Novel and recurrent mutations in GJB3 and GJB4 cause erythrokeratodermia variabilis et progressiva

Sir,

Erythrokeratodermia variabilis et progressiva comprises a group of genetically heterogeneous skin disorders characterized by the coexistence of erythematous patches and persistent hyperkeratotic plaques. It can be caused by mutations in *GJB3*, *GJB4*, *GJA1*, *KDSR*, and *KRT83*, encoding connexin 31, connexin 30.3, connexin 43, 3-ketodihydrosphingosine reductase, and keratin 83, respectively.[1-3] We herein report three unrelated families with this condition harboring one recurrent mutation in *GJB3* and two novel mutations in *GJB4*.

Three families of Chinese Han ethnicity were referred to the Peking University First Hospital in Beijing, China. They were clinically diagnosed to have erythrokeratodermia variabilis et progressiva [Figure 1]. The age of onset ranged from at birth to adolescence. All the affected individuals exhibited persistent hyperkeratotic plaques as well as transient symmetric red-brown erythematous patches which lasted hours to months. Two probands had relatively restricted lesions which predominated in body folds (proband 1) [Figure 2a and dorsal feet (proband 3) Figure 2b], whereas proband 2 showed progressive lesions extending over the limbs and trunk with mild skin peeling and scaling [Figure 2c and d]. Proband 2 had palmoplantar keratosis also. Seasonal changes and emotional stress caused exacerbation of the lesions.

After obtaining written informed consent for genetic testing from the probands and the approval from institutional ethics committee of Peking University First Hospital, a screening was done for exons and their flanking regions of *GJB3* and *GJB4*, the most common causative genes of erythrokeratodermia variabilis et progressiva, in all the probands. Sanger sequencing revealed two previously unreported heterozygous mutations, c.77C>A (p.Ser26Tyr) and c.182C>G (p.Pro61Arg) in *GJB4,* in the first and second proband respectively and one recurrent heterozygous mutation c.256T>A (p.Cys86Ser) was seen in *GJB3* in the third proband. [Figure 3a]. Co-segregation of the mutations with phenotype was confirmed in all three families. The two novel missense mutations, c.77C>A and c.182C>G in *GJB4,* were absent in all public databases including ExAC, gnomAD, and 1000G and were predicted to be "disease causing" by MutationTaster.

Gap junction channels, which mediate direct intercellular signaling, play important role in many biological processes including development, differentiation, and cell synchronization. Gap junction channel is structured by two hemichannels docking end-to-end, each formed by six connexins oligomerized together.[4] Connexin 31 and 30.3, encoded by *GJB3* and *GJB4*, respectively, are members of the highly homologous connexin protein family, which share a common structure topology characterized by four transmembrane domains (M1–M4) linked by two extracellular loop (E1 and E2) and one intracellular loop [Figure 3b]. The transmembrane and extracellular domains along with the N-terminus are defined as the conservative domains. To date, we have found more

