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Nonmosaic Trisomy 19p13.3p13.2 Resulting from a Rare Unbalanced t(Y;19)(q12;p13.2) Translocation in a Patient with Pachygyria and Polymicrogyria

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Nonmosaic trisomy 19p · Pachygyria · Polymicrogyria · Unbalanced t(Y;19)

Abstract
Nonmosaic trisomy involving 19p13.3p13.2 is a very uncommon abnormality. At present, only 12 cases with this genetic condition have been reported in the literature. However, the size of the trisomic fragment is heterogeneous and thus, the clinical spectrum is variable. Herein, we report the clinical and cytogenetic characterization of a 5-year-old boy with nonmosaic trisomy 19p13.3p13.2 (7.38 Mb), generated by a derivative Y chromosome resulting from a de novo unbalanced translocation t(Y;19)(q12;p13.2). We demonstrated the integrity of the euchromatic regions in the abnormal Y chromosome to confirm the pure trisomy 19p. Our patient shares some clinical features described in other reported patients with pure trisomy 19p, such as craniofacial anomalies, developmental delay, and heart defects. Different to previous reports, our case exhibits frontal pachygyria and polymicrogyria. These additional features contribute to further delineate the clinical spectrum of trisomy 19p13.3p13.2.

Chromosome 19 has a higher gene density compared to other human chromosomes [Puvabanditsin et al., 2009]. Presumably, triplication of chromosomes with very high gene density does not allow the embryo to survive long enough to be identified as a miscarriage. In this context, in live-born individuals the gain of chromosome 19 genes can only be present as partial trisomies [Migeon et al., 2017]. Trisomy 19p is very uncommon; most of the reports of patients with this condition describe mosaic cases with supernumerary ring or marker chromosomes, as well as cases with the clinical features of trisomy 19p coexisting with phenotypic manifestations of other autosomal imbalances [Salbert et al., 1992; Brown et al., 2000; Quigley et al., 2004; Novelli et al., 2005; Puvabanditsin et al., 2009; Seidel et al., 2014]. In this report, we describe a patient with nonmosaic trisomy 19p, resulting from a de novo unbalanced translocation t(Y;19)(q12;p13.2), and include a literature review of previously reported patients with similar cytogenetic and clinical conditions.

