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

Table I. Types of cutis laxa and their manifestations

	ADCL	ARCL-IA	ARCL-IB	ARCL-IIA	ARCL-IIB	ARCL-III (DBS)	XLCL	ATS	URDS	MACS
Gene defect	*ELN*	*FBLN4*	*FBLN5*	*ATP6V0A2*	*PYCR1*	Unknown	*ATP7A*	*SLC2A10*	*LTBP4*	*RIN2*
Skin laxity	+++	++	+++	+++	+++	+++	+++	+++	+++	+++
Retrognathia	No	+++	No	+++	+++	No	No	+++	+++	No
Hypertelorism	No	+++	No	No	No	No	No	++	+++	No
Prominent ears	+++	+	+++	No	No	No	++	+	+	No
Emphysema	++	++	+++	No	No	No	No	No	+++	No
Aortic aneurysm	++	+++	No	+	No	No	No	++	No	No
SVAS	No	No	+++	No	No	No	No	No	No	No
Arterial tortuosity	No	+++	+	No	No	No	++	+++	No	No
Hernias	++	+++	+++	+++	++	++	+++	++	+++	+
Bladder diverticula	No	No	+	+	No	No	+++	No	+++	No
Mental retardation	No	No	No	+++	+++	+++	+++	No	No	No
Delayed motor development	No	+	+	+++	No	+++	+++	No	No	No
Postnatal growth delay	No	++	+	+++	+++	+++	+	No	+++	No
Congenital hip dislocation	No	+	No	+	+++	++	No	No	No	No
Patent anterior fontanelle	No	No	No	+++	No	++	++	No	++	No
Joint laxity	No	+	No	+++	+++	++	++	+++	++	+++
IUGR	No	No	No	+++	+++	+++	No	No	+	No
Hypotonia	No	+	No	+++	No	++	++	No	+++	No
Glycosylation defects	No	No	No	++	No	No	No	No	No	No
Athetoid movements	No	No	No	No	+	+++	No	No	No	No
Corneal opacification	No	No	No	No	+	+++	No	No	No	No
Occipital horns	No	No	No	No	No	No	+++	No	No	No
Short and broad clavicles	No	No	No	No	No	No	+++	No	No	No
Osteoporosis	No	No	No	No	++	No	++	No	No	+
Macrocephaly	No	No	No	No*	No*	No*	No	No	No	+++
Alopecia	No	No	No	No	No	No	No	No	No	+++
Scoliosis	No	No	No	++	+	++	++	++	No	+++
Gingival hyperplasia	No	No	No	No	No	No	No	No	No	+++

ADCL, Autosomal dominant cutis laxa; *ARCL*, autosomal recessive cutis laxa; *ATS*, arterial tortuosity syndrome; *DBS*, De Barsy syndrome; *IUGR*, intrauterine growth retardation; *MACS*, macrocephaly-alopecia-cutis laxa-scoliosis syndrome; *No*, not present; *SVAS*, supravalvular aortic stenosis; *URDS*, Urban-Rifkin-Davis syndrome; *XLCL*, X-linked cutis laxa; +, rare case reports; ++, multiple case reports; +++, common finding.
*May have microcephaly.

interacts with tropoelastin, fibrillin-1, and lysyl oxidase-like-1,[35-37] and facilitates the deposition of tropoelastin onto a scaffold of fibrillin-1 microfibrils.[4] Fibulin-4 is also required for mature elastic fiber formation, and can bind tropoelastin, lysyl oxidase, and fibrillin-1.[38] Fibulin-4 may help recruit lysyl oxidase, and regulate tropoelastin expression and TGF-β signaling.[34,38-40]

Some patients who are homozygous or compound heterozygous for mild *FBLN4* mutations show arterial tortuosity, stenosis, and aneurysms without CL.[34] Patients with *FBLN5* mutations commonly have supravalvular aortic stenosis.[24,29,30] In contrast, patients with FBLN4/EFEMP2 mutations do not have supravalvular aortic stenosis but can have aortic aneurysms.[31-34] Based on this distinct cardiovascular presentation, we recommend calling *FBLN4/EFEMP2*-related CL "autosomal recessive cutis laxa type IA" and calling *FBLN5*-related CL "autosomal recessive cutis laxa type IB."

Recently, homozygous *ELN* mutations were identified in a mild, unusual form of ARCL in a single consanguineous pedigree.[41]

ARCL type II

Clinical findings. There are 2 forms of ARCL-II: ARCL-IIA (MIM219200, Debre type) and ARCL-IIB (MIM612940). Unlike ARCL-IIB, ARCL-IIA may have defects of N- and O-glycosylation, which can be detected by isoelectric focusing analysis of serum proteins transferrin (N-glycosylation) and apolipoprotein CIII (O-glycosylation).[42] Other distinguishing features of ARCL-IIA include more frequent motor nervous system abnormalities, cardiovascular abnormalities, patent anterior fontanel, and female predominance. ARCL-IIA may be associated with

