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Isolated renal phosphate wasting presenting with palpitations and light-headedness in a male with digenic heterozygous missense mutations in *SLC34A1* and *SLC34A3*

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Clinical Presentation

The patient is a 46 year (y.) old male with atrial fibrillation (AFib) and ulcerative colitis. He reportedly had bowing of the lower extremities at age 5 y., which had resolved spontaneously. At age 33 he presented with AFib and was started on sotalol and warfarin. He sustained a tibial plateau fracture at age 41 while running on a treadmill. He denied any personal history of kidney stones. His family history includes kidney stones in his father, diabetes in his mother, colon cancer in his brother, and a sister with ulcerative colitis. There is no family history of skeletal disorders and all family members achieved average adult heights. In the months prior to his hospital admission, he had several emergency room visits for light-headedness and palpitations with a heart rate of 160 beats per minute picked up by his smart-watch. Electrocardiogram (ECG) showed sinus tachycardia during these visits. On one of these visits, his phosphorus levels were checked and found to be extremely low (0.9mg/dL; normal 2.2 – 4.5 mg/dL). He was admitted for cardiac monitoring and since he continued to have low serum phosphorus levels, he was discharged with oral phosphate supplements and calcitriol, and referred to our endocrinology clinic for further evaluation.

Differential diagnosis of Renal Phosphate Wasting Disorders

PTH-dependent

- Hyperparathyroidism (primary or secondary)
- PTHrP-dependent hypercalcemia of malignancy

FGF23-dependent

- Familial hypophosphatemic rickets (i.e. XLH, ADHR, ARHP1-3)
- Tumor-induced osteomalacia (TIO)
- Fibrous dysplasia (McCune-Albright Syndrome)

FGF23-independent

- Fanconi Syndrome (i.e. RTA, Dent's disease)
- Idiopathic infantile hypercalcemia (IIH) due to *SLC34A1*/NPT2a mutation
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) due to *SLC34A3*/*NPT2c* mutation

PTH – parathyroid hormone; PTHrP – parathyroid hormone related peptide; FGF23 – Fibroblast growth factor 23; XLH – X-Linked hypophosphatemia, ADHR – autosomal dominant hypophosphatemic rickets; ARHP1-3 – autosomal recessive hypophosphatemic rickets; NPT2a – Sodium-dependent phosphate co-transporter 2a, NPT2c – Sodium-dependent phosphate co-transporter 2c; RTA - rental tubular acidosis.

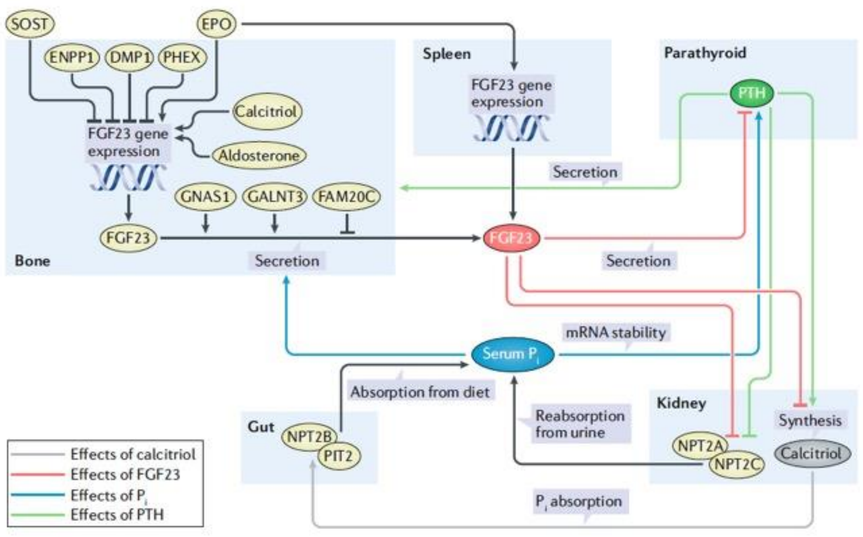
Results

	Presentation	Off Supplementation	On Supplementation	Reference
Phosphorus	0.9	1.9 - 2.1	2.3- 3.1	2.2 - 4.5 mg/dL
Ca	9.3	8.7 - 9	8.9	8.8 - 10.2 mg/dL
Cr	1.18	1.22 - 1.24	1.27-1.3	0.40 1.30 mg/dL
1,25-D	-	57	49	25 - 66 pg/mL
iPTH	-	27.7	33.5	15 - 65 pg/mL
FGF23	-	76 - 77	101 - 116	< 180 RU/mL
TRP%	-	67.8 - 70.8	44.9-61.7	85 -95%
Urine Ca/Cr	-	0	0 - 0.05	< 0.14

