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Hypophosphatemia: Mouse model for human familial hypophosphatemic (vitamin D-resistant) rickets

(X-linkage/phosphate transport/animal model)

EVA M. EICHER*, JANICE L. SOUTHARD*, CHARLES R. SCRIVER†, AND FRANCIS H. GLORIEUX‡

* The Jackson Laboratory, Bar Harbor, Maine 04609; † Departments of Biology and Pediatrics, McGill University, and the deBelle Laboratory for Biochemical Genetics, McGill University-Montreal Children's Hospital Research Institute, 2300 Tupper Street, Montreal, P.Q., Canada H3H 1P3; and ‡ The Genetics Unit, Shriners Hospital, 1529 Cedar Avenue, and Departments of Pediatrics and Experimental Surgery, Faculty of Medicine, McGill University, Montreal, Canada

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ABSTRACT **A new dominant mutation in the laboratory mouse, hypophosphatemia (gene symbol *Hyp*), has been identified. The *Hyp* gene is located on the X-chromosome and maps at the distal end. Mutant mice are characterized by hypophosphatemia, bone changes resembling rickets, diminished bone ash, dwarfism, and high fractional excretion of phosphate anion (low net tubular reabsorption). Phosphate supplementation of the diet from weaning prevents the appearance of severe skeletal abnormalities. The hypophosphatemic male mouse resembles human males with X-linked hypophosphatemia and the *Hyp* gene is presumably homologous with the X-linked human gene. The mouse model should facilitate study of the defect in transport of plasma inorganic phosphate anion.**

Familial vitamin D-resistant rickets or X-linked hypophosphatemia (XLH) is characterized by X-linked dominant inheritance. Affected individuals have essentially normal serum calcium levels, hypophosphatemia, impaired net renal tubular reabsorption of phosphate anion, shortened stature, and vitamin D nonresponsive rickets or osteomalacia (1, 2). Although several hypotheses have been put forth, precise etiology of the disease remains unknown.

We report the discovery of an X-linked dominant mutation named hypophosphatemia (gene symbol *Hyp*) in the laboratory mouse. Our findings indicate that the disease seen in the hypophosphatemic mouse is similar to XLH. Because both diseases are inherited as X-linked dominants, it is highly probable that the human and mouse diseases are caused by mutations affecting the homologous gene. Accordingly, the mouse should be a valuable model for elucidation of the basic defect in human XLH.

MATERIALS AND METHODS

Origin and Genetics. In 1966, six male mice with shortened trunk and hind limbs were noted in a linkage experiment at the Jackson Laboratory. By appropriate crosses, the new mutation was shown to be dominant and X-linked. Because the affected mice had a low serum phosphorus concentration, the mutation was named hypophosphatemia, gene symbol *Hyp*. Soon after its discovery, the mutant *Hyp* allele was transferred to the C57BL/6J inbred strain by repeated matings of *Hyp*/+ females to C57BL/6J +/Y males. All growth and physiological studies were conducted on mice of the C57BL/6J-*Hyp* strain.

Diet. Unless otherwise noted, all mice were fed the mouse diet Old Guilford 96W containing 22.5% protein, 7.5% fat, 0.6% vitamin supplement, 0.22% calcium, and 0.74% phosphorus (wt/wt). The drinking water was acidified. Food and water were available *ad libitum*.

Linkage. In order to determine the position of *Hyp* on the X chromosome, the following experiment was conducted. Females that were + + *Hyp*/+ + + were mated to a *Ta Bn* +/Y male (*Ta* = tabby; *Bn* = bent-tail). The (*Ta Bn* +/+ + *Hyp*)F_1 females were mated to + + +/Y CBA/J males. All offspring were classified for *Ta* (coat texture and color), *Bn* (bent, shortened tail), and *Hyp* (shortened hind limbs).

Body Weight. Offspring produced by matings of *Hyp*/+ females to +/Y males were weighed at birth, toe-clipped for future identification, and weighed weekly until 43 days of age. The young were isolated from their parents at 21 days of age and separated by sex.

