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Short communication

Clinical and molecular delineation of duplication 9p24.3q21.11 in a patient with psychotic behavior

Lizeth Martínez-Jacobo [a], Rocío Ortíz-López [a,b], Alfredo Rizo-Méndez [c], Viridiana García-Molina [c], Sandra K. Santuario-Facio [b], Fernando Rivas [d], Augusto Rojas-Martínez [a,b,*]

[a] Departamento de Bioquímica y Medicina Molecular, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Mexico
[b] Unidad de Genómica, Centro de Investigación y Desarrollo en Ciencias de la Salud, Universidad Autónoma de Nuevo León, Monterrey, Mexico
[c] Servicio de Psiquiatría, Hospital Civil de Guadalajara, Guadalajara, Mexico
[d] Hospital General de Occidente, Secretaría de Salud Jalisco, Guadalajara, Mexico

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ABSTRACT

This article describes a 19-year-old female with mild facial dysmorphism, asociality, decreased school performance, and psychotic behavior in whom the karyotype showed an extra-chromosomal marker characterized as 9p24.3–9q21.11 duplication by array-CGH. The 69 Mbp duplicated segment in this patient includes the critical 9p duplication syndrome region, the *GLDC* and *C90RF72* genes associated with psychotic behavior and other conduct disorders, and a potential locus for autism.

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1. Introduction

The 9p trisomy represents the 4th most common life-compatible autosomal trisomy and one of the most clinically characterized chromosomal abnormalities after trisomies 21, 13, and 18 (Temtamy et al., 2007; San Román Muñoz et al., 2004). Its severity correlates with the extension of the involved chromosomal segment (Temtamy et al., 2007). Craniofacial abnormalities and intellectual disability (ID) are common, but to date only one case of 9p duplication featuring autism (Abu-Amero et al., 2010) has been described in trisomy 9p. Most of the 9p duplication cases originate as meiotic unbalances in parents with balanced translocations (Haddad et al., 1996). This article describes a young female patient affected by ID, psychotic episodes, and craniofacial dysmorphism.

2. Case presentation

A 19 year-old-female patient from a rural area was attended at the Psychiatric Service of the Hospital Civil de Guadalajara (Mexico) due to an acute psychotic episode started on the day before the visit. The episode consisted of disorganized speech, auditory and visual hallucinations, mystic and persecutory delusions and disorientation. Once the medical causes were discarded, including neuroinfection and encephalitis by magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis, the patient received treatment with olanzapine and valproate showing a significant improvement after the first week of therapy. There were previous psychotic episodes with full interepisode remission. The patient is referred to have poor socialization, but there are no additional symptoms. The patient is a single child from a non-consanguineous and reportedly healthy couple. After a surveilled pregnancy, the patient was delivered by cesarean section due to acute fetal distress, and birth weight and size are not known. In addition to persistent enuresis until 7 years old, the remaining psychomotor development is unnoticeable. She started scholarity at age 4 y.o. and showed poor learning and social disabilities. Menarche happened at 10 y.o. and sexual development was normal. Physical examination showed a well oriented girl with a cooperative attitude during the interview, but psychomotor hyperreactivity and alterations in logical reasonings were noted. Patient was 1.55 cm tall and her weight was 49.5 kg, with a BMI of 20.6. The exam showed micrognathia, arched palate, bulbous nose, downturned corners of mouth, low set ears, short neck and brachymesodactyly. An umbilical hernia was also observed. The rest of

Abbreviations: Array-CGH, array based comparative genomic hybridization; BMI, body mass index; C9orf123 gene, chromosome 9 open reading frame 72; C9orf66 gene, chromosome 9 open reading frame 66; C9orf72 gene, chromosome 9 open reading frame 72; CNVs, copy number variations; DECIPHER, DatabasE of Genomic variants and Phenotype in Humans Using Ensembl Resources; DOCK8 gene, dedicator of cytokinesis 8; FOXD4 gene, forkhead box D4; GLDC gene, glycine dehydrogenase; ID, intellectual disability; KANK1 (ANKRD15) gene, KN motif and ankyrin repeat domains 1; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; PTPRD gene, protein tyrosine phosphatase receptor type D; UCSC Genome Browser, University of California Santa Cruz Genome Browser.

