Cytogenetic and Genome Research

Novel Insights from Clinical Practice

Cytogenet Genome Res 2020;160:589–596
DOI: 10.1159/000511235

Received: April 8, 2020
Accepted: August 20, 2020
Published online: December 14, 2020

Partial 5p Gain and 15q Loss in Three Patients from a Family with a t(5;15)(p13.3;q26.3) Translocation

Fernanda T. Bellucco Bianca P. Favilla Eduardo Perrone Maria I. Melaragno

Genetics Division, Department of Morphology and Genetics, Universidade Federal de São Paulo, São Paulo, Brazil

Established Facts

- Duplications spanning from 5p15.33 to 5p13.3 usually show a mild and relatively indistinct phenotype.
- 15q26 deletions, due to haploinsufficiency of the *IGF1R* gene, have been associated with multiple congenital anomalies, including growth deficiency, intellectual disability, and anomalies of the hands and feet.
- There is only 1 patient reported in the literature with a partial 5p13 gain associated with a terminal 15q26 loss.

Novel Insights

- We report 3 new cases of a partial 5p gain concomitant with a 15q loss due to a familial reciprocal translocation.
- In the 15q26.3 region, the *CHSY1* gene, in addition to *IGF1R*, may be responsible for the well-known clinical features that patients with 15q26 deletion present and should be considered in the genotype-phenotype correlation of these patients.
- We can not support previous reports that associated *SNRPA1* gene haploinsufficiency with the development of congenital heart defects.

Keywords
Familial reciprocal translocation · Genotype-phenotype correlation · SNP-array · 5p duplication · 15q deletion

Abstract
Several patients with 5p duplication or 15q deletion have been reported in the literature, involving different chromosome regions and clinical features. Here, we describe a family in which we identified a 30-Mb 5p15.33p13.3 gain and a 2.5-Mb 15q26.3 loss in 3 individuals, due to a balanced familial translocation between chromosomes 5p and 15q. They presented a similar combination of clinical findings related to their genetic imbalances, but there were also phenotypic differences between them. Our analyses show that their clinical picture is mostly caused by the loss in 15q and not the gain in 5p, despite its much larger size. Our findings suggest that other genes, besides the *IGF1R* gene, in the 15q26.3 re-

F.T.B. and B.P.F. contributed equally to this article.

karger@karger.com
www.karger.com/cgr

Maria I. Melaragno
Department of Morphology and Genetics
Universidade Federal de São Paulo, Rua Botucatu 740
Sao Paulo, SP 04023-900 (Brazil)
melaragno.maria@unifesp.br

gion, such as the *CHSY1* gene, may have a great impact on the clinical picture of the syndrome. Our data emphasize the importance of detailed cytogenomic and clinical analyses for an accurate diagnosis, prognosis, and genetic counseling, providing an opportunity to improve genotype-phenotype correlations of patients with partial 5p duplication and 15q deletion syndromes.

Introduction

There are few reports of patients with 5p duplication and 15q deletion in the literature, involving different chromosomal regions and a great variety of clinical features.

Trisomy of the short arm of chromosome 5 was first described by Lejeune et al. [1964], with less than 50 cases with complete or partial 5p duplications reported since then. Lorda-Sánchez et al. [1997], comparing patients with partial 5p duplications, defined a critical region (between 5p13.1 and 5p10) for the 5p duplication syndrome phenotype. Chromosome 5p13 duplication syndrome (OMIM #613174), a contiguous gene syndrome involving duplication of several genes in chromosome 5p13, including the nipped-B-like (*NIPBL*) gene (OMIM *608667), has been described in rare patients with developmental delay, learning disability, behavioral problems, and facial dysmorphisms. The clinical findings in cases with complete 5p duplication and with duplications involving the 5p13.1p10 segment are more severe than the cases with duplications spanning from 5p15.33 to 5p13.3 [Izzo et al., 2012].

Terminal deletions of the long arm of chromosome 15, on the other hand, are responsible for a variety of clinical features and multiple congenital abnormalities [Tümer et al., 2004; Li et al., 2008], being associated with growth deficiency, intellectual disability, breathing problems at birth, feeding difficulties, abnormal facial features, and anomalies of the hands and feet [Poot et al., 2013; Szabó et al., 2018]. Chromosome 15q26 deletion syndrome (OMIM #612626) has been described in a few patients with such clinical features. Although its molecular basis relies on a 5.8-Mb deletion of this region, encompassing the insulin-like growth factor 1 receptor (*IGF1R*) gene (OMIM *147370), smaller deletions that do not include this gene have also been described and associated with variable phenotypes of the syndrome [Poot et al., 2013; Szabó et al., 2018]. There is great clinical variability among the patients with 15q26 deletions, even when they present deletions of the same size. Thus, even though the size of the deletion and the haploinsufficiency of the genes within the region may have a phenotypic effect, other genetic mechanisms may also be involved and need to be investigated [Poot et al., 2013].

To the best of our knowledge, there is only 1 report in the literature of partial 5p trisomy associated with terminal 15q monosomy [Sagi-Dain et al., 2017]. Here, we describe a family with 2 generations of affected individuals with a 15q loss and 5p gain due to a familial balanced translocation t(5;15)(p13.3;q26.3).

