# Pseudohypoparathyroidism: A Variation on the Theme of Hypoparathyroidism

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Pseudohypoparathyroidism is characterized by an inability of the body to respond appropriately to parathyroid hormone (PTH), the principal hormone that regulates calcium and phosphorous levels in the body. PTH is made by the parathyroid glands in the neck. There are usually four parathyroid glands, but we probably only need one or two of the glands. PTH is missing, or too low, in patients with hypoparathyroidism. Therefore, the fundamental difference between hypoparathyroidism and pseudohypoparathyroidism is that PTH is absent in hypoparathyroidism, but the body will respond to it; and PTH is plentiful in pseudohypoparathyroidism, but the body cannot respond to it!

PTH acts directly on the bone and kidneys to control blood levels of calcium and phosphorous, and to regulate bone mass and strength. PTH also acts indirectly on the intestine and skeleton by stimulating production of the active form of Vitamin D (calcitriol) in the kidney. Calcitriol stimulates absorption of calcium and phosphorous from the intestine and also increases the release of calcium and phosphorous from storage pools in the skeleton (Figure 1). In the bone, PTH stimulates specific bone cells called osteoclasts to break down or "resorb" bone to release the minerals calcium and phosphorus into the blood stream. Osteoclasts resorb bone when extra minerals are needed in the blood or when it is necessary to remodel bone, such as during growth or repair of a fracture. Working closely with the osteoclasts are osteoblasts, the cells that create new bone tissue after osteoclasts remove old or damaged bone. PTH also acts in the kidney, where it increases calcium reabsorption (prevents loss into the urine) and increases urinary phosphate excretion (loss into the urine) to avoid elevated levels of phosphorous in the blood. The kidney is a very important control valve to maintain normal levels of blood calcium and phosphorous. The kidney filters the blood, like a colander, and keeps large particles such as blood cells. The filtered "water" contains both waste products and minerals. The kidney reclaims or reabsorbs the important things, such as water and minerals, and gets rid of, or excretes, what it does not need, such as waste products and extra minerals. It knows how much of each mineral to excrete by signals from hormones such as PTH. An increase in PTH saves, or reabsorbs, the calcium and excretes extra phosphorus.

The kidney is an important part of vitamin D metabolism. There are special cells in the kidney that make the active form of vitamin D (calcitriol or 1, 25 dihydroxy Vitamin D) in response to PTH. Calcitriol acts in the intestine where it increases absorption of dietary calcium and, to a lesser extent, phosphorous. Vitamin D is important because it also helps the osteoblasts build strong bones. Finally, when the blood levels of calcium

and calcitriol are satisfactory, they both signal the parathyroid glands to decrease the amount of PTH produced and released.

