LRP5 gene

LDL receptor related protein 5

Normal Function

The *LRP5* gene provides instructions for making a protein that is embedded in the outer membrane of many types of cells. This protein is known as a co-receptor because it works with another receptor protein, frizzled-4 (produced from the *FZD4* gene), to transmit chemical signals from outside the cell to the cell's nucleus. Frizzled-4 and the LRP5 protein participate in the Wnt signaling pathway, a series of steps that affect the way cells and tissues develop. Wnt signaling is important for cell division (proliferation), attachment of cells to one another (adhesion), cell movement (migration), and many other cellular activities.

The LRP5 protein plays an important role in the development and maintenance of several tissues. During early development, it helps guide the specialization of cells in the retina, which is the light-sensitive tissue that lines the back of the eye. The LRP5 protein is also involved in forming blood vessels in the retina and in the inner ear. Additionally, this protein helps regulate bone mineral density, which is a measure of the amount of calcium and other minerals in bones. The minerals give the bones strength, making them less likely to break.

Health Conditions Related to Genetic Changes

Familial exudative vitreoretinopathy

Multiple variants (also called mutations) in the *LRP5* gene have been identified in people with the eye disease familial exudative vitreoretinopathy. This disorder affects the retina and can cause vision loss that worsens over time.Some of these variants change single protein building blocks (amino acids) in the LRP5 protein, while others insert or delete genetic material in the gene. Most of these variants reduce the amount of functional LRP5 protein that is produced within cells.

A reduction in the amount of LRP5 protein disrupts chemical signaling in the developing eye, which interferes with the formation of blood vessels at the edges of the retina. The resulting abnormal blood supply to this tissue can lead to retinal damage and vision loss. Because the LRP5 protein plays a role in bone formation, *LRP5* gene variants also cause reduced bone mineral density and other features of a condition called osteoporosis-pseudoglioma syndrome (described below) in some people with familial

exudative vitreoretinopathy.

Juvenile primary osteoporosis

LRP5 gene variants have been found to cause juvenile primary osteoporosis. Individuals with this condition have low bone mineral density and thinning of the bones (osteoporosis) beginning in childhood. Osteoporosis causes the bones to be brittle and to break easily. The *LRP5* gene variants that cause this condition produce in an LRP5 protein that is unable to transmit chemical signals along the Wnt signaling pathway. The resulting reduction in signaling disrupts the regulation of bone mineral density, leading to osteoporosis at a young age.

Osteoporosis-pseudoglioma syndrome

Multiple *LRP5* gene variants that cause osteoporosis-pseudoglioma syndrome have been identified. Beginning in childhood, people with this condition have extremely low bone mineral density and osteoporosis, which leads to multiple bone fractures. Affected individuals also have eye abnormalities that cause vision impairment from birth or early infancy.

Many of the *LRP5* gene variants that cause osteoporosis-pseudoglioma syndrome prevent cells from making any LRP5 protein. Other variants lead to changes in single amino acids in the LRP5 protein. These abnormal proteins cannot insert themselves into the outer membrane of the cell, which makes them unable to perform their function. Loss of LRP5 protein function disrupts the chemical signaling pathways that are needed for the formation of bone and for normal retinal development, leading to the bone and eye abnormalities characteristic of osteoporosis-pseudoglioma syndrome. It is unclear why some *LRP5* gene variants affect eye development and others do not.

Other disorders

Studies suggest that changes in the *LRP5* gene may influence the risk of developing osteoporosis in adulthood. Other genetic and environmental factors likely contribute to this common disorder.

Other *LRP5* gene variants cause disorders associated with an increase in bone mineral density. These include autosomal dominant osteopetrosis type 1 and autosomal dominant osteosclerosis. In some cases, these conditions can cause abnormal bone growth and related skeletal abnormalities. Rarely, affected individuals have hearing loss or circulation problems in the brain. Other people with increased bone mineral density do not have any associated health problems. The *LRP5* gene variants responsible for increased bone mineral density syndromes overactivate the LRP5 protein, which increases Wnt signaling within cells and enhances bone formation.

Other Names for This Gene

- BMND1
- EVR1

- EVR4
- HBM
- low density lipoprotein receptor-related protein 5
- low density lipoprotein receptor-related protein 7
- LR3
- LRP5_HUMAN
- LRP7
- OPS
- OPTA1
- VBCH2

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of LRP5 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4041[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28LRP5%5BTIAB%5D%29+OR+%28low+density+lipoprotein+receptor-related+protein+5%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 5; LRP5 (https://omim.org/entry/603506)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/4041)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=LRP5[gene])

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Genomic Location

The *LRP5* gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

Last updated February 5, 2024