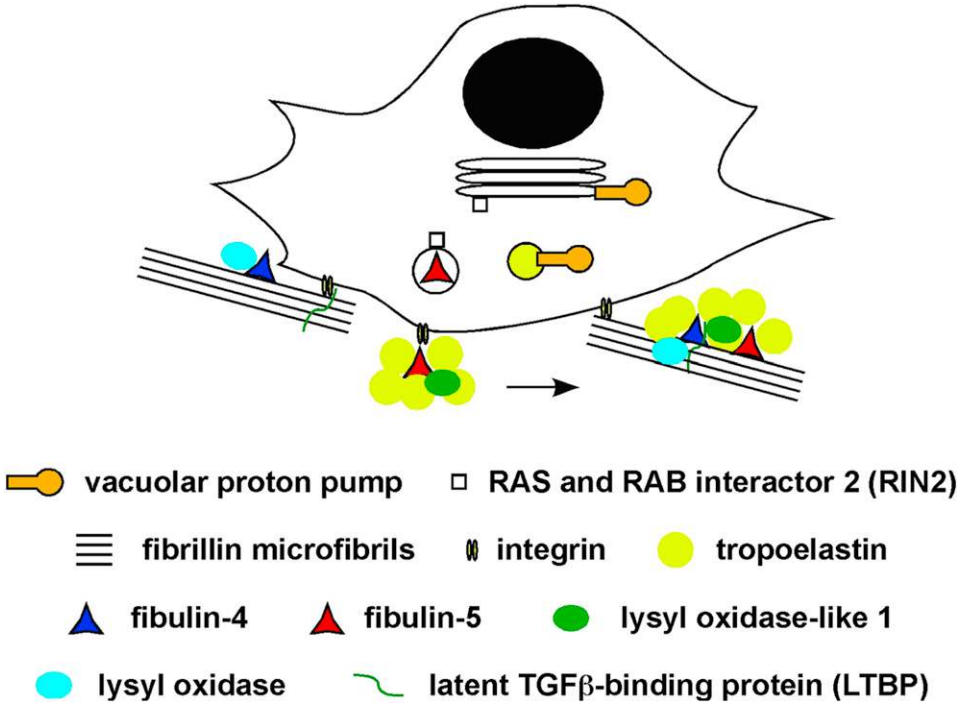

Fig 1. Working model of function of cutis laxa–related molecules. RIN2 and ATP6V0A2 (part of vacuolar proton pump) are located in Golgi apparatus and in secretory vesicles and may be necessary for proper sorting and efficient secretion of elastic fiber components. Extracellular assembly of elastic fibers is cell-directed process that occurs on template of microfibrils. Microassembly involves formation of globular assemblies containing tropoelastin, which are deposited and fashioned into long-range structures as part of macroassembly. Individual fibulins, latent transforming growth factor (*TGF*)-β binding proteins (*LTBP*), and lysyl oxidases may play role at different stages of this hierarchical process.[133]

severe central nervous system defects such as pachygyria (Fig 5), microcephaly, hypotonia, seizures, myopia, neurodegeneration, and Dandy-Walker malformation.[43,44]

Features of ARCL-IIB overlap those of geroderma osteodysplasticum, ARCL-IIA/wrinkled skin syndrome, and De Barsy syndrome (DBS). ARCL-IIB is characterized by wrinkled inelastic skin, especially on the dorsal acral surfaces and abdomen; hip dislocation; intrauterine and postnatal growth retardation; and developmental delay.[45-50] Distinctive features include osteoporosis and triangular dysmorphic facies, with progeroid appearance, bulbous nose, prognathism, hypotelorism, epicanthal folds, blue sclera, large ears, and microcephaly.[45-50]

Etiology. ARCL-IIA is a result of mutations in *ATP6V0A2*,[43,51] which encodes a proton pump in vesicles.[43,51] ATP6V0A2 mutations impair vesicular trafficking, causing tropoelastin accumulation in the Golgi.[43,51] ARCL-IIB is a result of mutations in *PYCR1*,[50] which encodes a mitochondrial enzyme involved in proline metabolism.[46,50]

ARCL type III (DBS)

Clinical findings. DBS is also known as ARCL-III (MIM219150), progeroid syndrome of De Barsy, or CL-corneal clouding-mental retardation syndrome.[52] Distinguishing features include bilateral corneal opacification, progeroid appearance, reduced subcutaneous fat, and athetoid movements early in life.[52-59]

Etiology. Although the genetic cause of DBS remains poorly defined, several publications identifying *ATP6V0A2* and *PYCR1* mutations in ARCL may have included some patients with DBS.[1,50,51,60]

Urban-Rifkin-Davis syndrome

URDS (MIM613177)—also known as CL with severe pulmonary, gastrointestinal, and urinary abnormalities—is a recently characterized autosomal recessive disorder caused by *LTBP4* mutations.[61] Respiratory complications are often fatal during infancy and include emphysema, atelectasis, tracheomalacia, and diaphragmatic hernia (Fig 6, *A* and *B*).[61] Gastrointestinal distension, diverticulosis, stenoses, and tortuosities are common (Fig 6, *C* and *D*).[61] Urinary tract abnormalities include hydronephrosis

