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Partial Monosomy 4p and Trisomy 12q due to a t(4;12)(p16.3;q24.31) Familial Translocation in Two Cousins

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Abstract
Wolf-Hirschhorn syndrome (WHS) is caused by a distal 4p monosomy usually involving the region of the *WHSC1* and *WHSC2* genes. About 40–45% of WHS patients show an unbalanced translocation leading to both 4p monosomy and partial trisomy of another chromosome arm. In this case report, we describe 2 female cousins (P1 and P2) with a derivative chromosome leading to a 4p16.3pter deletion and 12q24.31qter duplication. Conventional karyotyping and genomic analyses showed that they both had the same rearrangement derived from a balanced parental translocation involving chromosomes 4 and 12, t(4;12)(p16.3;q24.31). The rearrangements occurred between 4p16.3pter and 12q24.31qter detected by array-CGH analysis, with a 2.7-Mb loss at 4p and a large 12.4-Mb gain at 12q. Both affected patients shared global developmental delay and craniofacial dysmorphisms with some distinct phenotypic findings associated with both WHS and 12qter trisomy. P2 was more severely impaired than P1, and she showed severe intellectual disability, seizures, midface hypoplasia, unilateral microtia, and deafness which were absent in P1. Previous studies of distal 4p monosomies have found phenotypic variability in WHS which does not correlate with haploinsufficiency of specific genes. Features of 12q trisomies are diverse with developmental and growth delay, intellectual disability, behavioral problems, and facial abnormalities. Collectively, our analysis of the literature of 3 similar translocations involving 4p and 12q, together with the clinical features of the affected cousins in this familial translocation, permits an evaluation of genes closely linked to *WHSC1* and *WHSC2* in the context of WHS and the genes involved in 12q trisomy.

Unbalanced t(4;12) translocations leading to monosomy of distal 4p16 and partial trisomy of 12q are extremely rare with only 3 previous reports in the literature [Melnyk et al., 1981; Tajara et al., 1985; Wilson and Oei, 1998]. In this study, we describe the genomic and clinical

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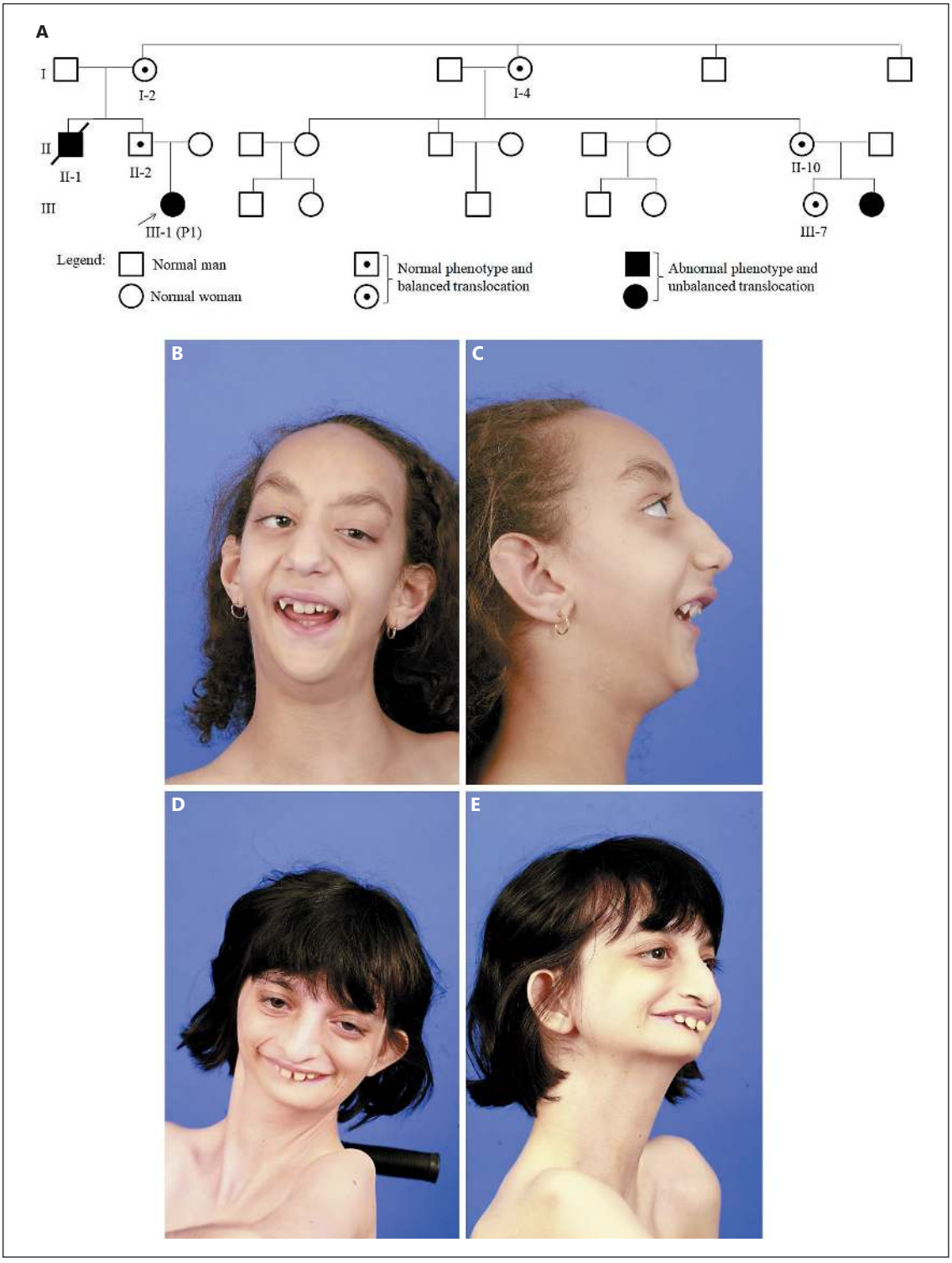


