

## Genetic Molecular Basis of Cutis Laxa and Surgical Management

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**Abstract:** *Cutis laxa is a rare condition involving the skin. There is loss of resilience, texture and quality of skin. The inherited form of cutis laxa is rather uncommon. Some 400 families have been reported in literature until now. The majority of the various subtypes of cutis laxa syndromes affect connective tissue development through structural gene defects. In most of the patients there is a strong histological evidence demonstrating an abnormal structure of elastin fibers and the associated extracellular matrix network of the skin.<sup>[1]</sup> Recently autosomal recessive cutis laxa syndrome type II (ARCL II; MIM 219200) emerged in the center of attention, due to the discovery of a unique underlying metabolic etiology.<sup>[2]</sup> This novel inborn error is a distinct form of the Congenital Disorders of Glycosylation (CDG). The defect is responsible for the phenotype in several patients diagnosed with the most common and viable form of the cutis laxa. Elastin gene mutations have been associated with a variety of phenotypes. Autosomal dominant cutis laxa (ACDL) is a rare disorder that presents with lax skin, typical facial characteristics, inguinal hernias, aortic root dilatation and pulmonary emphysema. In most of the patients, frameshift mutations are found in the 3' region gene of the elastin gene (exons 30-34) which result in C-terminally ended proteins. Menkes disease was the first metabolic disease reported with old-looking, wrinkled skin. Cutis laxa has recently been found in patients with abnormal Glycosylation. The discovery of the COG7 defect in patients with wrinkled, inelastic skin was the first genetic link with the Congenital Disorders of Glycosylation (CDG). Since then several inborn errors of metabolism with cutis laxa have been described with variable severity. These include P5CS, ATP6V0A2-CDG and PYCR1 defects. In spite of the evolving number of cutis laxa-related diseases a large part of the cases remain genetically unsolved. In metabolic cutis laxa syndromes the clinical and laboratory features might partially overlap, however there are some distinct, discriminative features.*

**Keywords:** *autosomal dominant cutis laxa, Cutis Laxa, Elastin, ELN, Phenotype, Genetic counseling*

### I. Introduction

The three primary components of dermal connective tissue layer are

- ✓ glycosaminoglycan gel
- ✓ elastic fibers
- ✓ Collagen.

They show progressive diminution or disruption. The total amount of ground substance composed of glycosaminoglycan and proteoglycans decreases with age. Elastic fibers are composed of at least two distinct proteins namely elastin and microfibrillar component. In adults, elastic fibers occupy 2% to 4% of the total volume of the dermis. The apparent role of elastic fibers is to maintain the waving of the collagen bundles; disruption of the elastic fibers results in loss of the physiological recoil and laxity of the skin. With the aging process, the finer oxytalan fibers that normally extend perpendicularly through the papillary dermis and into the epidermis are depleted or absent. Because so much collagen is lost, the elastic component can seem to be increased in older skin. These intrinsic degenerative changes begin at approximately age 30 years.

Skin resilience, texture, and quality are determined by the elastic fiber network of the dermis. Elastic fibers undergo minimal remodeling in adult life. Alterations to elastic fibers as the result of photo damage or several forms of cutis laxa produce a dramatic aging phenotype that cannot be remedied without surgical intervention.<sup>[3]</sup> Wound healing is reportedly unaffected in cutis laxa patients since the collagen metabolism is not affected.<sup>[4,5]</sup> Elastic fibers are among the last structural elements to appear at sites of injury in human skin, often taking years to reappear to any significant level.<sup>[6]</sup> In marked contrast, vascular and pulmonary tissue can respond rapidly to injury or mechanical stress by compensatory augmentation of the elastic fiber network arrangement.<sup>[7]</sup> Elastic fiber arrangement and abundance are more disturbed in circumstances of excess scarring. The early wound and scar are sites of intense matrix remodeling. Elastic fibers are structures designed for long-term stability. They are incompatible with rapid tissue turnover. Cutis laxa or elastolysis is a rare, inherited or acquired connective tissue disorder in which the skin becomes inelastic and hangs loosely in folds. The clinical

presentation and the mode of inheritance show considerable heterogeneity. Autosomal dominant, autosomal recessive and X-linked recessive patterns have been noted in inherited forms. A serine to proline amino acid substitution in the fibulin 5 (FBLN5) gene has been associated with problems in normal elastogenesis, resulting in a recessive form of cutis laxa in humans.<sup>[8]</sup> Autosomal recessive cutis laxa is a genetically heterogeneous condition.<sup>[9]</sup> A combined disorder of N- and O-linked Glycosylation has been described in children with congenital cutis laxa in association with severe central nervous system involvement, brain migration defects, seizures, and hearing loss. The X-linked form is currently classified in the group of copper transport diseases.

