



## PITX1 gene

paired like homeodomain 1

### Normal Function

The *PITX1* gene provides instructions for making a protein that plays a critical role in development of the lower limbs. The PITX1 protein is found primarily in the developing legs and feet. The protein acts as a transcription factor, which is a protein that attaches (binds) to specific regions of DNA and helps control the activity of particular genes. Specifically, PITX1 regulates the activity of genes to direct the shape and structure of tissues in the lower limbs, including the bones, muscles, and tendons (the bands of tissue that connect muscles to bones).

The PITX1 protein is also found in the developing pituitary gland, which is a hormone-producing gland located at the base of the brain, and in an embryonic structure called the branchial arch. The PITX1 protein may play a role in formation of the pituitary gland and tissues derived from the branchial arch, such as the roof of the mouth, the jaw, and parts of the inner ear.

### Health Conditions Related to Genetic Changes

#### Liebenberg syndrome

Changes in the DNA near the *PITX1* gene cause Liebenberg syndrome, a rare condition characterized by abnormal development of the arms, resulting in short fingers (brachydactyly), joint deformities called contractures that limit movement of the elbows and wrists, and other bone and muscle abnormalities. These genetic changes delete, insert, or rearrange genetic material near the *PITX1* gene; at least five such mutations have been identified in affected individuals. These changes affect regions of DNA known as regulatory elements, which help turn on or turn off genes (known as enhancers or repressors, respectively). They control when and where certain genes are active. The mutations that cause Liebenberg syndrome likely relocate enhancers that promote the activity of genes involved in upper limb development to be near the *PITX1* gene. Alternatively, mutations may remove repressors that normally turn off the *PITX1* gene during upper limb development. As a result, the *PITX1* gene is abnormally active during arm and hand development. Because the PITX1 protein normally directs lower limb structure, bones, muscles, and tendons in the arms and hands develop more like those in the legs and feet, leading to the features of Liebenberg syndrome. Development of the lower limbs is normal in people with this condition.

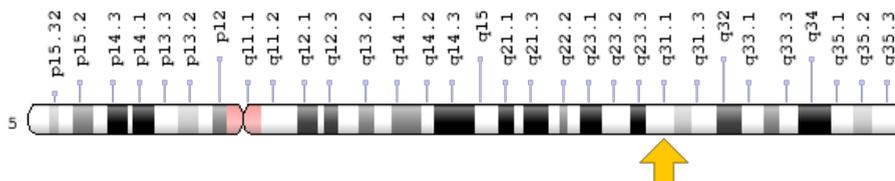
## Other disorders

*PITX1* gene mutations have been found to cause lower limb abnormalities, including an inward- and upward-turning foot (clubfoot) and absence or severe shortening of a bone in the lower leg called the tibia (tibial hemimelia). These gene mutations have also been found in people with extra toes (polydactyly), specifically a severe form of the abnormality called mirror-image polydactyly. These mutations delete a large part of the *PITX1* gene or the whole gene, or change a single protein building block (amino acid) in the *PITX1* protein. Unlike the mutations that cause Liebenberg syndrome (described above), these genetic changes reduce the amount of functional *PITX1* protein, which disrupts normal development of the lower limbs. The upper limbs are normal in individuals with these *PITX1* gene mutations.

## Chromosomal Location

Cytogenetic Location: 5q31.1, which is the long (q) arm of chromosome 5 at position 31.1

Molecular Location: base pairs 135,027,734 to 135,034,274 on chromosome 5 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

## Other Names for This Gene

- BFT
- hindlimb-expressed homeobox protein backfoot
- hindlimb expressed homeobox protein backfoot
- homeobox protein PITX1
- paired-like homeodomain 1
- paired-like homeodomain transcription factor 1
- pituitary homeo box 1
- pituitary homeobox 1
- pituitary otx-related factor
- POTX

- Ptlx
- PTX1

## **Additional Information & Resources**

### Educational Resources

- An Introduction to Genetic Analysis (seventh edition, 2000): Distance-Independent Cis-Acting Elements  
[https://www.ncbi.nlm.nih.gov/books/NBK21780/#\\_A2026\\_](https://www.ncbi.nlm.nih.gov/books/NBK21780/#_A2026_)
- Developmental Biology (sixth edition, 2000): Anatomy of the Gene: Promoters and Enhancers  
[https://www.ncbi.nlm.nih.gov/books/NBK10023/#\\_A751\\_](https://www.ncbi.nlm.nih.gov/books/NBK10023/#_A751_)
- The Cell: A Molecular Approach (second edition, 2000): Regulation of Transcription in Eukaryotes  
<https://www.ncbi.nlm.nih.gov/books/NBK9904/>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28PITX1%5BTIAB%5D%29+OR+%28paired+like+homeodomain+1%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

