FACT SHEET

What are the possible signs and symptoms?
Everyone with familial hypophosphatemia (X-linked or autosomal) has a low serum phosphorus level or hypophosphatemia. It is a whole-life, whole-body disorder, with symptoms that may include lower limb deformities, waddling gait, short stature, spontaneous tooth abscesses, bone pain, fatigue, calcifications, and muscle pain or weakness.

Can someone have familial hypophosphatemia when it has never occurred in the family before?
Yes. This is how each family's history begins. A spontaneous mutation occurs at conception, causing the familial hypophosphatemia to develop, and it is then heritable for future generations in that family.

How is familial hypophosphatemia passed on?
The gene responsible for XLH is located on the X chromosome and is inherited in a dominant manner:

> **An XLH father** will: Always pass the affected gene to his daughters and never pass the affected gene to his sons.
>
> **An XLH mother** will *with each pregnancy*: have a fifty percent chance of passing the affected gene to either sons or daughters.

There are also three ultra-rare versions where the genetic defect is not on the X chromosome, but is autosomal, and may be either dominant or recessive.

What causes familial hypophosphatemia?
Familial hypophosphatemia is a genetic (inherited or heritable) metabolic phosphate-wasting disorder generally caused by a mutation of the PHEX gene on the X chromosome, although it may also be a DMP1 or ENPP1 mutation. The mutation leads dysregulated vitamin D synthesis and elevated circulating levels of FGF23, a novel phosphate-regulating hormone. Elevated FGF23 leads to the inability of the kidney to retain phosphorus which leads to problems with bone/tooth mineralization, muscle formation and energy levels.

Is familial hypophosphatemia curable?
Not at present. However, the genes that carry the mutations have been identified, and dedicated researchers around the world continue their efforts to understand how they work. We remain hopeful that a cure will be found one day.

Is familial hypophosphatemia treatable?
Yes. A newly approved treatment known as burosumab has shown promising results in both children and adults. Burosumab is a monoclonal antibody that binds with the excessive Fibroblast Growth Factor 23 to reduce phosphate-wasting and improve vitamin D metabolism.

Before burosumab, the only treatment available was a delicate balance of activated vitamin D (calcitriol) and oral phosphate supplements. That treatment had potential adverse side-effects, including secondary hyperparathyroidism, hypercalcemia, and nephrocalcinosis. It also did not reduce the widespread, potentially disabling calcifications experienced by adults, including enthesopathy (calcification of tendons and ligaments) and osteophytes. The most commonly affected sites include the knees, ankles and spine.

How is familial hypophosphatemia diagnosed?
Genetic testing is available. Otherwise, the following may indicate a genetic cause of hypophosphatemia: Low serum phosphorus with elevated alkaline phosphatase and normal calcium; high urine phosphorus and a low tubular resorption rate for phosphorus; normal 25-hydroxy vitamin D levels, but low or inappropriately normal 1,25 dihyodroxy vitamin D levels; and elevated serum FGF23.

If an adult's serum (blood) phosphorus is above 2.5 mg/dL, can familial hypophosphatemia be present?
Yes. Serum phosphorus can sometimes be in the lower end of the normal range. Values as high as 3.1 mg/dL have been observed in XLH patients.

How should diagnostic tests be performed?
Blood should be drawn in the morning (phosphorus levels are lowest then) with the patient fasting (foods can affect the results). Results must be compared to age-appropriate reference ranges. Many labs only include an adult reference range for phosphorus, which is lower than the pediatric reference range.

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