The precise cause is unknown, but it may be due to abnormal elastin metabolism resulting in markedly reduced dermal elastin content. Autosomal dominant congenital cutis laxa (ADCL) is genetically heterogeneous and shows clinical variability. Mutations in the elastin gene (ELN) have been described<sup>[10]</sup> In the inherited type and the acquired type, the internal organs are frequently involved. Cutis laxa may be preceded by an inflammatory rash or it may develop spontaneously.

## **II. Inheritance of cutis laxa**

Cutis laxa (CL) is inherited in many different ways, depending on the type of cutis laxa. There are autosomal dominant (AD), autosomal recessive (AR), and X-linked recessive (XLR) forms of inherited cutis laxa. In general, autosomal recessive forms of cutis laxa tend to be more severe than the autosomal dominant form. Cutis laxa can also be acquired by an individual who does not have one of the inherited forms of CL. The cause of the acquired form of CL is unknown, affects older adults following a severe illness with fever and rash.

These individuals may have damage to their connective tissue from some environmental cause such as exposure to certain medications, infections, cancer treatments, or secondary to an autoimmune disease such as lupus or rheumatoid arthritis.

## **III. Different types of Cutis Laxa**

Hyper extensible skin should also be distinguished from that observed in the cutis laxa syndromes and in De Barsy syndrome, in which the redundant skin hangs in loose folds and only returns very slowly to its former position. In these syndromes, the skin is not fragile, and wound healing is normal. The cutis laxa syndromes result from the loss or fragmentation of the elastic fiber network. They are variably associated with pulmonary, cardiac, arterial, and gastrointestinal abnormalities. Syndromic cutis laxa comprises a group of distinct but clinically overlapping disorders within which inelastic, wrinkled and redundant skin is a common feature (Mohamed et al. 2011). It is genetically heterogeneous and can be categorized according to autosomal dominant, recessive, or X-linked modes of inheritance. Within the category of autosomal recessive CL, Type I (ARCL1, MIM219100, 614437, 613177) is associated with pulmonary emphysema and poor prognosis. It is caused by mutations in ELN (MIM 130160), FBLN5 (MIM 604580), EFEMP2 (MIM 604633), or LTBP4 (MIM 604710) which encode secreted proteins that interact with the extracellular matrix (ECM)<sup>[11,12]</sup>

3.1.1 ARCL 1A or FBLN5-Related Cutis Laxa is characterized by cutis laxa, hernias, and pulmonary involvement such as emphysema from a young age. However, there is some variability in onset age for this symptoms. ARCL1A is caused by mutations in the FBLN5 gene.

3.1.2 ARCL 1B or FBLN4 (EFEMP2)-related cutis laxa is characterized by cutis laxa and the involvement of other body parts, namely the cardiovascular system (arterial problems such as tortuosity, aneurysms and stenosis), skeletal system (loose joints, long thin fingers, hernias, and bone fragility), and some distinctive features involving the face and head (small chin, high-arched palate, and widely spaced eyes). ARCL1B can be extremely severe resulting in death soon after birth, or it can be limited to only the blood vessel and facial features noted above. ARCL1B is caused by mutations in the FBLN4 (EFEMP2) gene.

3.1.3 ARCL 1C or LTBP4-Related Cutis Laxa is characterized by cutis laxa, as well as severe pulmonary, gastrointestinal, and urinary problems. ARCL1C is also known as Urban-Rifkin-Davis Syndrome (URDS). ARCL1C is caused by mutations in the LTBP4 gene.

3.2 Type II (ARCL2, MIM 219200, 612940) is associated with developmental delay, skeletal abnormalities and characteristic facies. ARCL2 can be caused by mutations in ATP6V0A2 (MIM 611716) which encodes a component of a Golgi-localized H<sup>+</sup>-ATPase (Kornak et al. 2008). A related disorder, Geroderma osteodysplasticum (GO, MIM231070) is caused by mutations in GORAB (MIM607983), which encodes a RAB6-interacting Golgin (Hennies et al. 2008).

