Mosaic \textit{PHEX} variants are important causes of X-linked hypophosphatemic rickets

Prentice P$^1$, Owens M$^\dagger$, Brain C$^\ddagger$, Allgrove J$^\S$, Gevers EF$^1,2,4$

$^1$Royal London Hospital – Barts Health NHS Trust, London, UK, $^2$Great Ormond Street Hospital for Children, London, UK, $^3$Royal Devon and Exeter NHS Foundation Trust, Exeter, UK, $^4$Queen Mary University London, William Harvey Research Institute, Centre for Endocrinology, London, UK

**Background**

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

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

**Case 1**

- Presented at 4 years of age with bowing legs, hypophosphatemia 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 \textit{PHX}/FG23 initially.
- The UK 100,000 genome project then suggested a \textit{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.

**Case 2**

- Presented at 6 years of age with mild tibial bowing and rickets. He had hypophosphatemia (0.75 mmol/L) and low TRP (81%) (table 1); FG23 146 RU/ml.
- He was initially given conventional treatment; then burosumab
- Sanger sequencing showed a low level (30%) \textit{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%.

**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%, FG23 149 RU/ml, table 1).
- Sanger sequencing showed a nonsense variant resulting in a premature stop codon \textit{PHEX}:c.1157G>A;(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%.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Case 1 (after starting treatment)</th>
<th>Case 2 (pre treatment)</th>
<th>Case 3 (pre treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.01</td>
<td>0.75</td>
<td>0.91</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>422</td>
<td>732</td>
<td>409</td>
</tr>
<tr>
<td>TRP (%)</td>
<td>60</td>
<td>81</td>
<td>67</td>
</tr>
<tr>
<td>Vitamin D (mmol/L)</td>
<td>4.6</td>
<td>63</td>
<td>108</td>
</tr>
<tr>
<td>PTH (pmol/L)</td>
<td>4.6</td>
<td>5</td>
<td>3.2</td>
</tr>
</tbody>
</table>

**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 \textit{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 \textit{PHEX} variants have been described, where \textit{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**