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Molecular characterization of the coexistence of 18q haploinsufficiency and 18p duplication, causal of a complex syndromic phenotype

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ABSTRACT

Since genomic SNPs/CNVs arrays were implemented as a diagnostic tool in clinical settings to search for the cause of idiopathic intellectual disability, chromosomal imbalances have been precisely described as being the cause of many new syndromes, especially when they are associated with multiple congenital anomalies and/or dimorphism. High-density SNPs/CNVs microarray was used to delineate genotype-phenotype correlation in a 2.5 year-old girl who carried a mosaic characterized by a predominant cell line representing 92% which carried a duplication of 12.5 Mb of the 18p11.32p11.21 chromosomal region (chr18:12602631_telomeric) and a deletion and a deletion of 20.3 Mb of the 18q21.32q23 chromosomal region (chr18:57691236_telomeric) and a second minor cell line (8%) presented a ring chromosome, carrying the deletion of 20.3 Mb of the 18q21.32q23 chromosomal region. The microarray analysis identified the genetic causes for the specific phenotype of the patient, whose more evident signs and symptoms were mainly associated to the genomic regions duplicated and in haploinsufficiency. Although the conventional karyotype is currently considered a diagnostic technique of support or second line, it was key to establish the etiology of the alteration that the patient carried. Its performance allowed the correct interpretation of the result of the array, whose characterization facilitated its correlation with the phenotypic features of the patient. From both tests, it was possible to conclude the existence of ring chromosome 18, as well as the percentage of the mosaic lines. The deleterious capabilities of the affected OMIM and dominant genes were evaluated along her period of life. A rigorous clinical following up in that patient included valorous phenotypic data to the array data bases, and will make less difficult to hypothesize about prognosis in other individuals who carry overlapping similar high risk genetic alterations.

Keywords: 18q haploinsufficiency, 18p duplication, SNP/CNV array, complex phenotype

INTRODUCTION

Last years, the development of microarray technology has improved the diagnosis and detection rate of chromosomal abnormalities over the conventional karyotype (Dhillon 2014). Clinical efficiency of the single-nucleotide polymorphism/copy number variation (SNP/CNV) array technology has been widely established. In our days, it constitutes the base of an efficient genetic diagnostic algorithm to intellectual disability, as a screening protocol in patients with syndromic phenotype. The obtained results describe the prevalence of the genetic etiologies in patients with syndromic intellectual disability of unknown etiology and detail the variability of cryptic chromosomal imbalances implicated. Characterizations of subcryptic chromosomal anomalies are also being

produced, and the exhaustive phenotypic correlation description of the new syndromes is progressively considered essential. New candidate susceptibility genes are appearing implicated in the development of dimorphic mental incapacity.

The description of the early-onset intellectual disability associated to the development of an extreme phenotype, allowed to detail the genotype-phenotype correlation focused on the clinical signs and symptoms apart from intellectual disability, as organ-specific developmental abnormalities and dimorphic traits description. In this regard, although SNP/CNV arrays have been implemented as a diagnostic tool to look for the cause of idiopathic intellectual disability in children (Shaffer 2007; D'Angelo 2012), the use of these arrays has not yet been rigorously used for the exhaustive characterization of the appearing syndromic phenotype. After improving the phenotypic data about analyzed patients, a variety of chromosomal imbalances have been accepted as the cause of many unaffiliated clinical alterations.

We report here a clinical case of a girl with a rare complex set of signs and symptoms, including deficient growth measures and haploinsufficiency for the OMIM genes *CTDP1*, *TNFRSF11A*, *MC4R*, *PIGN*, *CDH19*, *TMX3*, *RTTN*, *ZNF407*, *TSHZ1*, *MBP* and *SALL3*.

We implemented array analysis as a first method of choice for a fast and accurate detection of chromosomal abnormalities in this patient and for a better phenotype/genotype characterization. However, the use of conventional karyotype was crucial to understand better this correlation and to observe big rearrangements such as the ring chromosome 18 presented in mosaic in the patient.

