

CASE REPORT

A paternal t(6;22)(q25.3;p12) leading to a deleted and satellited der(6) in a short-lived infant

María Guadalupe Domínguez¹ | Horacio Rivera^{1,2} | Rosa María Dávalos-Pulido¹ | Ingrid Patricia Dávalos-Rodríguez^{1,2}

¹División de Genética, CIBO, Instituto Mexicano del Seguro Social, Guadalajara, México

²Doctorado en Genética Humana, CUCS, Universidad de Guadalajara, Guadalajara, México

Correspondence

Ingrid Patricia Dávalos-Rodríguez, Sierra Mojada 800, Independencia Oriente, Guadalajara, Jalisco, México, 44340.
Email: ingriddavalos@hotmail.com

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Abstract

Background: Non-acrocentric satellited chromosomes mostly result from familial balanced insertions or translocations with p12 or p13 of any acrocentric. Although all non-acrocentrics have been involved, only 12 instances of chromosome 6 involvement are known.

Case presentation: A female infant exhibited clinical features typical of 6qter deletions and also generalized hypertrichosis and synophrys, traits seldom reported in patients with similar imbalances or haploinsufficiency of *ARID1B* located in 6q25.3. She had a paternal derivative satellited 6q of a t(6;22)(q25.3;p12)pat entailing a 6q terminal deletion, karyotype 46,XX,der(6)t(6;22)(q25.3;p12)pat [16].ish del 6q subtel-.

Conclusion: Male and female carriers of reciprocal translocations or insertions between chromosome 6 and the short arm of any acrocentric have few unbalanced offspring mostly by adjacent-1 segregation. In addition, spontaneous abortions or male infertility was present in 7/13 instances of satellited chromosome 6.

KEYWORDS

6q deletion, chromosome 6, non-acrocentric satellited chromosomes, nucleolus organizer regions in 6q, satellited 6q

1 | BACKGROUND

Non-acrocentric satellited chromosomes result from the translocation between a non-acrocentric chromosome and the short arm of any acrocentric.¹ Regardless of the breakpoint location in the non-acrocentric chromosome, carriers usually exhibit a normal phenotype.²

Most non-acrocentric chromosome arms, particularly 4p/4q and Yp/Yq, have sometimes acquired stalks and/or satellites usually located on pter or qter and mostly derived from chromosome 15; yet, it must be remarked that the sole presence of satellites in some derivatives may go unnoticed.²⁻⁴ Regarding chromosome 6, eleven familial and one sporadic instance are on record,

including an exceptional case featuring interstitial NORs at 6p22 (Table 1).¹⁻¹²

About 37 patients with a 6q pure 6q25/6q26→qter deletion encompassing up 11 Mb and usually diagnosed postnatally are known.¹³⁻²¹ These patients have mainly exhibited developmental delay, intellectual disability, dysmorphic features, microcephaly, hydrocephalus, abnormal corpus callosum, retinal abnormalities, high or cleft palate, complex partial seizures, and hypotonia.^{13,15,16,18} We present a patient with a satellited 6q who exhibited typical features of 6qter deletions but also generalized hypertrichosis and synophrys, traits seldom reported in patients with haploinsufficiency of *ARID1B* located in 6q25.3.^{20,21}

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TABLE 1 Balanced and unbalanced rearrangements of chromosome 6 with the short arm of any acrocentric (n=13)

Proband's karyotype	Carrier's sub fertility	References
46,XY,t(6;14)(q13;p10)	1M ^c	Li et al ⁶
46,XX,der(15)t(6;15)(p21;p12)pat	None	Chiyo et al ⁷
46,XY,ins(6)(q15stk)pat ^a	None	Prieto et al ¹
46,XY,der(15)t(6;15)(q23;p12)pat ^a	1M ^d	Pivnick et al ⁸
46,XX,t(6;21)(q12;p11)mat	1F ^d	Osztovcics et al ⁹
46,XY,der(21)t(6;21)(q22;p12)mat ^a	1F ^d	Taysi et al ¹⁰
46,XY,t(6;21)(p21.1;p13)mat	4M ^c /2F ^d	Paoloni-Giacobino et al ³
46,XY,t(6;21)(p21.1;p13)mat ^a	3M ^c	Dahoun et al (cited by Sarri et al ²)
46,XY,der(22)t(6;22)(q21;p13)mat	None	Stamberg et al ¹¹
46,XY,der(22)t(6;22)(q26;p12)mat ^a	None	Turleau and de Grouchy ¹²
46,XY,t(6;22)(q16.2;p13)mat	None	Hooper et al ⁴
46,XX,ins(6)(p22stk)pat ^{a,b}	1F ^d	Chen et al ⁵
46,XX,der(6)t(6;22)(q25.3;p12)pat ^a	None	Present case

^aSatellites visible on der(6).^bSee text for details.^cSterile/subfertile males.^dPregnancy loss.

