2q32 microdeletion syndrome in a patient from the western Amazon

Wilyan Dias Cosmo de Oliveira, Christian Rogers Gomes da Silva, Christopher Harrison Salomão Andrade, Edilson Moreira Borges, Gabriele Batista de Sá, Joshua Werner Bicalho da Rocha

ABSTRACT

Introduction: Interstitial deletions involving the 2q31q32 region are recognized as a clinical disorder involving several manifestations, such as intellectual disability, growth retardation, behavioral disorders, and facial dysmorphologies. The reduced number of reports of patients affected by this syndrome contributes to the difficulty of making genotype-phenotype correlations. **Case report:** Patient with inversion of the long arm of chromosome 2 [46, XX,inv(2)(q21q33)]. On physical examination, he had a prominent forehead, epicanthus, low nasal bridge, long nasolabial philtrum and thin upper lip. Neurological examination showed hypotonia. **Discussion:** A correct chromosomal interpretation can identify the microdeletion syndrome and rule out or confirm possible differential diagnoses, highlighting the need and importance of recognizing and documenting cases.

Keywords: Genetics, Chromosome deletion, Human chromosomes pair 2.

INTRODUCTION

During cell division, breaks may occur in structural chromosomal abnormalities, resulting in deletions, insertions, or translocations. Deletions represent genetic material loss, insertions represent genetic material addition, and translocations correspond to the addition or replacement of genetic material from one chromosome to another chromosome[1].

According to Ferreira et al.[2], interstitial deletions involving the 2q31q32 region are pathogenic and result in a clinical disorder, with the most common symptoms being an intellectual disability, growth retardation, distinct facial dysmorphisms, and behavioral disorders.

Van Buggenhout *et al.*[3] first described the deletion syndrome in this region based on the report of four patients with 2q32q33 deletions. Following the identification of two additional patients, the clinical phenotype was designated as 2q31.2q32.34 Deletion Syndrome[4].

Approximately 40 patients have been described in the literature; however, according to Cormack *et al.*[5], a significant number of these cases are not highly resolving, making genotype-phenotype correlations difficult to establish.

Advances in molecular cytogenomics enabled higher resolution in the characterization of minor rearrangements and a more precise genotype-phenotype characterization[6].

The Microarray-based Comparative Genomic Hybridization (CGH) technique is a relatively new and high-resolution analytical technique that permits detailed analysis of the entire genome, detecting microscopic and submicroscopic chromosomal changes that cause disease. It is possible to detect losses (deletions) and/or gains (duplications) of genetic material in all chromosomes simultaneously, with significantly increased sensitivity and specificity compared to conventional cytogenetic tests[7].

In this study, we describe a patient with chromosomal inversion of chromosome 2's long arm and deletion syndrome of the same chromosome's long arm. A term of free and informed consent was presented to the parents of the patient, and after they signed it, a copy was retained by the parents and a copy was attached to the patient's medical record. Due to the fact that it is a single-arm case report study, it was not submitted to the Research Ethics Committee (EC).

Universidade Federal de Rondônia (UNIR). Departamento de Medicina, Porto Velho (RO), Brasil.

https://doi.org/10.11606/issn.2176-7262.rmrp.2023.190243

CASE STUDY

A 1-year-and-three-month-old female with a clinical history of facial dysmorphisms evident at birth. During our initial evaluation, the parents complained of a delay in neuropsychomotor development, stating that the patient required cephalic support at 3 months, sat unassisted at 7 months, uttered his first words at 1 year, and has not been able to stand without assistance to this day.

The 33-year-old mother's gynecological and obstetrical antecedents were G3P1A2 (8 and 12-week spontaneous abortions). Due to a previous diagnosis of hypothyroidism, she received prenatal care beginning in the first trimester and used levothyroxine 50mcg throughout her pregnancy. The patient in question was born by cesarean section at term (38 weeks), with a birth weight of 3,170 grams, a length of 51 centimeters, a head circumference of 35 centimeters, and an Apgar score of 8/9.

In the patient's pathological and family history, the patient's mother was previously diagnosed with hypothyroidism. In addition, there are no similar cases or genetic diseases in the mother's family. The parent was 39 years old and had no comorbid conditions. However, he had a first cousin with autism spectrum disorder (ASD) but no other cases or family history of genetic diseases.

The patient weighed 8.950 grams (p15), measured 77 centimeters in height (p50), and had a head circumference of 46 centimeters (p50). She was in good general health, with moist and ruddy mucous membranes, and was cooperative. She had a prominent forehead, discrete bilateral epicanthus, a low nasal bridge, a long nasolabial philtrum, and a thin upper lip, as determined by a dysmorphological physical examination (Figure 1). On a neurological exam, she was found to have hypotonia.

