

## Autosomal Recessive Cutis Laxa Type II: Report of Novel Mutation in a Child

### Abstract

Autosomal recessive cutis laxa type-II (ARCLII) is a spectrum of clinical disorders with prenatal and postnatal growth retardation, cutis laxa, dysmorphism, and skeletal abnormalities. We report the case of a 14-month-old boy with developmental delay, hypotonia, dysmorphism, and loose skin. A novel homozygous variant was observed in *ATP6VOA2* gene. Clinical spectrum of ARCLII is highly heterogeneous and molecular analysis should be done to confirm the diagnosis.

**Keywords:** *Autosomal recessive cutis laxa, dysmorphism, novel mutation*

### Introduction

Autosomal recessive cutis laxa (ARCL) is a genetically heterogeneous condition with variable phenotype.<sup>[1]</sup> Three common types are known, and generalized loose skin with increased elasticity is a common feature in all the three types. ARCL type I is a severe form and fatal at an early age due to cardiopulmonary complications. ARCL type II is a spectrum of clinical entities with variable severity of cutis laxa, developmental delay, and associated skeletal abnormalities. ARCL Type III (De Bary syndrome) has progeroid appearance with presence of athetoid movements and corneal clouding. Patients with ARCL type II can be divided in two major groups – children with ARCL type II associated with a combined N- and O-linked glycosylation defect (CDG type II) and without the presence of metabolic disorder. So far, all ARCL II cases with combined glycosylation defect harbour mutations on both alleles of the *ATP6VOA2* gene. In the nonmetabolic group, the underlying genetic defect is not yet known.<sup>[2,3]</sup> Several genetic defects have been described in patients with ARCL II. Here, we present a child with clinical features of ARCL Type II and a novel mutation (c.2293+5G>A) in the homozygous state.

### Case Report

A 14-month-old boy presented with predominant motor developmental delay

and seizures. Child also had stridor and indirect laryngoscopy suggested laryngomalacia. The child was born of a second-degree consanguineous marriage at 33 weeks gestation with birth weight of 1.1 kg. Birth history was uneventful, and no significant illness was present in the family. Child had generalized loose skin with prominent skin folds. Weight, length, and head circumference were less than third centile for his age. Child had dysmorphism in the form of sagging cheeks, maxillary hypoplasia, prognathism, posteriorly placed large and low set ears, hypertelorism, down slanting palpebral fissures, wide open anterior fontanelle, medial epicanthal folds, depressed nose, long philtrum, and small mouth [Figure 1a]. He also had a small umbilical hernia [Figure 1b], generalized laxity of all joints [Figure 1c], and generalized hypotonia with hyporeflexia. Magnetic resonance imaging of the brain showed frontal dysmyelination [Figure 1d]. Skin biopsy showed mild hyperkeratosis and mild mononuclear inflammatory infiltrates in the papillary dermis, small and diminished elastic fibres, and deficient elastin with globular appearance [Figure 2a and b].

In presence of characteristic skin biopsy features, mutation screening in the *ATP6VOA2* gene revealed presence of mutation (c.2293+5G>A) in homozygous state in the patient and in heterozygous state in both parents.

**Rakesh Kumar,  
Sheetal Sharda,  
Vimlesh Soni,  
Kaniyappan  
Nambiyar<sup>1</sup>**

*Departments of Paediatrics and  
Histopathology, Post Graduate  
Institute of Medical Education  
and Research, Chandigarh,  
India*

#### Address for correspondence:

*Dr. Rakesh Kumar,  
Department of Paediatrics,  
Post Graduate Institute  
of Medical Education and  
Research, Chandigarh, India.  
E-mail: drakesh.pgi@  
gmail.com*

#### Access this article online

**Website:** www.idoj.in

**DOI:** 10.4103/idoj.IDOJ\_334\_16

#### Quick Response Code:



**How to cite this article:** Kumar R, Sharda S, Soni V, Nambiyar K. Autosomal recessive cutis laxa Type II: Report of novel mutation in a child. *Indian Dermatol Online J* 2017;8:352-4.