3.2.1 ARCL2A or ATP6V0A2-related cutis laxa is caused by mutations in the ATP6V0A2 gene. Individuals with this type of cutis laxa have wrinkly skin over the entire body, which typically improves with age. Other

features in these children include an enlarged anterior fontanel, dislocation of the hips that is present at birth, hernias, and nearsightedness. Many individuals with this condition have severe developmental delay and seizures. Wrinkly Skin Syndrome, which causes wrinkled skin, small head size, and mental retardation, as well as muscle and skeletal problems, is caused by mutations in the same ATP6V0A2 gene.

3.2.2 ARCL2B or PYCR1-related cutis laxa is caused by mutations in the PYCR1 gene. Clinical features of this disease include cutis laxa leading to an aged appearance, growth delay, developmental delay, joint and skeletal problems, small head size, large forehead, triangular-shaped face, and large ears.

3.3 Type III ARCL, also known as De Barsy syndrome, is associated with cognitive impairment and motor deficits in addition to developmental delay and abnormal facies.

3.3.1 ARCL3 or De Barsy syndrome has overlapping features with ARCL2A and ARCL2B. It causes cutis laxa with growth retardation, moderate to severe mental retardation, cataracts, and loose joints. Other skin problems in addition to the cutis laxa contribute to an aged appearance. There are typically neither cardiovascular nor pulmonary symptoms. Some patients initially diagnosed with De Barsy syndrome were later found to have mutations in PYCR1 (ARCL2B), ATP6V0A2 (ARCL2A), or ALDH18A1. ARCL3A (MIM 219150) is caused by mutations in ALDH18A1 (MIM 138250) and

ARCL3B (MIM 614438) is caused by mutations in PYCR1 (MIM179035). These genes encode mitochondrial enzymes involved in proline synthesis,  $\Delta^1$ -pyrroline-5-carboxylatesynthase (P5CS) and pyrroline-5-carboxylate reductase 1, respectively (Baumgartner et al. 2000; Reversade et al. 2009). Mutations in PYCR1 are a more frequently reported cause of ARCL3 than mutations in ALDH18A1. PYCR1 mutations have been described as causing ARCL2B (MIM 612940) and GO as well as ARCL3B.<sup>[13]</sup>

Arterial Tortuosity Syndrome (ATS; MIM #208050) is a very rare autosomal recessive connective tissue disorder (CTD) characterized mainly by tortuosity and elongation of the large and medium-sized arteries, aneurysm formation and vascular dissection. ATS also has additional signs that are shared with other connective tissue disorders namely Cutis laxa, Dysmorphic facial features, cleft palate and abdominal hernias and skeletal anomalies.

### **3.4 Occipital Horn Syndrome (OHS)**

Usually begin within the first decade of life, and include cutis laxa, skeletal problems (bony growths on the back of the skull, loose joints, and short stature), and pulmonary (lung), cardiovascular (heart), and gastrointestinal problems such as emphysema, aneurysms, and hernias. There can also be muscle weakness, and intelligence ranges from low normal to mild mental retardation. OHS is a disorder of copper metabolism caused by mutations (changes) in the ATP7A gene.

3.5 Autosomal Dominant Cutis Laxa (ADCL): symptoms of ADCL begin anytime between birth and young adulthood. Symptoms include only cutis laxa in some of these patients. However, some families also exhibit specific facial features mainly involving the nose and ears, and cardiovascular and pulmonary problems such as aortic aneurysm and emphysema. Echocardiography and pulmonary function testing is recommended for these patients in order to identify heart and lung complications before they become life-threatening. Although most cases of ADCL result from mutations in the elastin (ELN) gene at least one family with ADCL has been found to have a mutation in the fibulin 5 (FBLN5) genes which is the cause of autosomal recessive cutis laxa type 1A (ARCL1A).

3.6 Geroderma Osteodysplasticum (GO): This type of cutis laxa occurs in babies or young children. These children have loose skin, mostly on the hands, feet, and stomach, as well as their face. Other features include a small jaw, hip dislocations, hernias, osteoporosis, fractures, and dwarfism. As with ARCL3, there are typically neither cardiovascular nor pulmonary symptoms. GO is also an autosomal recessive condition caused by mutations in the GORAB (SCYL1BP1) gene.

3.7 MACS Syndrome is macrocephaly (large head), alopecia (sparse hair), cutis laxa, and scoliosis. Other features include puffy eyelids, flat feet, loose joints, and short stature. MACS is an autosomal recessive disorder caused by mutations in the RIN2 gene.

