

Duplication 12p and Pallister–Killian syndrome: A Case Report and Review of the Literature Toward Defining a Pallister–Killian Syndrome Minimal Critical Region

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Pallister–Killian syndrome (PKS) is a multisystem sporadic genetic condition characterized by facial anomalies, variable developmental delay and intellectual impairment, hypotonia, hearing loss, seizures, pigmentary skin differences, temporal alopecia, diaphragmatic hernia, congenital heart defects, and other systemic abnormalities. PKS is typically caused by the presence of a supernumerary isochromosome composed of the short arms of chromosome 12 resulting in tetrasomy 12p, which is often present in a tissue limited mosaic state. The PKS phenotype has also often been observed in individuals with complete or partial duplications of 12p (trisomy 12p rather than tetrasomy 12p) as the result of an interstitial duplication or unbalanced translocation. We have identified a *proposita* with PKS who has two small *de novo* interstitial duplications of 12p which, along with a review of previously reported cases, has allowed us to define a minimum critical region for PKS.

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Key words: 12p duplication; isochromosome 12p

INTRODUCTION

Pallister–Killian syndrome (PKS) (OMIM#601803) is a multisystem sporadic genetic disorder characterized by facial anomalies (prominent forehead with sparse temporal hair, broad nasal bridge, hypertelorism, wide mouth), variable developmental delay and intellectual impairment, hypotonia, seizures, pigmentary skin differences, diaphragmatic hernia, congenital heart defects, and other systemic abnormalities [Pallister et al., 1977; Teschler-Nicola and Killian, 1981; Mathieu et al., 1997].

PKS is typically caused by the presence of a supernumerary isochromosome composed of the short arms of chromosome 12

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resulting in tetrasomy 12p, which is often present in a tissue limited mosaic state [Peltomäki et al., 1987]. The PKS phenotype has also been observed in individuals with complete or partial duplications of 12p (trisomy 12p rather than tetrasomy 12p) as the result of an interstitial duplication or unbalanced translocation, although some patients with duplication of 12p can have features that differ significantly from that of PKS [Zumkeller et al., 2004; Inage et al., 2010]. Given that the full PKS phenotype can be observed in individuals carrying such duplications, it is likely that a subset of genes on 12p are responsible for the PKS phenotype and that trisomic non-mosaic dosage is equivalent to the tetrasomic mosaic dosage in terms of pathogenicity. However, delineation of a candidate genomic region responsible for the PKS phenotype has

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been hampered by the paucity of reports of interstitial duplication of 12p.

We have identified a probanda with a PKS phenotype who has two small de novo interstitial duplications of 12p which, along with a review of previously reported cases, has allowed us to define a minimum critical region that, when duplicated, generates many of the manifestations of PKS. This newly defined PKS critical region likely contains the critical gene or genes responsible for this diagnosis when present in greater than two copies.

MATERIALS AND METHODS

Clinical Report

The probanda was born to a 25-year-old G2P0 to1 mother by cesarean after 37 weeks of pregnancy. The mother had a prior history of a spontaneous abortion at 4 months gestation; the family history was otherwise noncontributory. Intrauterine growth retardation was noted early in the pregnancy. Fetal echocardiography made a prenatal diagnosis of Ebstein anomaly. The Apgar scores were 3, 5, and 7 at 1, 5, and 10 min, respectively. Due to poor respiratory effort, she was intubated at birth. Her birth weight was 2,965 g (60th centile), length was 50.5 cm (80th centile), and head circumference was 33 cm (50th centile). Physical examination revealed many dysmorphic features including frontal bossing, asymmetric brachycephaly with a flat occiput, small anterior fontanel, sparse scalp hair, low-set short ears with prominent anti-helices and overfolded superior helices, sparse eyebrows, widely spaced eyes, wide nasal bridge, short nose, anteverted nares, short neck, excess nuchal skin, wide spaced nipples, and broad hallux (Fig. 1). Her neurological exam showed limited arousal, poor purposeful motor responses, and hypotonia; however, due to sedation, neurologic evaluation was limited. Postnatal echocardiography revealed a large atrial septal defect, right atrial dilation, severe tricuspid regurgitation and right ventricular dilation, consistent with the diagnosis of severe Ebstein anomaly. Brain MRI showed partial agenesis of the corpus callosum and mild inferior cerebellar vermian hypoplasia in addition to intraventricular hem-