**Received:** September, 2016. **Accepted:** January, 2017.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com



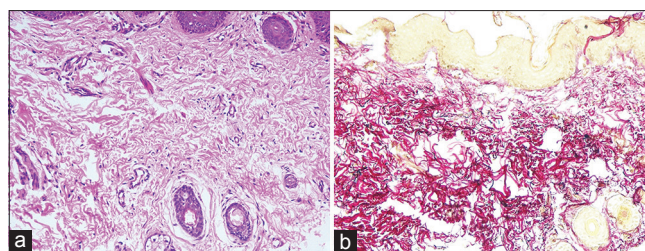
**Figure 1:** (a) Facial dysmorphism of the child at 14 months of age. (b) Redundant and loose skin over abdomen with small umbilical hernia. (c) Joint laxity and prominent loose skin folds. (d) MRI T2-weighted images showing features of dysmyelination prominent in frontal lobes with mild ex-vacuo enlargement of lateral ventricles

During follow-up at 4 years of age, the child still had mild developmental lag in motor sector with no seizure recurrence. Laryngomalacia and inspiratory stridor settled slowly by 2½ years. Parents were counselled regarding the 25% chance of recurrence of the disease in subsequent pregnancy and genetic counselling regarding antenatal diagnosis was done.

## Discussion

The index patient presented with seizures and generalized hypotonia. Presence of generalized loose skin and central nervous system (CNS) involvement made us think of ARCL type II, as CNS involvement with seizures is a prominent feature of type II form of this syndrome, and this was supported by skin biopsy findings. Further confirmation was provided by mutation in the *ATP6V0A2* gene. ARCL II is represented by a spectrum of clinical phenotype with variable severity of cutis laxa, abnormal growth, and developmental delay. Apart from this, persistent wide fontanelles, frontal bossing, slight microcephaly, downward-slanted palpebral fissures, inverted-V eyebrows, low and posteriorly placed ears, and dental caries are characteristic features of this type of cutis laxa.

ARCL type II has features overlapping with wrinkly skin syndrome; as a result, they are regarded as one disorder



**Figure 2:** (a) Skin biopsy shows diminished elastic fibres and mild mononuclear inflammatory infiltrates in the dermis (H and E, ×20). (b) Skin biopsy shows sparse fragmented elastic fibres (Verhoeff van Gieson, ×20)

with a variable spectrum of severity by some authors.<sup>[4]</sup> Because of the many phenotypic similarities in Geroderma osteodysplastica and wrinkly skin syndrome, it has been proposed that these two conditions represent the same disorder.<sup>[5]</sup>

Morava *et al.* reported phenotypic features of 10 children with ARCL II who had associated glycosylation defects.<sup>[1]</sup> Additional features found in their series were strabismus, myopia, hypermetropia, liver involvement, and coagulation abnormalities, which were not seen in our case. Hence, depending on the presence or absence of glycosylation defects, these patients can be divided into two groups: ARCL IIA comprising those with a CDG type II and ARCL IIB comprising those without a metabolic disorder. The migration defects leading to cortex dysgenesis in *ATP6V0A2* mutations could be associated both with normal intelligence or severe intellectual disability. The combination of cobblestone-like brain dysgenesis with late closure of the fontanel and microcephaly might suggest an underlying glycosylation defect in children with cutis laxa; however, migration defects have been described in children with ARCL type II without a glycosylation defect also. Glycosylation studies could not be performed in the index child. Recently, Fischer *et al.* have reported 13 patients of ARCL II, in whom they found 17 different *ATP6V0A2* mutations, and 14 among these, were novel mutations.<sup>[6]</sup>

Our patient has mild phenotypic variant of ARCL II, suggesting that the novel mutation seen in the index case may lead to milder phenotype of the syndrome. Because the clinical spectrum of ARCLII is highly heterogeneous, molecular analysis should be done to confirm the diagnosis.

## 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.

## Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Morava E, Guillard M, Lefeber DJ, Wevers RA. Autosomal recessive cutis laxa syndrome revisited. *Eur J Hum Genet* 2009;17:1099-110.
2. Kornak U, Reynders E, Dimopoulou A, van Reeuwijk J, Fischer B, Rajab A, *et al.* Impaired glycosylation and cutis laxa caused by mutations in the vesicular H<sup>+</sup>-ATPase subunit ATP6V0A2. *Nat Genet* 2008;40:32-4.
3. Rajab A, Kornak U, Budde BS, Hoffmann K, Jaeken J, Nürnberg P, *et al.* Geroderma osteodysplasticum hereditaria and wrinkly skin syndrome in 22 patients from Oman. *Am J Med Genet A* 2008;146:965-76.
4. Hamamy H, Masri A, Ajlouni K. Wrinkly skin syndrome. *Clin Exp Derm* 2005;30:590-2.
5. Al-Gazali L I, Sztriha L, Skaff F, Haas D. Geroderma osteodysplastica and wrinkly skin syndrome: Are they the same? *Am J Med Genet* 2001;101:213-20.
6. Fischer B, Dimopoulou A, Egerer J, Gardeitchik T, Kidd A, Jost D, *et al.* Further characterization of ATP6V0A2-related autosomal recessive cutis laxa. *Hum Genet* 2012;131:1761-73.