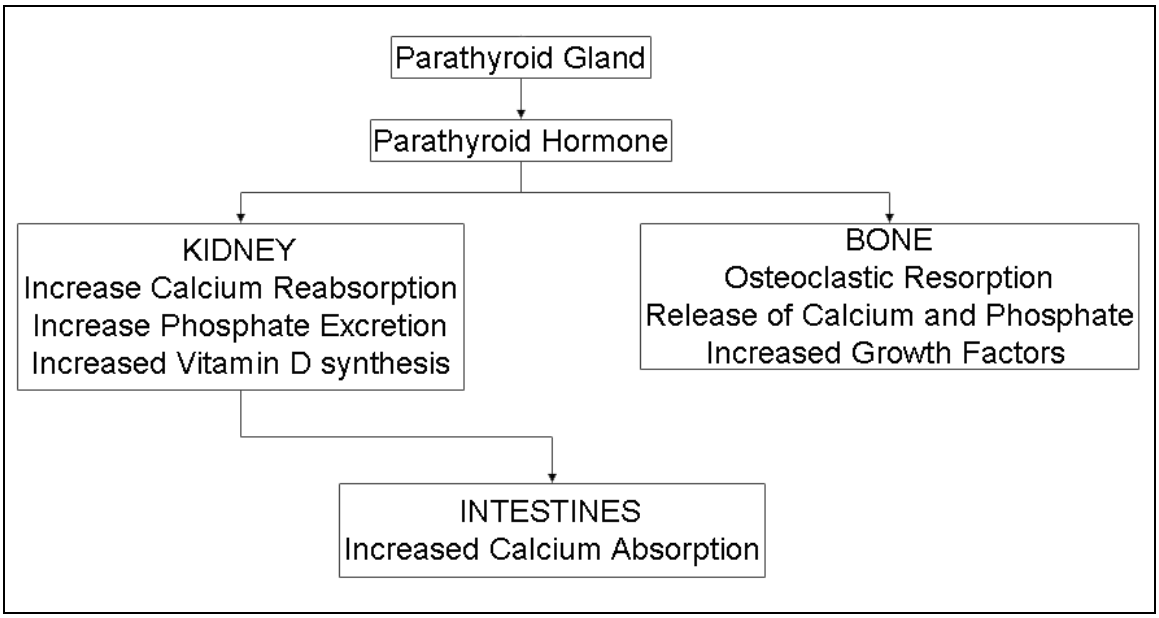


**Figure 1. PTH actions in normal subjects.**

There are several variants of PHP, but the most common forms are PHP type 1a and PHP type 1b. In patients with PHP type 1a and type 1b, the kidneys are not fully responsive to PTH. Therefore, the kidneys do not excrete phosphorus or produce adequate amounts of calcitriol. Together, this causes the serum calcium to become low and the serum phosphorous to become high. Some kidney responses to PTH remain normal, however. For example, the kidneys can respond to PTH to increase reabsorption of calcium, so levels of calcium in the urine are LOW. By contrast, levels of calcium in the urine can be HIGH in patients with more typical hypoparathyroidism where there is a lack of PTH (Figure 2). Moreover, some elements of the skeleton can also respond to PTH, so over time bone can become thin or weak, particularly if patients are not treated with sufficient calcium and vitamin D to lower levels of PTH. On the other hand, patients with hypoparathyroidism (who lack PTH) have heavier, more dense bones.

Pseudohypoparathyroidism is called “pseudo” hypoparathyroidism because the blood chemistry values (low to normal serum calcium and high serum phosphorous) resemble the more common disorder hypoparathyroidism in which PTH is absent or low, but PTH is actually elevated because the kidney cannot fully respond to PTH.

