Two siblings with congenital syndromic hypopituitarism and TBC1D32 mutations

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Introduction

New genes underlying hypopituitarism are discovered at burgeoning pace, yet a significant amount of congenital hypopituitarism causes remain unraveled (1). We hypothesized that a pituitary developmental gene defect underlies previously unexplained congenital hypopituitarism in two siblings with associated extra-pituitary phenotypes, and investigated the siblings' genomes by using whole genome sequencing.

Results

Table 1. Pituitary hormone deficiencies and phenotypic features of the patients

	Patient #1 (male)*	Patient #2 (female)
Biochemical hormone deficiencies	ACTH, TSH, GH, FSH/LH	TSH, GH
Gonads	Micropenis Bilateral testis retention	Unremarkable Prepubertal
Brain MRI	Sella turcica and pituitary not detectable Ectopic neurohypophysis	Sella turcica and pituitary not easily identifiable Ectopic neurohypophysis Slightly small optic chiasm
Additional phenotype	Communicating hydrocephalus Developmental delay Slight bilateral astigmatia	Motoric difficulties Retinal dystrophy Slight lumbal scoliosis Lower limb length difference

*exitus at 3 years of age

Whole-genome sequencing revealed compound heterozygous variants in both patients in *TBC1D32* gene (c.1165_1166dupGT p.(Gln390Phefs*32)(A) and c.2151delA p.(Lys717Asnfs*29)(B)). Both variants are predicted to lead to a frameshift and a premature stop codon and loss-of-function of the gene. The mother carried the c.2151delA mutation and the father the c.1165_1166dupGT mutation in the heterozygous state.

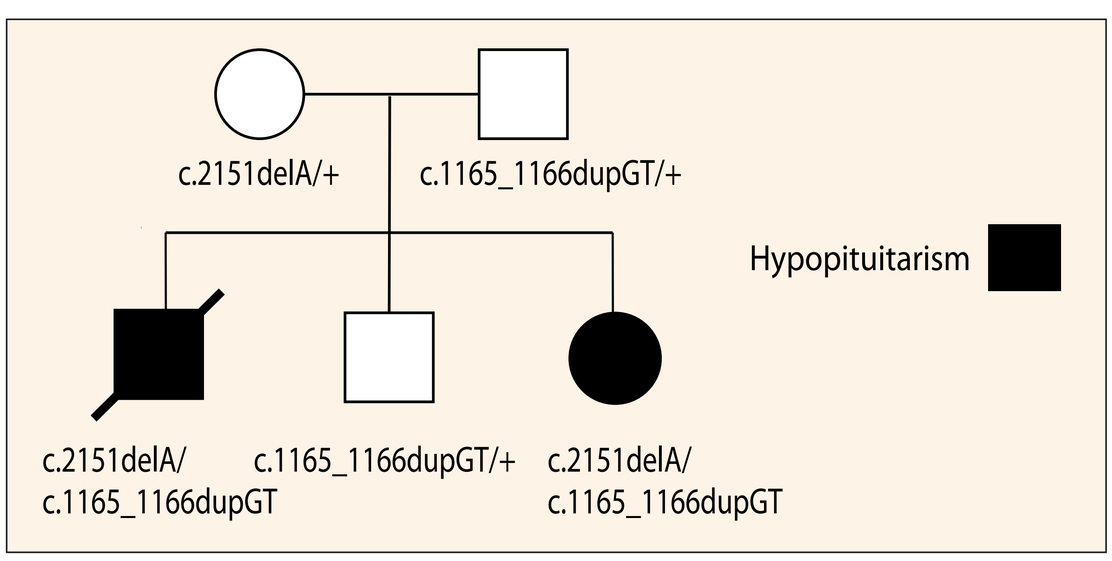

Figure 1. The pedigree of the patients with syndromic hypopituitarism and TBC1D32 mutations

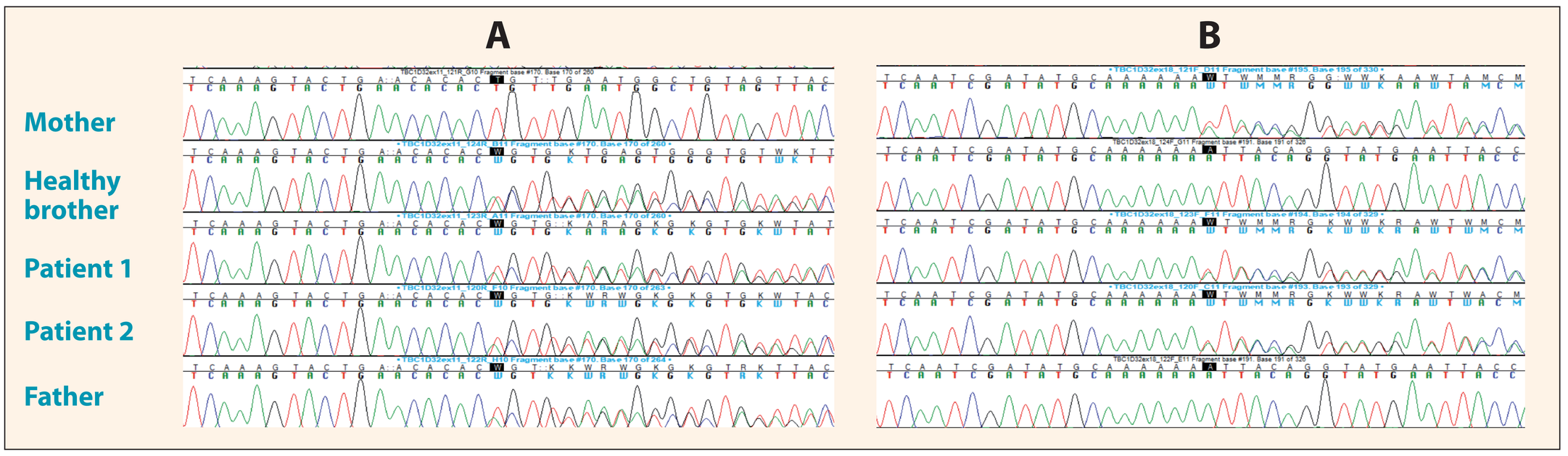

Figure 2. The identified disease-causing variants, c.1165_1166dupGT p.(Gln390Phefs*32) (A) and c.2151delA p.(Lys717Asnfs*29)(B)

Discussion/Conclusions

A homozygous splice site mutation in *TBC1D32* resulting in a truncated protein has previously been described in one male patient with the ciliopathy oro-facio-digital syndrome type IX (2). This patients phenotype was overlapping with our patients. The mouse *Tbc1d32* gene (*Bromi*) has been shown to be necessary for appropriate Sonic hedgehog signaling activation by Gli proteins, especially Gli2 (3). In mice, Gli2 induces pituitary progenitors in oral ectoderm as well as Bmp4 and Fgf8 expression in the ventral diencephalon. Mice with inactivated *Gli2* had hypoplastic anterior pituitary and absent posterior pituitary. (4) In humans, *GLI2* mutations cause hypopituitarism and/or holoprosencephaly (5).
We conclude that *TBC1D32* adds to ciliary genes involved in hypopituitarism.

PEDIATRIC RESEARCH CENTER

References

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Conflicts of interest: The authors have nothing to disclose.