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Early Multisystem Presentation of Frank-ter Haar Syndrome with a Novel Compound Heterozygous SH3PXD2B Variant: A Case Report

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Abstract

Background: Frank-Ter Haar syndrome (FTHS; OMIM #249420) is an ultra-rare autosomal recessive disorder caused by biallelic variants in SH3PXD2B, which encodes the podosome adaptor protein TKS4. Fewer than 50 molecularly confirmed cases have been reported.

Case presentation: We describe a 6-year-old girl, born at term to non-consanguineous parents, who had low-set ears and craniofacial dysmorphism at birth. A neonatal skull radiograph showed a copper-beaten calvarium and abdominal ultrasonography incidentally noted bowel-wall thickening; no diagnosis was reached at the time and echocardiography was normal. At 6 years she presented with global developmental delay, mild intellectual disability and recurrent lower respiratory tract infections. A repeat skeletal survey confirmed brachycephaly and a persistent copper-beaten skull, with an incidental asymmetry of carpal ossification not previously described in this condition. Paroxysmal inconsolable crying prompted ophthalmological review, which revealed bilateral glaucoma with significant refractive error. Chest radiography and CT thorax were normal. Whole-exome sequencing identified a novel missense variant in SH3PXD2B (exon 13; c.2690C>T, p.(Ser897Phe)) in trans with a paternally inherited nonsense variant (c.1219C>T, p.(Arg407*)), confirmed by segregation and consistent with autosomal recessive FTHS.

Conclusions: This case expands the mutational spectrum of SH3PXD2B and shows that non-specific neonatal radiological findings may antedate the recognisable FTHS phenotype by years. Paroxysmal crying as the presenting sign of occult glaucoma underscores the need for proactive ophthalmological screening in skeletal dysplasia syndromes.

Keywords: Frank-ter Haar syndrome; SH3PXD2B; TKS4; Congenital glaucoma; Copper-beaten skull; Compound heterozygous; Whole-exome sequencing

Introduction

Frank-Ter Haar Syndrome (FTHS) is a rare multisystem disorder first described by Frank et al. and ter Haar et al. and later attributed to biallelic loss-of-function variants in SH3PXD2B on chromosome 5q35.1[1-3]. The encoded protein, TKS4, is a Src-kinase substrate and podosome adaptor required for pericellular matrix remodelling, EGFR signalling and neural crest cell migration, mechanistically linking a single cytoskeletal scaffold protein to the craniofacial, skeletal and ocular phenotype of FTHS [4,5].

The classic phenotype, brachycephaly, craniofacial dysmorphism, a calvarial 'copper-beaten' appearance, skeletal dysplasia and megalocornea with or without glaucoma, is usually recognised only once the full triad emerges in early childhood [6,7]. We report a child in whom striking neonatal radiological abnormalities

preceded clinical suspicion of FTHS by several years, with diagnosis ultimately established by identification of a novel SH3PXD2B missense variant in trans with a truncating allele.

Case Presentation

The proband was the first child of non-consanguineous, healthy parents, born at term by normal vaginal delivery (birth weight 2.8 kg). There was no family history of a similar disorder. At birth, low-set ears and mild craniofacial dysmorphism were noted; cardiovascular and neurological examination were otherwise unremarkable.

A neonatal cranial neurosonogram was normal. Abdominal ultrasonography incidentally showed



diffuse bowel-wall thickening without obstruction or other acute pathology; the infant remained asymptomatic gastrointestinally. A skull radiograph showed a pronounced copper-beaten calvarium. Baseline echocardiography was structurally and functionally normal. No syndromic diagnosis was made at this stage.

At 6 years of age, the child presented with global developmental delay, mild intellectual disability and recurrent lower respiratory tract infections. Examination confirmed persistent brachycephaly and craniofacial dysmorphism. A repeat skeletal survey confirmed the persistent copper-beaten calvarium and additionally identified an asymmetry of carpal

ossification, most marked at the trapezoid, not previously documented in this child or, to our knowledge, reported as a feature of FTHS.

The parents described recurrent episodes of inconsolable crying without an obvious precipitant, together with apparent blurring of vision. Examination under sedation revealed bilateral glaucoma with elevated intraocular pressure and significant refractive error, without overt buphthalmos or corneal clouding, an association previously reported in FTHS [8]. Chest radiography and CT thorax, performed in view of the recurrent infections, were normal and repeat echocardiography remained unremarkable. Summary of clinical findings are mentioned in **Table 1**.

Table 1: Summary of clinical findings.