3.8 Acquired Cutis laxa typically occurs in older adults. Although its cause is unknown, it has been observed in some individuals after certain environmental exposures, such as some medications, infections, or autoimmune diseases. Acquired cutis laxa is not inherited. However, one aspect of Dr. Urban's research is to determine whether some individuals may have a genetic susceptibility to developing cutis laxa after certain exposures.

### 3.9 Unknown or Undescribed Types of Cutis Laxa

Some patients cannot be assigned to any of the above types. These individuals may have mutations in genes that have not been identified as possible causes of cutis laxa.

## IV. Cardiac Involvement in Cutis Laxa

Not every person with cutis laxa will have cardiac involvement. Certain forms of cutis laxa have specific cardiac involvement namely aortic dilation and aneurysm, supravalvular aortic stenosis, arterial stenosis and arterial tortuosity. Echocardiogram detects these cardiac conditions. Aortic Aneurysm can happen if the elastic fibers in the aorta cause it to become stretched. Forms of cutis laxa that may involve aortic dilation are:

- FBLN4 (recessive type 1A)
- ELN (dominant type)

Acquired form of Pulmonary Artery Stenosis can be found in some people with URDS cutis laxa (Urban-Rifkin-Davis Syndrome) which is in the geneLTBP4. Supravalvular Aortic Stenosis (SVAS) is seen in people who have recessive type 1B (FBLN5) and dominant type (ELN). Arterial (or Vascular) tortuosity is seen in people who have recessive cutis laxa type 1A (FBLN4).Regurgitation is seen in people with dominant cutis laxa.

## V. Molecular Genetic Basis of Cutis Laxa

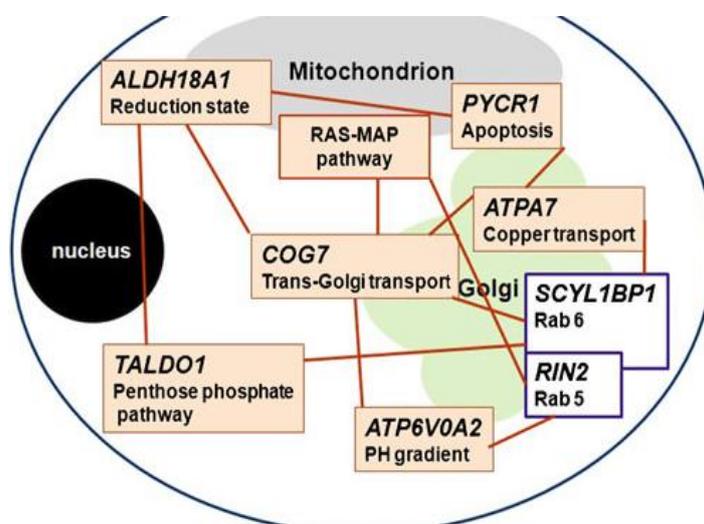


Figure 1: Genetic defects related to biochemical pathways or inborn errors of metabolism in patients with cutis laxa and their suggested pathomechanism

Cutis laxa can be inherited either in an X-linked, autosomal dominant, or autosomal recessive fashion. In autosomal dominant forms of cutis laxa (ADCL) mutations in genes encoding diverse components of the extracellular matrix are found. Autosomal recessive cutis laxa (ARCL) is more heterogeneous in terms of clinical manifestations and the underlying genetic defect. The disease spectrum can be subdivided into autosomal recessive cutis laxa types I and II. Autosomal recessive cutis laxa type I (ARCL1; OMIM 219100) is mainly characterized by severe systemic involvement including pulmonary emphysema, cardiovascular problems, and gastrointestinal manifestations. It is caused by mutations in Fibulin-5 (FBLN5) and EGF-containing fibulin-like extracellular matrix protein 2 gene (EFEMP2) (formerly fibulin-4 (FBLN4)), which results in a more severe phenotype. Another form of ARCL1 is caused by mutations in latent transforming growth factor-beta binding protein-4 (LTBP4). The mutations identified in ARCL2 affect intracellular gene products with functions in Golgi apparatus, endosomes, or mitochondria. Geroderma osteodysplastica (GO; OMIM 231070) resides at the milder end of the ARCL2 phenotypic spectrum. The condition is characterized by lax skin and wrinkles at the dorsa of hands and feet, spontaneous bone fractures due to osteoporosis, jaw hypoplasia and usually normal intellectual development. Hennies and colleagues described disease-causing mutations in GORAB, encoding a newly identified golgin and interaction partner of RAB6.

