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CASE REPORT

Intellectual disability and dysmorphisms in a child with 14q32.31-q32.33 deletion: a case report

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Comparative Genomic Hybridization, Cytogenetics, Intellectual Disability, Sequence, Deletion.

Abstract

Introduction: Intellectual disability and global developmental delay are frequent causes of genetic consultation requested by pediatricians. Around 30% of severe intellectual disability and 70% of mild intellectual disability do not present a defined diagnosis. **Objectives:** Chromosome microarray comparative genomic hybridization test is now the standard diagnosis for patients presenting unexplained global developmental delay or intellectual disability, autism spectrum disorders, and multiple congenital anomalies due to the tests sensibility, increasing the chance for a diagnosis and elucidating size and region affected. **Case Report:** This paper reports a girl with intellectual disability, prominent hypotonia, postnatal growth retardation and several dysmorphisms with a small subtelomeric 14q terminal deletion whose diagnosis was sought during six years and only became possible through the chromosome microarray test.

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INTRODUCTION

Intellectual disability (ID) or global developmental delay (GDD) are common causes of a genetic consultation. A proportion of ID cases, ranging from 17-50%, is attributable to genetic etiology[1]. However, around 30% of severe ID and 70% of mild ID do not present an ethnologic diagnosis[2]. Cytogenetic studies are recommended but a significant percentage of these patients are not diagnosed because conventional techniques are limited and cannot identify chromosomal abnormalities, involving less than 5Mb. Chromosome microarray test is the standard diagnosis for patients presenting unexplained global developmental delay or ID, autism spectrum disorders, and multiple congenital anomalies because it presents increases in sensibility[3]. Herein is reported a girl with ID, hypotonia and dysmorphisms with a small subtelomeric deletion whose diagnosis was sought during six years and only became possible through the array comparative genomic hybridization (array-CGH).

CASE REPORT

Female, 11 years old, the first child of healthy unrelated parents; she was born at term, by normal delivery; Apgar score at 5' was 8. Table 1 shows anthropometry and developmental milestones at different ages. The antenatal period was unremarkable and the mother was 23 years old at delivery. The father has a healthy 7 years old girl from his second marriage. There was no family history of GDD/ID or congenital anomalies.

The proband was referred to genetic evaluation, at two years old, due to (GDD). At first evaluation, she presented global hypotonia, was unable to stand up or walk and presented an incomprehensible speech. Physical examination showed microcephaly, high forehead, narrow bifrontal diameter, blepharophimosis, bilateral epicanthi, short bulbous nose with anteverted nares, elongated face, high and arched palate, thin upper lip, asymmetric ears and joint laxity (Photography 1). There were no internal anomalies. It was reported several respiratory infections from birth to five years old. Concerning adaptive behavior, she eats by herself, plays alone and with other children, and draws scribbles, but she is unable to recognize alphabet letters or numbers at 6 years old. Intelligent quotient at age of 7, by Wechsler Intelligent Scale version III (WISC-III), was 44 and the presence of anxiety was noticeable.



Photography 1. Proband at two-years-old. Note the high forehead, narrow bifrontal diameter, bilateral epicanthal, short bulbous nose with anteverted nares and broad nasal bridge.

Table 2 shows the proband's main features, comparing to other cases published in the literature. In a first investigation at 2 years old, an electromyogram suggested myopathy, and muscle enzymes presented borderline results; GTG karyotype was normal (46, XX). It was prescribed physical therapy and follow-up at a genetics clinic. When the patient was 8 years old, another investigation was done and a blood sample was collected for cytogenetic molecular analysis, elucidating the diagnosis. Then, she was referred to an occupational therapist and to an ophthalmologist, who diagnosed myopia. She was enrolled at regular school and received all different kinds of pedagogical assistance where she is presenting improvement. At 10 years old, she has still presented anxiety, and she was unable to read or write.

Table 1. Anthropometry from birth to 11 years old and developmental milestones.

	Weight (p)	Length (p)	Head circumference (p)	Developmental milestones
At born	2985g	48cm	33cm (5)	
2 years-old	9400g (3.5)	80.5cm (3.2)	44.2cm (↓ p 3)	Sits without support
3 years old	11.300g (0.6)	92cm (1.3)	47cm (p 10)	Stands with support/speaks 4 words
6 years-old				Speaks sentences
8 years-old	22Kg (↓p 5)	122.3cm (p 10-25)	49cm (↓ 50)	Sphincter control
11 years-old		136cm (p 3-15)	50cm (↓ 50)	Unable to read/write anxiety

Legend: p = Percentile.

Table 2. Proband features compared to other cases reported in the literature.

