Mosaic *PHEX* variants are important causes of X-linked hypophosphataemic rickets

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Background

X-linked hypophosphataemic rickets (XLH) is due to mutations in the *PHEX* (Phosphate-regulating Endopeptidase homolog; X-linked) gene. It causes reduced renal phosphate reabsorption and loss of bone and dentin mineralisation. Mosaic *PHEX* variants are reported in only a few case reports in the literature.

We report three male cases, with de novo mosaic pathogenic *PHEX* variants, showing the importance of considering this in the diagnosis of XLH.

Case 1

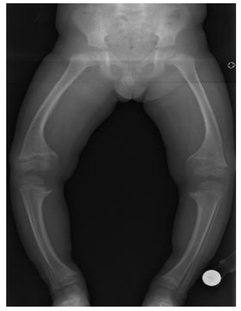
- Presented at 4 years of age with bowed legs, hypophosphataemia and low tubular reabsorption of phosphate (TRP).
- He had difficulty tolerating conventional treatment (phosphate/alfacalcidol) and continued to have rickets and bone deformities.
- No variants were found in *PHEX/FGF23* initially
- The UK 100,000 genome project then suggested a *PHEX* variant.
- Reanalysis with Sanger-sequencing showed a low level (35%) de novo mosaic pathological splice donor site variant: c.1173+5G>C in PMBCs. The functional effect of this variant is difficult to predict but it may cause skipping of exon 10, leading to a shift in the reading frame and the introduction of a premature termination (stop) codon. The mRNA product would likely to be subject to nonsense-mediated decay.
- 5 years after diagnosis he was then eligible for burosumab.
- Now 10 years of age, he is on 0.5 mg/kg/dose burosumab, with healing rickets and height SD of -1.65.

Table 1	Case 1 (after starting treatment)	Case 2 (pre treatment)	Case 3 (pre treatment)
Phosphate (mmol/L)	1.01	0.75	0.91
ALP (U/L)	422	732	409
TRP (%)	60	81	67
Vitamin D (nmol/L)		63	108
PTH (pmol/L)	4.6	5	3.2

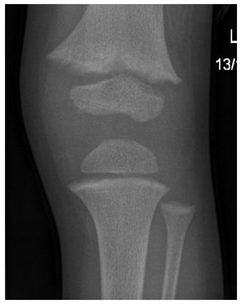
Case 2

- Presented at 6 years of age with mild tibial bowing and rickets. He had hypophosphataemia (0.75 mmol/L) and low TRP (81%) (table 1); FGF23 146 RU/ml.
- He was initially given conventional treatment; then burosumab
- Sanger sequencing showed a low level (30%) *PHEX* mosaic splice donor site variant in PMBCs:c.1645+1G>A, predicted to cause skipping of exon 15 and likely nonsense mediated mRNA decay.
- Now 13 years of age, he is taking 0.7 mg/kg/dose of burosumab and has a height of +1 SD. He has healed rickets and his TRP increased to 95%.

Figures 1-2 showing rachitic changes and bowing of the legs



Patient 1



Patient 3

Case 3

- Presented at 11 months with macrocephaly, scaphocephaly and short stature
- Biochemistry and X-rays suggested XLH (phosphate 0.91 mmol/L, TRP 67%, FGF23 149 RU/ml, table 1).
- Sanger sequencing showed a nonsense variant resulting in a premature stop codon *PHEX*:c.1157G>A;p.(Trp386*), with a 59% level mosaicism in PMBCs. It is expected to result in an absent or disrupted protein product (ClinVar).
- Now 5 years of age, he is on 1.3 mg/kg/dose of burosumab, has a height SD of -2.65 and his last TRP was 85%.

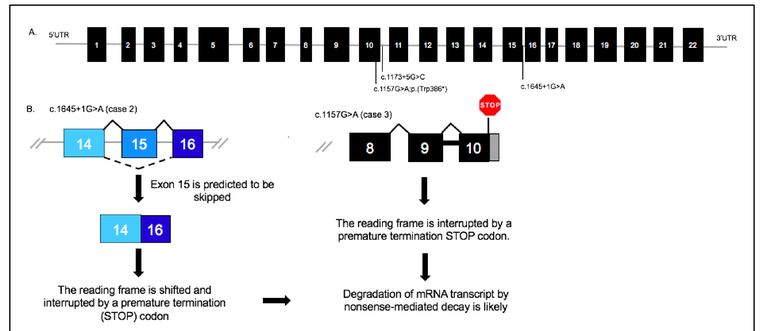


Figure 3: A: Schematic representation of the *PHEX* gene and location of the variants identified in the three cases. B: The variant identified in case 2 (c.1645+1G>A) and case 3 (c.1157G>A) are predicted to result in the introduction of a premature termination codon. The consequence of the variant identified in case 1, c.1173+5G>C is not predictable but it is possible that it results in aberrant splicing. Numbered boxes, exons; introns, grey lines; solid black lines, expected splicing, broken lines, predicted splicing effect of variant.

Discussion

Although these splice site and nonsense variants have been reported previously in XLH (1-3), this is the first time they have been found as mosaic variants.

Mosaic *PHEX* variants can be difficult to identify (4) but these cases suggest that mosaicism may not be extremely rare and give rise to similar phenotypes as non-mosaic mutations.

Of note, only boys with mosaic *PHEX* variants have been described, whereas *PHEX* variants in girls are not always rescued by X-chromosome inactivation.

Case 1 highlights the importance of considering mosaicism and splice site variants when there is a high clinical suspicion for XLH. Delayed diagnosis resulted in initial ineligibility for burosumab treatment.

References

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