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# Recurrent Copy Number Variants Associated with Syndromic Short Stature of Unknown Cause

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**Keywords**

Short stature · Chromosomal microarray · Copy number variants · Recurrent copy number variants · Array-based comparative genomic hybridization · Single nucleotide polymorphism array

**Abstract**

***Background/Aims:*** Genetic imbalances are responsible for many cases of short stature of unknown etiology. This study aims to identify recurrent pathogenic copy number variants (CNVs) in patients with syndromic short stature of unknown cause. ***Methods:*** We selected 229 children with short stature and dysmorphic features, developmental delay, and/or intellectual disability, but without a recognized syndrome. All patients were evaluated by chromosomal microarray (array-based comparative genomic hybridization/single nucleotide polymorphism array). Additionally, we searched databases and previous studies to recover recurrent pathogenic CNVs associated with short stature. ***Results:*** We identified 32 pathogenic/probably pathogenic CNVs in 229 patients. By reviewing the literature, we selected 4 previous studies which evaluated CNVs in cohorts of patients with short stature. Taken together, there were 671 patients with short stature of unknown cause evaluated by chromosomal microarray. Pathogenic/probably pathogenic CNVs were identified in 87 patients (13%). Seven recurrent CNVs, 22q11.21, 15q26, 1p36.33, Xp22.33, 17p13.3, 1q21.1, 2q24.2, were observed. They are responsible for about 40% of all pathogenic/probably pathogenic genomic imbalances found in short stature



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patients of unknown cause. ***Conclusion:*** CNVs seem to play a significant role in patients with short stature. Chromosomal microarray should be used as a diagnostic tool for evaluation of growth disorders, especially for syndromic short stature of unknown cause. 

## Introduction

Short stature is a common reason for children to be evaluated by a specialist. The etiology of short stature is heterogeneous and, usually, the diagnostic approach to this condition is based on clinical evaluation complemented by laboratory and radiological exams [1–3]. Even though many short stature cases remain without a specific diagnosis, it is estimated that a large fraction of this short stature of unknown etiology has a genetic cause. The genetic evaluation of short stature is important not only for diagnosis, but also to provide additional information to the patients and their families regarding natural history, prognosis, available treatment, and precise genetic counseling [4]. For decades, candidate gene approaches have been applied in the molecular-genetic investigation of children with growth disorders. However, the genetic heterogeneity in short stature conditions, the rarity of some diseases, and the considerable variability in phenotypes may impair an etiological diagnosis based only on this approach [5, 6]. Recently, with the advent of new technologies, a genomic approach arose as an important strategy for genetic investigation and to establish the etiology of growth disorders [5, 6].

In this scenario, analyses of chromosomal copy number variants (CNVs) have provided an opportunity to identify the genetic basis of several human diseases. Array-based genomic copy number analyses, including array-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism arrays (SNPa), allow detecting and mapping submicroscopic deletions and duplications with higher sensitivity and resolution [7]. Recent studies have identified pathogenic or probably pathogenic CNVs in 10–16% of children with short stature of unknown cause [8–11], usually in patients with additional malformations and/or neurodevelopmental disorders. Results have shown that rare CNVs contribute as significant genetic causes to short stature in these patients and also reveal novel potential candidate related-genes and/or loci [8–12].

Based on these observations, the objective of this study was to determine the frequency of rare CNVs and to describe novel CNVs in a large cohort of patients with syndromic short stature of unknown cause. We also reviewed the scientific literature regarding CNVs in short stature, to identify recurrent pathogenic or probably pathogenic CNVs associated with this condition.

## Materials and Methods

*Subjects*

The Local Ethics Committee approved this study, and the patients and/or their guardians gave written informed consent. The cohort consisted on 229 patients from a pediatric endocrinology outpatient clinic ($n$ = 62) and from a University Genetic Center ($n$ = 167) referred for molecular genetic investigation. The patients from the pediatric endocrinology outpatient clinic were included based on the following criteria: short stature at the age of 2 years or above (height standard deviation score ≤2) and presence of dysmorphic features, developmental delay, and/or intellectual disability, but without a recognized syndrome. The patients from the University Genetic Center were referred for chromosome microarray analysis for presenting intellectual disability or developmental delay; included among them in this study were those patients with short stature (standard deviation score ≤2), many of them presenting additional clinical signs. All patients had normal G-banded karyotyping.