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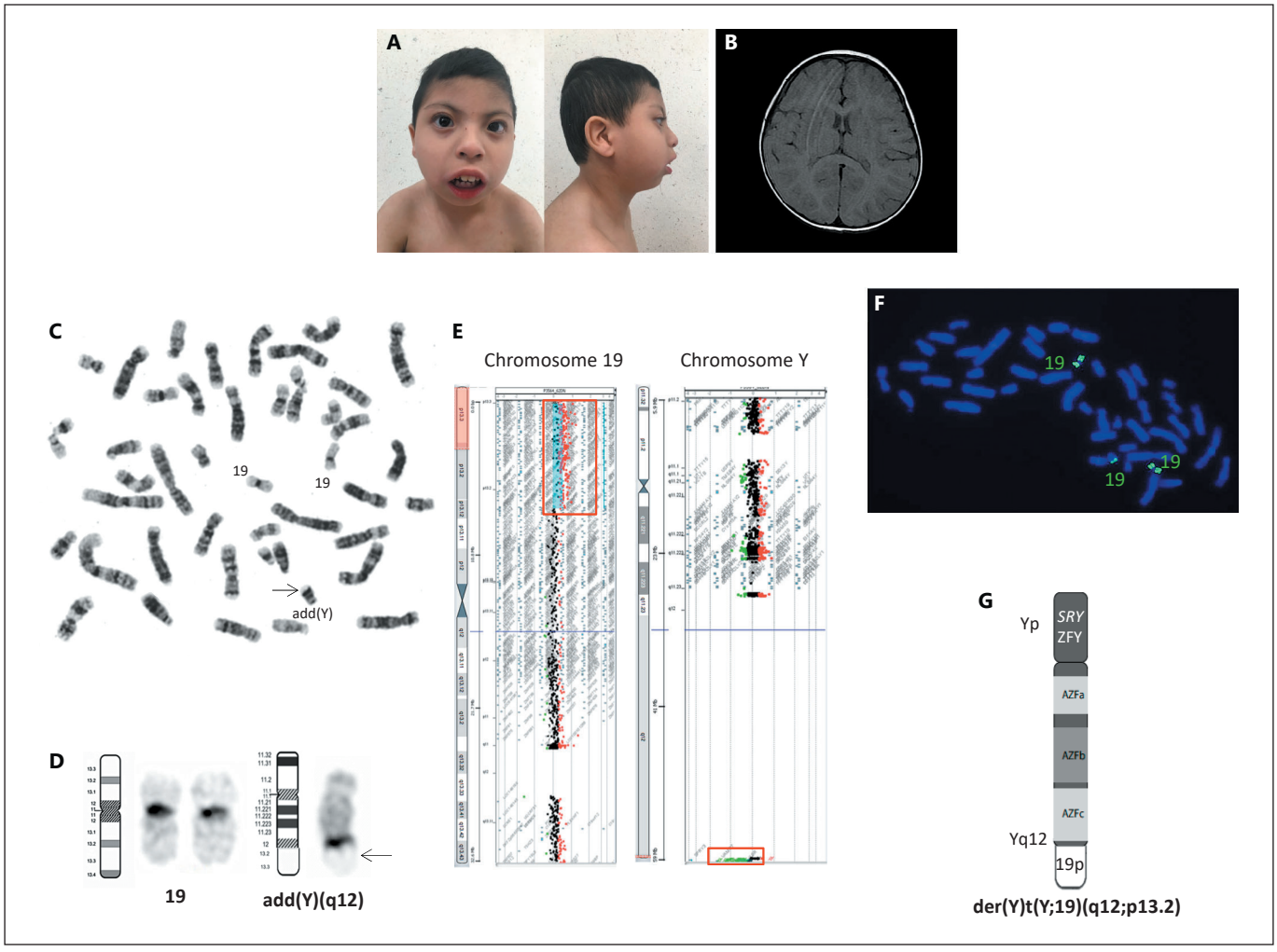

Fig. 1. Clinical features, cytogenomic and molecular analysis of the proband. **A** The patient showing microcephaly, arched eyebrows, telecanthus, micrognathia, retrognathia, and low-set ears. **B** Resonance magnetic imaging showing pachygyria and polymicrogyria. **C** Complete metaphase showing both normal chromosomes 19 and the abnormal chromosome Y. **D** Partial karyotype. **E** aCGH analysis showing a copy number gain at 19p13.3p13.2 and copy number loss at Yq12 (red boxes). **F** WCP19 FISH analysis showing hybridization on both normal chromosomes 19 and additional material on the Y chromosome. **G** Diagram of the derivative Y chromosome.

Case Report

We report on a 5-year-old boy, first child of healthy and nonconsanguineous parents. His mother was 19 years old and his father was 21 years old when he was born. Family and gestational history are unremarkable. Because of fetal bradycardia, the patient was born by cesarean delivery at 38 weeks of gestation. His birth weight was 2.050 kg ($Z = -1.79$), length 47 cm ($Z = -0.2$), APGAR 8/9, and occipitofrontal circumference unknown. He was referred to the National Pediatric Institute (Mexico City, Mexico) at 3 months of age for evaluation due to a heart murmur that suggested a congenital heart disease. At physical examination his weight was 2.840 kg ($Z = -4.3$), height 53 cm ($Z = -3.5$), and head circumference 32.5 cm ($Z = -8$). He presented microcephaly, arched eyebrows, upslanting palpebral fissures, anteverted nostrils, micrognathia, and low-set ears (Fig. 1A). An echocardiogram showed a 3-mm atrial septal defect and a 3-mm ventricular septal defect with hemodynamic repercussion, and thus he started pharmacological management with furosemide, spironolactone, and captopril. An echocardiogram at 3 years of age showed a 7-mm ventricular septal defect. As the patient was asymptomatic, the medication was suspended. In addition, at 1 year of age, the patient started with seizures, which are currently under control with valproic acid. His follow-up included a cranial magnetic resonance image showing frontal pachygyria and polymicrogyria (Fig. 1B); his ophthalmological evaluation was normal. At present, his weight is 12.200 kg ($Z = -4.26$), height 98 cm ($Z = -3.06$), and head circumference 44 cm ($Z = -6.05$). He exhibits developmental delay, requiring support for standing, and his communication is sign-based.

