Novel ATP2A2 mutation in a large Chinese pedigree with extensive Darier's disease

Sir,

Darier's disease (OMIM 124200) is an autosomal dominant genodermatosis characterized by warty papules and plaques in seborrheic areas such as central part of trunk, flexures, scalp and face. Heat and sweating may exacerbate the disease. The mutations responsible for Darier's disease have been identified in the ATP2A2 gene on chromosome 12q23-24.1. This gene encodes the sarco/endoplasmic reticulum Ca2+ ATPase type-2 isoform (SERCA2), which transports Ca2+ from the cytosol into the endoplasmic reticulum lumen and plays a pivotal role in intracellular calcium signalling.

A 43-year-old Chinese man presented with extensive pruritic eruption mostly on seborrheic areas of 30 years duration. These lesions first developed on his face at the age of 13 and later progressed to involve trunk, scalp and flexures. Sun exposure and sweating aggravated his condition. He was born at full term and had no history of neuropsychiatric abnormalities. Multiple erythematous and hyperpigmented scaly papules were present on his scalp, face, neck and trunk [Figure 1a]. Flat-topped and verrucous papules were present on the dorsum of his hands and nails showed longitudinal ridging and fissuring [Figure 1d]. Oral mucosa was uninvolved. His sister and nephew also had a similar clinical presentation [Figure 1b and c]. There were six individuals in his family, including four males and two females, affected with similar lesions[Figure 2]. The other affected members of this family were diagnosed by dermatologists with histopathological confirmation [Figure 1e].

We carried out sequencing studies to find out the pathogenic gene of a large Chinese pedigree with severe Darier's disease. This study was approved by the ethics committee of Peking Union Medical College and conducted according to the principles of the Declaration of Helsinki. After obtaining informed consent from the proband, his parents, his sister and the son of his sister, ethylenediaminetetraaceticacid anticoagulated venous blood samples were collected from all participants. Genomic DNA was extracted from peripheral blood lymphocytes by standard procedures using Flexi Gene DNA kits (Qiagen, California, USA). The primer of all coding exon and intron-exon boundaries of ATP2A2 was designed using the web-based version of the Primer 3.0 program (http://www. genome. wi. mit. edu/cgibin/primer/primer3_www.cgi). The primer was amplified by polymerase chain reaction (PCR). After the amplification, the PCR products were purified with a QIAquick PCR purification kit (Qiagen) and directly sequenced on ABI PRISM 3730 automated sequencer (Applied Biosystems). Sequence comparisons and analysis were performed by Phred-PhrapConsed program, V.12.0. As a result, sequence analysis of the ATP2A2 gene revealed a novel heterozygous mutation in ATP2A2 (exon 19: c. 2747C > T: Ser916Phe) [Figure 3]. A subsequent search of the published work in PubMed (www. ncbi. nlm. nih. gov/pubmed/) and ATP2A2 sequence information (University of California Santa Cruz Genome Browser Home [http://genome.ucsc.edu/]) led to the identification of this mutation as novel.

In addition, we sequenced another four affected and four unaffected family members from this family. We identified the same missense mutation in all affected members but not in unaffected members. Meanwhile, we sequenced the mutation in additional 200 unrelated, ethnically and geographically matched healthy controls and found that the mutation was absent in these 200 subjects.

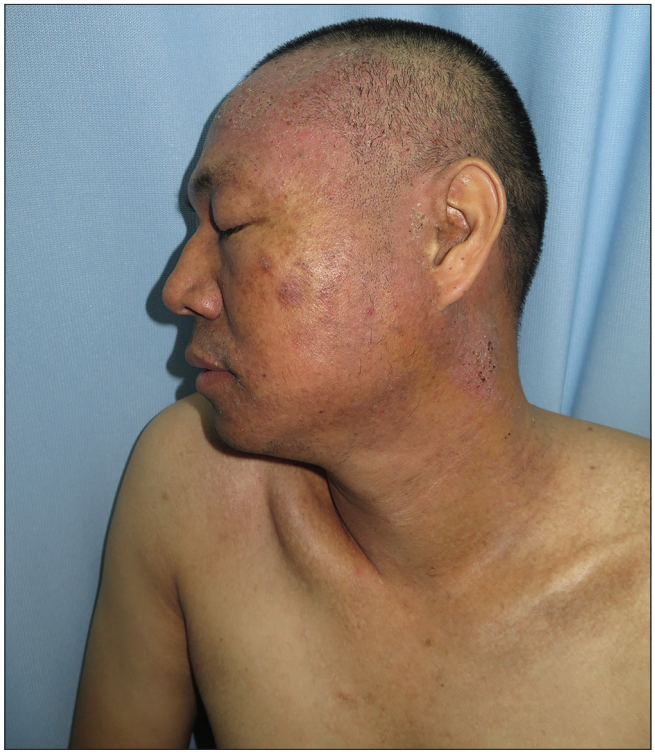

Figure 1a: Erythematous and hyperpigmented scaly papules in seborrheic areas of the proband

