Novel severe skeletal dysplasia with under-mineralisation associated with *in utero* calcium transport and *TRPV6* compound heterozygous variants

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Clinical Case

- Antenatal skeletal abnormalities and recurrent polyhydramnios
- Postnatal severe thoracic insufficiency with significant skeletal and biochemical abnormalities
- Normal parental biochemistry
- Treatment included pamidronate, cinacalcet (calcimimetic), calcium and Vitamin D supplementation
- Required tracheostomy and long term ventilation strategies

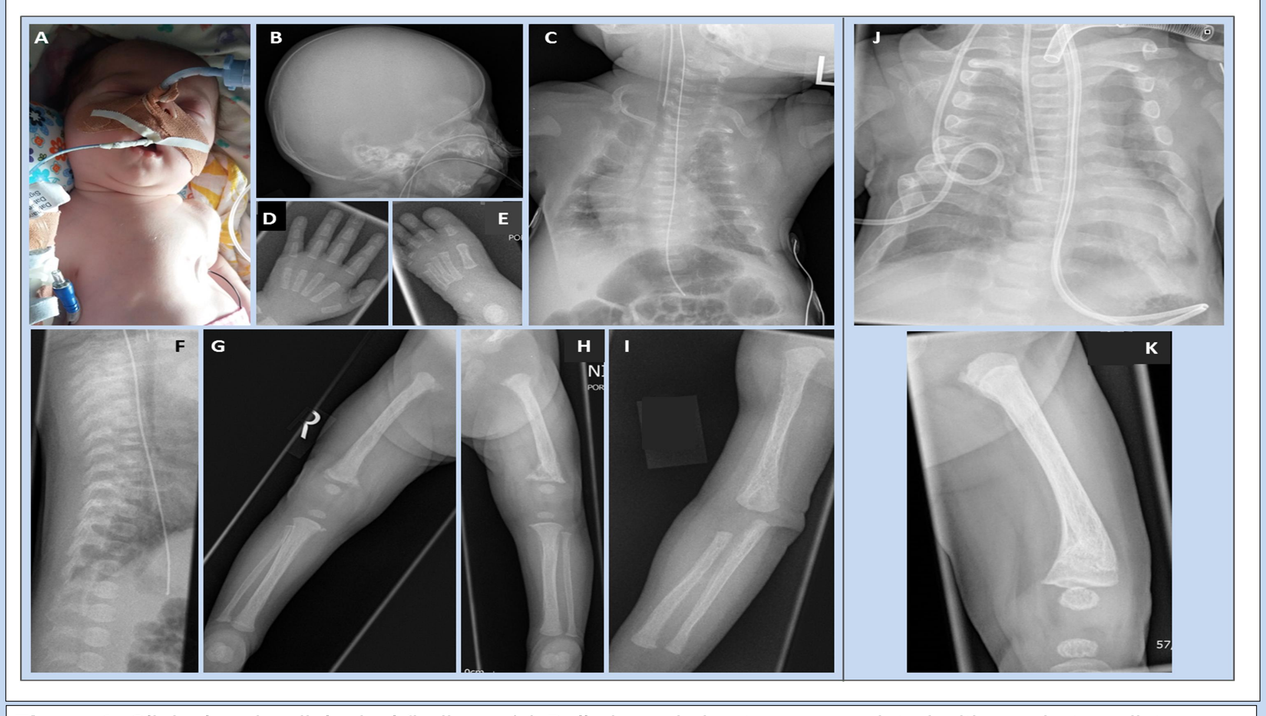

Figure 1: Clinical and radiological findings. (a) Bell-shaped chest was associated with respiratory distress. (b–i) Skeletal survey aged 2 weeks showed generalised under-mineralisation, short, thin, and fractured ribs, absence of Wormian bones and normal vertebrae. The long bones showed a similar pattern of metaphyseal irregularities with corner fractures and periosteal reaction, especially diaphyses of femora, tibiae and humeri. (j, k) Chest and femur X rays aged 10 weeks showed broader, longer ribs, improved bone mineralisation and improved metaphyseal lesions[1]

