E-P04.22 - Mosaicism in the *PHEX* gene. Is it more common than we thought?

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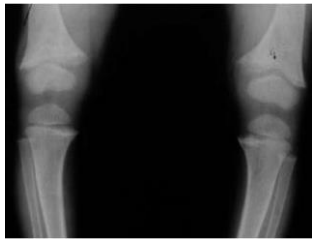
INTRODUCTION

Familial X-linked hypophosphatemic rickets (XLHR) is defined as a group of disorders characterized by rickets with bone deformities, short stature, dental anomalies, hypophosphatemia and increased activity of serum alkaline phosphatases. According to the bibliography, pathogenic variants in the *PHEX* gene are the most common cause of XLHR and only a few cases of mosaicism have been identified worldwide. In this publication, we present two unrelated family cases from The Canary Islands (Spain) referred with XLHR clinical suspicion where mosaic variants have been identified.

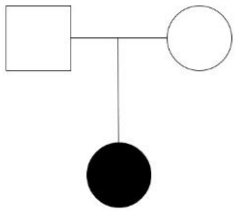


MATERIALS AND METHODS

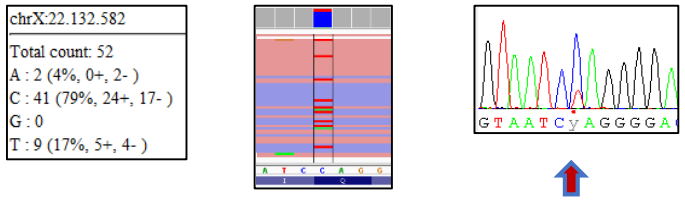
Two unrelated Canary Island patients were requested for *PHEX* sequencing. Case A corresponds to an 18 year old woman with short stature and clinical suspicion of XLHR. Case B corresponds to an 11 year old boy with clinical suspicion of XLHR whose mother was studied to investigate segregation.
Genomic DNA was isolated from EDTA blood using a standard protocol. Next Generation Sequencing (NGS) was used to analyse *PHEX* gene in the probands of both families. Sanger sequencing was used to perform the study in the mother's proband in case of family B.

RESULTS

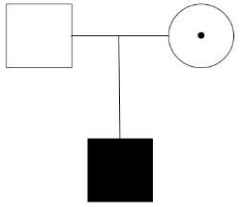
Family A: Analysis by NGS revealed that in chrX:22132582, the proband had 79% of reads with wildtype Cytosine nucleotide, meanwhile 17% of the reads had Thymine. The aforementioned proportion is typical in mosaic changes.
Sanger sequencing confirmed proband was mosaic for a nonsense pathogenic variant c.1180C>T p.(Gln394Ter) in the *PHEX* gene.



PHEX: c.1180=/C>T p.(Gln394Ter)

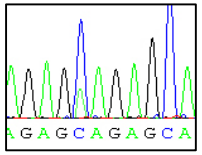


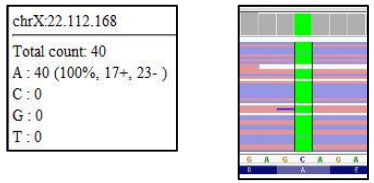
Family B: Analysis by NGS revealed that proband had 100% of reads with a nucleotide change in the chrX:22112168 position. He was hemizygous for a c.800C>A p.(Ala267Glu) in *PHEX* gene, a missense variant of uncertain significance (VUS). The family analysis of this variant by Sanger sequencing reveals that his unaffected mother was a mosaic.



PHEX: c.800C>A p.(Ala267Glu)

PHEX: c.800=/C>A p.(Ala267Glu)





CONCLUSIONS

- **The identified cases are the first families with mosaic variants in *PHEX* gene reported in Spain.**
- **Genetic counselling context: the "recurrence" of mosaicism in *PHEX* gene, emphasize to consider unaffected males as possible mosaic carriers.**
- **The advantage of performing analysis by NGS is noteworthy: allow detection of mosaic variants with high sensibility and reliability, as well as it enables discarding aneuploidy, for example a possible Klinefelter karyotype.**

REFERENCES

- Yang M, et al. A novel of novo mosaic mutation in *PHEX* in a Korean patient with hypophosphatemic rickets. Annals of Pediatric Endocrinology & Metabolism. 2018.
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- Goji K.*et al.* Somatic and germline mosaicism for a mutation of the *PHEX* gene can lead to genetic transmission of X linked hypophosphatemic rickets that mimics an autosomal dominant trait. J Clin Endocrinol Metab. 2006.