During this first evaluation, the mother brings with her some complementary exams that were requested at birth. Among these exams, the echocardiogram showed a patent ductus arteriosus without hemodynamic repercussions and a normal transfontanellar ultrasonography.

A normal echocardiogram, ultrasound of the kidneys and urinary tract, computed tomography of the skull, nuclear magnetic resonance imaging of the skull, electroencephalogram, and abdominal ultrasound were requested during subsequent evaluations.

In light of the results of the normal complementary tests and the dysmorphological findings, the possibility of Down syndrome was raised and a karyotype with G-banding was requested (Figure 2). The result indicated that the long arm of chromosome 2 was inverted [46, XX,inv(2)(q21q33)].

Due to the observed change in the patient's karyotype, examinations of the parents' karyotypes were requested and revealed normal results. In light of the patient's condition, the investigation was supplemented with a chromosomal microarray (SNP-array) analysis that revealed a pathogenic microdeletion of the long arm of chromosome 2 arr[GRCh37] 2q32.1q32.3 (185870918 196963028) x1 (Figure 3).

The SNP-array 750k result interpretation reveals the 2q32.1q32.3 deletion with a minimum size of 11,092Kb (1858870918_196963028, GRCh37). In this region, 52 genes, pseudogenes, and miRNAs are present. CALCRL (114190), COL3A1 (120180), COL5A2 (120190), F5TP2 (615796), GLS (138280), HIBCH (610690), MSTN (601788), STATI (500555), and STAT4 (601788) are OMIM-

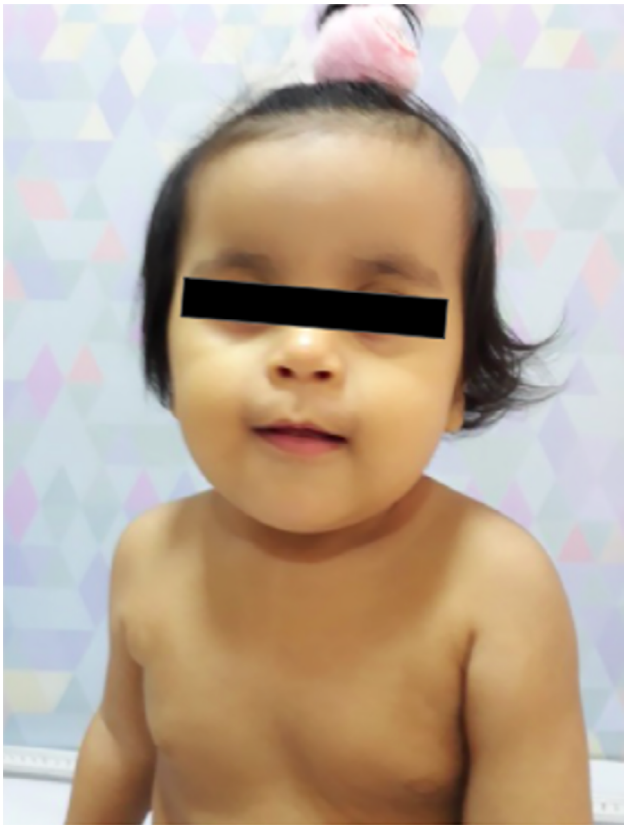

Figure 1. Phenotype of the patient.

recognized genes associated with conditions with known molecular bases (500558).

In the ClinGen, CLInVar, and Decipher databases, there are records of pathogenic deletions smaller than the one detected in the patient under study. In contrast, neither the DGV population control database nor the CNV control group contains records of deletions of comparable size. Consequently, the 2q32.1q2.3 deletion meets the criteria for pathogenicity.