Features	Proband	Ortigas et al., 1997[4]	Cheon et al., 2011[5]	Van Karnebeek et al., 2002[X]	Zada et al., 2014[X]	Engels et al., 2012[7] (n=5)	Riegel et al., 2014[10]
Age	11-year	3-year	5-year	9-month	20-year		6-year
14q distal breakpoint		Qter	Qter	Qter	q32.31		q24.3
14q proximal breakpoint	q32.31	q32.3	q32.33	q32.31	q32.2	q32.31(n=3) q32.33(n=1) q32.31-q32.32(n=1)	q31.3
Microcephaly	+	+	+	+	+	1/5	-
High forehead	+	+	+	+	+	5/5	-
Narrow bifrontal diameter	+	NR	+	+	NR	NR	-
Blepharophimosis	+	+	NR	+	NR	2/5	-
Bilateral epicanthi/telecanthus	+	+	-	+	NR	5/5	-
Short bulbous nose with anteverted nares/ broad nasal bridge	+	+	+	+	NR	5/5	+
Elongated face	+	NR	NR	NR	NR	NR	NR
High and arched palate	+	+	-	NR	NR	3/2	-
Thin upper lip/ vermilion	+	NR	-	NR	+	4/5	+
Asymmetric/abnormal ears	+	NR	NR	+	NR	4/5	+
Myopia/other eye anomalies	+	+	NR	NR	NR	1/5	-
Hypotonia	+	+	+	+	+	5/5	+
Post-natal growth retardation	+	-	+	_	+	1/5	-
Abnormal EEG	-	-	+	-	NR	1/5	-
Seizure	-	-	+	-	NR	NR	-
Delayed milestones	+	+	+	+	+	5/5	-
Intellectual disability	+	NR	+	+	+	5/5	+
Behavior	Anxiety	NR	Hyperactivity	NR	NR	NR	Attention deficit

Legend: NR = Not reported.

Molecular cytogenetic analysis and the result

The molecular cytogenetic investigation was performed using customized Agilent 60-mer oligonucleotide-based microarrays with a theoretical resolution of 40 kb (8X60K, Agilent Technologies Inc., Santa Clara, CA). Labeling and hybridization were performed according to protocols provided by Agilent. Arrays were analyzed with a microarray scanner (G2600D) and Feature Extraction software (v. 9.5.1) (both from Agilent Technologies). Image analysis was performed using Agilent Genomic Workbench Lite Edition 6.5.0.18 with the statistical algorithm ADM-2 and sensitivity threshold 6.0. Map position was based on the UCSC Genome Browser, Feb. 2009, gh19 (NCBI Build GRCH37-reference sequence).

The result showed 14q32.31-q32.33 deletion (Figure 1)