orrhage. Ophthalmologic examination was unremarkable. Skull X-ray demonstrated bilateral coronal synostosis with harlequin eyes (uplifting of orbital roof). The probanda passed away at 6 days of age after withdrawal of medical treatment. Autopsy was not performed as per the parental request.

LITERATURE REVIEW

A review of the literature was undertaken using PubMed searching for terms “chromosome 12p”, “duplication chromosome 12p” “triplication 12p” “trisomy 12p” and cross referencing back from relevant identified articles. All articles with relevant cases (well defined cytogenetic and clinical characterization) were included in this review. However, case reports with mosaic duplication of 12p and prenatal cases of 12p duplication were not included in this review. Unbalanced translocations involving monosomy of short arm of the acrocentric chromosomes were included; however, cases with unbalanced translocations causing monosomy of the other chromosomal region or with marker chromosomes involving other chromosomal regions were excluded.

RESULTS

Molecular and Cytogenetic Analysis

G-band karyotype was 46, XX. Given the phenotypic similarity of Seathre–Chotzen syndrome, we conducted *TWIST* gene sequencing analysis and targeted mutational analysis of p.Pro250Arg in *FGFR2*; however, no mutation was identified. We also tested for the p.Pro250Arg *FGFR1* mutation, and sequenced exon 8 and 10 of *FGFR2* as well as the *GLI3* gene, all of which were within normal limits. BAC array comparative genomic hybridization was performed, and revealed a 12p13.31 microduplication and a 16p13.11 microdeletion. To further refine the breakpoint of microduplication, single nucleotide polymorphism (SNP) microarray analysis was performed. SNP array genotyping was carried out by the Center for Applied Genomics using the Illumina Infinium SNP genotyping platform (HumanHap550 chips and BeadStation Scanner and BeadStudio analysis software). The HumanHap550 chip contains 555,352 SNP probes, distributed with an average interSNP distance of 6 kb. Three microduplications in 12p13.31 (chr12: 6362208–6742773, chr12: 7888157–8017012, and chr12: 8496483–8912792) and microdeletion of 16p13.11p12.3 (chr16: 15387380–18174650) were confirmed (Fig. 2). One of the microdeletions in 12p13.31 (chr12: 7888157–8017012) was identified in the phenotypically normal mother, and the microdeletion of 16p was found in the father.

Literature Review

In addition to the new case reported here, we identified 21 reports describing a total of 26 individuals with 12p duplications of varying sizes (15 cases were partial 12p duplication, one case had partial 12p triplication and 10 cases had duplication of the entire 12p) [Armendares et al., 1975; Biederman et al., 1977; Tenconi et al., 1977; Hansteen et al., 1978; Parslow et al., 1979; Dallapiccola et al., 1980; Stengel-Rutkowski et al., 1981; Ray et al., 1985; Rivera et al., 1987; Tayal et al., 1989; Pfeiffer et al., 1992; Zelante et al., 1994; Allen



FIG. 1. Facial appearances of the probanda. Note brachycephaly, frontal bossing, flat occiput, sparse scalp hair, low-set short ears with prominent anti-helices overfolded superior helices, sparse eyebrows, widely spaced eyes, wide nasal bridge, short nose, and anteverted nares.