2 | MATERIALS AND METHODS

2.1 | Case presentation

The 3-month-old proband was the 2nd child born to non-consanguineous parents aged 22 (she) and 23 years. Her older brother had generalized hypertrichosis, redundant skin in posterior neck and imperforate anus, and died at 5 days after birth from pneumonia. During the 2nd trimester, a cystic hygroma and intrauterine growth restriction were diagnosed by ultrasound. The patient was obtained by cesarean section at the 36th week because of oligohydramnios. At birth, she had a weight of 2120 g (below 3rd centile) and a length of 41 cm (below 3rd centile). At 2 months, she presented pneumonia and was hospitalized. One month later, her weight (3400 g), length (44 cm), and head circumference (31.5 cm) were still below the 3rd centile; because of poor sucking, she required a nasogastric tube for feeding. Physical examination (Figure S1) showed generalized hypertrichosis, microcephaly, redundant skin in posterior neck, thick eyebrows, synophrys, hypertelorism, broad and depressed nasal bridge, downturned angle of the mouth, micrognathia, clinodactyly of fifth fingers, and digitized thumbs. Cardiological evaluation reported a structurally normal heart. She died at 5 months from complicated pneumonia.

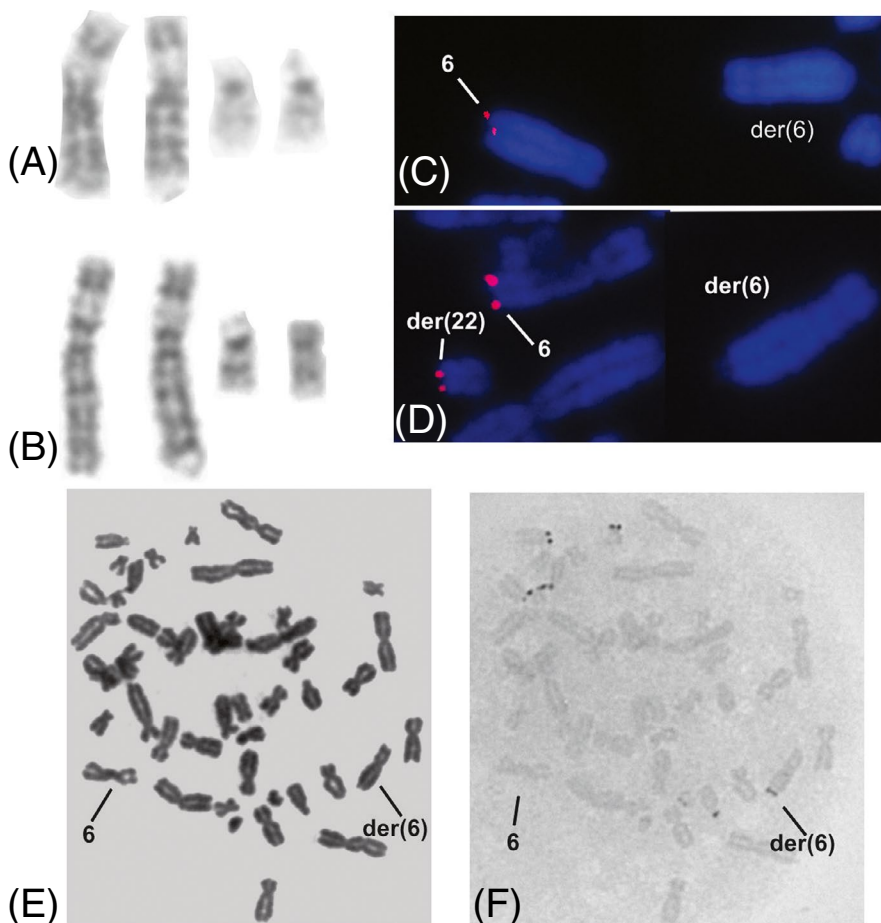


FIGURE 1 GTG-banding, Ag-staining, and FISH results in the family. A and C, Chromosomes 6 and 22 from the patient; note that the der(6) had terminal satellites at 6q25.3 and lacked the 6q subtelomeric signal. B and D, Chromosome pairs 6 and 22 from the father with the t(6;22)(q25.3;p12); note the loss of the 6q subtelomeric signal in the satellited 6q. E and F, Plain Giemsa and silver nitrate staining of a paternal metaphase. The der(6) exhibited an active nucleolar organizing region and satellites attached at 6q25.3

