Danon disease

Description

Danon disease is a condition characterized by weakening of the heart muscle (cardiomyopathy); weakening of the muscles used for movement, called skeletal muscles (myopathy); and intellectual disabilities. People with Danon disease may develop the condition at different ages. Signs and symptoms of this condition appear about 15 years earlier in individuals with a Y chromosome (typical for males) than in individuals with two X chromosomes (typical for females). People with a Y chromosome first experience health problems in childhood or adolescence; without treatment, these individuals typically live into early adulthood. People with two X chromosomes start experiencing health problems in early adulthood and typically survive into mid-adulthood without treatment.

Cardiomyopathy is the most common symptom of Danon disease, and it occurs in all people with a Y chromosome and in most people with two X chromosomes. Beginning in childhood, most affected individuals with a Y chromosome develop hypertrophic cardiomyopathy, which is a thickening of the heart muscle that may make it harder for the heart to pump blood. Others with Danon disease may have dilated cardiomyopathy, which is a condition that weakens and enlarges the heart, preventing it from pumping blood efficiently. About half of people with Danon disease who have two X chromosomes have hypertrophic cardiomyopathy, and the other half have dilated cardiomyopathy. Rarely, individuals with hypertrophic cardiomyopathy later develop dilated cardiomyopathy. Either type of cardiomyopathy can lead to heart failure and premature death.

Individuals with Danon disease can have other heart-related signs and symptoms, including a sensation of fluttering or pounding in the chest (palpitations), an abnormal heartbeat (arrhythmia), or chest pain. Many affected individuals have abnormalities of the electrical signals that control the heartbeat (conduction abnormalities). Affected individuals often have a specific conduction abnormality known as cardiac preexcitation. The type of cardiac preexcitation most often seen in people with Danon disease is called the Wolff-Parkinson-White syndrome pattern.

Skeletal myopathy occurs in most people with Danon disease who have one Y chromosome and in some affected individuals with two X chromosomes. The weakness typically occurs in the muscles of the shoulders, neck, and upper thighs. Many individuals with Danon disease who have one Y chromosome have elevated levels of an enzyme called creatine kinase in their blood, which often indicates muscle disease.

Most people with Danon disease who have one Y chromosome have mild intellectual disabilities, but this is much less common in affected individuals with two X chromosomes.

There can be other signs and symptoms of the condition in addition to the three characteristic features. Several affected individuals have had gastrointestinal disease, breathing problems, or visual abnormalities.

Frequency

Danon disease is a rare condition, but the exact prevalence is unknown.

Causes

Danon disease is caused by variants (also called mutations) in the *LAMP2* gene. The *LAMP2* gene provides instructions for making a protein called lysosome-associated membrane glycoprotein 2 (LAMP-2). As its name suggests, this protein is found in the membrane of cellular structures called lysosomes. Lysosomes are compartments in the cell that digest and recycle different types of materials. The LAMP-2 protein helps transport cellular materials or digestive enzymes into the lysosome. Three slightly different versions (isoforms) of the LAMP-2 protein are produced. These isoforms have slightly different functions and are found in different tissues throughout the body. The main isoform is needed to transport materials into lysosomes using a formation of cellular structures called autophagic vacuoles (or autophagosomes). Cellular material is first enclosed in an autophagic vacuole inside the cell. The vacuole then attaches (fuses) to a lysosome to transfer the cellular material into the lysosome. The LAMP-2 protein is involved in the fusion between autophagic vacuoles and lysosomes.

Variants in the *LAMP2* gene lead to the production of very little or no functional LAMP-2 protein. Studies have shown that fusion between autophagic vacuoles and lysosomes occurs more slowly in cells without the LAMP-2 protein, which causes autophagic vacuoles to accumulate in these cells. Accumulation of these vacuoles in the heart likely causes heart muscle cells to expand and eventually die, leading to the enlarged and weakened heart common in people with Danon disease. Similarly, in skeletal muscle cells, this accumulation likely leads to the breakdown of the muscle cells, causing muscle weakness. The cause of the other signs and symptoms of Danon disease is unclear, but it is likely related to the accumulation of vacuoles in other affected tissues.

Learn more about the gene associated with Danon disease

- LAMP2

Inheritance

This condition is inherited in an X-linked pattern. A condition is considered X-linked if the altered gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In individuals who have one X chromosome, a

variant in the only copy of the gene in each cell is sufficient to cause the condition. In people who have two copies of the X chromosome, a variant in one of the two copies of the gene can cause the condition, although the features may be less severe than in individuals with both copies altered. A characteristic of X-linked inheritance is that people with Y chromosomes cannot pass X-linked traits to their children with Y chromosomes.

Other Names for This Condition

- Glycogen storage disease type 2B
- Glycogen storage disease type IIb
- Lysosomal glycogen storage disease with normal acid maltase
- Lysosomal glycogen storage disease without acid maltase deficiency
- X-linked pseudoglycogenosis II
- X-linked vacuolar cardiomyopathy and myopathy

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Danon disease (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0878677/)

Genetic and Rare Diseases Information Center

- Glycogen storage disease due to LAMP-2 deficiency (https://rarediseases.info.nih.gov/diseases/9730/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- DANON DISEASE (https://omim.org/entry/300257)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Glycogen+Storage+Disease+Type+IIb%5BMAJR%5D%29+AND+%28Danon+disease%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

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