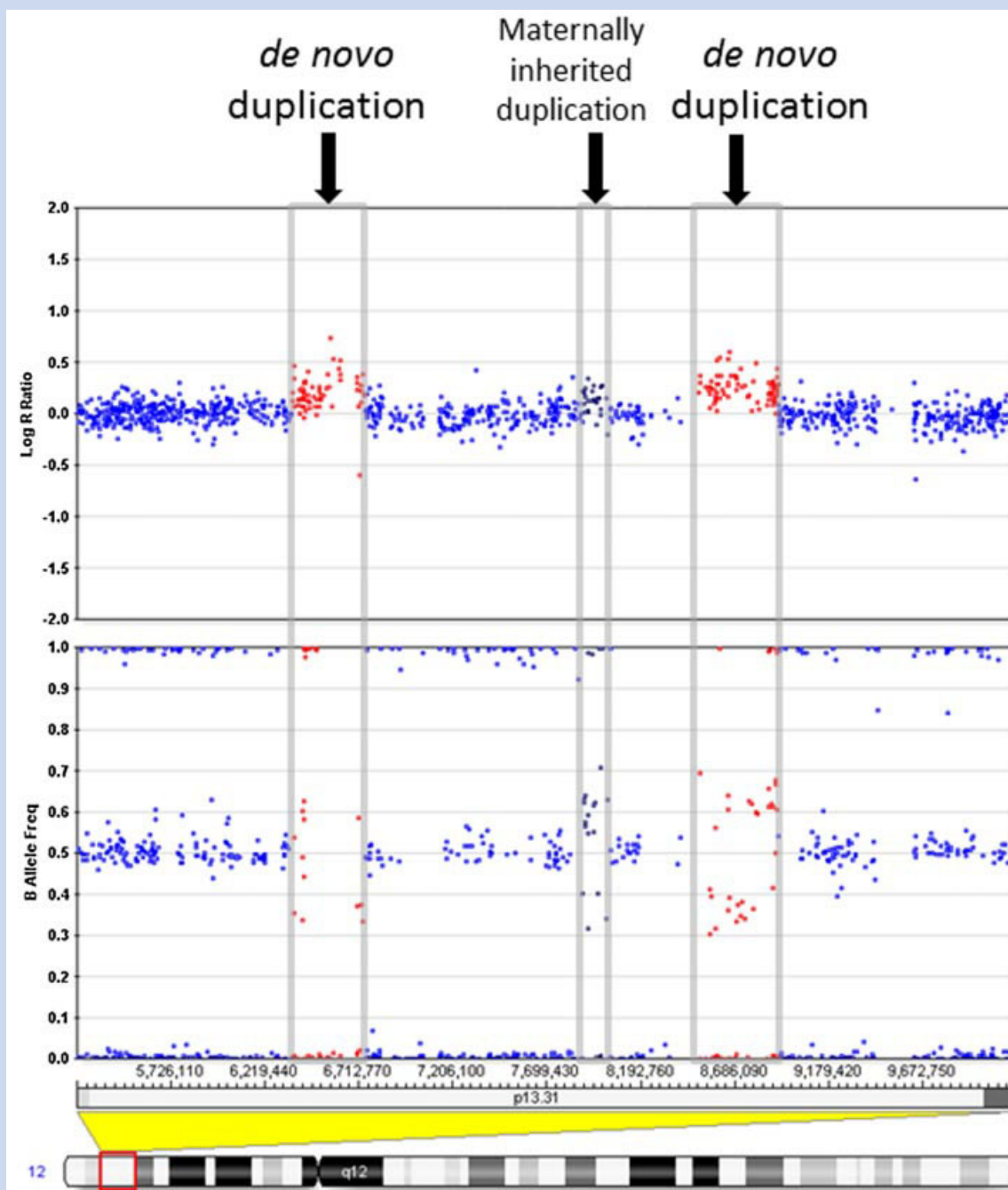


FIG. 2. SNP array result demonstrating chromosome 12p13.31 duplications. Within 12p13.31, three microduplications were identified which can be seen as an elevation in the Log R ratio and the split B-allele frequency. The proximal and distal duplications were de novo, and the middle duplication was inherited from the mother.

