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 3,350 g (50th centile), length of 52 cm (75th centile), and head circumference of 33 cm (10th centile). Bilateral anophthalmia and relative microophthalmia 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 unpointed 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.

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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