Fig. 1. A Pedigree of the family showing the patients, balanced translocation carriers, and normal individuals. The arrow indicates the index case (P1). All the individuals shown in the pedigree were cytogenetically investigated. FISH and array CGH were also performed on the balanced translocation carries and affected patients. **B**, **C** Craniofacial anomalies in P1, showing microcephaly, triangular face, ptosis, strabismus, retrognathia, and dysplastic ears. **D**, **E** Craniofacial anomalies in P2, showing ocular proptosis, beaked nose, macrostomia, microretrognathia, and prominent left ear.

features of another example of a t(4;12) translocation in 2 cousins who both inherited an unbalanced der(4)t(4;12)(p16.3;q24.31), leading to a combination of partial monosomy 4p and partial trisomy 12q.

Deletions in 4p16 are associated with Wolf-Hirschhorn syndrome (WHS). The clinical features of WHS include a characteristic facial appearance, delayed growth and development, intellectual disability, hypotonia, and seizures [reviewed in Battaglia et al., 2015]. The genomic size of monosomy 4p16 varies among patients with WHS, and recent studies suggest that larger deletions may lead to more severe features [Corrêa et al., 2018].

Clinical presentations of patients with 12q trisomies may include developmental delay, intellectual disability, behavioral problems, and growth delay, together with distinctive facial features. The severity can also depend on the size, gene content, and the location of the trisomy [Bouman et al., 2013].

In this case report, we describe the clinical and genomic features of patient 1 (P1), a 13-year-old girl, and patient 2 (P2), her 20-year-old female cousin; both carry the same inherited unbalanced chromosomal translocation 46,XX,der(4)t(4;12)(p16.3;q24.31), but each patient has distinct clinical findings. We also compare the phenotypic effects of 3 other similar unbalanced t(4;12) translocation cases that also have monosomy of distal 4p16 and partial trisomy 12q with the clinical findings of our cases P1 and P2.

Patients and Methods

Clinical Reports

We describe 2 related patients with a familial unbalanced translocation of chromosomes 4 and 12 with clinical findings marked by intellectual disability, microcephaly, distinctive facial features, and hearing loss. The index case, P1 was referred to the department for genetic evaluation due to failure to thrive, psychomotor developmental delay, dysmorphic facial features, precocious puberty, and behavioral disorder. An extended analysis of the family revealed no occurrence of miscarriages, but there was a paternal uncle who died at the age of 2 due to unspecified congenital malformations. Our analysis also found that the second cousin (P2) of our index case had some similar phenotypic features (Fig. 1A), prompting a more extensive genetic study of both cases.