Another form of ARCL, wrinkly skin syndrome/autosomal recessive cutis laxa Debré type (ARCL2A; OMIM 219200), is due to mutations in ATP6V0A2. This gene encodes the V-type H<sup>+</sup>-ATPase subunit a2, which resides in the Golgi apparatus of skin fibroblasts and plays a role in Golgi membrane trafficking. Clinical hallmarks are generalized cutis laxa, delayed closure of the enlarged anterior fontanel, varying degree of

developmental delay, cobblestone-like brain malformations and occasionally a neurodegenerative phenotype with seizures and dementia. On biochemical evaluation a specific combined defect of N- and O-Glycosylation of serum proteins (CDG type II) is found in these patients. Macrocephaly, alopecia, cutis laxa, and scoliosis syndrome (MACS; OMIM 613075) is caused by mutations in RIN2. RIN2 is localized on endosomal vesicles and deficiency of this Rab5 effector protein causes a very rare phenotype with a typical facial coarsening, sagging chin, thick lips, mild alterations in serum protein Glycosylation and mental retardation.

At the most severe end of the ARCL spectrum resides the De Barsy syndrome (DBS; OMIM 219150), which has been also referred to as ARCL type III (ARCL3). The clinical hallmarks are a progeroid appearance with short stature, corneal clouding, hypotonia, a movement disorder and pronounced intellectual disability. The etiology of DBS is not fully understood. Mutations in ATP6V0A2 were described to cause a DBS-like phenotype in a patient with a severe form of ARCL2A. Recently, mutations in PYCR1 (ARCL2B; OMIM 612940) encoding the pyrroline-5-carboxylate reductase 1 were identified in patients initially diagnosed with DBS. In addition, ALDH18A1 (P5CS) mutations also cause a syndrome with severe progeroid and neurocutaneous features highly comparable with ARCL2B and the spectrum of De Barsy-like pathologies.

### **Genetics/Basic Defects**

Genetic heterogeneity is the hallmark of the genetic defects in Cutis Laxa

a. Autosomal recessive cutis laxa: the most common type

- Type I autosomal recessive cutis laxa: less frequent than type II
- Type II autosomal recessive cutis laxa

b. Autosomal dominant cutis laxa

c. X-linked recessive cutis laxa

- Previously called occipital horn syndrome
- At present, best termed as Ehlers-Danlos syndrome type IX 2.

### **Biochemical and molecular defects**

a. Autosomal recessive cutis laxa type I: molecular studies in a large consanguineous Turkish family demonstrated the presence of a homozygous missense mutation (T998C) in the fibulin-5 (FBLN5) gene, resulting in a serine-to-proline (S227P) substitution in the fourth calcium-binding epidermal growth factor-like domain of fibulin-5 protein

b. Autosomal dominant cutis laxa

- i. Can be caused by mutations in the elastin gene
- ii. Molecular heterogeneity cannot be excluded

c. X-linked recessive cutis laxa

- i. Caused by mutations in the ATP7A gene
- ii. Characterized by diminished activity of lysyl oxidase in the skin from affected males
- iii. Reduced serum copper and ceruloplasmin in affected males, suggesting that the lysyl oxidase deficiency may be secondary to a defect in copper metabolism
- iv. Now known to be allelic to Menkes disease  
(Atlas of Genetic diagnosis and Counseling, Harold Chen)

## **VI. Pathophysiology**

Cutis laxa is characterized by degenerative changes in the elastic fibers resulting in loose, pendulous skin. The skin is sagging, redundant, and stretchable, with reduced elastic recoil. The cutaneous findings of cutis laxa may be striking, but the elastic fiber network is even more important for pulmonary and cardiovascular function. In most cases of cutis laxa, the biochemical and molecular basis of the skin changes are unclear.

However, the histopathological analysis of the skin in several patients reveals alterations in the quantity or the morphology of elastin in which fragmentation or a loss of elastic fibers is present. Additionally, evidence of abnormal cross-linking of elastin exists in some patients with cutis laxa. Several factors such as copper deficiency, lysyl oxidase, elastases, and elastase inhibitors, contribute to abnormal elastin degradation. Lysyl oxidase, a copper-dependent enzyme, is important in the synthesis and cross-linking of elastin and collagen. Therefore, low levels of serum copper could lead to diminished elastin synthesis. However, only a few patients with cutis laxa have demonstrated low serum copper levels. Defective copper utilization may also lead to

