Isolated Growth Hormone Deficiency

Subjects: Genetics & Heredity
Contributor: Camila Xu

Isolated growth hormone deficiency is a condition caused by a severe shortage or absence of growth hormone.

Keywords: genetic conditions

1. Introduction

Growth hormone is a protein that is necessary for the normal growth of the body's bones and tissues. Because they do not have enough of this hormone, people with isolated growth hormone deficiency commonly experience a failure to grow at the expected rate and have unusually short stature. This condition is usually apparent by early childhood.

There are four types of isolated growth hormone deficiency differentiated by the severity of the condition, the gene involved, and the inheritance pattern.

Isolated growth hormone deficiency type IA is caused by an absence of growth hormone and is the most severe of all the types. In people with type IA, growth failure is evident in infancy as affected babies are shorter than normal at birth.

People with isolated growth hormone deficiency type IB produce very low levels of growth hormone. As a result, type IB is characterized by short stature, but this growth failure is typically not as severe as in type IA. Growth failure in people with type IB is usually apparent in early to mid-childhood.

Individuals with isolated growth hormone deficiency type II have very low levels of growth hormone and short stature that varies in severity. Growth failure in these individuals is usually evident in early to mid-childhood. It is estimated that nearly half of the individuals with type II have underdevelopment of the pituitary gland (pituitary hypoplasia). The pituitary gland is located at the base of the brain and produces many hormones, including growth hormone.

Isolated growth hormone deficiency type III is similar to type II in that affected individuals have very low levels of growth hormone and short stature that varies in severity. Growth failure in type III is usually evident in early to mid-childhood. People with type III may also have a weakened immune system and are prone to frequent infections. They produce very few B cells, which are specialized white blood cells that help protect the body against infection (agammaglobulinemia).

2. Frequency

The incidence of isolated growth hormone deficiency is estimated to be 1 in 4,000 to 10,000 individuals worldwide.

3. Causes

Isolated growth hormone deficiency is caused by mutations in one of at least three genes. Isolated growth hormone deficiency types IA and II are caused by mutations in the *GH1* gene. Type IB is caused by mutations in either the *GH1* or *GHRHR* gene. Type III is caused by mutations in the *BTK* gene.

The *GH1* gene provides instructions for making the growth hormone protein. Growth hormone is produced in the pituitary gland and plays a major role in promoting the body's growth. Growth hormone also plays a role in various chemical reactions (metabolic processes) in the body. Mutations in the *GH1* gene prevent or impair the production of growth hormone. Without sufficient growth hormone, the body fails to grow at its normal rate, resulting in slow growth and short stature as seen in isolated growth hormone deficiency types IA, IB, and II.

The *GHRHR* gene provides instructions for making a protein called the growth hormone releasing hormone receptor. This receptor attaches (binds) to a molecule called growth hormone releasing hormone. The binding of growth hormone releasing hormone to the receptor triggers the production of growth hormone and its release from the pituitary gland.

Mutations in the *GHRHR* gene impair the production or release of growth hormone. The resulting shortage of growth hormone prevents the body from growing at the expected rate. Decreased growth hormone activity due to *GHRHR* gene mutations is responsible for many cases of isolated growth hormone deficiency type IB.

The *BTK* gene provides instructions for making a protein called Bruton tyrosine kinase (BTK), which is essential for the development and maturation of immune system cells called B cells. The BTK protein transmits important chemical signals that instruct B cells to mature and produce special proteins called antibodies. Antibodies attach to specific foreign particles and germs, marking them for destruction. It is unknown how mutations in the *BTK* gene contribute to short stature in people with isolated growth hormone deficiency type III.

Some people with isolated growth hormone deficiency do not have mutations in the *GH1*, *GHRHR*, or *BTK* genes. In these individuals, the cause of the condition is unknown. When this condition does not have an identified genetic cause, it is known as idiopathic isolated growth hormone deficiency.

3.1. The genes associated with Isolated growth hormone deficiency

- BTK
- GH1
- GHRHR

4. Inheritance

Isolated growth hormone deficiency can have different inheritance patterns depending on the type of the condition.

Isolated growth hormone deficiency types IA and IB are inherited in an autosomal recessive pattern, which means both copies of the *GH1* or *GHRHR* 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.

Isolated growth hormone deficiency type II can be inherited in an autosomal dominant pattern, which means a mutation in one copy of the *GH1* gene in each cell is sufficient to cause the disorder. This condition can also result from new mutations in the *GH1* gene and occur in people with no history of the disorder in their family.

Isolated growth hormone deficiency type III, caused by mutations in the *BTK* gene, is inherited in an X-linked recessive pattern. The *BTK* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- dwarfism, growth hormone deficiency
- dwarfism, pituitary
- growth hormone deficiency dwarfism
- isolated GH deficiency
- isolated HGH deficiency
- isolated human growth hormone deficiency
- isolated somatotropin deficiency
- isolated somatotropin deficiency disorder

References

1. Alatzoglou KS, Dattani MT. Genetic causes and treatment of isolated growthhormone deficiency-an update. Nat Rev Endocrinol. 2010 Oct;6(10):562-76. doi:10.1038/nrendo.2010.147. Review.
2. Alatzoglou KS, Turton JP, Kelberman D, Clayton PE, Mehta A, Buchanan C, AylwinS, Crowne EC, Christesen HT, Hertel NT, Trainer PJ, Savage MO, Raza J, BanerjeeK, Sinha SK, Ten S, Mushtaq T, Brauner R, Cheetham TD, Hindmarsh PC, Mullis PE,Dattani MT. Expanding the spectrum of mutations in GH1 and GHRHR: geneticscreening in a large cohort of patients with congenital isolated growth hormonedeficiency. J Clin Endocrinol Metab. 2009 Sep;94(9):3191-9. doi:10.1210/jc.2008-2783.
3. Hamid R, Phillips JA 3rd, Holladay C, Cogan JD, Austin ED, Backeljauw PF,Travers SH, Patton JG. A molecular basis for variation in clinical severity ofisolated growth hormone deficiency type II. J Clin Endocrinol Metab. 2009Dec;94(12):4728-34. doi: 10.1210/jc.2009-0746.
4. Mullis PE. Genetic control of growth. Eur J Endocrinol. 2005 Jan;152(1):11-31.Review.
5. Mullis PE. Genetics of isolated growth hormone deficiency. J Clin Res Pediatr Endocrinol. 2010;2(2):52-62. doi: 10.4274/jcrpe.v2i2.52.
6. Seaver LH, Irons M; American College of Medical Genetics (ACMG) ProfessionalPractice and Guidelines Committee. ACMG practice guideline: genetic evaluation ofshort stature. Genet Med. 2009 Jun;11(6):465-70. doi:10.1097/GIM.0b013e3181a7e8f8. Erratum in: Genet Med. 2009 Oct;11(10):765.
7. Wit JM, Kiess W, Mullis P. Genetic evaluation of short stature. Best Pract ResClin Endocrinol Metab. 2011 Feb;25(1):1-17. doi: 10.1016/j.beem.2010.06.007.Review.