CLINICAL REPORT

A 6-month-old girl was referred for clinical assessment and treatment. She was the second daughter of unrelated young and healthy parents. Pregnancy was well tolerated and controlled. The normal vaginal delivery was at 36+6 weeks of gestation. Birth weight was 2.240 g (P10); length 44 cm (P10-25) and head circumference 31 cm. Apgar score were 9/9 at one and five minutes respectively. In the neonatal period she presented transient tachypnea and non-immune neonatal jaundice that required phototherapy for less than 24 hours. During hospitalization, she suffered a staph and epidermidis sepsis, which was treated with intravenous antibiotics without complications.

Physical examinations showed moderate axial hypotonia and highlighted many dimorphic features such as hypertelorism, flat nasal bridge, dysplastic ears, and redundant skin fold. At abdominal level a minimal umbilical hernia was noted. The patient had an anorectal malformation consistent in a perineal fistula, with an ectopic anal opening in backplane fourchette. At locomotor level, she had irreducible abducts and severe valgus feet. Cerebral ultrasound detected the cavity of *septum pellucidum* and vergae. The otoacoustic emissions and brainstem auditory evoked potential pathology, showing a conductive hearing loss. The temporary rock TAC showed stenosis of both ear canals. An echocardiogram was performed and an atrial septal defect, *ostium secundum* type and patent *ductus arteriosus* were diagnosed.

The patient wore hearing aids from 5 months of age due to conductive hearing loss. Flat feet valgus was resolved through bandages and physiotherapy. She had a mild bronchiolitis episode at 8 months old and has had several mild-moderate episodes of bronchospasm. She was admitted at hospital twice with 11 and 12 months of age. She had psychomotor delay (she held her head up at the age of 8 months, sat up at 17 months and could get up at 3 years), language delay (she only babbles) and was hypotonic. A brain magnetic resonance imaging (MRI) showed hypoplasia of the corpus callosum, intermediate mass thalamus hypertrophy and poor differentiation between gray and white matter. The electroencephalogram was normal.

The girl showed growth delay, at the age of 2 years her weight was of 9kg (below P1, corresponding to -2.52 SD) and her size presented a fall from 9 months of age, having a height of 80 cm at 2 years (in p1, co-

rresponding to -2.35 SD). Microcephaly was appreciated, remaining the percentiles from birth below p1 (-3.64 SD). The cardiological examination was normal after Inter-Auricular Communication (CIA) and dose-area product (DAP). The dismorphologic examination at 2.5 years showed: microcephaly, asymmetric positional plagiocephaly and less development of left hemiface. She continued using headphones. There were horizontal palpebral fissures, small eyes with bilateral epicanthus, strabismus on the left eye, depressed and broad nasal root, small nasal tip and small mouth with high palate. She had mild micrognathia and low-set ears. There was normal chest with increased internipples distance and normal abdomen. The anus was very small and near to fourchette. Limbs were normal.

The last dismorphologic examination at 4.6 years showed better general and global state. Most dismorphic traits persevered. Changes in the patient's phenotype included normocephaly, improvement of asymmetric positional plagiocephaly, normal eyes with bilateral epicanthus and mild strabismus. In addition, short philtrum was described.

CYTOGENETIC AND MOLECULAR STUDIES

After obtaining informed consent, peripheral blood lymphocyte cultures of the patient and the parents were set up by standard techniques for karyotyping with high resolution GTG banding (Figure 1). Chromosomal alteration was molecularly characterized using the Affymetrix Cytogenetics Whole-Genome 2.7 M Array (Affymetrix Inc., Santa Clara, CA, USA) (Figure 1). Data was collected using Gene Chip Scanner 3000 Dx and CEL files were analyzed using Chromosome Analysis Suite software (ChAS v1.1, Affymetrix Inc, Santa Clara, CA, USA). The annotation file used was hg19. Detected CNVs were compared with the Database of Genomic Variants (DGV; http://projects.tcag.ca/variation) and with the International Standards for Cytogenomic Arrays Consortium (Public ISCA database; https://www.iscaconsortium.org). The Database of Chromosomal Imbalance and Phenotype in Humans (DECIPHER; https://decipher.sanger.ac.uk) was used as main resource for evaluating the clinical significance of the detected alterations.

