

Contribuição dos autores: DBAR designed the study, participated of data collection, analyzed and interpreted the data and drafted the initial manuscript. PLD and AER participated of data collection. VCCFS, CBV, ABC-S and BFM participated of the cytogenetic analysis. ACF-C conceptualized and designed the study, supervised data collection, participated in the investigation, critically reviewed and wrote the manuscript as submitted. All authors read and approved the manuscript.

Contato para correspondência:
Dante Bruno Avansso R Rosan

E-mail:
danterosan@gmail.com

Conflito de interesses: Não

Financiamento: Recursos próprios

Recebido: 24/01/2020
Aprovado: 17/06/2021



Síndrome de Down resultante de uma translocação não Robertsoniana rara t(11;21)(p13;q22)

Down syndrome resulting from a rare non Robertsonian translocation t(11;21)(p13;q22)

Dante Bruno Avansso Rosan¹, Priscila L. Dourado¹, Andréa Engracia Ruiz¹, Valéria C.C. Ferrarezi da Silva², Cristina Benitez Vendrame², Andréa B. Carvalho-Salles², Brasilina de F. Mafei², Agnes Cristina Fett-Conte²

RESUMO

Introdução: A síndrome de Down (SD) é um distúrbio genético comum, ocorrendo em aproximadamente 1 em 700 nascimentos. Resulta de uma cópia extra de todo ou de parte do braço longo do cromossomo 21, causada por diferentes alterações citogenéticas: trissomia livre, translocações robertsonianas, mosaicism, duplicação da região crítica e outros rearranjos estruturais. Translocações cromossômicas não-Robertsonianas são eventos muito raros, com poucos casos relatados. **Objetivo:** Descrever uma paciente com SD resultante da translocação não-Robertsoniana t(11; 21)(p13; q22). **Relato De Caso:** Uma menina encaminhada com diagnóstico clínico de trissomia do 21 apresentou dois cromossomos 21 e a translocação não-Robertsoniana t(11; 21)(p13; q22). A criança desenvolveu distúrbio mieloproliferativo transitório aos 17 meses. A análise citogenética foi realizada em metafases obtidas de linfócitos e de células da medula óssea, de acordo com procedimento padrão - bandamento G e hibridização in situ fluorescente. O estudo do cariótipo dos pais revelou que sua mãe, fenotipicamente normal, é portadora da mesma translocação recíproca. **Conclusão:** Este é o segundo relato da translocação t(11; 21)(p13; q22), o primeiro resultando na SD. Essa descrição amplia o conhecimento sobre a variabilidade citogenética na etiologia da síndrome de Down. Estudos futuros são necessários para investigar os efeitos clínicos a longo prazo da trissomia do cromossomo 21 associada com a t(11; 21)(p13; q22).

Palavras-Chave: Trissomia; Cromossomos Humanos Par 11; Translocação Genética; Aconselhamento genético.

ABSTRACT

Introduction: Down syndrome (DS) is a common genetic disorder, occurring in approximately 1 in 700 births. It results from an extra copy (triplication) of the whole or part of the long arm of chromosome 21 caused by different cytogenetic alterations: free trisomy, Robertsonian translocations, mosaicism, duplication of the critical region and other structural rearrangements. Non-Robertsonian chromosome translocations are very rare events with few cases reported. **Case report:** We identified the non-Robertsonian translocation t(11;21)(p13;q22) and two chromosomes 21 in a female child referred with a clinical diagnosis of trisomy 21. The infant developed the transient myeloproliferative disorder at 17 months. Cytogenetic analysis was performed in lymphocytes and bone marrow metaphases according to standard procedure - G banding and fluorescence in situ hybridization. The karyotype study of the parents revealed that her phenotypically normal mother carries the same reciprocal translocation. **Conclusion:** This is the second report of the translocation t(11;21)(p13;q22), the first one resulting in DS. This description expands knowledge about cytogenetic variability in the etiology of DS. Future studies are needed to investigate the long-term clinical effects of the trisomy 21 associated with t(11;21)(p13;q22).

