Trichothiodystrophy

Description

Trichothiodystrophy, commonly called TTD, is a rare inherited condition that affects many parts of the body. The hallmark of this condition is hair that is sparse and easily broken.

In people with trichothiodystrophy, tests show that the hair is lacking sulfur-containing proteins that normally gives hair its strength. A cross section of a cut hair shows alternating light and dark banding that has been described as a "tiger tail."

The signs and symptoms of trichothiodystrophy vary widely. Mild cases may involve only the hair. More severe cases also cause delayed development, significant intellectual disability, and recurrent infections; severely affected individuals may survive only into infancy or early childhood.

Mothers of children with trichothiodystrophy may experience problems during pregnancy including pregnancy-induced high blood pressure (preeclampsia) and a related condition called HELLP syndrome that can damage the liver. Babies with trichothiodystrophy are at increased risk of premature birth, low birth weight, and slow growth. Most children with trichothiodystrophy have short stature compared to others their age.

Intellectual disability and delayed development are common in people with trichothiodystrophy, although most affected individuals are highly social with an outgoing and engaging personality. Some people with trichothiodystrophy have brain abnormalities that can be seen with imaging tests. A common neurological feature of this disorder is impaired myelin production (dysmyelination). Myelin is a fatty substance that insulates nerve cells and promotes the rapid transmission of nerve impulses.

Trichothiodystrophy is also associated with recurrent infections, particularly respiratory infections, which can be life-threatening. People with trichothiodystrophy may have abnormal red blood cells, including red blood cells that are smaller than normal. They may also have elevated levels of a type of hemoglobin called A2, which is a protein found in red blood cells. Other features of trichothiodystrophy can include dry, scaly skin (ichthyosis); abnormalities of the fingernails and toenails; clouding of the lens in both eyes from birth (congenital cataracts); poor coordination; and skeletal abnormalities including degeneration of both hips at an early age.

About half of all people with trichothiodystrophy have a photosensitive form of the disorder, which causes them to be extremely sensitive to ultraviolet (UV) rays from sunlight. They develop a severe sunburn after spending just a few minutes in the sun. However, for reasons that are unclear, they do not develop other sun-related problems such as excessive freckling of the skin or an increased risk of skin cancer. Many people with trichothiodystrophy report that they do not sweat.

Frequency

Trichothiodystrophy has an estimated incidence of about 1 in 1 million newborns in the United States and Europe. About 100 affected individuals have been reported worldwide.

Causes

Variants (also called mutations) in at least 10 genes have been found to cause trichothiodystrophy. Most cases of the photosensitive form of trichothiodystrophy result from variants in one of three genes: *ERCC2*, *ERCC3*, or *GTF2H5*. The proteins produced from these genes work together as part of a group of proteins called the general transcription factor 2 H (TFIIH) complex. This complex is involved in the repair of DNA damage, which can be caused by UV rays. The TFIIH complex also plays an important role in gene transcription, which is the first step in protein production.

Variants in the *ERCC2*, *ERCC3*, or *GTF2H5* genes reduce the amount of TFIIH complex within cells, which impairs both DNA repair and gene transcription. An inability to repair DNA damage probably underlies the sun sensitivity in affected individuals. Studies suggest that many of the other features of trichothiodystrophy may result from problems with the transcription of genes needed for normal development before and after birth.

Variants in at least seven genes have been reported to cause non-photosensitive forms of trichothiodystrophy. Variants in the *MPLKIP* gene account for fewer than 20 percent of all cases of non-photosensitive trichothiodystrophy. The protein produced from the *MPLKIP* gene does not appear to be involved in DNA repair. This protein interacts with another protein that is involved in processing and repairing RNA molecules, which are chemical cousins of DNA. Some forms of non-photosensitive trichothiodystrophy are caused by variants in genes that are also involved in RNA repair and protein production.

In some cases, the genetic cause of trichothiodystrophy is unknown.

Learn more about the genes associated with Trichothiodystrophy

- ERCC2
- ERCC3
- GTF2H5
- MPLKIP

Additional Information from NCBI Gene:

- AARS1
- CARS1
- GTF2E2
- MARS1
- RNF113A
- TARS1

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell must have a variant to cause the disorder. 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.

Other Names for This Condition

- Amish brittle hair syndrome
- BIDS syndrome
- Brittle hair-intellectual impairment-decreased fertility-short stature syndrome
- IBIDS
- PIBIDS
- TTD

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Trichothiodystrophy 4, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1313961/)
- Genetic Testing Registry: Trichothiodystrophy 7, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5231403/)
- Genetic Testing Registry: Trichothiodystrophy 8, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5562057/)
- Genetic Testing Registry: Trichothiodystrophy 9, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5562058/)
- Genetic Testing Registry: Trichothiodystrophy 1, photosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866504/)
- Genetic Testing Registry: Trichothiodystrophy 2, photosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225344/)

- Genetic Testing Registry: Trichothiodystrophy 3, photosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4017171/)
- Genetic Testing Registry: Trichothiodystrophy 5, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225420/)
- Genetic Testing Registry: Trichothiodystrophy 6, nonphotosensitive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4310785/)

Genetic and Rare Diseases Information Center

- Trichothiodystrophy (https://rarediseases.info.nih.gov/diseases/12109/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- TRICHOTHIODYSTROPHY 1, PHOTOSENSITIVE; TTD1 (https://omim.org/entry/601675)
- TRICHOTHIODYSTROPHY 4, NONPHOTOSENSITIVE; TTD4 (https://omim.org/entry/234050)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28DNA+Repair-Deficiency+Disorders%5BMAJR%5D%29+AND+%28%28trichothiodystrophy%5BTIAB%5D%29+OR+%28bids+syndrome%5BTIAB%5D%29+OR+%28IBIDS+syndrome%5BTIAB%5D%29+OR+%28ttd%5BTIAB%5D%29+OR+%28amish+brittle+hair+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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