Lacrimo-Auriculo-Dento-Digital Syndrome

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Lacrimo-auriculo-dento-digital (LADD) syndrome is a genetic disorder that mainly affects the eyes, ears, mouth, and hands. LADD syndrome is characterized by defects in the tear-producing lacrimal system (lacrimo-), ear problems (auriculo-), dental abnormalities (dento-), and deformities of the fingers (digital).

genetic conditions

1. Introduction

The lacrimal system consists of structures in the eye that produce and secrete tears. Lacrimal system malformations that can occur with LADD syndrome include an underdeveloped or absent opening to the tear duct at the edge of the eyelid (lacrimal puncta) and blockage of the channel (nasolacrimal duct) that connects the inside corner of the eye where tears gather (tear sac) to the nasal cavity. These malformations of the lacrimal system can lead to chronic tearing (epiphora), inflammation of the tear sac (dacryocystitis), inflammation of the front surface of the eye (keratoconjunctivitis), or an inability to produce tears.

Ears that are low-set and described as cup-shaped, often accompanied by hearing loss, are a common feature of LADD syndrome. The hearing loss may be mild to severe and can be caused by changes in the inner ear (sensorineural deafness), changes in the middle ear (conductive hearing loss), or both (mixed hearing loss).

People with LADD syndrome may have underdeveloped or absent salivary glands, which impairs saliva production. A decrease in saliva leads to dry mouth (xerostomia) and a greater susceptibility to cavities. Individuals with LADD syndrome often have small, underdeveloped teeth with thin enamel and peg-shaped front teeth (incisors).

Hand deformities are also a frequent feature of LADD syndrome. Affected individuals may have abnormally small or missing thumbs. Alternatively, the thumb might be duplicated, fused with the index finger (syndactyly), abnormally placed, or have three bones instead of the normal two and resemble a finger. Abnormalities of the fingers include syndactyly of the second and third fingers, extra or missing fingers, and curved pinky fingers (fifth finger clinodactyly). Sometimes, the forearm is also affected. It can be shorter than normal with abnormal wrist and elbow joint development that limits movement.

People with LADD syndrome may also experience other signs and symptoms. They can have kidney problems that include hardening of the kidneys (nephrosclerosis) and urine accumulation in the kidneys (hydronephrosis), which can impair kidney function. Recurrent urinary tract infections and abnormalities of the genitourinary system can

also occur. Some people with LADD syndrome have an opening in the roof of the mouth (cleft palate) with or without a split in the upper lip (cleft lip). The signs and symptoms of this condition vary widely, even among affected family members.

2. Frequency

LADD syndrome appears to be a rare condition; at least 60 cases have been described in the scientific literature.

3. Causes

Mutations in the *FGFR2*, *FGFR3*, or *FGF10* gene can cause LADD syndrome.

The *FGFR2* and *FGFR3* genes provide instructions for making proteins that are part of a family called fibroblast growth factor receptors. The *FGF10* gene provides instructions for making a protein called a fibroblast growth factor, which is a family of proteins that attaches (binds) to fibroblast growth factor receptors. The receptors are located within the membranes of cells, where they receive signals that control growth and development from growth factors outside the cell. The signals triggered by the *FGFR2*, *FGFR3*, and *FGF10* genes appear to stimulate cells to form the structures that make up the lacrimal glands, salivary glands, ears, skeleton, and many other organs.

Mutations in the *FGFR2*, *FGFR3*, or *FGF10* gene alter the proteins produced from these genes and disrupt the signaling within cells. As a result, cell maturation and development is impaired and the formation of many tissues is affected, leading to the signs and symptoms of LADD syndrome.

3.1. The genes associated with Lacrimo-auriculo-dento-digital syndrome

- FGF10
- FGFR2
- FGFR3

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means a mutation in one copy of the *FGFR2*, *FGFR3*, or *FGF10* gene in each cell is sufficient to cause the disorder.

In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

5. Other Names for This Condition

- lacrimoauriculodentodigital syndrome
- LADD syndrome
- Levy-Hollister syndrome

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