Clinical Report

All patients were evaluated by the geneticists of the Medical Genetics Center of the Universidade Federal de São Paulo. The summarized clinical data of the patients are presented in Table 1, and the family's pedigree is shown in Figure 1a.

Patient 1 (IV-1)

The proband, a male patient, was first referred for genetic assessment at the age of 6 years and 10 months due to neurodevelopmental delay and obesity. Pre- and neonatal periods were unremarkable. During the first years of his life, he presented failure to thrive, but at age 5 years, he developed hyperphagia, starting to gain weight. On review of his milestones, he was sitting without support at 9 months, walking at 1 year and 4 months, and saying his first words at age 3 years, with a significant neurodevelopmental delay. By the age of his first evaluation, he was still not elaborating complete sentences, and as soon as he started going to school, a learning disability became evident. On physical examination, his measurements revealed short stature (1.08 m, –2.49 SD), normal occipital frontal circumference (51 cm), and obesity (27 kg, +1.85 SD; BMI 23.2 kg/m^2, +3.37 SD). On morphological examination, he showed malar flattening, depressed nasal bridge, sparse and arched eyebrows, convergent strabismus, downslanting palpebral fissures, retrognathia and high palate, downturned corners of the mouth, tapering fingers, brachydactyly with fifth finger clinodactyly, absent fourth finger distal interphalangeal creases, short neck, and typical male genitalia. Complementary exams showed normal ophthalmological evaluation, brain CT, skeletal X-ray, and echocardiography. At the age of 18 years (Fig. 1b–d), he still showed obesity (BMI 36.7 kg/m^2, +3.22 SD) and presented proportionate short stature (1.58 m, –2.44 SD). Due to obesity, he presented sleep apnea episodes, demanding an otorhinolaryngological evaluation. An abdominal ultrasound was performed, unveiling mild liver steatosis, probably due to obesity as well. He was still having poor academic performance as he had not learned reading or writing yet.

Patient 2 (IV-5)

This patient is the proband's sister. She was referred to our clinic because of her brother's history of neurodevelopmental delay. At age 1 year and 3 months, she presented short stature (66.5 cm, –3.77 SD) and was underweight (6.3 kg, –3.54 SD); her OFC was 44.5 cm (–1 SD). A neurodevelopmental delay was suggested since she was not able to walk, and she could only sit with support at 8

Table 1. Clinical features of patients with 15q26.2qter monosomy and/or 5p13pter trisomy

Clinical features	15q26.2qter deletion (with *IGF1R* deletion)[a]	15q26.3qter deletion (no *IGF1R* deletion)[b]	15q26 deletion and 5p13.3 duplication				5p13.3pter duplication[c]
			present article			Sagi-Dain et al., 2017	
			patient 1	patient 2	patient 3		
Number of patients	16	12				1	12
Sex	11 F, 5 M	9 F, 3 M	M	F	M	M	7 F, 4 M
Intrauterine growth restriction	4/12	3/3	–	–	–	+	0/7
Neurodevelopmental delay	15/16	6/6	+	+	NA	+	6/7
Intellectual disability	9/9	5/5	+	+	+	NA	9/10
Hypertonia	0/11	0/1	–	–	NA	+	5/10
Central nervous system anomalies	3/6	1/1	–	–	–	+	2/4
Obesity (truncal obesity)	6/16	2/4	+	+	+	–	0/7
Polyphagia	2/13	0/1	+	–	NA	–	0/7
Mild chronic gastritis	0/0	0/1	–	–	–	+	0/0
Short stature	16/16	8/9	+	+	+	+	4/12
Malar flattening	0/12	0/3	+	–	NA	–	0/11
Broad forehead	1/12	0/3	–	–	NA	+	1/6
Bulbous nose	0/12	0/3	+	+	NA	–	5/12
Broad/depressed nasal bridge	6/12	1/3	+	–	NA	+	3/12
Hypermetropia	0/3	0/0	–	+	NA	–	1/6
Strabismus	3/11	1/4	–	+	NA	–	3/12
Hypertelorism	3/11	1/3	–	+	NA	–	1/12
Eyebrow abnormalities	3/11	0/3	+	+	NA	–	2/11
Downslanting palpebral fissures	3/11	0/3	+	+	NA	–	1/12
Ear anomalies	4/12	0/3	–	+	NA	–	7/12
Hearing impairment	3/3	0/0	–	–	NA	+	0/0
Retrognathia/micrognathia	5/13	2/3	+	+	NA	–	5/12
High/arched palate	0/11	2/3	+	–	NA	–	5/9
Downturned corners of the mouth	4/12	1/4	+	+	NA	–	1/12
Short neck	3/12	0/3	+	+	NA	–	4/12
Pectus excavatum	0/11	0/3	–	+	NA	–	0/5
Joint hypermobility	3/11	0/0	–	–	NA	+	0/2
Small hands	4/13	0/0	+	+	+	–	0/10
Tapering fingers	2/13	0/1	+	–	NA	–	0/10
Brachydactyly	5/12	0/1	+	+	+	–	0/10
Fifth finger clinodactyly	7/13	0/1	+	+	NA	–	6/10
Absent distal interphalangeal crease	1/13	0/1	+	–	NA	–	0/10

