Cutis laxa

Description

Cutis laxa is a disorder of connective tissue, which is the tissue that provides structure and strength to the muscles, joints, organs, and skin. Most cases are inherited, but some are acquired, which means they do not appear to be caused by genetic variations. While signs and symptoms of inherited cutis laxa are often noticeable in infancy or childhood, acquired cutis laxa typically appears later in life. This summary primarily describes inherited forms of cutis laxa.

The term "cutis laxa" is Latin for loose or lax skin, and this condition is characterized by skin that is sagging and not stretchy (inelastic). The skin often hangs in loose folds, causing the face and other parts of the body to have a droopy or wrinkled appearance. Extremely wrinkled skin may be particularly noticeable on the neck and in the armpits and groin.

Cutis laxa can also affect connective tissue in other parts of the body, including the heart, blood vessels, intestines, and lungs. The disorder can cause heart problems and abnormal narrowing, bulging, or tearing of critical blood vessels. Affected individuals may have soft out-pouchings in the lower abdomen (inguinal hernia) or around the belly button (umbilical hernia). Sacs called diverticula can also develop in the walls of certain organs, such as the bladder and intestines. During childhood, some people with cutis laxa develop a life-long lung disease called emphysema, which can make it difficult to breathe. Depending on which organs and tissues are affected, the signs and symptoms of cutis laxa can range from mild to life-threatening.

Researchers have described several different forms of cutis laxa. The forms are often distinguished by their pattern of inheritance: autosomal dominant, autosomal recessive, or X-linked. In general, the autosomal recessive forms of cutis laxa tend to be more severe than the autosomal dominant forms, although some people with autosomal dominant cutis laxa are severely affected. In addition to the features described above, people with autosomal recessive cutis laxa can have delayed development, intellectual disability, seizures, problems with movement, or eye or bone abnormalities.

The X-linked form of cutis laxa is often called occipital horn syndrome. This form of the disorder is considered a mild type of Menkes syndrome, which is a condition that affects copper levels in the body. In addition to sagging and inelastic skin, occipital horn syndrome is characterized by wedge-shaped calcium deposits in a bone at the base of the skull (the occipital bone), coarse hair, and loose joints.

Other rare conditions, including arterial tortuosity syndrome, geroderma osteodysplastica, and *RIN2* syndrome, are sometimes classified as cutis laxa-related conditions, because affected individuals can have loose, sagging skin. These conditions each have a particular pattern of signs and symptoms affecting different tissues and body systems.

Frequency

Cutis laxa is a rare disorder. More than 450 affected families worldwide have been reported.

Causes

Cutis laxa can be caused by variants (also known as mutations) in several genes. Autosomal dominant cutis laxa (ADCL), the most common form of the disorder, is primarily caused by variants in the *ELN* gene. Very rarely, *FBLN5* and *ALDH18A1* gene variants are associated with autosomal dominant forms of the disorder. Autosomal recessive cutis laxa (ARCL) can be caused by variants in the *FBLN5*, *EFEMP2*, *LTBP4*, *ATP6V0A2*, *PYCR1*, or *ALDH18A1* gene.

Many of the genes associated with autosomal dominant and autosomal recessive forms of cutis laxa are involved in the formation and function of elastic fibers, which are slender bundles of proteins that provide strength and flexibility to connective tissue throughout the body. Elastic fibers allow the skin to stretch, the lungs to expand and contract, and arteries to handle blood flowing through them at high pressure.

The major component of elastic fibers, a protein called elastin, is produced from the *ELN* gene. Other proteins involved in cutis laxa that have critical roles in the assembly of elastic fibers are produced from the *EFEMP2*, *FBLN5*, *LTBP4*, and *ATP6V0A2* genes. Variants in any of these genes disrupt the formation, assembly, or function of elastic fibers. A shortage of these fibers weakens connective tissue in the skin, arteries, lungs, and other organs. These defects in connective tissue underlie the major features of cutis laxa.

Two other genes involved in cutis laxa, *ALDH18A1* and *PYCR1*, provide instructions for making proteins that have important roles in cells. The proteins are critical in the formation of the protein building block (amino acid) proline, which is a key component of elastic fiber proteins. The proteins produced from the *ALDH18A1* and *PYCR1* genes are also important for the function of cell structures called mitochondria, which are the energy-producing centers of cells. Alterations in these genes appear to disrupt mitochondrial function, which could lead to the death of cells in the connective tissue that supports the skin. It is unclear if disruption of proline formation plays a role in the development of cutis laxa.

