Gordon Holmes syndrome

Description

Gordon Holmes syndrome is a rare condition characterized by reproductive and neurological problems. One of the key features of the condition is reduced production of hormones that direct sexual development (hypogonadotropic hypogonadism). Many affected individuals have a delay in development of the typical signs of puberty, such as the growth of facial hair and deepening of the voice in males, and the start of monthly periods (menstruation) and breast development in females. Some never undergo puberty. While some people with Gordon Holmes syndrome seem to have normal puberty, they develop other problems with the reproductive system later in life.

In early adulthood, individuals with Gordon Holmes syndrome develop neurological problems, usually beginning with speech difficulties (dysarthria). As the condition worsens, affected individuals have problems with balance and coordination (cerebellar ataxia), often leading to difficulties with activities of daily living and a need for wheelchair assistance. Some affected individuals also develop memory problems and a decline in intellectual function (dementia).

Frequency

Gordon Holmes syndrome is a rare condition. Its prevalence is unknown.

Causes

Gordon Holmes syndrome can be caused by mutations in the *RNF216* or *PNPLA6* gene. Some people with the condition do not have mutations in these genes, indicating that mutations in other genes are likely involved in the condition.

The protein produced from the *RNF216* gene is involved in a cellular process, called ubiquitination, by which unneeded proteins are tagged with a molecule called ubiquitin. The ubiquitin tag signals for the protein to be broken down. One of several proteins tagged by RNF216 is a protein found in nerve cells (neurons) that plays a role in a process called synaptic plasticity. Synaptic plasticity is the ability of the connections between neurons (synapses) to change and adapt over time in response to experience. This process is critical for learning and memory.

RNF216 gene mutations impair the ability of the RNF216 protein to tag unneeded proteins to be broken down. Impaired breakdown of the neuronal protein disrupts

normal synaptic connections and plasticity, which likely contributes to dementia in people with Gordon Holmes syndrome. It is unclear how a lack of RNF216 protein function causes hypogonadotropic hypogonadism or cerebellar ataxia.

The *PNPLA6* gene provides instructions for making a protein called neuropathy target esterase (NTE), which helps regulate the amount of certain fats (lipids) that make up the outer membrane surrounding cells. The correct levels of these lipids are critical to the stability and function of cell membranes. NTE is found most abundantly in the nervous system and is thought to help maintain the stability of membranes surrounding neurons. NTE is also thought to play a role in the release of hormones from the pituitary gland, a process that requires particular changes in the cell membrane. The pituitary gland is located at the base of the brain and produces several hormones, including those that help direct sexual development and growth.

PNPLA6 gene mutations are thought to impair NTE's function. Researchers speculate that such an impairment alters the balance of lipids in the cell membrane. This imbalance may damage neurons in the brain, causing cerebellar ataxia, and impair the pituitary gland's release of hormones involved in sexual development, leading to hypogonadotropic hypogonadism. Individuals with Gordon Holmes syndrome caused by *PNPLA6* gene mutations do not appear to develop dementia.

Learn more about the genes associated with Gordon Holmes syndrome

- PNPLA6
- RNF216

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- Cerebellar ataxia and hypogonadotropic hypogonadism
- Deficiency of luteinizing hormone-releasing hormone with ataxia
- LHRH deficiency and ataxia

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Cerebellar ataxia-hypogonadism syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1859305/)

Genetic and Rare Diseases Information Center

- Cerebellar ataxia-hypogonadism syndrome (https://rarediseases.info.nih.gov/diseases/3314/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- GORDON HOLMES SYNDROME; GDHS (https://omim.org/entry/212840)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Gordon+Holmes+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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