+, present; –, absent; NA, not available. [a] Pinson et al., 2005; Rujirabanjerd et al., 2007; Rump et al., 2008; Walenkamp et al., 2008; Ester et al., 2009; Bruce et al., 2010; Lin et al., 2010; Dateki et al., 2011; Rudaks et al., 2011; Poot et al., 2013; O'Riordan et al., 2017; Santos et al., 2020. [b] Lucaccioni et al., 2015; Szabó et al., 2018; DECIPHER: 270050, 265742, 401263, 251400, 353687, 331451, 331238, 286496, 280979. [c] Chia et al., 1987; Webb et al., 1988; Rethoré et al., 1989; Zenger-Hain et al., 1993; Chen et al., 1995; Baialardo et al., 2003; Cervera et al., 2005.

months. Her morphological evaluation showed low-set ears, pectus excavatum, and sparse eyebrows. At 14 years and 4 months (Fig. 1e–g), her morphological evaluation revealed proportionate short stature (1.35 m, –3.2 SD) and obesity (BMI 27.9 kg/m^2, +2.03 SD). The patient, unlike her brother, did not present hyperphagia at the time of evaluation. Her learning disability, on the other hand, had become more evident, as the patient was not able to read or write. Her morphological examination revealed convergent strabismus, ocular hypertelorism, low-set ears, short neck, downturned corners of the mouth, downslanting palpebral fissures, retrognathia, brachydactyly, and fifth finger clinodactyly. The patient was treated with growth hormone, owing to growth hormone deficiency. An ophthalmological examination showed hypermetropia and convergent strabismus.

Patient 3 (III-12)

Patient 3 is the uncle of patients 1 and 2, and the only available clinical information is the presence of intellectual disability, short stature (1.48 m; <2 SD), and obesity (BMI 31 kg/m^2). We could not properly evaluate this patient, but his blood samples were collected for karyotype.

