

Letters to the Editor

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Clouston syndrome with dental anomalies, micropores of hair shafts and absence of palmoplantar keratoderma

Dear Editor,

A 3-year-old Thai girl presented with hypotrichosis, pale and slow-growing hair. At birth she had normal hair, but she progressively lost it. Her hair stayed short. Hair loss commenced

in the temporo-occipital areas (Fig. 1a). Her fingernails were narrow and hyperconvex, but toenails were normal (Fig. 1b). Scanning electron microscopy (SEM) of scalp hair showed hypoplastic cuticles (Fig. 1c). Oral examination showed



Figure 1. (a) The proband with hypotrichosis, pale and slow-growing hair. Hypodontia of the mandibular right lateral incisor (arrow). (b) Fingernails are narrow and hyperconvex, but toenails are unremarkable. (c) Scanning electron microscopy (SEM) of scalp hair shows hypoplastic cuticles. (d) Panoramic radiograph shows hypodontia of the mandibular right deciduous lateral incisor (yellow arrow). The successor of the missing deciduous tooth is observed (red arrow). (e) The mother of the proband is of normal appearance. Skin and hair appears essentially normal. (f) SEM of her scalp hair shows absence of cuticles. Note numerous micropores on the hair shafts near hair follicles. Micropores are smaller than 5 μm . (g) Fingernails and toenails are narrow and hyperconvex. (h) Panoramic radiograph shows single-rooted maxillary permanent molars (arrows).

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hypodontia of the mandibular right deciduous lateral incisor. Interestingly, the successor of the missing deciduous tooth was radiographically present (Fig. 1a,d). Intelligence, sweating and hearing were unremarkable. The mother had normal skin and hair (Fig. 1e). SEM of her scalp hair showed numerous micropores along the hair shafts near hair follicles (Fig. 1f). Her fingernails and toenails were narrow and hyperconvex (Fig. 1g). A panoramic radiograph showed single-rooted maxillary permanent molars (Fig. 1h).


Following approval of the ethics committee, obtaining informed consent and in full accordance with the Declaration of Helsinki, whole-exome sequencing was performed on the proband's DNA. Whole-exome sequencing showed a heterozygous single base substitution in *GJB6* (c.31G>A; p.Gly11Arg) (Fig. S1) and *GJB2* (c.109G>A; p.Val37Ile) (Fig. S2). Sanger sequencing revealed the presence of *GJB2* and *GJB6* variants in the proband and her mother, but not the father.

The c.31G>A; p.Gly11Arg missense mutation in *GJB6* has been known to be the cause of Clouston syndrome (Mendelian Inheritance in Man #129500). It is characterized by hypotrichosis, pale, brittle and slow-growing hair, abnormal nails and palmoplantar keratoderma. Four *GJB6* mutations (Gly11Arg, Val37Glu, Asp50Asn, Ala88Val) have been reported.¹ The allele frequencies of the *GJB2* variant according to ExAC and gnomAD are 0.00659 and 0.00772, respectively. According to the Leiden Open Variation Database, this *GJB2* variant has been reported to be pathogenic for hearing impairment in a number of reports. Single-rooted maxillary permanent molars and micropores on the scalp hair shafts found in the mother have never been reported in patients with Clouston syndrome. The micropores may be places where cuticle cells have fallen off the hairs as a result of poorly formed gap junction connections. Whole-exome sequencing excluded the effects of other known hypodontia-associated genes including *WNT10A*, *WNT10B*, *AXIN2*, *PAX9*, *MSX1*, *GREM2* and *TFAP2B*.² It is convincing that the dental anomalies found in this family were the effects of *GJB6* mutation. The absence of a deciduous tooth with the presence of its permanent successor implies the differential role of *GJB6* in development of the primary dentition, but not the permanent one. Up till now, hypodontia has only been reported in Thai patients who carried the p.Ala88Val mutation.¹ Dental anomalies, micropores on the hair shafts and the absence of palmoplantar keratoderma might have been the effects of racial background or the combined effects of *GJB6* and *GJB2* variants.³ The dental and hair findings raise the importance of *GJB6* in tooth and hair development and this hypothesis is supported by the findings that *GJB6* is a potential direct target gene of TP63⁴ and dental and hair anomalies are common in patients with *TP63* mutations.⁵ *GJB2* may function as a

modifier gene because *GJB2* itself is not expressed in teeth during early tooth development.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. A heterozygous single base substitution in *GJB6* (c.31G>A; p.Gly11Arg) in the patient and her mother (arrows).

Figure S2. A heterozygous single base substitution in *GJB2* (c.109G>A; p.Val37Ile) in the patient, her mother, and a normal control (arrows).