Partial Trisomy 13q/Monosomy 3p Resulting from a Paternal Reciprocal 3p;13q Translocation in a Boy with Facial Dysmorphism and Hypertrophic Cardiomyopathy

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Established Facts

- Individuals with 3p deletion show a great clinical variability, patients with partial trisomy 13q usually have a phenotype resembling complete trisomy 13.
- Partial trisomy 13 regularly presents with heart defects.

Novel Insights

- We report a type of cardiomyopathy not previously reported.
- Few cases have been reported with chromosome imbalance due to a p3;q13 translocation.
- This is the first case with a 3p deletion and 13q duplication

Keywords

Trisomy 13q · Monosomy 3p · Translocation

Abstract

Individuals with 3p deletion show a great clinical variability. Apparently, a 1.5-Mb terminal deletion, including the *CRBN* and *CNTN4* genes, is sufficient to cause this syndrome. Partial trisomy 13q is a rare chromosomal abnormality with a vari-

able phenotypic expression, but in most cases, patients have a phenotype resembling complete trisomy 13. The aim of the present study is to describe a 9-month-old Mexican male patient with 3p deletion/13q duplication and a novel clinical finding. He presented with facial dysmorphism and multiple congenital alterations. Echocardiogram revealed cardiac insufficiency with hypertrophic cardiomyopathy and pulmonary hypertension, not previously reported. Karyotype from the patient and his father were 46,XY,add(3)(p26) and

46,XY,t(3;13), respectively. Microarray assay of the proband exhibited an approximately 2.6-Mb loss at terminal 3p26.3 and a 27.7-Mb gain of the long arm in terminal chromosome 13 at q31.1q34. A chromosomal imbalance with a partial trisomy 13q31.1q34 and monosomy 3p26.3 of paternal origin were detected. Microarray assay of both parents were normal. The proband has a cardiomyopathy not previously reported. These data enrich the spectrum of clinical manifestations in 3p deletion/3q duplication chromosomopathy.

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Introduction

Chromosomal alterations that result in genomic imbalances are a major cause of congenital and developmental anomalies [Liu et al., 2016]. 3p deletion syndrome (OMIM 613792) is a contiguous gene syndrome associated with intellectual disability, developmental delay, intrauterine growth restriction, facial dysmorphism, skeletal abnormalities and other defects such as hypogenitalia, atrioventricular septal defects, hiatal hernia, optic atrophy, and polycystic renal dysplasia [Chen et al., 2012b; Moghadas et al., 2014]. The spectrum of defects depends upon the overall size of the deleted segment [Kaur and Khetarpal, 2013]. The phenotype of individuals with 3p deletions varies from normal to severe [Cuoco et al., 2011]. It has been suggested that a 1.5-Mb minimal terminal deletion including the genes *CRBN* and *CNTN4* in chromosome 3 is enough to cause this syndrome [Kaur and Khetarpal, 2013].

Partial trisomy 13q is a rare chromosomal abnormality with a variable phenotypic expression. It may result from parental reciprocal translocations and pericentric or paracentric inversions. Partial trisomy 13q has been shown to have a distinctive and common phenotype resembling that of complete trisomy 13. Common phenotypic features described for partial trisomy 13q are craniofacial dysmorphism, short neck, hemangioma, hexadactyly, urinary tract/kidney anomalies, umbilical/inguinal hernia, intrauterine growth retardation, and oligohydramnios. Other phenotypic features in child and adult patients are psychomotor retardation, hypoacusia, hypochromic anemia, splenomegaly, ocular anomalies, convulsions, and fatty acid disturbances [Machado et al., 2010; Douglas et al., 2017].

This paper aims to describe a case with partial monosomy 3p and partial trisomy 13q with novel clinical data.

Fig. 1. Patient at 3 months of age showing anteverted nares.

Case Presentation

The proband, a 9-month-old male child, is the fourth child of young nonconsanguineous and healthy parents. No family history of congenital malformations was recorded. The child was born at 35 weeks after an uneventful pregnancy. At birth, he had a weight of 3,100 g (10th–25th centile), length of 50 cm (50th centile), occipitofrontal head circumference (OFC) of 33 cm (50th centile), and Apgar score of 9 at 5 min. At the age of 2 months, he was referred to the hospital for hepatosplenomegaly, cholestasis, and facial dysmorphism.