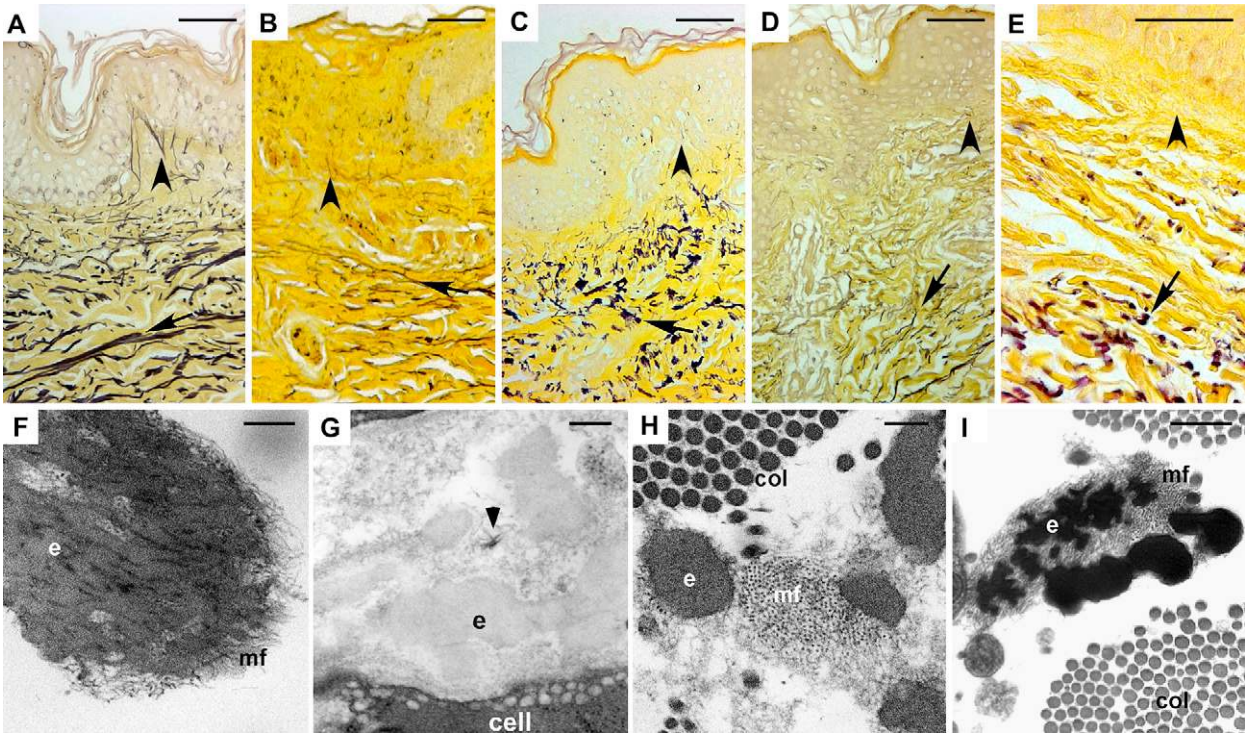

Fig 2. Histochemical and electron microscopic analysis of elastic fibers in cutis laxa (CL). Hart elastin (*e*) stain of skin sections from healthy donor **(A)**, patient with autosomal dominant CL (ADCL) and *elastin* mutation **(B)**, patient with autosomal recessive CL (ARCL)-I and *fibulin-5* mutation **(C)**, patient with ARCL-I and *fibulin-4* mutation **(D)**, and patient with Urban-Rifkin-Davis syndrome (URDS) and *LTBP4* mutation **(E)**. *Arrowheads* indicate elaunin fibers in papillary dermis, and *arrows* show elastic fibers in reticular dermis. Note paucity of elaunin fibers in CL skin **(B** to **E)** and either underdeveloped **(B** and **D)** or globular **(C** and **E)** elastin deposits in reticular dermis. Electron microscopic analysis of elastic fibers from healthy donor **(F)**, patient with ADCL and elastin mutation **(G)**, patient with ARCL-I and fibulin-5 mutation **(H)**, and patient with URDS and *LTBP4* mutation **(I)**. Note the close association of microfibrils (*mf*) with elastin in the control and elastin deposits devoid of microfibrils in all 3 CL samples. *col*, Collagen fibrils. Magnification bars: 50 μm **(A** to **D)**, 20 μm **(E)**, and 200 nm **(F** to **I)**. Taken with permission from following references: **(A** and **D)**,[31] **(B** and **G**, with permission of the BMJ Publishing Group**)**,[13] **(C**, **F**, and **H**, by permission of Oxford University Press**)**,[8] **(E** and **I)**.[61]

and diverticulosis (Fig 6, *E*).[61] *LTBP4* encodes the latent TGF-β binding protein 4, which helps localize the latent TGF-β complex to fibrillin microfibrils in the extracellular matrix.[61-65]

MACS syndrome

Basel-Vanagaite et al[66] described MACS syndrome in an Israeli-Arab family with age-dependent redundant skin, macrocephaly, down-slanting palpebral fissures, droopy eyelids, everted lips, gingival hypertrophy, dental anomalies, sparse hair, joint hypermobility, scoliosis, and high-pitched voice. There were no ocular, neurologic, or respiratory abnormalities.[66] Homozygous *RIN2* mutations were identified.[66] RIN2 plays a role in endocytic trafficking and serves as a guanine exchange factor for Rab5, a guanosine triphosphate that regulates membrane and protein trafficking.[66,67]

Arterial tortuosity syndrome

ATS (MIM208050) is an autosomal recessive condition characterized by elongation and tortuosity of major arteries and variable skin laxity.[68-74] Distinctive complications include vascular aneurysms, dissections, and stenoses.[70-72,74] Death may occur in early childhood,[71] although milder phenotypes have been described.[74]

ATS is caused by inactivating mutations in *SLC2A10*, which encodes GLUT10, a member of the glucose transporter family.[73,74] GLUT10 was recently shown to be localized in the mitochondria transporting dehydroascorbic acid, an oxidized form