1,25-D - 1,25(OH)2-vitamin D; iPTH – intact parathyroid hormone, FGF23 – fibroblast growth factor 23; TRP% - tubular reabsorption of phosphate; Ca – calcium, Cr - creatinine

FDG-PET	No hypermetabolic masses or lymphadenopathy
Genetic Testing	SLC34A3:NM_080877:exon13:c.C1402T:p.R468W SLC34A1:NM_003052:exon8:c.G874A:p.G292S

Figure 1. Pathways of total body phosphate homeostasis [3]



Discussion

The patient described here had a tubular reabsorption of phosphorus of 67.8-76.6% (85 – 95%) which, in light of severe hypophosphatemia, is diagnostic for renal phosphorus wasting [1]. There was no evidence of non-gap acidosis, aminoaciduria, or glucosuria making Fanconi syndrome unlikely. Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) are the major phosphaturic hormones that promote renal phosphate excretion by inhibiting sodium-dependent phosphate co-transporters 2A (NPT2a) and 2C (NPT2c) in the proximal tubule [2]. These transporters are expressed in the proximal renal tubule and are important for phosphate reabsorption. Since PTH was within normal limits, and he presented in adulthood with an inappropriately normal FGF23 we initially suspected the acquired FGF23-dependent disorder tumor-induced osteomalacia (TIO), which is caused by vascular phosphaturic mesenchymal tumors (PMTs) that produce FGF23 in a paraneoplastic fashion leading to isolated hypophosphatemia. FDG-PET testing however did not show any hypermetabolic masses. Although TIO tumors are often small and difficult to identify, we decided to proceed with genetic testing for a panel of genes involved in other hypophosphatemic disorders. This genetic test detected heterozygous missense mutations in *SLC34A1* and *SLC34A3* that encode NPT2a and NPT2c respectively. Biallelic mutations in *SLC34A1* cause idiopathic infantile hypercalcemia (IIH). Biallelic *SLC34A3* mutations cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH). Heterozygous carriers of mutations in these transporters have milder symptoms often causing hypercalciuria and kidney calcifications. Our patient is the second report of an individual with digenic heterozygous mutations in *SLC34A1* and *SLC34A3* [4].

Conclusions

Biallelic mutations in *SLC34A1* and *SLC34A3* have been classically associated with autosomal recessive hypophosphatemic rickets and hypercalciuria. Mild rickets as a child, which resolved spontaneously, and absence of hypercalciuria and renal calcifications illustrate the high degree of phenotypic variability in our patient. His atypical presentation with AFib at age 31 furthermore highlights the importance to include phosphorus in the initial evaluation of arrythmias [5].

References

1. Bergwitz, C. and K. I. Miyamoto (2019). "Hereditary hypophosphatemic rickets with hypercalciuria: pathophysiology, clinical presentation, diagnosis and therapy." Pflugers Arch 471(1): 149-163.
2. Melmed, S., Melmed, S., Melmed, S., Larsen, P. R., Kronenberg, H., Larsen, P. R., . . . Polonsky, K. S. (2015). *Williams textbook of endocrinology*. Philadelphia, PA: Elsevier.
3. Chande, S. and C. Bergwitz (2018). "Role of phosphate sensing in bone and mineral metabolism." Nat Rev Endocrinol 14(11): 637-655.
4. Gordon, R. J., et al. (2020). "Digenic Heterozygous Mutations in SLC34A3 and SLC34A1 Cause Dominant Hypophosphatemic Rickets with Hypercalciuria." J Clin Endocrinol Metab 105(7).
5. Schwartz, A., et al. (2014). "Association between Hypophosphatemia and Cardiac Arrhythmias in the Early Stage of Sepsis: Could Phosphorus Replacement Treatment Reduce the Incidence of Arrhythmias?" Electrolyte Blood Press 12(1): 19-25.