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Hidrotic ectodermal dysplasia in a Chinese pedigree: A case report and literature review

Hidrotic ectodermal dysplasia in a Chinese pedigree

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Abstract

BACKGROUND

We report on a large family of Chinese Han individuals with hidrotic ectodermal dysplasia (HED) with a variation in *GJB6* c.31G>A. The patients in the family had a triad of clinical manifestations of varying degrees. Although similar variation loci have been reported, the clinical manifestations of this family were difficult to distinguish from congenital thick nail disorder, palmoplantar keratosis, and congenital hypotrichosis.

CASE SUMMARY

This investigation involved a large Chinese family of 46 members across five generations and included 12 patients with HED. The proband (IV4) was a male patient with normal sweat gland function and dental development, no skeletal dysplasia, no cognitive disability, and no hearing impairments. His parents were not consanguineously married. Physical examination of the proband revealed thinning hair and thickened grayish-yellow nails and toenails with some longitudinal ridges, in addition to mild bilateral palmoplantar hyperkeratosis. *GJB6*, *GJB2*, and *GJA1* have been reported to be the causative genes of HED; therefore, we subjected the patient's samples to Sanger sequencing of these three genes. In this family, the variation locus was at *GJB6* c.31G>A (p.Gly11Arg). Overexpression vectors of wild-type *GJB6* and its variants were established and transfected into HaCaT cell models, and the related mRNA and protein expression changes were determined using western blotting and RT-qPCR.

CONCLUSION

We report another HED phenotype associated with *GJB6* variations, which can help clinicians to diagnose HED despite its varying presentations.

Key Words: Hidrotic ectodermal dysplasia; GJB6; Connexin; Gene sequencing; Cell transfection; Case report

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Core Tip: We report on a Chinese family with hidrotic ectodermal dysplasia (HED), with patients in the family presenting varying degrees of hair dysplasia, nail dysplasia, and palmoplantar hyperkeratosis. In addition, we performed a literature review of other reported HED genotypes and their corresponding phenotypes, which lays a foundation for subsequent studies on these associations. Overexpression vectors of the *GJB6* gene and its variants (variation sites: c.31G>A, c.263C>T, c.110T>A) were established and transfected into a HaCaT cell model. The expression changes of related mRNA and proteins before and after gene editing were obtained by western blotting and RT-qPCR to provide clues for subsequent pathogenesis studies.

INTRODUCTION

To date, four variations in *GJB6* (G11R, A88V, V37E, and D50N), a *GJA1* (V41L) variation combined with a *GJB2* (R127H) variation, and an independent *GJB2* (V27I) variation have been found to trigger hidrotic ectodermal dysplasia (HED)[1]. The typical clinical presentation of HED is a triad of symptoms: hair development disorders, palmoplantar hyperkeratosis, and finger/toenail dysplasia[2]. The variant locus of the investigated case has been reported previously; however, the clinical presentation characteristics of the investigated family differed from those previously reported. Each patient in the family exhibited a triad of symptoms, with varying degrees of severity; when a patient is characterized by one of the clinical manifestations of hyperkeratosis of the palm and toes, sparse hair, or hypoplasia of the finger (toe) nails, it is difficult to distinguish the disease from congenital thick nail disease, palmoplantar keratosis, or congenital oligodactyly based on clinical symptoms.

CASE PRESENTATION

Chief complaints

A 32-year-old Chinese man presented with sparse hair, grayish-yellow, thickened nails, and hyperkeratosis of the palmoplantar from birth.

History of present illness

The patient had normal sweat gland function and dental development, no cognitive disability, no hearing impairments, and no skeletal dysplasia. His parents were not consanguineously married.

History of past illness

No special.

Personal and family history

In the five generations of the 46 members of the proband's family, 12 HED patients (nine males and three females) were included (Figure 1A). The proband (IV4) and his affected family members had varying degrees of hair dysplasia, nail dysplasia, and palmoplantar hyperkeratosis from birth (Table 1).

