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Chromosomal imbalance report

Oesophageal atresia with tracheoesophageal fistula and anal atresia in a patient with a *de novo* microduplication in 17q12

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ABSTRACT

Oesophageal atresia (OA) and tracheoesophageal fistula (TOF) are foregut malformations with a heterogeneous etiology. OA/TOF may occur as an isolated anomaly or as part of a syndrome. Chromosomal anomalies have been reported in 6–10% of OA/TOF. Several genes have been implicated in cases of syndromic OA/TOF, but no single specific chromosomal and monogenic defect has been confirmed as a main etiological factor. We described a patient with a 1.4 Mb duplication at 17q12 detected by SNP-array study and validated using qRT-PCR, who presented with an oesophageal atresia accompanied with tracheoesophageal fistula and anal atresia as well as other symptoms resembling VATER association (thumb hypoplasia, sacral bone defect, cryptorchidism). Genomic rearrangements of chromosome 17q12 are associated with a variety of clinical phenotypes. Only few cases with OA patients with the duplication in 17q12 have been reported. The 17q12 region comprised 15 genes. We propose to consider a role for selected genes such as *AATF* (cell proliferation and apoptosis) and *TADA2L* (Wnt pathway) at the 17q12 region as well as developmental and transcriptional pathways represented by these genes, in the development of OA/TOF and VATER association.

1. Introduction

Oesophageal atresia (OA) and tracheoesophageal fistula (TOF) are foregut malformations with a heterogeneous etiology. OA/TOF may occur as an isolated anomaly or as part of a syndrome. Several syndromes have OA/TOF as a clinical feature. The best known is the VACTERL association that is seen in 10–30% of OA/TOF. Chromosomal anomalies have been reported in 6–10% of OA/TOF. Several genes have been implicated in cases of syndromic OA/TOF, but no single specific chromosomal and monogenic defect has been confirmed as a main etiological factor. It is thought that a combination of genetic and environmental factors plays a role in the etiology of OA/TOF [1–5]. Advances in surgical techniques and perioperative care have increased survival rates to over 95% for isolated cases. Lower survival rates are reported for patients with multiple anomalies.

We report a male infant presenting the combination of multiple congenital defects (OA/TOF, anal atresia, thumbs hypoplasia, tracheomalacia, sacral bone defect, cryptorchidism) resembling VATER association, diagnosed with 17q12 microduplication.

2. Clinical description

The propositus was born at 33 weeks of gestation by cesarean delivery because of fetal multiple congenital defects diagnosed by ultrasonography. At birth his weight was 1010 g (<3rd centile), length was 39 cm (<3rd centile), and skull circumference 29 cm (<3rd centile). Physical and diagnostic examinations after birth revealed OA/TOF, anal atresia, sacral bone defect and cryptorchidism. The clinical symptoms resembled VATER association, but at first day of life he was suspected of Edwards syndrome that was finally excluded in cytogenetic analysis. Further examination showed mild facial dysmorphism, thumb hypoplasia and tracheomalacia (he needed tracheostomy tube).

He was operated on the first day of live. The TOF was closed and esophageal anastomosis were performed by thoracoscopic

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approach. During the same procedure a sigmoidostomy was created. The postoperative course was complicated by long respiratory insufficiency. The tracheomalacia was diagnosed and a tracheostomy was created. Later he had staged repair of anal atresia according to Pena's procedure. He was also diagnosed with gastroesophageal reflux and cholecystitis. Thus, fundoplication and cholecystectomy is planned for this patient.

Follow-up at 2 years showed a delayed psychomotor, but normal social development, hypotonia, short stature and mild facial dysmorphism. In the 20th month of life his height was 69.5 cm (below 3rd percentile), the weight 6.8 kg (<3rd percentile), skull circumference 47 cm (3rd centile) (Fig. 1).

Clinical evaluation at 32 month of life showed short stature and low weight. His height was 78.4 cm (−3.16 SDS to the standard for children born between 32 and 37 weeks of pregnancy) and weight 9.2 kg (−4.4 SDS). Bone age was delayed. Reduced levels of growth hormone in glucagon stimulation test (max. 9.0 ng/ml) along with IGF1, IGFBP3, TSH and fT4 in the normal range were noticed.

3. Methods and genomic rearrangement

Chromosome analysis showed a normal, male karyotype (46,XY). No subtelomeric imbalances were detected by using MLPA.

