Deletion of 16q22.2q23.3 in a Boy with a Phenotype Reminiscent of Silver-Russell Syndrome

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Established Facts

- Interstitial 16q deletions are rare copy number variations.
- Most common features are global developmental delay, short stature, minor anomalies of the ears and forehead, and feeding difficulties in infancy.

Novel Insights

- A patient with a 16q22.2q23.3 microdeletion presented with a facial phenotype reminiscent of Silver-Russell syndrome.
- Additional individual features found in the patient were a weak cry, sleeping disturbance, and delayed tooth eruption.

Keywords

Chromosome 16q · Deletion · Copy number variation · Growth delay · Neurodevelopmental disorders

Abstract

A 15-month-old boy presented with growth and global developmental delay, feeding difficulties, sleep disturbance and several minor anomalies, including a large anterior fontanel, relative macrocephaly, and a triangular face. Clinical suspicion prompted genetic investigations for Silver-Russell syndrome and related disorders. SNP array analysis led to the diagnosis of an approximately 10-Mb large deletion of the long arm in chromosome 16q22.2q23.3. Interstitial deletions of 16q show a wide variability of related features; however,

considering the differences in size and location of the deletions in the known patients, the phenotypic overlap is surprising. Here, we report a novel microdeletion, compare the proband with data from scientific literature and international databases, and discuss possible diagnostic implications.

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Introduction

Interstitial deletions of chromosome 16q have been reported in scientific literature since the late 1970s [Lin et al., 1983; Ionasescu et al., 1987; Casamassima et al., 1990; Fujiwara et al., 1992; Callen et al., 1993; Monaghan et al., 1997; Werner et al., 1997; Chen et al., 1998; Mori et al.,

Fig. 1. Frontal and profile view of the proband showing facial characteristics.

2019]. Despite variable deletion breakpoints, there is great phenotypic overlap between the known patients: low birth weight, poor sucking and feeding difficulties, failure to thrive, slower somatic development during childhood, and sometimes short stature in adolescence/adulthood; intellectual disability/developmental delay (ID/DD); large anterior fontanel and/or delayed closure of the cranial sutures, high and broad forehead, frontal bossing, low-set ears with morphological abnormalities, hypertelorism, short neck, narrow thorax, wide intermamillary distance, and minor anomalies of the hands and feet (e.g., finger clinodactyly, broad hallux, overlapping toes, etc.) are very common regardless of the deletion's exact location. A nearly study proposed 16q22.1q22.2 as a critical region [Werner et al., 1997], while the Online Inheritance in Man database (www.omim.org) lists "chromosome 16q22 deletion syndrome" (#614541) as a separate entity. However, most abovementioned case studies date back to a time when high-definition characterization of the deletion breakpoints was not yet possible. We report a child with clinical features reminiscent of Silver-Russell syndrome (SRS) carrying a large loss of chromosome 16q22.2q23.3.

Case Presentation

The patient (listed in the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources [Firth et al., 2009]; DECIPHER ID #414204) was referred to our clinic with growth and global developmental delay, and feeding difficulties. He is the second of 3 children born to a healthy nonconsanguineous couple. He was born after 38 weeks of uncomplicated gestation per vias naturales; labor, however, was prolonged, and the umbilical cord was wrapped around the newborn's neck. He weighed 2,700 g (−1.4 SD for gestational age), had a length of 49 cm (+0.6 SD for gestational age), a head circumference of 33.5 cm (+0.2 SD), and Apgar scores of 8/9. He had moderate combined acidosis and was observed in a neonatal intensive care unit for a short period of time after birth. Postnatal screening examinations (brainstem evoked response audiometry; ophthalmological, cardiac, echocardiographic, and abdominal and cranial ultrasound examinations) were all normal. His growth delay first became evident after 2 months of age. As an infant, he had a wide anterior fontanel. Upon first physical examination at 15 months of age, we noted the following characteristics: relative macrocephaly; broad, high and prominent forehead; wide nasal bridge; low-set and short ears; prominent antihelix; micrognathia; high palate; single transverse palmar crease on the left hand; 4th–5th toe syndactyly of the left foot, and 4 small café-au-lait spots (Fig. 1.). He had slightly delayed eruption of primary teeth (10 months of age). The parents also observed sleep disturbance and a weak cry. He has been receiving early intervention services since the age of 1 year and is showing consistent improvement in all developmental areas. He underwent additional neurological examinations due to an absence-like episode, but his EEG was normal. Brain MRI showed mild dilation of

[illegible]

D, DECIPHER; ID/DD, intellectual disability/developmental delay; -, absent; +, present. * Excluding hyperteletorism; ** For more detailed phenotypic information, see online supplementary Table 3.

the lateral and the third ventricles and small (<3 mm) aspecific focal hyperintensities in the superior frontal gyrus. GHRH-arginine stimulation test excluded the possibility of GH deficiency. At the most recent follow-up, the proband was 2 years and 6 months old, his head circumference was 48.5 cm (between the 15th–50th percentile for age and sex; –0.79 SD), he weighed 9.4 kg (below the 3rd percentile; –3.48 SD), his height was 77.3 cm (below the 3rd percentile; –4.13 SD), and his body mass index was 15.73 kg/m² (25th–30th percentile). Follow-up abdominal ultrasound was normal and there was no indication for a further echocardiogram. His older brother and younger sister are healthy; family history is negative for genetic disease and congenital anomalies.