Plasma Inorganic Phosphate and Calcium. Plasma inorganic phosphate (P_i) was determined by the method of Mattenheimer (3), modified for 50- to 100-μl samples, on *Hyp*/+ and +/+ females and *Hyp*/Y and +/Y males ranging in age from 20 to over 400 days. Plasma calcium was measured with the Monitor calcium kit (Fisher Scientific Co.) on 35- to 300-day-old individuals. Unless otherwise noted, plasma was collected between 10:00 a.m. and 1:00 p.m.

Renal Excretion of P_i. Mice (10 *Hyp*/Y, 10 +/Y, 200 days of age) were housed in Gelman metabolic cages while urine was collected for 6 hr, in the morning, under fasting conditions. At the end of the collection period, blood was drawn by orbital sinus puncture. Serum was separated from the cells immediately and urine was acidified for phosphate measurement.

Renal Cortex P_i. The P_i concentration in supernatants of 5% cold trichloroacetic acid homogenates of renal cortex was determined by the method of Vestergaard-Bogind (4).

Effect of Diet Composition on Serum and Urine P_i. The effect of dietary calcium and phosphate on levels of serum and urine P_i was examined in two sets of eight *Hyp*/Y males and two sets of six +/Y males (240–270 days of age) fed one of two diets (described in Table 4) for 7 days before the experiment. Urine was collected as described above.

Phosphate-Supplemented Drinking Water. A phosphate-supplemented diet ameliorates the rickets (or osteomalacia) in XLH human subjects (5). This therapy, therefore, was applied to hypophosphatemic male mice. Eight *Hyp*/Y and three +/Y males, 3–4 weeks of age, were given acidified drinking H_2O *ad libitum* containing phosphate salts (Na_2HPO_4, 6.75 g and KH_2PO_4, 2.0 g per liter). Four *Hyp*/Y and three +/Y males of the same age were kept on acidified drinking H_2O. The mice were observed weekly by one of us (E.M.E.) for obvious changes in their hind limbs. Representatives of each genotype and treatment were killed after 11 or 18 weeks of phosphate therapy. Skeletons were prepared according to the method of Green (6), as modified by Eicher and Beamer (7).

Other Measurements. Serum immune reactive parathyroid hormone was measured in three *Hyp*/Y and three +/Y males with CH-12M antiserum at the Shriners Hospital by standard immunoradioassay. The chicken antiserum, kindly provided by Dr. Claude Arnaud of the Mayo Clinic, senses COOH- and

Abbreviation: XLH, X-linked hypophosphatemia.

