Cutis laxa: A review

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Cutis laxa is a rare disorder of elastic tissue resulting in loose, redundant, hypoelastic skin. Both acquired and inherited forms exist, some of which have significant systemic manifestations. Here, we review the various forms of cutis laxa, with focus on the inherited forms. Recent molecular studies have provided many new insights into the causes of cutis laxa and revealed greater genetic heterogeneity than previously appreciated. (J Am Acad Dermatol 2012;66:842.e1-17.)

Key words: cutis laxa; elastic tissue; elastin; fibulin-4; fibulin-5; genodermatosis.

INTRODUCTION AND CLASSIFICATION OF CUTIS LAXA

Cutis laxa (CL) is characterized by abnormal elastic fibers resulting in loose, redundant, hypoelastic skin. Typically, the skin in CL can easily be pulled away from underlying tissue and only slowly returns to its original position. Unlike some conditions in the differential diagnosis, CL is not characterized by easy bruising or abnormal scarring. Redundant skin is often most noticeable on the neck, hands, and groin, but can also be seen on the face, creating a premature aging appearance.

CL may be inherited or acquired. Inherited forms include autosomal dominant CL (ADCL); autosomal recessive CL (ARCL)-I, -IIA, and -IIB; Urban-Rifkin-Davis syndrome (URDS); macrocephaly-alopecia-CL-scoliosis (MACS) syndrome; and arterial tortuosity syndrome (ATS) or X-linked CL (XLCL) (Table I). Although all of the inherited forms of CL are rare, ARCL has most commonly been reported, particularly ARCL-II.[1] Because of significant overlap among these types, precise clinical classification can be difficult.

Abbreviations used:

ACL:	acquired cutis laxa
ADCL:	autosomal dominant cutis laxa
ARCL:	autosomal recessive cutis laxa
ATS:	arterial tortuosity syndrome
CL:	cutis laxa
DBS:	De Barsy syndrome
EDS:	Ehlers-Danlos syndrome
MACS:	macrocephaly-alopecia-cutis laxa-scoliosis
PXE:	pseudoxanthoma elasticum
TGF:	transforming growth factor
URDS:	Urban-Rifkin-Davis syndrome
XLCL:	X-linked cutis laxa

ULTRASTRUCTURAL REVIEW OF ELASTIC FIBERS

The extracellular matrix of the dermis is composed of various elements including collagen, proteoglycans, laminin, fibrillin, and elastic fibers.[2] Elastic fibers comprise 2% to 4% of the skin's weight, and provide elasticity and resilience to the skin, lungs, and large blood vessels. Elastic fibers contain 2 ultrastructurally distinguishable constituents.[3] The amorphous core, so named because it lacks any repeating structure or banding pattern, is composed primarily of elastin and comprises 90% of the elastic fiber. The second component consists of microfibrils located around the periphery and embedded within the amorphous component. Microfibrils provide scaffolding for elastin deposition, and contain fibrillin, microfibril-associated glycoproteins, and other proteins.[4] Molecules such as emilins, collagen VIII

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(in vasculature), and fibulins are located at the elastic fiber interface and involved in elastin deposition onto the microfibrillar scaffold and elastic fiber-cell surface interactions (Fig 1).[4]

Elastin is synthesized and secreted as tropoelastin by fibroblasts and smooth muscle cells.[5] Tropoelastin is extensively cross-linked by the oxidation of lysyl residues, and contributes to the resiliency and insolubility of elastic fibers. This cross-linking is mediated by copper-dependent lysyl oxidase enzymes (Fig 1), which also cross-link collagen.[6] Most elastin is accumulated during fetal growth with little turnover after birth.

The dermal elastic complex is composed of elastic, elaunin, and oxytalan fibers.[5,7] In the papillary dermis, microfibril bundles, known as oxytalan fibers, are perpendicular to the dermoepidermal junction and not associated with elastin.[5,7] The reticular dermis contains elastic fibers in a complex interwoven pattern (Fig 2, *A*).[5,7] In the papillary dermis, elastic fibers are smaller, contain less elastin, and are called "elaunin fibers."[5,7] These fibers are oriented perpendicular to the dermoepidermal junction and connect elastic and oxytalan fibers.[5,7]

CAPSULE SUMMARY

- Cutis laxa (CL) is characterized by hypoelastic, loose skin and may be inherited or acquired, with variable systemic manifestations.
- This review summarizes recent genetic studies regarding inherited CL, which have shifted the historically clinical classification to a more molecular classification.
- It is important to distinguish between inherited CL and acquired CL, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and other conditions with lax or wrinkled skin.

HISTOPATHOLOGY OF CL

Because normal elastic tissue is invisible with hematoxylin-eosin staining, special elastic fiber stains such as orcein, Verhoeff-van Gieson, Weigert, or Hart elastin stains are needed to evaluate diseases of elastic tissue (Fig 2). In CL, microscopic findings include loss of elaunin fibers and sparse, fragmented elastic fibers in the reticular dermis. All types of CL show some elastic abnormalities and no findings are specific for individual types of CL. Mild abnormalities of elastic fibers are difficult to detect by histochemical staining. Thus, failure to demonstrate elastic fiber abnormalities does not necessarily exclude the diagnosis of CL.[1] Antibody staining for molecules known to be involved in CL may become a technique of choice to rapidly diagnose specific types.[8]

INHERITED FORMS OF CL

Autosomal dominant CL

Clinical findings. ADCL (MIM123700) may present from birth to early adulthood with predominantly skin findings.[9-11] Patients have loose, inelastic, redundant skin that typically worsens with age.[12,13] Characteristic facial features include an aged appearance, long philtrum, high forehead, large earlobes, and beaked nose (Fig 3, *A*).

Systemic manifestations can range from mild to severe, including cardiac and pulmonary complications, such as bronchiectasis and emphysema (Fig 3, *B*).[14-16] Many patients live normal life spans,[17] although some patients with ADCL experience more serious systemic problems including aortic aneurysms (Fig 3, *C*),[13] severe congenital lung disease, and pulmonary artery disease.[18] To prevent life-threatening complications, echocardiography and pulmonary function testing are recommended. There is marked intrafamilial variability of skin and other systemic manifestations (Fig 3, *D*). Approximately 30% of patients with ADCL have de novo mutations with no family history (Fig 3, *D*).

Etiology. Most ADCL mutations are frameshifts located in the last few exons of *ELN* and result in the replacement of the C-terminus of tropoelastin with an extended missense peptide sequence.[19] This mutant tropoelastin is deficient in fibrillin binding but has enhanced self-association properties.[20] Incorporation of mutant elastin into elastic fibers leads to increased compliance and reduced stiffness of tissues leading to increased transforming growth factor (TGF)-β signaling.[21]

ARCL type I

Clinical findings. Manifestations of ARCL-I (MIM219100) begin at birth with abnormal facies, redundant folds around the face and neck, and an aged appearance (Fig 4, *A* to *C*).[22-24] Compared with ADCL, ARCL-I is more often associated with severe systemic complications, especially emphysema and diaphragmatic defects, arterial tortuosity, and aneurysms (Fig 4, *D* and *E*).[23,25,26] Joint laxity and muscular hypotonia is also observed (Fig 4, *C*). Many patients die from pulmonary or cardiac complications in early childhood[23,25,26] Mental and motor development are usually normal.[22,27,28]

Etiology. Some cases of ARCL-I result from *FBLN5*[24,29,30] or *FBLN4/EFEMP2*[31-34] mutations, which encode fibulin-5 and fibulin-4, respectively. Fibulin-5

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