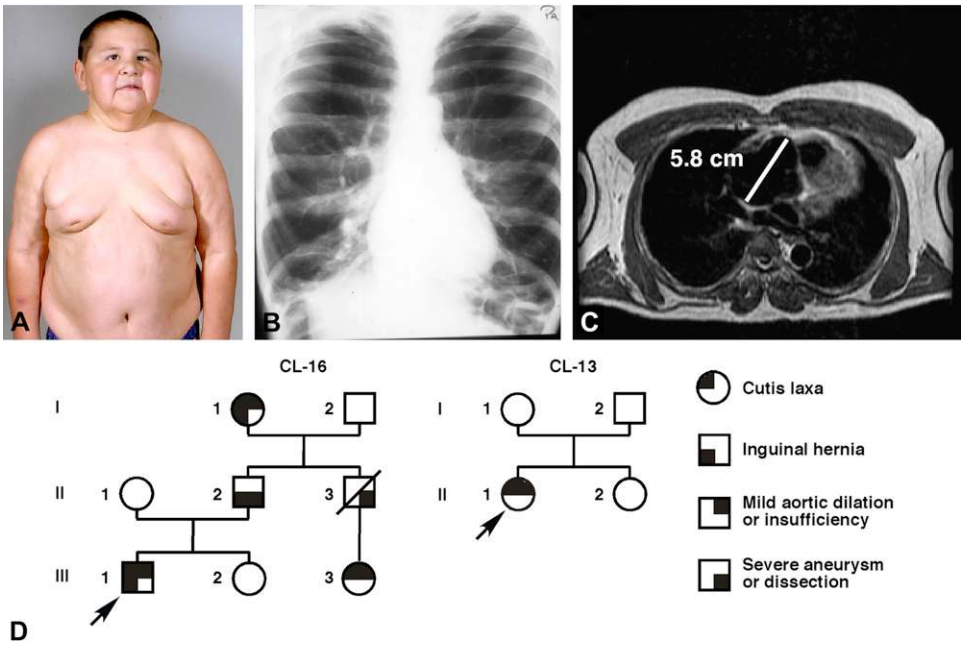

Fig 3. Manifestations and inheritance of autosomal dominant (AD) cutis laxa (*CL*). **A**, Photograph of patient at age 13 years. **B**, Chest X-ray of 51-year-old patient with severe emphysema shown by bilateral hyperexpanded lung fields (reprinted with permission[16]). **C**, Magnetic resonance imaging of aortic root in patient indicates aneurysm of 5.8 cm (*white bar*). **D**, Pedigrees of family with AD inheritance with variable expression (CL-16) and family with ADCL caused by de novo *elastin* mutation (CL-13) (reprinted with permission[13]).

of vitamin C.[75] Mutations lead to misregulation of glucose-responsive genes and activation of the TGF-β signaling pathway.[73] Clinically, ATS resembles Loeys-Dietz syndrome, which is caused by mutations in the TGF-β receptors and characterized by generalized arterial tortuosity, hypertelorism, bifid uvula, and cleft palate.[76]

XLCL (occipital horn syndrome)/Menkes disease

Clinical findings. XLCL (MIM304150) (Table II), also called occipital horn syndrome, was formerly classified as Ehlers-Danlos syndrome (EDS) type IX. XLCL and Menkes disease (MIM309400) are allelic, existing along a spectrum, with XLCL representing the mildest form.[77] Patients with XLCL demonstrate downward-pointing exostoses on the occipital bones, within the tendinous insertions of the sternocleidomastoid and trapezius muscles.[78] Patients with Menkes disease may also demonstrate occipital horns. Occipital horns become more prominent with age and can be palpated or found on radiographs.[79-81] Although patients with XLCL mainly have connective tissue problems, patients with Menkes disease have more severe neurologic defects, typically presenting at 2 to 3 months of age with developmental delay, hypotonia, seizures, and failure to thrive (Fig 7, *A*).[77] Menkes disease is often fatal by 4 years of age.

Patients with XLCL display hyperextensible wrinkled skin with droopy facies at birth.[77-79,82-87] With age, additional findings are seen: bladder diverticulae, urinary tract infections, inguinal hernias, orthostatic hypotension, diarrhea, and skeletal abnormalities.[77-79,82-87] Coarse, kinky hair with pili torti can be seen.[77-79,84,86]

Etiology. XLCL and Menkes disease are caused by mutations in *ATP7A*, which encodes a copper-transporting adenosine triphosphatase.[81] ATP7A functions in copper absorption from the small intestine, copper secretion from nonhepatic tissues, and copper transport across the blood-brain barrier.[77,88] Defective ATP7A results in functional copper deficiency, impairing copper-dependent enzymes such as lysyl oxidase, dopamine β-hydroxylase, and tyrosinase.[77,88] Intracellular copper levels are markedly elevated, except in the liver and brain.[84,89,90] In XLCL, the activity of lysyl oxidase is usually less than 6% of normal.[82,91]

Serum copper and ceruloplasmin levels are low to normal in patients with XLCL, while urine copper levels are elevated.[77] Ceruloplasmin is decreased because of decreased hepatic copper uptake.[92] Deficient dopamine β-hydroxylase results in a

