
Clouston syndrome (CS) and keratitis-ichthyosis-deafness (KID) syndrome are rare autosomal dominant ectodermal dysplasias caused by germline mutations in the connexin genes GJB6 and GJB2, respectively, which encode the closely related gap junction proteins Cx30 and Cx26.1,2 The triad features of CS are nail dystrophy, hair loss, and palmoplantar keratoderma (PPK). Usually, photophobia and sensorineural hearing loss (SNHL) are lacking in CS. We describe herein a patient with CS, photophobia, and SNHL.

Report of a Case | The patient was a 24-year-old Japanese woman born to nonconsanguineous, unaffected parents after an uneventful pregnancy. From the time of her birth, her skin had been dry, and her nails dystrophic. She had no scalp hair, eyebrows, or eyelashes. Her total absence of hair was congenital. She had PPK from infancy, and its severity has been stable over her lifetime. She also had mild photophobia.

At age 24 years, she underwent a dermatologic examination, which revealed a complete absence of body and scalp hair (Figure 1A), eyebrows, and eyelashes. Several fingernails had been shed, and the remaining ones, as well as the toenails, were short and thickened and demonstrated distal onycholysis (Figure 1B). The patient had diffuse PPK with a cobblestone surface (Figure 1C). Neither follicular keratosis nor hyperpigmentation was observed. The oral mucosa was unremarkable. Her teeth were normal in number and shape. Audiologic testing revealed mild prelingual bilateral SNHL, but her speech was normal.

Following ethical approval, informed consent was obtained from the patient, in compliance with the Declaration of Helsinki guidelines. The entire coding regions of GJB6 and GJB2, including the exon/intron boundaries, were sequenced using genomic DNA samples from the patient. The mutation analysis revealed that the proband harbored the heterozygous mutation p.Ala88Val (c.263C>T) in GJB6. The patient was diagnosed as having CS resulting from the heterozygous missense mutation p.Ala88Val in GJB6. In addition, the patient was found to be heterozygous for p.Val27Ile (c.79G>A) in GJB2. This substitution, also found in unaffected controls in a homozygous or heterozygous state, represents a common single-nucleotide polymorphism (SNP) in the Japanese population.3

Discussion | In general, GJB2 and GJB6 mutations result in KID syndrome and CS, respectively.1,2 However, the symptoms of patients with GJB2 or GJB6 mutations vary from case to case, according to the nature of the mutations. Details of the pathogenetic pathway of GJB2 as well as GJB6 mutations and the complex genotype/phenotype background of connexin disorders and SNHL have been summarized by van Steensel et al.4 Furthermore, in cases with both GJB2 and GJB6 mutations or variants, the clinical features and symptoms are more complicated. The heterozygous mutation p.Val27Glu in GJB6 has been detected in a patient with CS without SNHL or photophobia5 (Figure 2). However, there is a report of a patient showing congenital atrichia, PPK, and nail dystrophy, as well as SNHL and mild prelingual SNHL.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the plastic surgeons and dermatologists who took time out of their busy schedules to complete the survey.

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Generally, a patient with CS and the GJB2 mutation p.Ala88Val but without the GJB2 variant p.Val27Ile has neither sensorineural hearing loss (SNHL) nor photophobia (red circle). In contrast, the present patient (yellow circle), with both the GJB6 mutation p.Ala88Val and the GJB2 variant p.Val27Ile, has SNHL and photophobia. CL indicates cytoplasmic loop; E1 and E2, extracellular domains 1 and 2; M1 through M4 indicate transmembrane domains 1 through 4; blue circle, keratitis-ichthyosis-deafness syndrome accompanied by congenital atrichia, palmoplantar keratoderma, and nail dystrophy; and white circles, CS.

In conclusion, the present case suggests that the coexistence of a GJB6 mutation and a heterozygous GJB2 variant in CS may lead to SNHL and photophobia in addition to the triad that typifies CS, even though the GJB2 variant is an SNP when it presents without any GJB6 mutation.

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Correction: This article was corrected on August 22, 2013, to correct an author’s name spelling.


CORRECTION

Incorrect Spelling of Author’s Name: In the article titled “Clouston Syndrome With Heterozygous GJB6 Mutation p.Ala88Val and GJB2 Variant p.Val27Ile Revealing Mild Sensorineural Hearing Loss and Photophobia,” posted online first in JAMA Dermatology on July 17, 2013 (doi:10.1001/jamadermatol.2013.4766), the first author’s name was spelled incorrectly throughout. The correct spelling is Kazumitsu Sugura, MD, PhD.