*Methods*

Genomic DNA was extracted from peripheral blood leukocytes of all patients using standard procedures. aCGH ($n$ = 71) or SNP array ($n$ = 168) were performed according to availability. All experiments were conducted according to the standard protocol of the manufacturer or previously published data [10, 13]. aCGH was performed in a whole-genome 180 K platform (Agilent Technologies, Inc., Santa Clara, CA, USA). Microarray-scanned images were processed using the Software Genomic Workbench (Agilent Technologies, Inc.). The SNP array used was the CytoSNP-850K BeadChip (Illumina, USA) or CytoScan HD array (Affymetrix Inc., Santa Clara, CA, USA). Microarray-scanned images were processed using Bluefuse Multisoftware v4.1 (Bluegnome, UK) or Affymetrix® Chromosome Analysis Software Suite (ChAS) v.3.0.0.42 (Affymetrix). The parameters used to call a duplication or a deletion were $\log_2$ ratio intensities of a given genomic segment >0.3 or <−0.3, respectively, and encompassing at least 3 probes. CNVs considered common were excluded, based on the Database of Genomic Variants [14] and an independent control cohort of 400 healthy individuals.

We collected genomic coordinates, size, genes encompassed and, when available, inheritance of the identified CNVs. The assessment of CNV pathogenicity was made by considering the criteria based on the Consensus Statement of Chromosomal Microarray [7] and the guidelines of the American College of Medical Genetics [15], consistent with clinical phenotype, and updated information on known short stature syndromes and growth impairment-related genes. Briefly, we classified the CNVs as follows: (1) pathogenic: CNVs that overlap with genomic coordinates for a known genomic-imbalance syndrome and CNVs ≥3 Mb and (2) probably pathogenic: CNVs between 1 and 3 Mb or CNVs ≥300 kb carrying Online Mendelian Inheritance in Man (OMIM) mor-

bid genes de novo or inherited from a parent with a similar phenotype. A total of 16 relatives of 8 patients were analyzed to investigate probably pathogenicity and inheritance of CNVs. Parents of patients who had clear pathogenic and large CNVs (more than 3 Mb) were not tested, since the classification of pathogenicity was not dependent on the inheritance in these cases.

*Literature Search Strategy*

We searched the literature for studies evaluating CNVs in cohorts of patients with short stature up to April 2017 using the following criteria: (1) published in English, (2) investigation of patients with short stature of unknown cause, and (3) contained enough information about the results and methodology used in the study. We excluded non-original studies, case reports, specific disease investigation, custom genome-wide microarrays, and articles not published in English. We used the following search terms: (short stature OR growth impairment OR growth restriction OR growth retardation OR height OR dwarfism OR dwarf) AND (copy number variants OR array comparative genomic hybridization OR aCGH OR single nucleotide polymorphism array OR SNPa OR chromosomal microarray OR molecular karyotyping). Furthermore, we manually searched the reference lists of every primary study for additional information.

Data of CNVs and their genomic positions were collected from all the selected studies. The recurrent loci were selected, and the genomic positions were analyzed by DECIPHER [16]. The protein coding genes situated in CNVs loci were analyzed by VarElect NGS Phenotyper Program [17]. We used the following phenotype terms for prioritization of genes: "short stature" OR "growth impairment" OR height OR dwarfism OR dwarf OR "growth restriction" OR "growth retardation." We selected the first 5 genes directly related to the phenotype. The assessment of gene function and the assessment of overlapping with other genomic disorders were performed using the OMIM and the PubMed databases.