* Corresponding author at: Facultad de Medicina and Centro de Investigación y Desarrollo en Ciencias de la Salud, Universidad Autónoma de Nuevo León, Carlos Canseco S.N., Colonia Mitras Centro, Monterrey C.P. 64460, Mexico.
E-mail addresses: arojasmtz@gmail.com, augusto.rojasm@uanl.mx (A. Rojas-Martínez).

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the clinical examination, electroencephalogram, cardiologic evaluation, and standard cranial radiographs and MRI studies were normal.

3. Material and methods

3.1. Chromosomal analysis

Before the studies, the patient's mother was informed about the genetic studies, including aCGH, and signed the consent. Initial cytogenetic analyses were performed by standard 72 h lymphocyte culture (PB-MAX, Gibco®) and G-banding on 30 metaphases, at a resolution of 450 bands approximately. An additional EDTA-anticoagulated blood sample was used for DNA isolation and aCGH studies. Parental samples for chromosome studies were not available.

3.2. Array CGH

Genomic DNA (250 ng) was obtained from 3 ml of peripheral blood by Qiagen DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany), digested with restriction enzymes Sty I and Nsp I (New England BioLabs, Ipswich, MA), and ligated to Sty I or Nsp I adaptors, respectively. After PCR amplification, random fragmentation, purification and labeling procedures, samples were hybridized to Affymetrix GenomeWide SNP 6.0 arrays (Affymetrix, Santa Clara, CA) for 16–18 h in a hybridization oven. Washing and staining of the arrays were performed using the fluidics station 450 (Affymetrix); array images were acquired using the Affymetrix GeneChip Scanner 3000; Affymetrix, and analyzed by using the Genotyping Console v4.0 software.

4. Results

The patient's 47,XX,+mar karyotype found in all cells was reinterpreted after molecular studies including a supernumerary marker 9pter–q21.11. The aCGH study demonstrated that the marker corresponded to a 69 Mb duplicated segment of chromosome 9 (genomic positions 46, 587-69, 186, 399), involving 31,069 markers and 280 genes (including miRNAs and hypothetic protein-genes) (NCBI36/hg18), indicative of a partial trisomy 9pter–q21.11 (Fig. 1). The final karyotype for this patient is 47,XX,+ mar.arr9p24.3q21.11 (46, 587-69, 186, 399) × 3 (Fig. 1). This duplication involves: a) the critical region for the 9p duplication syndrome, b) the GLDC gene associated with non-ketotic hyperglycinemia (NKH) (Kure et al., 1997), c) the C90RF72 gene associated with psychotic behavior (Galimberti et al., 2013), d) a locus associated with autism (Abu-Amero et al., 2010), and e) several genes associated with ID and to additional disturbances of conduct, like *KANK1*, *DOCK8*, *FOXD4*, *C9orf123*, and *PTPRD*. Similar duplications have been also reported (Lin et al., 1977; Stoll et al., 1992; Temtamy et al., 2007; Bonaglia et al., 2002; Di Bartolo et al., 2012) (Fig.2). No additional genomic disturbances were observed.

