DIAGNOSTIC OF CHROMOSOME 7Q11.23 DUPLICATION SYNDROME - A CASE REPORT*

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Resumo: a Síndrome da Duplicação do Cromossomo 7q11.23, também conhecida como Síndrome da duplicação de WBS, é uma desordem rara causada pela duplicação de um segmento de 1.5 Mb e caracterizada por deficiência intelectual, dificuldade na fala e anomalias craniofaciais moderadas. Ao realizar a técnica de CMA em amostras de uma família que tem uma criança com deficiência intelectual, foi observado uma microduplicação de novo de 1.428,9 Kbp no cromossomo 7q11.3.


The Chromosome 7q11.23 Duplication Syndrome (MIM 609757) is a genomic disorder caused by the duplication of a common 1.5 Mb segment spanning 26 genes (Mervis *et al*., 2011). The microduplication of 7q11.23 was first reported in 2005 (Somerville *et al*., 2005), and 36 cases have been reported to date (Kirchoff *et al*., 2007; van der AA *et al*., 2009; Berg *et al*., 2007; Depienne *et al*., 2007; Kriek *et al*., 2006; Torriero *et al*., 2007; Torriero *et al*., 2008; Orellana *et al*., 2008; Thomas *et al*., 2006; Merritt *et al*., 2008). This region is also associated with the Williams-Beuren Syndrome (WBS) (MIM 194050) which is caused by deletion of a 1.5 Mb DNA segment at 7q11.23. Theoretically, duplications of the WBS region should occur at the same frequency as deletions based on an interchromosomal nonallelic homologous recombination mechanism, leading to 1:13,500 affected new born in a given population (Inoue *et al*., 2002).
The duplication at 7q11.23 is associated with neurocognitive and behavioral impairment, specifically, intellectual disability. Many patients have cognitive deficit ranging from mild mental retardation to autism, although some may have normal cognitive abilities. This particular developmental disorder shows variable clinical manifestations most common being speech delay and mild craniofacial anomalies (VAN der AA et al., 2009). Herein, we report a rare case of 7q11.23 microduplication detected by Cytoscan™ HD array GeneChip (Affymetrix, USA) in Central Brazil.

MATERIALS AND METHODS

Clinical Case

A 16 years old male patient born to non-consanguineous parents, at 36 weeks gestation, his birth weight was 3450 g and crown-heel length 49 cm. Child delivery was carried out through a caesarean section procedure. His mother had pre eclampsia. The patient showed moderate intellectual disability, mild facial dysmorphisms with broad forehead, high- broad nose, short philtrum, straight eyebrows, delay in speech development and expressive language problem. The family history was unremarkable on both sides.

Molecular and Cytogenetics Studies

With Pontifícia Universidade Católica de Goiás ethics approval (CAAE 0051.0.168.000-11) and informed consent, convencional cytogenetics studies were carried out using peripheral blood, following standardized procedures (VERMA; BABU, 1995). Chromosomal analysis was done using the software IKAROS® Metasystems Germany. After the karyotyping, the array analysis were performed on patient and his parents, in order to determine the origin of potential DNA imbalances, either de novo or inherited. Blood samples were obtained and genomic DNA was isolated using QIAamp® DNA Mini kit (QIAGEN, Germany). Total DNA (250ng) was amplified, labeled and hybridized using GeneChip CytoScan™ HD array protocols (AFFYMETRIX, USA) according to the manufacturer’s instructions. The array was designed specifically for cytogenetic research, including ≈ 2,696,550 CNV markers, 743,304 SNP markers, and > 1,953,246 non-polymorphic markers. CEL files obtained by scanning the arrays were analyzed using the Chromosome Analysis Suite (ChAS) software (AFFYMETRIX, USA). Gains and losses that affected a minimum of 50 and 25 markers, respectively, in a 100 kb length were initially considered.

