Terminal Osseous Dysplasia

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Terminal osseous dysplasia is a disorder primarily involving skeletal abnormalities and certain skin changes. It is a member of a group of related conditions called otopalatodigital spectrum disorders, which also includes otopalatodigital syndrome type 1, otopalatodigital syndrome type 2, frontometaphyseal dysplasia, and Melnick-Needles syndrome. In general, these disorders involve hearing loss caused by malformations in tiny bones in the ears (ossicles), problems in the development of the roof of the mouth (palate), and skeletal abnormalities involving the fingers or toes (digits), although not every condition in the spectrum has all of these features.

genetic conditions

1. Introduction

Terminal osseous dysplasia occurs only in females; males with the condition do not survive to birth. The skeletal abnormalities in people with this condition typically include permanently bent fingers and toes (camptodactyly) and underdevelopment (hypoplasia), shortening, or fusion of the bones in the wrists and hands. The outer layer of bone (cortex) in other parts of the skeleton may be abnormal, and some affected individuals have bowed arms or legs or are shorter than their peers.

Skin abnormalities are also common in terminal osseous dysplasia. Many individuals with the condition have dark patches of skin on their face, often near the temples. In addition, affected infants commonly develop noncancerous (benign) tumors called fibromas on their fingers or toes. The tumors may reappear after being removed, but they tend to go away and stop reoccurring in childhood.

Other signs and symptoms can occur in people with terminal osseous dysplasia, including extra oral frenulae, which are the thin pieces of tissue in the mouth that connect the inside of the lips to the gums; widely spaced eyes; and hair loss. Some people with this condition have an abnormality in the muscular wall (septum) that separates the right and left sides of the heart (cardiac septal defect).

2. Frequency

Terminal osseous dysplasia is a rare disorder. Its prevalence is unknown.

3. Causes

Terminal osseous dysplasia is caused by a mutation in the *FLNA* gene. This gene provides instructions for producing the protein filamin A, which helps build the network of protein filaments (cytoskeleton) that gives structure to cells and allows them to change shape, move, and interact with neighboring cells. Filamin A attaches (binds) to another protein called actin, and helps the actin form the branching network of filaments that make up the cytoskeleton. Filamin A also links actin to many other proteins to perform various functions within the cell.

The *FLNA* gene mutation that causes terminal osseous dysplasia changes a single DNA building block (nucleotide), which alters the way the blueprint for making the filamin A protein is put together. The version of the protein made using this blueprint is abnormally short. Researchers suspect the altered protein may not be able to interact with other molecules normally. It is thought that the inability to bind to other proteins disrupts important processes involved in skeletal development and cell growth, leading to the bone and skin abnormalities characteristic of terminal osseous dysplasia.

3.1 Learn more about the gene associated with Terminal osseous dysplasia

- FLNA

4. Inheritance

Terminal osseous dysplasia is inherited in an X-linked dominant pattern. The *FLNA* gene is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell is thought to be lethal very early in development.

Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, so that each X chromosome is active in about half the body's cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation.

In terminal osseous dysplasia, skewed X-inactivation allows for the normal copy of the *FLNA* gene to be active (expressed) and leads to the production of the normal filamin A protein in most cells in affected females. Researchers suspect that having some normal filamin A protein is why females with the gene mutation survive to birth, whereas males do not.

A feature of X-linked conditions is affected girls cannot inherit the mutation from their fathers. In some cases, mothers of daughters with terminal osseous dysplasia are unaffected or have only mild symptoms. Researchers suspect that unaffected mothers have the mutation only in their egg cells, which is a phenomenon known as

germline mosaicism. Mildly affected mothers may also have the mutation in some, but not all, of their body cells, which is known as somatic mosaicism.

5. Other Names for This Condition

- DCD
- digitocutaneous dysplasia
- terminal osseous dysplasia and pigmentary defect syndrome
- terminal osseous dysplasia and pigmentary defects
- terminal osseous dysplasia with pigmentary defects
- terminal osseous dysplasia-pigmentary defects syndrome
- TODPD

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