Cytogenetic and Molecular Analysis

Cytogenetic analyses of the patient and his parents were performed in peripheral blood lymphocytes. GTG-banded metaphases were analyzed and interpreted according to the International System for Human Cytogenomic Nomenclature 2016 [ISCN, 2016]. A total of 50 metaphases were analyzed to exclude chromosomal mosaicism higher than 5%.

Array-CGH (aCGH), FISH, and multiplex PCR were performed to finely characterize the chromosomal rearrangement. DNA was isolated from blood using a Qiagen Kit (Qiagen™, Valencia, CA, USA) according to manufacturer's instructions. aCGH was carried out with an Oligo 60K array using Agilent Technologies™ (Santa Clara, CA) and annotated using Human Genome Build GRCh37/hg19. Copy number losses and gains were determined by decrease or increase in the log R ratio, respectively. To validate the aCGH results, we performed FISH under standard procedures using a whole chromosome 19 painting probe (WCP19; Oncor™, Paris, France) on metaphases of the patient and his father. To confirm the integrity of the Y chromosome, amplification of the *SRY* gene and 22 sequence-tagged sites belonging to AZFa, AZFb, and AZFc regions and the Yq12 heterochromatin (sY160) was performed by multiplex PCR (conditions available upon request) according to primer sequences reported by Hellani et al. [2005] and Krausz et al. [2014].

Results

Conventional cytogenetic analysis of the patient at a resolution level of 450 to 550 bands disclosed the karyotype 46,X,add(Y)(q12) (Fig. 1C, D). Cytogenetic analyses of both parents revealed normal karyotypes. The paternity was confirmed by analysis of 15 autosomal short tandem repeat sequences using multiplex PCR (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000507561 for all online suppl. material). Therefore, additional material on the Y chromosome was considered as a de novo abnormality.

The cytogenetic identity of the additional material on the Y chromosome was determined by aCGH. The result was arr[GRCh37] 19p13.3p13.2(275925_7660356)×3, Yq12(59103588_59327772)×1 (Fig. 1E), revealing a 7.38-Mb terminal duplication of the short arm of chromosome 19 from p13.2 to p13.3 that involved 209 protein-coding genes. A 224.2-kb deletion of Yq12 at constitutive heterochromatin, involving only 2 protein-coding genes, *SPRY3* and *VAMP7*, was detected as well. The aCGH showed an amplification ratio greater than 0.5 and a deletion ratio lower than –0.5 [Mean Log Ratio], suggesting that the abnormalities detected are not in mosaic. Conventional cytogenetics and FISH analyses in 50 metaphases confirmed a nonmosaic state of the partial trisomy 19.

Multiplex PCR did not reveal microdeletions in *SRY*, nor in the sequence-tagged sites located in AZFa, AZFb, AZFc regions and Yq12; these results confirm the intactness of Yp, the euchromatic regions in Yq, and Yq12 as far as the *DAZ1* marker (online suppl. Fig. 2). FISH analysis with the WCP19 probe showed specific hybridization on both normal chromosomes 19 and on the additional material of the abnormal Y chromosome in the patient (Fig. 1F); the father presented a normal pattern with positive hybridization only on both chromosomes 19. The cytogenomic and molecular analyses suggested that the derivative Y chromosome is composed of Yp, an intact euchromatic Yq region, Yq12, and the 19p13.3p13.2 region (Fig. 1G). These results were used to define the karyotype 46,X,der(Y)t(Y;19)(q12;p13.2).ish der(Y)t(Y;19)(q12;p13.2)(wcp19+).arr[GRCh37] 19p13.3p13.2(257952_7660356)×3,Yq12(59103588_59327772)×1 dn. In conclusion, the patient presents a de novo constitutive trisomy 19p13.2 to 19p13.3 and the absence of a distal fragment of Yq12 constitutive heterochromatin.

