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**Artigo Original**

# 3q27.3.3q29 duplication and 2q37.2q37.3 deletion in a child with developmental delay and hypotonia in Manaus, Brazil

Duplicação 3q27.3q29 e deleção 2q37.2q37.3 em uma criança com atraso no desenvolvimento e hipotonia em Manaus, Brasil

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## ABSTRACT

**Introduction:** Cytogenomic analyses play a fundamental role in the detection of genetic disorders. **Objective**: Report the case in a female child with developmental delay and hypotonia and relate the existence of copy-number variations to understand their contribution to the appearance of the phenotype. **Material and Methods**: Female patient aged 10 months of age at first appointment, the only child of non-consanguineous couples and with no history of genetic diseases in the family. Her mother reported uneventful pregnancy with obstructed cesarean delivery and neonatal jaundice. Physical examination, patient presented developmental delay, hypotonia, loose skin, hyperextensible joints, micrognathia, ankyloglossia, umbilical hernia, camptodactyly and involuntary convulsive seizures. Cytogenetic (G-banding karyotype) and cytogenomic ( SNP array) analyzes were performed. **Results**: G-banding karyotype was normal (46, XX). SNP array revealed a duplication in 3q27.3.3q29 and a deletion in 2q37.2.2q37.3, both considered pathogenic. **Conclusion**: Therefore, of the patient presented duplication in 3q27.3.3q29 and deletion in 2q37.2.2q37.3, both considered pathogenic, rare alterations. The altered regions contain genes that are sensitive to dosage and/or gene haploinsufficiency, contributed to the phenotype of the patient. SNP array proved to be paramount in the diagnostic elucidation of patient, and made it possible to therapeutic management and genetic counseling.

**Keywords** SNP Array; Duplication; Deletion; Pathogenic Variants.

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## RESUMO

**Introdução:** Análises citogenômicas desempenham papel fundamental na detecção de desequilíbrios genéticos. **Objetivo**: Relatar o caso de uma criança do sexo feminino com atraso de desenvolvimento e hypotonia e relacionar a existência de variações no número de cópias para entender a sua contribuição com o aparecimento do fenótipo. **Descrição**: Paciente de sexo feminino com 10 meses na primeira consulta, filha única de casais não consanguíneos e sem histórico de doenças genéticas na família. Sua mãe relatou gravidez sem intercorrências com parto cesariano distorcido e icterícia neonatal. Ao exame físico, a paciente apresentou atraso de desenvolvimento, hipotonia, pele frouxa, articulações hiperextensíveis, micrognatia, anquiloglossia, hérnia umbilical, camptodactilia e crises convulsivas involuntárias. Análises citogenéticas (cariótipo por bandeamento G) e citogenômicas (SNP array) foram realizadas. **Resultados**: O cariótipo por bandeamento G foi normal (46, XX). SNP array revelou duplicação em 3q27.3.3q29 e deleção em 2q37.2.2q37.3, ambas consideradas patogênicas. **Conclusão**: Portanto, o paciente apresentou duplicação em 3q27.3.3q29 e deleção em 2q37.2.2q37.3, ambas alterações consideradas patogênicas e raras. As regiões alteradas contêm genes sensíveis à dosagem e / ou haploinsuficiência gênica, contribuindo para o fenótipo do paciente. O SNP array mostrou-se primordial na elucidação diagnóstica do paciente, possibilitando o manejo terapêutico e o aconselhamento genético.


**Palavras-chave:** SNP Array; Duplicação; Deleção; Variantes Patogênicas.

## INTRODUCTION

Cytogenomic imbalance, for the most part, are associated with certain phenotypes such as congenital anomalies, autism, intellectual disability, developmental delay and hypotonia[1]. These cytogenomic imbalance can be identified by several strategies, including single nucleotide polymorphisms (SNPs) array. SNP array is a cytogenomic analysis with high resolution, accuracy and sensitivity that detects changes or variations of the genome[1-3]. These variations are based on genetic polymorphisms, which can be SNP and copy-number variations (CNVs).

CNVs are regions of the genome that may be deleted, with loss of genetic material and/or duplicated with a gain in genetic material in relation to the reference genome[4]. They can be large (> 1 megabases) or small (<500 base pairs) CNVs, and originate from mutation, homology-and non-homology-directed meiotic recombination, repair of double-stranded DNA breaks and/or replication errors[3-5]. CNVs can be classified as having benign, pathogenic and uncertain clinical significance[6,7]. They are important contributors to genetic variability and disease susceptibility. In this context, the present study reported the case of a female child with developmental delay and hypotonia, in order to verify whether there is a relationship between the variations in the number of copies of the genome present in this patient and their contribution to the appearance of the phenotype.

