

# Paget Disease of Bone

Subjects: Genetics & Heredity

Contributor: Rita Xu

Paget disease of bone is a disorder that causes bones to grow larger and weaker than normal. Affected bones may be misshapen and easily broken (fractured).

Keywords: genetic conditions

---

## 1. Introduction

The classic form of Paget disease of bone typically appears in middle age or later. It usually occurs in one or a few bones and does not spread from one bone to another. Any bones can be affected, although the disease most commonly affects bones in the spine, pelvis, skull, or legs.

Many people with classic Paget disease of bone do not experience any symptoms associated with their bone abnormalities. The disease is often diagnosed unexpectedly by x-rays or laboratory tests done for other reasons. People who develop symptoms are most likely to experience pain. The affected bones may themselves be painful, or pain may be caused by arthritis in nearby joints. Arthritis results when the distortion of bones, particularly weight-bearing bones in the legs, causes extra wear and tear on the joints. Arthritis most frequently affects the knees and hips in people with this disease.

Other complications of Paget disease of bone depend on which bones are affected. If the disease occurs in bones of the skull, it can cause an enlarged head, hearing loss, headaches, and dizziness. If the disease affects bones in the spine, it can lead to numbness and tingling (due to pinched nerves) and abnormal spinal curvature. In the leg bones, the disease can cause bowed legs and difficulty walking.

A rare type of bone cancer called osteosarcoma has been associated with Paget disease of bone. This type of cancer probably occurs in less than 1 in 1,000 people with this disease.

Early-onset Paget disease of bone is a less common form of the disease that appears in a person's teens or twenties. Its features are similar to those of the classic form of the disease, although it is more likely to affect the skull, spine, and ribs (the axial skeleton) and the small bones of the hands. The early-onset form of the disorder is also associated with hearing loss early in life.

## 2. Frequency

Classic Paget disease of bone occurs in approximately 1 percent of people older than 40 in the United States. Scientists estimate that about 1 million people in this country have the disease. It is most common in people of western European heritage.

Early-onset Paget disease of bone is much rarer. This form of the disorder has been reported in only a few families.

## 3. Causes

A combination of genetic and environmental factors likely play a role in causing Paget disease of bone. Researchers have identified changes in several genes that increase the risk of the disorder. Other factors, including infections with certain viruses, may be involved in triggering the disease in people who are at risk. However, the influence of genetic and environmental factors on the development of Paget disease of bone remains unclear.

Researchers have identified variations in three genes that are associated with Paget disease of bone: *SQSTM1*, *TNFRSF11A*, and *TNFRSF11B*. Mutations in the *SQSTM1* gene are the most common genetic cause of classic Paget disease of bone, accounting for 10 to 50 percent of cases that run in families and 5 to 30 percent of cases in which there

is no family history of the disease. Variations in the *TNFRSF11B* gene also appear to increase the risk of the classic form of the disorder, particularly in women. *TNFRSF11A* mutations cause the early-onset form of Paget disease of bone.

The *SQSTM1*, *TNFRSF11A*, and *TNFRSF11B* genes are involved in bone remodeling, a normal process in which old bone is broken down and new bone is created to replace it. Bones are constantly being remodeled, and the process is carefully controlled to ensure that bones stay strong and healthy. Paget disease of bone disrupts the bone remodeling process. Affected bone is broken down abnormally and then replaced much faster than usual. When the new bone tissue grows, it is larger, weaker, and less organized than normal bone. It is unclear why these problems with bone remodeling affect some bones but not others in people with this disease.

Researchers are looking for additional genes that may influence a person's chances of developing Paget disease of bone. Studies suggest that genetic variations in certain regions of chromosome 2, chromosome 5, and chromosome 10 appear to contribute to disease risk. However, the associated genes on these chromosomes have not been identified.

### The Genes Associated with Paget Disease of Bone

- *SQSTM1*
- *TNFRSF11A*
- *TNFRSF11B*

## 4. Inheritance

In 15 to 40 percent of all cases of classic Paget disease of bone, the disorder has an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means that having one copy of an altered gene in each cell is sufficient to cause the disorder.

In the remaining cases, the inheritance pattern of classic Paget disease of bone is unclear. Many affected people have no family history of the disease, although it sometimes clusters in families. Studies suggest that close relatives of people with classic Paget disease of bone are 7 to 10 times more likely to develop the disease than people without an affected relative.

Early-onset Paget disease of bone is inherited in an autosomal dominant pattern. In people with this form of the disorder, having one altered copy of the *TNFRSF11A* gene in each cell is sufficient to cause the disease.

## 5. Other Names for This Condition

- osseous Paget's disease
- osteitis deformans
- Paget disease, bone
- Paget's disease of bone
- PDB

---

## References

1. Daroszewska A, Ralston SH. Mechanisms of disease: genetics of Paget's disease of bone and related disorders. *Nat Clin Pract Rheumatol*. 2006 May;2(5):270-7. Review.
2. Goode A, Layfield R. Recent advances in understanding the molecular basis of Paget disease of bone. *J Clin Pathol*. 2010 Mar;63(3):199-203. doi:10.1136/jcp.2009.064428.
3. Ralston SH, Albagha OM. Genetics of Paget's disease of bone. *Curr Osteoporos Rep*. 2014 Sep;12(3):263-71. doi: 10.1007/s11914-014-0219-y. Review.
4. Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. *Lancet*. 2008 Jul 12;372(9633):155-63. doi:10.1016/S0140-6736(08)61035-1. Review.
5. Ralston SH. Pathogenesis of Paget's disease of bone. *Bone*. 2008 Nov;43(5):819-25. doi: 10.1016/j.bone.2008.06.015.
6. Singer FR, Bone HG 3rd, Hosking DJ, Lyles KW, Murad MH, Reid IR, Siris ES; Endocrine Society. Paget's disease of bone: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014 Dec;99(12):4408-22. doi:10.1210/jc.2014-2910.
7. Whyte MP. Clinical practice. Paget's disease of bone. *N Engl J Med*. 2006 Aug 10;355(6):593-600. Review.

