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# The Clinical Manifestation of p.Asp50Asn Heterozygous Mutation of *GJB2* Gene in 3 Members of a Family Is Similar to That of Clouston Syndrome

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Keratitis-ichthyosis-deafness (KID) syndrome has genetic heterogeneity, and the clinical manifestations of some patients may overlap with Clouston syndrome. A 34-year-old female patient came to our department with a complain of "sparse hair, rough skin, photophobia and deafness for more than 30 years." We found that the proband and two other family members (57-year-old mother and 4-year-old daughter) had similar clinical manifestations: systemic hair loss, generalized skin hyperkeratosis, especially in the metacarpophalangeal area. Subungual hyperkeratosis, finger/toenail dystrophy, as well as photophobia and epiphora. According to the investigation, one of the family members also had similar clinical manifestations (grandfather of the proband) and he's died. The other three members of the family had no hearing impairment, and all patients had typical nail dystrophy, hair loss and palmoplantar hyperkeratosis, similar like as seen in Clouston syndrome, so we suspected to diagnose the case as Clouston syndrome. However, after genetic testing, it was found that the proband, his mother and daughter all had p.Asp50Asn heterozygous mutations in the *GJB2* gene, and no mutation was detected in *GJB6*. The modified diagnosis was KID syndrome.

**Keywords:** Clouston syndrome, *GJB2* gene, Connexin 26

## INTRODUCTION

At present, the diagnosis of keratitis-ichthyosis-deafness (KID) syndrome is still a challenge. KID syndrome and Clouston syndrome have many overlapping phenotypes, and their prognosis and disease management are very different, when we face patients with phenotype similar to Clouston syndrome, we need to screen several connexin genes with known skin phenotype for definite diagnosis. Early diagnosis and active treatment of KID syndrome is essential, prenatal diagnosis should be carried out if necessary. The reported p.Asp50Asn mutations mainly occur in sporadic cases, and our findings are of great significance to the practice of medical genetics. Among the 4 patients in this family, the hair, nail and skin lesions are very similar to Clouston syndrome. Our report can provide clinical data for clinicians to correctly diagnose the two diseases.

## CASE REPORT

The proband, a 34-year-old female, went to see a doctor because of "sparse hair, rough skin, photophobia and deafness for more than 30 years." The mother of the proband complained that at birth, the patient had only a small amount of fine hair covering the scalp, no eyebrows and eyelashes, rough skin, dark color and dark skin lines, and the patient was born in well lighted room, so she closed her eyes and burst into tears. In infancy, parents found that the patient's ears did not respond to sound, and his throat could make a sound, but could not speak. With the increase of age, the roughness of the skin all over the body gradually aggravated, the fingernail gradually thickened, the yellow substance accumulated under the nail, and the deck was gradually damaged. The amount of hair did not increase in the past 30 years, and axillary hair and

pubic hair did not grow. Ophthalmic examination revealed vascular keratitis (Fig. 1). The patient had no history of head trauma from childhood, no history of special medication, normal mental development, normal teeth and sweating. Parents are not consanguineous. Four in four generations of the family have the disease (Fig. 2).

Specialist physical examination (Fig. 3, 4): the hair of the scalp is sparse, thin and short, and flaky pigmentation and needle-tip-sized granular keratins can be seen on the top of the scalp. Milky papules of 1 to 2 mm size are scattered around the eyes. The protruding side of the tongue is scattered with circular leukoplakia of the size of 1 to 4 $cm^2$, with white ridges at the edges, and fissures of different lengths of 0.5~2 cm can be seen during this period. The skin all over the body is dark and dark brown patches can be seen on the back, especially on the waist and back. Hands and feet are rough in touch, thickened nails with subungual hyperkeratosis of both hand and toe nails, partial deck damage; short and thick first finger and toe segments.

DNA test: After obtaining the consent of the patients and their families, the peripheral blood of the proband, the

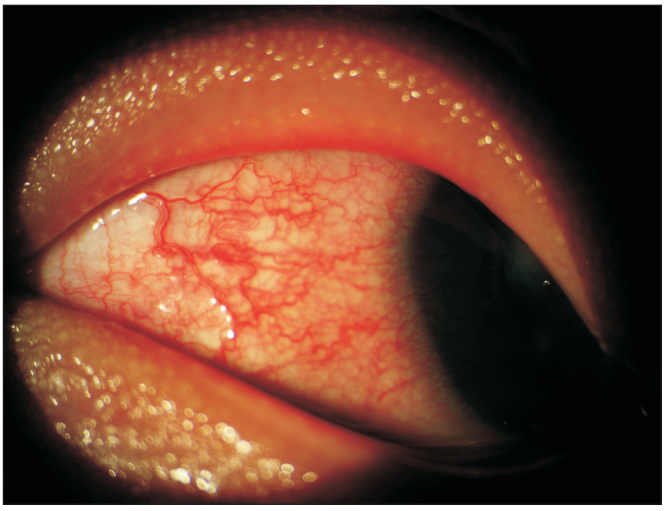

**Fig. 1.** Eyes of a patient with keratitis-ichthyosis-deafness (KID) syndrome. Eyes exhibit palpebral hyperkeratotic lesions, no eyelashes, and absence of meibomian glands. New blood vessels can be seen in both eyes.

