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Genetic Disorders of Renal Phosphate Transport

TO THE EDITOR: In their comprehensive review of genetic disorders of renal phosphate transport, Prié and Friedlander (June 24 issue)¹ claim that the role of NPT2a in renal phosphate handling has been shown by the association between heterozygous mutations in *NPT2a* and renal phosphate leak.² However, Virkki et al.³ found no dominant negative effect of these *NPT2a* variants, which indicates that they are polymorphisms. Lapointe et al.⁴ also identified *NPT2a* variants in patients with renal phosphate leak, but ruled out their functional significance by the finding of normal renal phosphate balance in family members carrying the same variants. The major contribution of *NPT2a* to renal phosphate balance was definitively established in a recent article in the *Journal* that reported autosomal recessive hypophosphatemic rickets with renal Fanconi's syndrome secondary to a loss-of-function mutation in *SLC34A1* (also known as *NPT2a*), the gene that encodes NPT2a (also known as NaPi-IIa).⁵

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No potential conflict of interest relevant to this letter was reported.

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4. Lapointe JY, Tessier J, Paquette Y, et al. NPT2a gene variation in calcium nephrolithiasis with renal phosphate leak. *Kidney Int* 2006;69:2261-7.
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5q35, which removed the *NSD1* and *NPT2a* genes. The cause of the Sotos syndrome, which is manifested by macrocephaly, bone overgrowth with advanced bone age, and mental retardation,² is haploinsufficiency of the *NSD1* gene.³ The index patient presented with severe hypophosphatemia in the neonatal period (serum phosphorus level, 0.4 to 0.9 mg per deciliter; normal range, 4.8 to 8.2), which persisted but was less pronounced during later years (3.7±0.6 mg per deciliter). The maximum tubular reabsorption of phosphate normalized for the glomerular filtration rate measured at the age of 4 years was 3.4 mg per deciliter (reference range for age, 4.6±0.6). Serum levels of calcium and parathyroid hormone remained in the normal range, but 1,25-dihydroxyvitamin D₃ levels were slightly elevated. Nephrocalcinosis, rickets, and osteoporosis were not present. Five other patients with the Sotos syndrome who had mutations that did not affect *NPT2a* had normophosphatemia. Our observation broadens the clinical spectrum of the Sotos syndrome and indicates that a haploinsufficiency of *NPT2a* is sufficient to cause hypophosphatemia.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The review by Prié and Friedlander discusses hypophosphatemia with nephrolithiasis and bone demineralization due to heterozygous mutations in *NPT2a*.¹ We observed hypophosphatemia in a boy with the Sotos syndrome due to a heterozygous microdeletion on

THE AUTHORS REPLY: Magen et al. reported on two relatives with a Fanconi's syndrome, renal insufficiency, and a homozygous mutation in *SLC34A1*, which encodes NPT2a.¹ This phenotype was more complex than that of patients with heterozygous *NPT2a* mutations.² It is surprising that

the decrease in NPT2a expression alone could explain the whole phenotype. These unexpected features might result from intracellular accumulation of this particular mutant protein and thereby in a toxic effect on renal cells. This property is not necessarily shared with other *NPT2a* mutants. In these highly consanguineous patients, additional mutations in genes other than *NPT2a* could also participate. This important paper was published while our review article was at an advanced stage of the publication process, thereby preventing us from discussing it.

We previously reported the association between heterozygous *NPT2a* mutations and renal phosphate loss.² These mutations decreased phosphate transport; the coexpression of wild-type and mutated *NPT2a* proteins in oocytes resulted in phosphate transport that was lower than expected, a result that we interpreted as a dominant negative effect of mutant *NPT2a*. Virkki et al. confirmed that the mutations we had identified markedly decreased *NPT2a* activity.³ These authors did not, however, detect a dominant negative effect of the *NPT2a* mutants by introducing a cysteine residue in *NPT2a*, under the assumption that this modification would reveal an interaction between wild-type and mutant *NPT2a*. However, the validity of an interaction between wild-type and mutant *NPT2a* is unknown.

Lapointe et al. found no association between hypophosphatemia and a previously unidentified

variant of *NPT2a*.⁴ No definitive conclusion can be drawn, however, regarding the consequences of other mutations.

The data reported by Levtschenko et al. suggest that *NPT2a* haploinsufficiency can induce hypophosphatemia, an observation consistent with the defect of renal phosphate transport seen in patients with *NPT2a* heterozygous mutations.

As detailed in our most recent review, mutations in genes other than *NPT2a* may lead to decreased *NPT2a* expression and thus to renal phosphate loss and hypophosphatemia. This enlightens the central role of *NPT2a* in phosphate homeostasis.

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Since publication of their article, the authors report no further potential conflict of interest.

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Acupuncture for Chronic Low Back Pain

TO THE EDITOR: In their review article, Berman et al. (July 29 issue)¹ discuss the use of acupuncture for chronic low back pain. Acupuncture, which originated in China, has been practiced there and in other Asian countries for thousands of years. The selection of acupuncture points and manual manipulation are performed according to the diagnosis and as determined by the theories of traditional Chinese medicine. However, when acupuncture is studied by practitioners of conventional medicine, insertion points are selected from lists of commonly used points on the basis of the diagnosis as determined by conventional medicine.²⁻⁶

In traditional Chinese medicine, the diagno-

sis, which is based on inquiry, inspection, olfaction, auscultation, percussion, palpation, and pulse examination, guides point selection and manual manipulation for every acupuncture point in each treatment session. The lack of a correct diagnosis on this basis could explain the reported result that real acupuncture was no more effective than sham acupuncture in the clinical trials that were cited by Berman et al.

The diagnostic assessments of both conventional and traditional Chinese medicine are required for tailored acupuncture treatment. Further studies to evaluate the efficacy of acupuncture should incorporate the diagnosis according to traditional Chinese medicine.