decreased activity of elastase inhibitor alpha-1 antitrypsin, resulting in destruction of elastic fibers. Cultured dermal fibroblasts from patients with cutis laxa have shown increased elastolytic activity compared with healthy skin, and elastolysis has been suggested to result from increased elastase activity. Inflammatory cells or their mediators might damage elastic fibers. Polymorph nuclear leukocytes and macrophages release elastases, which could damage elastic fibers with subsequent phagocytosis. Excessive loss of cutaneous elastin in patients with cutis laxa appeared to be related to the combined effects of low lysyl oxidase activity with high levels of cathepsin G, an elastolytic protease. Variations in the morphology of the elastic fibers among skin samples from individuals with cutis laxa suggest that the biochemical basis of the disorder may be heterogeneous. Cutis laxa could result from mutations that affect the synthesis, the stabilization, or the degradation of elastic fibers.

FBLN5-Related cutis laxa is characterized by Cutis laxa, early childhood-onset of pulmonary emphysema, peripheral pulmonary artery stenosis and generalized connective tissue disorder such as inguinal hernias and hollow viscus diverticula of intestine and bladder. FBLN5-Related cutis laxa is inherited as an autosomal recessive (most common) or autosomal dominant manner. FBLN5 is the only gene in which pathogenic variants cause this disorder. Supravalvular aortic stenosis may also occur. In severe cases, death occurs in childhood due to pulmonary or cardiac complications.

In the past, cutis laxa subtypes were defined by clinical symptoms recently, they are separated based upon the molecular basis of the disorder i.e. muted genes. The following are the subdivisions of cutis laxa:

- ✧ Acquired cutis laxa
- ✧ ALDH18A1-related cutis laxa
- ✧ ATP6VOA2-related cutis laxa
- ✧ Autosomal dominant cutis laxa (ADCL)
- ✧ Autosomal recessive cutis laxa type 1A (ARCL1A)
- ✧ Autosomal recessive cutis laxa type 1B (ARCL1B)
- ✧ Autosomal recessive cutis laxa type 1C (ARCL1C)
- ✧ Autosomal recessive cutis laxa type 2A (ARCL2A)
- ✧ Autosomal recessive cutis laxa type 2B (ARCL2B)
- ✧ Autosomal recessive cutis laxa type 3
- ✧ Debre-type cutis laxa
- ✧ EFEMP2-related cutis laxa
- ✧ ELN-related cutis laxa
- ✧ Geroderma osteoplasticum
- ✧ LTBP4-related cutis laxa
- ✧ MACS syndrome
- ✧ PYCR1-related cutis laxa
- ✧ RIN2-related cutis laxa
- ✧ Urban-Rifkin-Davis Syndrome
- ✧ Wrinkly Skin Syndrome

## **VII. Histopathological Analysis**

Classical histological findings of cutis laxa are

- small and diminished elastic fibers
- deficient elastin with globular appearance
- tangled microfilaments,
- Excessive micro fibrils with abnormal orientation and fragmentation of the elastin structure.

The histopathological analysis of the skin reveals alterations in the quantity and morphology of elastin in which fragmentation or a loss of elastic fibers is present. Abnormal cross-linking of elastin exists in some patients with CL. Cultured dermal fibroblasts from patients with CL have shown increased elastolytic activity and elastolysis due to increased elastase activity. No specific histological abnormality is seen on routine stains with hematoxylin and eosin. On elastic fiber stains, all types of CL show a reduction in the number of elastic fibers throughout the dermis, with remaining fibers being shortened, clumped, granular, or fragmented. In severe cases, no elastic fibers may be present, but only fine, dust like particles scattered throughout the dermis can be seen. In cases preceded by an inflammatory eruption, such as urticaria or vesicles, the inflammatory infiltrate may be mononuclear (lymphocytes and histiocytes) or mixed, containing neutrophils. Electron microscopic examination reveals degenerative changes in the elastic fibers, which are variable from case to case. However, the most significant finding is the presence of electron-dense amorphous or granular aggregates that are irregularly distributed in the vicinity of the elastic fibers. Skin stained with Elastic stain, Dako Code AR163.

Verhoeff's hematoxylin method has been counterstained with Van Gieson's picro-fuchsin. The Elastic

stain is based on Verhoeff's technique optimized for the Artisan™ Staining System. Elastin fibers and elastic lamina in histological specimens are stained black, while remaining tissue elements are stained as follows: nuclei - blue/black, collagen - red, other tissue elements - yellow.

