Meta Gene 9 (2016) 185–190

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Inherited Xq13.2-q21.31 duplication in a boy with recurrent seizures and pubertal gynecomastia: Clinical, chromosomal and aCGH characterization

Natália D. Linhares [a,*], Eugênia R. Valadares [b,c], Silvia S. da Costa [d], Rodrigo R. Arantes [c], Luiz Roberto de Oliveira [c], Carla Rosenberg [d], Angela M. Vianna-Morgante [d], Marta Svartman [e]

[a] Setor de Citogenética/Laboratório Central do Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[b] Departamento de Propedêutica Complementar, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[c] Ambulatório de Erros Inatos do Metabolismo, Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[d] Departamento de Genética e Biologia Evolutiva, Instituto de Biociências, Universidade de São Paulo, São Paulo, Brazil
[e] Departamento de Biologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

ARTICLE INFO

Article history:
Received 28 April 2016
Revised 4 June 2016
Accepted 7 July 2016
Available online 7 July 2016

Keywords:
Xq13-q21 duplication
Prader-Willi syndrome
Mitochondrial disease
ATRX protein
PCDH11X protein

ABSTRACT

We report on a 16-year-old boy with a maternally inherited ~18.3 Mb Xq13.2-q21.31 duplication delimited by aCGH. As previously described in patients with similar duplications, his clinical features included intellectual disability, developmental delay, speech delay, generalized hypotonia, infantile feeding difficulties, self-injurious behavior, short stature and endocrine problems. As additional findings, he presented recurrent seizures and pubertal gynecomastia. His mother was phenotypically normal and had completely skewed inactivation of the duplicated X chromosome, as most female carriers of such duplications. Five previously reported patients with partial Xq duplications presented duplication breakpoints similar to those of our patient. One of them, a fetus with multiple congenital abnormalities, had the same cytogenetic duplication breakpoint. Three of the reported patients shared many features with our proband but the other had some clinical features of the Prader-Willi syndrome. It was suggested that *ATRX* overexpression could be involved in the major clinical features of patients with partial Xq duplications. We propose that this gene could also be involved with the obesity of the patient with the Prader-Willi-like phenotype. Additionally, we suggest that the *PCDH11X* gene could be a candidate for our patient's recurrent seizures. In males, the Xq13-q21 duplication should be considered in the differential diagnosis of Prader-Willi syndrome, as previously suggested, and neuromuscular diseases, particularly mitochondriopathies.

© 2016 Published by Elsevier B.V.

1. Introduction

Males with Xq13-q21 duplications have short stature, intellectual disability, developmental delay, speech delay, generalized hypotonia, infantile feeding difficulties, endocrine problems, short palpebral fissures, epicanthic folds, ptosis, tented vermilion of the upper lip and downturned corners of the mouth, and genital anomalies such as hypoplastic genitalia with undescended testes. On the other hand, most of the female carriers are asymptomatic with an inactive duplication-bearing X chromosome.

Interestingly, patients with X-linked intellectual disability associated or not with alpha-thalassemia (MIM 301040, MIM 309580) have a phenotype similar to those with the Xq13-q21 duplication, including features such as short stature, intellectual disability, developmental delay, hypotonia, hypogonadism, cryptorchidism, epicanthic folds, ptosis and inverted V-shaped upper lip (Lugtenberg et al., 2009). This disorder comprises several syndromes reported separately, including Chudley-Lowry, Juberg-Marsidi, Carpenter-Waziri, Holmes-Gang and Smith-Fineman-Myers, found to be caused by mutations in the *ATRX* gene, located at Xq21.1 (alpha thalassemia/mental retardation syndrome X-linked, MIM 300032).

We report on a boy with an Xq13.2-q21.31 duplication inherited from his phenotypically normal mother. His chromosome rearrangement was identified by routine chromosome analysis and characterized by high resolution karyotyping and oligonucleotide aCGH analysis. We compare the patient's phenotype to five previously reported patients with molecularly delimited similar duplications.

2. Materials and methods

This study was approved by the Research Ethics Committee of the *Universidade Federal de Minas Gerais* (project number 0007.0.203.000-10). The written informed consent was undersigned by the patient's parents.

http://dx.doi.org/10.1016/j.mgene.2016.07.004
2214-5400/© 2016 Published by Elsevier B.V.

2.1. Clinical report

The 16-year-old boy (Fig. 1) was the fourth child of a non-consanguineous healthy couple. He was born at term by elective Cesarean section, with weight of 3020 g (25–50th centile), length of 45 cm (10–25th centile) and head circumference of 35 cm (75–90th centile). A previous male sibling died of an unknown cause, 17 h after birth, and two sisters were phenotypically normal. In the newborn period he presented feeding difficulties, with poor sucking, and at age 15 days he weighed 1900 g (<3rd centile). Neonatal screening for hypothyroidism and phenylketonuria were negative.

His growth and neuropsychomotor development were delayed; he walked without support and spoke his first words at age 3 years. Although calm, he had a self-injurious behavior (for instance, he bit himself and hit his head on the wall), first noted when he was 4 years old. At age 2 years, the diagnosis of hypothyroidism was established, and he made use of levothyroxine until the age of 5 years and 6 months, when the thyroid function normalized. He underwent surgical correction of cryptorchidism and bilateral inguinal hernia at 6 years. From age 7 to 13 years he presented recurrent seizures, treated by carbamazepine since the first episode.