On physical examination, at the age of 4 months, his weight was 4.2 kg (<3rd centile), length 53 cm (<3rd centile), and OFC 40 cm (3rd centile), he presented with upslanting palpebral fissures with long eyelashes, anteverted nares, high and narrow palate, heart murmur, umbilic hernia, and bilateral inguinal hernia with right cryptorchidism (Fig. 1). During hospitalization, he had cardiac insufficiency; an echocardiogram revealed hypertrophic cardiomyopathy and pulmonary hypertension. He had a normal hepatic ultrasound and a brain CT with cortical atrophy. He also had gastroesophageal reflux and needed gastrostomy for feeding. At 9 months, he persisted with low weight (5.6 kg; 3rd centile) and a low length (59 cm; <3rd centile).

Materials and Methods

Chromosome analysis was performed by routine GTG-banding at a band resolution of approximately 500. Genomic DNA was extracted with TRIzol reagent (Life Technologies, Santa Clara, CA, USA). Array analysis was carried out using CytoScan HD array (Affymetrix, Santa Clara, CA, USA), and scanned with the Affymetrix GeneChip Scanner 3000 7 G. Data were analyzed using GTYPE (GeneChip Genotyping Analysis Software, v1.0.12) to detect copy number aberrations.

Fig. 2. Karyotypes. **a** Patient: 46,XY,add(3)(p26). **b** Father: 46,XY,t(3;13).

Fig. 3. **a** Microarray assay exhibiting a 2.6-Mb loss at terminal 3p26.3. **b** 27.7-Mb gain of the long arm in terminal chromosome 13 at q31.1q34. Genes involved are described in the text.

Results

Conventional cytogenetic analysis showed a karyotype of 46,XY,add(3)(p26) (Fig. 2a). Karyotype of the parents showed 46,XX (mother) and 46,XY,t(3;13) (father) (Fig. 2b). The oligonucleotide SNP array had a 1.15-kb resolution, and the result was: arr[hg19] 3p26.3(61,891_2,312,694)×1,13q31.1q34(87,427,188_115,107,733)×3, exhibiting an approximately 2.6-Mb loss at terminal 3p26.3 and a 27.7-Mb gain of the long arm of terminal chromosome 13 at q31.1q34 (Fig. 3a, b). These data show a chromosomal imbalance with a partial trisomy 13q31.1q34 and a monosomy 3p26.3 of paternal origin. Genes involved are shown in Table 1. The microarray analysis of both parents was normal.

Discussion and Conclusion

The 3p deletion syndrome is a rare contiguous gene syndrome caused by deletions with variable size in 3p25pter; the deletion ranges from one to several megabases. There are no common breakpoints, and it mostly occurs de novo; only a few familial cases have been reported [Cuoco et al., 2011]. The minimal deletion region is thought to be 1.5 Mb in size and includes the *CRBN* and *CNTN4* genes [Kashevarova et al., 2014]. To better define the genetic basis of 3p deletion syndrome, a cohort of 14 patients with visible distal 3p deletions has been studied by SNP array. Among the different haploinsufficient genes, a deletion involving *CRBN* and *CNTN4* seems to be enough to produce the typical clinical features, while

Table 1. Disease-causing genes

OMIM	Gene	Disease	Inheritance
3p	<i>CHL1</i>	3p deletion syndrome: Developmental delay, intellectual disability, microcephaly, and various facial dysmorphisms and limb abnormalities	
	<i>CNTN6</i>	3p deletion syndrome ASD candidate gene	
	<i>CNTN4</i>	3p deletion syndrome ASD candidate gene	
13q			
258315	<i>GPC6</i>	Omodisplasia 1	AR
619165	<i>TYRP2</i>	Oculocutaneous albinism, type VIII	AR
616145	<i>TGDS</i>	Catel-Manzke syndrome	AR
617671	<i>CLDN10</i>	HELIX syndrome	AR
610840	<i>DZIP1</i>	Mitral valve prolapse 3	AD
619102		Spermatogenic failure 47	AR
616192	<i>DNAJC3</i>	Ataxia, combined cerebellar and peripheral, with hearing loss and diabetes mellitus	AR
609637	<i>ZIC2</i>	Holoprosencephaly 5	AD
606054	<i>PCCA</i>	Propionicacidemia	AR
616570	<i>ERCC5</i>	Cerebrooculofacioskeletal syndrome 3	AR
278780		Xeroderma pigmentosum, group G	AR
		Xeroderma pigmentosum, group G/Cockayne syndrome	AR
606593	<i>LIG4</i>	LIG4 syndrome	AR
125853	<i>IRS2</i>	Diabetes mellitus, noninsulin-dependent	AD
618321	<i>NAXD</i>	Encephalopathy, progressive, early-onset, with brain edema and/or leukoencephalopathy, 2	AR
614483	<i>COL4A2</i>	Brain small vessel disease 2	AD
616672	<i>CARS2</i>	Combined oxidative phosphorylation deficiency 27	AR
275355	<i>ING1</i>	Squamous cell carcinoma, head and neck, somatic	
227500	<i>F7</i>	Factor VII deficiency	AR
227600	<i>F10</i>	Factor X deficiency	AR
609307	<i>FGF14</i>	Spinocerebellar ataxia 27	AD
614024	<i>PROZ</i>	Protein Z deficiency	
613411	<i>GRK1</i>	Oguchi disease-2	
181500	<i>DAOA</i>	Schizophrenia	AD
180000	<i>COL4A1</i>	Tortuosity of retinal arteries	AD
611773		Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps	AD
175780		Brain small vessel disease with or without ocular anomalies	AD
618564		Microangiopathy and leukoencephalopathy, pontine	AD
616579	<i>CHAMP1</i>	Mental retardation 40	AD