Discussion and Conclusion

Chromosome 19 abnormalities are very uncommon compared to those found in other chromosomes of the human karyotype [Orellana et al., 2015]. In addition, Y;autosome translocations are infrequent genomic rearrangements that appear in 1/2,000 individuals in the general population and commonly involve an acrocentric chromosome [Wang et al., 2017]. To our knowledge, no patients have been previously reported showing a de novo unbalanced translocation t(Y;19) involving the 19p13.2 and heterochromatic Yq12 regions. Our patient presents this chromosome rearrangement in a nonmosaic state, and the patient's father has a normal karyotype in his peripheral blood lymphocytes. Gonadal mosaicism confined to germ cells carrying the unbalanced Y;19 translocation could explain the presence of this abnormality in a nonmosaic state in the patient; however, this possibility was not confirmed in the present study.

The mechanism of origin of this translocation is uncertain, however, chromosomes Y and 19 contain an unusual density of repeated sequences that could promote chromosome rearrangements. The Yq12 region presents HSAT/Alu/AT-rich and HSAT II satellite DNA sequences, which are very similar to satellite DNA in the pericentromeric regions of acrocentric chromosomes and in the 22q11.2 locus; these regions are frequently involved in chromosome rearrangements [Babcock et al., 2007].

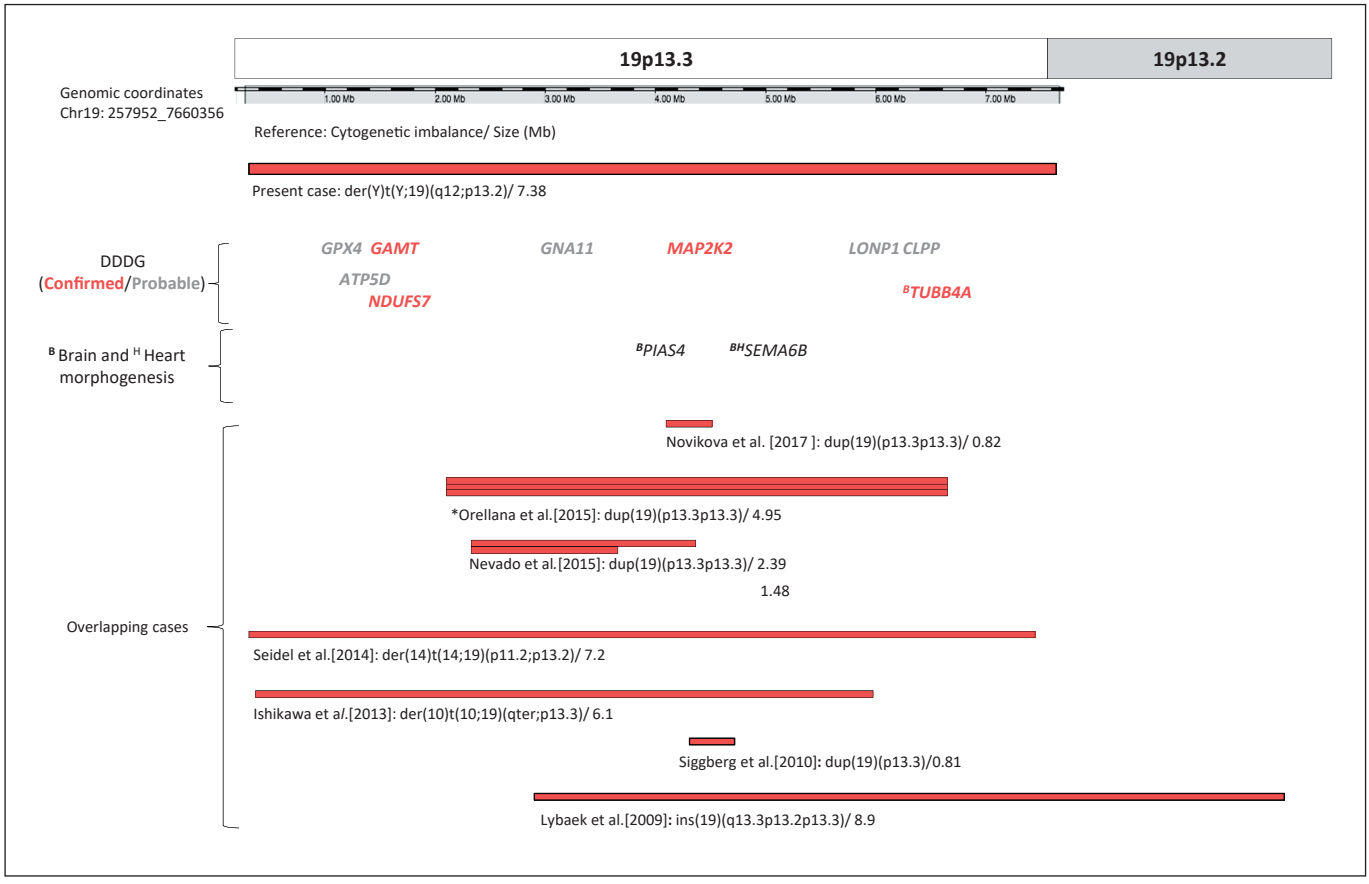

Fig. 2. Genomic coordinates of the reported cases with pure trisomy 19p13.3p13.2 that overlap with the present case (Chr19: 257952_7660356), and genes in this region associated with developmental disorders and with brain or heart morphogenesis implication. * Orellana et al. [2017] described 3 cases with the same genomic coordinates. The cases reported by Stratton et al. [1995] and Andries et al. [2002] are not shown because the genomic coordinates were not available in the original reports. DDDG, DECIPHER Developmental Disorder Genes.

Also, almost 55% of chromosome 19 contains repetitive elements, while chromosomes 6, 7, 14, 20, 21, and 22 present repeat contents ranging from 40 to 46%. Alu repeats make up 25.8% of chromosome 19, compared with 13.8, 13.3, 9.5, and 16.8% observed in chromosomes 7, 14, 21, and 22, respectively [Grimwood et al., 2004].