### VIII. Consultations

Cutis Laxa needs a Multi-specialty evaluation and management. Consult a dermatologist for diagnosis of cutis laxa. Consult an internal medicine specialist for evaluation of the underlying cause of cutis laxa and internal organ involvement. Cutis laxa increases the risk for aortic aneurysm; therefore, regular cardiac monitoring is recommended to avert a potentially fatal aortic rupture. Affected individuals may require a consultation with a pulmonologist. Consultation with a geneticist is suggested, particularly for patients presenting in childhood.

### IX. Case Report

A 30 years old male patient from West Bengal was referred from Dermatology Department for surgical management of cutis Laxa. The patient has been suffering from acquired cutis laxa for the past ten years. Skin Biopsy taken from the abdominal wall confirmed the diagnosis of Cutis Laxa by Verhoff Van Gieson (EVG) Stain method. The patient's main concern was his aged appearance for his chronological age. On examination the patient had an 'old man' appearance. Patient had prominent forehead creases. There were folds of lax and wrinkled skin over the face, neck, around eyelids chin region and arms. There is Sagging of the excess malar area skin and also over hanging of naso-labial folds seen in the patient. Sagging of ear lobules was noted and ear lobules were large measuring 6cm by 4cm. Skin could be easily stretched and showed delayed recoiling. Urticarial wheals were noticed. Ophthalmic examination showed Blepharochalasis and entropion of upper eyelid, folds of loose hanging skin over the upper eyelid. There were no hernias, no hyper-extensibility of joints. Oral cavity, genitalia, hair, nail and systemic examination was normal. Blood sugars, liver function tests, renal function tests, lipid profile, urine analysis were within normal limits. ANA was negative, no thyroid abnormality. Chest x-ray (PA), ECG, Echocardiography was normal. Serum IgE and AEC levels were elevated. Skin biopsy with special stain Verhoff-Van Gieson showed very few attenuated fragments of elastic fibers in dermis. There was no evidence of inflammation, morphological features was consistent with cutis laxa. The patient was treated with Tab. Levocetirizine 5mg and moisturizers by the Dermatologist and then referred to Plastic surgery department for surgical procedures.

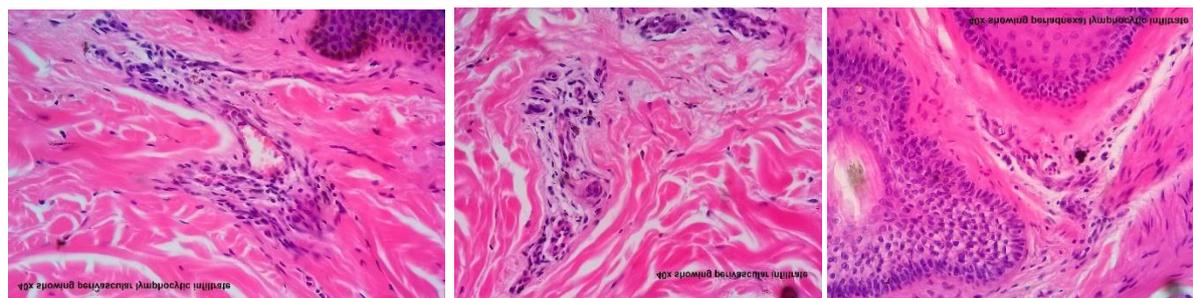


Fig.2:Pre-operative picture of the patient with bilateral sagging of the upper eyelids, nasolabial folds and ear lobule.





- A) Van Geison stain showing occasional elastic fibers in 40X
- B) Van Geison Stain showing decreased elastic fibers in 10X
- C) Scanner view displaying epidermis and dermis



- D) 40X showing Perivascular lymphocytic infiltration
- E) 40X showing Perivascular infiltrate
- F) 40X showing Perivascular Lymphocytic Infiltrate

Fig.3: Histopathological features of Cutis Laxa.

## X. Differential Diagnosis

### 10.1 Ehlers-Danlos syndrome

Cutis laxa is, in many ways, the opposite of Ehlers-Danlos syndrome. The main histopathological finding in cutis laxa is degeneration of the elastic fibers in the dermis. Affected persons have generalized loose skin in all regions of the body. Unlike the skin in cases of Ehlers-Danlos syndrome, the skin in cases of cutis laxa is inelastic and does not spring back into position after stretching. Hyper extensibility of the joints is absent, and skin healing progresses in a relatively normal manner. The defective elastic tissues present as a coarsely textured, drooping skin all over the body that is evident in the neonatal period. Affected infants frequently have associated aneurysms, pneumothorax, emphysema, congenital heart disease, and hernias.