## Results

*Analysis of 229 Patients with Short Stature of Unknown Cause*

Among 229 patients with short stature studied by chromosomal microarray analysis, we observed 77 rare CNVs in 73 patients (1–4 per patient). We classified 25 CNVs as pathogenic and 7 as probably pathogenic. Moreover, 2 patients have maternal uniparental disomies. Pathogenic/probably pathogenic CNVs presented the following main characteristics: sizes ranged from 0.5 to 6.7 Mb (84.4% were over 1 Mb); 26 were deletions while 6 were duplications. Nineteen CNVs overlapped with genomic coordinates for a known microdeletion/microduplication syndrome already associated with short stature (Table 1).

The most recurrent phenotypes associated with short stature among patients with pathogenic/probably pathogenic CNVs were developmental delay and/or intellectual disability ($n$ = 29, 85.3%), dysmorphic facial features ($n$ = 23, 67.6%), microcephaly ($n$ = 9, 26.5%), cardiac congenital anomalies ($n$ = 3, 8.8%), and cryptorchidism ($n$ = 2, 5.9%). Fifty patients presented with minor anomalies, such as strabismus, pectus excavatum, clinodactyly, sacral dimple, hypothyroidism, and 1 patient had renal malformation. The online supplementary Table (for all online suppl. material, see www.karger.com/doi/10.1159/000481777) summarizes clinical and genetic features of all children with detected pathogenic/probably pathogenic CNVs.

*Analysis of Recurrent CNVs Associated with Risk for Short Stature*

Reviewing the literature, we found 6,029 studies which used chromosome microarray technologies. Of these 258 included patients with growth disorders or short stature. We performed a manual curation based on abstracts. They were analyzed according to our including and excluding criteria previously cited. This strategy resulted in a final selection of 4 eligible studies to be included in the CNV recurrence analysis [8–11] (Table 2). These studies and the present one reported a total of 671 patients with short stature of unknown cause evaluated by chromosome microarray technologies (SNPa or aCGH). Pathogenic/probably pathogenic CNVs were identified in 87 patients (13%; 95% confidence interval of 10.4–15.5%). We identified 7 recurrent CNVs in short stature (Table 3). Four of these recurrent CNVs were described in multiple studies (22q11, 15q26, Xp22.33, 1p36.33, and disomy in chromosome 14) and 2 recurrent CNVs were found in a single study and involved unrelated patients (1q21.1 and 17p13.3).

## Discussion

In the past few years, since the genomic approaches have been advancing, an increasing number of causative genetic alterations have been identified in many diseases. It has been demonstrated that CNVs (i.e., deletions or duplications of chromosomal segments) have a strong relationship with genome variability and contiguous gene syndrome and might be responsible for several conditions associated with short stature [18]. In 2009, the American College of Medical Genetics published the first practice guideline for genetic evaluation of short stature, which includes the recommendation for CNV investigation in patients with proportional short stature and other physical or developmental defects with an unrecognized syndrome [4].

