Identification of *GJB6* gene mutation in an Indian man with Clouston syndrome

Sir,

Clouston syndrome (MIM 129500), also known as hidrotic ectodermal dysplasia, is a rare autosomal dominant genetic disorder characterized by generalized hypotrichosis, dystrophic nails and hyperkeratotic palms and soles. It is particularly common in the French Canadian population of Southwest Quebec. We present an Indian man with typical clinical features of Clouston syndrome who was found to have a known mutation in the *GJB6* gene.

A 45-year-old man presented to the dermatology outpatient department of Geetanjali Medical College and Hospital in Udaipur, Rajasthan, with complaints

of excessively thickened skin of the palms and soles. The thickened skin restricted movements of his fingers and disrupted his daily functioning. He gave a history of similar features in one of his children. There was no history of similar lesions in any of his siblings, parents or other family members. None of his family members could be examined.

On examination, the patient was found to have severe hyperkeratosis of the palms and soles which led to clawing of the hands [Figure 1]. Nails were dystrophic in both hands and feet. The fingernails were thickened, overcurved, discolored [Figure 2] and associated with tufting of the terminal phalanges [Figure 1]. Further, the patient had thin and sparse scalp hair [Figure 3a]. Other hair-bearing regions (eyebrows, eyelids, axillae, pubic region) also had very minimal hair [Figure 3b]. There was no history of consanguinity, hypohidrosis, abnormal dentition and any hearing or visual complaints. A provisional diagnosis of hidrotic ectodermal dysplasia was made.

A peripheral blood sample was collected in an ethylenediaminetetraacetic acid (EDTA) tube and DNA was isolated by the salting out method.[1] Coding exon 3 of the *GJB6* gene was amplified by polymerase chain reaction (PCR) and the amplification checked on 2% agarose gel. Primers used are shown in Table 1. The polymerase chain reaction-amplified product was incubated with exonuclease I and shrimp alkaline phosphatase to remove the unincorporated primers and nucleotides. Bidirectional Sanger deoxyribonucleic acid sequencing was done using ABI Prism BigDye Terminator Cycle sequencing ready reaction kit v3.1 (Applied Biosystems, USA), followed by ethanol/ethylenediamine tetraacetic acid/sodium acetate precipitation. The precipitate was dissolved in 10 μL Hi-Di formamide with denaturation and capillary electrophoresis using an ABI 3130 Genetic Analyzer. Sequencing results were analyzed using Chromas Pro software (http://technelysium.com.au) and compared with the reference sequence of *GJB6* in the NCBI database (http://www.ncbi.nlm.nih.gov/). A reported heterozygous missense mutation c. 31G>A (p.G11R) was identified, resulting from a glycine-to-arginine amino acid change [Figure 4].

Clouston syndrome is a rare genetic disease caused by mutations in connexin genes. Connexins or gap junction proteins are a family of structurally related transmembrane proteins which establish direct cell-to-cell communication and are responsible for the movement of molecules and ions across adjacent cells. They may be classified into three major groups (GJA, GJB and GJC) based on sequence homology. Each combination of connexins has different qualities of permeability highly significant in terms of function. Mutations in connexins result in hereditary

Table 1: Primer sequence for connexin 30 (GJB6) gene

Primer name	Primer sequence (5' and 3')
Cx 30-3F	CCTTAAAATAAAGTTGGCTTCAGTC
Cx 30-3R	CAAACTCTTCAGGCTACAGAAGG
Cx 30-3IF	TGCATGTGGCCTACTACAGG
Cx 30-3IR	AAGCAGCATGCAAATCACAG

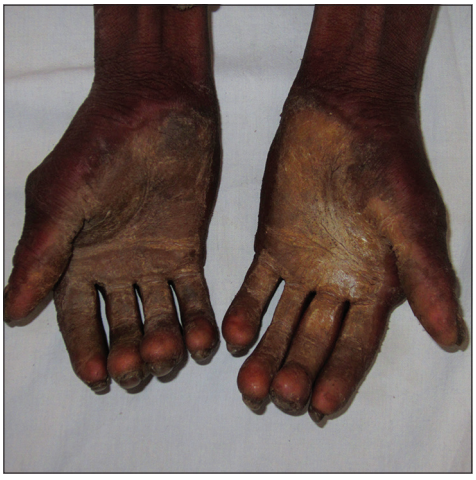

Figure 1: Severe hyperkeratosis of palms leading to clawing, along with bulbous terminal phalanges