5. Discussion

A patient with mild features of 9p duplication syndrome and psychotic episodes had an extra marker 9pter → q21.11 showing partial trisomy of chromosome 9. In spite of the marker chromosome's size, its identification using only G bands was not possible. Similar cases of partial trisomies of chromosome 9 in which marker chromosomes were identified by complementary techniques have been reported by Lin et al. (1977) and Temtamy et al. (2007). The proposita's karyotype showed a likely stable extra 9p marker. The marker's mitotic stability indicates that the broken end is capped with a functional telomere be it a neotelomere or captured from 9q or another chromosome. Although we did not analyze the chromosomes of the patient's parents and therefore cannot exclude a parental translocation (e.g., Teraoka et al., 2001; family 2 in Vázquez-Cárdenas et al., 2007), the family history rather supports a de novo origin as it has been documented for other extra 9p chromosomes (patient 4 in Temtamy et al., 2007; Abu-Amero et al., 2010). The region shares a duplicated segment with the 9p duplication syndrome critical region (9p22.3–9p22.2) (Abu-Amero et al., 2010), which partially explains her dysmorphic features. The clinical picture of the 9p duplication syndrome mainly includes ID, craniofacial malformations as microcephaly, micrognathia, downturned corners of the mouth among others, and distal phalangeal hypoplasia (Sirisena et al., 2013). There is only one report of autism (Abu-Amero et al., 2010) but no cases of psychotic disturbances in patients with 9p duplication.

The search of related cases in DECIPHER (Firth et al., 2009) database displays 186 cases related to the duplicated segment in this patient. In addition to the physical malformations described in them, there are 20 instances of autism, 5 of psychosis, and 10 related to other psychiatric conditions, such as aggressive behavior. Among the genes involved in this duplicated region, *GLDC*, *C9orf66*, *DOCK8*, *FOXD4*, *C9orf72*, and *KANK1* have been associated with altered neurodevelopment.

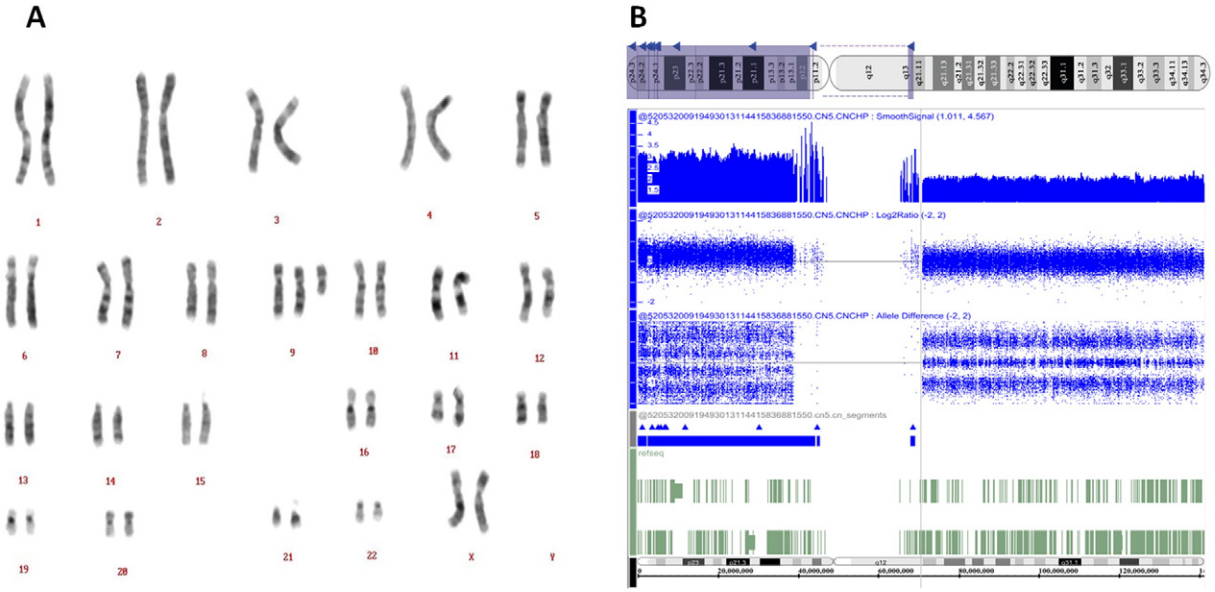

Fig. 1. (A) Patient's karyotype showing a marker chromosome. (B) Microarray image of duplicate region of chromosome 9 from Genotyping Console v.4 Software.

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