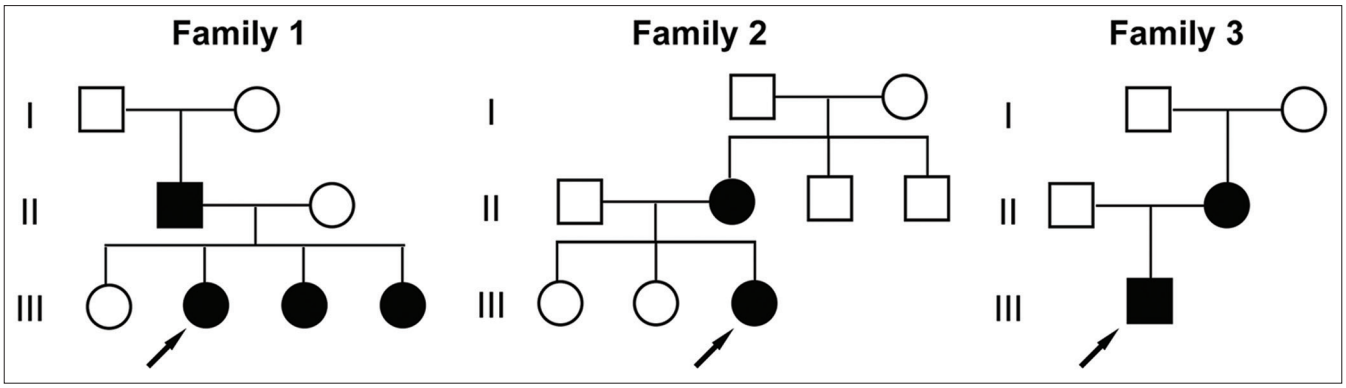

Figure 1: Pedigrees of the three families with erythrokeratodermia variabilis et progressiva

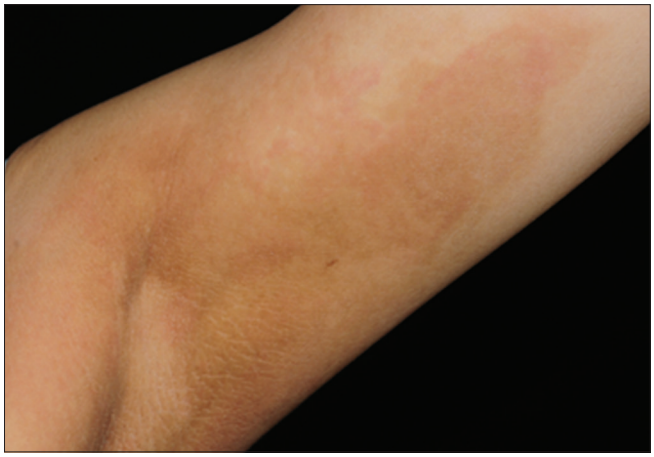

Figure 2a: Erythematous patches with mild hyperkeratosis in the axilla of proband 1

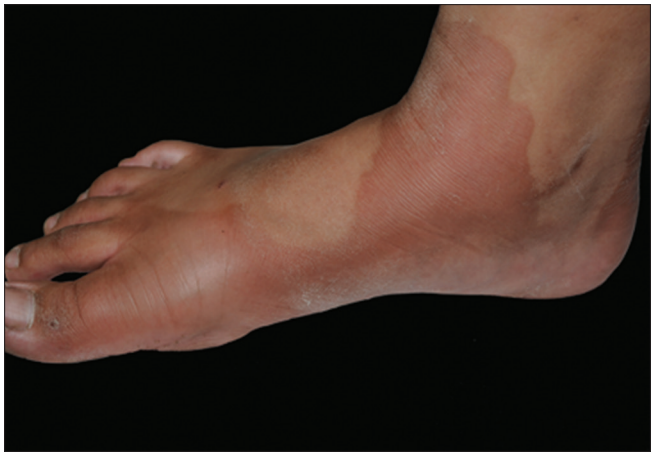

Figure 2b: Symmetrically distributed well-demarcated erythematous plaques over the ankles and dorsa of feet of proband 3

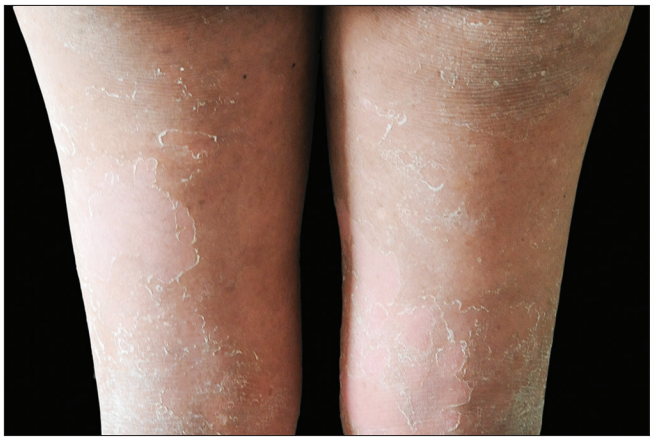

Figure 2c: Erythematous patches and hyperkeratotic scaly plaques on the proximal part of lower extremities of proband 2

