Anophthalmia, abnormal pituitary development and suboptimal response to growth hormone therapy in two children with microdeletions of 14q22q23

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Introduction

The morphogenesis of midline brain structures, eyes, optic nerves and optic tracts is governed by a cascade of transcription factors including *SOX2*, *OTX2* and *BMP4*. Congenital anophthalmia, which is among the most severe consequences of defects in this cascade, is often accompanied by pituitary dysfunction and growth failure due to growth hormone (GH) deficiency.

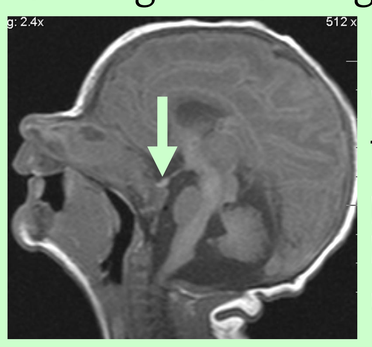
Patient 1

The girl was born to healthy parents in the 41st week of gestation with a weight of 3,500 g (50th centile), length of 52 cm (75th centile), and head circumference of 33 cm (10th centile). Bilateral anophthalmia and relative microcephaly were noted at birth. Brain MRI revealed absence of optic nerves, optic chiasm and optic tracts. The sella was flat, the pituitary stalk and posterior pituitary were present and normally located, but the anterior pituitary was undetectable.

She showed profound hypotonia and very large, low-set dysplastic ears, high prominent forehead, high frontal hairline, and wide nose with horizontal nostrils, but no cardiac or genital defects. Radiography revealed the presence of 13 pairs of ribs and unpent arcs of vertebral corpus Th1. At 6 months of age she had normal hearing at the left side and moderate hearing loss at the right side.

Patient 2

The boy was born to healthy parents in the 37th week of gestation by Caesarean section due to intrauterine growth retardation (IUGR) with a weight of 2,060 g and length of 44 cm (both below the 3rd centile for the gestational age), bilateral anophthalmia and hypotonia.

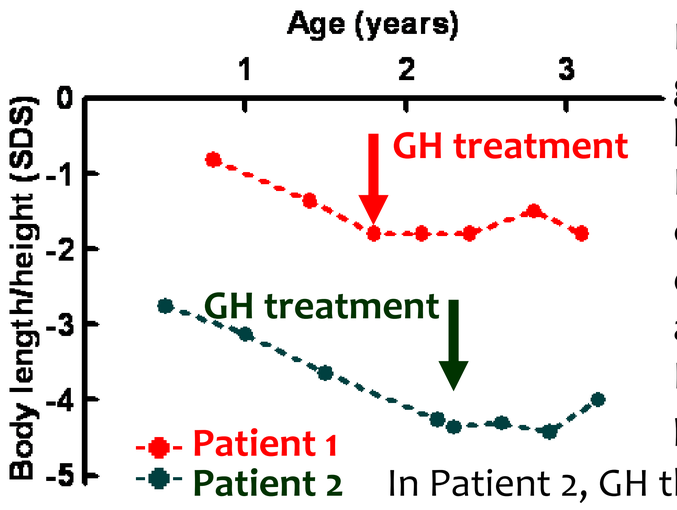


Brain MRI revealed absent optic chiasm; however, extraocular muscles were preserved. The sella was flat, the pituitary stalk and posterior pituitary were present and normally located, but the anterior pituitary was undetectable (marked by arrow).

Patient 2 showed mesocephaly with prominent narrow forehead, a small narrow face and a wide nasal bridge. He had no apparent morphological ear abnormalities and no cardiac, spinal, abdominal, or genital defects. His bilateral testicular retention required surgical management.

Growth and endocrine characteristics

Initially, the growth of the Patient 1 was normal. However, it started to decelerate to –0.8 SD (70 cm) at 10 months, –1.4 SD (76.3 cm) at 1.4 years and –1.8 SD (79 cm) at 1.8 years of age. Endocrine assessment revealed GH deficiency (3.53 ug/l following insulin-induced hypoglycemia at 17 months of age) and IGF-I deficiency (11 ug/l; –1.79 SD) but normal other pituitary functions (TSH 1.19 mIU/l, fT4 12.2 pmol/l, FSH 8.9 IU/l, LH 0.9 IU/l, cortisol 555 nmol/l, prolactin 4.7 ug/l).