Considering the spatial disposition of chromosomes in the cell nucleus of somatic cells, the Yq12 region containing HSAT1/Alu/AT-rich repeats is located in the nuclear periphery during interphase, distant from the other chromosomes, thus preventing recombination through their highly unstable satellite repeats. However, Mudrak et al. [2012] described the chromosome territories of chromosomes 1, 3, 6, 17, 18, 19, X, and Y in nuclei of human sperm using FISH with WCP probes and detected that in the longitudinal axis of the sperm nuclei the chromosomes 19 and Y tend to be grouped in the anterior half, near to the acrosomal tip. It is possible that the repeated sequences and nucleus position of Yq12 and 19p13.2 regions predispose to nonallelic homologous recombination, resulting in a translocation between the most gene rich human chromosome and the heterochromatic portion of the Y chromosome.

In our patient, the deleted region of the Y chromosome involves 2 protein-coding genes: *SPRY3*, encoding the sprouty RTK signaling antagonist 3 protein, and *VAMP7*, encoding the vesicle associated membrane protein 7. Both genes are located in the centromeric boundary of X/Y PAR2; however, according to the literature, the Y-related alleles are transcriptionally silenced by epigenetic mechanisms [De Bonis et al., 2006], and the alleles of the X chromosome are intact in our patient. Ad-

ditionally, according to the DECIPHER database (https://decipher.sanger.ac.uk), these genes do not show a high score of haploinsufficiency (62.78 and 56.22% for *SPRY3* and *VAMP7,* respectively). Moreover, DECIPHER reports 17 patients with deletions of similar size (144.83 to 313.14 kb) and with involvement of *SPRY3* and *VAMP7* genes. These CNVs are classified as benign, likely benign or with unknown significance, considering that some of them are inherited from a normal father with the deletion in a constitutive state. Apparently, in the present case, the deleted region of the Y chromosome only involves phenotypically irrelevant Yq12 heterochromatin; and thus, we consider that the patient's clinical phenotype could be completely attributed to the trisomy of 19p13.3p13.2.

