X-linked Hypophosphatemic rickets (XLH), a sex-linked dominant disorder of phosphate homeostasis, is the most common form of inherited rickets with an incidence of 1 in 20,000. The disorder is characterized by defective renal phosphate handling and vitamin D metabolism leading to growth retardation, rachitic and osteomalacic bone disease, and hypophosphatemia. Inactivating mutations of the neutral endopeptidase gene, PHEX, are responsible for the XLH phenotype. Conventional combined treatment of 1, 25 dihydroxyvitamin D3 (Rocaltrol) and inorganic phosphate salts has been well established to improve linear growth and heal rachitic skeletal abnormalities; however severe growth retardation is common in some patients even with early medical intervention.

Our study had three main goals: 1) to describe pattern of growth in patients with XLH, 2) to evaluate factors (medication dose, duration of treatment, and laboratory results) that may influence growth pattern and final height in XLH, and 3) to report and correlate PHEX mutations associated with treatment response and/or complications of therapy. Forty-eight patients with a diagnosis of Hypophosphatemic rickets were ascertained for the study. Twenty patients, with final height attainment, were evaluated for growth pattern. Thirty patients from 20 families (20 individuals from 10 families with
multiple affected individuals and 10 sporadically affected individuals) were enrolled in the PHEX mutation study.

Our analysis describes a subset of patients (60% of patients with final height) demonstrating an abnormal growth rate pattern leading to an earlier age of final adult height compared to the normal growth pattern. One-sample t-test analysis demonstrated an earlier attainment of final height compared to normal reference values [age 13 years for females (p=0.028) and age 16 years for males (p=0.024)]. Mean medication dose, duration of treatment, and growth rate per year were variables evaluated for growth rate pattern. The combined treatment of Rocaltrol and inorganic phosphate was not statistically significant (p=/439 and p=.469, respectively) with respect to growth rate pattern and final height outcome; however the mean phosphate dose was found to have a significant (p=0.0001) negative correlation with height standard deviation values. In addition, mean phosphate dose was significantly correlated (p=0.0001) with height standard deviation for the total study population, indicating that a higher phosphate dose was given to patients with lower height standard deviation values. Growth rate analysis was significant (p=0.007) for growth pattern between patients with reduced growth rate pattern and patients with normal growth rate pattern. Due to sample size, our study did not compare variations in phosphate dose to growth and height standard deviation. Future analysis potentially may delineate the effect of phosphate dose on growth and complications of therapy.

Eleven different PHEX mutations were detected with 80% of mutations identified in familial cases and 50% of mutations in sporadic cases. The types of mutations detected included: missense, nonsense, abnormal splicing, frameshifts, and deletions. Mutation
types were compressed into two main groups; missense and protein truncation. Mutation type was not significantly correlated with the development of nephrocalcinosis (p=.530) or PTH levels (p=.586), however 10 patients with protein truncation mutations had a history of elevated PTH levels compared to 2 patients with missense mutations. Testing additional patients for PHEX mutations and correlating with treatment regimen and laboratory values is needed to determine if our genotype/phenotype observation is significant.