We initially assessed him for SRS due to a score of 4 out of 6 points on the Netchine-Harbinson clinical scoring system [Wake-ling et al., 2017]: postnatal growth failure, relative macrocephaly at birth, protruding forehead, and severe feeding difficulties. His additional features suggestive of SRS were micrognathia, a triangular face, and global DD.

Materials and Methods

Methylation-specific and quantitative MLPA was performed with ME030-C3 and ME032-A1 MLPA probemixes (MRC Holland, Amsterdam, the Netherlands) and SNP analysis using the Affymetrix CytoScan HD microarray system (Thermo Fisher Scientific, Inc.; Waltham, MA, USA) at the Institute of Human Genetics, Uniklinik, RWTH Aachen. Patient and parental karyotypes were determined by analysis of 20 Giemsa-stained metaphases each from standard 72-h peripheral blood lymphocyte cultures.

MLPA analysis had negative results for abnormal methylation or copy number changes in chromosome 11p15, for maternal uniparental disomy of chromosome 7 and for maternal uniparental disomy of chromosome 14. SNP analysis was then performed and revealed a 9,993-Mb large deletion of chromosome 16 between genomic positions 72,155,844 and 82,148,404 Mb. The adjacent oligos showing a normal copy number were located at 72,152,836 and 82,148,451 Mb. The deletion was confirmed by conventional G-banding, and his karyotype was determined as 46,XY,del(16)(q22.2q23.3).arr[GRCh37/hg19] 16q22.2q23.3(72155844_82148404)×1. G-banding analysis of the parents gave normal results <http://genome-euro.ucsc.edu/index.html>.

Discussion

Among the 71 genes found within the presented patient's deleted chromosome segment, 49 are protein coding, and 16 are known disease-causing genes (online suppl. Fig. 1. (<http://genome-euro.ucsc.edu/index.html>); for all online suppl. material, see www.karger.com/doi/10.1159/515941). Mutations in *WWOX* (*605131), a putative oxidoreductase and tumor suppressor, can cause 2 autosomal recessive disorders, early infantile epileptic encephalopathy 28 (#616211) and spinocerebellar ataxia 12 (#614322). An infant with West-syndrome and ~7-Mb

large loss of 16q22.2q23.1 encompassing *WWOX* has been reported recently; however, the authors found no pathogenic mutations in the other allele of the *WWOX* gene, and seizures are not a common finding in 16q deletions [Mori et al., 2019]. *MAF* (*177075) encodes a transcription factor involved in the differentiation of various T-cell subtypes and chondrocytes, and in the development of the eye. Specific mutations of this gene are associated with autosomal dominant disorders: cataract 21, multiple types (#610202) and Aymé-Gripp syndrome (#601088). This syndrome is characterized by congenital cataracts, sensorineural hearing loss, DD/ID, behavioral disorders, seizures, reduced growth/short stature, brachycephaly, a distinct facial phenotype (flat face, short nasal tip, abnormalities of the ears, small mouth, long philtrum), and variable cardiac and skeletal anomalies (e.g., pericardial effusion and radioulnar synostosis [Niceta et al., 2015; Amudhaval- li et al., 2018]). Aymé-Gripp syndrome shows a partial phenotypic overlap with 16q deletions, highlighting *MAF* as a potential key gene. For information about further encompassed genes associated with neurodevelopmental disorders, see online supplementary Table 1.

DECIPHER and the dbVar public databases each list approximately 100 overlapping deletions. For comparison with the presented patient, we have narrowed down this large pool of cases to 19 individuals who carry CNVs of similar size and/or have ~50% or more overlap with the proband's deletion (online suppl. Table 2). Phenotypic information is available for 18 of them (an overview of the proband and the 18 overlapping cases can be seen in Table 1.; for more detailed phenotypes see online suppl. Table 3). The most frequent feature amongst them was ID/DD, listed in 15 cases. Growth abnormalities and morphological anomalies of the forehead occurred in 9/19 cases, while muscular hypotonia and morphological anomalies of the ears each affected 8 patients. Six individuals had a wide anterior fontanel and/or delayed closure of the fontanel; a high anterior hairline was likewise noted in 6 cases. Anomalies of the genitourinary tract occurred in 5 patients and included cryptorchidism, renal hypoplasia, ectopic anus, hydro-nephrosis and multicystic kidney dysplasia. Microcephaly was listed in 4 patients. Four individuals had a heart defect, 2 of which were atrioventricular canal defects. Further minor anomalies that affected several patients included hypertelorism (6/19), short neck (4/19), wide intermamillary distance (4/19), and variable abnormalities of the hands and feet (8/19). Two individuals had cataracts; both of their deletions encompassed *MAF*.

In conclusion, we present a novel specific 16q22.2q23.3 microdeletion phenotype. Global DD dominated the

child's clinical picture and a facial phenotype reminiscent of SRS. Moreover, he presented additional individual features such as a weak cry, delayed tooth eruption, and sleep disturbance. Considering the phenotypic overlap with SRS, physicians might consider the 16q deletion syndrome as an alternative diagnosis after obtaining negative test results, especially in the absence of body asymmetry.

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Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. As this paper included only diagnostic testing of the patient and his parents, Hungarian regulations do not require additional approval from an ethics committee for publication. Written informed consent was

obtained from the patient's parents for the publication of this case report and the publication of identifying photographs.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

A.L., É.P., G.F., and I.H. conceptualized the project. G.F. and I.H. conducted the project. A.L. and É.P. are the attending physicians, they organized the tests, and wrote the clinical description. A.L. prepared the manuscript and the figures. T.E. conducted and analyzed the genetic tests. All authors critically revised the manuscript and approved the final version.

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