Parathyroid Hormone (PTH)	53.4-101pmol/L
Corrected Calcium	2.43mmol/L
Alkaline Phosphatase (ALP)	289IU/L
Urinary Ca/Creat Ratio	1.05
Vitamin D	29nmol/L

Figure 2: Initial postnatal biochemistry
- markedly elevated PTH
- predominantly normocalcaemia
- normal ALP
- normal calcium/creatinine ratio
- Vitamin D insufficiency

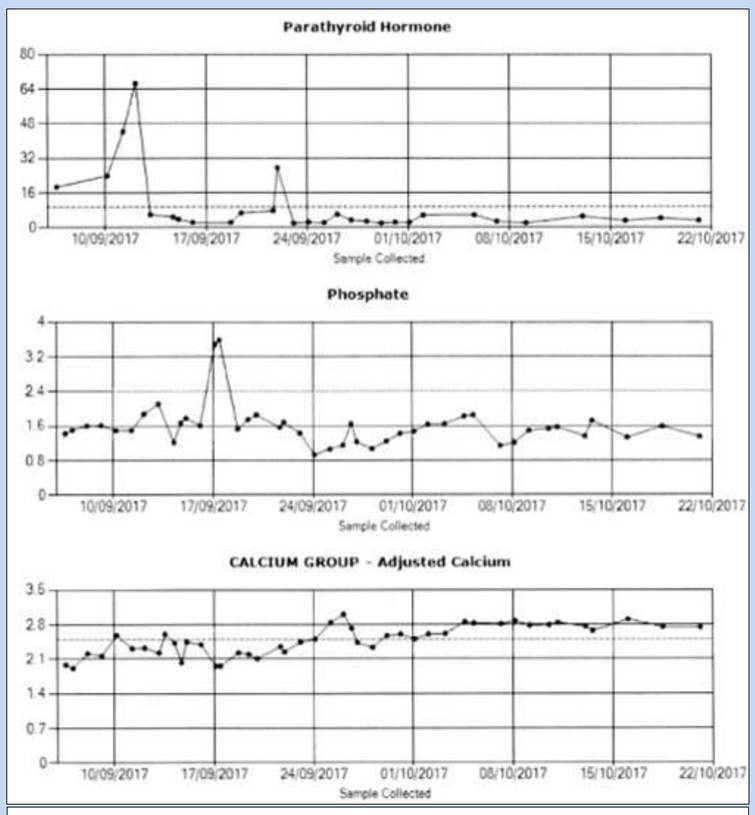

Figure 3: Resolution of biochemical abnormalities- Prompt PTH normalisation with ongoing normocalcaemia, including following cinacalcet cessation

Initial Genetic Investigations

- No abnormality on antenatal CGH array and UDP14 testing
- Molecular genetic analysis excluded Neonatal Severe Hyperparathyroidism (CASR, GNA11, APS21)
- Mucolipidosis Type II excluded biochemically and genetically (GNPTG)
- Whole exome sequencing (WES) using 336 gene skeletal dysplasia panel detected no abnormalities

- Changing clinical picture with resolution of biochemical abnormalities and progressive skeletal mineralisation radiologically
- Alternative hypothesis of *in utero* pathology proposed

Relevance of *TRPV6*

- Fetal skeletal development and mineralisation depends on placental calcium transfer
- *TRPV6* (Transient Receptor Potential Vanilloid family 6th member) functions in tetramer form and has been recently identified in calcium transport[2]
- Not previously linked with skeletal development disorders