Examined at 10 years of age, his height was 118.2 cm (<3rd centile), and his weight was 20.2 kg (<3rd centile). He presented intellectual disability, impaired social interaction, language impairment (spoke a few words), facial and generalized hypotonia, normal tendon reflexes, bilateral ptosis, tented mouth, high-arched palate, low-set protruding ears, *pectus excavatum*, *genu varum* and joint hyperextensibility. Ophthalmologic examination and brain computed tomography (CT) scan did not show abnormalities; nuclear magnetic resonance (NMR) of the brain documented mild dilatation of lateral ventricles, spectroscopy showed an increased lactate peak and the electroencephalogram showed the presence of nonspecific changes. Venous blood gases, ammonia, lactate, ions, complete blood count with platelets, blood glucose, uric acid, creatine phosphokinase-total (CKT), urine qualitative reactions and chromatography of oligosaccharides in urine and blood amino acid were normal. TSH, T3, T4 and T3-reverse were performed at 12-years of age and the results were within the normal range. He entered puberty at age 12 and since then presented bilateral generalized gynecomastia (Fig. 1). Currently at age 16, his height is 152 cm (<3rd centile), his weight is 53 kg (10–25th centile) and he has adult genitalia, axillary hair, and thin mustache (beardless).

Chromosome analysis revealed a 46,XY,dup(X)(q13q23) karyotype. His mother presented the same tandem duplication. His maternal grandmother karyotype was normal, and his grandfather refused examination. Recently, his sister had a hypotonic male child that needed gastrostomy diet due to poor sucking; his karyotype showed the same duplication.

2.2. Cytogenetic analysis

Chromosome preparations from the patient and his mother were obtained from cultured peripheral blood lymphocytes. In order to obtain high-resolution chromosomes we combined thymidine cell synchronization with ethidium bromide addition. Chromosome analysis was performed after GTG-banding and fluorescence in situ hybridization (FISH) was carried out with a flow-sorted whole-human X chromosome probe labeled and detected according to standard procedures.

2.3. X chromosome inactivation

The X chromosome inactivation pattern was analyzed in the patient's mother after 5-bromodeoxyuridine (5-BrdU) incorporation and acridine orange staining, according to Latt (1973) with modifications. Briefly, leukocytes were cultured for 40 h in medium with 0.2 mg/ml 5-BrdU (Sigma-Aldrich, Saint Louis, MO, EUA) and then for 6 h in 5-BrdU free medium containing 0.2 mg/ml thymidine (Sigma-Aldrich). The X inactivation pattern was analyzed in 50 cells. The methylation status of the androgen-receptor gene was determined in a DNA sample extracted from peripheral blood, as previously described (Allen et al., 1992). The resulting PCR products were analyzed on an ABI-310 Genetic Analyzer, and product length and peak areas were obtained using the Gene Mapper Software v4.0 (Applied Biosystems, Foster City, CA).

2.4. aCGH analysis

Genomic DNA was isolated from the patient's and his mother's blood cells using the Qiagen DNA extraction kit (Santa Clara, CA). Microarray-based comparative genomic hybridization (aCGH) was performed using an X-chromosome dedicated 44K microarray (custom design 2008) and the Whole Human Genome CGH Microarray 60K (Agilent Technologies Inc., Santa Clara, CA, USA), following the manufacturer's protocol. Scanned images of the arrays were processed with the Feature Extraction software (Agilent Technologies). We applied the Genomic Workbench software (Agilent Technologies) for calling CNVs using the Aberration Detection Method 2 statistical algorithm (sensitivity threshold of 6.7). Duplications or deletions were considered when the log2 ratio of the Cy3/Cy5 intensities of a region encompassing at least three probes was >0.3 or <−0.3, respectively. Mapping data were analyzed using the UCSC genome browser - NCBI Build 37, hg19.

3. Results

High resolution chromosome analysis of the patient showed a partial duplication of the X chromosome long arm [46,XY,dup(X)(q13.3q22.1)]. The same duplication was detected in his

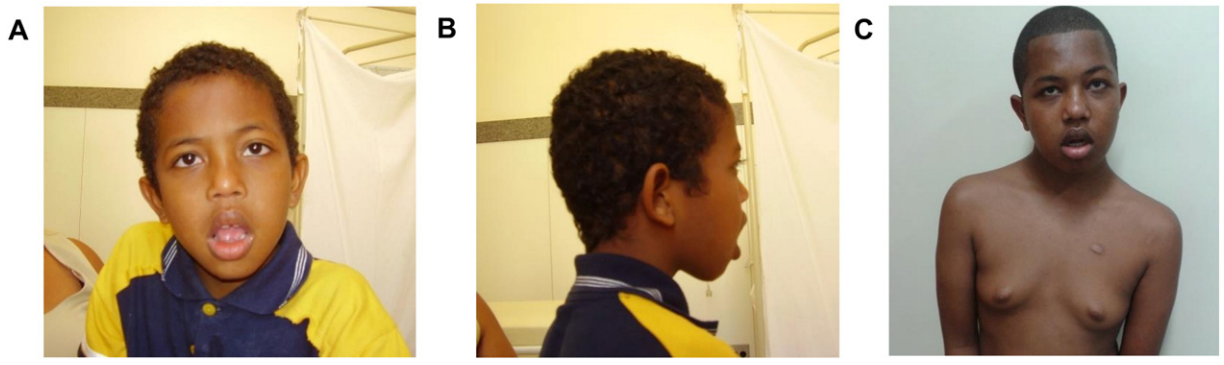

Fig. 1. (A, B) Frontal and lateral views of patient at 12-years of age, showing facial hypotonia, bilateral ptosis, low-set protruding ears and tented mouth. (C) Patient at 16-years of age, showing gynecomastia.

Download English Version:

https://daneshyari.com/en/article/8389316

Download Persian Version:

https://daneshyari.com/article/8389316

Daneshyari.com