**Table 1.** Description of the genomic imbalances classified as pathogenic/probably pathogenic

| Cytogenetic position | Genomic position (hg 19)[1] | Size, Mb | Gain/ loss | Pathogenicity | Affected genes, *n* | Protein coding/ OMIM genes, *n* | MD syndrome[2] |
|---|---|---|---|---|---|---|---|
| 1p36.33 | chr1:1018337-2188572 | 1.1 | Loss | Pathogenic | 49 | 43/13 | 1p36 microdeletion syndrome |
| 1p36.33p36.32 | chr1:82154-2366316 | 2.2 | Loss | Pathogenic | 80 | 58/35 | 1p36 microdeletion syndrome |
| 2p15p16.1 | chr2:60910033-64133562 | 3.2 | Loss | Pathogenic | 37 | 20/17 | 2p15-16.1 microdeletion syndrome |
| 2q24.1q24.2 | chr2:156761199-163169595 | 6.4 | Loss | Pathogenic | 54 | 28/24 | |
| 2q24.2q24.3 | chr2:161229701-167823275 | 6.6 | Loss | Pathogenic | 44 | 24/22 | |
| 2q24.3q31.1 | chr2:169465503-170164641 | 0.7 | Gain | Pathogenic | 9 | 7/7 | Chr 2q31.1 duplication syndrome |
| 2q37.2q37.3 | chr2:236798070-242717216 | 6.7 | Loss | Pathogenic | 80 | 58/42 | |
| 4p16.3p16.2 | chr4:49450-5516502 | 5.5 | Loss | Pathogenic | 93 | 62/49 | Wolf-Hirschhorn syndrome |
| 7q36.1q36.2 | chr7:150412317-152604342 | 2.2 | Loss | Probably pathogenic | 47 | 31/28 | |
| 8q23.3q24.13 | chr8:117628200-122637676 | 5.0 | Loss | Pathogenic | 32 | 21/18 | |
| 9q22.2q22.33 | chr9:93184497-99876878 | 6.7 | Gain | Pathogenic | 89 | 46/30 | |
| 10q22.2 | chr10:76540987-77666682 | 1.1 | Loss | Probably pathogenic | 15 | 8/6 | |
| 10q26.3 | chr10:131188376-135253581 | 4.1 | Loss | Pathogenic | 45 | 28/19 | |
| 12q14.2q15 | chr12:64082220-69757429 | 5.7 | Loss | Pathogenic | 64 | 32/29 | 12q14 microdeletion syndrome |
| 12q24.23q24.31 | chr12:120308438-122331128 | 2.2 | Gain | Probably pathogenic | 57 | 38/34 | |
| 14q24.3q32.33 | chr14:73972535-107287663 | 33.3 | UPD | Pathogenic[2] | 620 | 224/168 | Temple syndrome |
| 14q31.3q32.33 | chr14:88045320-107285437 | 19.2 | UPD | Pathogenic[2] | 505 | 148/114 | Temple syndrome |
| 15q11.1q11.2 | chr15:20212798-23226254 | 3.0 | Loss | Pathogenic | 62 | 10/5 | Spastic paraplegia 6 |
| 15q11.2q13.1 | chr15:23656946-29006093 | 5.3 | Loss | Pathogenic | 117 | 15/12 | Chr 15q11.2 deletion syndrome |
| 15q13.3 | chr15:32018731-32513233 | 0.5 | Gain | Probably pathogenic | 2 | 2/2 | |
| 15q26.2q26.3 | chr15:96128092-100200967 | 4.1 | Loss | Pathogenic[2] | 27 | 10/5 | |
| 15q26.3 | chr15:98969215-102399819 | 3.4 | Loss | Pathogenic[2] | 38 | 22/14 | |
| 16p11.2 | chr16:29326560-30198151 | 0.9 | Loss | Probably pathogenic | 38 | 31/28 | |
| 16p13.3 | chr16:247888-3061591 | 2.8 | Gain | Probably pathogenic | 146 | 117/86 | |
| 17p11.2 | chr17:16578397-20234743 | 3.7 | Loss | Pathogenic | 107 | 49/38 | Smith-Magenis syndrome |
| 17q11.2q12 | chr17:29533718-34346267 | 4.8 | Loss | Pathogenic | 80 | 56/46 | NF1 microdeletion syndrome |
| 17p13.3 | chr17:148092-2363821 | 2.2 | Loss | Pathogenic[2] | 50 | 38/33 | Miller-Dieker syndrome |
| 17p13.3 | chr17:525-2294143 | 2.3 | Loss | Pathogenic[2] | 50 | 38/34 | Miller-Dieker syndrome |
| 19q13.32 | chr19:51842509-52739293 | 0.9 | Gain | Probably pathogenic[2] | 43 | 30/16 | |
| 22q11.21 | chr22:18626108-21798907 | 3.2 | Loss | Pathogenic[2] | 96 | 49/44 | 22q11 deletion syndrome |
| 22q11.21 | chr22:18844632-21608479 | 2.8 | Loss | Pathogenic | 86 | 45/41 | 22q11 deletion syndrome |
| 22q11.21 | chr22:18886915-21463730 | 2.6 | Loss | Pathogenic | 82 | 44/40 | 22q11 deletion syndrome |
| 22q11.21 | chr22:19024793-21800471 | 2.8 | Loss | Pathogenic | 86 | 45/40 | 22q11 deletion syndrome |
| Xp22.33 | chrX:61396-612228 | 0.6 | Loss | Pathogenic | 7 | 4/1 | Leri-Weill dyschondrosteosis |