System	Neonatal Period	6 Years of Age
Craniofacial	Low-set ears; mild dysmorphism	Brachycephaly; persistent dysmorphism
Skeletal	Copper-beaten skull	Persistent copper-beaten skull; carpal ossification asymmetry
Gastrointestinal	Thickened bowel wall (US), asymptomatic	No GI symptoms
Cardiac	Echocardiogram normal	Echocardiogram normal
Neurodevelopmental	Neurosonogram normal	GDD; mild intellectual disability
Ophthalmological	Not assessed	Bilateral glaucoma; refractive error; paroxysmal crying
Respiratory	Not applicable	Recurrent LRTI; CXR/CT thorax normal

Trio whole-exome sequencing identified two variants in SH3PXD2B (NM_001017995): A maternally inherited missense variant in exon 13, c.2690C>T, p.(Ser897Phe) and a paternally inherited nonsense variant in exon 8, c.1219C>T, p.(Arg407*). Sanger sequencing confirmed both variants and their parent-of-origin, with each parent a heterozygous carrier of only one variant, consistent with the two residing in trans and with autosomal recessive inheritance.

The nonsense variant truncates TKS4 well before the fourth SH3 domain, consistent with the predominantly truncating nature of previously reported pathogenic SH3PXD2B alleles [6,9]. The missense variant was absent from population reference databases, was predicted deleterious by in silico tools and has not, to our knowledge, been previously reported, extending the mutational repertoire of SH3PXD2B. On the basis of phenotype, segregation and predicted effect, the genotype was classified as likely pathogenic for autosomal recessive FTHS, per ACMG/AMP guidance [10].

Discussion

This case illustrates three points of clinical relevance. First, a markedly abnormal skull radiograph

and incidental bowel-wall thickening were present at birth, years before FTHS was clinically suspected. The copper-beaten calvarium reflects exaggerated digital convolutional markings against a thin, poorly mineralised vault and is a recognised, if non-specific, correlate of the generalised osteopenia of FTHS [6,7]; its presence in the neonatal period, before the craniofacial gestalt was apparent, suggests skeletal imaging may be a more sensitive early clue than dysmorphism alone, particularly in non-consanguineous families without a raised prior probability of an autosomal recessive disorder. We did not identify a comparable prior report of a neonatal copper-beaten skull in FTHS and present it here as a candidate early radiological clue rather than an established sign.

Second, the carpal ossification asymmetry identified on this child's skeletal survey has not, to our knowledge, been documented in FTHS, where reported carpal findings are typically crowding of the carpal bones and broadened metacarpals rather than focal ossification asymmetry [6]. We report it descriptively as a novel observation rather than a corroborated feature, since the phenotypic boundaries of an ultra-rare syndrome are defined incrementally through such individual observations.



Third, the only clinical clue to this child's bilateral glaucoma was paroxysmal, otherwise unexplained crying, without overt buphthalmos or photophobia. Ocular disease, principally megalocornea with or without glaucoma, is among the most consistently reported and visually consequential features of FTHS and early surgical intervention is sight-saving when diagnosis is timely [8,11]. In pre-verbal or cognitively impaired children, elevated intraocular pressure may present exclusively as non-specific behavioural distress, supporting scheduled, proactive ophthalmological screening in FTHS rather than reliance on overt ocular signs.

Genetically, the architecture identified here, a presumed-null truncating allele in trans with a novel missense variant, is consistent with the broader pattern reported for SH3PXD2B, in which truncating alleles predominate and at least one previously characterised missense variant has been shown to reduce protein expression and alter intracellular localization [5,9].

We did not perform functional studies (for example, podosome formation or EGFR-signalling assays in patient-derived fibroblasts) to directly confirm the consequence of the p.(Ser897Phe) substitution, which we regard as a limitation of this report. This case is further limited by its single-patient design, precluding firm conclusions about the generalisability of the neonatal and carpal findings described; longitudinal follow-up and further case reports will be needed to clarify whether these represent consistent early or expanded features of FTHS.

Conclusion

We report a child with FTHS confirmed by a novel compound heterozygous SH3PXD2B genotype, c.2690C>T, p.(Ser897Phe) in trans with c.1219C>T, p.(Arg407*). Striking but non-specific radiological findings were present from birth, years before the syndrome was clinically suspected and an unreported carpal anomaly was identified on follow-up imaging. Occult bilateral glaucoma presenting only as paroxysmal crying underscores the value of scheduled, proactive ophthalmological surveillance in this and related skeletal dysplasia syndromes.

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Conflicts of Interest / Competing Interests

The authors declare that they have no competing interests.

Ethics Approval

Ethics committee approval was waived as this is a single case report with anonymized clinical data.

Consent to Participate

Written informed consent for participation in clinical management and reporting of anonymized data was obtained from the patient's parents/legal guardians.

Written Consent for Publication

Written informed consent for publication of clinical details and images was obtained from the patient's parents/legal guardians.

Availability of Data and Material

All data generated or analyzed during this study are included in this published article.

Code Availability

Not applicable.

Large Language Model (LLM) use; No large language model was utilized. The scientific content, interpretation and final manuscript preparation were performed by the authors.

Declaration of generative AI and AI-assisted technologies in manuscript preparation; the authors didn't used generative AI tools. No AI tools were used for data generation, analysis or interpretation.

Authors' Contributions

Rohan Acharya – Conceptualization, data curation, literature review, original draft writing

Kapil Bhalla – Clinical supervision, critical review, editing

Priyanka Panda – Radiological input, literature support, editing all authors read and approved the final manuscript.

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