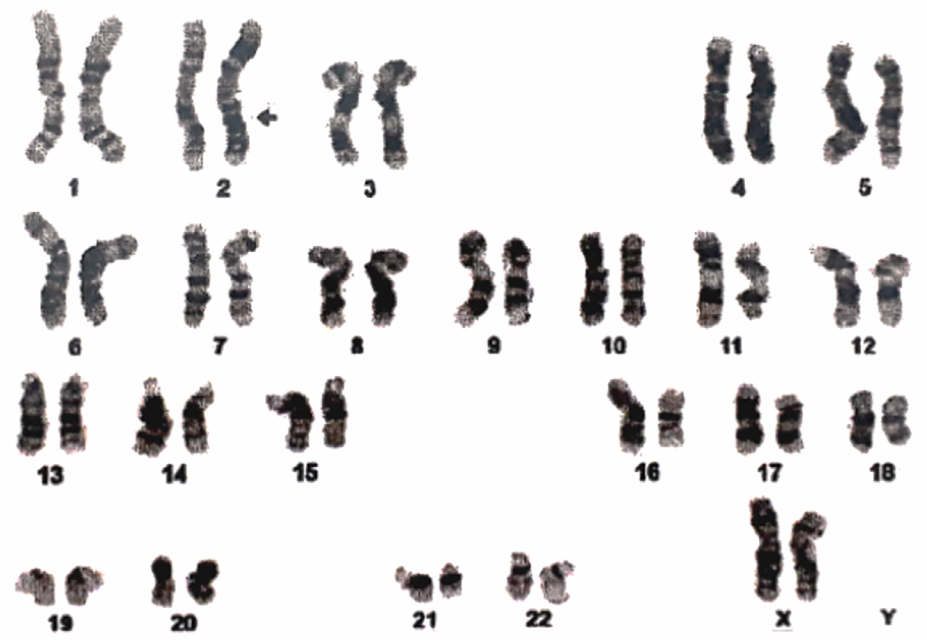

Figure 2. Karyotype including a G band

arr [GRCh37] 2q32.1q32.3 (185870918_196963028) x 1	
Presence of the deletion on chromosome 2, band q32,1q32.3, region 185870918_196963028.	
Several regions with loss of heterozygosity were identified, as shown in the table below	
Description of regions with loss of heterozygosity (LOH)	
Genetic position	**Size (Kb)**
arr [GRCh37] 2q32. 3q33.1 (194818763_197828651) x2 hmz	3.009
arr [GRCh37] 3q24 (143489746_146574234) x2 hmz	3.084
arr [GRCh37] 3q26.1 (163350125_ 166598939) x2 hmz	3.248
arr [GRCh37] 4q32.1 (157929783_161422597) x2 hmz	3.492
arr [GRCh37] 6q16.1q16.2 (95122845_99687240) x2 hmz	4.564
arr [GRCh37] 11p11.2p11.12 (47236567_51550787) x2hmz	4.314
arr [GRCh37] 11q13.1q13.3 (65845636_68860872) x2 hmz	3.015
arr [GRCh37] 11. q22.3q23.2 (109680151_113317745) x2 hmz	3.637
arr [GRCh37] 12q24.11q24.21 (111154787_114916300) x2 hmz	3.761
arr [GRCh37] 15q15.1q21.1 (42760158_47590896) x2 hmz	4.830
arr [GRCh37] 19q13.2q13.31 (40357662_44311132) x2 hmz	3.953
arr [GRCh37] Xp11.22p11.1 (53821794_58227320) x2 hmz	4.405
arr [GRCh37] xq11.1q12 (62036670_67384857) x2 hmz	5.348
arr [GRCh37] xq13.1q13.3 (70273716_75287494) x2 hmz	5.013

Figure 3. Chromosomal analysis SNP-array 750k

DISCUSSION

A chromosomal microarray investigation confirmed the patient's diagnosis as chromosome 2 microdeletion syndrome {arr[GRCh37] 2q32.1q32.3 (185870918 196963028)x1}. Cases of patients with microdeletions involving the 2q32.1q32.3 region have been reported in the medical literature, and here we will examine the predominant clinical manifestations of these patients. Regarding the skull and face, asymmetric and flat bones, a high forehead, bitemporal constriction, midface hypoplasia, limited maxillary opening, hemifacial microsomia, a small mouth, and a rectangular and prominent forehead were more prevalent. Concerning the eyes, hypertelorism, dacryocystitis, palpebral fissures sloping downward, bilateral cataracts, and esotropia were observed. There is a description of minor outer ear abnormalities in relation to the ears. In addition, oligodontia, tooth crowding, bifid uvula, cleft palate, micrognathia, sparse hair, and interventricular septal defects were identified[2,3,6–10].

When compared to the patient's findings, the dysmorphological exam revealed a prominent forehead, distinct bilateral epicanthus (more on the left), a low nasal bridge, a long nasolabial philtrum, and a thin upper lip, but no other apparent dysmorphias. Neurological examination reveals appendicular hypotonia and unsupported sitting[2]. Several of the findings already described in the literature for patients with the same syndrome are absent in this patient population, which can be explained by the vast array of clinical findings that patients with microdeletions in this region may exhibit.

Regarding the behavior of these patients as described in the literature, the following may be mentioned: aggressive and unpredictable mood, uncontrolled eating habits, anxiety, self-mutilation, obsessive-compulsive disorder, hyperactivity, autistic behavior, or even a report of the absence of behavioral disorders. There are reports ranging from absence of speech to normal and active speech[6-8].

The nonspecificity and phenotypic variability of chromosome 2 microdeletion syndrome demonstrate the significance and difficulty of obtaining the diagnosis [2,10]. Even if these tests are expensive and inaccessible, and only a small number of centers have the infrastructure to perform them, it is essential to perform identification and careful analysis of the clinical picture supported by a test of high sensitivity. In any case, the significance of the diagnosis lies in its ability to facilitate appropriate clinical management of these patients and accurate genetic counseling.