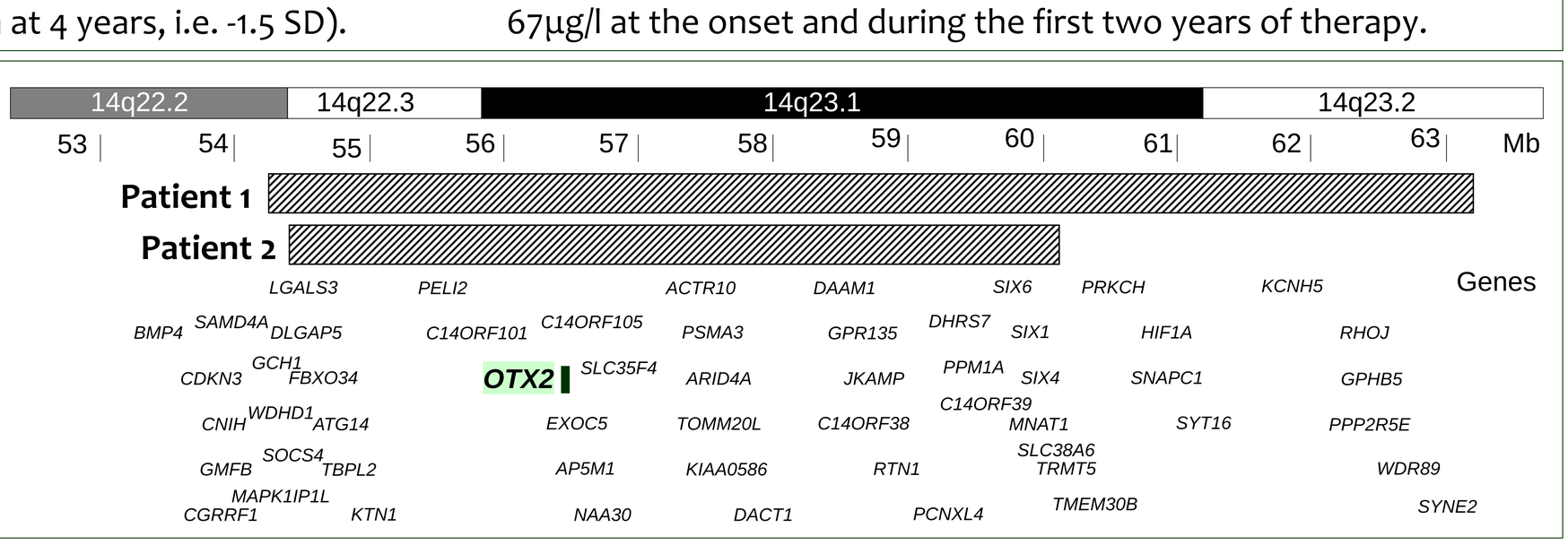
IUGR of Patient 2 was followed by severe postnatal growth failure: at the age of 7 weeks the boy had a length of 48.4cm(–3.7 SD), and weight of 3,010 g. He suffered from GH deficiency (1.79 ug/l following clonidine stimulation at 2.3 years of age) and IGF-I deficiency (2 ug/l). Other pituitary functions were apparently normal (TSH 2.75 mIU/l, fT411.8pmol/l, FSH 0.48IU/l, LH 0.07IU/l, cortisol 201 nmol/l, prolactin 5.7 ug/l).

In Patient 1, the GH therapy at a dose of 25µg/kg/day was initiated at the age of 1.8 years. It improved the growth rate and the serum IGF-I level (5.75 and 116 µg/l at the onset, 12 and 24 months of therapy, respectively) but did not lead to catch-up growth (99 cm at 4 years, i.e. -1.5 SD).

In Patient 2, GH therapy at a dose of 25µg/kg/day was initiated at the age of 2.3 years. His height velocity on therapy was atypical, with only a moderate increase within the first year of GH administration but a marked increase thereafter (92.0 cm at 4.1 years, i. e. -3.17 SD). Serum IGF-I levels were gradually increasing to 6, 19, 33, 56 and 67µg/l at the onset and during the first two years of therapy.

Genetic findings

Array comparative genomic hybridization (aCGH) revealed that Patient 1 had a deletion of 8.9 Mb affecting *OTX2* gene. Patient 2 had a 5.8 Mb long deletion removing also *OTX2* gene. Using independent methods, all deletions were confirmed in the patients but not in any of the parents indicating the *de novo* nature of the aberrations.



Conclusion

Genotype-phenotype description of two patients with deletions of 14q22q23 demonstrated that *OTX2* gene defects alone could explain most of the reported clinical features, although their expressivities are very variable. GH deficiency is remarkable in these patients but growth failure may be difficult to correct with GH therapy, probably due to an additional negative influence of some other deleted gene(s).

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