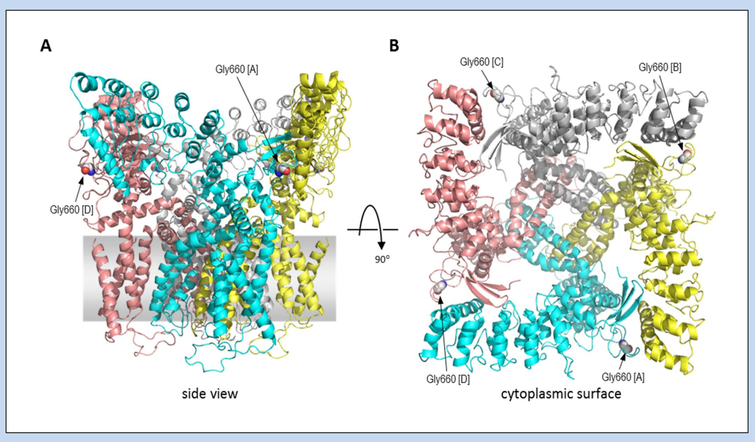

Figure 4: Human*TRPV6* tetramer structure. (a) Structure in open form, complex oriented to show view in the plane of the membrane (represented by the grey bar) with the cytoplasmic region at the top. (b) As (a), but rotated to show the view from the cytoplasm; the ion channel lies at the centre of the tetramer[1]

Making the Diagnosis

- Trio exome analysis identified compound heterozygous *TRPV6* likely pathogenic variants, confirming recessive inheritance:
  - A novel maternally inherited missense variant c.1978G>C p.(Gly660Arg)
  - A paternally inherited nonsense variant c.1528C>T p.(Arg510Ter)
- The p.(Gly660Arg) generates a large side chain protruding from the C-terminal hook into the interface with the adjacent *TRPV6* subunit[1]
- *In silico* protein modelling suggests steric clashes between interface residues, decreased C-terminal hook and *TRPV6* tetramer stability; predicting profound loss of *TRPV6* function[1]

Conclusion

- First reported case of *TRPV6* compound heterozygous variants in a novel skeletal dysplasia
- Astute clinical interpretation remains valuable in complex calcium and bone pathophysiology and helps inform whole exome sequence interpretation[1]

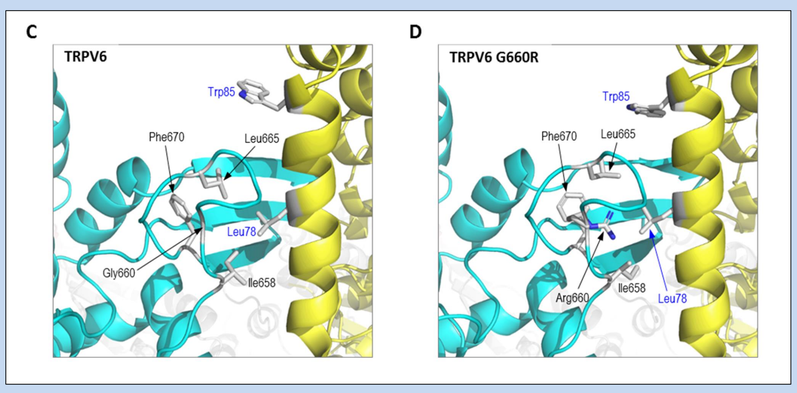

Figure 5: Location of Gly660 and effect of p.(Gly660Arg) substitution. (c) Detail of the interface between the C-terminal hook of subunit A and the N-terminal helix of subunit B; the position of the Gly660 backbone is indicated, and side chains shown in stick format. (d) As (c), but showing detail of the p.(Gly660Arg) variant[1]

References

1. Burren CP, Caswell R, Castle B, Welch CR, Hilliard TN, Smithson SF, Ellard S. TRPV6 compound heterozygous variants result in impaired placental calcium transport and severe undermineralization and dysplasia of the fetal skeleton. Am J Med Genet A. 2018 Aug 25. doi: 10.1002/ajmg.a.40484. PubMed PMID: 30144375.
2. Fecher-Trost, C., Wissenbach, U., & Weissgerber, P. (2017). TRPV6: From identification to function. Cell Calcium, 67, 116–122. https://doi.org/10.1016/j.ceca.2017.04.006.