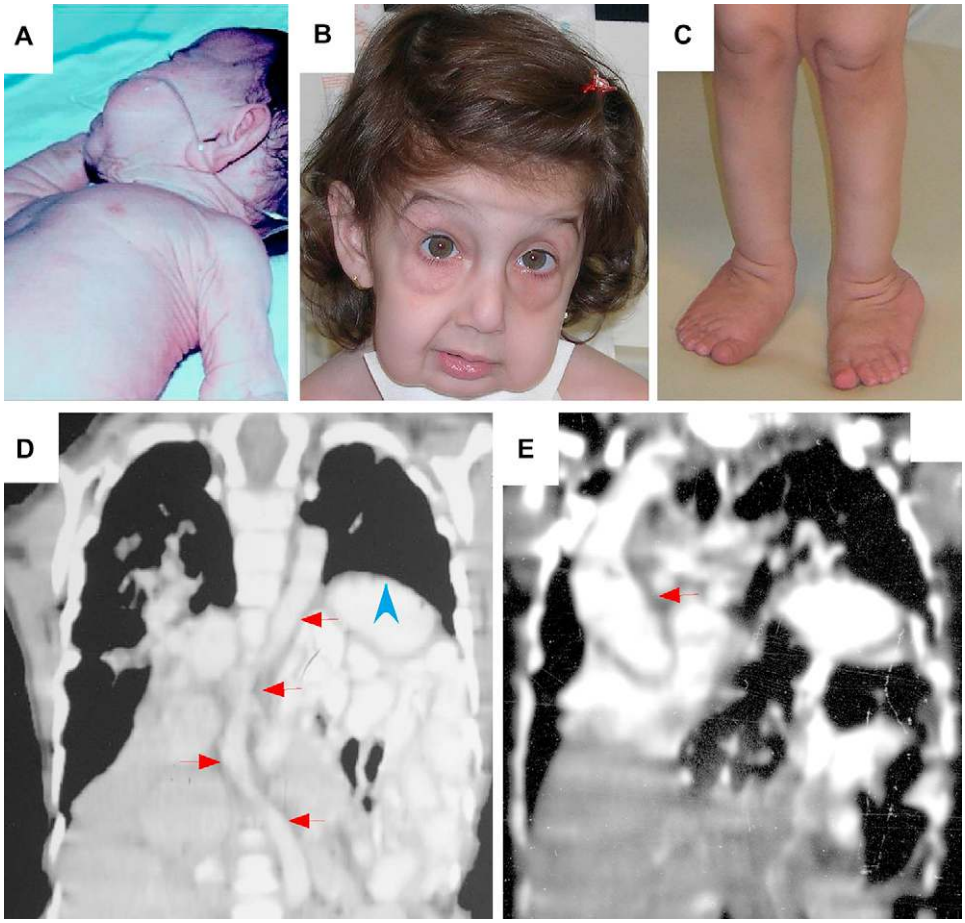

Fig 4. Manifestations of autosomal recessive cutis laxa type I. **A**, Redundant skin and large ears in patient with *fibulin-5* mutation (reprinted with permission[23]). **B**, Sagging cheeks and periorbital area, reverse-V eyebrows, long philtrum, and large ears in patient with *fibulin-4* mutation. **C**, Redundant skin and joint laxity on the legs of a patient with ARCL-I (reprinted with permission[31]). Computed tomography images of tortuous aorta (*arrows*) and diaphragmatic hernia (*arrowhead*) in patient with *fibulin-4* mutation **(D)** and aortic aneurysm (*arrow*) in patient with *fibulin-4* mutation **(E)**.

characteristic plasma neurochemical profile including a high ratio of dihydroxyphenylacetic acid to dihydroxyphenylglycol, and a high ratio of dopamine to norepinephrine.[93-95]

TREATMENT OF CL

Treatment for CL is limited. In some cases, especially in ARCL-II, the laxity improves with time.[12,96] Excision of lax skin is helpful, but repeated procedures are often required.[96,97] Unlike persons with related connective tissue disorders, patients with CL generally heal well after surgery. Botulinum toxin has been helpful in one case.[98] Early copper-histidine treatment may benefit patients on the XLCL-Menkes disease spectrum, especially newborns with some residual ATP7A function.[95,99,100]

ACQUIRED CL

Acquired CL (ACL) is a rare disorder with insidious onset that most often occurs in adulthood and may be associated with various conditions and drugs (Table III).[101-118] ACL often starts on the face and progresses caudally.[105] Some patients have systemic involvement with emphysema, intestinal diverticula, hernias, and vascular dilatations.[101] Earlier onset may be associated with decreased disease severity.[105] Half of cases are associated with an inflammatory dermatosis.[105,119]

Marshall syndrome is a type of ACL affecting young children and characterized by postinflammatory elastolysis after a neutrophilic dermatosis (Fig 7, *B*).[113,114,117] Patients with ACL may demonstrate low lysyl oxidase activity, high cathepsin G levels, and reduced alpha-1-antitrypsin, presumably contributing to decreased cutaneous elastin.[120] One patient

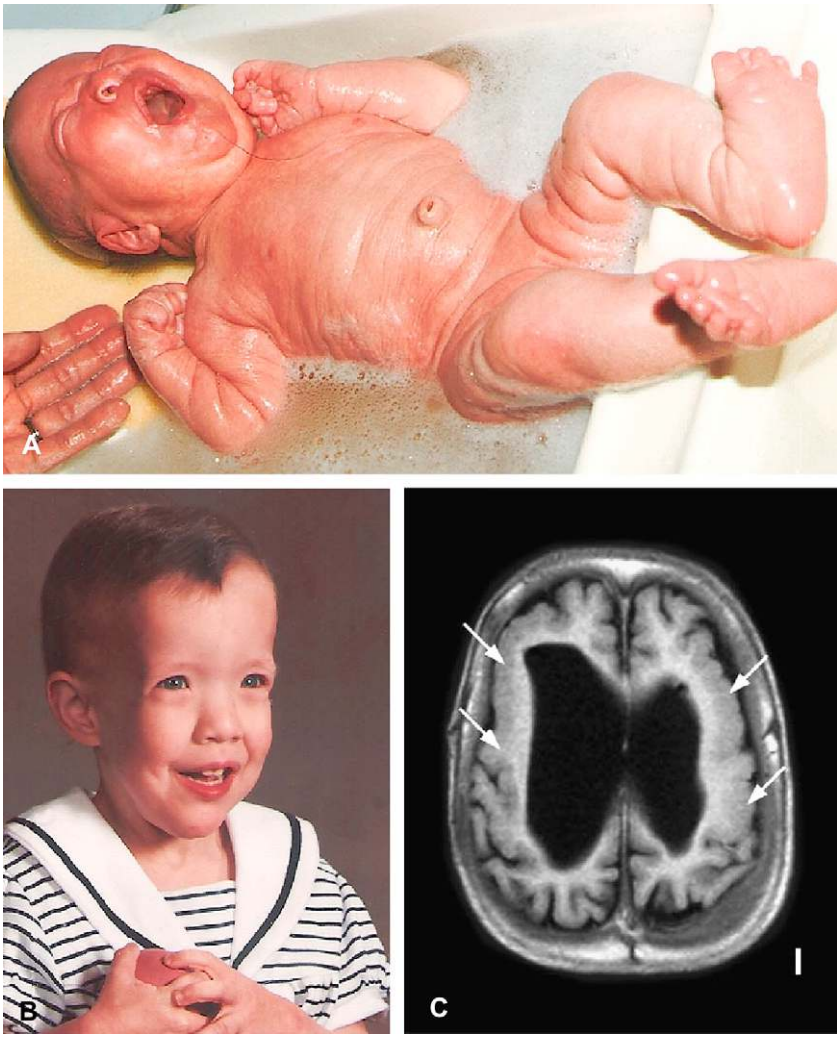

Fig 5. Manifestations of autosomal recessive cutis laxa type II. **A**, Redundant and wrinkled skin in patient. **B**, Craniofacial features include short nose, broad nasal bridge, down-slanting palpebral fissures, bitemporal narrowing, broad forehead, and retrognathia. **C**, Brain magnetic resonance imaging showing thickening of gray matter and pachygyria (image reprinted with permission[44]).

with ACL demonstrated missense mutations in *ELN* and *FBLN5*, suggesting that mild mutations in CL genes may increase susceptibility to inflammatory destruction of elastic fibers.[121] Histologically, elastic fibers are reduced in ACL, especially in the papillary dermis.[101]

OTHER SYNDROMES WITH LAX AND/OR WRINKLED SKIN

Other syndromes have lax or wrinkled skin as a predominant finding (Table IV).