et al., 1996; Rauch et al., 1996; Back et al., 1997; Rivera et al., 1999; Tekin et al., 2001; Zumkeller et al., 2004; De Gregori et al., 2005; Tsai et al., 2005; Eckel et al., 2006; Liang et al., 2006; Cetin et al., 2011]. Ages of the patients described in the previously published case reports ranged from birth to 34 years. We also identified three reports of individuals with partial tetrasomy 12p [Dufke et al., 2001; Vermeesch et al., 2005; Huang et al., 2007]. Duplication sizes ranged

from the entire short arm to microduplications of about 10 Mb, many of which are associated with characteristic traits of PKS (Table I).

Amongst the 25 cases of 12p duplication cases and one partial 12p triplication, common facial features include prominent forehead/frontal bossing (15/26 cases), full cheeks (14/26 cases), epicanthus (12/26 cases), low-set ear (14/26 cases), wide/depressed

TABLE I. Comparison of phenotypic features among the cases of partial 12p duplication, 12p duplication of entire arm and partial 12p tetrasomy due to marker chromosome

Partial 12p duplication

Year of publication	Present case	Eckel ^a	Liang Propositus	Liang Son	De Gregori	Tsai	Tekin	Back	Rauch Case1 1996/(Pfeiffer 1992)	Rauch Case2	Allen	Zelante	Tajel	Dallapiccola	Hansteen Case No1	Hansteen Case No3	Tenconi
Age	Newborn	4yo	34yo	15mo	4yo	2.5yo	10mo	12.5yo	5.5yo	9mo	9yo	7yo	14yo	12mo	3.5yo	12mo	2y.4mo
Gender	Female	Male	Male	Male	Female	Female	Male	Male	Female	Female	Male	Female	Male	Male	Male	Male	Male
Head			(+)	(+)			(+)		(+)		(+)		(+)				
Sparse scalp hair	(+)								(+)		(+)						
Prominent forehead/Frontal bossing	(+)		(+)				(+)		(+)		(+)						
Round face	(+)					(+)	(+)		(+)		(+)				(+)		
Full cheeks	(+)						(+)		(+)		(+)			(+)			
Turricephaly	(+)								(+)		(+)			(+)			(+)
Eye																	
Widely spaced eye	(+)	(+)									(+)						(+)
Upslanted palpebral fissure	(-)								(+)								
Downslanted palpebral fissure	(+)													(+)			(+)
Epicanthus	(-)	(+)							(+)		(+)						(+)
Sparse eyebrow/Sparse eyelash	(+)																
Prosis	Unknown																
Blepharophimosis	Unknown					(+)	(+)			(+)							
Strabismus	Unknown					(+)								(+)			(+)
Nystagmus	Unknown																(+)
Ear																	
Low-set ear	(+)								(+)								(+)
Overfolded helix	(+)								(+)								(+)
Increased posterior angulation of ear	(+)								(+)								(+)
Hearing loss	Unknown																
					Mild conductive hearing loss	Normal hearing	Unilateral moderate to severe sensorineural hearing loss										
Nose																	
Wide/Depressed nasal bridge	(+)		(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Short nose	(+)		(+)	(+)			(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Anteverted nares	(+)		(+)	(+)			(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Mouth																	

(Continued)

TABLE I. (Continued)