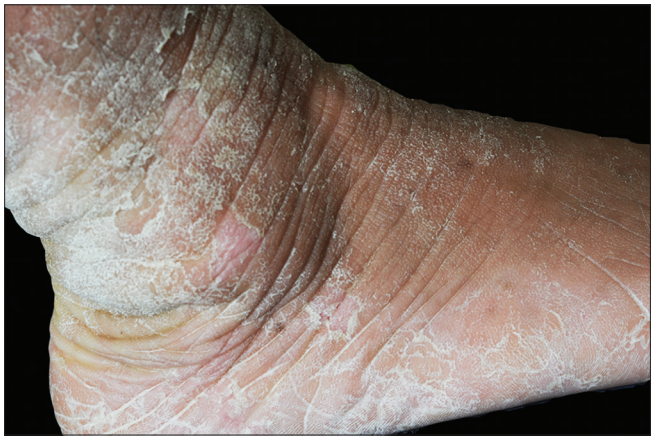

Figure 2d: Erythematous hyperkeratotic scaly plaques on the feet of proband 2

than 30 previous reports of mutations in *GJB3* and *GJB4* to be associated with erythrokeratodermia variabilis et progressiva, including the two novel mutations reported here. Most of these mutations occurred in the conservative regions [Figure 3b]. Nevertheless, none of the previously reported *GJB4* mutations occurred in extracellular domains, which function as essential element in the formation of the gap junction pore.[5] Among all previously reported mutations associated with erythrokeratodermia variabilis et progressiva, the novel mutation c.182C>G (p.Pro61Arg) reported here is the first to be located in the first extracellular (E1) domain of *GJB4* and also the first in the extracellular domain of the protein. The other novel mutation of *GJB4* (p.Ser26Tyr)