DIFFERENTIAL DIAGNOSIS OF CL

Ehlers-Danlos syndrome

Unlike CL, EDS includes hyperelastic skin, which extends easily and snaps back into place after being stretched (Fig 7, *C*).[122] In EDS, wound healing is impaired, and broad, atrophic scars are characteristic (Table V).[122]

EDS is classified into 6 major subtypes, although other subtypes exist (eg, X-linked, fibronectin-deficient, and periodontitis types).[122,123] The classic and hypermobile subtypes comprise 90% of cases. Defects include collagen genes (*COL5A1*, *COL5A2*, *COL3A1*, *COL1A1*), enzymes (lysyl hydroxylase, procollagen N-peptidase), and tenascin-X.

Pseudoxanthoma elasticum

Like CL, pseudoxanthoma elasticum (PXE) (MIM264800) is characterized by abnormal elastic fibers (Table V). Skin lesions are often the initial finding, presenting in the second decade.[124] Patients

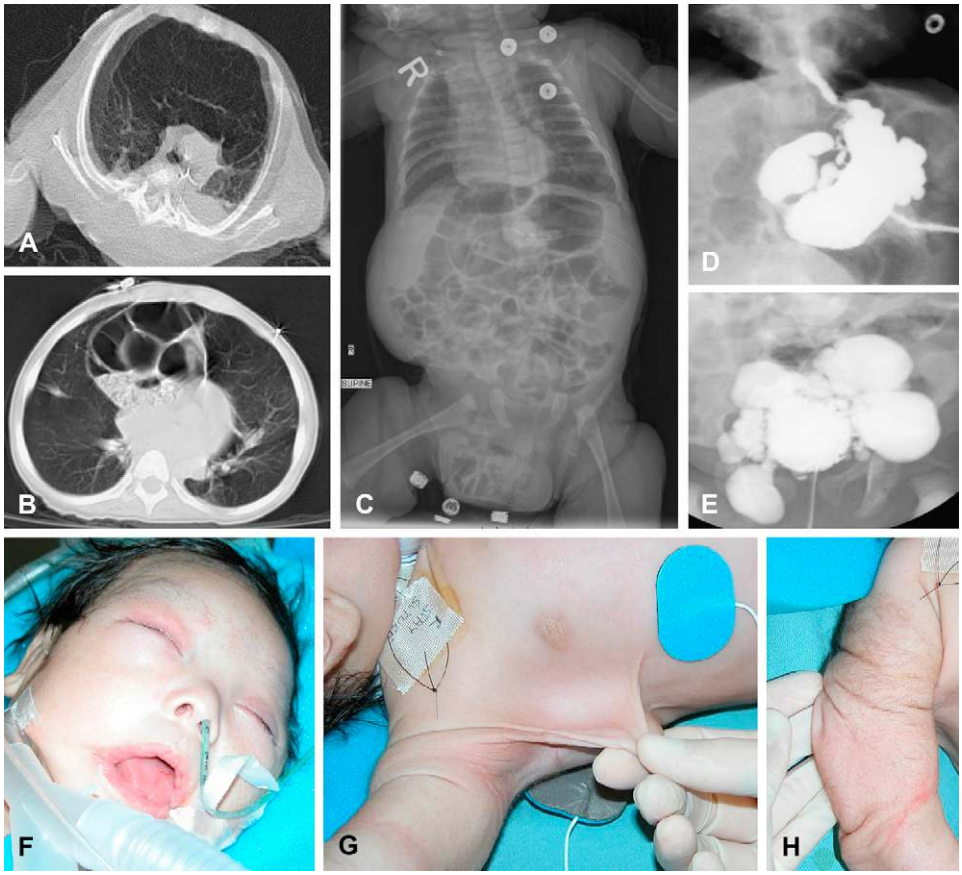

Fig 6. Manifestations of Urban-Rifkin-Davis syndrome. Chest computed tomography images showing hyperinflation of anterior and atelectasis of posterior lung **(A)** and parasternal diaphragmatic hernia and cystic and atelectatic changes in lung **(B)**. **C**, X-ray image of patient with dilated intestines, laterally displaced liver, and inguinal hernia. **D**, Stomach diverticula. **E**, Bladder diverticula. **F**, Craniofacial features include flattened mid face, wide nasal bridge, long philtrum, micrognathia, hypertelorism, periorbital fullness, and receding forehead. **G** and **H**, Redundant skin. Images reprinted with permission.[61]

demonstrate yellow, xanthoma-like plaques on the neck and flexural folds (Fig 7, *D*).[124-126] As PXE progresses, the skin loses elasticity. Other features include yellow papules on the inner lower lip and elastosis perforans serpiginosa.[124-126] Vascular, ocular, and cardiac manifestations can cause considerable morbidity and mortality.[125,126] Microscopy reveals clumped, fragmented, and calcified elastic fibers in the mid and reticular dermis.[127] PXE is caused by recessive inactivating mutations in *ABCC6*.[128-130]

A novel PXE-like entity was recently identified that consists of fragmented, calcified dermal elastic fibers, generalized skin laxity, and clotting factor deficiency (MIM610842).[131,132] Although cutaneous features are more severe than in PXE, ocular features are milder.[131,132] This autosomal recessive condition is caused by mutations in the gamma-glutamyl carboxylase enzyme, which facilitates carboxylation of gla-proteins including vitamin K–dependent clotting factors and matrix gla-proteins involved in protecting soft tissues from calcification.[131,132]