To the best of our knowledge, there are 12 patients reported in the literature with pure and nonmosaic trisomy 19p13.3p13.2. In 10 cases, the trisomy was identified by chromosomal microarray analysis, whereas FISH was used in 2 cases. Regarding the genetic features, in 8 patients the cytogenetic imbalance was an interstitial duplication of the 19p13.3 segment; one case presented a duplication derived from an unbalanced intrachromosomal insertion of 19p13.3p13.2; and the other 3 cases showed an unbalanced translocation between the 19p segment and a chromosome region without phenotype relevance (satellite p arm or telomeric regions). Most of these cases involving the trisomy 19p13.3p13.2 occurred de novo, and the sizes of the trisomic segments were heterogeneous (0.81 to 8.9 Mb) (Fig. 2) [Stratton et al., 1995; Seidel et al., 2014; Novikova et al., 2017]. Additionally, we searched in DECIPHER, ISCA (http://dbsearch.clinicalgenome.org/search/), and NCBI dbVAR (https://www.ncbi.nlm.nih.gov/dbvar/) databases, and we found another 30 reports of gain of copy number variants, classified as pathogenic and involving the overlapping region. Unfortunately, not all cases displayed the detailed information about the status of pure trisomy 19p, nonmosaic state and/or the major clinical features.

Considering our patient and the reported cases with constitutional trisomy 19p13.3p13.2, the age ranges from 21 months to 39 years old, with an average of 8 years. These cases present intrauterine growth retardation (63%), growth delay with short stature, and low weight (75 and 100%, respectively). The shared craniofacial findings include short or flat philtrum, abnormal nose, low-set ears, microretrognathia, tall prominent forehead, and hypertelorism or telecanthus. All of the cases have a psychomotor developmental delay and/or intellectual disability, and some of them also present microcephaly (76%). Other neurological features described in these patients are seizures (27%), hypotonia (80%), and cerebral imaging abnormalities, such as hypoplastic inferior vermis and slightly extended temporal lobe; however, our patient differs from others reported due to the presence of pachygyria and polymicrogyria. In addition to the spectrum of minor clinical features, major clinical findings are observed in some patients, including congenital heart defects (like atrial ventricular septal defect or a systolic murmur, 66%), ophthalmologic features, kidney abnormalities, hip dysplasia, and recurrent infections [Stratton et al., 1995; Seidel et al., 2014; Novikova et al., 2017]. Our patient also presents major clinical findings, specifically congenital heart defects (Table 1).

In the case reported by Seidel et al. [2014], a primary immunodeficiency was diagnosed associated with trisomy of the 19p13.3p13.2 region. Other patients with this genetic entity presented recurrent infections that suggest an immunologic compromise; our patient does not show these or other symptoms associated with an immune compromise (Table 1). Our patient shares most of the clinical features with the previously reported patients with constitutional pure trisomy 19p, in particular, the neurodevelopmental and psychomotor delay, microcephaly, and facial dysmorphism, but differs from these by the presence of pachygyria and polymicrogyria and the absence of kidney and hip abnormalities (Table 1).

To relate the craniofacial features, congenital heart defects, and cortical brain anomalies present in our patient with the genes involved in the trisomy 19p, we searched for genes associated with developmental disorders or with the morphogenesis of heart or brain. The 19p trisomic segment includes 9 genes classified by the DECIPHER database as developmental disorder genes; these are from telomere to centromere: *GPX4*, *ATP5D*, *GAMT*, *NDUFS7*, *GNA11*, *MAP2K2*, *LONP1*, *CLPP*, and *TUBBB4A* (Fig. 2, a complete list of OMIM morbid genes is included in online supplementary Table 1). Of these genes, *MAP2K2* is located in 19p13.3 and is associated with cardiofaciocutaneous syndrome 4 (CFC4; OMIM 615280); our patient and all the reported cases with trisomy 19p13.3 disclose some overlapping clinical features with CFC4, including developmental delay, intellectual disability, low-set ears, tall forehead, long appearing face, hypertelorism, and cardiac abnormalities comprising septal defects (Fig. 2; Table 1). However, they do not present a typical CFC4 phenotype because they lack other distinctive features, such as thin and curly hair [Siggberg et al., 2010; Nowaczyk et al.,

