GHR Gene

Subjects: Genetics & Heredity
Contributor: Vivi Li

Growth hormone receptor genes

1. Normal Function

The GHR gene provides instructions for making a protein called the growth hormone receptor. This receptor is embedded in the outer membrane of cells throughout the body and is most abundant in liver cells.

The growth hormone receptor has three major parts: An extracellular region that sticks out from the surface of the cell, a transmembrane region that anchors the receptor to the cell membrane, and an intracellular region that transmits signals to the interior of the cell. The extracellular region attaches (binds) to a substance called growth hormone, fitting together like a lock and its key. The binding of growth hormone triggers signaling via the intracellular region of the receptor that stimulates the growth and division of cells. This signaling also leads to the production, primarily by liver cells, of another important growth-promoting hormone called insulin-like growth factor I (IGF-I).

Growth hormone and IGF-I have a wide variety of effects on the growth and function of many parts of the body. For example, these hormones stimulate the growth and division of cells called chondrocytes, which play a critical role in producing new bone tissue. Growth hormone and IGF-I also influence metabolism, including how the body uses and stores carbohydrates, proteins, and fats from food.

Researchers have identified two major versions (isoforms) of the growth hormone receptor. The two isoforms differ by the presence or absence of a particular segment known as exon 3, which is located in the extracellular region of the receptor. The version of the receptor that includes exon 3 is known as the full-length isoform (fl-GHR), while the version that is missing exon 3 is known as the exon 3-deficient isoform (d3-GHR). Both isoforms are relatively common in most populations. Each individual can have fl-GHR only, d3-GHR only, or a mix of both isoforms. The two isoforms bind to growth hormone in the same way on the surface of cells, but for reasons that are unclear, d3-GHR is associated with enhanced signaling within cells compared with fl-GHR.

2. Health Conditions Related to Genetic Changes

2.1 Laron Syndrome

At least 70 mutations in the *GHR* gene have been found to cause Laron syndrome, a rare form of short stature that is also characterized by obesity, a distinctive facial appearance, and other signs and symptoms affecting multiple body systems. All of the identified mutations impair the function of the growth hormone receptor. Most of the mutations affect the extracellular region of the receptor, preventing it from binding to growth hormone effectively. A few mutations affect the intracellular region of the receptor, reducing or eliminating its ability to trigger the signals that promote growth.

Although people with *GHR* gene mutations produce growth hormone, the defective receptors prevent cells from responding to the hormone by producing IGF-I or triggering cell growth and division. The cells' inability to react to growth hormone, which is described as growth hormone insensitivity, disrupts the normal growth of many different tissues. Short stature results when growth hormone cannot adequately stimulate the growth of bones. Changes in metabolism caused by insensitivity to growth hormone and the resulting shortage of IGF-I cause many of the other features of the condition, including obesity.

Studies suggest that people with Laron syndrome have a significantly reduced risk of cancer and type 2 diabetes. Affected individuals appear to develop these common diseases much less frequently than their unaffected relatives, despite having obesity (a risk factor for both cancer and type 2 diabetes). Researchers are working to determine how mutations in the *GHR* gene may protect people with Laron syndrome from developing these diseases. Studies suggest that insensitivity to growth hormone may help prevent the uncontrolled growth and division of cells that can lead to the development of cancerous tumors. Growth hormone insensitivity also appears to alter how the body responds to insulin, which is a hormone that regulates blood sugar levels. Resistance to the effects of insulin is a major risk factor for type 2 diabetes. People with Laron syndrome have the opposite situation, an increased sensitivity to insulin, which likely helps explain their reduced risk of this disease.

2.2 Other Disorders

The two isoforms of the growth hormone receptor have been studied in several conditions involving problems with growth. These conditions include short stature resulting from a shortage (deficiency) of growth hormone, slow growth starting before birth (small for gestational age), and short stature of unknown cause (idiopathic short stature). Some studies have found that children with these disorders respond differently to treatment depending on which isoform of the growth hormone receptor they have. Specifically, d3-GHR has been associated with faster growth during treatment compared with fl-GHR. Other studies have not found a difference in growth, although all of the studies used different methodologies and included relatively few participants.