Patient 1 is a 13-year-old girl, the only child of nonconsanguineous healthy parents. The pregnancy was unremarkable, and she was born at 38 weeks' gestation by elective C-section with no complications. Her birth weight was 2,500 g (between the 25th and 50th centile), OFC was 31cm (10th centile), and Apgar scores were 6 and 9. Hypotonia, feeding difficulties, facial dysmorphisms, and cleft palate were observed. Her neuropsychomotor development was globally delayed (she walked within 31 months and spoke her first words when she was 8 years old). A physical examination was performed when she was 12 years old, which showed microcephaly with moderate intellectual disability and failure to thrive with all parameters <3rd centile (weight: 27.5 kg, height: 140.5 cm, and OFC: 49 cm). Dysmorphic features are detailed in Table 1 (also see Fig. 1B, C). Transthoracic echocardiography revealed an atrial septal defect (3 mm) and brainstem evoked response audiometric testing showed a moderate bilateral sensorineural hearing loss. Abdominal ultrasound and cranial MRI were normal.

Patient 2 is a 20-year-old girl, the second child of nonconsanguineous healthy parents. The pregnancy was unremarkable, and she was born at 38 weeks' gestation. No adverse events in the antenatal period were noticed. Her birth weight was 2,050 g (<3 centile), length 45 cm (10th centile), and OFC was 33 cm (50th centile). She also presented with hypotonia, feeding difficulties, and dysmorphic features. All developmental milestones were more significantly delayed in comparison to P1 (she never walked or was able to speak). Seizures were observed when she was 8 months old. All her current growth parameters are <3rd centile (weight: 19.1 kg, height: 130 cm, and OFC: 45 cm), and her craniofacial dysmorphisms include a characteristic appearance called the "Greek warrior helmet", comprising a high forehead with prominent glabela and a beaked nose that is typical of WHS. The clinical features are detailed in Table 1 (see Fig. 1d, e). Neurological investigation showed temporal lobe epilepsy and tomography of the temporal bone showed atresia of the external auditory canal on the right side with severe bilateral sensorineural hearing loss.

Methods

Cytogenetic analysis of peripheral blood samples was performed according to standard methods. The karyotypes were interpreted according to the International System for Human Cytogenetic Nomenclature [ISCN, 2016]. We used LSI probes (Cytocell, UK) specific for the regions 4pter (4p16.3 LPT04PR, SpectrumRed) and 12qter (12q24.33 LPT12QG, SpectrumGreen) according to the manufacturer's instructions. Array CGH was performed on P1, P2, and their relatives (balanced translocation carriers) using Agilent Array Kit, 2x400K according to manufacturer's recommendations. Data were analyzed using Nexus Copy Number version 7.0 software (BioDiscovery, El Segundo, CA, USA). All genomic coordinates for copy number changes are reported using human reference sequence hg19/GRCh37.

Results

Cytogenetic and Cytogenomic Findings

The karyotype analysis revealed that both P1 and P2 carried extra material derived from chromosome 12 on the short arm of chromosome 4. Subsequent cytogenetic analysis performed on their relatives showed that the father of P1 was a carrier of an apparently balanced translocation defined as 46,XY,t(4;12)(p16.3;q24.31). Further cytogenetic studies indicated that the paternal grandmother of P1 and both the sister and the mother of P2 had the same balanced rearrangement, resulting in triso-

