

## FGF23, PEX and Hypophosphatemic Rickets

Hypophosphatemia occurs in a number of clinical settings, perhaps most apparent to pediatric endocrinologists and medical geneticists in X-linked and in the less common autosomal dominant forms of hypophosphatemic rickets, XLHR and ADHR, respectively. Both conditions are characterized by short stature, bow legs, hypophosphatemia, and radiographic changes of rickets and osteomalacia. A picture that explains the pathogenesis of these 2 inherited disorders and relates them to tumor-induced osteomalacia is beginning to emerge, and it involves an unlikely candidate, a relatively new member of the fibroblast growth factor (FGF) family, FGF23.

The recent story begins in 1995 with the identification by the HYP Consortium of mutations in a gene that maps to chromosome Xp22.1 in patients with XLHR.<sup>1</sup> The gene, which encodes a protein whose amino acid sequence suggests it is a neutral endopeptidase, was called *PEX* for "phosphate regulating gene with homologies to endopeptidases on the X chromosome." However, the substrates for *PEX* were not known. A number of mutations have subsequently been found that predict loss of function for the putative enzyme.<sup>2</sup>

The next chapter occurred in late 2000 with the positional cloning of FGF23 as the gene that harbors mutations responsible for ADHR.<sup>3</sup> Of note was that the mutations in 4 families studied mapped to 1 of 2 closely spaced arginine residues at positions 176 or 179 of FGF23.

Most recently, Shimada et al have shown that FGF23 is produced abundantly in tumor-induced osteomalacia.<sup>4</sup> They first cloned a highly expressed cDNA from an osteomalacia-inducing tumor, showing that it encoded FGF23. Next, they demonstrated that injection of FGF23 into mice reduced serum phosphate levels within 12 hours. They then showed that trans-

plantation of CHO cells expressing and secreting FGF23 into nude mice led to hypophosphatemia; increased phosphate renal clearance; high alkaline phosphatase and inappropriately low 1,25-dihydroxy-vitamin D levels in association with bone deformities; osteomalacia; and widening of the growth plate typical of rickets. Shimada et al were unable to demonstrate direct effects of FGF23 on phosphate transport in renal epithelial cells (OK cells) in culture, raising the possibility that FGF23 acts indirectly on renal phosphate transport. However, in an independent study, Bowe et al documented that FGF23 does block phosphate resorption in this cell culture model of renal proximal tubule epithelia.<sup>5</sup>

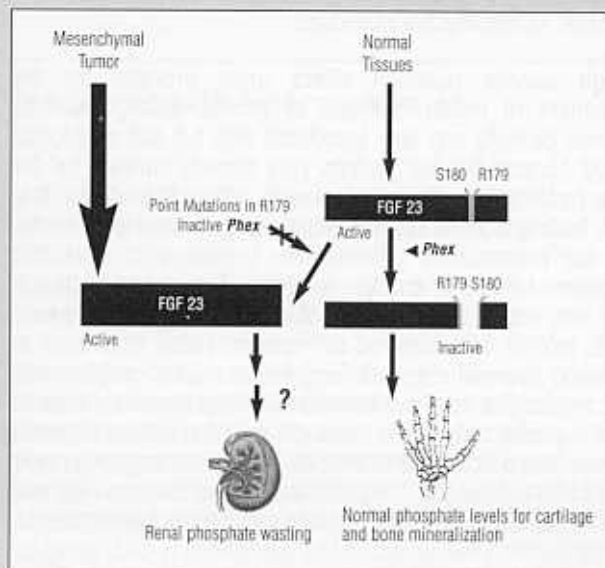
As this story evolved, the idea emerged that FGF23 is a substrate for *PEX* and that loss of *PEX* function in XLHR leads to an accumulation of FGF23 in serum and in kidney tissues, where it blocks renal phosphate resorption. Supporting this possibility is that the arginine residues (Arg176 and Arg179) that are mutated in all 4 families with ADHR are part of a consensus recognition sequence for endopeptidases, such as *PEX*. Indeed, Bowe et al have now confirmed that FGF23 is a substrate for *PEX* cleavage and that FGF23 harboring the Arg179Gln missense ADHR mutation is not cleaved in an *in vitro* assay.<sup>5</sup>

1. HYP Consortium. *Nat Genet* 1995;11:130-136.
2. White KE, et al. Autosomal dominant hypophosphatemic rickets is associated with mutations in FGF23. *Nat Genet* 2000;26:345-348.
3. Sabbagh Y, Jones AO, Tenenhouse HS. *Hum Mutat* 2000;16:1-6.
4. Shimada T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Nat Acad Sci USA* 2001;98:6500-6505.
5. Bowe AE, et al. FGF-23 inhibits renal tubular phosphate transport and is a *PEX* substrate. *Biochem Biophys Res Commun* 2001;284:977-981.

Figure  
Proposed Pathogenesis of Renal  
Phosphate Wasting

Mesenchymal tumors produce renal phosphate wasting by overproduction of FGF23 levels can also be increased by mutations in *Phex*, a protease that cleaves and inactivates the molecule, or by mutations at key arginine residues that render FGF23 resistant to cleavage by *Phex*. FGF23 excess causes phosphate wasting either directly or by inducing another phosphaturic factor.

