University Hospitals Bristol NHS
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Novel p.Asn628Ser heterozygous mutation in *FGFR1* is associated with Hartsfield syndrome and tumoral calcinosis

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Introduction

Hartsfield syndrome (#OMIM 615465) describes the rare co-occurrence of holoprosencephaly (failure of complete separation of the 2 cerebral hemispheres) with ectrodactyly, associated with a spectrum of developmental defects including specific pituitary dysfunction.

Novel homozygous and heterozygous mutations in *FGFR1* have recently been associated with the condition in six patients (1). Loss-of-function *FGFR1* mutations have also been associated with a spectrum of clinical phenotypes including Kallman syndrome, in which gonadotrophin deficiency is also a feature (2) Fibroblast growth factor signalling plays an important role in embryonic development with downstream effects on cell motility, cell survival and cell mitosis. Downstream signalling cascades are FGF-, FGFR- and cell-specific.

Case Report

Holoprosencephaly, Ectrodactyly, Pituitary Dysfunction

Our patient, a male infant, born to non-consanguineous Caucasian parents, has several congenital abnormalities including bilateral cleft lip and palate, right sided microtia, bilateral ectrodactyly of the hands and feet and semilobar holoprosencephaly (Fig 1). At the age of 5 weeks he was diagnosed with cranial diabetes insipidus and gonadotrophin deficiency.

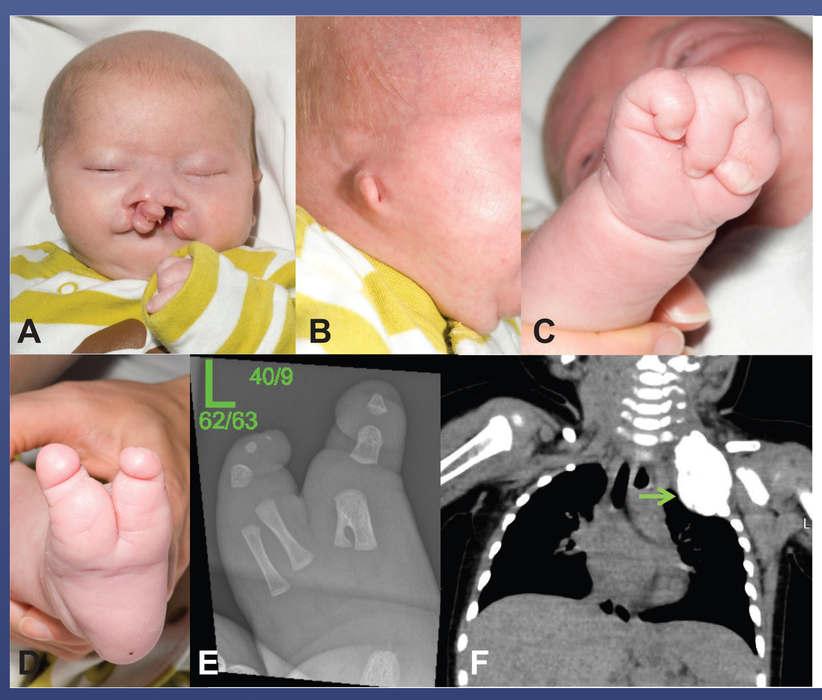

Fig 1. Clinical phenotype of Hartsfield syndrome in our patient. The clinical features of Hartsfield syndrome in our patient, in addition to pituitary dysfunction and holoprosencephaly include (A) bilateral cleft lip and palate, (B) right sided microtia, (C) ectrodactyly of the hands and (D) feet, pictured with (E) representative radiograph of the left foot and (F) tumoral calcinosis as seen on CT Chest.

Tumoral Calcinosis

Aged 16 months our patient presented with a lesion in the posterior first rib. Histology from the biopsy taken was in keeping with **tumoral calcinosis**.

Methods

Direct Sanger sequencing of *FGFR1*, incisional biopsy (histology consistent with tumoral calcinosis) and serum for bone biochemistry and C-terminal/ intact FGF23 levels was taken.

Results

c.1883A>G; p.Asn628Ser mutation in *FGFR1*

Direct Sanger sequencing of *FGFR1* in our patient reveals a novel, *de novo* heterozygous missense mutation, c.1883A>G; p.Asn628Ser (Fig 2A). The p.Asn628Ser mutation affects an amino acid residue located in the ATP binding pocket of the intracellular tyrosine kinase domain, with predicted impairment of FGFR1 kinase activity.
Disease-associated mutations in the kinase domain interfere with normal signalling activity *in vivo* in zebrafish models, with findings supporting a dominant negative mechanism (3).