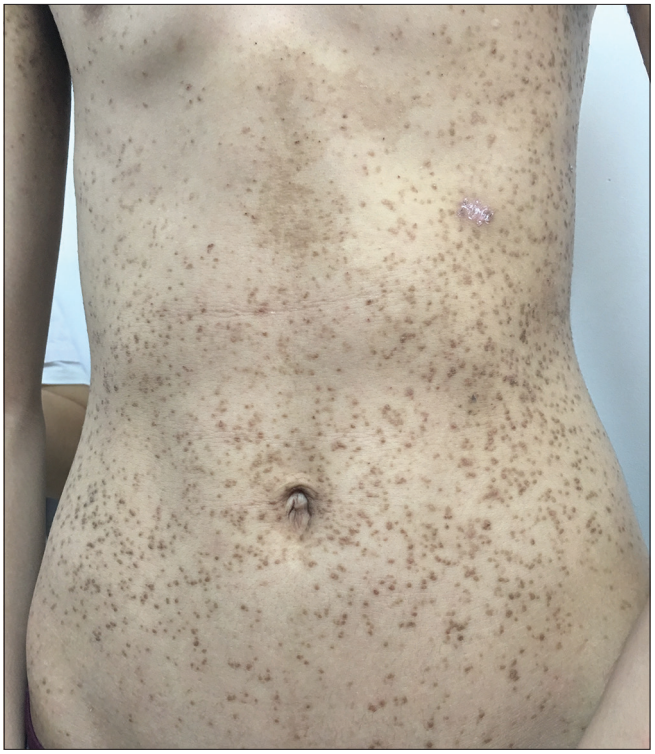

Figure 1b: Hyperpigmented scaly papules on trunk of the proband's nephew

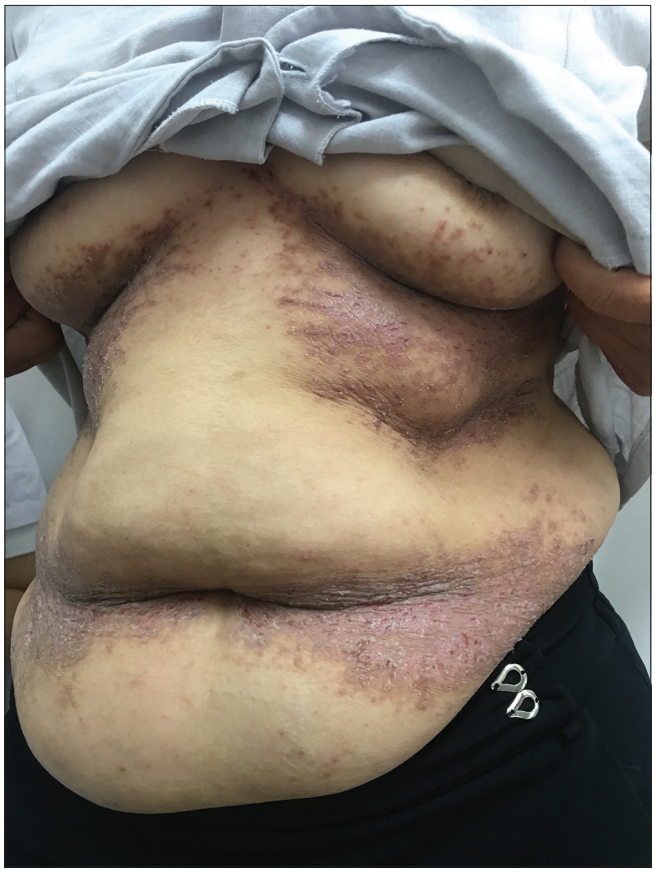

Figure 1c: Erythematous scaly papules and plaques on trunk of the proband's sister

Darier disease is a rare skin condition with autosomal dominant inheritance that manifests in childhood or adolescence. More than 248 pathogenic mutations have been described so far throughout the gene including missense, nonsense, substitution, insertion and deletion involving both frame-shift and inframe.[1-3] In general, these mutations are scattered over the entire ATP2A2 gene, without any clearly identified genotype–phenotype correlation. ATP2A2 mutations could