## DESCRIPTION

Female patient with first geneticist's evaluation at 10 months of age for investigation of developmental delay and hypotonia. She is the daughter of non-consanguineous parents and has no family history of genetic disease. Mother reported uneventful pregnancy with obstructed cesarean delivery and neonatal jaundice. On physical examination, the patient presented loose skin, hyperextensible joints, micrognathia, ankyloglossia, umbilical hernia, camptodactyly and involuntary convulsive seizures. Two tests were requested for the patient: karyotyping with G-band and SNP array. The result of karyotyping with G-banding was normal (46, XX). Result of SNP array Illumina HumanCytoSNP850K beadchip showed a duplication of 10.2 megabases in size in the terminal region of the long arm of chromosome 3 arr[GRCh37]3q27.3q29(187615000-197838262)x3 (Figure 1A and B; Figure 2) and a deletion of 7.2 megabases in the terminal region of the long arm of chromosome 2

arr[GRCh37]2q37.2q37.3(235805656-243048760)x1 (Figure 1C and D; Figure 3), changes found were classified as pathogenic variants.

**Figure 1.** SNP array result of present case. Copy number profile showing 3q27.3q29 duplication (A) and 2q37.2q37.3 deletion (C). SNP genotyping pattern showing 3q27.3q29 duplication (B) and 2q37.2q37.3 deletion (D). Bar means identification of duplication and deletion.

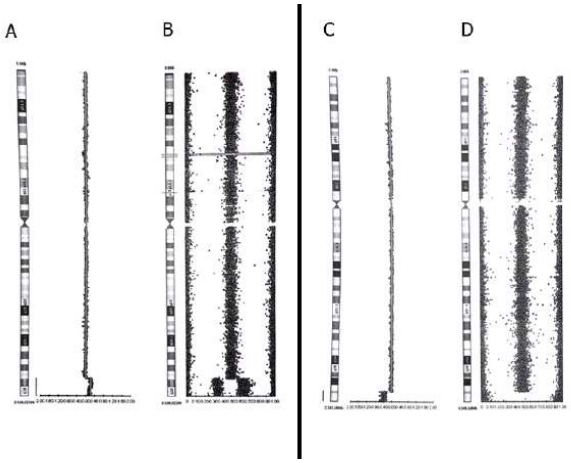



**Figure 2.** Database information presenting the ideogram of the chromosome, the position of the CNV in the chromosome, the size of the region comprising the CNV and summary of the genes involved in 3q27.3q29 duplication.