2.2 | Cytogenetic studies

Metaphases from peripheral blood lymphocytes from the patient and her parents were stained for GTG-banding at a resolution of 500-550 bands (ISCN).^{22,23} In addition, father's chromosomes were stained with plain Giemsa and silver nitrate for nucleolar organizing regions (NORs).²⁴ FISH studies in the patient and her father were performed using the 6q subtelomeric probe; paternal chromosomes were also tested with the alpha satellite 14/22 probe (Cytocell).

3 | RESULTS

The patient had a chromosome 6 with terminal stalks and satellites attached to 6q25.3; that is, there was a 6q25.3→qter deletion (Figure 1A). The father was a carrier of a t(6;22)(q25.3;p12) (Figure 1B) in which the satellited der(6) was Ag-positive (Figure 1E,F); maternal chromosomes were normal. FISH studies revealed loss of the 6q subtelomere in the satellited 6q in both the patient (Figure 1C) and her father (Figure 1D). In addition, all four expected alphoid signals were present in the latter (images not shown). The patient's final karyotype was 46,XX,der(6)t(6;22)(q25.3;p12)pat [16].ish del 6q subtel-.

4 | DISCUSSION

The present patient's clinical manifestations were similar to those reported in other subjects with a 6q terminal deletion even if some features such as seizures and retinal abnormalities were either not present or not looked for.^{15,18,19} A comparable clinical picture was observed in five patients with intellectual disability and *ARID1B* haploinsufficiency secondary to intragenic deletions.^{14,20,21} Our patient's deletion likely included *ARID1B*, *THBS2*, *DLL1*, *C6orf70*, and *PHF10* genes related to brain development and neuronal migration.¹⁵ In contrast with the usual long survival of patients with monosomy 6q25→qter,¹⁵ our patient and her brother had a short survival.

Our observation is the 13th report of a satellited chromosome 6 and the 4th involving chromosome 22 (Table 1).¹⁻¹² Although six of these patients had an imbalance resulting from an adjacent-1 segregation of a familial translocation, only ours had a 6qter loss (the other five had a 6qter or 6pter gain). Two familial 6p21 translocations were ascertained via male infertility. In the former, there were four males with infertility perhaps secondary to the preferential association of the (6;21) quadrivalent with the XY bivalent and asynapsis; significantly, the *ZNF165* gene mapped at 6p21.1 and expressed during spermatogenesis was neither disrupted nor deleted.³ In the latter, Dahoun et al (cited by Sarri et al²) reported a t(6;21)(p21.1;p13) in a mother and all her five children, including three infertile sons. A further sporadic t(6;14)(q13;p10) was diagnosed in an oligozoospermic patient.⁶ Another adverse reproductive outcome of some chromosome 6 translocations is excessive miscarriage.^{3,9} Lastly, a familial balanced translocation (6;22)(q16.2;p13) concurred with a 6q16.1

deletion of 400 kb located 1.2 Mb distal to the breakpoint and responsible for either Tourette syndrome or obsessive-compulsive disorder.⁴

To summarize, male and female carriers of reciprocal translocations or insertions between chromosome 6 and the short arm of any acrocentric have had few unbalanced offspring mostly by adjacent-1 segregation. Indeed, empiric data showed that when a 6q25-6q26 duplication or deletion is fully viable, then there will be an equal number of offspring due to alternate or adjacent-1 segregation.²⁵ In addition, spontaneous abortions or male infertility were present in 7/13 instances of satellited chromosome 6 (Table 1).¹⁻¹² Molecular studies such as MLPA or aCGH are required to precisely determine pure deletions and duplications in patients with a non-acrocentric satellited chromosome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

MGD, HR, RMDP, and IPDR made substantial contributions to the conception and design of the manuscript; acquisition and interpretation of data; revised it critically for important intellectual content, and revised and approved the final version of the manuscript.

ETHICAL APPROVAL

This case report has been approved by our ethical review committee (R-2017-785-088) on 28 august 2017. In addition, parental informed consent was obtained.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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