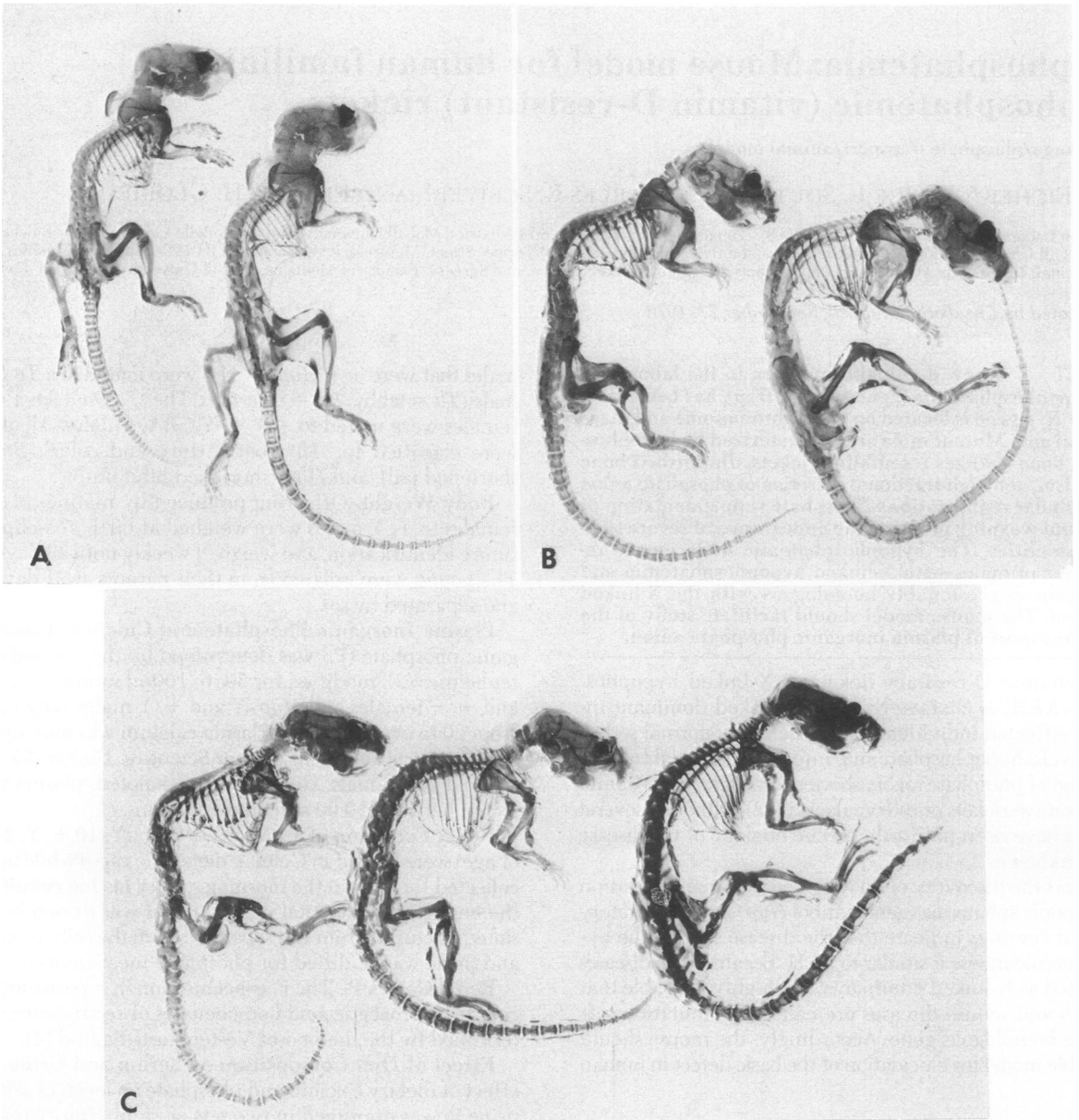

FIG. 1. Skeletal preparations from *Hyp*/Y and +/Y males. The left fore limbs and hind limbs of those mice in panels B and C were removed. (A) One-month-old *Hyp*/Y (left) and +/Y littermate. (B) Five-month-old *Hyp*/Y male (left) and +/Y littermate. In both cases, the *Hyp*/Y male is significantly smaller than his +/Y littermate. Comparison of the *Hyp*/Y males in panels A and B reveals the kyphosis of the spine and rachitic rosary that develops as the disease progresses. (C) Two *Hyp*/Y males and one +/Y littermate (right) 4 months old. The *Hyp*/Y male in the center has been on a phosphate-supplemented diet since he was 1 month old. In this male there is no kyphosis of the spine, reduced rachitic rosary, and evidence of growth of the long bone (note femur) compared to his *Hyp*/Y male sibling maintained on a normal diet.

NH_2-terminal fragments and the whole molecule of chicken parathyroid hormone, and it crossreacts with rodent and human parathyroid hormones. Bone ash weight and the calcium: phosphorus ratio were measured by standard methods.