In this regard, the inclusion of reports such as this one in the scholarly literature contributes significantly to the dissemination of information. In order to enable the long-term comparison of existing cases, it is of the utmost importance that not only the pertinent characteristics of frequent signs and symptoms but also treatment plans are precisely described. In addition, the significance of accurate chromosomal interpretation is emphasized can identify the 2q32.1q32.3 microdeletion syndrome and exclude or confirm potential alternative diagnoses.

REFERENCES

1. Kuczynski E. Sporadic chromosomal abnormalities associated with the autistic syndrome. Infanto - Journal of Child and Adolescent Neuropsychiatry [Internet]. 1996 [quoted July 06, 2021];4(2):26-36. Available in: http://www.psiquiatriainfantil.com.br/revista/edicoes/Ed_04_2/in_10_07.pdf
2. Ferreira SI, Matoso E, Venâncio M, Saraiva J, Melo JB, Carreira IM. Critical region in 2q31.2q32.3 deletion syndrome: Report of two phenotypically distinct patients, one with an additional deletion in Alagille syndrome region. Mol Cytogenet [Internet]. 2012 [quoted July 06, 2021];5:25. Available in: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3460744/#B1
3. Van Buggenhout G, Van Ravenswaaij-Arts C, Mc Maas N, Thoelen R, Vogels A, Smeets D, et al. The del(2)(q32.2q33) deletion syndrome defined by clinical and molecular characterization of four patients. Eur J Med Genet [Internet]. 2005 [quoted July 07, 2021];48: 276– 289. Available in: https://www-sciencedirect.ez8.periodicos.capes.gov.br/science/article/pii/S1769721205000832
4. Prontera P, Bernardini L, Stangoni G, Capalbo A, Rogaia D, Ardisia C, et al. 2q31.2q32.3 deletion syndrome: Report of an adult patient. Am J Med Genet A [Internet]. 2009 [quoted June 07, 2021];149A:706-712. Available in: https://www-sciencedirect.ez8.periodicos.capes.gov.br/science/article/pii/S1769721205000832?via%3Dihub
5. Cormack AM, Taylor J, Gregersen N, George AM, Love DR. Delineation of 2q32q35 Deletion Phenotypes: Two Apparent "Proximal" and "Distal" Syndromes. Case Reports in Genetics [Internet]. 2013 [quoted July 07, 2021]. Available in: https://www.hindawi.com/journals/crig/2013/823451
6. Cocchella A, Malacarne M, Forzano F, Marciano C, Pierluigi M, Perroni L, et al. The Refinement of the Critical Region for the 2q31.2q32.3 Deletion Syndrome Indicates Candidate Genes for Mental Retardation and Speech Impairment. Am J Med Genet B Neuropsychiatr Genet [Internet]. 2010 [quoted June 07, 2021];153B:1342-1346. Available in: https://doi.org/10.1002/ajmg.b.31107

7. Array Comparative Genomic Hybridization - aCGH - Tempo Digital Magazine from the Federal University of Bahia [Internet]. 2021 [quoted June 12, 2021];4(2):26-36. Available in: https://genetica.hupes.ufba.br/hibridizacao-genomica-comparativa-em-array-acgh

8. Rifai L, Port-Lis M, Tabet A, Bailleul-Forestier I, Benzacken B, Drunat S, et al. Ectodermal dysplasia-like syndrome with mental retardation due to contiguous gene deletion: further clinical and molecular delineation of del(2q32) syndrome. Am J Med Genet A [Internet]. 2010 [quoted July 14, 2021];152(1):111–117. Available in: https://www.ncbi.nlm.nih.gov/pubmed/20034071

9. Mencarelli MA, Caselli R, Pescucci C, Hayek G, Zappella M, Renieri A, Mari F. Clinical and molecular characterization of a patient with a 2q31.2-32.3 deletion identified by array-CGH. Am J Med Genet A [Internet]. 2007 [quoted July 14, 2021];143A(8):858-65. Available in: https://pubmed.ncbi.nlm.nih.gov/17352388

10. Balasubramanian M, Smith K, Basel-Vanagaite L, Feingold MF, Brock P, Gowans GC, et al. Case series: 2q33.1 microdeletion syndrome-further delineation of the phenotype. J Med Genet [Internet]. 2011 [quoted July 14, 2021];48(5):290–298. Available in: https://www.ncbi.nlm.nih.gov/pubmed/21343628

Corresponding Author:
Wilyan Dias Cosmo de Oliveira
academico.wilyan.unir@gmail.com

Editor:
Ada Clarice Gastaldi

Received in: aug 31, 2021
Approved in: aug 10, 2022