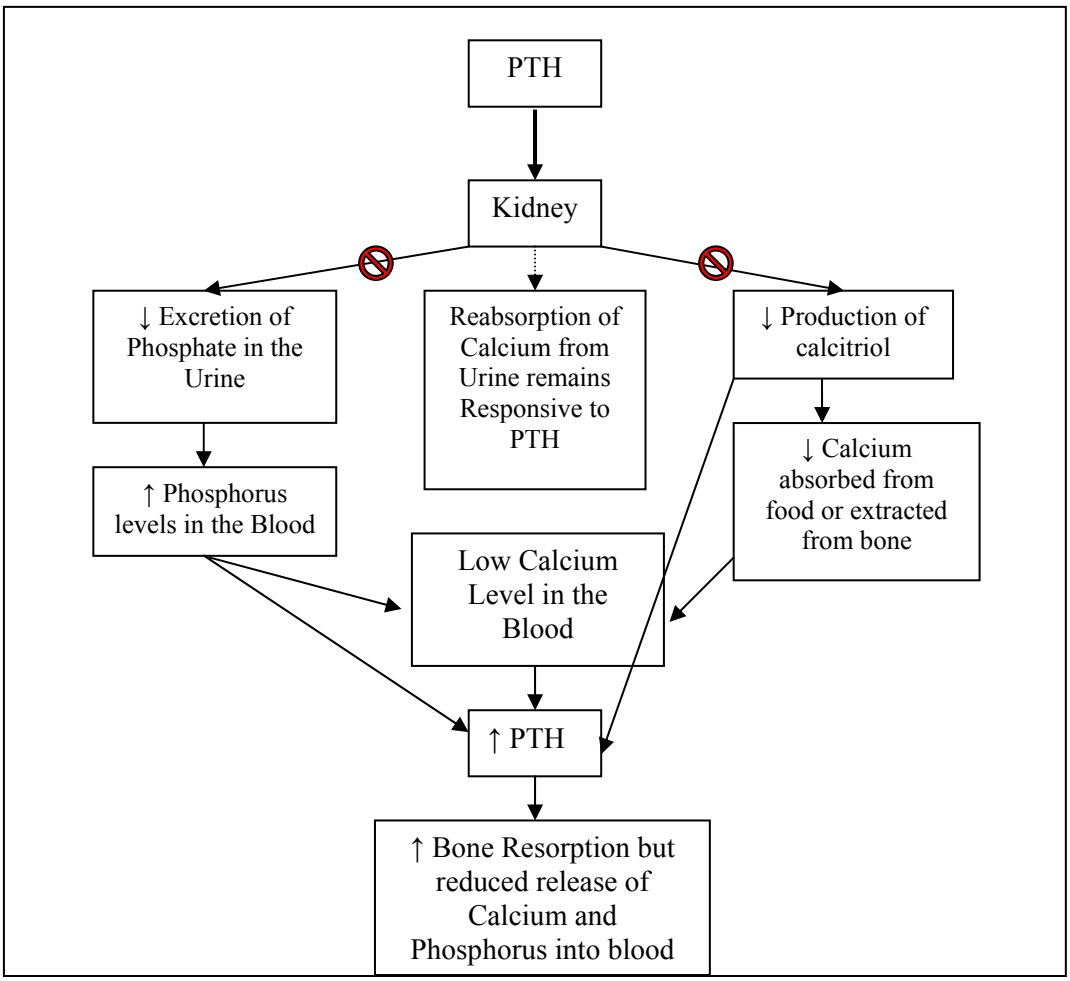


**Figure 2. Consequences of PTH resistance in PHP 1.**

Patients with PHP type 1a have a defect in the *GNAS* gene that leads to a widespread deficiency of Gsα, a signaling protein that is required by many hormone receptors to trigger the cell's response to a hormone. Because this deficiency occurs in many cells, patients not only fail to respond to PTH, but also do not respond well to thyroid stimulating hormone (causing mild hypothyroidism), gondadotropins (causing problems with fertility and sexual development), calcitonin (regulates calcium balance with PTH), glucagon (increases the blood sugar), and GHRH, the hormone that signals release of growth hormone from the pituitary gland. Therefore, in addition to a low serum calcium levels, patients with PHP type 1a often have low thyroid hormone levels, low levels of estrogen or testosterone, and short stature due to growth hormone deficiency. They also have a variety of physical features termed "Albright hereditary osteodystrophy" that consist of a round face, shortened fingers and/or toes, hard lumps of bone that form underneath the skin, obesity, short stature, and some problems with learning.

A second major form of PHP is type 1b. Patients with PHP type 1b generally have a normal appearance, but sometimes a finger or toe may be shortened. Patients have genetic defects that alter

expression of *GNAS* in a more restricted manner, and hormone problems are usually limited to an inability of the kidney to respond fully to PTH.

PHP type 1a and type 1b can be inherited, but the genetics are quite unusual (and often confusing!) because transmission does not follow the typical dominant or recessive laws of inheritance that were first described by Gregor Mendel (1822-1884)! Humans have about 35,000 genes that are distributed among 23 pairs of chromosomes. In general, each parent (mother and father) contributes equally to the chromosomes and genes of a baby. There are some exceptions, however. For example, a mother gives each child one of her two X chromosomes, while the father gives his daughters his X chromosome and his sons his Y chromosome. In this manner each parent contributes something unique. Parents also contribute genetic uniqueness through about 100 other genes that are more or less active depending upon the parent of origin. These genes are "imprinted" so that they remember whether they came from the mother or father, and *GNAS* is one of these special genes. Imprinting is a process that controls whether genes are active or not, and the imprint is determined by "switches" that are set by whether the gene came from the mother or the father. In many cells only the copy of *GNAS* that is inherited from the mother is active or "turned on." If the *GNAS* gene from the mother has a mutation the child will develop PHP type 1a, and will have the hormone problems discussed above plus the features of Albright hereditary osteodystrophy. However, if a defective *GNAS* is inherited from the father the child will ***not*** develop hormone problems, but will have only the features of Albright hereditary osteodystrophy (See Figure 3). In this case the child has a condition that is like PHP type 1a, so it is called "pseudo" PHP type 1a! The child will develop the features of Albright hereditary osteodystrophy because during the developmental process, *BOTH* of the *GNAS* genes are required.

Sometimes a child has a defective *GNAS* gene but neither parent has the mutation. This mutation could have occurred in the sperm or egg that was fertilized to produce the child. In some cases the mother will carry the *GNAS* mutation but not have any hormone problems (*i.e.* she has pseudo PHP), and will have only some features of Albright hereditary osteodystrophy. These mothers have likely inherited the defective *GNAS* gene from their fathers. So the severity of the disorder can vary by generation, but is always determined by the parent of origin of the mutant *GNAS* gene rather than by the process of inheritance *per se*.

Patients with PHP type 1b have mutations that are near *GNAS* and which alter the expression of G$\alpha$s protein. These mutations can be inherited from a mother who is a carrier, or may arise as a new mutation on a maternal gene.

If a woman has PHP type 1a or type 1b, she has the potential to pass the defective gene on to half of her children, who will develop the complete syndrome with hormone resistance. If a man has PHP type 1a or type 1b, he has the potential to pass the defective gene on to half of his children, but these children will be mildly affected. Children who inherit a defective *GNAS* gene from their father will not have hormone problems,

and will have pseudoPHP type 1a. Children who inherit a gene defect from a father with PHP type 1b will be normal carriers, but can pass the gene on to their children.