MD, microdeletion; chr, chromosome; Mb, megabase; *n*, number; OMIM, Online Mendelian Inheritance in Man; UPD, uniparental disomy. [1] Genomic positions are given according to Human Genome Building GCRh37, hg19. [2] Confirmed as de novo CNVs.

**Table 2.** Characteristics of all the selected studies about CNVs in short stature patients of unknown cause as well as the present study

| First author [Ref.] | Patients, *n* | | aCGH/ SNPa | Patients' selection criteria |
|---|---|---|---|---|
| | total enrolled | with pathogenic CNV | | |
| Zahnleiter et al., 2013 [8] | 200 | 20 (10%) | SNPa | Short stature of unknown origin, either born with a normal birth size or born SGA, associated with dysmorphic features and/or developmental delay, but without criteria for the diagnosis of known syndromes |
| van Duyvenvoorde et al., 2014 [9] | 142 | 17 (12%) | SNPa | Short stature of unknown origin, either born with a normal birth size or born SGA |
| Canton et al., 2014 [10] | 51 | 8 (16%) | aCGH | Prenatal and postnatal growth retardation associated with dysmorphic features and/or developmental delay, but without criteria for the diagnosis of known syndromes |
| Wit et al., 2014 [11] | 49 | 8 (16%) | SNPa | Short stature patients born small for gestational age |
| Present study | 229 | 34 (15%) | aCGH/ SNPa | Short stature of unknown origin, either born with a normal birth size or born SGA, associated with dysmorphic features and/or developmental delay, but without criteria for the diagnosis of known syndromes |

CNV, copy number variants; SNPa, single nucleotide polymorphism array; aCGH, array-based comparative genomic hybridization; SGA, small for gestational age.

**Table 3.** Recurrent submicroscopic genomic imbalances classified as pathogenic/probably pathogenic identified in 5 studies that investigated patients with short stature of unknown cause

| Recurrent cases, *n* (%) | Locus | Common (critical) region | Size, Mb | Protein coding/ OMIM genes, *n* | Main candidate genes[1] | Ref. |
|---|---|---|---|---|---|---|
| 9 (10.3) | 22q11.21 | chr22:21,011,217-21,440,656 | 4.3 | 9/9 | *LZTR1, SNAP29* | 8–11, present study |
| 8 (9.2) | 15q26 | chr15:98,456,575-101,003,122 | 2.5 | 10/5 | *IGF1R* | 9, 11, present study |
| 3 (3.4) | Xp22.33 | chrX:61,396-612,228 | 0.5 | 4/4 | *SHOX* | 9, 11, present study |
| 3 (3.4) | 1p36.33 | chr1:1,018,337-2,188,572 | 1.2 | 43/30 | *B3GALT6, DVL1* | 8, present study |
| 3 (3.4) | UPD14 | NA | NA | NA | NA | 11, present study |
| 2 (2.3) | 1q21.1 | chr1:146,101,228-147,831,171 | 1.7 | 10/10 | *GJA5, GJA8, CHD1L, BCL9* | 8 |
| 2 (2.3) | 2q24.2 | chr2:161,229,701-163,169,595 | 1.9 | 9/9 | *IFIH1* | present study |
| 2 (2.3) | 17p13.3 | chr17:148,092-2,294,143 | 2.1 | 37/33 | *SERPINF1, DPH1, YWHAE, WDR81, VPS53* | present study |

UPD, uniparental disomy; NA, not applicable; *n*, number; chr, chromosome; Mb, megabase; OMIM, Online Mendelian Inheritance in Man. [1] Main candidate genes involved in growth impairment using the VarElect NGS Phenotyper Program.