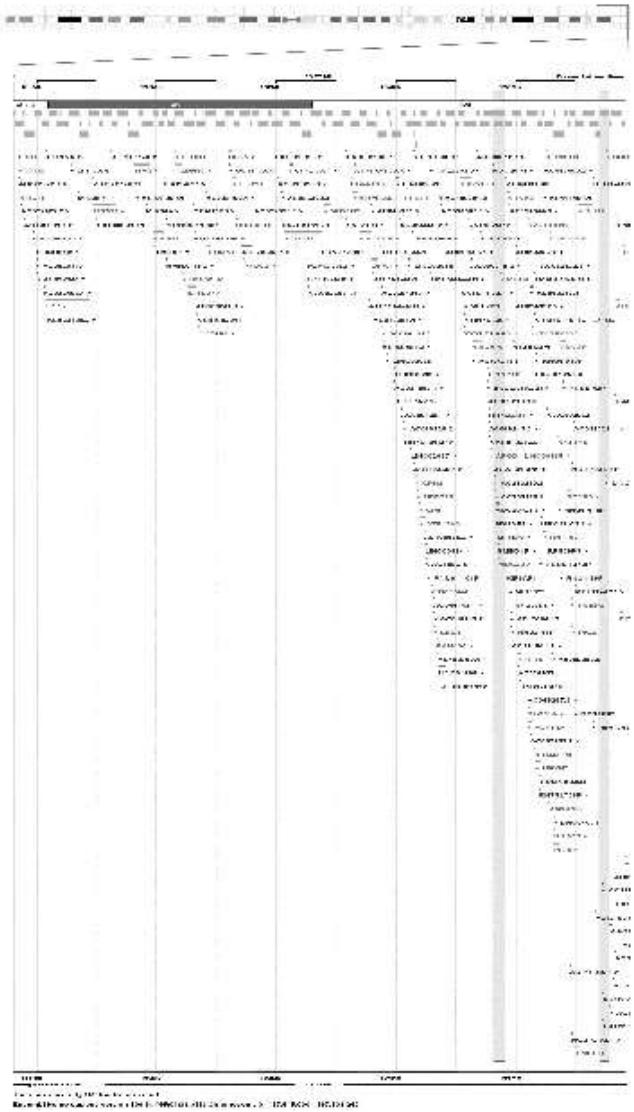
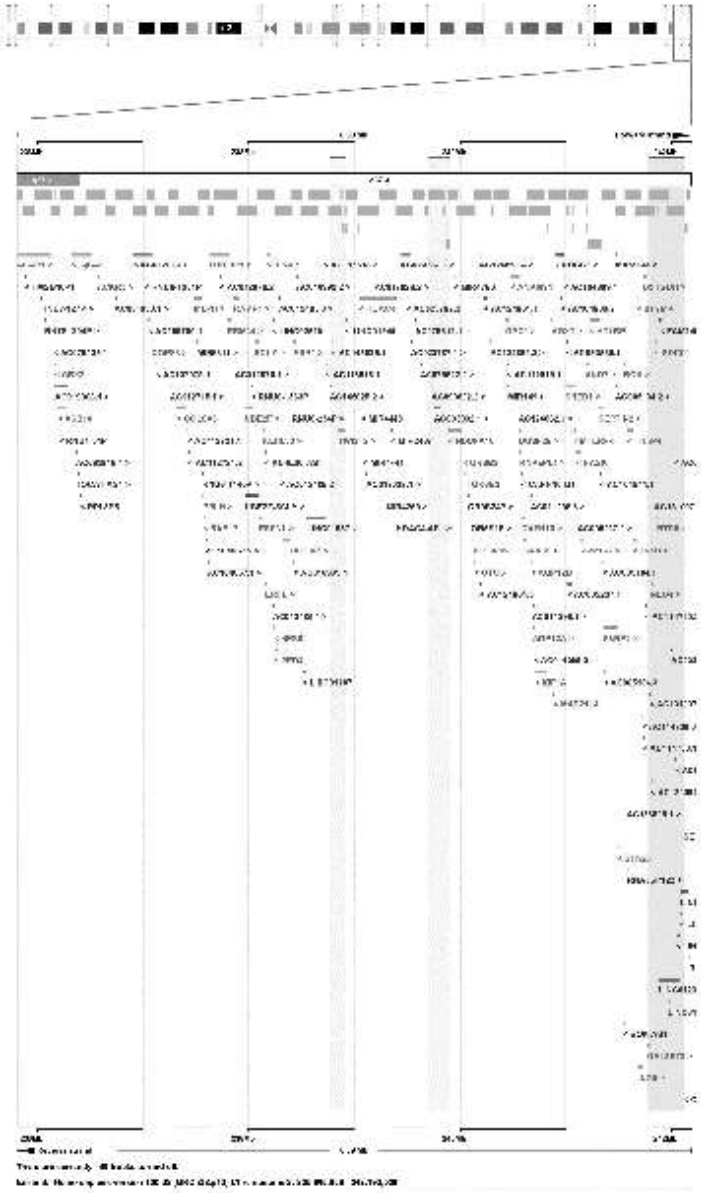


**Figure 3.** Database information presenting the ideogram of the chromosome, the position of the CNV in the chromosome, the size of the region comprising the CNV and summary of the genes involved in 2q37.2q37.3 deletion.



The classification of CNVs was determined based on the type of alteration, chromosomal region, size of alteration, gene content and clinical relevance of CNVs in public databases (ClinGen – Clinical Genome Resource, https://www.clinicalgenome.org; ClinVar - https://www.ncbi.nlm.nih.gov/clinvar/; DECIPHER - Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources, https://decipher.sanger.ac.uk/; DGV - Database of Genomic Variants, http://projects.tcag.ca/variation; OMIM - Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim; UCSC Genome Bioinformatics, http://genome.ucsc.edu/.). Currently, the patient is being followed up with a multi-professional approach, in order to provide a better quality of life. The study was approved by the Research Ethics Committee of the Amazonas State University, under the authorization number 4.288.698 (CAAE: 95704617.0.0000.5016).

## DISCUSSION

Cytogenomic analyses using SNP array are routinely performed in the investigation of cytogenomic imbalance in patients with multiple congenital malformations, autism, intellectual disability, developmental

delay and hypotonia without etiological diagnosis[1]. In the present study, the SNP array test identified two copy-number variations in the patient, duplication and deletion in distinct proportions.

It is increasingly perceived that duplications are more common events in the human genome than deletions. However, deletions are more likely to result in a more severe phenotype than duplications, which usually result in a less severe phenotype[9]. It has been suggested that these changes when associated with coding or regulatory regions, may cause gene haploinsufficiency, gene dosage, gene interruption, position effects, recessive allele unmasking or potential transvection effects, and which seem to influence gene expression and phenotypic variability[4,10,11]. Other regions of the genome, such as repetitive regions, may also favor the emergence of deletions and duplications[12].

