Mutation-Proved Clouston Syndrome in a Large Indian Family with a Variant Phenotype

Sangeeta Khatter, Ratna Dua Puri, Sunita Bijarnia Mahay, Pratibha Bhai, Renu Saxena, Ishwar C Verma

Abstract
Hereditary ectodermal dysplasias, a group of disorders affecting skin, hair, nails, and teeth, consist of two main clinical forms – hypohidrotic and hidrotic. Clouston syndrome is a hidrotic ectodermal dysplasia characterized by a triad of generalized hypotrichosis, palmoplantar hyperkeratosis, and nail dystrophy. This paper reports a large Indian family with Clouston syndrome but with the absence of palmoplantar keratoderma, one of the features of the typical triad, thus representing phenotypic heterogeneity, in spite of the presence of a common known mutation in GJB6 gene (p.Gly11Arg).

Key Words: Clouston syndrome, gjb6, hidrotic ectodermal dysplasia, hypotrichosis, keratoderma

Introduction
Ectodermal dysplasias are divided into two main groups: hypohidrotic and hidrotic. Hypohidrotic ectodermal dysplasias are common, and numerous cases have been reported in the Indian literature, either by dermatologists, pediatricians, or dentists. Inheritance can be X-linked (80% cases), but rarely autosomal recessive and autosomal dominant forms have been described. The hidrotic form, also called Clouston syndrome, is much rare. To date, only a few reports of mutation-proved Clouston syndrome in Asian Indians have been published. One was of a large Gujarati family with 41 affected individuals across five generations. Using this family, the chromosomal location of the gene was determined by linkage studies. The second report described a p.A88V mutation detected by Lamartine et al. in a patient of Indian ethnicity. The third case with typical features was a sporadic one with mutation studies. The fourth case was recently reported by Arif et al. but no mutation studies were done. We describe a large Indian family with mutation-proved Clouston syndrome but with the absence of palmoplantar keratoderma, thus representing phenotypic heterogeneity, in spite of the presence of a common known mutation in GJB6 gene (p.Gly11Arg).

Case Report
A 27-year-old Asian Indian woman presented for preconceptional counseling, with sparse hair on the scalp and eyebrows and dysplastic nails since birth. On examination, she (the proband) had very thin hair on scalp, eyebrows, and eyelashes. Her nails were dysplastic and discolored both on hands and on toes [Figure 1], but there was the absence of palmoplantar keratoderma [Figure 2]. There were no other abnormal features.

Family history revealed that on her mother’s side, multiple family members were affected in an autosomal dominant pattern [Figure 3], but there was a great variability of clinical features. Her mother, maternal aunt, and her children had a history of dystrophic nails and sparse hair, but the maternal uncles and their children had only dystrophic nails since birth. None of them had palmar hyperkeratosis.

Due to atypical nature of the presentation, molecular testing of the proband was carried out by the study of the gene panel for ectodermal dysplasias at MedGenome Labs, Bangalore. A heterozygous missense variation in exon 5 of the GJB6 gene, c. 31G>A (p.Gly11Arg), was identified, which was sanger validated in molecular laboratory at Sir Ganga Ram Hospital. This variation has previously been reported as recurrent heterozygous mutation in patients with Clouston syndrome (OMIM*604418). This is an autosomal dominant disorder, and the proband was counseled accordingly, with 50% chance of transmission of the disorder to the offspring in each pregnancy.

Address for correspondence: Dr. Ishwar C. Verma, Institute of Genomics and Medical Genetics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India. E-mail: icverma@gmail.com

How to cite this article: Khatter S, Puri RD, Mahay SB, Bhai P, Saxena R, Verma IC. Mutation-Proved Clouston syndrome in a large Indian family with a variant phenotype. Indian J Dermatol 2019;64:143-5.

Received: October, 2017. Accepted: August, 2018.
Khatter, et al.: Clouston syndrome in Indian family and variant phenotype

Indian Journal of Dermatology | Volume 64 | Issue 2 | March-April 2019

She subsequently returned when she was pregnant. Chorionic villus sampling was done, and analysis of the extracted DNA showed that the baby had inherited the normal allele from the mother.

