A novel heterozygous missense mutation of the desmoglein 1 gene in a Chinese family with diffuse nonepidermolytic palmoplantar keratoderma

Sir,

Palmoplantar keratoderma is a heterogeneous group of skin disorders characterized by epidermal hyperkeratosis of the palms and soles. Clinically, there are four types – diffuse, focal, punctuate and striate. Diffuse palmoplantar keratoderma can either be epidermolytic or nonepidermolytic depending on pathological changes. Diffuse nonepidermolytic palmoplantar keratoderma (DNEPPK: OMIM 148700) is comparatively rare and exhibits incredible genetic heterogeneity. Mutations affecting the *keratin1*, *loricrin*, *aquaporin 5* and *desmoglein 1* genes have been identified as thepossible etiologic factors.[1-4] Only 2 cases of diffuse palmoplantar keratoderma, associated with *DSG1* mutation, have been reported till date.[4,5] Here, we report a novel heterozygous missense mutation of the *DSG1* gene in a Chinese family with diffuse nonepidermolytic palmoplantar keratoderma.

The proband was a 59-year-old female born to nonconsanguineous parents. She presented with slowly progressive thickening and fissuring of palms and soles since the age of 2 years. She denied any associated palmoplantar hyperhidrosis or fungal infection. There was no evidence of any hearing abnormality. Her parents were not affected and had passed away, however her only son developed similar lesions on palms and soles [Figure 1a]. Systemic examination was noncontributory. Cutaneous examination demonstrated diffuse yellowish hyperkeratotic and scaly plaques on both palms and soles, with sparing of the thenar areas [Figure 1b and c]. Histology from lesional skin showed orthokeratotic hyperkeratosis, hypergranulosis and acanthosis. Widening of the intercellular spaces was noted in some areas, but without epidermolysis [Figure 2a and b]. A diagnosis of nonepidermolytic palmoplantar keratoderma was made, based on clinico-pathological features.

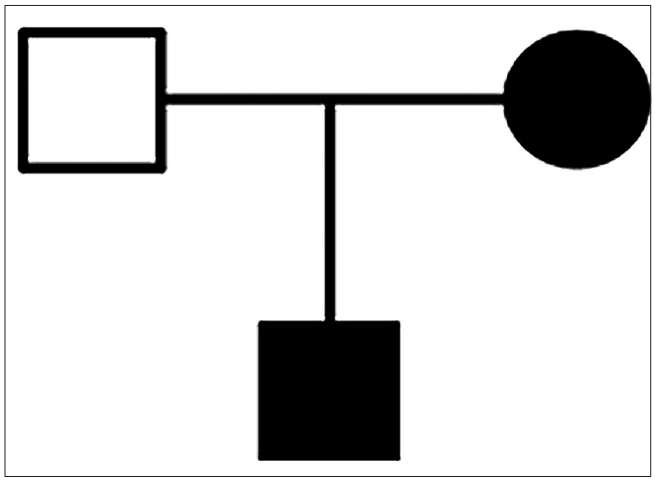

Figure 1a: Pedigrees of the Chinese family with diffuse nonepidermolytic palmoplantar keratoderma

After obtaining informed consent and approval of the institutional ethical committee, peripheral blood samples were obtained from three members of the family and 120 unrelated controls. Genomic DNA was isolated from these samples following standard guidelines. All exons and flanking intronic regions of the *KRT1, LOR, AQP5,* and *DSG1* genes were amplified using polymerase chain reaction and sequenced. Both the proband and her son were found to carry a heterozygous missense mutation c.547G>A (NM_001942.3**:** g28911693), which caused a D183N substitution in the *DSG1* gene. The mutation has not been reported in recent literature and online mutation databases. Moreover, this mutation was absent in 120 population-matched healthy controls and the proband's unaffected husband [Figure 3a-c]. The mutation was situated in a part of the gene that is highly conserved between different species [Figure 3d]. *In-silico* analysis was used to predict the functional consequences of the mutation. Polyphen2 (http://genetics.bwh.harvard.edu/pph2) predicted it to be "probably damaging" with a score of 0.998, SIFT (http://sift.bii.a-star.edu.sg) predicted it would "affect protein function" with a score of 0.00.

