

Masked β -Thalassemia Carrier Status Due to Coinherited *HBD* Variant Identified Through Whole Exome Sequencing A Paediatric Case Report

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INTRODUCTION

- β -thalassemia carrier screening in Sri Lanka primarily relies on High-Performance Liquid Chromatography (HPLC), with elevated HbA₂ levels considered the diagnostic hallmark.
- Variants affecting δ -globin synthesis can reduce HbA₂ levels, masking β -thalassemia carrier status and leading to false-negative screening results.
- Increasing use of genomic testing has enabled the identification of these hidden genetic interactions, improving diagnostic accuracy.

CASE PRESENTATION

- 6-year-old female
- posthumous WES performed following sudden death due to suspected familial cardiomyopathy
- history of sudden death in a younger sibling

Primary Clinical Finding

WES identified a homozygous likely pathogenic splice-site variant in *NRAP* gene, consistent with autosomal recessive dilated cardiomyopathy.

Incidental Carrier Findings

HBB Variant (β -globin gene)

Heterozygous pathogenic splice variant
c.92+5G>C

Consistent with β -thalassemia trait

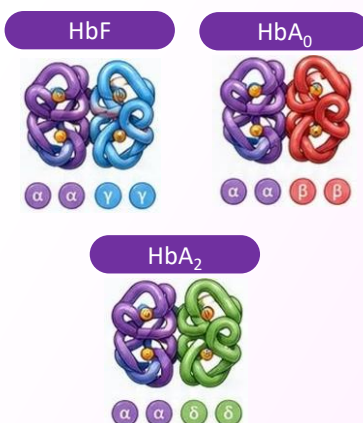
HBD Variant (δ -globin gene)

Heterozygous likely pathogenic missense variant
c.82G>T (Hb A2-Yialousa)

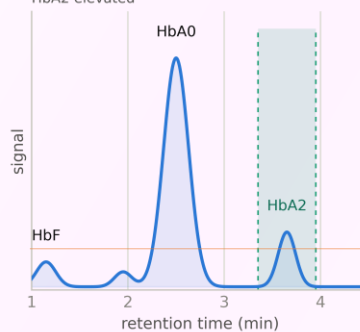
Known to reduce δ -globin production

Effect of Coinheritance

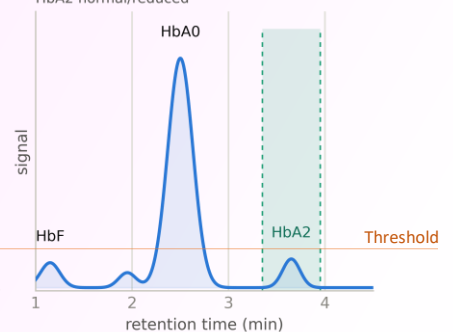
Coinheritance of *HBB* (β -thalassemia trait) and *HBD* (Hb A2-Yialousa) variants is associated with normal or low HbA₂ levels, potentially resulting in false-negative β -thalassemia screening on routine HPLC testing



Beta thalassemia trait
HbA₂ elevated



Beta thalassemia masked by an *HBD* variant
HbA₂ normal/reduced



(an illustration - not derived from the presented case)

CONCLUSIONS

- ✓ This case highlights an important limitation of HbA₂-based β -thalassemia screening, where coinherited *HBD* variants can mask carrier status.
- ✓ Molecular testing should be considered in individuals with discordant laboratory findings or relevant family history.
- ✓ Increased awareness of such genetic interactions is essential to improve the accuracy of thalassemia screening programs in high-prevalence settings.