RESULTS

General Phenotype. In matings of *Hyp*/+ female by +/Y male on the C57BL/6J inbred background, *Hyp*/+ and *Hyp*/Y individuals can be distinguished from their normal siblings at 21 days of age by their shortened hind limbs and tail (Fig. 1). On a hybrid background (observed as a consequence of the linkage experiments, see below), 10–20 more days are necessary in order to note a clear difference. Irrespective of background, the reduced body size persists throughout life. Kyphosis of the thoracic vertebrae, rachitic rosary, and prominent bowing of the femur develop with age in mutant mice (Fig. 1). These skeletal abnormalities are more uniformly severe in the male compared to the female. Mutant animals may eventually develop extreme impairment of mobility from what appears to be a "locking" of the femur to the pelvic girdle. This condition did not appear to reduce the life span of hypophosphatemic males and females, since both survived to well over 2 years of age. Bone ash is reduced in *Hyp*/Y males (39.8% wt/wt) compared to +/Y siblings (59.1% wt/wt). In addition, the calcium:phosphorus ratio is similar in both (about 2:1). The values are the mean of triplicate determinations in 30-mg samples of bone from three male mice of each genotype.

Hyp/+ females are fertile and raise their young. Not all

Table 1. X-Linkage of *Hyp*

Chromosome from ♀ parent	Number of offspring ♀	♂	Total
Bn *Ta* +	47	31	78*
+ + *Hyp*	54	69	123
+ *Ta* +	22	8	30
Bn + *Hyp*	9	1	10*
Bn *Ta* *Hyp*	14	14	28*
+ + +	34	23	57
+ *Ta* *Hyp*	3	1	4
Bn + +	3	1	4*
Total	186	148	334

Cross: *Bn Ta* +/+ + *Hyp* ♀ × + + +/Y ♂.

* One hundred twenty offspring used to calculate gene order and distance.

Hyp/Y males successfully sire offspring. Those that do may sire only one or two litters.

Linkage. The X-linked loci *Ta* and *Bn* were used to locate the position of *Hyp* on the X chromosome. The offspring produced from the cross *Bn Ta* +/+ + *Hyp* female × + + +/Y male are given in Table 1. Because the *Bn* mutation does not have complete penetrance, only the animals known to receive the *Bn* rather than the + allele from their mother were considered in calculated gene order and distance. The order of loci as percentage recombination ± standard error of the mean is: *Bn*—11.8 ± 2.9—*Ta*—26.7 ± 4.0—*Hyp*. This places *Hyp* at the distal end of the mouse X chromosome.

Growth. The mean weight values obtained for the hypophosphatemia females and males and their normal siblings are given in Fig. 2. The body weight of *Hyp*/Y males as compared to +/Y male siblings is significantly reduced by 8 days of age ($P < 0.05$) and remains so through 43 days of age. The weight of *Hyp*/+ females as compared to +/+ female siblings is significantly reduced by 22 days of age ($P < 0.01$) and remains so up to 43 days of age. Thus, the effect of the *Hyp* mutation is evident before weaning in the *Hyp*/Y males, and by weaning in *Hyp*/+ females. A single dose of the + allele in the *Hyp*/+ females does enhance growth up to weaning. A normal sexual dimorphism of body weight between normal female and male C57BL/6J mice is observed by 36 days of age (7); this finding was not observed in the hypophosphatemic females and males.

Plasma Calcium and Phosphorus. Data for plasma calcium and P_i are given in Tables 2 and 3. The *Hyp*/+ females have