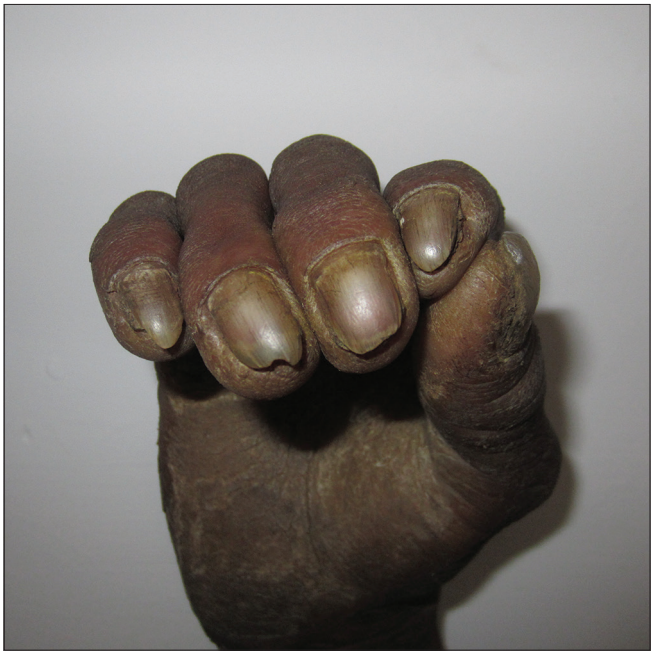

Figure 2: Thickened, overcurved and discolored finger nails

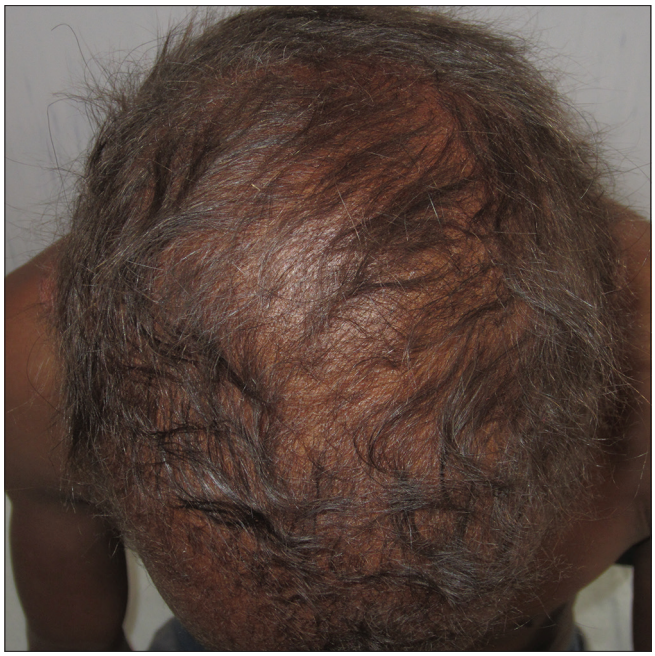

Figure 3: (a) Thin and sparse scalp hair

Figure 3: (b) Sparse eyebrows, eyelashes and facial hair

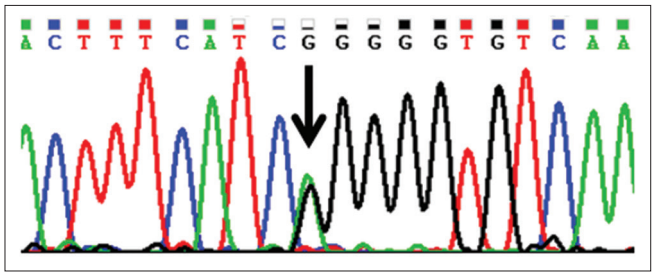

Figure 4: A heterozygous c. 31G>A change in the *GJB6* gene

peripheral neuropathy, complex conotruncal heart malformations, autosomal dominant forms of cataract and hearing loss. Erythrokeratoderma variabilis, keratitis-ichthyosis-deafness syndrome, Vohwinkel syndrome and Clouston syndrome are cutaneous disorders resulting from connexin mutations.

Mutations in *GJB6* gene (and in some cases, *GJA1* and *GJB2* genes) are responsible for Clouston syndrome. To date, five different mutations have been reported in *GJB6* gene with phenotypic features of Clouston syndrome. Mutations p.G11R and p.A88V have been described by Lamartine *et al*. in multiple ethnic populations, p.V37E by Smith *et al*. in Scottish patients and p.D50N by Baris *et al*. in Israeli patients.[2-4] Recently, Liu *et al*. have found that the combination of a novel mutation N14S in GJB6 and a mutation F191L in GJB2 played a pathogenic role in Clouston syndrome.[5] Mutations in *GJA1* (p.V41L) and an R127H heterozygous variants of *GJB2* have also been found responsible for Clouston syndrome.[6] Out of all these, p.G11R is the most commonly reported mutation, seen in the French Canadian population as well as in many other ethnic populations of the world.

We could find only two previous reports of Clouston syndrome in Indians. One was of a large Gujarati family with 41 affected individuals spanning five generations, but genetic mutations were not explored in this family.[7] The other report described a p.A88V mutation detected by Lamartine *et al*. in a patient of Indian ethnicity.[2]

Our patient presented with typical features, and since he denied any similar features in his parents, it was probably a sporadic case. The mutation detected, c. 31G>A (p.G11R) in the *GJB6* gene, is a known mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Nidheesh Agarwal, Pawan Kumar Singh[1], Kalpana Gupta, Neerja Gupta[1], Madhulika Kabra[1]

Department of Dermatology, Venereology and Leprosy, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, [1]Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Nidheesh Agarwal, Flat No. 001, Fateh Apartment, New Fatehpura, Udaipur, Rajasthan, India.
E-mail: nidheeshagarwal@gmail.com

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