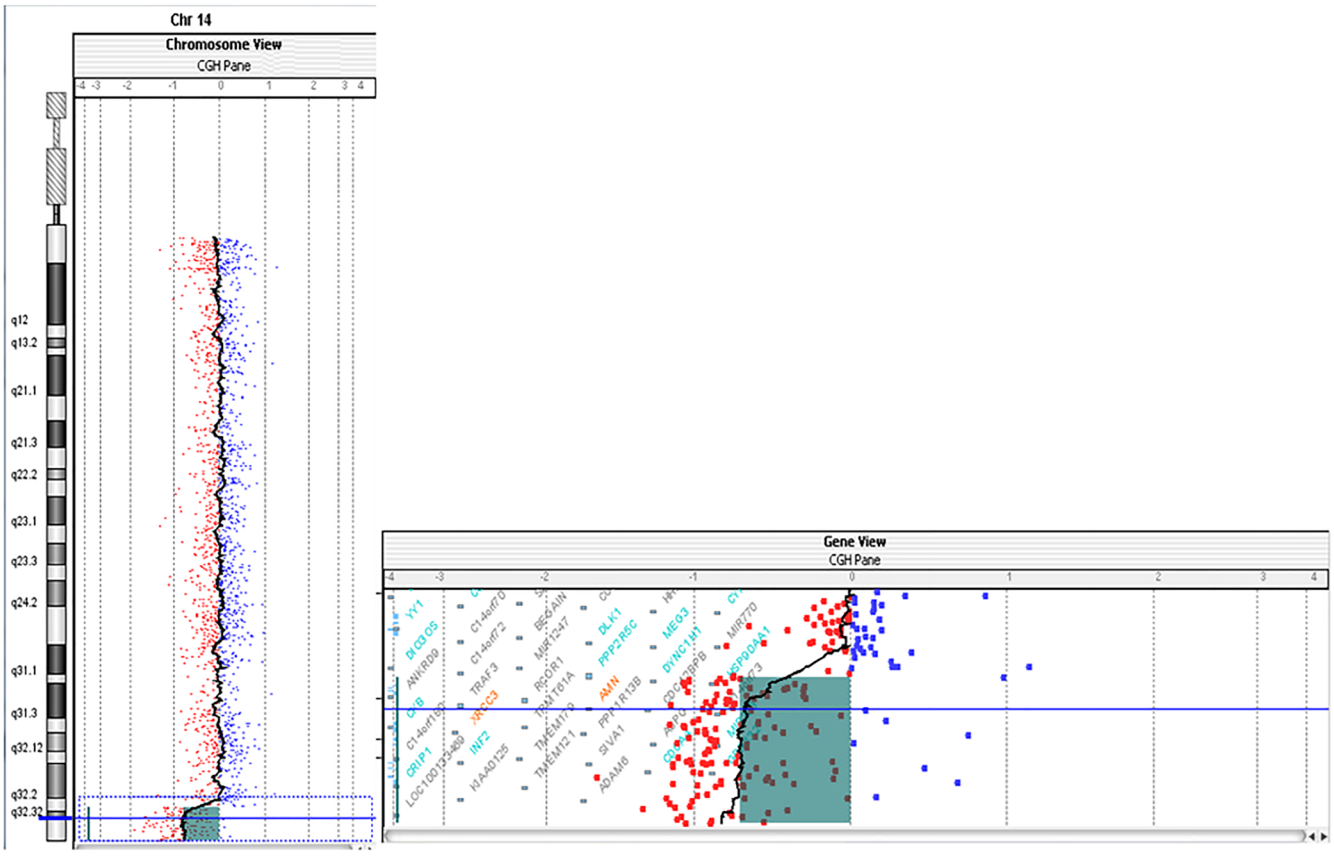


Figure 1. Chromosome 14 aCGH profile of the patient (in red) and a reference DNA sample from a normal female (in blue). The figure shows (A) a copy number loss corresponding to the segment 14q32.31-q32.33 in a genomic segment with the median log2 ratio shifted to -0.7 (black line). The probe log2 ratios were plotted according to genomic coordinates (based on the UCSC Genome Browser, December 2013, NCBI Build 38 reference sequence). In (B), detail of the 14q32.31-q32.33 region showing the deleted region of ~4.67 Mb.

DISCUSSION

The focus of this paper is to report an additional case of 14q terminal deletion and discuss array-CGH importance for diagnosis, which, has been searched since this patient's second year of life. 14q deletions are relatively rare and it is a result of rearrangements (balanced translocations) or de novo deletions, which lead to a broad and inconsistent spectrum of clinical features, according to local breakpoint and deletion size. It can be an interstitial deletion with variable breakpoints and variable sizes or apparently terminal deletion of variable size[4]. Sometimes, chromosome 14 deletion may present as a ring[4]. Hypotonia is an important sign in the first months of life as presented by this patient. The most recognizable features during childhood are intellectual disability and dysmorphisms. Major congenital malformations are uncommon[5]; however, ophthalmologic and heart defects, brain, gastrointestinal, and male genitourinary malformations had been reported[6]. Some features are more specific in cases due to 14q deletion with ring chromosomes, like seizures and retinitis pigmentosa[4]. Patients with 14 chromosome terminal deletions usually share a significant number of clinical features, varying according to the affected region[5]. Some of these features like elongated face became evident as the patient grows older[7]. Typical clinical features include ID, microcephaly, postnatal growth retardation, muscular hypotonia, and dysmorphisms like high forehead, blepharophimosis, epicanthic fold and short bulbous nose[8]. Most of these features are present in this proband. Respiratory infections were rarely reported[4].

Such techniques as array-CGH allow localization and size definition as well as involved genes, which could be helpful for genotype-phenotype correlations[9]. Excluding pseudogenes, chromosome 14 presents a mean gene density of 10 genes per Mb, and 21 of these genes are associated with genetic diseases[10]. In the present case, array-CGH was fundamental considering that the patient presented minor anomalies and ID without a definitive diagnosis, which, in this kind of situation, currently is supported by data as more profitable compared to the traditional investigation, as karyotype[2]. This diagnosis allowed appropriate genetic counseling, clarifying there was no recurrence risk for the family, and patient follow-up, avoiding further unnecessary laboratory investigations. It is important to emphasize the pediatrician should seek an ethnologic diagnosis, asking for genetic consultation, if available, and using molecular cytogenetic tools.

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Conflict of interest

The authors declare that there no conflicts of interest to disclose.

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Ethical committee's approval

The present study is part of the project "*Deficiência mental em uma coorte de nascimentos: prevalência, etiologia e determinantes* (Mental deficiency in a birth cohort: prevalence, etiology and determinants)" and was approved by the ethical committee from the local institution according to the Resolution 196/96 from the National Health Council.

Informed consent from the guardian

The patient's guardian signed a consent form allowing the child medical photographs made; understanding that the information could be used for publication in medical journals and by consenting to these medical photographs understood that will not receive payment from any part. And, in case of refusal to consent would not in no way affected the medical care that will receive. And, if would have any question or wish to withdraw the consent in the future would contact the responsible researcher.

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