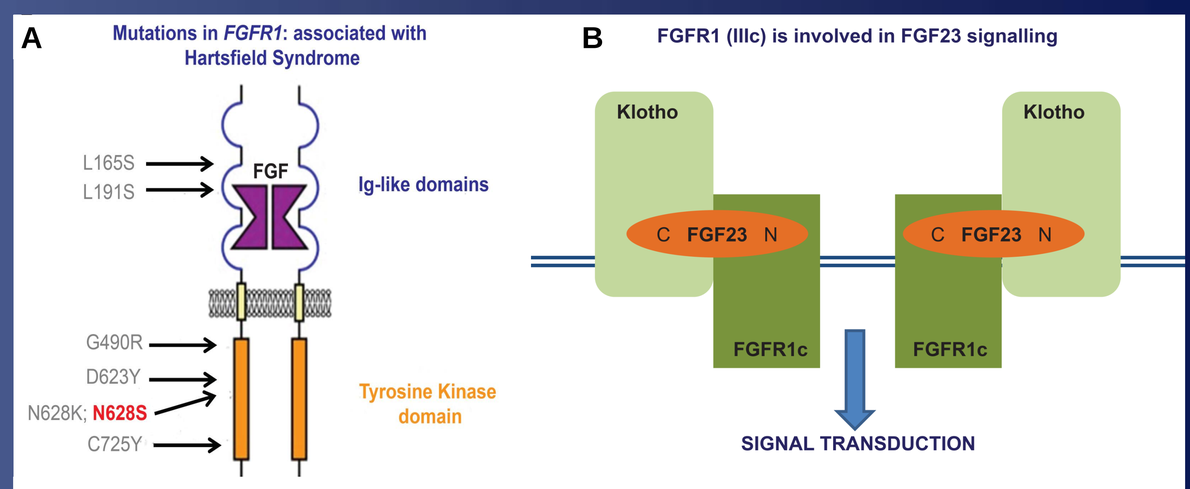

Fig 2. *FGFR1* A) heterozygous and homozygous mutations are associated with Hartsfield Syndrome (previously described mutations in grey, our patient's mutation in red). **(B)** is involved in FGF23 signalling and phosphate homeostasis.

Biochemistry in keeping with tumoral calcinosis

Biochemical findings in our patient indicate **normo-calcaemia** (Corrected calcium 2.44 mmol/L, normal range 2.20-2.70) and **hyperphosphataemia (serum phosphate 2.10 mmol/L**; normal range 0.9-1.8), with a normal 1, 25 Vitamin D level of 139 pmol/L and normal PTH (2.7 pmol/L), and **low fractional excretion of phosphate** (0.58%) as is typically seen in **familial forms of tumoral calcinosis.**

The circulating factor FGF23 normally promotes excretion of phosphate. C-terminal levels of FGF23 (accounting for both the bioactive intact form of FGF23 and C-terminal fragments present in the circulation) are raised in inherited forms of tumoral calcinosis, either as a consequence of increased proteolytic processing of FGF23 or end-organ resistance. **Raised C-terminal FGF23 levels of 111 relative units/mL** (reference range <100) were found in our patient, again supporting a diagnosis of tumoral calcinosis. **Intact FGF23 was 81.7 pg/mL**; whilst this is within the normal adult range no paediatric reference range exists. Bone biochemistry of both parents was within normal limits.

Loss of FGFR1 function potentially contributes to tumoral calcinosis

For the first time we report tumoral calcinosis in a patient with Hartsfield Syndrome. **Tumoral calcinosis (# OMIM 211900)** can be inherited in an autosomal recessive manner involving loss of function mutations in ***FGF23, KLOTHO* and *GALNT3*** (4-7). The circulating factor FGF23 promotes phosphate excretion. Klotho directly converts the splice variant FGFR1 (IIIc) into the FGF23-specific receptor (8) (Fig 2B), raising the possibility that an inactivating *FGFR1* mutation may contribute to tumoral calcinosis development. Activating heterozygous missense mutations in *FGFR1* are associated with osteoglophonic dysplasia (# OMIM 166250), an autosomal dominant condition where increased serum levels of FGF23 can lead to hypophosphatemia

Studies have implicated FGFR1 activation in regulating *FGF23* gene transcription which may account for the paucity of elevation of FGF23 seen despite increased renal phosphate reabsorption.

Conclusion

This novel mutation in *FGFR1* provides further compelling evidence of the association of *FGFR1* mutations with Hartsfield syndrome. We also expand the phenotype with the first report of tumoral calcinosis with mildly raised C-terminal FGF23 levels, which may reflect loss of function of FGFR1.

Disclosure: Nothing to declare

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