Case Report

GJB6 mutation A88V for hidrotic ectodermal dysplasia in a Chinese family

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Case Report

We report a four-generation family consisting of five patients (three men and two women, among them one was deceased) and 13 healthy controls. The proband (Fig. 1) was a 5-year-old boy. From the time of his birth, his hair, eyebrows, and eyelashes were totally absent, and his fingernails and toenails were thick with yellow discoloration and demonstrated distal onycholysis (Fig. 2a–c). He had decreased cold intolerance during the winter months and had recurrent nail infections. Sweating, teeth, ears, eyes, and mucosa were normal. The other affected individuals were adults with similar symptoms and additionally showed hyperkeratosis of the palms with a cobblestone surface (Fig. 2d and e). The mode of inheritance was autosomal dominant. Genomic DNA was isolated from peripheral blood, and the candidate genes of GJB6 and GJB2 were sequenced. The GJB6 gene sequencing results revealed that all the affected members harbored a heterozygous base mutation from C to T in 263 (c.263C>T), causing a amino acid substitution from alanine to valine in 88 (p. A88V) (Fig. 3a), which was not found in healthy controls. The GJB2 sequencing showed that the affected members had no F191L mutation but held a heterozygous missense mutation p. V37I (c. 109 G>A) in GJB2 gene.

Discussion

The clinical symptoms of the affected individuals in the family fulfilled the clinical criterion for the diagnosis of hidrotic ectodermal dysplasia (HED), also known as Clouston syndrome (CS; MIM 129500), which was first described in 1895 and later...
recorded in detail by Clouston in 1929. It is a rare autosomal dominant disease. It is characterized by a triad of major clinical signs: nail dystrophy, partial to total alopecia capitis, and palmo-plantar hyperkeratosis. Nail abnormalities include thickening, brittleness, discoloration, splitting, and onycholysis. Sweat glands and teeth of patients with HED are usually normal. Since 2000, four mutations in GJB6 gene, which cluster at chromosome 13q11 and encode gap junction protein connexin 30, have been reported to cause HED: G11R, V37E, A88V, and D50N (Table 1). Connexin 30 contains two extracellular domains, three cytoplasmic domains, and four hydrophobic transmembrane domains (M1–M4) (Fig. 4). The mutation A88V, introducing a highly hydrophobic residue in the transmembrane M2 domain, may change the polarity of connexin channels and affect communication between cells or induce CX30 apoptosis through an endoplasmic reticulum-independent mechanism. A mouse model for HED carrying GJB6 mutation A88V revealed hyperproliferative and enlarged sebaceous glands as well as a mild palmo-plantar hyperkeratosis. A88V was only reported in two Chinese families. Here, we report another one.

The GJB2 gene, also located in 13q11, encodes a gap junction protein CX26, mutations which can cause keratitis–ichthyosis–deafness which share a few overlapping features, such as nail dystrophy, hair loss, and palmo-plantar keratoderma, with HED. N14S mutation in GJB6 accompanied by F191L mutation in GJB2 may also cause HED. The F191L mutation of GJB2 was not detected in this family. A V37I mutation of GJB2, which is the most frequent variant in Asian population, was found in both the affected patient and a normal

Figure 2 Clinical symptoms of the affected individuals. a, b, and c from IV 1 (proband). (a) Alopecia, complete absence of body, eyebrows, and eyelashes. (b) Fingernails were short and thickened, discolored, and demonstrated distal onycholysis; (c) Short, thickened, and brittle toenails; d and e from III 1. (d) Hyperkeratosis of the palms with a cobblestone surface; (e) Short, thickened, and brittle toenails

Figure 3 Molecular genetic analysis of GJB6 and GJB2 from proband. (a) Heterozygous missense mutation c.263C>T of GJB6 that predicts amino acid change A88V. (b) Heterozygous missense mutation 79G>A of GJB2 predicting the amino acid change V27I
control, while a V27I mutation of GJB2 was found only in affected individuals in this family. A V27I mutation in GJB2 is regarded as a common benign single nucleotide polymorphism.\textsuperscript{14–18} Although few reports showed that V27I mutation of GJB2 might have contribution to skin diseases,\textsuperscript{19,20} the GJB2 mutations that are associated with skin symptoms all cause deafness (Table 1); however, in a recent study deafness was not found. Therefore, we speculated that V27I mutation of GJB2 might have been a polymorphism and had no contribution to the phenotypic characteristics in this family.

In conclusion, the mutation p.A88V in GJB6 played a pathogenic role in the Chinese HED family.

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### Table 1 Since 2000, the detected gene mutations associated with HED

| GJB6  | GJB2  | Number of family | Affected members | Ethnic group   | Year and reference |
|-------|-------|------------------|------------------|----------------|-------------------|
| G11R  |       | 2                | 22               | French         | 2000\textsuperscript{3,21} |
|       | 2     | More than 3      |                  | Moroccan, Dutch| 2003\textsuperscript{3} |
| 1     | 18    |                  |                  | Chinese        | 2002\textsuperscript{3} |
| 1     | 8     |                  |                  | Chinese        | 2009\textsuperscript{22} |
| 1     | 8     |                  |                  | Chinese        | 2013\textsuperscript{23} |
| 1     | 2     |                  |                  | Chinese        | 2013\textsuperscript{24} |
| 1     | 1     |                  |                  | Chinese        | 2014\textsuperscript{25} |
| 1     | 17    |                  |                  | Chinese        | 2016\textsuperscript{27} |
| 1     | 1     |                  |                  | Chinese        | 2016\textsuperscript{28} |
| 1     | 2     |                  |                  | Indian         | 2016\textsuperscript{29} |
| 1     | 19    |                  |                  | Taiwanese      | 2015\textsuperscript{30} |
| V37E  |       | 1                | 1 with deafness  | Scottish       | 2002\textsuperscript{4} |
| V27I  |       | 1                | 1 with deafness  | Ashkenazi Jews | 2008\textsuperscript{5} |
| D50N  | 1     | 2                |                  | Indian, Malaysian, Walsh | 2000\textsuperscript{3,21} |
| A88V  | 3     | 3                |                  | Dutch          | 2003\textsuperscript{3} |
|       | 1     | 1                |                  | Chinese        | 2006\textsuperscript{6} |
|       | 1     | 2                |                  | Russian        | 2012\textsuperscript{11} |
| V27I  | 1     | 1                | 1 with deafness  | Japanese       | 2019\textsuperscript{31} |
|       | 2     |                  |                  | Chinese        | 2015\textsuperscript{31} |

### Figure 4

The location of four gene mutations in CX30. CL, Cytoplasmic loop; E1 and E2, extracellular domains 1 and 2; M1–M4, Transmembrane domains 1–4. The red ☆ indicates the present patient.
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