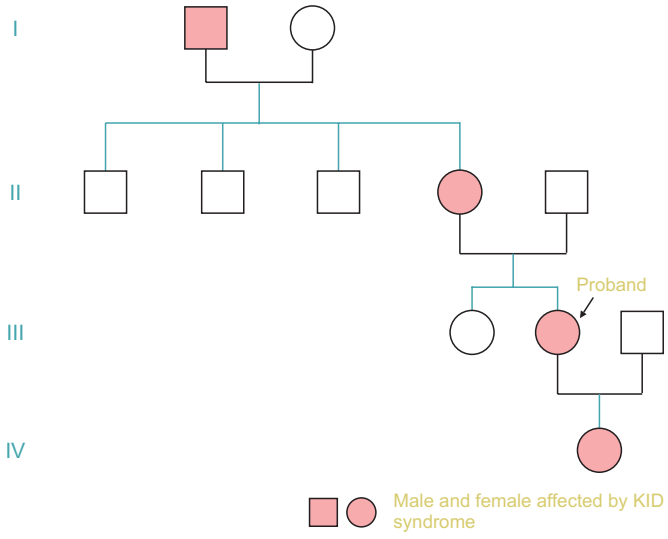


**Fig. 2.** Family tree: there are four affected by keratitis-ichthyosis-deafness (KID) syndrome in four generation.

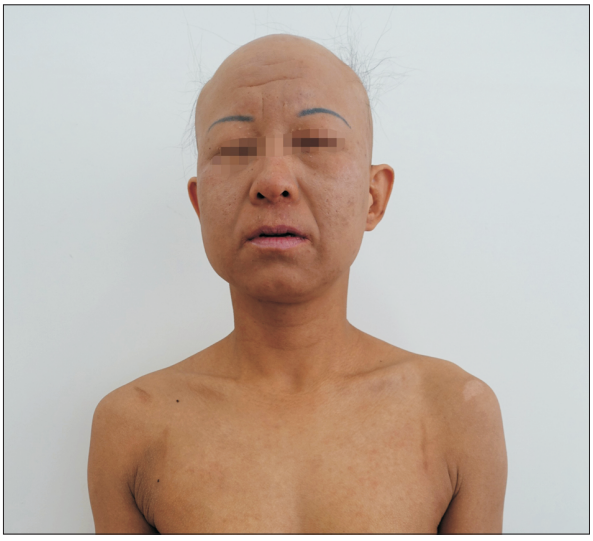

**Fig. 3.** The patient has thin hair, no eyebrows or eyelashes.

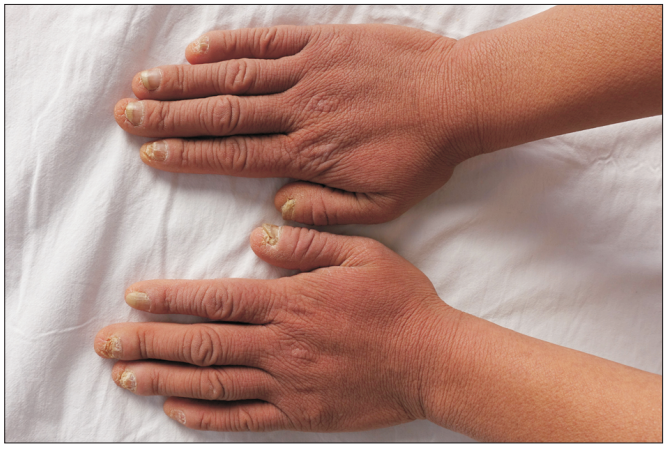

**Fig. 4.** Hands and feet are rough in touch, thickened nails with subungual hyperkeratosis of both hand and toe nails, partial deck damage; short and thick first finger and toe segments.

proband's parents and their daughters were extracted and sequenced. A heterozygous mutation of c.G148A (nucleotide mutation at position 148 in the coding region from G to A) was detected in the proband *GJB2* gene. First-generation sequencing tests showed that both the mother and daughter of the proband were heterozygous at this locus (Supplementary Fig. 1).

