Cutis Laxa: An Overview

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What is Cutis Laxa?

- Cutis Laxa (CL) is a rare disorder of connective tissue.
- Connective tissue, or the extracellular matrix, provides the structural framework for the skin, muscles, joints, blood vessels, and even the internal organs.
- There are many different types of CL, including an acquired form as well as several inherited forms.
- The involvement of which, if any, additional body systems depends on the type of CL and the genetic cause.
What are the Symptoms of CL?

- The most obvious symptom of cutis laxa is loose wrinkled skin, especially around the face, trunk, arms, and legs, which hangs in folds and causes an aged appearance.
- Additional body areas affected by CL can include the respiratory, skeletal, intestinal, and cardiovascular systems.
- The involvement of which, if any, additional body systems again depends on the type of CL.
How is Cutis Laxa Inherited?

- 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.
- Cutis laxa can also be acquired by an individual who does not have one of the inherited forms of CL.
Acquired Cutis Laxa

- Causes of the acquired form of CL are unknown, but it typically affects older adults following a severe illness with fever and rash.
- Individuals with Acquired CL may have incurred damage to their connective tissue from an environmental cause, such as:
  - Exposure to certain medications,
  - Infections,
  - Cancer treatments, or
  - From an autoimmune disease such as Lupus or Rheumatoid Arthritis.
- One aspect of our research is to determine if there is a genetic susceptibility to developing Acquired CL.
Inherited Cutis Laxa

• There are many forms of inherited CL
  • Occipital Horn Syndrome (OHS)
  • Autosomal Dominant Cutis Laxa (ADCL)
  • Autosomal Recessive Cutis Laxa (ARCL)
  • Gerodermia Osteodysplastica (GO)
  • MACS Syndrome

• Let’s review the (relatively) more common inherited forms of ADCL and ARCL.
Picture of Chromosomes
Autosomal Dominant Inheritance

- 2 copies of each gene
- 1 copy has a mutation that causes disease
- \( \frac{1}{2} \) or 50% chance of inheriting disease with each pregnancy.
- Equally affects males and females
- Disease is often seen in multiple generations
ADCL

- Symptoms begin anytime between birth and young adult.
- Symptoms include only cutis laxa in some of these patients.
- Some families also exhibit:
  - specific facial features mainly involving the nose and ears, and
  - blood vessel and lung problems (such as aortic aneurysm and emphysema).
- Echocardiography and pulmonary function testing (PFT) is recommended for these patients in order to identify heart and lung complications before becoming 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 single, possibly dominant, mutation in the Fibulin-5 (*FBLN5*) gene, which is the cause of autosomal recessive cutis laxa type 1B (ARCL1B).
**Autosomal Recessive Inheritance**

- 2 copies of each gene
- Both copies have to have a mutation to cause disease
- 1 copy of mutation = healthy carrier
- ¼ or 25% chance of inheriting disease with each pregnancy.
- Equally affects males and females
- Usually seen in only 1 family member or sometimes siblings
ARCL

- ARCL is divided into several subtypes, based both on specific symptoms and the gene which causes the condition.
- ARCL is divided into ARCL₁, ARCL₂, and ARCL₃, which are then further divided into additional subtypes, such as ARCL₁A, ARCL₁B, etc.
- Again, recessive forms of CL require TWO gene mutations, one inherited from each parent, and are therefore rarely seen in other family members, except occasionally in other siblings.
- There are 4 types of ARCL that we see the most.
ARCL1A

- Also called \textit{FBLN}_4 \textit{(EFEMP}_2\textit{)}-related cutis laxa
- ARCL1A is characterized by cutis laxa and the involvement of other body systems, namely
  - the cardiovascular system
    - arterial problems such as tortuosity, aneurysms, and stenosis
  - the skeletal system
    - loose joints, long thin fingers, hernias, and bone fragility
  - some distinctive features involving the face and head
    - small chin, high-arched palate, and widely spaced eyes
- ARCL1A can be extremely severe (fatal in infancy), or it can be limited to only the blood vessel and facial features noted above.
- ARCL1A is caused by mutations in the \textit{FBLN}_4 \textit{(EFEMP}_2\textit{)} gene.
ARCL1B

- Also called $FBLN_5$-Related Cutis Laxa
- Characterized by cutis laxa, hernias, and pulmonary involvement such as emphysema from a young age.
- There is a high degree of variability in onset age for these symptoms, even within the same family.
- ARCL1B is caused by mutations in the $FBLN_5$ gene.
ARCL1C

- Also called $LTBP_4$-Related Cutis Laxa
- 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 $LTBP_4$ gene.
ARCL2A

- Also called \textit{ATP6VoA2}-related cutis laxa
- Caused by mutations in the \textit{ATP6VoA2} 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 (soft spot on head), dislocation of the hips that is present at birth, hernias, decreased bone density, and nearsightedness.
- Some individuals with this condition have developmental delay and/or seizures.
How do you diagnose CL?

- Diagnosis of cutis laxa is typically made by physical examination of the skin by a physician such as a geneticist or dermatologist, often followed by a skin biopsy for microscopic analysis of the elastic fibers.
- The specific type of cutis laxa is determined by the associated features, family history information, electron microscopy, and in some cases can be confirmed by genetic testing.
- As you all here know, some patients with or without a clinically identified cutis laxa gene mutation choose to enroll in Dr. Urban's cutis laxa research study at the University of Pittsburgh.
Treatment/Management of CL

- After initial diagnosis, patients with cutis laxa typically receive cardiovascular and pulmonary evaluations, such as echocardiograms and lung function testing.
- Management of individuals with cutis laxa includes treatment of symptoms, such as
  - surgical repair of hernias
  - medications such as beta-blockers may be considered to prevent growth of aortic aneurysms, and
  - pulmonary emphysema is treated symptomatically
- Regular cardiovascular and pulmonary follow-up should begin at birth or immediately after diagnosis.
Treatment/Management of CL

- Environmental triggers should be avoided, such as
  - cigarette smoking, which can worsen emphysema, and
  - sun bathing, which can damage the skin
- Some individuals with cutis laxa may choose to undergo plastic surgery. Although the results from plastic surgery are typically very good, they may not be permanent, as the loose skin may reoccur.
Support Group and Resources

- **Cutis Laxa Internationale**: [http://asso.orpha.net/cutislax](http://asso.orpha.net/cutislax)
The goal of Cutis Laxa Internationale is to bring together individuals with cutis laxa from all over the world, and raise both awareness and money for cutis laxa research. Marie-Claude Boiteux, Chair of Cutis Laxa Internationale, can be reached by email at: **MCJLBoiteux@aol.com**.

- **Facebook - Cutis Laxa Group**: The cutis laxa facebook page is a forum for cutis laxa patients and their families to reach out to others facing similar medical issues. Susan Dickison Nunner is one of the administrators of the cutis laxa facebook page and can also be reached by email at: **smnuner@yahoo.com**.

- **University of Pittsburgh - Cutis Laxa Research Study**: [www.cutislaxa.pitt.edu](http://www.cutislaxa.pitt.edu)