Keywords: Trisomy; Chromosomes, Human, Pair 11; Translocation, Genetic; Genetic counseling.

INTRODUCTION

Down syndrome (DS) is caused by the presence of an extra copy of all or segments of the long arm of human chromosome 21 (trisomy 21). It is highly prevalent worldwide, appearing in about 1 in 700 newborns. It is the most common genetic cause of intellectual disability attributable to an imbalance in gene dosage. There is remarkably wide variability in the phenotypic and it can result in high medical, healthcare, and socioeconomic costs^{1,2}. Most cases result from aneuploidy (free trisomy, 90-95% of cases; mosaicism, 3-5%) and

Robertsonian translocations (4%). Duplications of the critical region and non-Robertsonian translocations are very rare events related to etiology^{3,4}. Although translocations between 11 and 21 are frequently reported in leukemic cells^{5,6}, constitutional translocations involving these chromosomes are very rare events. As far as we know, there is only one description of constitutional translocation involving chromosomes 11 and 21 with breakpoints at 11p13 and 21q22⁷. In this study, we report the second case of this non-Robertsonian translocation, the first one resulting in DS.

CASE REPORT

A four-month-old female infant was referred to the Genetic Service of Hospital de Base of Medicine School (São José do Rio Preto, São Paulo, Brazil) because a suggestive phenotype of DS. She was born by a full-term vaginal delivery following a normal pregnancy, with 45cm and 2,415g. She is the only child of young and healthy non-consanguineous parents, with no reported familial history of DS or miscarriages. The physical examination revealed the presence of multiple birth defects in a typical phenotype of the trisomy 21 (Figure 1).

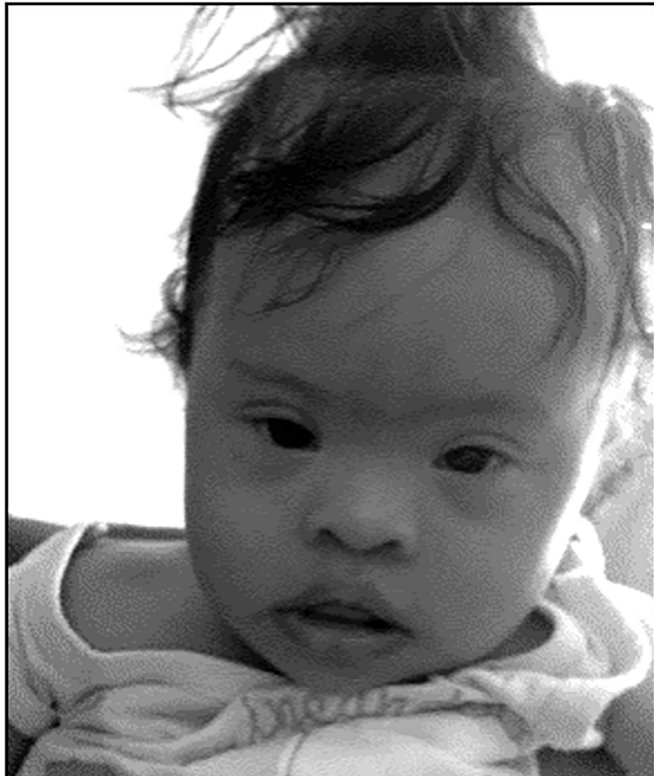


Figure 1. Patient with a characteristic facial phenotype of Down syndrome.

An echocardiogram identified congenital heart disease: atrial septal defect, persistent ductus arteriosus, and mitral insufficiency. Ultrasonography of the brain, abdomen, and kidneys was normal. Routine hematological exams and auditory evaluation were normal.

G-banding technique (20 cells) was performed in metaphases from stimulated peripheral blood culture according to standard procedures and demonstrated 47,XX,t(11;21)(p13;q22),+21 in all analyzed cells (Figure 2).