ASD, autism spectrum disorder; AD, autosomal dominant; AR, autosomal recessive. Reference, UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38). Assembly, <https://genome.ucsc.edu/>.

the *CHL1* gene has been suggested to contribute to mental development [Cuoco et al., 2011; Tassano et al., 2014].

To explain the variability in the phenotype from severe to normal, chromosomal non-penetrance and gene modification have been proposed [Sims et al., 2012].

In our case, the copy number loss involves *CHL1*, *CNTN6*, *CNTN4* and *CNTN4-AS2*. *CNTN4* mRNA transcript is a member of the immunoglobulin superfamily of neuronal cell adhesion molecules; it participates in axon growth, guidance, and fasciculation in the central nervous system (CNS). The *CNTN4* disruption is associated

with the 3p deletion syndrome phenotype; knockouts of homologous neuronal adhesion molecules in mouse have resulted in viable mutants demonstrating morphological, neurological and behavioral abnormalities. This indicates an important role for *CNTN4* in CNS development [Fernandez et al., 2004]. This gene may play a role in 3p deletion syndrome with low birth weight, microcephaly, trigonocephaly, hypertelorism, ear abnormalities, hypotonia, psychomotor and growth retardation, among others [Cervantes et al., 2014; Iype et al., 2015]. Our patient has microcephaly, psychomotor and growth retardation.

Table 2. Comparative table between the proband and 3p deletion and 13q duplication syndrome

Phenotype	3p deletion syndrome [Fernandez et al., 2004]	Proband	13q duplication [Tharapel et al., 1986; Douglas et al., 2017]
Growth	Low birth weight Growth retardation	Growth retardation	
Psychomotor development	Psychomotor retardation	Psychomotor retardation	Psychomotor retardation Intellectual disability
Craniofacial	Trigonocephaly Microcephaly Ptosis Telecanthus, hypertelorism Downslanting palpebral fissures Preauricular pits Ears malformed or low set Abnormal nose Micrognathia Cleft palate	Microcephaly Upslanting palpebral fissures Anteverted nares High-arched palate	Microcephaly Bushy eyebrows Long curled eyelashes Prominent nasal bridge Long philtrum Thin upper lip High-arched palate
Neurological	Hypotonia Seizures	Hypotonia Cortical atrophy	Hypotonia Seizures
Cardiovascular	Congenital heart defects (especially atrioventricular septal defects)	Hypertrophic cardiomyopathy and pulmonary hypertension	Tetralogy of Fallot Ventricular septal defect
Gastrointestinal	Feeding problems	Cholestasis Umbilic hernia	Umbilical/inguinal hernia
Renal	Renal malformation		Urinary tract/kidney anomalies Renal hypoplasia
Musculoskeletal	Postaxial polydactyly Clinodactily		Polidactily Single palmar crease
Genital	Cryptorchidism	Cryptorchidism	
Column	Sacral dimple		Spina bifida Scoliosis

The region distal to the disrupted *CNTN4* gene contains *CNTN6* and *CHL1*; they are neuronal cell adhesion molecules that also contain Ig and FNIII domains. Analyses of *CHL1* knockout mice have identified anomalies in axonal organization in various brain regions as well as subtle behavioral abnormalities in homozygous null animals [Fernandez et al., 2004].