In the present study, the prevalence of chromosome imbalances was 14.8%, showing their relevant contribution as a possible genetic mechanism in short stature. Other studies that investigated the impact of CNVs in children with short stature of unknown origin, regardless of physical or developmental defects, also identified a high rate of pathogenic or probably pathogenic CNVs (10–16%) [8–11].

Recently, studies have recognized recurrent pathogenic or probably pathogenic CNVs associated with neurodevelopment disorders, ovarian cancer, and heart diseases, indicating that there might be some genetic "hotspots"

predisposing to different diseases [19–21]. Analyzing the 4 selected studies on short stature as well as the present study, 7 recurrent CNVs and 1 uniparental disomy were identified in patients with short stature of unknown cause. These CNVs were characterized as large, de novo, and individually rare, similar to those from other conditions in which there might be genetic "hotspots" for chromosomal imbalances [19, 20]. These loci corresponded to 40.2% of the total pathogenic or probably pathogenic CNVs described in all studies in which the short stature phenotype was the main emphasized phenotype.

In this study, we did not test inheritance in all patients. However, these patients had clear pathogenic, large CNVs (more than 3 Mb) and healthy parents. In 2010, a guideline about chromosomal microarray was published. In this consensus, the vast majority of inherited CNVs are described as much smaller than 500 kb, whereas most pathogenic CNVs are larger than 1 Mb and most occur de novo [7].

Among the recurrent CNVs identified in these studies, the 22q11 deletions were the most prevalent. The 22q11 deletion is described to be related to the DiGeorge syndrome (OMIM 188400)/velocardiofacial syndrome (OMIM 192430). This is one of the most common recurrent microdeletions in humans, with an estimated incidence of ~1:4,000 births. Although it is described as a well-known genetic syndrome, patients with 22q11 deletions usually have features with widely variable expressivity [22]. None of the patients with 22q11 deletion identified in studies of children with short stature of unknown cause have the typical signs associated with this syndrome [22, 23]. Also, several of these patients had some unspecific findings associated with 22q11 deletions (dysmorphic facial features, postnatal growth restriction, microcephaly, developmental and learning disabilities, psychiatric and/or behavioral problems) that could be confounded with other syndromes with a similar phenotype.

Another recurrent CNV identified was the 15q26 rearrangement. The insulin-like growth factor-1 receptor (*IGF1R*) gene, a well-known gene related to growth pathway, is located on chromosome 15q26.3. Haploinsufficiency of the *IGF1R* gene (OMIM 147370) is associated with impaired prenatal and postnatal growth [24]. Furthermore, there is a large spectrum of associated abnormalities, and it might be a confounding factor on clinical diagnosis [25–28]. The haploinsufficiency of the *IGF1R* gene has been described to be involved with developmental delay, facial and skeletal dysmorphisms, microcephaly, congenital heart disease, epilepsy, diaphragmatic hernia, renal anomalies, neonatal lymphedema, and aplasia cutis congenita [25, 26].

Xp22.33 rearrangement is also a common recurrent CNV, in which the *SHOX* gene is located, another well-known gene related to short stature [29, 30]. It has been mapped at the pseudoautosomal region 1 (*PAR1*) of sexual chromosomes X (Xp22.33) and Y (Yp11.2) [29, 30]. It is assumed that the heterozygous loss of the *SHOX* gene is responsible for Leri-Weill dyschondrosteosis (OMIM 127300), whereas homozygous loss leads to Langer mesomelic dysplasia (OMIM 249700), both being characterized by disproportionate short stature [29, 30]. Defects on the *SHOX* gene have also been identified in idiopathic short stature [31, 32]. Patients with identified Xp22.33 rearrangements usually had some additional features of disproportionate short stature that mask the suspicion of heterozygous loss of the *SHOX* gene.

