Published in final edited form as:

Pediatr Dermatol. 2014 ; 31(3): 347–349. doi:10.1111/pde.12334.

A Novel Elastin Gene Mutation in a Vietnamese Patient with Cutis Laxa

Mark L. Siefring, M.D.¹, Elizabeth C. Lawrence, B.A.², Tom C. Nguyen, M.D.¹, Doanh Lu, M.D.¹, Giang Pham, M.D.¹, Christa Lorenychick, B.S.², Kara L. Levine, M.S.², and Zsolt Urban, Ph.D.²

¹Stamford Skin and Medical Centre, Ho Chi Minh City, Vietnam

²Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA, USA

Abstract

We report a 3-year-old girl from Vietnam with severe congenital cutis laxa, no cardiovascular, pulmonary, neurological or visceral involvement and no family history of cutis laxa. Mutational analysis of the elastin (*ELN*) gene identified heterozygosity for a previously unreported, *de novo* c. 2184delT mutation in exon 30, not present in either parent.

Keywords

Connective tissue disorders; Developmental defects; Genetic diseases/mechanisms; Genodermatoses

Cutis laxa comprises a group of conditions characterized by loose, inelastic, redundant and wrinkled skin, caused by mutations in a group of genes, crucial to the genesis of elastic fibers (1-3) (Table 1).

A 3-year-old Vietnamese female from the Mekong River Delta area was initially diagnosed clinically with progeria syndrome due to her markedly aged physical appearance. Neither her parents nor her two older siblings were affected. Her mother noticed lax skin at the age of 4 months, with no history of antecedent infections or inflammatory conditions.

At the age of 2 years, the proband developed an inguinal hernia, which was repaired 1 month prior to evaluation at our facility. She exhibited age-appropriate development. On physical examination no cardiovascular, respiratory, intra-abdominal, or neurologic deficits were detected. There was no hair loss. She had mild frontal bossing, a long philtrum, prominent nasolabial folds, and fine wrinkles across her forehead. Deep skin wrinkling was observed on her body, with multiple marked skin folds across her chest, abdomen, back, and extremities. On her torso and lower extremities the skin folds were especially excessive and

Corresponding author: Zsolt Urban, PhD, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, 130 De Soto Street, Crabtree Hall A300, Pittsburgh, PA 15261, USA., Tel.: +1-412-648-8269; Fax: +1-412-624-3020; urbanz@pitt.edu.

Conflict of interest statement: The authors declare no conflict of interest.

the skin lacked elastic rebound (Fig. 1). Total body anterior-posterior X-ray study and abdominal-thoracic cavity ultrasound were performed, and there were no emphysematous changes, aortic structural deformities or diaphragmatic abnormalities.

Cutis laxa was strongly suspected. Based on the absence of bone fragility, alopecia, and lipodystrophy, the diagnosis of progeria was excluded. The absence of severe cardiovascular or pulmonary manifestations made autosomal recessive cutis laxa type 1 unlikely, and the lack of growth and developmental delay excluded autosomal recessive cutis laxa types 2 and 3 as well as geroderma osteodysplasticum. Her gender made X-linked cutis laxa less likely and the lack of macrocephaly, alopecia and scoliosis led to the elimination of macrocephaly-alopecia-cutis laxa-scoliosis syndrome as a possible diagnosis, making autosomal dominant cutis laxa the most likely candidate (Table 1).

Blood samples from the patient, both parents and both siblings were obtained under consent. The last 5 exons of the elastin gene (*ELN*), where most cutis laxa mutations are localized, were subjected to mutational analysis by direct DNA sequencing. A single nucleotide deletion c.2184delT (ENST00000358929) was found in exon 30 (Fig. 2a). The parents and siblings of the patient were negative for the mutation, indicating that the proband was heterozygous for a *de novo* mutation. Although this mutation is novel, it is predicted to behave similarly to other previously described frameshift mutations within exon 30 of *ELN* (4, 7).

Mutations in *ELN* predominate as the underlying cause of autosomal dominant cutis laxa (4-6). Approximately 30% of patients with ADCL have been found to carry *de novo* dominant mutations in *ELN* (1, 2). A recent study reported 5 *de novo* *ELN* frame shift mutations in 6 ADCL-affected individuals, including a pair of identical twins (4). These findings highlight the importance of considering *de novo* dominant mutations in as a cause of disease in individuals with cutis laxa and a lack of family history.

Acknowledgments

We thank the patient and family members for their participation in the study. This work was funded in part by a National Heart, Lung and Blood Institute grant (HL090648).

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Figure 1.
Generalized skin laxity and wrinkling in the proband.

Table 1
Types of inherited cutis laxa and characteristics relevant to this case

Disorder [*]	Distinguishing Clinical Features	Gene
ADCL	Pulmonary and cardiovascular manifestations absent, milder or later onset	<i>ELN</i>
ARCL1A	Supravalvular aortic stenosis, lethal developmental emphysema	<i>FBLN5</i>
ARCL1B	Arterial tortuosity, lethal pulmonary hypertension, bone fragility	<i>FBLN4</i> <i>EFEMP2</i>
ARCL1C Urban-Rifkin-Davis syndrome	Severe gastrointestinal and urinary malformations, lethal developmental emphysema mild cardiovascular involvement	<i>LTBP4</i>
ARCL2A	Growth and developmental delay, abnormal glycosylation of serum proteins	<i>ATP6V0A2</i>
ARCL2B	Growth and developmental delay, triangular face, normal glycosylation	<i>PYCR1</i>
XLCL	Occipital exostoses, pili torti	<i>ATP7A</i>
ARCL3A DeBary syndrome	Growth and developmental delay, corneal clouding, athetoid movements	<i>ALDH18A1</i>
Geroderma osteodysplasticum	Bone fragility, short stature	<i>GORAB</i>
Macrocephaly alopecia cutis laxa scoliosis syndrome	Macrocephaly, alopecia, scoliosis	<i>RIN2</i>

* ADCL, autosomal dominant cutis laxa; ARCL, autosomal recessive cutis laxa; XLCL, X-linked cutis laxa;