Table 1. Clinical features of patients with 4p;12q translocations

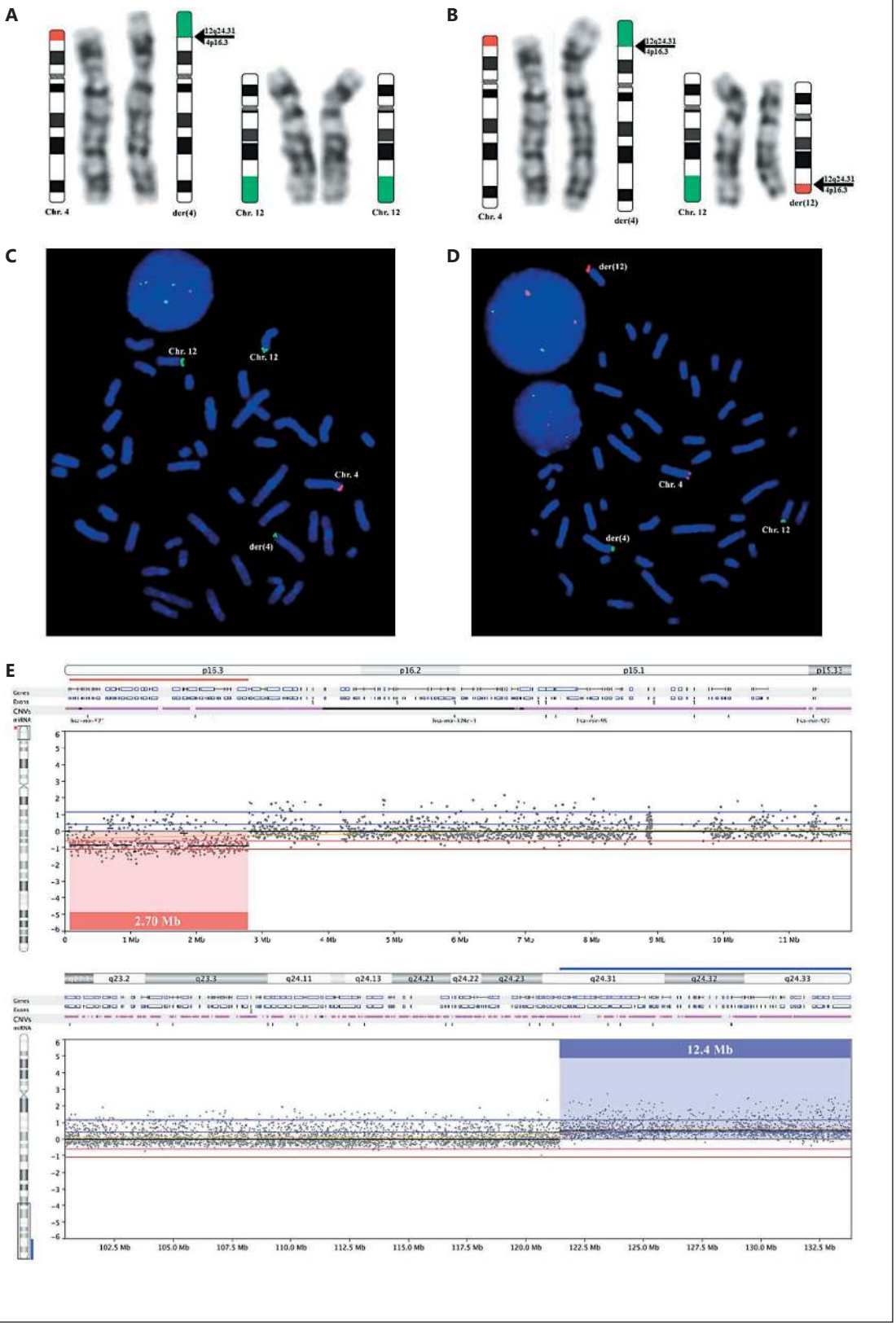
	Melnyk et al., 1981	Tajara et al., 1985	Wilson and Oei, 1998	This study	
				P1	P2
Neurological features					
Hypotonia	+	n.d.	n.d.	+	+
Developmental delay	+	+	n.a.	+	+
Intellectual disability	+	+	n.a.	+	+
Seizures	+	+	n.a.	–	+
Behavioral disorder	n.d.	n.d.	n.a.	+	–
Neurosensorial deafness	n.d.	n.d.	n.a.	–	+
Craniofacial features					
Microcephaly	+	+	+	+	+
Prominent forehead	+	+	+	+	+
Low-set and/or malformed ears	+	+	+	+	+
Hypertelorism	+	+	+	–	–
Strabismus	n.d.	+	n.d.	+	–
Flat nasal bridge	+	+	+	+	+
Wide mouth with downturned corners	+	+	n.d.	–	+
Cleft palate	–	–	+	+	–
Micrognathia	+	+	+	+	+
Musculoskeletal and limb features					
Single palmar creases	+	+	n.d.	–	–
Clinodactyly	+	+	n.d.	+	+
Hyperextensibility	+	n.d.	n.d.	+	–
Sacrococcygeal anomalies	+	+	–	+	+
Feet deformity	+	+	+	+	+
Subluxation of hips	n.d.	n.d.	+	–	–
Genitourinary anomaly	+	+	–	–	–
Cardiovascular anomaly	+	–	n.d.	+	–
Other features					
Failure to thrive	+	+	+	+	+
Widely spaced nipples	+	+	+	–	–
Loose skin at nape	–	+	–	–	–
Chromosomal abnormality					
4p deletion	4p16pter	4p16pter	4p15.2pter	4p16.3pter	4p16.3pter
12q duplication	12q24.1qter	12q24.31qter	12q21.3qter	12q24.31qter	12q24.31qter

n.a., Not available, patient died 12 h after birth; n.d., not discussed; +, present; –, absent.

my of 12qter for both patients: 46,XX,der(4)t(4;12)(p16.3;q24.31) (Fig. 2A, B).