Two recurrent CNVs were identified in chromosome 1: 1p36 (OMIM 607872) and 1q21.1 (OMIM 612474) deletions. They are among the most frequently described genomic disorders. The 1p36 deletion is characterized by craniofacial dysmorphism, developmental delay, and mental retardation [33], while in 1q21.1 deletion, the presence of psychiatric or behavior alterations and cardiac abnormalities are remarkable [34, 35]. Some clinical characteristics such as developmental delay, heart defects, seizures, skeletal anomalies, and short stature were described in both syndromes [33–37]. The wide phenotypic spectrum with variable penetrance and expressiveness and the overlapping of features make the clinical diagnosis more difficult.

Another recurrent variation found was a maternal uniparental disomy of chromosome 14. Although Temple syndrome (OMIM 616222) is a well-known short stature syndrome, the real incidence has probably been underestimated. The phenotype is variable, relatively mild, and age-dependent [38]. Both patients diagnosed with Temple syndrome in this study have a mild phenotype and a young age, which probably led to a misdiagnosis. These patients were clinically suspected of having Silver-Russell syndrome (SRS; OMIM 180860); however, both analyses for 11p15 ICR1 hypomethylation and uniparental disomy of chromosome 7 (UPD7) were negative. Some Temple syndrome features clinically overlap with SRS, including pre- and postnatal growth retardation, hypotonia, delay in the development of motor skills, and early puberty. Recently, the first SRS Consensus was published, and it suggested that Temple syndrome should only be investigated when SRS has been excluded due to the clinical overlap between both syndromes [39].

In this study, we used, SNPa and aCGH platforms, both proven to be efficient to detect copy number changes. However, it is known that SNP arrays have the advantage of also detecting stretches of homozygosity, which might represent uniparental disomy [7]. It is possible that if all studies had been done using SNP arrays, we would have more uniparental disomy diagnoses.

Two recurrent CNVs were exclusive for the present study: 17p13.3 and 2q24.2 rearrangements. The 17p13.3 rearrangement has been described in the Miller-Dieker lissencephaly (OMIM 247200). Although it is responsible for a well-defined syndrome, this diagnosis was not suspected for the patients. This syndrome is characterized by facial dysmorphisms, microcephaly, short stature, seizures, cardiac malformations, and, mainly, different severity grades of agyria in lissencephaly [40, 41]. However, our patients had some relatively nonspecific features and, most importantly, they do not have lissencephaly. The *LIS1* gene, responsible for lissencephaly and subcortical laminar heterotopia, was preserved in our patients. Regarding the 2q24.2 rearrangement, there are only few studies describing patients with mental retardation, generalized hypotonia, seizures, characteristic dysmorphic features, and delayed growth. In addition, other findings such as pulmonary emphysema have also been described [42]. Our 2 patients had some additional features, such as coloboma, scoliosis, microcephaly, and cardiopathy, showing a widely variable phenotype among these affected patients. In both cases, the atypical phenotype made the clinical diagnosis difficult.

In addition, there were 4 other studies about CNVs in short stature patients which did not fulfill our inclusion criteria, because either they used a custom genome-wide microarray or studied a specific growth disorder. Similarly, they also identified 6 of the 7 recurrent CNVs described in our study [43–46], indicating that theses CNVs might be common in patients with the short stature phenotype.

In conclusion, chromosomal microarray made it possible to identify the etiology of syndromic short stature condition in 13% of the cases in whom the clinical approach was unable to establish a diagnosis due to relatively nonspecific features or a mild phenotype. Moreover, we observed some recurrent CNVs associated with this condition, corresponding to 40.2% of the total pathogenic or probably pathogenic CNVs described in all studies in which the short stature phenotype was the main emphasized phenotype. Among these recurrent CNVs, we identified deletions involving genes clearly associated with the short stature phenotype: *IGF1R* and *SHOX* [24, 29]. Additionally, novel candidate genes were suggested, and further studies should be performed to evaluate their role in growth disorders.

## Statement of Ethics

Study was approved by the Ethics Committee for Analysis of Research Projects (CAPPesq) of the School of Medicine, University of Sao Paulo (USP) (#1645329).

## Disclosure Statement

The authors declare that they have no competing interests.


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