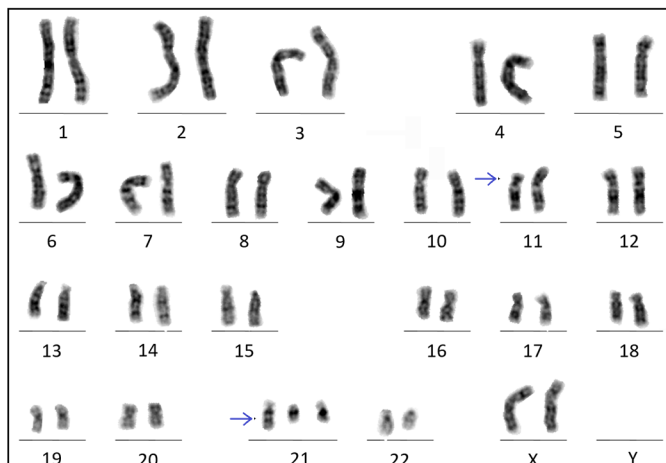


Figure 2. GTG banding karyotype obtained from peripheral blood showing the 47,XX,t(11;21)(p13;q22)mat,+21. As arrows indicate the chromosomal segments involved in the translocation.

The 21-year-old phenotypically normal mother was found to be the carrier of the balanced reciprocal translocation and presented the karyotype 46,XX,t(11;21)(p13;q22) (Figure 3).

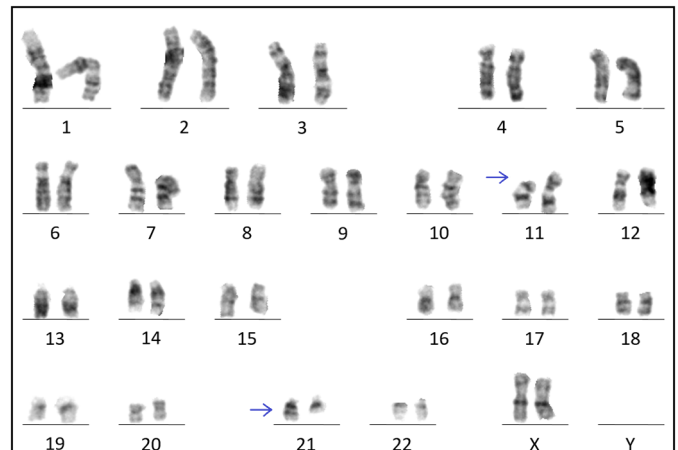


Figure 3. GTG banding karyotype obtained from peripheral blood of the patient's mother showing the 46,XX,t(11;21)(p13;q22). The arrows indicate the translocated chromosomal segments.

The karyotype of her father was normal. The fluorescence *in situ* hybridization (FISH) also was performed according to a standard protocol using the LSI ETO (8q22) SpectrumOrange/ LSI AML1 (21q22) SpectrumGreen probe (Abbott Molecular), which identified the presence of three signals of 21 chromosome segment (Figure 4).

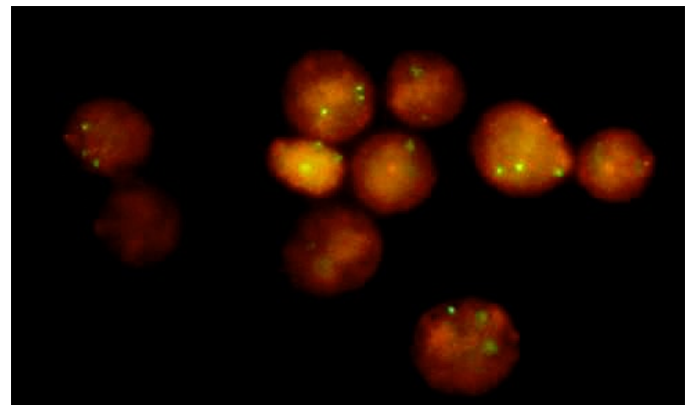


Figure 4. Fluorescence in situ hybridization experiment showing peripheral blood cells with three green signals corresponding to the chromosomes 21q22