- PAIRED-LIKE HOMEODOMAIN TRANSCRIPTION FACTOR 1  
<http://omim.org/entry/602149>

### Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology  
[http://atlasgeneticsoncology.org/Genes/GC\\_PITX1.html](http://atlasgeneticsoncology.org/Genes/GC_PITX1.html)
- ClinVar  
<https://www.ncbi.nlm.nih.gov/clinvar?term=PITX1%5Bgene%5D>
- HGNC Gene Symbol Report  
[https://www.genenames.org/data/gene-symbol-report/#!/hgnc\\_id/HGNC:9004](https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:9004)
- Monarch Initiative  
<https://monarchinitiative.org/gene/NCBIGene:5307>
- NCBI Gene  
<https://www.ncbi.nlm.nih.gov/gene/5307>
- UniProt  
<https://www.uniprot.org/uniprot/P78337>

## Sources for This Summary

- Alvarado DM, McCall K, Aferol H, Silva MJ, Garbow JR, Spees WM, Patel T, Siegel M, Dobbs MB, Gurnett CA. Pitx1 haploinsufficiency causes clubfoot in humans and a clubfoot-like phenotype in mice. *Hum Mol Genet.* 2011 Oct 15;20(20):3943-52. doi: 10.1093/hmg/ddr313. Epub 2011 Jul 20. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21775501>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3177645/>
- DeLaurier A, Schweitzer R, Logan M. Pitx1 determines the morphology of muscle, tendon, and bones of the hindlimb. *Dev Biol.* 2006 Nov 1;299(1):22-34. Epub 2006 Jul 14. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/16989801>
- Duboc V, Logan MP. Pitx1 is necessary for normal initiation of hindlimb outgrowth through regulation of Tbx4 expression and shapes hindlimb morphologies via targeted growth control. *Development.* 2011 Dec;138(24):5301-9. doi: 10.1242/dev.074153. Epub 2011 Nov 9. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22071103>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222209/>
- Infante CR, Park S, Mihala AG, Kingsley DM, Menke DB. Pitx1 broadly associates with limb enhancers and is enriched on hindlimb cis-regulatory elements. *Dev Biol.* 2013 Feb 1;374(1):234-44. doi: 10.1016/j.ydbio.2012.11.017. Epub 2012 Nov 27. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23201014>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3640454/>
- Klopocki E, Kähler C, Foulds N, Shah H, Joseph B, Vogel H, Lüttgen S, Bald R, Besoke R, Held K, Mundlos S, Kurth I. Deletions in PITX1 cause a spectrum of lower-limb malformations including mirror-image polydactyly. *Eur J Hum Genet.* 2012 Jun;20(6):705-8. doi: 10.1038/ejhg.2011.264. Epub 2012 Jan 18. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22258522>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3355260/>
- Lanctôt C, Moreau A, Chamberland M, Tremblay ML, Drouin J. Hindlimb patterning and mandible development require the Ptx1 gene. *Development.* 1999 May;126(9):1805-10. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/10101115>
- OMIM: PAIRED-LIKE HOMEODOMAIN TRANSCRIPTION FACTOR 1  
<http://omim.org/entry/602149>
- Spielmann M, Brancati F, Krawitz PM, Robinson PN, Ibrahim DM, Franke M, Hecht J, Lohan S, Dathe K, Nardone AM, Ferrari P, Landi A, Wittler L, Timmermann B, Chan D, Mennen U, Klopocki E, Mundlos S. Homeotic arm-to-leg transformation associated with genomic rearrangements at the PITX1 locus. *Am J Hum Genet.* 2012 Oct 5;91(4):629-35. doi: 10.1016/j.ajhg.2012.08.014. Epub 2012 Sep 27. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23022097>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3484647/>
- Szeto DP, Rodriguez-Esteban C, Ryan AK, O'Connell SM, Liu F, Kioussi C, Gleiberman AS, Izpisua-Belmonte JC, Rosenfeld MG. Role of the Bicoid-related homeodomain factor Pitx1 in specifying hindlimb morphogenesis and pituitary development. *Genes Dev.* 1999 Feb 15;13(4):484-94. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/10049363>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC316471/>

---

Reprinted from Genetics Home Reference:  
<https://ghr.nlm.nih.gov/gene/PITX1>

Reviewed: September 2016

Published: May 14, 2019

Lister Hill National Center for Biomedical Communications

U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services