Partial 12p duplication

Year of publication	Present case	Eckel ^a	Liang Propositus	Liang Son	De Gregori	Tsai	Tekin	Back	Rauch Case 1 1996/(Pfeiffer 1992)	Rauch Case 2 1996	Allen	Zelante	Tajel	Dallapiccola	Hansteen Case No 1	Hansteen Case No 3	Tenconi
	Unknown	2006	2006	2006	2005	2005	2001	1997 (+)		1996	1996	1994	1989 (+)	1980	1978	1978	1977
	Wide mouth							(+)									
	Long/deep philtrum							(+)									
	Short philtrum		(+)	(+)	(+)	(+)	(+)	(+)									
	Thin upper lip vermillion																
	Everted/thick lower lip vermillion	(+)	(+)	(+)													
	Downturned corners of the mouth	(+)															
	Micrognathia	(-)															
	Prognathism	(-)					(+)							(+)			(+)
	Neck	(+)						(+)									(+)
	Short neck																(+)
	Heart	(+)															
	Congenital heart disease																
	Genitourinary	(-)						(+)									
	imperforate anus																
	Cryptorchidism																
	Extremities																
	Broad finger/foot	(-)						(+)									(+)
	Short finger	(-)															(+)
	Broad hallux	(+)										(+)					(+)
	Joint hyperextensibility	(-)															
	Growth																
	Macrosomia at birth	No	No	Yes	No	No	No	No	No	Yes	Yes (with maternal diabetes)	No	No	No	No	No	No
	BW >+2SD																
	or 97th percentile																
	Short stature (HT <3rd centile)	Unknown	No	No	No	No	No	Yes	No	No	No	No	Yes				No
	Poor weight gain (Wt <3rd)	Unknown	No	No	No	No	No	No	Yes	No	No	No	No				No
	Microcephaly (HCX <3rd)	Unknown	No	No	No	No	No	No	No	Yes	No	No	No				No
			(macrocephaly)	(macrocephaly)	(at 3rd percentile)												(macrocephaly at 98th centile)
	Skin																
	Pigmentation abnormality	(-)															

(Continued)

TABLE I. (Continued)

Year of publication	12p duplication of entire arm						Partial 12p tetrasomy due to marker chromosome						
	Cetin	Zumkeller	Rivera	Ray	Stengel-Rutkowski Case1	Stengel-Rutkowski Case2		Parslow Case1	Parslow Case2	Biederman	Armendares	Huang	Vermeesch
(+)	2011 (+)	2004	1999/1987	1985	1981 (+)	1981 (+)	1979	1979	1977	1975	2007	2005	2001 (+)
Downturned corners of the mouth													
Micrognathia	(+)		(+)		(+)	(+)					(+)		
Prognathism													
5													
Neck													
Short neck	(+)	(+)	(+)	(+)	(+)	(+)		(+)					
Heart													
Congenital heart disease	PDA				VSD				Congestive heart failure, PDA, incomplete right branch block			No heart defects	Narrow pulmonary artery, slight supraventricular stenosis, small ASD
Genitourinary													
imperforate anus													
Cryptorchidism													
Extremities													
Broad finger/foot					(+)	(+)				(+)			(+)
Short finger					(+)	(+)							
Broad hallux		(+)			(+)	(+)							
Joint													
Hyperextensibility													
Growth													
Macrosomia at birth BW > +2SD or 97th percentile	No		No	No	No	Yes	No	Yes	No	Yes	Yes	No	No
Short stature													
(Ht < 3rd centile)	No	Yes	Yes	No	No	No	Yes	Yes	No	No	No	>97th	No
Poor weight gain (Wt < 3rd)	No	Yes	No	No	No	No	Yes	No	No	No	No	>97th	No at 97th centile
Microcephaly (HCX < 3rd)	No	No	No	No	No	No	No	(macrocephaly at 98th centile)	No	No	Yes	No	Yes
Skin													
Pigmentation abnormality	(+)												
Supranumerary nipple			(+)						(+)	(+)			
6													
Neuro													
Developmental delay	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Died at 11 days old													

(Continued)

TABLE I. (Continued)