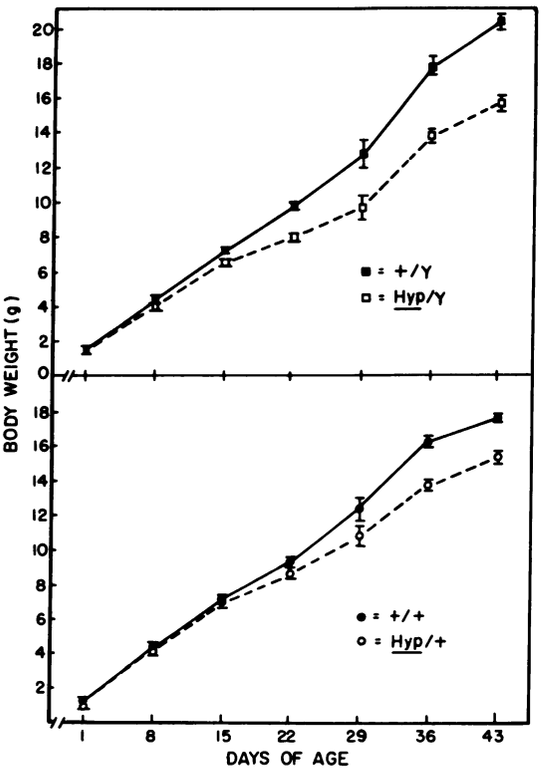

FIG. 2. Growth of hypophosphatemic mice and their normal sibling controls, 1–43 days of age. Open circles and squares are *Hyp*/+ and *Hyp*/Y individuals, respectively. Closed circles and squares are +/+ and +/Y individuals, respectively. Standard errors are shown for each point.

slightly but significantly lower plasma calcium than do +/+ females by 35–49 days of age ($P < 0.05$), and lower values continue to over 200 days of age. The same is true for *Hyp*/Y compared to +/Y males. Plasma P_i is significantly reduced in *Hyp*/+ compared to +/+ females ($P < 0.05$) and *Hyp*/Y compared to +/Y males ($P < 0.05$) by 20–49 days of age. These differences persist up to and beyond 400 days of age.

Our data show that plasma P_i in C57BL/6J mice is higher during rapid growth that in mature adults, as it is in the growing human subject. Furthermore, the plasma P_i in mice appears to decline slowly between 20 and 400 days in +/+ and +/Y individuals. Although *Hyp*/Y males and *Hyp*/+ females do appear to have a decline in plasma P_i between 20 and 100 days, a continual decline after 100 days was not apparent.

Phosphaturia and Urine Composition. Urinary P_i excretion

Table 2. Plasma phosphate levels (mg/100 ml) of hypophosphatemic and normal mice

Sex	Genotype	Age in days* 20–49	50–99	100–199	200–299	300–399	400–750
♀	*Hyp*/+	4.81 ± 0.14 (33)	4.47 ± 0.13 (27)	3.99 ± 0.30 (12)	3.68 ± 0.28 (10)	4.21 ± 0.14 (13)	3.97 ± 0.12 (14)
	+/+	8.11 ± 0.23 (23)	7.00 ± 0.21 (22)	6.03 ± 0.28 (10)	6.25 ± 0.39 (6)	6.15 ± 0.22 (11)	5.83 ± 0.60 (3)
♂	*Hyp*/Y	4.13 ± 0.09 (43)	3.77 ± 0.12 (25)	3.29 ± 0.17 (17)	3.36 ± 0.27 (5)	3.60 ± 0.17 (20)	4.26 ± 0.73 (5)
	+/Y	7.86 ± 0.17 (25)	6.62 ± 0.26 (17)	6.96 ± 0.39 (9)	5.60 (1)	6.43 ± 0.16 (14)	5.73 ± 0.18 (4)

* Values are presented as mean ± SEM. The values of *Hyp*/+ compared to +/+, and *Hyp*/Y compared to +/Y are significantly different ($P < 0.05$) for each age group by *t*-test for groups of unequal size. Numbers in parentheses are numbers of individuals tested.

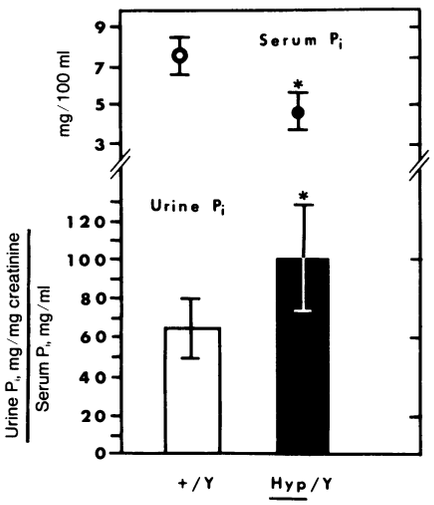

FIG. 3. Urinary P_i excretion in relation to serum P_i in 10 +/Y and 10 *Hyp*/Y mice. The mice (200 days of age) were fed a diet containing 0.72% (wt/wt) phosphorus and 0.67% (wt/wt) calcium. P_i excretion is increased relative to serum P_i in *Hyp*/Y animals. * Indicates statistical significance of finding ($P < 0.001$).