Regarding the size of CNVs, we can note that the patient presented CNVs greater than 7 megabases, being considered large CNVs. Large CNVs involve a segment that encompasses several genes or regulatory regions, and this increases the likelihood of altering a gene, leading to phenotypic consequences[13]. This is probably due to the chromosomal region that the alteration covers and the genes present in that region, and not necessarily to the size of the alteration. This is because small CNVs can also generate phenotypic alterations due to the pathogenicity of the altered gene[14].

The CNVs found in the patient were classified as pathogenic, considered those in which cytogenomic imbalanced explain the observed clinical phenotype. In the case presented, duplication in the 3q27.3q29 region covers 183 genes, but these have not been fully characterized for such duplication. However, candidates genes for 3q27.3q29 duplication are the genes *CLDN16* (Claudin 16 and *CLDN1* (Claudin 1). Similar duplications appear in the literature, but with different sizes than in the present case. In the literature, it was reported the case of a girl of 4 years and 8 months with a duplication of 15.3 Mb in the 3q27.3q29 region, whose phenotype was developmental delay, hypotonia, dysmorphic features of hypertelorism, downward inclined eyelid fissures, epicanthic folds, broad nasal bridge, bulbous nasal tip and brachydactyly[15]. In another work, it was described a report of a fetus diagnosed with trisomy partial 3q (3q27.3q29, 11.3 megabases) and partial 14q monosomy (14q31.3q32, 19.5 megabases), which is associated with the phenotype of developmental delay, hypotonia, scoliosis, hyperextensible joints, dysmorphic facial, ventricular septal defect, pulmonary stenosis, clenched hands, clubfoot, a swelling of the scalp, and hydronephrosis in the right kidney[16]. It was also observed that duplication in 3q27.3q29 is localized in the critical region of the 3q duplication syndrome, defined in the 3q21q29 region. Clinical features of this syndrome involve developmental delay, intellectual disability, genitourinary abnormalities, microcephaly and facial dysmorphisms[17].

The other change found, deletion in the 2q37.2q37.3 region, overlaps the region of the 2q37.2q37 microdeletion syndrome. The microdeletion syndrome is characterized by developmental delay, hypotonia, brachydactyly of the third to fifth digits or the toes, short stature, obesity, facial dysmorphism, skeletal malformations, autism spectrum disorder and epilepsy[18]. The 2q37.2q37.3 region has 138 genes and the exact function of many of them is still unknown. Considered candidates for 2q37 microdeletion syndrome are the genes *AGXT* (alanine glyoxylate and serine pyruvate aminotransferase), *COL6A3* (collagen type VI alpha-3 chain), *D2HGDH* (D-2-hydroxyglutarate dehydrogenase), *KIF1A* (kinesin family member 1A), *MLPH* (melanophilin), *NDUFA10* (NADH ubiquinone oxidoreductase subunit 10), *PASK* (PAS domain-containing serine/threonine kinase), *PER2* (period circadian regulator 2) and *TWIST2* (twist family bHLH transcription factor 2)[18,19]. Notwithstanding, the *HDAC4* gene (histone deacetylase 4) is responsible for regulating cardiac, muscular, neurological and bone development that, when in haploinsufficiency, can generate phenotypes of developmental delay, intellectual disabilities and behavioral abnormalities[20].

Considering the size of the changes and, consequently, the amount of genes affected, they determine the pathogenic correlation for the clinical changes presented by the patient, besides being rare alterations. These changes may contain genes sensitive to expression dosage and/or gene haploinsufficiency, whose such genomic imbalances contributed to the phenotype of the patient in this study, enabling the diagnosis for the patient.

## CONCLUSION

Therefore, of the patient presented duplication in 3q27.3.3q29 and a deletion in 2q37.2.2q37.3, both considered pathogenic, being that the duplication in 3q27.3.3q29 it's a rare alteration. Both the duplicated and deleted regions may contain genes that are sensitive to expression dosage and/or gene haploinsufficiency, whose such genomic imbalanced contributed to the phenotype of the patient in this study. Even so, the SNP array proved to be paramount in the diagnostic elucidation of the patients in question, providing better therapeutic management and aiding in genetic counseling for the family.

### Contributions

NDMC: Substantial contributions to the design, data analysis; writing and final approval of the publication version.

ICAD: Substantial contributions to the design, data analysis; writing and final approval of the publication version.

VMGP: Substantial contributions to the design, data analysis; writing and final approval of the publication version.

CF: Substantial contributions to the design, data analysis; writing and final approval of the publication version.

### Conflict of Interest

Authors declare no conflict of interest.

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