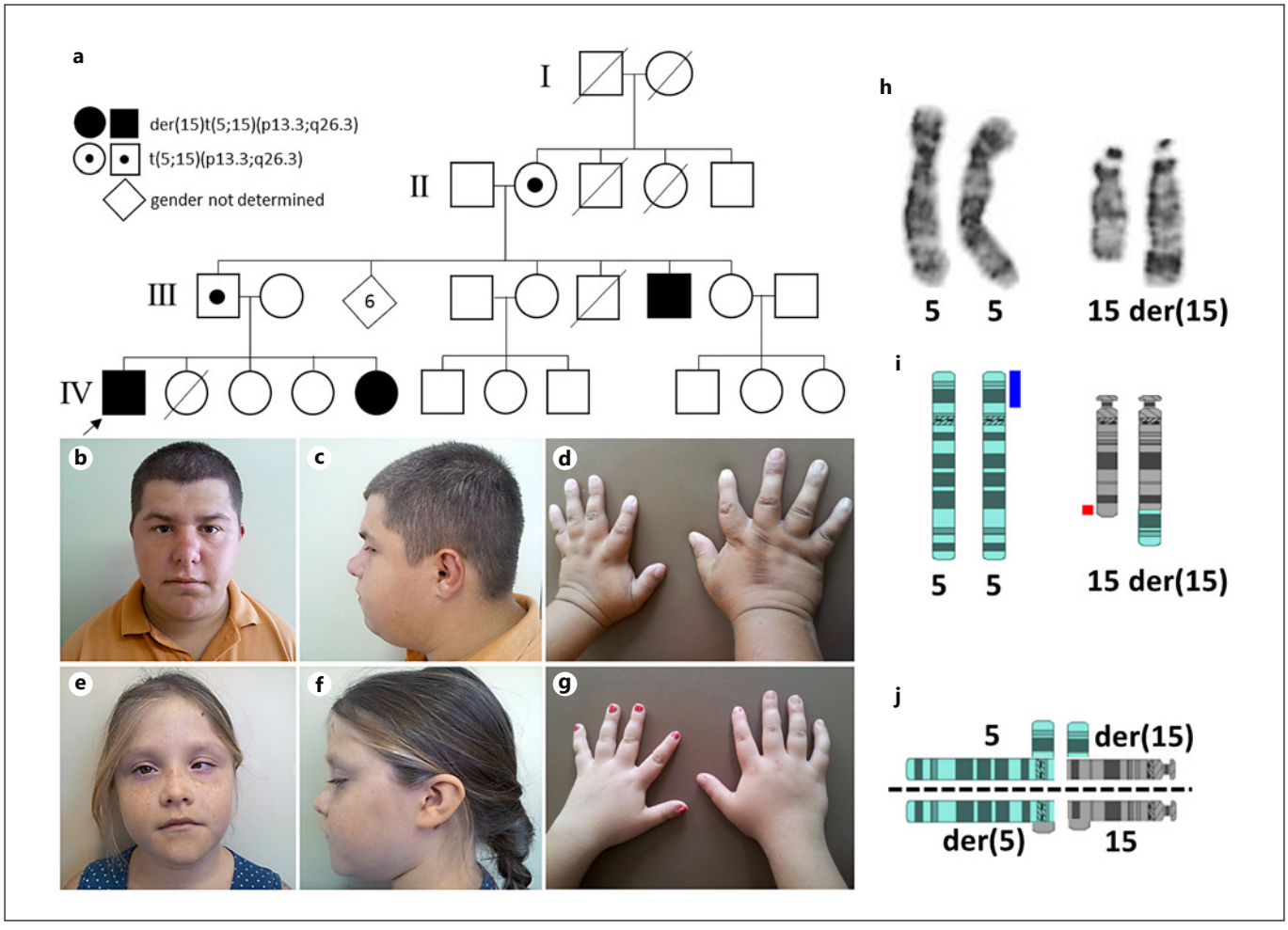

Fig. 1. a Family pedigree. **b–g** Patients IV-1 (**b**–**d**) and IV-5 (**e**–**g**) showing facial dysmorphisms, fifth finger clinodactyly, and brachydactyly. **h**, **i** Partial karyotype (**h**) and idiograms (**i**) of the chromosomes involved in the translocation. Blue and red bars indicate the gain and loss on chromosomes 5 and 15, respectively. **j** Scheme of chromosomes 5 and 15 paired in pachytene during meiosis. The dashed line along the longest chromosome arms in the quadrivalent figure indicates the preferential 2:2 adjacent-1 segregation mode.

Cytogenetic and Gene Pathogenicity Analysis

A G-banding karyotype was performed using peripheral blood lymphocyte cultures according to standard procedures. The results showed a der(15)t(5;15)(p13.3;q26.3) in the proband (IV-1), originating from a balanced reciprocal translocation between 5p13.3 and 15q26.3 found in his father (III-1). Further cytogenetic analyses in the family also identified the balanced t(5;15)(p13.3;q26.3) translocation in the proband's grandmother (II-2) and the derivative chromosome 15 in the proband's paternal uncle (III-12) and in one of his sisters (IV-5). His mother and his 2 other sisters had normal results (Fig. 1a, h, i).

DNA was isolated from peripheral blood using the Gentra Puregene kit (Qiagen Sciences Inc., Germantown, MD, USA), and the array assay was performed using the Genome-Wide Human SNP 6.0 array (Affymetrix, Santa Clara, CA, USA) for the proband and his affected sister. The array showed a terminal 5p15.33p13.3 gain of about 30 Mb and a terminal 15q26.3 loss of about 2.5 Mb. The cytogenomic result of the affected patients was given as 46,XX or XY,der(15)t(5;15)(p13.3;q26.3).arr[GRCh37] 5p15.33p13.3 (15519_30629115)×3,15q26.3(99829402_102400037)×1, according to ISCN [2016].

The pathogenicity of the 15q loss and the 5p gain was assessed using the AnnotSV tool (Version 2.3), which

compiles regulatory and clinically relevant information for the annotation and ranking of structural variations, considering the genes present in the deleted or duplicated region and the data from the DGV, DDD, dbVar, ExAC, ClinGen, gnomAD, and OMIM databases [Geoffroy et al., 2018]. In our patients' rearrangement, a slightly higher intolerance to the 15q26.3qter loss (*Z* score: 1.17×10^{14}) compared to the 5p15.33p13.3 gain (1.09×10^{14}) was observed, according to the ExAC's gene intolerance annotation. Regarding the genes within the regions, 76 coding genes were reported and classified according to the tool's parameters. Thirteen coding genes were reported in the 15q region, and 63 coding genes in the 5p region. Among those, 4 genes were classified as pathogenic (3 in the 15q26.3 region, 1 in the 5p15.2 region), and 6 as likely pathogenic (3 in the 15q26 region and 3 in the 5p15.3 region). Since the AnnotSV classification relies on the gene's morbidity, whether it is related to the nature of the variant (i.e., loss or gain) or not, we also evaluated the genes regarding their haploinsufficiency (pLI score and haploinsufficiency index) or triplosensitivity (triplosensitivity score) scores based on their location. Online supplementaryTable1(seewww.karger.com/doi/10.1159/000511235) sums up these data.

Discussion

Here, we describe 3 patients in the same family with a concomitant 5p15.33p13.3 gain and a 15q26.3qter loss due to a balanced familial translocation between chromosomes 5p and 15q.

According to the family's pedigree (Fig. 1a), all the individuals with the unbalanced translocation presented a normal chromosome 5 and the derivative chromosome 15. This chromosome constitution originated from 2:2 adjacent-1 segregation of the balanced translocation. This segregation mode, which results in gametes with one normal chromosome and the nonhomologous derivative chromosome from the other pair involved in the translocation, is most capable of originating viable abnormal offspring [Gardner and Amor, 2018]. In the translocation t(5;15)(p13.3;q26.3), adjacent-1 segregation results in the smallest gain and loss of material, consequently, being the most viable imbalance. The zygotes formed with the corresponding opposite combination of imbalances, with a normal chromosome 15 and a derivative chromosome 5, would result in a loss of 5p together with a gain of 15q, a situation that can be less compatible with life even though monosomy 5p is a viable genomic imbalance, but probably less viable than its correspondent gain (Fig. 1j).