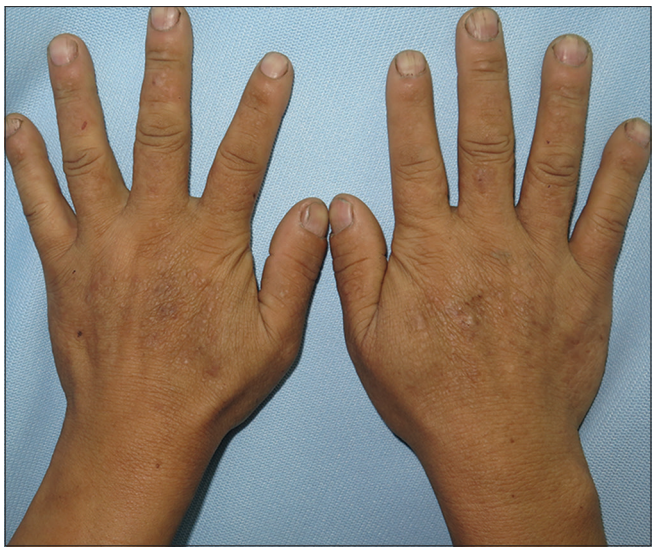

Figure 1d: Multiple flat-topped and verrucous papules on the dorsum of the hands and longitudinal ridging and fissuring of the nails of the proband

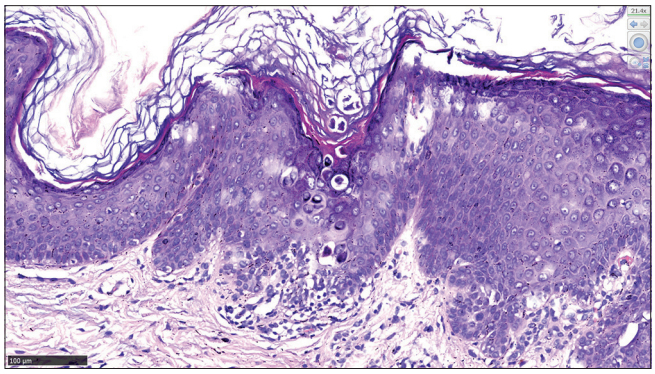

Figure 1e: Corps ronds and grains in the epidermis (H and E, ×100)

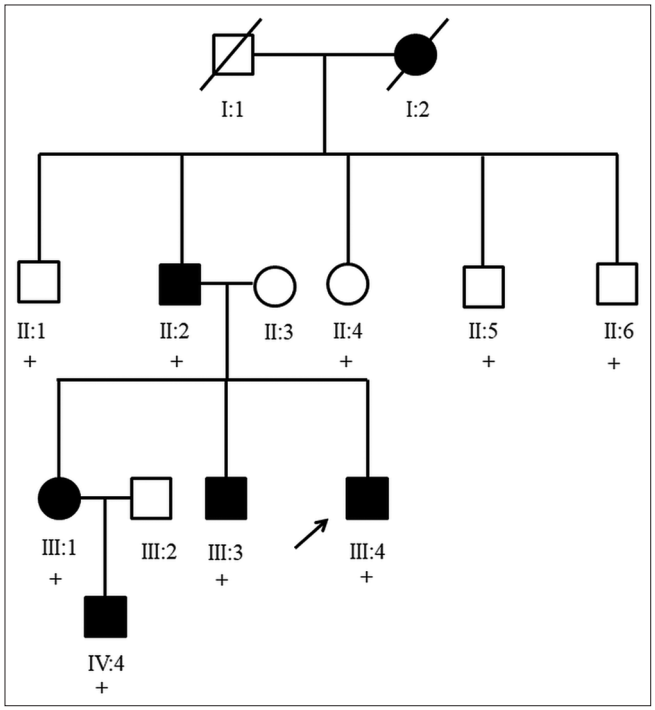

Figure 2: Genealogical tree of Darier's disease. "+" in pedigree indicates those who have undergone Sanger sequencing

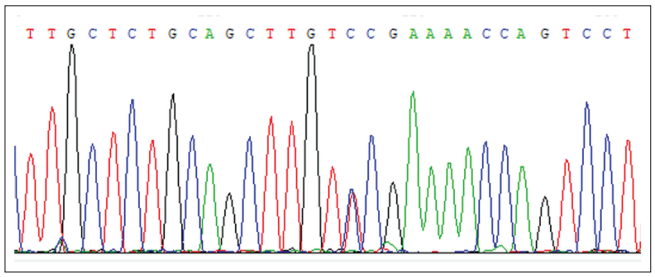

Figure 3: Sanger sequencing revealed a heterozygous mutation in ATP2A2 (exon 19:c.2747C>T: Ser916Phe)

be associated with acrokeratosis verruciformis of Hopf.[4] Nail changes include longitudinal red and/or white lines, longitudinal ridging, fissuring and wedge-shaped subungual hyperkeratosis. The nails are brittle and tend to break distally, forming V-shaped notches.[5] This study showed a novel heterozygous mutation in ATP2A2 (exon 19: c.2747C>T: Ser916Phe) in a large Chinese pedigree, which was linked with a phenotype of extensive Darier's disease as well as multiple flat-topped verrucous plaques on the dorsum of the hands, a presentation of acrokeratosis verruciformis. These results contribute to expand the database of ATP2A2 mutations and identify the genotype–phenotype correlation in the future.

Acknowledgement

We are most grateful to all the patients with Darier's disease and their family members for their support of this study.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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