Bidirectional sequence analysis of genomic DNA including the whole exonic region of the *MC4R* gene was performed on the patient. Primer sequences used for amplification were designed with Primer 3 software (Untergasser 2012) (primer sequences available upon request). Sequencing was performed on an ABI 3130 DNA Analyzer (Applied Biosystems, Foster City, CA, USA) using Big Dye Terminator v3.1 Cycle Sequencing Chemistry (Applied Biosystems, Foster City, CA, USA), according to protocols recommended by the manufacturer. Base calling was performed with Sequencing Analysis v5.2 (Applied Biosystems, Foster City, CA, USA). The obtained sequences were analyzed with the Staden package software (Staden, 1996) and the SeqScape Software v2.5 (Applied Biosystems, Foster City, CA, USA), and compared with the normal sequence (ENSG00000166603).

RESULTS

High-resolution karyotype by standard and GTG banding techniques evidenced that the patient had two mosaic cell lines: 92% of the cells had an abnormal chromosome 18 with a 18p duplication and 18q deletion and 8% had a ring chromosome 18. Karyotyping revealed was mos 46,XX,der(18)add(18)(q21.3)del (18)(q21.3)dn[46]/46,XX,r(18)(p?q21.32)dn[4], following the International System for Human Cytogenetic Nomenclature (ISCN). Therefore, the 18p duplication of the derivative chromosome was localized in the 18q21.3 regions after the deletion in the 18q arm. Chromosomal study was normal in parents.

The array analysis defined the derivative 18 chromosome characterized by a duplication of 12.5 Mb of the short arm (from chr18:12602631 to the telomeric terminal end) and moreover showed a deletion of 20.3 MB of the long arm (from chr18:57691236 to the telomeric terminal end). The deletion was presented in both derivative and ring chromosomes. The SNP/CNV whole-genome array's molecular formula was arr[GRCh37]18p11.32p11.21(chr18:136226_12602631)x3,18q21.32q23(chr18:57691236_78014123)x1, using