FISH analysis showed that both patients had a partial monosomy 4p at the 4p16.3 cytoband that had not been detected by G-banding. FISH analysis also showed that the carriers of the balanced translocation with a normal phenotype did not carry a detectable monosomy at 4p (Fig. 2C, D).

Array-CGH analysis showed a partial 4p terminal loss (2.7 Mb) involving 53 genes and a partial 12q gain (12.4 Mb) comprising 139 genes for both patients: defined as arr[GRCh37] 4p16.3(73629_2780849)×1;12q24.31q24.33(121446691_133851895)×3 (Fig. 2E, F). The loss in chromosome 4 comprised the WHS critical region (OMIM 194190) including the *WHCS1*, *WHSC2*, and *LETM1* genes. No evidence of genomic alterations was found in the breakpoint regions of the relatives with apparently balanced translocation.



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Discussion

In this study, we report 2 cousins, both with partial 4p monosomy and 12q trisomy and distinct clinical phenotypes. Analysis of the family suggests that this rearrangement was likely caused by the abnormal chromosome segregation of an inherited parental balanced translocation.

Partial trisomy 12q is a rarely observed chromosomal anomaly. Of the 50 previous cases of partial trisomy 12q, there are 13 that overlap with the same duplicated region present in our patients (12q24.31q24.33) [Zabel and Baumann, 1981; Tajara et al., 1985; Jardine et al., 1993; Rodriguez et al., 2003; Ireland et al., 2004; Lagier-Tourenne et al., 2004; Bao and Schorry 2005; Sathanoori et al., 2007; Semerci et al., 2010]. The sizes of the trisomies in the previous cases vary from 2.3 to 67.9 Mb, with more severe phenotypic effects being reported for more extensive trisomies. The phenotypes typically associated with 12q trisomies are an abnormally shaped skull, hypertelorism, a flat nasal bridge with a downturned or prominent nasal tip, downturned mouth, skeletal and limb abnormalities, sacral dimples, single palmar crease, and occasional brain and heart defects [Bouman et al., 2013]. The duplicated region in both our probands includes 139 genes. Of these genes, 15 are reported in the OMIM database as possibly disease-causing genes (*ORAI1*, *C12orf65*, *SCARB1*, *P2RX2*, *POLE*, *HPD*, *PUS1*, *BCL7A*, *ANKLE2*, *WDR66*, *EIF2B1*, *DIABLO*, *TCTN2*, *VPS33A*, and *ATP6V0A2*). Mutations in *DIABLO* and *P2RX2* are associated with developmental anomalies leading to sensorineural hearing deficits [Cheng et al., 2011; Faletra et al., 2014]. Since both our patients have trisomy of this region, their hearing loss may be related to gene dosage effects. It is likely that although this trisomy occurs in both cousins, the large number of genes duplicated may have resulted in synergistic action of multiple genes contributing to the variation in phenotypes between P1 and P2. In addition, the influence of other genetic mechanisms and environmental factors should not be disregarded.

The variability of phenotypic findings in WHS has been associated with the extent of the partial deletion in 4p. About 40–45% of the WHS cases involve an unbalanced translocation and a deletion of 4p as well as partial trisomy of a different chromosome arm [Battaglia et al., 2015]. The core phenotype is defined by a broad, flat nasal bridge, a prominent high forehead, and hypertelorism which has led to the descriptive term Greek warrior helmet appearance.

The association of the 4p monosomy and 12q trisomy has been previously reported in only 3 cases [Melnyk et al., 1981; Tajara et al., 1985; Wilson and Oei, 1998], analyzed by classical cytogenetics (Table 1). The phenotypic findings are very similar among the patients including developmental delay, intellectual disability, and craniofacial dysmorphisms. Prominent forehead, flat nasal bridge, micrognathia, and malformed ears were described in all cases. Three patients presented with seizures, and cleft palate was reported in 2. Microtia and deafness was exclusively observed in case P2. Ou et al. [2011] suggest that sequence homologies present in low-copy repeat clusters at 4p16 may make this region prone to chromosomal rearrangements.