is similar in +/Y and *Hyp*/Y mice, when expressed as a coefficient of creatinine excretion (9). However, when P_i excretion is related to plasma P_i, the urinary excretion is significantly elevated in *Hyp*/Y mice (Fig. 3). Fractional excretion of phosphate in bladder urine, determined by an infusion method at endogenous plasma P_i in the anesthetized mouse, is 0.20 ± 0.09 (mean ± SEM) in normal mice and 0.35 ± 0.08 in *Hyp*/Y ($P < 0.01$) (three pairs of one +/Y and one *Hyp*/Y males were used). These values are comparable to fractional P_i excretion in bladder urine of normal and XLH human subjects, respectively.

Urinary P_i excretion in relation to serum P_i remained elevated in *Hyp*/Y mice as compared to +/Y mice under various conditions of dietary phosphate and calcium intake (Table 4). Plasma P_i is diminished and urinary P_i excretion is increased at the usual dietary Ca:P_i ratio of 0.3. Hypophosphatemia and hyperphosphaturia are still apparent when the dietary Ca:P_i ratio is raised to 1.06. Since there is no histological evidence for parathyroid hyperplasia on the low-calcium diet, a change in cellular calcium in the kidney of *Hyp*/Y males may be a factor influencing the degree of phosphaturia. Calcium modulates the phosphaturia in XLH in man (9).

Solutes other than P_i (e.g., amino acids or glucose) were not present in excess in urine of *Hyp*/Y males compared to normal male siblings.

Table 4. Urine excretion of phosphate in relation to serum phosphate concentration and diet calcium and phosphate

Diet composition (%, wt/wt)		Serum P_i (mg/100 ml, mean ± SEM)		Urine P_i (excretion index)*	
Calcium	Phosphate	+/Y	*Hyp*/Y	+/Y	*Hyp*/Y
0.22	0.74	6.2 ± 0.6	2.4 ± 0.1	111	367
0.72	0.67	7.6 ± 0.9	4.6 ± 0.9	71	111

Litter mates were 240–270 days of age when placed on the diets. A total of eight *Hyp*/Y and six +/Y males were used.

* Excretion index = (mg P_i mg^{-1} creatinine in urine)/(mg P_i ml^{-1} in serum) was calculated using pooled urine and plasma obtained from the mice placed in metabolic cages.

Tissue Phosphate. Renal cortex P_i is 46.6 ± 1.0 nmol/mg of protein (mean ± SEM) in eight +/Y mice and 46.6 ± 1.1 nmol/mg of protein in six *Hyp*/Y individuals (no significant difference). This finding suggests that, while the tubular transport defect in *Hyp*/Y males compromises *net* reclamation of phosphate from the tubule lumen, it does not perturb the total cellular uptake of P_i anion from the combined peritubular and urinary surfaces of renal cortical epithelium. In fact, cellular P_i is greater than normal relative to plasma P_i in *Hyp*/Y males. Moreover, we have shown that renal cortex slices, which expose only the basolateral membranes of epithelial cells to the medium (10), accumulate $^{32}P_i$ into organic and inorganic pools equivalently when prepared from kidneys of *Hyp*/Y and +/Y males (9). This finding suggests that the presumed P_i transport defect is not expressed significantly in the basolateral membrane under conditions of incubation *in vitro*.

Therapy. After 11 weeks on phosphate-supplemented drinking H_2O, growth of hind limbs in *Hyp*/Y males had occurred. In addition, kyphosis of the thoracic spine did not appear to develop. Skeletal preparations (Fig. 1) verified these visual observations and revealed that long bones, tail bones, and skull bones of *Hyp*/Y males were more normal, the rachitic changes were more reduced, and the spinal kyphosis was absent. No differences were noted in the skeletons on +/Y males kept on phosphate-supplemented drinking water compared to those on normal diet.