At 17 months following birth, the infant was referred to the same Hospital presenting high fever and petechiae all over the body. Laboratory examination showed hemoglobin of 10g/dL, a platelet count of 28.000 mm³, hematocrit of 29% and a leukocyte count of 4,700 (54% of neutrophils, 30% of lymphocytes, 3% of eosinophils and 10% of monocytes), with 6.5% of blasts. A bone marrow aspirate showed 7,66% of lymphocytes, 0,66% of plasmocytes, 22,3% of blasts, 0,66% of promyelocytes, 4% of mielocytes, 7,33% of metamielocytes, 23,6% of rod, 28% of segmented, 1,66% of eosinophils, 0% of basófilos and 4% de monocytes. Flow cytometry showed myeloid origin of the blasts. The blasts were positive for cell surface antigens CD 34, CD45, CD117, CD33, CD36 CD42b, HLA-DR, partial CD13, CD71, CD38 CD7 and CD4 with evidence of megakaryocytic markers, which was consistent with the diagnosis of transient myeloproliferative disorder (TMD). Bone marrow cells aspirate withdrawn from the patient was used for G-banding cytogenetic analysis (30 cells) after a 24-h unstimulated culture and disclosed only the same alterations observed in her peripheral blood. After continual monitoring, the disease entered in spontaneous remission in 13 months.

DISCUSSION AND CONCLUSION

Although our patient presents DS resulting from a trisomy 21 involving a rare rearrangement, her congenital defects are compatible with those already reported in this condition ⁴. Although we did not carry out a patient's genome study, we can estimate that it presents the trisomy of most of chromosome 21, including those of the critical region responsible for the syndrome. In the consulted databases (PubMed and Scielo) there were no reports of DS cases resulting from translocation involving chromosomes 11 and 21, which prevents the comparison of her clinical signs.

Non-Robertsonian translocations involving chromosomes 11 and 21 have already been described in cancer cells and in patients with birth defects ⁸. Ramadevi et al. ⁷ described the first report involving a balanced translocation between chromosomes 11p and 21q in a female child with regression of milestones. Her father was carrier of the same translocation and he was phenotypically normal. The fact that DS always affects the neurodevelopment, in different levels of gravity, does not prevent from assigning an effect of the balanced translocation in the patient's clinic, but an additional effect of the same cannot be ruled out.

Balanced translocations can result in disruption of functional genes located in break points regions or in gene inactivation, resulting in disease associated with balanced chromosome rearrangements of carrier individuals ^{9,10}. Identification of the target genes is fundamental to evaluate the expressed characteristics in these cases, but the family of our patient did not authorize further genetic investigations.

Translocation, including those involving 21q22, can increase the risk of malignancy ¹¹. Our patient presented TMD, which is a pre-leukemia disorder that may occur in DS or non-DS infants ¹². Thus, it is not possible to relate the patient's myeloid disorder to the translocation, but rather to the resulting trisomy 21 itself.

TMD in our patient entered in spontaneous remission in 13 months. This disorder may enter in spontaneous remission or it can to develop into acute myeloid leukemia (AML) in 16-30% of cases. Following spontaneous remission of TMD, subsequent AML can evolve from a preexisting residual TMD clone through the acquisition of additional mutations involving multiple cohesion components and epigenetic regulators. Continual monitoring of the patients is required ^{13,14}.

As the mother of the patient, carriers of balanced translocation should be oriented toward the increasing risk of birth defects in their children, increased risk of infertility, and recurrent miscarriages. Genetic counseling is very important to assist the families deal in these risk situations.

As research into the molecular genetics of Down's syndrome (Trisomy 21) progresses, more and more diseases have been shown to be significantly linked to the trisomy 21 phenotype. Future studies and the follow-up in the long term are needed to investigate the clinical effects of this rare non-Robertsonian translocation that resulted in DS.