		12p duplication of entire arm										Partial 12p tetrasomy due to marker chromosome	
Year of publication	Cetin	Zumkeller	Rivera	Ray	Stengel-Rutkowski Case1	Stengel-Rutkowski Case2	Parslow Case1	Parslow Case2	Biederman	Armendares	Huang	Vermeesch	Dufke
Seizure	2011 No	2004 (+) Absent seizure	1999/1987 (+)	1985	1981 (+)	1981	1979 (+)	1979	1977 (+)	1975	2007 No	2005 No	2001 (+)
Hypertonia	(+)	(+)	(+)		(+)	(+)			(+)	(+)	(+)	(+)	(+)
Hypotonia				Normal cranial US		Enlarged right lateral ventricle	Moderate ventriculomegaly					Normal head CT	
Brain anomaly	Periventricular white matter hyperintense lesions around frontal horn of left lateral ventricle atrium by brain MRI												
Others	Bilateral grade III hydronephrosis, hypocalcaemia	Umbilical hernia, macroglossia, transient insulin-dependent diabetes mellitus	Congenital hip luxation, wide space teeth	Absent right index finger due to amniotic band	Meckel's diverticulum, incomplete intestinal torsion	Slight hypospadias, wide spaced nipples	Hypothyroid, ovarian dysgerminoma, hypertensive encephalopathy	Flattened occiput, right facial weakness, prominent nasal bridge	Single umbilical artery	Bilateral genu valgum, bilateral pes planus, talus valgus	Unusual fat accumulation on thighs	Persistent leukopenia, unusual fat accumulation on buttocks and hip, slow hair growth	Left hip dislocation

In all columns, the name refers to the first author of the paper—see References.

nasal bridge (20/26 cases), short nose (19/26 cases), anteverted nares (16/26 cases), long/deep philtrum (19/26 cases), and everted/thick lower lip (21/26 cases). Among the 13 cases of partial 12p duplication/triplication encompassing 12p13.31, the frequency of the above mentioned facial features are as follows: Prominent forehead/frontal bossing (5/13 cases), full cheeks (9/13 cases), epicanthus (5/13 cases), low-set ear (8/13 cases), wide/depressed nasal bridge (11/13 cases), short nose (9/13 cases), anteverted nares (9/13 cases), long/deep philtrum (11/13 cases), everted/thick lower lip (9/13 cases). Developmental delay was a universal feature of 12p duplication including partial 12p duplication, although one patient described by Stengel-Rutkowski et al. died at 11 days of age, and hence developmental parameters could not be measured.

DISCUSSION

Here we describe a child with clinical features of PKS caused by two *de novo* microduplications of 12p13.31. Individuals with larger duplications of 12p often exhibit phenotypic overlap with PKS; however, those with smaller duplications also exhibit many of the same characteristics, implying that there are a subset of genes, or even a single gene, that when present in three or more copies results in the PKS phenotype. Since our proposita manifested with striking

facial dysmorphism resembling that of PKS, limb anomaly, congenital heart defect, and brain anomaly, we hypothesized that the duplication of the genes located within 12p13.31 might be sufficient to result in the core phenotype of PKS.

Upon review of reported cases with 12p duplications in the literature, in general, most cases shared similar phenotypic features such as prominent forehead, frontal bossing, round face, full cheeks, widely spaced eye, epicanthus, low-set ears, wide/depressed nasal bridge, short nose, anteverted nares, long philtrum, thin upper lip vermilion, everted/thick lower lip, short neck, developmental delay, and hypotonia, although the degree of phenotypic description was quite variable in each article, complicating the comparison of phenotypes throughout the cases. However, irrespective of the deletion size, there seems to be common phenotypic features with a specific facial pattern, supporting the notion that the duplication of a subset of genes is responsible for the facial phenotype. Interestingly, among the previously published cases with 12p duplication/triplication, 23 of the 26 cases have duplication of 12p13.31 in common (Fig. 3). The majority of the cases with partial 12p duplication encompassing 12p13.31 manifested with the typical facial features for 12p duplication/PKS, supporting the hypothesis that 12p13.31 harbors genes that play a critical role in the pathogenesis of 12p duplication/PKS.