The two isoforms of the growth hormone receptor have also been studied in adults with acromegaly, a disorder characterized by increased levels of growth hormone. The abnormally high levels are most often caused by a noncancerous tumor in the pituitary gland, which is the part of the brain where growth hormone is produced. In response to the excess growth hormone, the bones of the hands, feet, and face grow unusually large. Other signs and symptoms of this condition can include thickened skin, increased sweating and body odor, enlargement of certain organs, muscle weakness, and excessive tiredness (fatigue). In adults with acromegaly, studies suggest

that having the d3-GHR isoform is associated with better response to treatment compared with having fl-GHR. However, having d3-GHR appears to increase the risk of certain complications of the disease compared with having fl-GHR. The reasons for these differences are not fully understood.

Whether a person has fl-GHR or d3-GHR does not seem to affect adult height in people without a growth disorder. Many genetic and non-genetic factors, some of which are unknown, influence how tall a person will be.

3. Other Names for This Gene

- GH receptor
- GHBP
- GHR_HUMAN
- growth hormone binding protein
- serum binding protein
- somatotropin receptor

References

1. Amselem S, Duquesnoy P, Attree O, Novelli G, Bousnina S, Postel-Vinay MC,Goossens M. Laron dwarfism and mutations of the growth hormone-receptor gene. NEngl J Med. 1989 Oct 12;321(15):989-95.
2. Brooks AJ, Waters MJ. The growth hormone receptor: mechanism of activation andclinical implications. Nat Rev Endocrinol. 2010 Sep;6(9):515-25. doi:10.1038/nrendo.2010.123.
3. Dos Santos C, Essioux L, Teinturier C, Tauber M, Goffin V, Bougnères P. Acommon polymorphism of the growth hormone receptor is associated with increasedresponsiveness to growth hormone. Nat Genet. 2004 Jul;36(7):720-4.
4. Filopanti M, Giavoli C, Grottoli S, Bianchi A, De Marinis L, Ghigo E, Spada A.The exon 3-deleted growth hormone receptor: molecular and functionalcharacterization and impact on GH/IGF-I axis in physiological and pathologicalconditions. J Endocrinol Invest. 2011 Dec;34(11):861-8. Review.
5. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, ChengCW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, LongoVD. Growth hormone receptor deficiency is associated with a major reduction inpro-aging signaling, cancer, and

diabetes in humans. Sci Transl Med. 2011 Feb16;3(70):70ra13. doi: 10.1126/scitranslmed.3001845.

6. Guevara-Aguirre J, Rosenbloom AL. Obesity, diabetes and cancer: insight intothe relationship from a cohort with growth hormone receptor deficiency.Diabetologia. 2015 Jan;58(1):37-42. doi: 10.1007/s00125-014-3397-3.
7. Jorge AA, Arnhold IJ. Growth hormone receptor exon 3 isoforms and theirimplication in growth disorders and treatment. Horm Res. 2009 Apr;71 Suppl2:55-63. doi: 10.1159/000192438.
8. Savage MO, Woods KA, Johnston LB, Postel-Vinay MC, Amselem S, Clark AJ.Defects of the growth hormone receptor and their clinical implications. GrowthHorm IGF Res. 1999 Apr;9 Suppl A:57-61. Review.
9. Wassenaar MJ, Biermasz NR, Pereira AM, van der Klaauw AA, Smit JW, RoelfsemaF, van der Straaten T, Cazemier M, Hommes DW, Kroon HM, Kloppenburg M, Guchelaar HJ, Romijn JA. The exon-3 deleted growth hormone receptor polymorphismpredisposes to long-term complications of acromegaly. J Clin Endocrinol Metab.2009 Dec;94(12):4671-8. doi: 10.1210/jc.2009-1172.
10. Wassenaar MJ, Dekkers OM, Pereira AM, Wit JM, Smit JW, Biermasz NR, Romijn JA.Impact of the exon 3-deleted growth hormone (GH) receptor polymorphism onbaseline height and the growth response to recombinant human GH therapy inGH-deficient (GHD) and non-GHD children with short stature: a systematic reviewand meta-analysis. J Clin Endocrinol Metab. 2009 Oct;94(10):3721-30. doi:10.1210/jc.2009-0425.