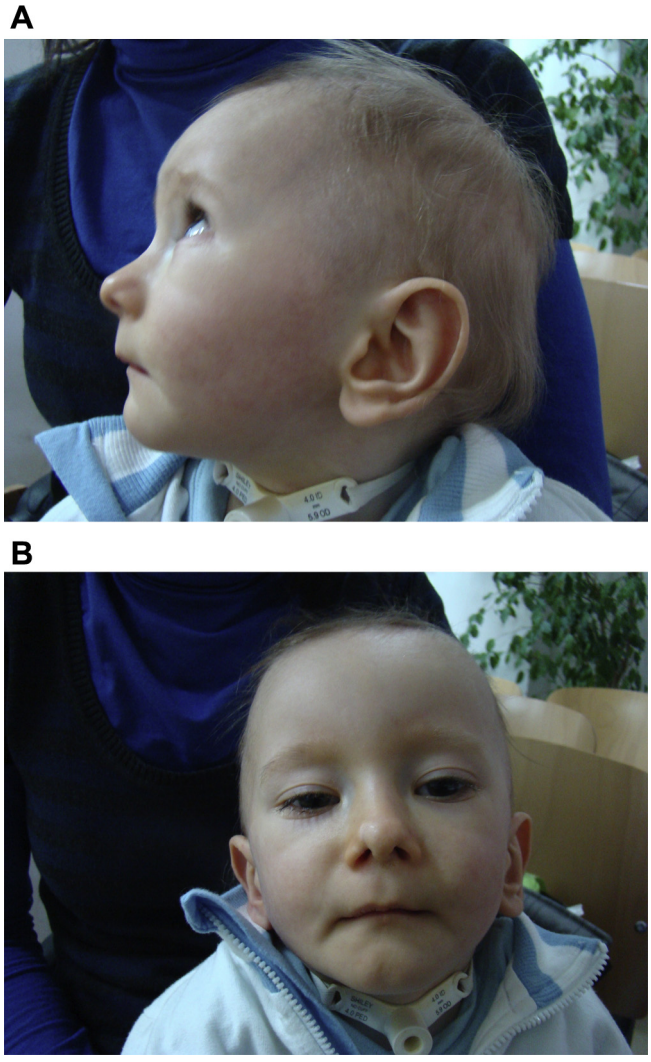

Fig. 1. Patient phenotype at 20 month of age.

Microarray analyses were carried out on the Affymetrix GeneChip 250k (NspI) SNP array platform (Affymetrix, Inc., Santa Clara, CA), containing 25-mer oligonucleotides representing a total of 262,264 SNPs. Hybridizations was performed according to the manufacturer's protocols. Copy numbers were determined using the 2.0 version of the CNAG (Copy Number Analyzer for Affymetrix GeneChip mapping) software package [6], by comparing SNP intensities from patient DNA with those of a sex-matched pooled reference DNA sample (DNA from either ten healthy male or ten healthy female individuals). The average resolution of this array platform is 150–200 kb. Genome wide array analysis showed a 1.4 Mb gain at 17q12 (position chr17:31.801.499-33.418.471) (Fig. 2). ArrayCGH result was validated using qRT-PCR (Illumina). This gain appeared to have occurred *de novo* – normal results in the patient's parents were obtained.

4. Discussion

The etiology and pathogenesis of esophageal atresia and treacheoesophageal fistula as well as VATER association are still unknown. About 50% of all patients with OA/TOF present with associated anomalies. About 10–30% of cases with OA/TOF are diagnosed as VATER/VACTERL association, comprising Vertebral defect, Anal atresia/stenosis, Tracheo-Esophageal fistula, Radial defects and Renal anomalies. Additional defects such as Cardiac defect and Limb anomalies are involved in VACTERL association [1–5].

We described a patient with a 1.4 Mb duplication at 17q12 detected by SNP-array study, who presented with an oesophageal atresia accompanied with tracheoesophageal fistula and anal atresia as well as other symptoms resembling VATER association (thumb hypoplasia, sacral bone defect, cryptorchidism).

Our patient also presents with short stature and growth hormone deficiency as seen in a glucagon stimulation test. Thus, further diagnostic procedures are planned. Microduplication in 17q12 region is likely to explain the clinical picture of our proband.

Genomic rearrangements of chromosome 17q12 are associated with a variety of clinical phenotypes. Deletions of 17q12 are associated with MODY, renal and liver abnormalities and pancreatic atrophy, while only few cases with the duplication in 17q12 have been reported [7,8]. Patients with a duplication of this region generally presented with cognitive impairment, renal disease and other minor anomalies [7,8,12]. Alterations in 17q12 region that is flanked by low-copy repeats have been described by Nagamani et al. in patients with epilepsy, brain abnormalities and intellectual disability [8]. Among these patients, one with a duplication of 17q12 presented with OA/TOF and vertebral defect [8]. Moreover, Faguer et al. presented a familial microduplication of 17q12 in a father with renal abnormalities and his child with OA and urinary tract defect [11]. The authors have focused their efforts at renal defects and they have screened *HNF1B* gene as a potential gene for renal hypodysplasia in nine patients with OA and various renal abnormalities but didn't find any mutations in this gene.

In our patient a 1.4 Mb duplication in 17q12 region has been shown. This region comprised 15 genes: *ZNHIT3*, *MYO19*, *PIGW*, *GGNBP2*, *DHRS11*, *MRM1*, *LHX1*, *AATF*, *ACACA*, *TADA2L*, *DUSP14*, *AP1GBP1*, *DDX52*, *HNF1B* and *LOC284100*. Overexpression of these genes could explain the congenital defects in our patient. Among these genes, *AATF* and *TADA2L* should be pointed as a potential candidate gene for OA/TOF and VATER association. However, an involvement of other genes located in duplicated region can't be excluded.

AATF encodes a transcription factor involved in regulation of cell proliferation and apoptosis. Overexpression of the *AATF* gene interferes with MAP3K12 inducing apoptosis [9]. It is proved that