Desmosomes are a type of epidermal cell adhesion molecule. They play a critical role in maintaining epidermal integrity and also some pivotal signal transduction pathways regulating cell growth

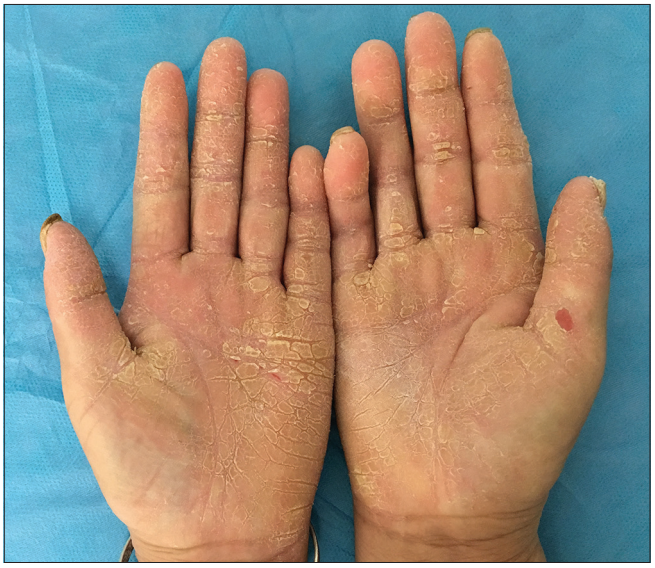

Figure 1b: Clinical features of the proband. Diffuse yellowish hyperkeratosis and scales were present on both palms

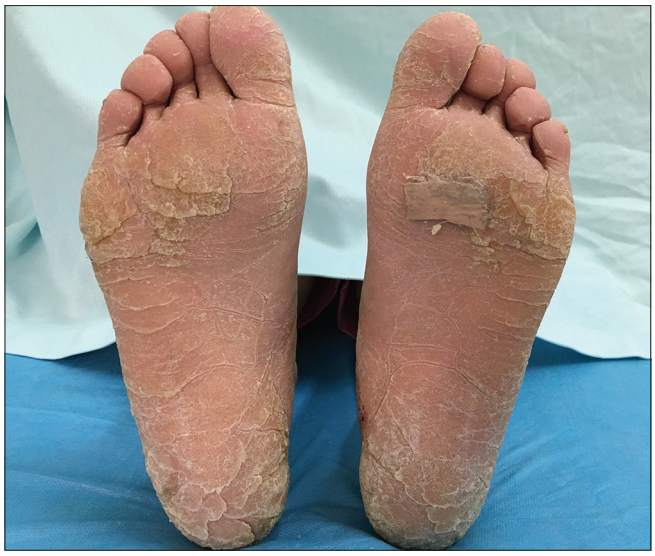

Figure 1c: Diffuse yellowish hyperkeratosis and scales were present on both soles

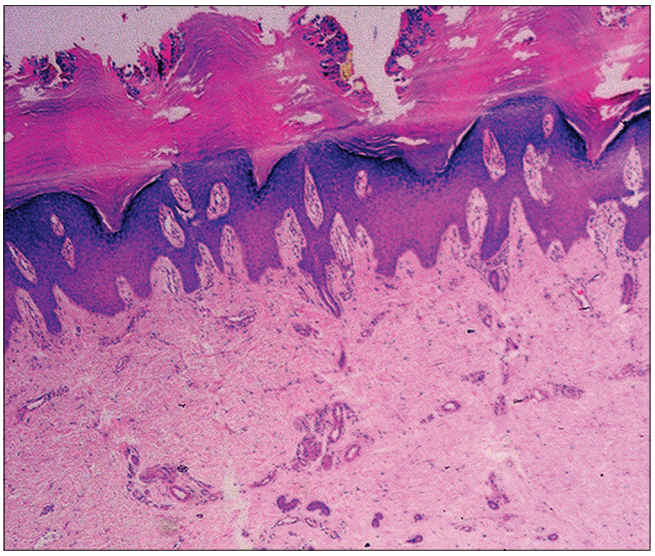

Figure 2a: Skin biopsy from the proband's left palm shows orthokeratotic hyperkeratosis, hypergranulosis and acanthosis (hematoxylin and eosin, ×25)

and differentiation. In accordance with their pleiotropic functions, abnormal desmosomes have been linked to a growing number of inherited and acquired skin diseases. Desmoglein 1, encoded by the *DSG1* gene, is a major component of this family, abundant in the upper epidermal layers and associated with the pathogenesis of at least three skin diseases – pemphigus foliaceus, staphylococcal scalded skin syndrome, and autosomal dominant hereditary palmoplantar keratoderma.[6] Till date, approximately 23 types of mutations in the *DSG1* gene have been reported to be associated with palmoplantar keratoderma. Striate palmoplantar keratoderma is the most common; however, focal or diffuse patterns have also been occasionally described.

Only 2 cases of diffuse palmoplantar keratoderma associated with *DSG1* mutations have been reported in the English literature so far. Keren *et al*. described an Israeli family with nonepidermolytic palmoplantar keratoderma, in which all affected individuals were found to carry a heterozygous nonsense mutation c.76C>T (p.R26X) in the *DSG1* gene.[4] Lovgren *et al*. reported seven unrelated pedigrees with dominantly inherited palmoplantar keratoderma due to mutations in the *DSG1* gene, among which one pedigree showed the phenotype of diffuse palmoplantar keratoderma.[5] Bergman *et al*. proposed that widening of the intercellular spaces and loosening of epidermal keratinocytes may serve as a histologic clue to palmoplantar keratoderma associated with *DSG1*mutations.[7] Similar kind of pathological change has also been observed in our case.