Even though there have been several reports of patients with deletions or duplications involving one of these chromosomes, there is only 1 patient reported in the literature, described by Sagi-Dain et al. [2017], who presented a 5p15.33p14.2 terminal gain associated with a 15q26.2q26.3 terminal loss.

Our patients and the one described by Sagi-Dain et al. [2017] present clinical features related to both 5p and 15q imbalances, but their clinical picture is quite different. They all present neurodevelopmental delay and short stature, but overall, they have different phenotypic characteristics: all our patients have obesity, intellectual disability, bulbous nose, sparse and arched eyebrows, downslanting palpebral fissures, retrognathia, short neck, and anomalies of the hands and feet, including brachydactyly and fifth finger clinodactyly, whereas Sagi-Dain's patient presented broad forehead, hearing impairment, and joint hypermobility (Table 1). Their facial abnormalities, as well as the neurodevelopmental delay, are commonly associated with both genetic imbalances [Zenger-Hain et al., 1993; Cervera et al., 2005; Ester et al., 2009; Poot et al., 2013], whereas the skeletal anomalies, hearing impairment, joint hypermobility, and short stature have been widely seen in patients with 15q26.3 deletion [Rump et al., 2008; Rudaks et al., 2011; O'Riordan et al., 2017]. The differences observed between our patients' phenotypic characteristics and those of the patient described by Sagi-Dain et al. [2017] (Fig. 1; Table 1) may be partially explained by the distinct sizes of the losses and gains that they present; although similar, our patients' rearrangement includes a much larger gain on 5p and a smaller loss on 15q.

It is also important to note that despite presenting the same rearrangement and breakpoint, the siblings reported here also have different clinical characteristics. The proband, for instance, is the only one who presents aplasia of the distal interphalangeal creases and malar flattening, which has never been described in either of the genetic imbalances. Likewise, tapering fingers, polyphagia, which has been recently associated with 15q26.3 deletion [O'Riordan et al., 2017; Santos et al., 2020], as well as depressed nasal bridge and high palate, which are common characteristics for both syndromes, were only identified in this patient. His sister, on the other hand, is the only one who presents abnormalities of the ears, which are associated with both syndromes, and pectus excavatum, which had been associated with the 15q26.3 deletions only (Table 1).

Such divergences, as well as the ones seen in patients with distinct breakpoints, can be due to each patient's dif-

ferent genetic background, which may play a role in the penetrance and the expressivity of the phenotypes, modulating them and leading to a variable clinical spectrum [Zlotogora, 2003; Klaassen et al., 2016] which is seen in both syndromes.

According to our pathogenicity analysis, the likely pathogenic genes in the 15q26.3 region have a high loss-of-function intolerance, indicated by the high gnomAD pLI score (online suppl. Table 1). However, concerning the genes classified as likely pathogenic within the 5p region, there is no evidence for pathogenicity related to gain, which can be noticed by their triplosensitivity scores (online suppl. Table 1).

All the genes classified as likely pathogenic by the AnnotSV tool in the 5p duplicated region are morbid genes, but their pathogenicity is related to nonfunctional proteins and not to increased dose. The dynein, axonemal, heavy chain 5 (*DNAH5*) gene (OMIM *603335), on the other hand, was classified as pathogenic due to the existence of 3 pathogenic copy number gain structural variants involving it, described in the dbVar. However, ciliary dyskinesia that is related to the copy number gain in the patients from dbVar cannot be seen in our patients. Thus, even though our patients present phenotypic characteristics that can be related to both, the 15q loss and the 5p gain, the 15q26.3 terminal loss seems to play a crucial role in establishing their clinical picture, despite being significantly smaller than the 5p gain.

In fact, depending on the size and the genes involved, patients with 5p13 duplications may present variable clinical features. It has been previously established that duplications encompassing the *NIPBL* gene (OMIM *608667) tend to cause a more severe phenotype, as well as duplications involving the 5p13.1p10 region or the whole short arm. Our patients' gain, on the other hand, spans from 5p15.33 to 5p13.3, which usually shows mild and relatively indistinct phenotypes [Izzo et al., 2012].

Patients with 15q26 monosomies also present a wide clinical variability that occurs even when the rearrangements have exactly the same breakpoint, which is the case of the siblings reported herein. As discussed previously, although other genetic mechanisms might be responsible for such variable phenotypes, making it hard to establish a clear correlation between the size of the deletion and the patients' clinical features, high-resolution mapping of the breakpoints supported the establishment of a contiguous gene 15q26 deletion model [Veenma et al., 2010].