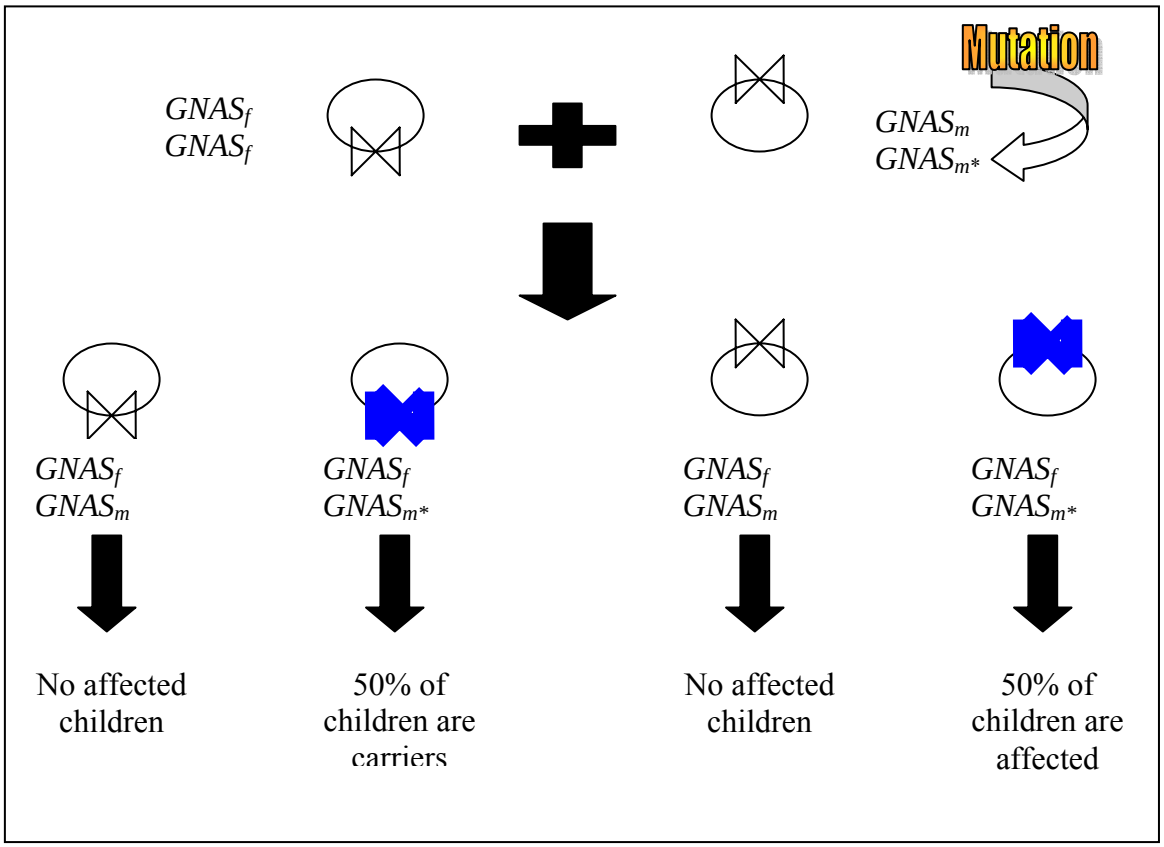


**Figure 3. Hypothetical Family Tree.**

This family tree shows a father and an unaffected mother who has a mutation in one of her *GNAS* genes (*GNAS*$_{m*}$). Either this is a mutation she inherited from her father, therefore does not have pseudohypoparathyroidism, or it occurs only in her eggs. They have 4 children, 2 boys and 2 girls. One of each are affected (colored bow/bowtie) because they have inherited the defective maternal gene (*GNAS*$_{m*}$). The other two are not affected. The affected girl will pass on the mutation to 50% of her children, who will develop PHP type 1a. The affected boy will pass the mutation to 50% of his children, who will develop pseudo PHP. The two unaffected children did not inherit the *GNAS*$_{m*}$ mutation, so their children will also be unaffected.

The treatment for pseudohypoparathyroidism relies on correcting the metabolic abnormalities – increasing calcium and vitamin D to normalize serum levels of calcium and phosphorous and at the same time to suppress (decrease) levels of PTH, which decreases bone destruction. Calcitriol supplements replace the deficient active vitamin D, increase calcium absorption and stimulate osteoblasts to build strong bones. Calcium supplements aid in the ability to increase calcium absorption from the gastrointestinal tract and increase the blood levels of calcium. The parathyroid glands respond to the increase in calcium, and decrease production and secretion of PTH. The decrease in PTH protects the bones from further damage that can result from a constantly high PTH (see Figure 2). Calcium and calcitriol supplements are successful in bringing the serum levels of calcium, calcitriol, and PTH to normal.

**References:**

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