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**Editor's comment:** These articles document that FGF23 is an important modulator of phosphate homeostasis and that this process is regulated at least in part by PEX through degradation of the growth factor. They further demonstrate that FGF23 levels and resulting phosphate homeostasis can be altered through several mechanisms, including excess production by tumors and by slowed degradation either because the enzyme that normally cleaves FGF23 is ineffective due to mutation or because the growth factor itself is mutated so that it is resistant to degradation. This concept is discussed in depth by Strewler and depicted in the Figure on page 47.

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Strewler GJ. FGF23, hypophosphatemia, and rickets: has phosphatonin been found? *Proc Nat Acad Sci USA* 2001;98:5945-5946.

**Second editor's comment:** This work illustrates the treasure trove of genetic data already available from the Human Genome Project waiting to be mined for relevance to human physiology and pathophysiology. PEX is expressed by osteoblasts, and it has been hypothesized that "phosphatonin" also may be

synthesized by these cells.<sup>1</sup> In normal mouse embryos, the murine homologue *Fgf23* maps to chromosome 6. The present investigators were unable to demonstrate expression of *Fgf23* in the tibiae of embryonic mice, perhaps suggesting that FGF23 is not "phosphatonin." Tumors that secrete a phosphate-wasting product leading to rickets or osteomalacia have been demonstrated by the same group to express FGF23 mRNA and to synthesize FGF23 protein.<sup>2</sup> However, it has not as yet been shown that FGF23 has phosphaturic activity or acts upon yet another molecule, the still elusive "phosphatonin."<sup>3</sup>

Allen W. Root, MD

1. Ecarot B, Desbarats M. 1,25-(OH)<sub>2</sub>D<sub>3</sub> down-regulates expression of PHEX, a marker of the mature osteoblast. *Endocrinology* 1999;140:1192-1199.
2. White KE, et al. The autosomal dominant hypophosphataemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. *J Clin Endocrinol Metab* 2001;86:497-500.
3. Quarles LD, Drezner MK. Pathophysiology of X-linked hypophosphatemia, tumor-induced osteomalacia, and autosomal dominant hypophosphatemia: a perPHEXing problem. *J Clin Endocrinol Metab* 2001;86:494-496. Editorial.

## Ethical Issues With Genetic Testing in Pediatrics

Advances in genetic research and emerging genetic technology are enabling testing and screening to be implemented before a full understanding of the ramifications has been developed. Clearly, new developments in genetics should be made available if they promote the best interest of the patient, in this case the child. The Committee on Bioethics of the American Academy of Pediatrics (AAP) reviewed the issues involved in genetic testing and put forward principles that should be considered before genetic testing is provided to an infant, child, or adolescent. Their report cites the Institute of Medicine's report of 1994 assessing genetic risks, implications for health, and social policy in which 3 principles were described for the introduction of new genetic tests: (1) Identification of the genetic condition must provide a clear benefit to the child; (2) a system must be in place to confirm the diagnosis; and (3) treatment and follow-up must be available for the affected individuals.

Although genetic research offers great promise for the improvement of health, the use of genetic testing must be considered carefully and only introduced with full and appropriate informed consent for the parents who provide consent for the child to have testing. There are several critical reasons for this. Genetic testing is different than other types of laboratory testing since the information obtained is familial and thus has implications for other family members. The risks of genetic testing may not be obvious but include psychosocial risks such as guilt, anxiety, and impaired self-esteem, social risks such as stigma, and financial risks involving insurance and employment. Genetic information may have limited predictive power since diseases are very complex and there are multiple environmental and genetic variables. Genetic conditions may be difficult to treat or prevent without additional research. The positive aspects of making a diagnosis should be demonstrated before screening tests are implemented.

The AAP committee report points out that there are insufficient numbers of genetic professionals (genetic counselors and

clinical geneticists) to have primary responsibility for managing the use of genetic testing, and, thus, primary care physicians must become knowledgeable about both the limitations and the positive aspects of genetic screening in children. It is particularly important to provide or refer children for counseling and testing only when it is in the best interest of the child and when testing and counseling can be provided without anticipated harm to the child.

The committee report is broken down into newborn screening, carrier screening, and predictive testing for late-onset disorders. Under newborn screening, it is reiterated that the purpose of newborn screening for genetic disorders is to limit the morbidity and mortality attributable to these inherited diseases. The report indicates that mandatory and voluntary screening should be distinguished. It strongly suggests that informed consent and voluntary screening occur rather than mandatory screening. The informed consent improves the efficiency of response to positive results and incorporates outcomes research if parents are already involved in making the decision to screen. Newborn screening protocols for phenylketonuria and hypothyroidism have been the model for early diagnosis, leading to improved treatable outcomes; however, the evaluation of the consequence of informed refusal is not yet available.

Screening programs to detect carriers are associated with significant concerns about the possibility for communities to misunderstand the carrier state, leading to stigma and discrimination against the identified carrier, as well as the possibility of adverse psychological reactions. Nevertheless, carrier testing for pregnant adolescents or adolescents who plan pregnancies may well be appropriate.

Predictive testing for late-onset disorders is as yet poorly understood and in general should be delayed until an autonomous decision by the individual to have this type of