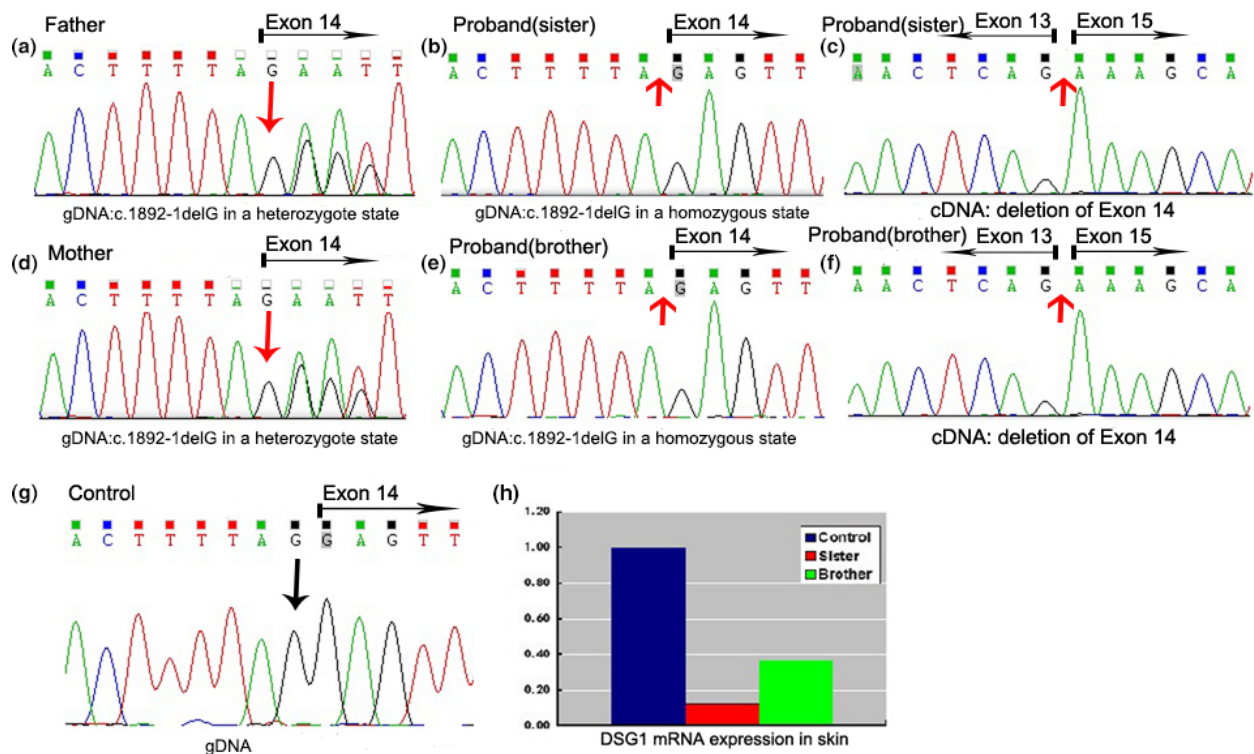


Figure 3. Sequence of desmoglein (DSG)1 in parents, probands and control; Quantitative reverse transcription polymerase chain reaction analysis for gene expression of DSG1 at mRNA level. (a,d) Analysis of DSG1 gene in DNA from peripheral blood of parents showed c.1892-1delG in a heterozygote state. (b,e) Analysis of DSG1 gene in DNA from peripheral blood of probands showed c.1892-1delG in a homozygous state. (c,f) Analysis of DSG1 gene in cDNA from skin of probands showed skip of exon 14. (g) Analysis of DSG1 gene in DNA from peripheral blood of normal control for contrast. (h) Expression of DSG1 gene at mRNA level is obviously downregulated in skin of probands compared with normal control.

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CONFLICT OF INTEREST: None declared.

REFERENCES

1 Samuelov L, Sarig O, Harmon RM *et al.* Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* 2013; **45**(10): 1244–1248.

- 2 Has C, Jakob T, He Y, Kiritsi D, Hausser I, Bruckner-Tuderman L. Loss of desmoglein 1 associated with palmoplantar keratoderma, dermatitis and multiple allergies. *Br J Dermatol* 2015; **172**(1): 257–261.
- 3 Schlipf NA, Vahlquist A, Teigen N *et al.* Whole exome sequencing identifies novel autosomal recessive DSG1 mutations associated with mild SAM syndrome. *Br J Dermatol* 2016; **174**(2): 444–448.
- 4 McAleer MA, Pohler E, Smith FJ *et al.* Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakoin domain of desmoplakin. *J Allergy Clin Immunol* 2015; **136**(5): 1268–1276.