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: 2 Date: 11 April 2011

Reviewer: Yves Sabbagh

Reviewer's report:

The authors provide a report regarding 36 index cases with hypophosphatemic rickets. The authors have identified 36 mutations in a very clear manner with emerging techniques that have helped identify mutations that would have been missed using classical methods of mutation detection, namely regular sequencing. Another important point that the paper makes is the presence of hyperparathyroidism in XLH patients prior to the start of treatment. The authors also demonstrate genotype-phenotype correlations between type of mutations with TRP and 1,25(OH)2D3 serum levels. This is the first report to demonstrate 100% of mutation identification in the PHEX gene in patients diagnosed with hypophosphatemic rickets.

Major Compulsory Revisions:

1. The paper does not address previous reports where the same mutation identified within a family or different families has different penetrance and severity of disease. This is in contrast to what has been described in the set of patients in this report. (an example: Filisetti D. Ostermann G. von Bredow M. Strom T. Filler G. Ehrich J. Pannetier S. Garnier JM. Rowe P. Francis F. Julienne A. Hanauer A. Econs MJ. Oudet C. Non-random distribution of mutations in the PHEX gene, and under-detected missense mutations at non-conserved residues. European Journal of Human Genetics. 7(5):615-619, 1999 Jul.)

2. In regards to the nephrocalcinosis which is present after treatments, it would have been helpful to state whether all patients were on similar standard of care or if there was any correlation with treatment regimens. The presence of nephrocalcinosis as suggested could be due to treatment regimen as well as other factors and not necessarily to the type of mutations as only 20% of patients with deletion mutations have nephrocalcinosis.

3. In the methods it states that 46 non affected family members were also analyzed. However, in the discussion section regarding the two novel missense mutations it is stated that these mutation were not found in 130 normal chromosomes. It should be stated in the methods sections how the nucleotide changes were confirmed as real mutations and not polymorphisms in the general population.
4. The authors chose to do genotype-phenotype correlation analysis based on predictive effect on protein rather than on a descriptive basis without providing a rationale for why they chose to do it that way.

5. It is not clear why patient #14, 15, and 31 were included in this study when no phenotypic features were present not even mention of skeletal deformity and in 2 cases no age at diagnosis. Some features must have been present to include these patients in the study and these need to be provided or mentioned in the paper.

Minor Essential Revisions:

1. Please check for spelling mistakes. In the discussion section XLHR is written as HXLR. In table 1 PTH parathormone should be parathyroid hormone.

2. In results section, under PHEX mutations, first paragraph, sentence starting with “Most of them (83.3%) resulted …” is incomplete.

3. In first paragraph of the discussion it says that 16 familial cases were identified when it should say 6 cases.

4. Figure legend 2 and 3 are inverted. In addition, in the figure legends it states that the mutation distribution for the upper panel is from the PHEX mutation database. However, in the discussion section the authors state that the distribution of the mutation are from the Human Genome Mutation Database. These 2 databases are distinct and clarification on which database was used to generate the figure needs to be addressed.

5. Please fix width of gender column.

Discretionary Revisions:

1. The authors state that exons 2 and 3 have high sequence homology, the percentage of homology should be stated and if possible a figure showing the alignment of the sequences will help drive the argument put forward.

Level of interest: An article whose findings are important to those with closely related research interests

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