Reviewer's report

Title: Genetic diagnosis of X-linked dominant hypophosphatemic rickets in a cohort study: Tubular reabsorption of phosphate and 1,25(OH)2D serum levels are associated with PHEX mutation type

Version: 3 Date: 4 July 2011

Reviewer: ERik Imel

Reviewer's report:

Major compulsory reviews.

1. The method of analysis precludes any ability to detect variation within persons with the same mutation, and is a limitation of the study. If significant variation within subjects with a mutation do exist, that could at least partly nullify the findings of this paper, and should be thoroughly discussed. In assessing the analysis: If the authors hypothesis is true, then including multiple family members with the same mutation would tend to overestimate the effect of a given mutation type. However if the hypothesis is false, the exclusion of multiple affected members from the same family could result in incorrectly excluding the null hypotheses and missing larger variation within genotype. Admittedly that might differ depending on the phenotypic variable being compared. TRP and 1,25D are directly modulated by FGF23, so it is plausible that these might relate to genotype more than some other phenotypic measures. However, from the point of view of the patients’ experience with the disease, the bone phenotype is probably the most relevant clinically. In the author response to reviewers, the authors summarize existing literature well that suggests there is variability between subjects with the same mutation. Since this is probably the most important issue that could limit generalization of the findings, there should be explicit statements and citations in the discussion that other authors have reported significant variation in phenotype within individuals with the same mutations.

Minor comments:

1. Clarify informed consent statement to indicate that the parents gave informed consent, as these were children.

2. In evaluating variation, was any attempt made to adjust for sex, or to confirm that sex did not contribute to the variation observed?

3. 130 control chromosomes should probably be clarified to number of patients(male and female), as well, since number of subjects cannot be assessed from the simple number of X chromosomes.

4. No standard of care is probably misleading as a phrase and might suggest erroneously that patients were receiving substandard care. It might be better to state that treatment regimens varied across the clinical sites according to local practices.
5. “No phenotypic data were available from all of the patients.” If that were true there would be no phenotype study….Actually what is meant is that for some patients, no phenotypic data were available.

6. Genotype-phenotype correlation: There is a typographical error: “The study of any possible correlation between the patient’s genotype and the type of mutation”…. Replace with phenotype and the type of mutation.

7. The statement is made that the data is not shown for male versus females for nephrocalcinosis, when actually the data is shown in the Table 1.

8. There are still multiple occurrences of the abbreviation HXLR, when XLHR is meant. Hyperoxaluria is misspelled in the text.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.