CONCLUSIONS

Recent studies have greatly contributed to our understanding, classification, and treatment of CL and related syndromes. In the last few years, *FBLN4*, *ATP6V0A2*, and *PYCR1* have been identified as causative genes in ARCL-I, ARCL-IIA, and ARCL-IIB, respectively. Moreover, URDS and MACS syndrome and their gene defects have been characterized. Functional insights from these genetic discoveries suggest that disruption of elastic fiber formation can occur at various levels in these syndromes ranging from secretion of

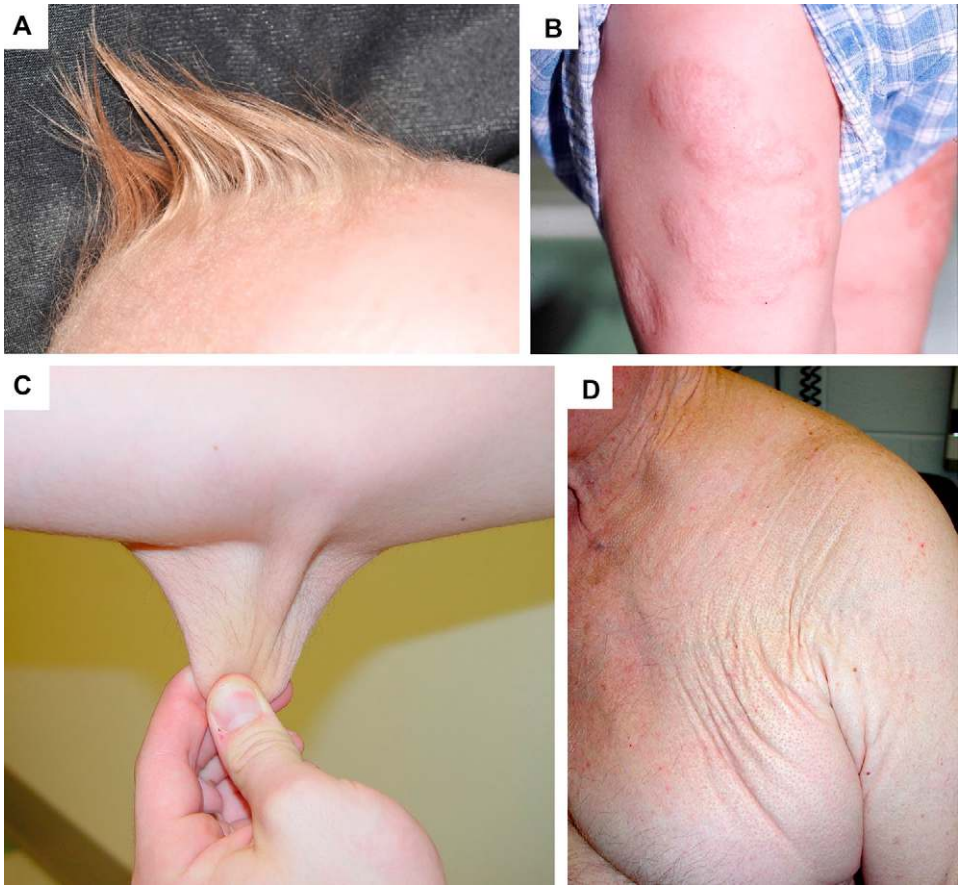

Fig 7. Phenotype in Menkes syndrome and other conditions with lax skin. **A**, Lightly pigmented, sparse hair and seborrheic dermatitis in 2-year-old boy with Menkes syndrome. **B**, Child with lax skin in areas of prior Sweet syndrome (Marshall syndrome). **C**, Hyperextensible skin in patient with Ehlers-Danlos syndrome. **D**, Thickened xanthoma-like plaques creating "plucked chicken"-like appearance in patient with pseudoxanthoma elasticum.

elastic fiber components (ARCL-IIA, and MACS syndrome) to assembly and cross-linking of the elastic fiber (ARCL-IA, ARCL-IB, URDS, and Menkes disease). Activation of the TGF-β signaling pathway is a common downstream consequence of CL gene mutations (ADCL, ARCL-IA, URDS). These advances have created new research questions, particularly regarding the pathogenesis of CL. It is unclear as to how secretory proteins regulate the sorting and trafficking of elastic fiber components and whether intracellular preassembly of these components occurs. It also remains to be understood as to how mitochondrial proteins such as PYCR1 and GLUT10 regulate extracellular matrix biogenesis and growth factor signaling. These molecular pathways provide exciting new targets for experimental therapeutic interventions in CL.

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Table II. X-linked cutis laxa (occipital horn syndrome)—associated abnormalities

Genetic defect—*ATP7A*; allelic to Menkes disease
Cutaneous abnormalities
Lax, inelastic skin
Abnormal facies
Dolichocephaly
Prominent forehead
High arched palate
Long philtrum
Hooked nose
Down-slanting palpebral fissures
Long neck
Protuberant ears
Coarse or kinky hair
Pili torti
Hypopigmented skin/hair
Loss of subcutaneous tissue
Prominent veins
Cardiovascular abnormalities
Elongation and kinking of carotid artery
Tortuosity of cerebral arteries
Splenic and hepatic artery aneurysms
Cardiac arrhythmias
Gastrointestinal abnormalities
Diarrhea
Gastric ulcer
Colon diverticulae
Pyloric stenosis
Musculoskeletal abnormalities
Occipital horns
Inguinal hernias
Short and broad clavicles
Joint hypermobility
Joint dislocations
Contractures of elbows and knees
Postnatal growth retardation
Pectus excavatum/carinatum
Pes planus
Genu valgum
Wormian bones
Osteopenia/osteoporosis
Coxa valga
Muscle atrophy
Patent anterior fontanelle
Gray enamel of teeth
Spicules on incisor teeth
Genitourinary abnormalities
Bladder diverticulae
Bladder rupture
Frequent urinary tract infections
Atonic bladder
Obstructive uropathy
Neurologic abnormalities
Mild intellectual deficiency
Emotional lability
Aggressive behavior
Motor development delay
Hypotonia
Hyperreflexia
Seizures
Spina bifida
Generalized muscle weakness
Ophthalmologic abnormalities
Prominent conjunctival vasculature