Physical examination

Physical examination revealed thinning hair, thickened grayish-yellow nails and toenails with some longitudinal ridges visible (Figure 1B, C), and mild bilateral palmoplantar hyperkeratosis (Figure 1D, E). The 11 surviving patients from the family had hair deficiency of varying severity and presentation, including sparse hair, slow growth, and/or easy breakage (Table 1). All 11 patients had thickened and brittle finger/toenails, with some patients having grayish-yellow finger/toenails and slow growth. All patients had varying degrees of palmoplantar keratinization, which decreased in severity in later generations (Figure 1F).

Laboratory examinations

Target genes were extracted using a DNA Blood Mini Kit (CWBIO, Beijing, China) and amplified *via* polymerase chain reaction, and mutated genes were detected *via* Sanger sequencing. A known heterozygous variation (c. 31G>A) in *GJB6* was found in all 11 patients with HED (Figure 2A, B) but not detected in any of the nine healthy individuals of the family.

Imaging examinations

Temporarily lacking.

FINAL DIAGNOSIS

Based on the current findings combined with the patient's medical history, the final diagnosis was HED.

TREATMENT

Because there is no effective treatment for this disease, the pedigree of patients was not treated after diagnosis.

OUTCOME AND FOLLOW-UP

Overexpression vectors of *GJB6* and its variants (c.31G>A, c.263C>T, and c.110T>A) were constructed. Empty loads were used as a normal control (NC) group, and cells grown in normal culture were used as a blank control group. Overexpression vectors of *GJB6* and its variants were transfected into HaCaT cells. After 24 h of cell transfection, the expression levels of *GJB6* mRNA and protein were detected *via* RT-qPCR and western blotting, respectively. The data were statistically analyzed using SPSS Statistics 19, GraphPad Prism 7, and Quantityone software. Significant differences between groups were analyzed *via* one-way ANOVA, and statistical significance was set at $P < 0.05$. The mRNA and protein expression levels of *GJB6* and its variant loci (c.31G>A, c.263C>T, and c.110T>A) are shown in Figure 2C, D.

Six months later, 11 patients from this pedigree were still alive.

DISCUSSION

In the reported family, the variation locus was at c.31G>A on *GJB6*, and although this variation locus has been reported previously, the clinical presentations of the patients of this family differed from those of other cases (Table 2). Table 2 shows that different variant loci lead to different clinical phenotypes and that the same variant locus can correspond to different clinical phenotypes, even in the same family. No one-to-one correspondence could be formed between the genotype and clinical phenotype of patients with HED.

Connexin 30 (Cx30) is the protein product of G*JB6* and is primarily utilized in the human cochlea and skin; therefore, deafness and skin problems may occur when there is a variation in *GJB6*. In this study, the conversion of guanine (G) at position 31 of G*JB6* to adenine (A) in patients of the family was detected using Sanger sequencing. This nucleotide base change results in the replacement of a normal glycine (Gly) with arginine (Arg), leading to an altered Cx30 product. This change affects the conformational and structural flexibility of the N-terminal of Cx30, which regulates the selectivity and gating polarity of the linker protein[3]. This leads to an abnormal transport activity through the skin gap junctions, which causes the phenotypic characteristics of HED. In addition, we performed a literature review of other reported genotypes of HED and their corresponding phenotypes, which may help clinicians diagnose the disease despite its varied presentations (Table 2). However, further study is required to determine how the pathogenesis of HED is affected by aberrant mRNA and protein expression because of *GJB6* variation.

CONCLUSION

There is no standard, effective treatment for HED, which can only be treated palliatively by wearing wigs, applying topical moisturizers, and following special nail care. Although HED is generally not life-threatening, it has serious physical and psychological effects on patients because of its effect on appearance. Sensorineural

deafness, cataracts, oral mucosal leukoplakia, mental retardation, impaired immune system, skeletal malformations, and pestle finger have also been reported in HED patients. Therefore, prenatal genetic counseling and genetic testing remain effective methods to reduce the transmission of this hereditary disease.

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