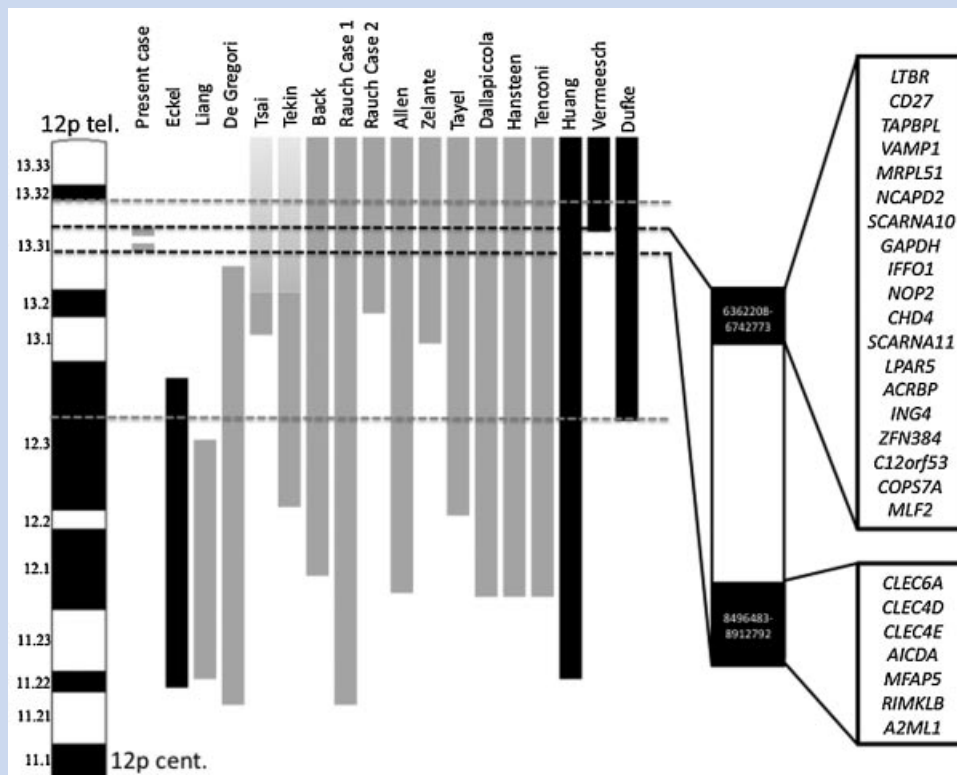


FIG. 3. Schematic diagram of the duplications seen in our proposita in relation to the previously reported partial 12p duplications/triplications [the name refers to the first author of the paper-see References]. Gray bars represent duplications and black bars represent triplications. Gray dashed lines indicate a previously proposed critical region. The telomeric boundary of the 12p duplications in the cases of Tsai et al. and Tekin et al. were mapped within 12p13.3, however, the precise mapping was not reported. The gene content within the proposita's duplication is shown on the right.

Among the cases of partial 12p duplication, it is worth mentioning the case reported by De Gregori et al. [2005]. They reported a case of partial 12p duplication from 12p11.21–12p13.31 with the telomeric breakpoint mapping to within 9.4 Mb of 12p13.31. It is unlikely that the duplication described in this case overlaps with that of our case reported herein. The patient described by De Gregori et al. [2005] had very minimal overlapping phenotypic features to that of 12p duplication and PKS, with full cheeks, wide nasal bridge, and developmental delay among the features frequently seen in 12p duplication. The absence of characteristic facial features in the case reported by De Gregori supports the hypothesis that the chromosomal region duplicated in the proposita described in this report represents a putative critical region for the PKS phenotype.