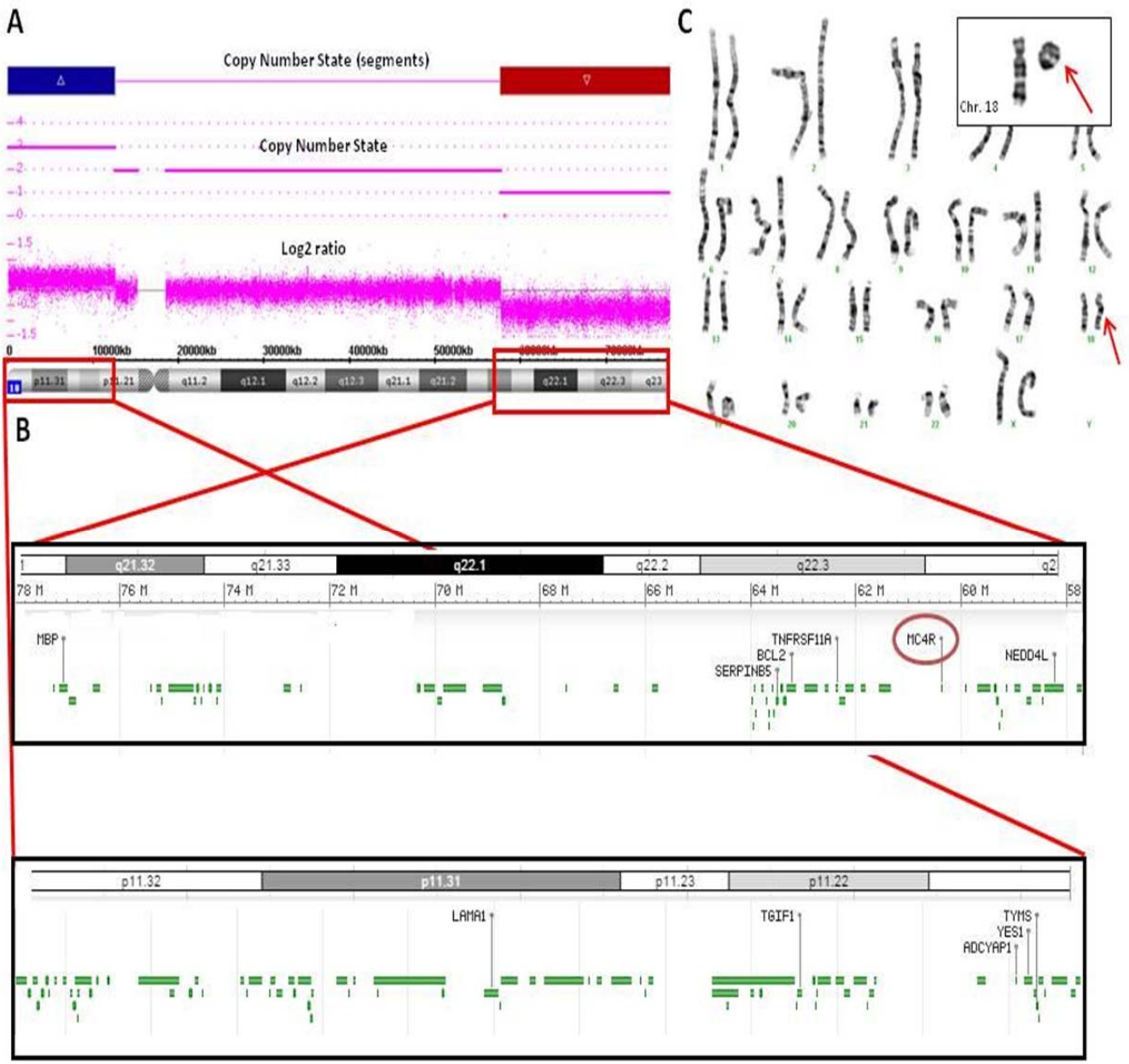

Figure 1. Molecular characterization of the patient by SNPs/CNVs microarray and conventional karyotype. A) Image obtained from the ChAS software showing the regions included in the deleted (bar in red) and duplicated (bar in blue) regions, both of which were carried by the patient. The formula of the microarray, arr[GRCh37]18p11.32p11.21(chr18:136226_12602631)x3,18q21.32q23(chr18:57691236_78014123)x1dn, represents the 18q subtelomeric 20.3 Mb deletion and 18p subtelomeric 12.5 Mb duplication. B) Representation of the OMIM deleted genes (upper panel) and OMIM duplicated genes (lower panel) (NC_000018.10 GRCh38). C) High-resolution karyotype of the patient with the cytogenetic formula mos 46,XX,der(18)add(18)(q21.3)del(18)(q21.3) dn[46]/ 46,XX,r(18)(p?q21.32) dn[4] evidenced two mosaic cell lines: 92% of the cells had an abnormal chromosome 18 with the 18p duplication, localized in the 18q21.3 region, and the 18q deletion and 8% a ring chromosome 18 with the 18q deletion and a 18p distal deletion non-detected by the array. The percentage of the ring was undetected by the array. The normal chromosomes are on the left and the rearranged copies are denoted by arrows on the right.

the ISCN (Figure 1). The rest of the complementary examinations were normal.

The duplicated area encompassed 12.5 Mb, comprising a total of 53 genes, including *NDUFV2*, *LPIN2*, *USP14*, *SMCHD1*, *TGIF1*, *APCDD1*, *GNAL*, *AFG3L2* and *IMPA2*, with entries in OMIM. The deletion size was 20.3 Mb and the proximal breakpoint was located at chromosome position 57,691,236 of the long arm of chromosome 18 (ChAS software (hg19)). The deleted area comprised a total of 32 genes, including *CTDP1*, *TNFRSF11A*, *MC4R*, *PIGN*, *CDH19*, *TMX3*, *RTTN*, *ZNF407*, *TSHZ1*, *MBP* and *SALL3*, with entries in OMIM (Figure 1).

Array results did not reveal any findings related to the molecular characterization of other cell line with a ring chromosome 18 because of the low percenta-

ge of the mosaic, around 8%. In this case, the cell line with the ring chromosome presented a distal 18p small deletion, non-detected by the array, and a distal 18q gross deletion, characterized by the array. The distal 18p deletion responsible of the origin of the ring chromosome is not revealed by the array because of its coincidence with the duplication.

The sequence of the *MC4R* gene, whose alteration is involved in the development of obesity, was normal, without any known or unknown mutations. Other genes *CTDP1*, *TNFRSF11A*, *PIGN*, *CDH19*, *TMX3*, *RTTN*, *ZNF407*, *TSHZ1*, *MBP* and *SALL3* were not considered candidate to be sequenced because their isolated functional capability in humans were not so well characterized.