The X-linked form of cutis laxa, occipital horn syndrome, is caused by variants in the *ATP7A* gene. This gene provides instructions for making a protein that is important for regulating copper levels in the body. Variants in the *ATP7A* gene result inpoor distribution of copper to the body's cells. A reduced supply of copper can decrease the

activity of numerous copper-containing enzymes that are necessary for the structure and function of bone, skin, hair, blood vessels, and the nervous system. The signs and symptoms of occipital horn syndrome are caused by the reduced activity of these copper-containing enzymes.

Variants in the genes described above account for only a small percentage of all cases of cutis laxa. Variants in other genes, some of which have not been identified, can also cause the condition.

About 20 percent of cases of cutis laxa are acquired, which means they do not appear to be caused by gene variants. Acquired cutis laxa appears later in life and is related to the destruction of normal elastic fibers. The causes of acquired cutis laxa are unclear, although it may occur after an infection or an episode of inflammation in the skin (such as eczema or hives), or as a side effect of treatment with certain medications, such as those that remove copper from the body (copper chelating drugs).

Learn more about the genes associated with Cutis laxa

- ALDH18A1
- ATP6V0A2
- ATP7A
- EFEMP2
- ELN
- FBLN5
- LTBP4
- PYCR1

Additional Information from NCBI Gene:

- ATP6AP1
- ATP6AP2
- ATP6V1A
- ATP6V1E1

Inheritance

Cutis laxa can have an autosomal dominant, autosomal recessive, or X-linked recessive pattern of inheritance.

Autosomal dominant inheritance means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases of this form of the disorder are caused by variants in the *ELN* gene. Rarely, cases of cutis laxa resulting from *FBLN5* gene variants or *ALDH18A1* gene variants can have an autosomal dominant pattern of inheritance.

Variants in the *FBLN5*, *EFEMP2*, *LTBP4*, *ATP6V0A2, PYCR1,* and *ALDH18A1*genes can cause autosomal recessive forms of cutis laxa.Autosomal recessive inheritance means both copies of the gene in each cell have variants. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition.

Occipital horn syndrome has anX-linked recessive pattern of inheritance. It results from variants in the *ATP7A* gene, which is located on the X chromosome. The X chromosome is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a variant would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- Dermatolysis
- Dermatomegaly

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Cutis laxa with osteodystrophy (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268355/)
- Genetic Testing Registry: Cutis laxa, autosomal dominant (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268350/)
- Genetic Testing Registry: Cutis laxa, autosomal recessive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3665335/)
- Genetic Testing Registry: Cutis laxa, X-linked (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268353/)

Genetic and Rare Diseases Information Center

- Cutis laxa (https://rarediseases.info.nih.gov/diseases/6227/index)
- Occipital horn syndrome (https://rarediseases.info.nih.gov/diseases/4017/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Cutis laxa%22)

Catalog of Genes and Diseases from OMIM

- CUTIS LAXA, AUTOSOMAL DOMINANT 1; ADCL1 (https://omim.org/entry/123700)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IA; ARCL1A (https://omim.org/entry/219100)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIIA; ARCL3A (https://omim.org/entry/219150)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIA; ARCL2A (https://omim.org/entry/219200)
- OCCIPITAL HORN SYNDROME; OHS (https://omim.org/entry/304150)
- CUTIS LAXA, AUTOSOMAL DOMINANT 3; ADCL3 (https://omim.org/entry/616603)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IC; ARCL1C (https://omim.org/entry/613177)
- CUTIS LAXA, NEONATAL, WITH MARFANOID PHENOTYPE (https://omim.org/entry/614100)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIB; ARCL2B (https://omim.org/entry/612940)
- CUTIS LAXA, AUTOSOMAL DOMINANT 2; ADCL2 (https://omim.org/entry/614434)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IB; ARCL1B (https://omim.org/entry/614437)
- CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIIB; ARCL3B (https://omim.org/entry/614438)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Cutis+Laxa%5BMAJR%5D%29+AND+%28cutis+laxa%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

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