Deletions of the 15q26.2qter region, for instance, have been described in a few patients with intrauterine and postnatal growth retardation, congenital heart defects, intellectual disability, triangular facial shape, skeletal anomalies such as clinodactyly and brachydactyly, and other minor abnormalities related to the shape of the nasal bridge and the eyes [Rump et al., 2008; Ester et al., 2009; Rudaks et al., 2011; Poot et al., 2013; O'Riordan et al., 2017; Szabó et al., 2018; Santos et al., 2020]. Haploinsufficiency of the *IGF1R* gene has been postulated as the main cause of most of these clinical features since they are similar to the ones caused by single mutations in this gene [Walenkamp et al., 2008] as well as its partial deletion [Veenma et al., 2010], especially in regard to growth deficiency.

However, when smaller deletions of the 15q26.3 region, not including the *IGF1R* gene, were considered, we noticed that they were also associated with short stature (Table 1). Among these patients, our patients also present short stature and some clinical features that are associated with *IGF1R* haploinsufficiency, such as clinodactyly, brachydactyly, and facial abnormalities, as postulated by Veenma et al. [2010], even though their 15q26.3 loss does not include the *IGF1R* gene. Szabó et al. [2018] described a patient with a 1-Mb terminal deletion of 15q26.3 and also observed that short stature can occur in patients with 15q26 deletions with no loss of the *IGF1R* gene, suggesting that its haploinsufficiency may not be the only cause of growth delay in those patients and that the deletion of the genomic region distal to the gene might as well play a role in growth disturbance.

By analyzing the overlap of the deletions in the patients with terminal 15q26.3 deletion and no loss of the *IGF1R* gene (Table 1), we could narrow down the region responsible for the short stature in 15q26.3 to 1 Mb, from 100.8 to 102 Mb. Within the narrowed 15q26.3 region, the chondroitin sulfate synthase 1 (*CHSY1*) gene (OMIM 608183), for example, is a good candidate for such a phenotype. It was classified as pathogenic by the AnnotSV tool, and it has already been associated with short stature, brachydactyly, micrognathia, and variable degrees of learning disabilities [Tian et al., 2010], being responsible for the Temtamy preaxial brachydactyly syndrome (OMIM #605282). Despite its association with an autosomal recessive phenotype and a mild intolerance to loss of function (pLI = 0.710) (online suppl. Table 1), it presents one of the highest intolerances to deletion in the 15q26.3 region, according to the ExAC database (*Z* score 0.68), which could indicate that the deletion of one allele may indeed have impacted its function.

The 15q26.3 deleted region in our patients includes 12 other coding genes, from which 3 were predicted to be likely pathogenic and 2 pathogenic, according to the AnnotSV

tool (online suppl. Table 1). Among the genes classified as pathogenic within the 15q26.3 region, the ADAM metallopeptidase with thrombospondin type 1 motif 17 (*ADAMTS17*) gene (OMIM 607511) presents 2 pathogenic copy number losses involving it, in the dbVar database. Besides that, homozygous mutations in this gene have already been associated with the Weill-Marchesani-like syndrome (OMIM #613195), an autosomal recessive disorder characterized by severe myopia, microspherophakia, glaucoma, cataract, and other features such as short stature and brachydactyly [Khan et al., 2012; Shah et al., 2014]. Although our patients present short stature and brachydactyly, the lack of more classical signs of the syndrome, especially the eye abnormalities, suggests that those features may be related to the haploinsufficiency of other genes as well.

The genes classified as likely pathogenic in the 15q26.3 region (*MEF2A*, *ASB7*, and *SNRPA1*) are genes that present high intolerance to loss of function and haploinsufficiency scores. The small nuclear ribonucleoprotein polypeptide A-prime (*SNRPA1*) gene, for instance, has a haploinsufficiency index of 10.5%, indicating that it is more likely to exhibit haploinsufficiency, and an ExAc pLI score of 0.990, which indicates that it is also extremely intolerant to loss of function. Even though there is no OMIM phenotype related to the gene, some of its polymorphisms have been associated with cardiovascular disease [Cox et al., 2013; Flaquer et al., 2013], and its haploinsufficiency was reported as a candidate for congenital heart defects in a patient with a 15q26 deletion [Szabó et al., 2018]. Our patients do not present any cardiac defects, despite the deletion of the gene, so we cannot confirm the role of *SNRPA1* in cardiac malformations. Regarding the other genes classified as likely pathogenic within the region, we could not identify any phenotypic characteristic related to their haploinsufficiency in our patients either.

Our data indicate that the variable clinical pictures seen in patients with 5p duplications and 15q deletions occur even when the patients share the same breakpoints. This highlights the importance of investigating other mechanisms that may impact the complete expression of a phenotype. Besides that, our findings emphasize the importance of detailed cytogenomic and clinical analyses for an accurate diagnosis, prognosis, and genetic counseling, and they also provide an opportunity to improve genotype-phenotype correlations of patients with partial 5p duplications and 15q terminal deletions.

Statement of Ethics

This study was approved by the Ethics Commission of the Universidade Federal de São Paulo, and informed written consent was obtained from the participating subjects.

Conflict of Interest Statement

All authors declare no conflict of interests.

Funding Sources

This work was supported by FAPESP, Brazil (grant #2014/11,572-8 to M.I.M.) and CAPES.