Table 1. Clinical features of overlapping cases with pure constitutional trisomy 19p13.3p13.2

References	Stratton et al. [1995]	Andries et al. [2002]	Lybaek et al. [2009]	Siggberg et al. [2010]	Ishikawa et al. [2013]	Seidel et al. [2014]	Nevado et al. [2015][a]	Orellana et al. [2015][b]	Novikova et al. [2017]	Present case	Total[c] (n = 13)
Growth delay											
IUGR	–	–	+	NR	+	+	A, B: –	A, B, C: +	NR	+	63%
Short stature	–	–	+	NR	+	+	A, B: +	A, B: +; C: –	+	+	75%
Low weight	+	NR	+	NR	+	+	A, B: +	A, B, C: +	+	+	100%
Facial dysmorphism	+	+	+	+	+	+	A, B: +	A, B, C: +	+	+	100%
Neurological features											
DD/ID	+	+	+	+	+	+	A, B: +	A, B, C: +	+	+	100%
Microcephaly	+	+	–	+	+	+	A: +; B: –	A, B, C: +	–	+	76%
Seizures	–	–	–	NR	–	+	A, B: –	A, C: –; B: +	–	+	27%
Cerebral imaging	Normal	NR	NR	NR	NR	Hypoplastic inferior vermis, slightly extended temporal lobe	NR	C: brain atrophy	NR	Pachygyria and polymicrogyria	NC
Hypotonia	–	NR	NR	NR	+	+	A, B: +	A, C: +; B: –	+	+	80%
Ophtalmologic features	Strabismus	–	NR	NR	Strabismus	Strabismus	A: -; B: + NS	A, C: myopia; B: –	Myopia	Strabismus	70%
Congenital heart defects	PDA, ASD, VSD	NR	VSD	NR	AVSD, PH, MVD	–	A: –; B: + NS	A,B, C: –	+ SM	+ ASD/VSD	66%
Kidney defects	NR	NR	NR	Unilateral renal agenesis	Ectopic kidney	Horseshoe kidney	A, B: NR	A,B, C: –	–	Normal	NC
Hip dislocation	NR	NR	Bilateral	NR	Bilateral	Bilateral	A, B: NR	A, C: –; B: right	–	Normal	NC
Data related to immunodeficiency	Died by viral pneumonia	NR	NR	NR	Recurrent respiratory infections	Primary immunodeficiency	A, B: NR	A, C: – B: recurrent infections	–	–	NC
Others								A, C: cleft palate			NC
			Eating problems			Eating problems	B: feeding problems			Feeding problems	
				Hearing loss		Hearing loss				Hearing loss	
					Kyphoscoliosis						
						Perineal hypospadias					

[a] Two cases. [b] Three cases. [c] Percentages calculated excluding the non-reported data. ASD, atrial septal defect; AVSD, atrioventricular septal defect; DD, developmental delay; ID, intellectual disability; IUGR, intrauterine growth retardation; MVD, mitral valve dyplasia; NC, not calculated; NR, not reported; NS, not specified; PDA, patent ductus arteriosus; PH, pulmonary hypertension; SM, systolic murmur; VSD, ventricular septal defect.

2014; Nevado et al., 2015; Orellana et al., 2015; Novikova et al., 2017].