In order to further investigate genotype-phenotype correlations in 3p deletion syndrome, Shuib et al. [2009] analyzed 14 patients with cytogenetically detectable deletions of 3p25 (including one patient with a normal phenotype) using Affymetrix 250K SNP microarrays. A candidate critical region for a congenital heart disease susceptibility gene was refined to approximately 200 kb and a candidate critical region for intellectual disability was mapped to an approximately 1-Mb interval containing

SRGAP3. Other 3p neuro developmental genes including *CHL1*, *CNTN4*, *LRRN1*, and *ITPR1* mapped outside the candidate critical interval. This current evidence suggests that *SRGAP3* is the major determinant gene of intellectual disability in distal 3p deletions [Shuib et al., 2009].

CHL1 is a member of the L1 family of cell adhesion molecules, these proteins play an important role in building and functioning of the brain. Due to the fact that migration and synaptogenesis require cell to cell and cell to matrix interactions, it has been suggested that these molecules are associated with intellectual defects in patients with 3p deletion syndrome [Cuoco et al., 2011; Gandawijaya et al., 2021].

CNTN6 is a neuronal membrane protein that functions as a cell adhesion molecule and may contribute to the formation of axon connections in the developing ner-

vous system. CNTN6, and other members of this protein family, have been identified as potential disease-causing genes in neurodevelopmental disorders. It has been suggested that these genes participate in pathways that are important for correct brain development. In mice, they are thought to participate in embryonic development and postnatal brain maturation. CNTN6 deficiency in mice causes profound motor coordination abnormalities and learning difficulties [Kashevarova et al., 2014].

There are previous reports of patients with 3p deletion syndrome and different congenital cardiopathies; Chen et al. [2012a] reported coarctation of the aorta, patent ductus arteriosus, peripheral pulmonary stenosis, and atrial septal defect. The oligonucleotide-based array CGH revealed a 4.79-Mb deletion of 3p26.2→pter encompassing *CHL1* and *CNTN4*, and a 19.56-Mb duplication of 5q34→qter encompassing *MSX2*, *NKX2-5*, and *NSD1*. The karyotype of the girl was 46,XX,der(3)t(3;5)(p26.2;q34)pat. The authors attribute the cardiopathy to the distal 5q duplication, not to the 3p deletion [Chen et al., 2012a]. Our patient had hypertrophic cardiomyopathy and pulmonary hypertension, not previously reported, maybe secondary to the 13q duplication.

Patients with distal 13q duplications typically show features overlapping those with full trisomy 13 [Helali et al., 1996]. Genomic rearrangements at chromosome 13q31.3q32.1 have been associated with multiple anomalies and a variable degree of mental disability [Tharapel et al., 1986; Brewer et al., 1999; Machado et al., 2010; Wei et al., 2012; Kannu et al., 2013].

Kannu et al. [2013] reviewed eight 13q duplication cases finding important phenotypic differences, 5 presented with facial dysmorphism, 4 of them had developmental delay, and only 1 had a nonspecified heart defect [Nikolis et al., 1991; Kannu et al., 2013].

Table 2 presents the symptoms between 3p deletion syndrome, 13q duplication syndrome and our patient.

McCorquodale et al. [1980] reported a child with partial trisomy involving the proximal segment of the long arm of chromosome 13 derived from a paternal translocation (p3;q13). The final karyotype was 47,XY,+der(13)t(3,13)(q24;q14). This boy had a clover-leaf shape of the head, CNS malformations, small sacral myelomeningocele, developmental delay, glaucoma, low nasal bridge, snub nose, prominent philtrum, narrow and high palate, a short neck with increased skin folds in the nape, asymmetric chest, small penis, right testis not palpable and left testis in the left inguinal canal, hands showed ulnar loops, hyperextension at interphalangeal joints, prominent heels, and hypotrophic toe nails. Above all these manifes-

tations, our patient also had developmental delay, high and narrow palate, and cryptorchidism.

In conclusion, we reported a case with 13q duplication and 3p deletion in a patient with hypertrophic cardiomyopathy and pulmonary hypertension, not previously reported. The presence of heart defect previously described indicates that this data could be part of this syndrome. It is important to mention that besides the proband is not the first case reported with this type of translocation; however, it is the first patient with a 3p deletion and 13q duplication.

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Statement of Ethics

Both parents gave their written informed consent prior to the realization of the studies and authorized to publish the case including images. This study protocol was reviewed and approved by Comité de Ética en Investigación and Comité de Investigación of Hospital General de México, approval number DI/17/310A/04/083.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Writing and original draft preparation: M.D.M., S.A.C., Z.C., K.A., L.M.G. O.M.B., and L.P.B. Critical review: M.D.M., K.A., and S.A.C. All authors analyzed and interpreted the data and approved the manuscript in its final form.

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