To conclude, we have identified a novel heterozygous missense mutation of the *DSG1* gene in a Chinese family with nonepidermolytic palmoplantar keratoderma. Our study expands the database on *DSG1* mutations and emphasizes the key role played by Dsg1 in maintaining the epidermal integrity. Furthermore, we suggest a low threshold for *DSG1* screening in nonepidermolytic palmoplantar keratoderma.

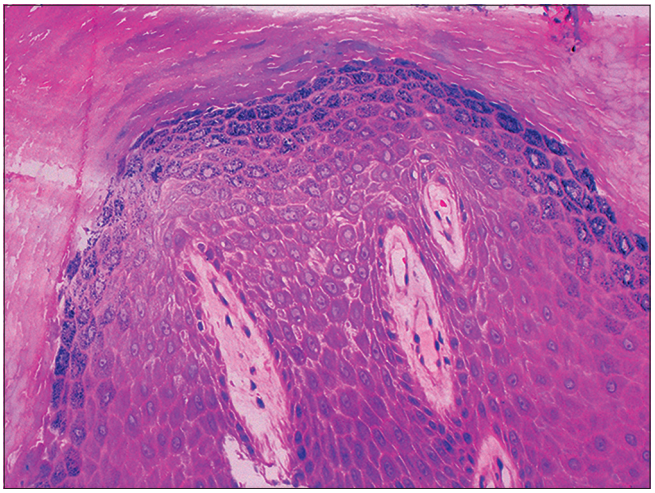

Figure 2b: Widening of the intercellular spaces of epidermal keratinocytes was noted (hematoxylin and eosin, ×200)

Our case was limited by the lack of functional tests. Therefore, further studies are needed to elucidate the exact pathogenesis of nonepidermolytic palmoplantar keratoderma resulting from mutations affecting the *DSG1* gene.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

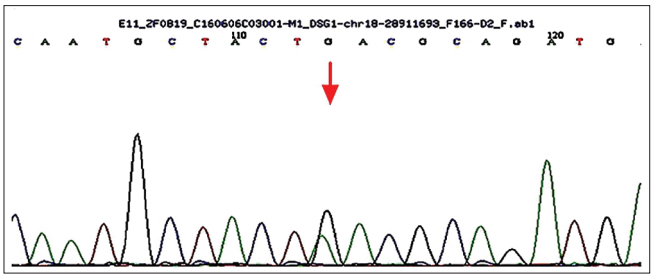

Figure 3a: Sequencing results of the *desmoglein 1* gene. The arrows indicate the G to A station substitution at c.547 leading to *D183N* mutation in desmoglein 1 in the proband

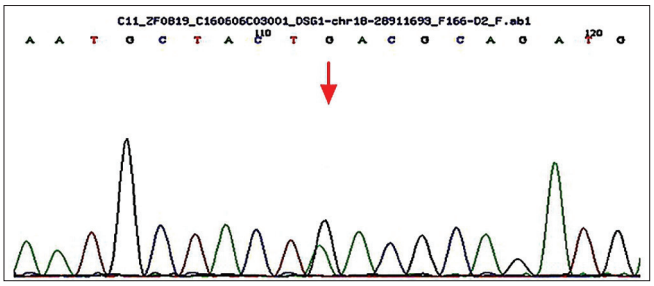

Figure 3b: Sequencing results of the *desmoglein 1* gene. The arrows indicate the G to A station substitution at c.547 leading to *D183N* mutation in *desmoglein 1* in the proband's son

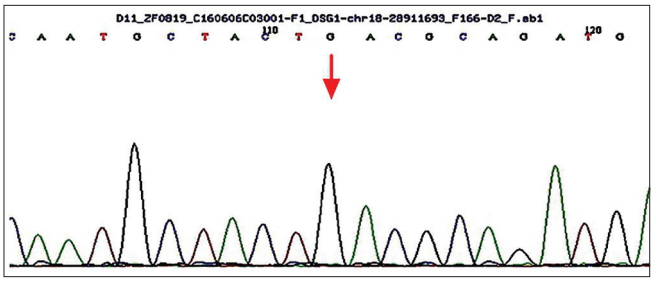

Figure 3c: The sequence of the normal control is given for comparison

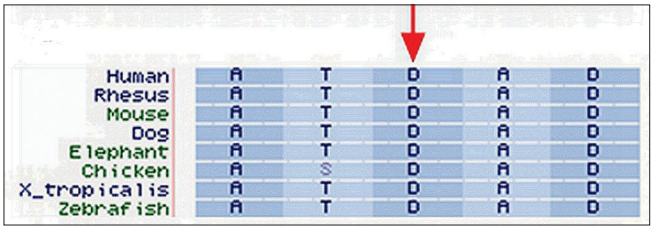

Figure 3d: The mutation was situated in a part of the gene that is highly conserved between different species

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Conflicts of interest

There are no conflicts of interest.

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