### 10.2 Idiopathic Skin Laxity

In 1977, Shelley and Wood first described wrinkles as being caused by an idiopathic loss of mid-dermal elastic tissue, and similar findings have been noted by Rae and Falanga. Affected individuals typically show patchy areas of mid-dermal elastolysis manifesting externally as localized fine wrinkling without systemic abnormalities. The cause of the disorder is undetermined, although an antecedent inflammatory event such as urticaria is suspected

**10.3** Occipital horn syndrome is also known as X-linked Cutis laxa, characterized by generalized cutis laxa. This syndrome is caused by mutations in ATP7A gene. This gene is involved in copper metabolism.

**10.4** Pseudoxanthoma elasticum, PXE: PXE, is an inherited disorder caused by mutations in the ABCC6 transporter gene that affects connective tissue in some parts of the body. Elastic tissues in the body are deposited with calcium and other minerals. The affected skin of PXE is hyper elastic.

**10.5** There are many other disorders in which cutis laxa or similar skin symptoms occur. They include Arterial tortuosity syndrome, Cantu syndrome, SCARF syndrome, Noonan syndrome, LEOPARD syndrome, Williams Syndrome, Barber-Say syndrome and Cardiofaciocutaneous (CFC) syndrome.

## **XI. Surgical Procedures**

The patient was evaluated and planned for surgery. The surgical procedure was explained to the patient. Patient was informed about the complications, the possibility of recurrence of slackness of skin and the need for further tightening procedures was also explained. Bilateral Brow-lift, blepharoplasty and face-lift with SMAS plication was done. The post-operative period was uneventful. The patient was pleased with the outcome of the surgery in the immediate post-operative period. The patient was asked to refrain from smoking and also to avoid direct sunlight.



Fig.4: Early post-operative follow-up of the patient.

## **XII. Genetic Counseling**

### **1. Recurrence risk**

#### **(a) Patient's siblings**

i. Autosomal recessive cutis laxa: 25%

ii. Autosomal dominant cutis laxa: not increased unless a parent is affected

iii. X-linked recessive cutis laxa

- When the mother is a carrier: 50% risk of brother will be affected and 50% of sisters will be carriers
- When mother is not a carrier: the recurrence risk is low but greater than that for the general population because the risk of Germline mosaicism in mother is not known

#### **(b) Patient's offspring**

- Autosomal recessive cutis laxa: not increased unless the spouse is a carrier or affected
- Autosomal dominant cutis laxa: 50%
- X-linked recessive cutis laxa: Males with occipital horn syndrome will pass the disease-causing gene to all of their daughters and none of their sons

### **2. Prenatal diagnosis**

- DNA-based analysis on fetal DNA obtained from amniocentesis or Chorionic villus sampling (CVS) for the previously characterized disease-causing mutation
- Fetal sex determination for X-linked recessive cutis laxa (occipital horn syndrome)

### **3. Management of Cutis Laxa**

a. Supportive therapy: antibiotic prophylaxis for bladder infection

b. Surgery for bladder diverticula

c. Plastic surgery to improve the cosmetic appearance

- Serial excisions of the skin
- Blepharoplasty
- Rhytidectomy
- Rhinoplasty
- Shortening of the upper lip
- Earlobe reduction
- Neck lift
- Correction of lower eyelid laxity, epiphora, and upper eyelid ptosis.<sup>[14]</sup>

## **XIII. Discussion**

Review of the world literature suggests only around 400 affected families being reported and only a striking minority of these patients has a known underlying molecular cause. Autosomal recessive cutis laxa type 3A is caused by mutations in *ALDH18A1*, a gene encoding the mitochondrial enzyme  $\Delta$ 1-pyrroline-5-carboxylate synthase (P5CS). It is a rare disorder with only six pathogenic mutations and 10 affected individuals

from five families previously described in the literature. Psychological and emotional aspects of patients have to be addressed. Males and females are affected in equal numbers. Cutis laxa affects individuals of all races and every ethnic group. Dapsone is reported to control acute swelling, which may support a role for neutrophil elastase. Botulinum toxin has been used to improve facial cosmesis. Plastic surgical procedures are indicated in patients with laxity of skin. The possibility of recurrence must be informed and the patients may require repeated surgical procedures for laxity of skin.

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