RESULTS

Karyotyping at > 550 band resolution showed a male karyotype (46,XY). Chromosomal Microarray Analayses (CMA) detected one genomic imbalance in the patient’s genome, corresponding to a de novo 1,428.9 kbp microduplication at 7q11.23 (72,718,277-74,147,166) (Figure 1), spanning over described 28 genes (NSUN5, TRIM50, FKBP6,
FZD9, BAZ1B, BCL7B, TBL2, MLXIPL, VPS37D, DNAJC30, WBSCR22, STX1A, MIR4284, ABHD11-AS1, ABHD11, CLDN3, CLDN4, WBSCR27, WBSCR28, ELN, LIMK1, EIF4H, MIR590, LAT2, RFC2, CLIP2, GTF2IRD1, GTF2I).

Figure 1: Chromosomal Microarray Analysis content of the 7q11.23 microduplication. Legend: (A) CMA showing a duplication segment at 7q11.23 from patient with intellectual disability and (B) Pink and blue light line plots indicated the CMA from mother and father, respectively, confirming a de novo origin for the genomic imbalance in their offspring (blue dark plots). Note: Image courtesy from Laboratory Núcleo de Pesquisas Replicon, Departamento de Biologia, Pontifícia Universidade Católica de Goiás.

DISCUSSION

Here we reported the first case of duplication of the Williams–Beuren critical region, resulting in chromosome 7q11.23 Duplication Syndrome in Central Brazil. The
case reported exhibited a clinical phenotype compatible with 7q11.23 microduplication group previously described, being milder, less distinct, and more variable than in WBS. Moreover, recent studies (CARTER et al., 2013; SANDERS et al., 2011) demonstrated the significant association of Autism Spectrum Disorders (ASDs) with de novo duplications of 7q11.23.

We identified de novo microduplication that seems to be more frequently observed than inherited ones (SOMERVILLE et al., 2005; TONIERO et al., 2007; DEPIEN-NE et al., 2007). Other authors (BERG et al., 2007), reported two of seven probands to have inherited duplications from their mothers. This observation demonstrates the importance of genomic evaluation from parents of a proband. In addition, researchers (ORELLANA et al., 2008), described duplication cases inherited from a healthy parent, which does not exclude the pathological condition of duplication. Incomplete penetrance or multifactorial influences might cause the observed of variability phenotypes and a mosaic condition may also contribute to mask phenotypes.

The size of the reported duplication (1,428.9 kbp) it is in agreement with earlier reports, ranging from 1.4-1.5 Mb (SOMERVILLE et al., 2005; VAN der AA et al., 2009; BERG et al., 2007; DIXIT et al., 2013). Some genes included in that genomic region have been shown to be implicated in Williams Beuren Syndrome. However, deletion or duplication in that region produce different degrees of impairment with variable phenotypes.

Microduplication at 7q11.23 was initially evaluated by a real-time PCR. The initial approach revealed duplications of markers within the WBS region (SOMERVILLE et al., 2005). However, with the advance of CMA newer cases are likely to be identified when proceeding with diagnostic investigation of children with developmental and neurobehavioral delays. Michelson et al., 2011 using CMA analysis found diagnostic abnormalities in 8% of subjects with learning disabilities and 11% in those with learning disability and dysmorphic features.

Recent findings suggest that the prevalence of dup(7)(q11.23) could be higher than previously expected. Our results demonstrated the involvement of 28 genes in the 7q11.23 region, showing a great variability in the genes that probably reflect phenotypic variability. The CMA analysis demonstrated genomic imbalances only identify using this technology, emphasize the strength of CMA in detecting imbalances genomics associated with intellectual disability phenotypes that other methods couldn’t identify. The authors believe that CMA is a powerful and efficient method to delineate phenotypic variation and to guide medical diagnosis.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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DIAGNÓSTICO DA SÍNDROME DA DUPLICAÇÃO DO CROMOSSOMO 7q11.23 - RELATO DE CASO

Abstract: *Chromosome 7q11.23 Duplication Syndrome, also known as WBS Duplication Syndrome, is a rare genomic disorder caused by the duplication of a common 1.5 Mb segment characterized by intellectual disability, speech delay and mild craniofacial anomalies. Using CMA on samples from a family who had a child with intellectual disability, we showed a de novo 1,428.9 kbp microduplication at 7q11.23.*

Keywords: CNV. Intellectual Disability. Microarray. Williams-Beuren Duplication Syndrome.

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