
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 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. 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 GJB2. The patient was diagnosed as having CS resulting from the heterozygous missense mutation p.Ala88Val in GJB2. 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.Val27Ile in GJB6 has been detected in a patient with CS without SNHL or photophobia2 (Figure 2). However, there is a report of a patient showing congenital atrichia, PPK, and nail dystrophy, as well as SNHL and
Generally, a patient with CS and the GJB6 mutation p.Ala88Val but without the GJB2 variant p.Val271le 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.Val271le, 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.

The present patient with CS carrying the GJB6 missense mutation p.Ala88Val and the GJB2 variant p.Val271le showed mild SNHL and photophobia. The identified GJB6 mutation p.Ala88Val was previously reported in a patient with CS without evidence of hearing disturbance or photophobia.1 Often, GJB2 mutations lead to SNHL in heterozygotes and homozygotes. Patients with GJB2 mutations are also known to show ocular involvement. Thus, in the present case, the additional symptoms of mild SNHL and photophobia might be attributable to p.Val271le in GJB2, although p.Val271le in GJB2 is a common SNP in the Japanese population.

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.Val271le 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 Sugiuira, MD, PhD.