The deleted region at 4p16.3 in our patients comprises 53 genes, including 3 major genes (*WHSC1*, *WHSC2*, and *LETM1*) known to be associated with the WHS phenotype. *WHSC1* is thought to regulate multiple processes in development [Battaglia et al., 2015], and its deletion may disrupt normal morphogenesis and neurodevelopment leading to some phenotypic features found in WHS [Zollino and Doronzio, 2018]. The *WHSC2* gene may be involved in more global aspects in WHS. The combined haploinsufficiency of *WHSC1* and *WHSC2* could significantly alter the "transcriptome landscape" during development, which may have an adverse overall impact on normal developmental processes in addition to having tissue-specific effects on different organs [Kerzendorfer et al., 2012].

The *LETM1* gene may play a role in the pathogenesis of seizures in patients with 4p deletion. The LETM1 protein regulates Ca^{+2}/H^{+} influx and efflux levels in the mito-

Fig. 2. G-banded chromosomes and FISH analysis. **A** G-banding results showing the derivative chromosome 4 with the addition of 12q in P1. **B** G-banded chromosomes showing the apparently balanced translocation between chromosomes 4 and 12 in P2's mother. **C**, **D** FISH analysis using LPT04PR-Red (4p16.3) and LPT12QG-Green (12q24.33) probes for patients and carriers. FISH analysis (P2) showing 3 green signals (**C**), one of them in the derivative chromosome 4 with the addition of the subtelomeric 12q region. The normal chromosomes 4 (red) and 12 (green) are also indicated. FISH analysis of P2's sister showing the derivatives and normal chromosomes (**D**). The derivative chromosome 4 with the addition of 12q is marked in green and the derivative chromosome 12 with addition of 4p in red. **E**, **F** Microarray mapping of P1. **E** The 2.7-Mb deletion in chromosome 4 (4p16.3) is indicated in red. **F** The 12.4-Mb duplication in chromosome 12 (12q24.31q24.33) is shown in blue.

chondria affecting cerebral activity [Jiang et al., 2013], but haploinsufficiency of *LETM1* by itself may be insufficient to lead to seizures [Andersen et al., 2014]. More recently, the genes *CTBP1*, *PIGG*, and *CPLX1,* all involved in neuronal synaptic activity, were suggested as additional candidates for the development of seizures [Bayindir et al., 2013; Zollino et al., 2014; Battaglia et al., 2015]. Ho et al. [2016] suggest that WHS patients are less likely to have seizures if the terminal 751 kb of the short arm of chromosome 4 remains intact. The terminal 4p deletions detected in P1 and P2 are the same at the genomic level and comprise all candidate genes for the onset of seizures, suggesting that other reasons may underlie why patient P1 did not have a phenotype involving seizures as observed in her cousin P2. There is some evidence that epileptic disorders act as an independent factor for the final degree of intellectual disability in patients [Oh et al., 2017], and this may explain the more severe neurodevelopmental impairment in case P2 in comparison to P1.

The deletion in 4p16.3 also includes the *FGFRL1* gene. It has been proposed that *FGFRL1* could contribute to the craniofacial phenotype and skeletal features in 4p deletions based on targeted deletion of *fgfrl1* in zebrafish [Hall et al., 2006] and mice [Catela et al., 2009]. The jaw malformations and defects in heart septation observed in these *fgfrl1* knockouts have similar features to clinical observations in P1, such as cleft palate and persistent interatrial communication.

Both P1 and P2 had some phenotypic features in common with other reported cases of monosomy 4p and trisomy 12q. Since both our patients carry the same genomic alterations and only P2 shows the distinctive Greek warrior helmet appearance typical of monosomy 4p, it seems possible that the large 12q trisomy has slightly different effects in P1 and P2.

Our study of this rare unbalanced t(4;12) translocation draws attention to several related genes that could help explain the genotype-phenotype correlations in patients with similar monosomies and trisomies at 4p and 12q.

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Statement of Ethics

This study was approved by the Ethic Committee for research involving human subjects at the Ribeirão Preto Clinical Hospital of the University of São Paulo (HCRP: 74/91/2015). Written informed consent was obtained from the parents for publication of this case report and any accompanying images.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Authors Contributions

All authors made substantive intellectual contributions to the study, read, and approved the final version of the manuscript. T. Mozer Joaquim participated in the design of the study, performed and analyzed FISH and array-CGH data, drafted the manuscript, and finalized it. C.H. Paiva Grangeiro acquired and interpreted clinical data. F. Gaona de Oliveira Gennaro and A. Galvão Gomes participated in performing and analyzing the array-CGH data. J.A. Squire participated in data analysis and critically read the manuscript. L.R. Martelli conceived the study, participated in its design and coordination, drafted the manuscript, and finalized it.

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