Author Contributions

All authors discussed the results and provided critical feedback to the manuscript. F.T.B. and B.P.F. contributed to the design of the work, the analysis and interpretation of the genomic data, and writing of the manuscript. E.P. performed the clinical evaluation of the patients and contributed to the genotype-phenotype correlation. M.I.M. contributed to the final version of the manuscript, revised the manuscript critically, and supervised the project.

References

Baialardo EM, Torrado MdV, Barreiro CZ, Gallego MS. Partial distal 5p trisomy resulting from paternal translocation (5;15)(p15.1;p13) in a boy with no mental retardation. Clin Dysmorphol. 2003;12(4):257–9.

Bruce S, Hannula-Jouppi K, Puoskari M, Fransson I, Simola KOJ, Lipsanen-Nyman M, et al. Submicroscopic genomic alterations in Silver–Russell syndrome and Silver–Russell-like patients. J Med Genet. 2010;47(12):816–22.

Cervera M, Sánchez S, Molina B, Alcántara MA, Del Castillo V, Carnevale A, et al. Trisomy of the short arm of chromosome 5 due to a de novo inversion and duplication (5)(p15.3 p13.3). Am J Med Genet A. 2005;136A:381–5.

Chen H, Hoffman WH, Kusyk CJ, Tuck-Muller CM, Hoffman MG, Davis LS. De novo dup (5p) in a patient with congenital hypoplasia of the adrenal gland. Am J Med Genet. 1995;55(4):489–93.

Chia NL, Bousfield LR, Johnson BH. A case report of a de novo tandem duplication (5p) (p14---pter). Clin Genet. 1987;31(2):65–9.

Cox AJ, Lehtinen AB, Xu J, Langefeld CD, Freedman BI, Carr JJ, et al. Polymorphisms in the selenoprotein S gene and subclinical cardiovascular disease in the Diabetes Heart Study. Acta Diabetol. 2013;50(3):391–9.

Dateki S, Fukami M, Tanaka Y, Sasaki G, Moriuchi H, Ogata T. Identification of chromosome 15q26 terminal deletion with telomere sequences and its bearing on genotype-phenotype analysis. Endocr J. 2011;58(3):155–9.

Ester WA, van Duyvenvoorde HA, de Wit CC, Broekman AJ, Ruivenkamp CA, Govaerts LC, et al. Two short children born small for gestational age with insulin-like growth factor 1 receptor haploinsufficiency illustrate the heterogeneity of its phenotype. J Clin Endocrinol Metab. 2009;94(12):4717–27.