DISCUSSION

In summary, we present a girl with a rare set of signs and symptoms resulting in a complex phenotype, who had a duplication of 18p11.32p11.21 localized in the 18q21.3 region and a deletion of 18q21.32q23, causing haploinsufficiency of the *CTDP1*, *TNFRSF11A*, *MC4R*, *PIGN*, *CDH19*, *TMX3*, *RTTN*, *ZNF407*, *TSHZ1*, *MBP* and *SALL3* genes, which apart from the derivative chromosome, originated a ring chromosome. The molecular characterization of a large deletion evaluates the deleterious capabilities of a set of contiguous OMIM genes acting under haploinsufficiency. The *de novo* deletion of 20.3 Mb arr[GRCh37] 18q21.32q23(chr18:57691236_78014123)x1 identified in the girl affected 32 genes. The last clinical examination at 4.6 years confirmed signs, symptoms and malformations from birth, correlated to the results obtained from microarray analysis.

The 18q deletion was compared to other detailed deletions including the widely described *MC4R* gene and their respective carrier individuals (Hale 2000; Versacci 2005; Cody 2009; Margarit 2012) to predict the genotype-phenotype relationship in our patient. Deleted genes in this region (18q21.32 to 18q23) have been associated with microcephaly, ear canal atresia, myelination disorders and other conditions (Hale 2000; Margarit 2012). The psychomotor and language delay, and neurological risk patient were also related to this loss (Cody 2007). The *TSHZ1* gene is associated with congenital aural atresia (CAA) consisting of a bilateral absence or incomplete formation of ear canal that may be associated or not to alterations in the middle ear (Feenstra 2011). It has been found in approximately 66% of patients with 18q terminal deletion (Veltman 2003).

Although obesity is a complex pathology manifested with or without intellectual disability and with a large number of involved genes, different obesity syndromes have been associated with chromosomal imbalances identified by arrays (D'Angelo 2012). Monogenic non-syndromic severe early-onset obesity is developed in carriers of punctual mutations and haploinsufficiency of the *MC4R* gene (Cody 1999). However, it is unclear whether the *MC4R* deficiency phenotype is due to haploinsufficiency or dominant-negative effects by the mutant receptor. Regarding that, there are reports of monogenic obesity related to haploinsufficiency in the MC4R gene, as a manner of MC4R deficiency (Abdullah 2016; Farooqi 2005; Turner 2015). Specific parameters to detect over growing evolution, signs or symptoms of an altered metabolic phenotype, and/or neurobehavioral impairment related to the haploinsufficiency of the MC4R gene were not identified in the patient. Additionally, the Sanger sequencing of *MC4R* gene confirmed the patient did not carry any mutation, being normal the unique copy of the gene. Therefore, the non-development of obesity in the patient could be due to the complex genotype, compensating the MC4R haploinsufficiency.

A delayed developmental milestone was still evident in the child. Among patients carrying the most frequent terminal 18q deletions in band q21 and beyond poor weight gain and physical growth failure after birth have been commonly detailed (http://www.rarechromo.org/information/Chromosome%2018/18q%20deletions%20from%2018q21%20and%20beyond%20FTNW.pdf); being attributed to the hypotonia, gastro-esophageal reflux and high-arched palate, which can lead to difficulties with sucking and swallowing, and/or latching on to the breast (Hale 2000; Feenstra 2007). Some of the adult patients had grown up to normal average or even overweight. In

fact, obesity has been described among an interesting number of individuals carrying 18q- (Feenstra 2007).

This chromosomal abnormality was more complex, as it also added a duplication of 12.5 Mb of the telomere region of the short arm (trisomy) of the same chromosome 18, localized in the 18q21.3 region. This alteration was presented in a 92% mosaic cell line. The 18p duplication is a rare chromosomal abnormality. There are few cases described in the literature (Mabboux 2007). Most patients have an apparent normal phenotype or some minor dimorphic features and may have intellectual disability to varying degrees. Our patient has an anorectal malformation consistent in a perineal fistula with an ectopic anal opening in backplane fourchette. There are some reported cases of partial trisomy of 18p-q12 region associated with anorectal malformations, even without knowing the critical region involved (Schramm 2011).

Duplication affects a broad set of genes, which we think may be of relevance, for instance the *IMPA2* gene, which has recently been associated with susceptibility to febrile seizures (Nakayama 2004).