Combined with medical history, signs and related auxiliary tests, the proband, the mother and daughter of the proband were diagnosed as KID syndrome.

We received the patient's consent form about publishing all photographic materials.

## DISCUSSION

KID syndrome is a very rare congenital syndrome. At present, most cases reported worldwide are sporadic, with less than 20 familial cases[1]. It is mainly caused by the GJB2 mutation that encodes the connexin 26. Sweating ectodermal dysplasia (HED) or Clouston syndrome is also a rare autosomal dominant disease, which is mainly caused by a mutation in the GJB6 gene encoding connexin 30[2]. Cx26 and Cx30 share 76% homology and have the typical structure of connexin: four transmembrane hydrophobic domains, two highly conserved extracellular hydrophilic rings and three relatively variable cytoplasmic domains[3]. KID syndrome[4] is characterized by skin, auditory and ophthalmic abnormalities. The most common clinical features are sensorineural deafness (90%), erythematous keratosis (89%), vascular keratitis (79%), hair loss (79%), and palmar reticular keratosis (41%). Clouston[5] is characterized by nail dystrophy, systemic hair loss and palmoplantar hyperkeratosis. Sparse hair and nail dystrophy begin to appear 1 month after birth, and progressive alopecia may lead to complete hair loss during puberty. Nail dystrophy and palmoplantar hyperkeratosis usually occur in childhood and aggravate with age. However, the clinical manifestations of each patient are different, even in the same family members, the clinical characteristics are not the same. KID syndrome and Clouston syndrome are caused by mutations in different connexin genes, but their symptoms may overlap (nail dystrophy, hair loss and palmoplantar hyperkeratosis), which may be due to the formation of isomers (consisting of more than one type of connexin) in their function and structure[6]. Some studies have shown that KID syndrome has genetic heterogeneity and can lead to different phenotypes. A dystrophy with hair loss usually indicates Clouston syndrome, but deafness is usually not part of the phenotype of Clouston syndrome. The proband is characterized by nail dystrophy, hair loss and palmoplantar keratoderma, which is a typical manifestation of Clouston syndrome. But, hair loss and reticulated palmoplantar hyperkeratosis are also included in the major diagnostic criteria of KID syndrome, but nails are predominantly affected Clouston syndrome, and the other three family members of the proband do not have hearing impairment, so they are suspected to be diagnosed with Clouston syndrome. Different from the skin manifestation, the eye and hearing impairment of KID syndrome is not consistent. The history of photophobia and tears in the eyes of the proband in this pedigree is later than that of the skin. More than 90% of patients can have varying degrees of hearing loss, which often affects the language function of patients. What is interesting is that in this family, only the proband has hearing impairment, and the other three patients are not affected, We think that the hearing loss phenotype has not yet come out in the three family members other than the proband. We will trace the family members. Compared with Clouston syndrome, KID syndrome can be associated with keratitis, hearing impairment, skin secondary infection, skin tumors and other serious complications, so all patients with KID syndrome should undergo ophthalmic evaluation and formal auditory tests, and then check regularly to track the progress of the disease[7]. This patient underwent ophthalmological examination, but no hearing test was performed because his hearing had been completely lost. KID eye features[8] are corneal epithelial defects, including scarring and neovascularization, which may lead to progressive loss of vision and may eventually lead to blindness. It can also be characterized by photophobia, dry eyes, blepharitis, corneal leukoplakia and conjunctivitis[9]. It can also be complicated with severe ocular infection. The decrease of host defense ability and enhancement of carcinogenic potential of KID syndrome indicate that gap junction communication plays a key role not only in epithelial dynamic balance and differentiation, but also in immune response and epidermal carcinogenesis[10-12]. Loss of Cx26 expression, disturbance of intercellular communication, and down-regulation of cadherin have been thought to explain uncontrolled epithelial growth and carcinogenesis in patients with KID syndrome. There is also evidence that intercellular signal disruption may interfere with the establishment of an

effective and timely immune response, thus increasing susceptibility to mucocutaneous infection. At present, there are no clear guidelines for the treatment and management of KID syndrome. Clinicians should pay attention to maintaining the skin barrier of patients, preventing or treating skin infections, and screening skin tumors[7,13,14]. Systemic use of retinoic acid, especially acitretin, is effective in diagonalization and cancer chemoprevention, and oral acitretin reverses visual impairment in KID syndrome and it is also used to treat systemic hyperkeratosis. Congenital sensorineural hearing loss may lead to social isolation and language delay, and cochlear implants may help children develop oral skills[15]. Some patient improves their visual acuity through local anti-inflammatory therapy and the use of scleral contact lenses. Cheung et al.[16] used ocular surface stem cell transplantation to treat keratitis in KID.

## SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-20-278-s001.pdf.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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