REFERENCES

- Saida S. Predispositions to leukemia in down syndrome and other hereditary disorders. *Curr Treat Options Oncol* [periódico na Internet]. 2017;18(7):1-13. doi: 10.1007/s11864-017-0485-x
- Delabar JM, Allinquant B, Bianchi D, Blumenthal T, Dekker A, Edgin J, et al. Changing paradigms in down syndrome: the First International Conference of the Trisomy 21 research society. *Mol Syndromol* [periódico na Internet]. 2016;7(5):251-61. doi: 10.1159/000449049
- Rupa D, Neeraja K, Deepak C, Swarna M. A rare balanced nonrobertsonian translocation involving acrocentric chromosomes: Chromosome abnormality of t(13;15)(p11.2;q22.1). *J Hum Reprod Sci* [periódico na Internet]. 2016;9(2):128-30. doi: 10.4103/0974-1208.183505
- Flores-Ramírez F, Palacios-Guerrero C, García-Delgado C, Morales-Jiménez AB, Arias-Villegas CM, Cervantes A, et al. Cytogenetic profile in 1,921 cases of trisomy 21 syndrome. *Arch Med Res* [periódico na Internet]. 2015;46(6):484-9. doi: 10.1016/j.arcmed.2015.08.001
- Imagama S, Abe A, Suzuki M, Hayakawa F, Katsumi A, Emi N, Kiyoi H. LRP16 is fused to RUNX1 in monocytic leukemia cell line with t(11;21)(q13;q22). *Eur J Haematol* [periódico na Internet]. 2007;79(1):25-31. doi: 10.1111/j.1600-0609.2007.00858.x
- Trivedi PJ, Brahmabhatt MM, Patel DM, Shukla SN, Patel PS. Acute myeloid leukemia with a masked type of three-way t(8;11;21) revealed by fluorescence in situ hybridizations using AML1-ETO probe. *J Assoc Genet Technol* [periódico na Internet]. 2014;40(1):11-5. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/26029947/>
- Ramadevi AR, Prabhakara K, Dutta U. Familial (11;21)(p13;q22)pat balanced reciprocal translocation in a female child with regression of milestones. *Ann Genet* [periódico na Internet]. 2002;45(1):13-5. doi: 10.1016/s0003-3995(02)01099-7
- Peng Y, Ma R, Zhou Y, Xia Y, Wen J, Zhang Y, et al. De Novo ring chromosome 11 and non-reciprocal translocation of 11p15.3-pter to 21qter in a patient with congenital heart disease. *Mol Cytogenet* [periódico na Internet]. 2015;8:88. doi: 10.1186/s13039-015-0191-y
- Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip J. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. A clinical, cytogenetical, and gene marker study. *Hum Hered* [periódico na Internet]. 1973;23(6):568-85. doi: 10.1159/000152624
- Bugge M, Bruun-Petersen G, Brøndum-Nielsen K, Friedrich U, Hansen J, Jensen G, et al. Disease associated balanced chromosome rearrangements: a resource for large scale genotype-phenotype delineation in man. *J Med Genet* [periódico na Internet]. 2000;37(11):858-65. doi: 10.1136/jmg.37.11.858
- Yamamoto K, Yakushijin K, Funakoshi Y, Sanada Y, Kawamoto S, Matsuoka H, et al. A new complex translocation t(8;11;21)(q22;q24;q22) in acute myeloid leukemia with RUNX1/RUNX1T1. *J Clin Exp Hematop* . [periódico na Internet]. 2014;54(2):167-70. doi: 10.3960/jslr.54.167
- Mast KJ, Taub JW, Alonzo TA, Gamis AS, Mosse CA, Mathew P, et al. Pathologic features of Down Syndrome myelodysplastic syndrome and acute myeloid leukemia: a report from the children's oncology group protocol AAML0431. *Arch Pathol Lab Med* [periódico na Internet]. 2020;144(4):466-72. doi: 10.5858/arpa.2018-0526-OA
- Salvatori G, Foligno S, Sirlito P, Genovese S, Russo S, Coletti V, et al. Sometimes it is better to wait: first Italian case of a newborn with transient abnormal myelopoiesis and a favorable prognosis. *Oncol Lett* [periódico na Internet]. 2017;13(1):191-5. doi: 10.3892/ol.2016.5401
- Watanabe K. Recent advances in the understanding of transient abnormal myelopoiesis in Down syndrome. *Pediatr Int* [periódico na Internet]. 2019;61(3):222-9. doi: 10.1111/ped.13776.