Historically, it is known that the human species tolerates better the excess of genetic material than its loss. Our case shows that the main clinical findings are primarily related to the loss of 18q material. However anorectal anomaly may be more in relation to the 18p duplication (Schramm 2011). As most cases, the patient's parents had no clinical or developmental problems with normal karyotypes, therefore the complex cytogenetic alteration was considered *de novo*.

Although high resolution karyotype has a key role in intellectual disability diagnosis, conventional karyotype had a key role in this case to identify the mosaicism, the 18p duplication rearrangement and the ring chromosome. Therefore, it is necessary to perform this conventional technique to confirm cytogenetically complex genotypes as the one we expose here and it allowed us to propose the molecular mechanism of the chromosome alteration formation.

So, predominant cell line, representing the 92%, appeared due to a duplication event in the 18p chromosome, which is localized in the 18q21.3 region after the 18q gross deletion. That was well-observed and well-characterized in the conventional karyotype and the whole-genome array. The minor cell line, representing an 8%, appeared by two deletion events, one in the distal 18q region, which is the gross deletion molecularly characterized by the array, and a small deletion in the 18p region non-detected by the array due to the small percentage of the cell line as well as the presence of the duplication of the majority cell line, masking the small deletion responsible of the ring chromosome .

CONCLUSION

We have described using SNPs/CNVs microarray the complex phenotype of a patient carrying two mosaic cell lines, the majority one containing a derivative chromosome 18 with 18p duplication and 18q deletion and a minor line with a ring chromosome originated by a gross 18q deletion and a small deletion in 18p distal region non-detected by the array. In these complex phenotypes, the conventional karyotype is still essential to solve the molecular diagnosis. Evaluation of OMIM genes included in the deletion shows that 18q haploinsufficiency correlates with most signs and symptoms of the patient's phenotype. Haploinsufficiency of *MC4R* gene has not altered the metabolism neither was related to the development of obesity in the patient. The description of this patient's genotype and phenotype characteristics will facilitate the evaluation of other patients carrying similar alterations.

DISCLOSURE

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RESUMEN

Desde que los arrays de SNPs/CNVs de genoma completo se han erigido como la principal estrategia diagnóstica en la práctica clínica en el ámbito de la neuropediatría, se han identificado numerosos desequilibrios cromosómicos causales de discapacidad intelectual considerada idiopática previamente. Su uso ha favorecido la descripción exhaustiva de las bases moleculares de numerosos nuevos síndromes, con especial eficiencia en aquellos asociados a múltiples anomalías congénitas y/o rasgos dismórficos. Para describir exhaustivamente la correlación fenotipo-genotipo en una paciente de 2.5 años cuyo cariotipo evidenció una alteración citogenética compleja con dos líneas en mosaico, se hibridó su ADN genómico en un microarray de alta densidad de SNPs/CNVs. El resultado del microarray detectó una duplicación de 12.5 Mb de la región cromosómica 18p11.32p11.21 (chr18:12602631_telómero) y una deleción de 20.3 Mb de la región cromosómica 18q21.32q23 (chr18:57691236_telómero). El cariotipo reveló la existencia de una línea celular con porcentaje del 92% portadora de la duplicación y de la deleción, y una segunda línea celular minoritaria (8%) que presentaba un cromosoma en anillo portador de la deleción detectada en el brazo q. La caracterización molecular de las regiones cromosómicas duplicadas y en haploinsuficiencia, identificaron las alteraciones causales de los principales signos y síntomas aparecidos en la paciente. Aunque el cariotipo convencional se considera actualmente una técnica diagnóstica de apoyo o segunda línea, fue clave para establecer la etiología de la alteración que portaba la paciente. En este caso permitió la interpretación correcta del resultado del array y sólo con ambas pruebas se pudo concluir la existencia del cromosoma 18 en anillo, así como el porcentaje exacto de mosaicismo de cada línea. La capacidad deletérea de los genes OMIM dominantes implicados, permitió el seguimiento clínico riguroso de la paciente y la descripción del fenotipo observado. La inclusión de tal información en las bases de datos específicas, junto a los resultados moleculares obtenidos del array, permite su comparación con alteraciones genéticas detectadas en otros pacientes y cuyas localizaciones cromosómicas sean solapantes.

Palabras clave: haploinsuficiencia 18q, duplicación 18p, SNP/CNV array, mosaicismo, fenotipo sindrómico