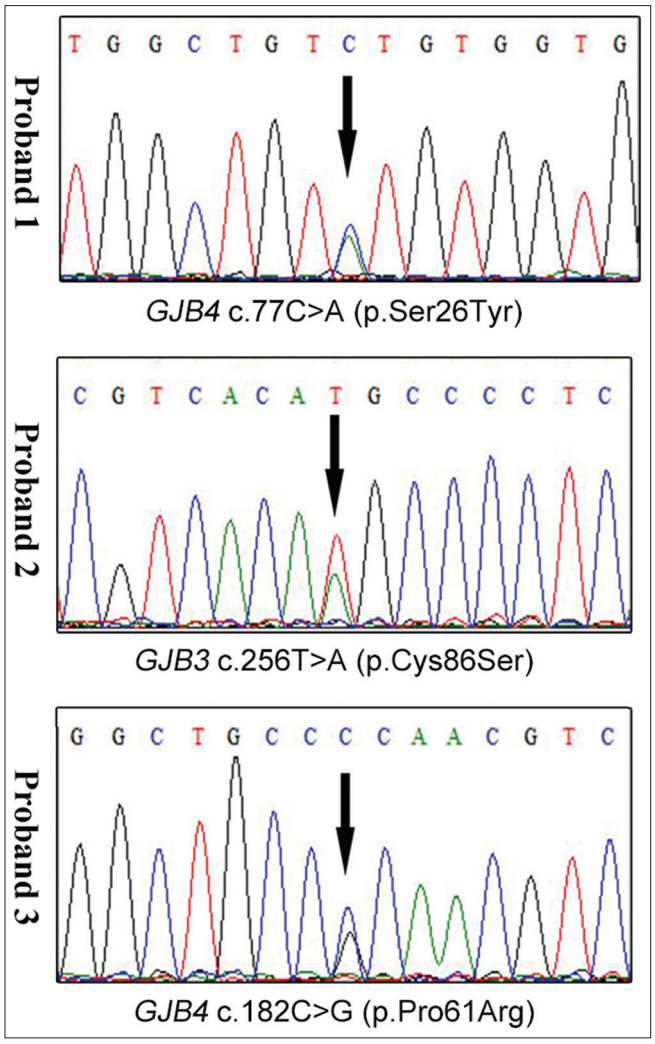

Figure 3a: Heterozygous missense *GJB4* mutations, c.77C>A (p.Ser26Tyr) (upper panel) and c.182C>G (p.Pro61Arg) (lower panel), in probands 1 and 3, respectively. Proband 2 harbors the heterozygous missense *GJB3* mutation c.256T>A (p.Cys86Ser) (middle panel)

is located in the transmembrane region, disruption of which is likely to interfere in channel gating.[5] The *GJB3* mutation (p.Cys86Ser) in proband 2 was repeatedly described elsewhere, and the severity of the condition varied greatly.[1] Proband 2 is the most severely affected, showing generalized erythema and hyperkeratosis, combined with other manifestations such as palmoplantar keratosis, scaling, and ridging in large skin folds. This corroborates the fact of great interfamilial phenotypic heterogeneity in erythrokeratodermia variabilis et progressiva. Although the general clinical presentation of patients with *GJB4* mutations was similar to those with *GJB3* mutations, previous studies have suggested certain correlation between genotype and phenotype of this disorder.[5] It has been reported that patients harboring the mutations, p.Gly12Asp and p.Phe137Leu in *GJB4,* seemed to manifest milder diseases than those with the corresponding mutations in *GJB3*.[5] By reviewing and comparing the phenotype of patients having mutations

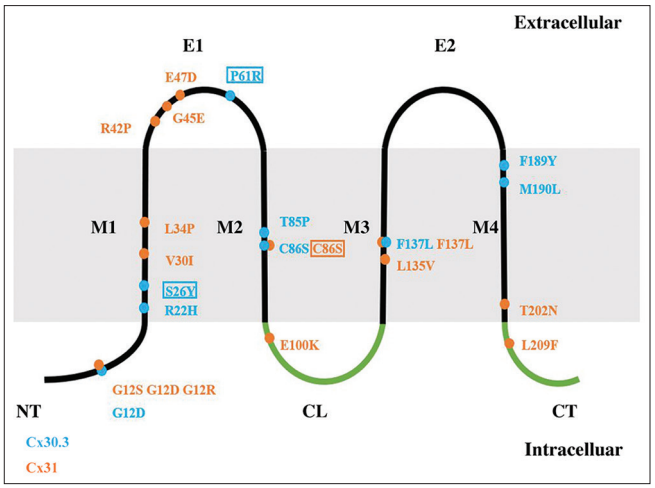

Figure 3b: Schematic diagram of connexin 31 (*GJB3*) and connexin 30.3 (*GJB4*) showing structural motifs and all reported mutations associated with erythrokeratodermia variabilis et progressiva. M1–M4: transmembrane spanning domains 1–4, E1–2: extracellular domains 1–2, CL: cytoplasmic loop, NT: N terminus, CT: C terminus. Domains in black lines are the conserved regions. Mutations in this study are shown in frames

in *GJB3* and *GJB4* affecting homologous residues in previous studies and our study it can be understood that those with mutations in *GJB3* tend to have more severe phenotype than those with mutations in *GJB4*. Hence we recommend a prior screening of *GJB3* in patients with generalized disease and palmoplantar keratosis in genetic counseling for erythrokeratodermia variabilis et progressiva in future.However, factors including age and previous treatment which might affect the clinical severity were not taken into account while comparing the phenotype of patients with GJB3 and GJB4 mutations. So further functional studies of the mutations are required to confirm this observation.

On the whole this study expands the mutation spectrum of *GJB3* and *GJB4* and further suggests a possible genotype–phenotype correlation in erythrokeratodermia variabilis et progressiva.

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 their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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