Another interesting gene located in 19p13.3 is *TUBB4A* (tubulin beta 4A class IVa), which encodes a member of the beta-tubulin family and shows specific high expression in the adult brain. The microtubules facilitate neurogenic division, drive neuronal migration, and are required for neuronal differentiation and circuit formation. Mutations in some members of the tubulin gene family (*TUBB*, *TUBA1A*, *TUBB2B*, *TUBB3*, *TUBG1*, *TUBA8*) reduce the microtubule stability, lead to inefficient dimerization, and have been associated with the presence of abnormal cortical phenotypes including pachygyria and polymicrogyria, which are features present in our patient [Breuss and Keays, 2014; Cushion et al., 2014]. In humans, there is still no evidence of the association of an extra copy of *TUBB4A* with microtubule instability; however, Weinstein and Solomon [1990] demonstrated in *S. cerevisiae* that the overexpression of genes that encode beta tubulin proteins at early development causes depolymerization and interferes with normal microtubule assembly. In humans, *TUBB4A* is expressed at low levels during CNS development. We cannot exclude that the overexpression of this gene resulting from trisomy 19p could have a deleterious effect on the stability of microtubules, which has been associated with brain malformation and abnormal neuron positioning. Regarding this, Orellana et al. [2015] and Seidel et al. [2014] described 2 patients with brain malformations and trisomy 19p that must involve the *TUBB4A* gene

(Fig. 2; Table 1). The majority of trisomy 19p13.3p13.2 patients were not screened for cerebral malformations but present neurological features that could be associated with this entity. Therefore, a cerebral imaging evaluation of these patients is of importance to achieve a complete clinical description of the brain malformations associated with trisomy 19p.

Additionally, the gene *PIAS4* (protein inhibitor of activated STAT4), which is associated with abnormal head size, is located in 19p13.3. This gene is highly conserved among different species. Xiong et al. [2012] reported in a frog embryo model that high doses of the protein encoded by the *PIAS4* orthologue reduce head structures. Moreover, Nevado et al. [2015] associated the presence of microcephaly or macrocephaly in patients with duplication or deletion of 19p13.3, respectively. Interestingly, in all the cases with trisomy 19p13.3p13.2 listed in Table 1 that show microcephaly and in whom analysis by microarrays was performed, the *PIAS4* gene is involved. Also, *SEMA6B* (semaphorin 6B) in 19p13.3 encodes a semaphorin protein family member, which is a protein that plays an important role as a regulator of morphogenesis and that is involved in neuronal connectivity and guidance of migrating neural crest and mesoderm cells [Koestner et al., 2008; Sun et al., 2018]. It is possible that copy number gains of this gene could contribute to the developmental delay and intellectual disability seen in trisomy 19p patients. The region 19p13.3p13.2 contains genes involved in epigenetic regulation (e.g., *CHAF1A*, *DOT1L*), transcription regulation (e.g., *AES*, *NFIC*), and immune response (e.g., *C3*, *TCF3*). It has been suggested that overexpression of these genes could be associated with the trisomy 19p patients' phenotypes [Seidel et al., 2014; Orellana et al., 2015].

In conclusion, this is the first reported patient with an unbalanced t(Y;19)(q12;p13.2) translocation, in whom complete characterization of a nonmosaic 19p trisomy genotype was achieved through cytogenomic and molecular analyses, and in whom genotype-phenotype correlations were studied. The genes present in the trisomic 19p region participate in neurological and heart morphogenesis, as well as in immune response. However, clinical manifestations vary in patients, even when they share trisomy of similar regions in 19p13.3p13.2. We contribute to the delineation of the spectrum of major clinical findings observed in patients with trisomy 19p13.3p13.2. Contrasting to previously reported cases, our patient demonstrates the importance of searching for pachygyria and polymicrogyria or other cortical abnormalities, which are features that have not been reported previously. This genetic entity is very uncommon, and the reports of patients with this genetic condition help to improve the description of the clinical spectrum of pure trisomy 19p, considering the relationship between the size of the chromosome segment and the genes involved.

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The authors thank the patient's family.

Statement of Ethics

Written informed consent was obtained from the parents for all genetic tests and to publish this case. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.M.A conceived the present study, performed the cytogenetic methods, interpreted the cytogenetic and cytogenomic data, and designed the figures. L.F.H. and A.G.d.A. diagnosed the patient, obtained the clinical data, and contributed a critical clinical analysis of the reported cases. M.A.A.O. performed the molecular experiments. V.U.A. contributed the conventional cytogenetic analysis. P.P.V. conceived the present idea and interpreted the cytogenomic data. D.M.A., L.F.H., A.G.d.A., M.A.A.O., and P.P.V. participated in drafting the manuscript.

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