Parathyroid Hormone and Gland Morphology. Parathyroid

Table 3. Plasma calcium levels (mg/100 ml) of hypophosphatemic and normal mice

Sex	Genotype	Age in days*			
		35–49	50–99	100–199	200–475
♀	*Hyp*/+	8.44 ± 0.12 (7)	9.09 ± 0.09 (8)	8.92 ± 0.09 (12)	9.19 ± 0.13 (15)
	+/+	9.03 ± 0.17 (4)	9.79 ± 0.17 (7)	9.42 ± 0.19 (6)	9.83 ± 0.10 (10)
♂	*Hyp*/Y	8.43 ± 0.12 (3)	8.64 ± 0.10 (16)	8.70 ± 0.09 (19)	8.46 ± 0.09 (9)
	+/Y	9.26 ± 0.11 (5)	9.38 ± 0.15 (12)	9.44 ± 0.13 (10)	9.44 ± 0.12 (7)

* Values are presented as mean ± SEM. The values for *Hyp*/+ compared to +/+ females and *Hyp*/Y compared to +/Y males are significantly different ($P < 0.05$) for each age group by *t*-test for groups of unequal size. Numbers in parentheses are numbers of individuals tested.

glands were dissected from *Hyp*/Y and +/Y mice and examined by light microscopy. There was no evidence of parathyroid hyperplasia in *Hyp*/Y mice. Serum parathyroid hormone was not elevated in hypophosphatemic males (<30 ng/ml) compared to +/Y (<50 ng/ml) (diet contained 0.74% calcium).

DISCUSSION

Hereditary hypophosphatemia in the mouse provides a new, well-defined nonhuman vertebrate model for a human disease (XLH) and, as such, it should be added to the existing compendia of such models (11, 12). The X-linked dominant mutant genes associated with hypophosphatemic bone disease in mouse and man are likely to be evolutionary homologues. Their phenotypes are nearly identical in terms of the relative time of appearance of manifestations after birth, including the presence of hypophosphatemia without striking hypocalcemia, the high urinary excretion P_i relative to serum P_i, the bone disease, and the dwarfism. The absence of significant hyperparathyroidism in the human disease (12) is apparently mimicked in the mouse, as shown by the normal morphology of their parathyroid glands and normal serum parathyroid hormone levels. The cause for the lower plasma calcium in *Hyp*/Y mice compared to +/Y males receiving a diet offering a low (0.3) calcium:phosphorus ratio has not been investigated. *Hyp*/Y animals would probably be vulnerable to impaired calcium absorption if luminal P_i in the intestine were elevated in the presence of an intrinsic intestinal defect in P_i absorption. However, the mild hypocalcemia in *Hyp*/Y mice did not provoke histological evidence of hyperparathyroidism.

The basic defect is still unknown in human XLH. Many investigators suspect that a defect in transepithelial transport of P_i anion in kidney, and perhaps also in the intestine and bone, is likely to be the most important determinant of the XLH phenotype in man (9, 13, 14). However is it undecided whether the primary defect involves (*a*) a luminal membrane-located anion carrier, (*b*) a disorder in cell responsiveness to agents that regulate P_i transport, (*c*) a postulated but as yet unidentified humoral modulator of phosphate transport, or (*d*) a disruption in vitamin D metabolism or function.

The presence of a mutant homologous nonhuman model of XLH should permit studies to be undertaken that cannot be performed in man. These would include the measurement *in vitro* of transepithelial P_i transport by intestine, where only uptake studies by mucosal biopsies have been done in man (15, 16), parabiosis (cross circulation) experiments to determine whether an abnormal circulating factor is present or a normal factor is missing, study of the homozygous female (*Hyp/Hyp*) to examine mutant gene dosage effects independent of possible sex-dependent modulation of the gene's expression, micropuncture studies to determine P_i handling at various sites in the tubule of *Hyp*/Y mice, and experiments to determine whether a defect in vitamin D metabolism exists in *Hyp*/Y and *Hyp*/+ mice.

The hypophosphatemia mutant mouse serving as a genetic probe should yield a clearer picture than exists at present about the events controlling P_i anion transport in the epithelia of metazoa.

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