Discussion

Clouston syndrome was first described in 1895 and later reported in Canadian families. It is characterized by the triad of nail dystrophy, generalized hypotrichosis, and palmoplantar hyperkeratosis. Sparse hair and nail dystrophy are present since the 1st month of life. Progressive loss of hair may lead to total alopecia at puberty. Nails gradually become dystrophic during childhood. Nail clubbing may occur. Palmoplantar keratoderma develops in childhood and progresses with age. Clinical features vary even within the same family members. Some patients may have skin hyperpigmentation over the joints. Strabismus, conjunctivitis, cataracts, deafness, polydactyly, and syndactyly may occur. Eccrine syringofibroadenomas have been reported in some patients. Epidermoid cysts were documented recently by Arif et al. Clouston syndrome occurs due to the mutation in GJB6 gene (GJA1 and GJB2 genes in a few cases). 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 in multiple ethnic populations, p.V37E in Scottish patients, and p.D50N in Israeli patients. Liu et al. found that the combination of a novel mutation N14S in GJB6 and a mutation F191L in GJB2 played a pathogenic role in Clouston syndrome. Another bigenic combination of mutations in connexin genes, i.e., GJA1 (p.V41L) and GJB2 (R127H), has also been observed in some cases. The p.G11R is the most commonly reported mutation, seen in the French Canadian population as well as in many other ethnic groups around the world. In vitro functional studies have revealed that mutant protein affected the proliferation and differentiation of cultured skin cells due to an aberrant leakage of Adenosine triphosphate (ATP) into the extracellular medium. In the present case, the same mutation was detected c.31G>A(p.G11R). However, proband in our family presented with only two features of the typical triad of Clouston syndrome, i.e., nail dystrophy and generalized hypotrichosis. Palmoplantar hyperkeratosis was not there in any of her family members. Multiple generations were affected, and variable presentation was seen among different family members such as only dystrophic nails in maternal uncle’s family and dystrophic nails and sparse hair in maternal aunt’s family. Familial variability of features is well-described previously, but the absence of palmoplantar hyperkeratosis is not seen in earlier cases. To conclude, we must think of the possibility of Clouston syndrome even if the patient has presented with nail dystrophy. This report might help physicians and dermatologists not to miss the diagnosis of Clouston syndrome even in cases presenting merely with nail dystrophies as seen in our patient family.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their 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.
Acknowledgment
The authors would like to acknowledge the patient and her family and staff members of Genetics, MedGenome Labs, Bangalore.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Clouston HR. The major forms of hereditary ectodermal dysplasia: (With an autopsy and biopsies on the anhydrotic type). Can Med Assoc J 1939;40:1-7.
2. Mukherjee SS, Chandrashekar BS. Despite the hair failing, nails thrive. Indian J Pediatr Dermatol 2017;18:121.
3. Chaudhary AK, Girisha KM, Bashyam MD. A novel EDARADD 5’-splice site mutation resulting in activation of two alternate cryptic 5’-splice sites causes autosomal recessive hypohidrotic ectodermal dysplasia. Am J Med Genet A 2016;170:1639-41.
4. Radhakrishna U, Blouin JL, Mehenni H, Mehta TY, Sheth FJ, Sheth JJ, et al. The gene for autosomal dominant hidrotic ectodermal dysplasia (Clouston syndrome) in a large Indian family maps to the 13q11-q12.1 pericentromeric region. Am J Med Genet 1997;71:80-6.
5. Lamartine J, Munhoz Essenfelder G, Kibar Z, Lanneluc I, Callouet E, Laoudj D, et al. Mutations in GJB6 cause hidrotic ectodermal dysplasia. Nat Genet 2000;26:142-4.
6. Agarwal N, Singh PK, Gupta K, Gupta N, Kabra M. Identification of GJB6 gene mutation in an Indian man with Clouston syndrome. Indian J Dermatol Venereol Leprol 2016;82:697-700.
7. Arif T, Amin SS, Adil M, Mohtashim M. Diffuse palmoplantar keratoderma, onychodystrophy, universal hypotrichosis and cysts. Acta Dermato-venereol Croat 2017;25:161-3.
8. der Kaloustian VM. Hidrotic ectodermal dysplasia 2. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, et al., editors. Gene Reviews® 2005. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1200. [Last accessed on 2014 Jun 06].
9. Andrade AC, Vieira DC, Harris OM, Pithon MM. Clouston syndrome associated with eccrine syringofibroadenoma. An Bras Dermatol 2014;89:504-6.
10. Liu YT, Guo K, Li J, Liu Y, Zeng WH, Geng SM, et al. Novel mutations in GJB6 and GJB2 in Clouston syndrome. Clin Exp Dermatol 2015;40:770-3.
11. Kellermayer R, Keller M, Ratajczak P, Richardson E, Harangi F, Mérei E, et al. Bicogenic connexin mutations in a patient with hidrotic ectodermal dysplasia. Eur J Dermatol 2005;15:75-9.