Continued

Table II. Cont'd

Table III. Reported associations with acquired cutis laxa

Medications
Isoniazid
Penicillin
Malignancies
Multiple myeloma
Lymphoma
Infections
Toxocara canis
Borrelia burgdorferi
Treponema pallidum
Onchocerca volvulus
Inflammatory diseases
Dermatitis herpetiformis
Sarcoidosis
Celiac disease
Sweet syndrome (Marshall syndrome)
Connective tissue diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Renal disease
Nephrotic syndrome
Enzyme disorder
Alpha-1 antitrypsin deficiency
Miscellaneous
Mastocytosis
Amyloidosis

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Table IV. Syndromes featuring lax or wrinkled skin

Syndrome	OMIM No.	Gene	Cutaneous findings	Other predominant findings
Wrinkly skin syndrome	278250	*ATP6V0A2*	Wrinkled skin especially on hands and feet, prominent venous pattern	MR, microcephaly, poorly developed skeletal musculature
Geroderma osteodysplasticum	231070	*SCYL1BP1*	Lax, nonhyperelastic skin most prominent over extremities; premature aging	Osteoporosis, joint laxity, AR inheritance
Cantu syndrome	114620		Hypertrichosis, wrinkled palms and soles	Delayed psychomotor development, short stature, large head, peculiar facies, cardiac abnormalities, mild MR, osteochondrodysplasia, AD inheritance
SCARF syndrome	312830		CL, webbed neck	Joint hyperextensibility, umbilical and inguinal herniae, skeletal abnormalities, craniosynostosis, ambiguous genitalia, retardation, facial abnormalities
Costello syndrome	218040	*HRAS* *H-ras oncogene*	CL most prominent over palms, soles, and neck; coarse craniofacial appearance; papillomata around mouth, nares, anus	Postnatal growth retardation, cardiovascular abnormalities, MR, AR inheritance
Williams syndrome (Williams-Beuren syndrome)	194050	Deletion of multiple genes in 7q11.23 including *ELN*	Premature wrinkling and aging, facial anomalies	AD inheritance, supravalvular aortic stenosis, multiple peripheral pulmonary artery stenosis, mental deficiency, short stature, dental malformations, infantile hypercalcemia
Patterson syndrome (pseudo-leprechaunism)	169170		Cutis gyrata of hands and feet, bronze hyperpigmentation	Hyperadrenocorticism, diabetes mellitus, bladder diverticuli, severe MR, major bony deformities
Hutchinson-Gilford syndrome	176670	*LMNA* *Lamin A*	Wrinkled, aged-looking skin; loss of subcutaneous fat; alopecia	Progeria, short stature, micrognathia, craniofacial disproportion, joint stiffness
Kabuki syndrome	147920		CL (rare), abnormal facies, dermatoglyphic abnormalities	MR, postnatal growth deficiency, skeletal anomalies, recurrent otitis media in infancy
Barber-Say syndrome	209885		Generalized hypertrichosis; ectropion of eyelids; redundant, lax skin	Ambiguous genitalia, macrostomia

Continued

Table IV. Cont'd

Syndrome	OMIM No.	Gene	Cutaneous findings	Other predominant findings
Congenital hemolytic anemia with emphysema and cutis laxa	235360		CL	Hemolytic anemia, emphysema, hemorrhagic necrosis of adrenals
Hereditary gelsolin amyloidosis (amyloidosis V)	105120	*GSN gelsolin*	Skin laxity	AD, corneal lattice dystrophy, cranial and peripheral polyneuropathy
Ablepharon macrostomia syndrome	200110		Redundant, lax skin; absence or hypoplasia of eyelids	Ambiguous genitalia, abnormal ears, rudimentary nipples, macrostomia
Lenz-Majewski hyperostotic dwarfism	151050		Thin, wrinkled, and atrophic skin; prominent cutaneous veins	Delayed closure of fontanelle, MR, progressive skeletal sclerosis with severe growth retardation
GAPO syndrome	230740		Redundant facial skin	Growth retardation, alopecia, pseudoanodontia, optic atrophy, facial dysmorphism, short stature, glaucoma

AD, Autosomal dominant; *AR*, autosomal recessive; *CL*, cutis laxa; *MR*, mental retardation; *OMIM*, Online Mendelian Inheritance in Man.

Table V. Differential diagnosis of cutis laxa

	Ehlers-Danlos syndrome (classic type)	Pseudoxanthoma elasticum
Gene	*COL5A1*; *COL5A2*; *COL1A1*	*ABCC6*
Inheritance	AD	AR
Pathogenesis	Abnormalities in collagen	Unknown
Cutaneous features	Skin hyperextensibility; widened atrophic scars; velvety skin; molluscoid pseudotumors; easy bruising	Yellowish papules coalescing to plaques on neck and flexural areas; lax skin with redundant folds in affected areas
Other cardinal features	Joint hypermobility; subcutaneous spheroids; muscular hypotonia; vascular abnormalities	Angioid streaks; cardiovascular disease
Histology	Large and irregular collagen fibers	Fragmented and calcified elastic fibers
Laboratory abnormalities	No routine laboratory testing	No routine laboratory testing
Disease course	Variable expressivity between affected patients; typically normal life span; morbidity from joint pain, early-onset arthritis, skin fragility	Range from mild manifestations to severe and occasionally lethal cardiovascular complications
Treatment	Physical therapy; disease and genetic counseling; no proven medical treatments	Genetic counseling; medical monitoring; no medical treatment available

AD, Autosomal dominant; *AR*, autosomal recessive.

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