Cowden syndrome

Description

Cowden syndrome is a genetic disorder characterized by multiple noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers.

Almost everyone with Cowden syndrome develops hamartomas. These growths are most commonly found on the skin and mucous membranes (such as the lining of the mouth and nose), but they can also occur in the intestine and other parts of the body. The growth of hamartomas on the skin and mucous membranes typically becomes apparent by a person's late twenties.

Cowden syndrome is associated with an increased risk of developing several types of cancer, particularly cancers of the breast, a gland in the lower neck called the thyroid, and the lining of the uterus (the endometrium). Other cancers that have been identified in people with Cowden syndrome include kidney cancer, colorectal cancer, and an agressive form of skin cancer called melanoma. Compared with the general population, people with Cowden syndrome develop these cancers at younger ages, often beginning in their thirties or forties. People with Cowden syndrome are also more likely to develop more than one cancer during their lifetimes compared to the general population. Other diseases of the breast, thyroid, and endometrium are also common in Cowden syndrome. Additional signs and symptoms can include an enlarged head (macrocephaly) and a rare, noncancerous brain tumor called Lhermitte-Duclos disease. A small percentage of affected individuals have delayed development, intellectual disability, or autism spectrum disorder, which can affect communication and social interaction.

Some people do not meet the strict criteria for a clinical diagnosis of Cowden syndrome, but they have some of the characteristic features of the condition, particularly the cancers. These individuals are often described as having Cowden-like syndrome. Both Cowden syndrome and Cowden-like syndrome are caused by mutations in the same genes.

The features of Cowden syndrome overlap with those of another disorder called Bannayan-Riley-Ruvalcaba syndrome. People with Bannayan-Riley-Ruvalcaba syndrome also develop hamartomas and other noncancerous tumors. Some people with Cowden syndrome have relatives diagnosed with Bannayan-Riley-Ruvalcaba syndrome, and other affected individuals have the characteristic features of both conditions. Based on these similarities, researchers have proposed that Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome represent a spectrum of

overlapping features known as *PTEN* hamartoma tumor syndrome (named for the genetic cause of the conditions) instead of two distinct conditions.

Frequency

Although the exact prevalence of Cowden syndrome is unknown, researchers estimate that it affects about 1 in 200,000 people.

Causes

Changes in the *PTEN*, *KLLN*, or *WWP1* gene are most commonly identified in people with Cowden syndrome or Cowden-like syndrome.

About 25 percent of Cowden syndrome and a small percentage of cases of Cowden-like syndrome result from mutations in the *PTEN* gene. The protein produced from the *PTEN* gene is a tumor suppressor, which means that it normally prevents cells from growing and dividing (proliferating) too rapidly or in an uncontrolled way. Mutations in the *PTEN* gene prevent the PTEN protein from regulating cell proliferation effectively, leading to uncontrolled cell division and the formation of hamartomas and cancerous tumors. The *PTEN* gene likely has other important functions within cells; however, research is needed to determine what role mutations in this gene play in causing the other features of Cowden syndrome, such as macrocephaly and intellectual disability.

Rarely, Cowden syndrome and Cowden-like syndrome result from a change involving the *KLLN* gene. This gene provides instructions for making a protein called killin. Like the protein produced from the *PTEN* gene, killin probably acts as a tumor suppressor. The genetic change that causes Cowden syndrome and Cowden-like syndrome leads to reduced production of the killin protein. A reduced amount of killin may allow abnormal cells to survive and proliferate inappropriately, which can lead to the formation of tumors.

A small percentage of Cowden syndrome and Cowden-like syndrome are associated with variants in the *WWP1* gene. The *WWP1* gene provides instructions for making a protein that is involved in the process that targets other proteins to be broken down (degraded) within cells. During this process, the WWP1 protein attaches (binds) to the PTEN protein, which impairs PTEN's function. *WWP1* gene variants are described as " gain-of-function" because they appear to enhance the activity of the WWP1 protein. Studies suggest that the altered protein binds to the PTEN protein more readily than normal. Excessive binding impairs PTEN's tumor suppressor activity, allowing cells to proliferate unchecked and, leading to the formation of tumors.

Mutations in a few other genes are each responsible for a very small percentage of cases of Cowden syndrome and Cowden-like syndrome. In the remaining cases, the genetic cause is unknown.

Learn more about the genes associated with Cowden syndrome

- AKT1
- KLLN
- PIK3CA
- PTEN
- SDHB
- SDHC
- SDHD
- SEC23B
- WWP1

Inheritance

Cowden syndrome and Cowden-like syndrome are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the condition and increase the risk of developing cancer. In some cases, an affected person inherits the mutation from one affected parent. Other cases may result from new mutations in the gene. These cases occur in people with no history of the disorder in their family.

Other Names for This Condition

- CD
- Cowden disease
- Cowden's disease
- Cowden's syndrome
- CS
- MHAM
- Multiple hamartoma syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Cowden syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0018553/)
- Genetic Testing Registry: Cowden syndrome 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/CN072330/)
- Genetic Testing Registry: Cowden syndrome 4 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3554517/)

- Genetic Testing Registry: Cowden syndrome 5 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3554518/)
- Genetic Testing Registry: Cowden syndrome 6 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3554519/)
- Genetic Testing Registry: Cowden syndrome 7 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225179/)

Genetic and Rare Diseases Information Center

- Cowden syndrome (https://rarediseases.info.nih.gov/diseases/6202/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- COWDEN SYNDROME 1; CWS1 (https://omim.org/entry/158350)
- COWDEN SYNDROME 4; CWS4 (https://omim.org/entry/615107)
- COWDEN SYNDROME 5; CWS5 (https://omim.org/entry/615108)
- COWDEN SYNDROME 6; CWS6 (https://omim.org/entry/615109)
- COWDEN SYNDROME 7; CWS7 (https://omim.org/entry/616858)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(Hamartoma+Syndrome,+Multiple%5BMAJR%5D)+AND+(Cowden+syndrome%5BTIAB%5D)+AND+english%5Bla%5D+AND+human%5Bmh%5D)

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