Flaquer A, Baumbach C, Piñero E, García Algas F, de la Fuente Sanchez MA, Rosell J, et al. Genome-wide linkage analysis of congenital heart defects using MOD score analysis identifies two novel loci. BMC Genet. 2013;14:44.
Gardner RJM, Amor DJ, editors. Chromosome Abnormalities and Genetic Counseling. 5th ed. New York: Oxford University Press; 2018.
Geoffroy V, Herenger Y, Kress A, Stoetzel C, Piton A, Dollfus H, et al. AnnotSV: an integrated tool for structural variations annotation. Bioinformatics. 2018;34(20):3572–4.
ISCN 2016. An International System for Human Cytogenomic Nomenclature. McGowan-Jordan J, Simons A, Schmid M, editors. Cytogenet Genome Res. 2016;149(1–2):1–140.
Izzo A, Genesio R, Ronga V, Nocera V, Marullo L, Cicatiello R, et al. 40 Mb duplication in chromosome band 5p13.1p15.33 with 800 kb terminal deletion in a foetus with mild phenotypic features. Eur J Med Genet. 2012;55(2):140–4.
Khan AO, Aldahmesh MA, Al-Ghadeer H, Mohamed JY, Alkuraya FS. Familial spherophakia with short stature caused by a novel homozygous ADAMTS17 mutation. Ophthalmic Genet. 2012;33(4):235–9.
Klaassen P, Duijff S, Swanenburg de Veye H, Beemer F, Sinnema G, Breetvelt E, et al. Explaining the variable penetrance of CNVs: Parental intelligence modulates expression of intellectual impairment caused by the 22q11.2 deletion. Am J Med Genet B Neuropsychiatr Genet. 2016;171:790–6.
Lejeune J, Lafourcade J, Berger R, Turpin R. Familial segregation of a 5–13 translocation determining partial monosomy and a trisomy of the short arm of the 5 chromosome: "cat cry" disease and its "receprocal". C R Hebd Seances Acad Sci. 1964;258:5767–70.
Li MM, Nimmakayalu MA, Mercer D, Andersson HC, Emanuel BS. Characterization of a cryptic 3.3 Mb deletion in a patient with a "balanced t(15;22) translocation" using high density oligo array CGH and gene expression arrays. Am J Med Genet A. 2008;146A:368–75.
Lin SY, Lee CN, Hung CC, Tsai WY, Lin SP, Li NC, et al. Epigenetic profiling of the H19 differentially methylated region and comprehensive whole genome array-based analysis in Silver-Russell syndrome. Am J Med Genet A. 2010;152A:2521–8.
Lorda-Sánchez I, Urioste M, Villa A, Carrascosa MC, Vázquez MS, Martínez A, et al. Proximal partial 5p trisomy resulting from a maternal (19;5) insertion. Am J Med Genet. 1997;68(4):476–80.
Lucaccioni L, Madeo SF, Stanghellini I, Bruzzi P, Predieri B, Iughetti L, et al. Familial short stature associated to terminal microdeletion of 15q26.3: variable phenotype not involving the IGF-1 receptor gene. ESPE Abstracts, P3-919. Horm Res Paediatr. 2015;84(suppl 1):446.
O'Riordan AM, McGrath N, Sharif F, Murphy NP, Franklin O, Lynch SA, et al. Expanding the clinical spectrum of chromosome 15q26 terminal deletions associated with IGF-1 resistance. Eur J Pediatr. 2017;176(1):137–42.
Pinson L, Perrin A, Plouzennec C, Parent P, Metz C, Collet M, et al. Detection of an unexpected subtelomeric 15q26.2 --> qter deletion in a little girl: clinical and cytogenetic studies. Am J Med Genet A. 2005;138A:160–5.
Poot M, Verrijn Stuart AA, van Daalen E, van Iperen A, van Binsbergen E, Hochstenbach R. Variable behavioural phenotypes of patients with monosomies of 15q26 and a review of 16 cases. Eur J Med Genet. 2013;56:346–50.
Rethoré MO, Blois MC, Peeters M, Popowski P, Pangalos C, Lejeune J. Pure partial trisomy of the short arm of chromosome 5. Hum Genet. 1989;82:296–8.
Rudaks LI, Nicholl JK, Bratkovic D, Barnett CP. Short stature due to 15q26 microdeletion involving IGF1R: report of an additional case and review of the literature. Am J Med Genet A. 2011;155A(12):3139–43.
Rujirabanjerd S, Suwannarat W, Sripo T, Dissaneevate P, Permsirivanich W, Limprasert P. De novo subtelomeric deletion of 15q associated with satellite translocation in a child with developmental delay and severe growth retardation. Am J Med Genet A. 2007;143A:271–6.
Rump P, Dijkhuizen T, Sikkema-Raddatz B, Lemmink HH, Vos YJ, Verheij JBGM, et al. Drayer's syndrome of mental retardation, microcephaly, short stature and absent phalanges is caused by a recurrent deletion of chromosome 15(q26.2-->qter). Clin Genet. 2008;74:455–62.
Sagi-Dain L, Goldberg Y, Berger R, Peleg A. Familial Translocation t(5;15)(p14.2;q26.2) Causing a Mirror Combination of Several Known Genetic Conditions. J Pediatr Neurol. 2017;15:332–7.
Santos JF, Acosta AX, Scheibler GG, Pitanga PML, Alves ES, Meira JGC, et al. Case of 15q26-qter deletion associated with a Prader-Willi phenotype. Eur J Med Genet. 2020;63:103955.
Shah MH, Bhat V, Shetty JS, Kumar A. Whole exome sequencing identifies a novel splice-site mutation in ADAMTS17 in an Indian family with Weill-Marchesani syndrome. Mol Vis. 2014;20:790–6.
Szabó A, Czakó M, Hadzsiev K, Duga B, Bánfai Z, Komlósi K, et al. Small supernumerary marker chromosome 15 and a ring chromosome 15 associated with a 15q26.3 deletion excluding the IGF1R gene. Am J Med Genet. 2018;176(2):443–9.
Tian J, Ling L, Shboul M, Lee H, O'Connor B, Merriman B, et al. Loss of CHSY1, a secreted FRINGE enzyme, causes syndromic brachydactyly in humans via increased NOTCH signaling. Am J Hum Genet. 2010;87(6):768–78.
Tümer Z, Harboe TL, Blennow E, Kalscheuer VM, Tommerup N, Brøndum-Nielsen K. Molecular cytogenetic characterization of ring chromosome 15 in three unrelated patients. Am J Med Genet A. 2004;130A(4):340–4.
Veenma DC, Eussen HJ, Govaerts LC, de Kort SW, Odink RJ, Wouters CH, et al. Phenotype-genotype correlation in a familial IGF1R microdeletion case. J Med Genet. 2010;47(7):492–8.
Walenkamp MJ, de Muinck Keizer-Schrama SM, de Mos M, Kalf ME, van Duyvenvoorde HA, Boot AM, et al. Successful long-term growth hormone therapy in a girl with haploinsufficiency of the insulin-like growth factor-I receptor due to a terminal 15q26.2->qter deletion detected by multiplex ligation probe amplification. J Clin Endocrinol Metab. 2008;93(6):2421–5.
Webb GC, Voullaire LE, Rogers JG. Duplication of a small segment of 5p due to maternal recombination within a paracentric shift. Am J Med Genet. 1988;30:875–81.
Zenger-Hain JL, Van Dyke DL, Wiktor A, Walker H, Feldman GL. Inverted duplication of chromosome 5p14p15.3 confirmed with in situ hybridization. Am J Med Genet. 1993;47(8):1198–201.
Zlotogora J. Penetrance and expressivity in the molecular age. Genet Med. 2003;5(5):347–52.