Of note, there are two articles describing three cases of 12p duplication without involvement of 12p13.31 [Eckel et al., 2006; Liang et al., 2006]. Eckel et al. [2006] described a 4-year-old male with an interstitial 12p triplication from 12p11.22–p12.3. He shared some facial findings with 12p duplication such as wide-spaced eyes, epicanthus, short nose, anteverted nares, and broad protruding lower lip. Liang et al. [2006] reported a father and son with an interstitial duplication of 12p12.3–p11.2, and they had some physical features characteristic of 12p duplication including high forehead, flat face, broad nasal bridge, short nose, thin upper vermilion, and broad everted lower lip; however, the degree of facial changes due to proximal 12p duplication is relatively mild. Therefore, some of the facial phenotypic features may be ascribed to the duplication of the genes located more proximally on 12p including 12p11.2–p12.3.

With the aim of narrowing down the candidate chromosomal region for PKS, we reviewed the literatures of partial tetrasomy 12p as well. The reports with partial tetrasomy of 12p are limited to only three cases to date [Dufke et al., 2001; Vermeesch et al., 2005; Huang et al., 2007]. Vermeesch et al. [2005] reported a patient with partial tetrasomy 12p of the smallest size (12p13.31–pter), although the authors concluded that the patient only had a partial PKS phenotype, given the lack of typical facial features, seizure, hearing loss, and skin pigmentation [Vermeesch et al., 2005]. The centromeric boundary of the partial tetrasomy 12p case reported by Vermeesch et al. was between 6.7 and 7.9 Mb, and they concluded that tetrasomy for genes located within 12p13.31 and 12p12.3 are likely contributing to the morphological abnormalities of the PKS phenotype (Fig. 3). This marker chromosome might not have included the genomic region duplicated in the proposita described here, explaining the atypical PKS phenotype of their case. Based on the findings of three cases of partial tetrasomy 12p, Huang et al. [2007] concluded that the pericentric region of 12p does not seem to contribute to the phenotypic features of PKS, which is in agreement with the conclusion derived from our systematic literature review of 12p duplication cases, and our proposed critical region.

The 12p13.31 chromosomal region has been strongly associated with the pathogenesis of various neoplasms, suggesting the presence of gene(s) important in cellular proliferation and differentiation [Gunduz et al., 2005; Korkola et al., 2006; Ye et al., 2008; Avet-Loiseau et al., 2009; Chen et al., 2011]. In fact, the chromosomal region of 12p13.31 is very rich in genes known to have functions in important cellular functions. Our proposita's duplication of

12p13.31 enables us to further narrow down the potential candidate genes for the PKS phenotype to 26 genes. While any of these genes may play a role in contributing to the PKS phenotype, three genes, *ING4*, *CHD4*, and *MAGP2* represent strong candidate genes, given their known function. *ING4* belongs to the family of inhibitor of growth (ING), which plays important roles in transcriptional regulation through associations with various binding partners including trimethylated histones and histone modifiers [Nozell et al., 2008; Hung et al., 2009]. The overexpression of *ING4* negatively regulates cell growth resulting in cell cycle arrest, and enhanced cell apoptosis [Zhang et al., 2004]. *CHD4* is a chromodomain helicase DNA binding protein, and constitutes a catalytic subunit of the nucleosome remodeling deacetylase (NuRD) transcriptional repressor complex, which plays an important role in chromatin remodeling [Tong et al., 1998]. *CHD4* is also known to play a role in the DNA-damage response and cell-cycle control [Larsen et al., 2010; Polo et al., 2010]. *MAGP2* is a microfibril-associate glycoprotein, and interacts with Notch1 [Miyamoto et al., 2006].

Our proposita had a 16p13.11–p12.3 deletion in addition to the 12p13.31 duplications. Copy number loss of 16p13.11 has been described in an association with a neurological phenotype including intellectual disability, microcephaly and seizures with very variable features [Hannes et al., 2009]. In agreement with previous studies describing the presence of the 16p13.11 deletion in apparently healthy controls, the same deletion was found in the father of the proposita. Similar deletions have been reported in five apparently healthy control subjects as well as one individual with schizophrenia and three epilepsy patients [de Kovel et al., 2010; Heinzen et al., 2010; Ingason et al., 2011]. The phenotype seen in our proposita with striking facial anomalies, congenital heart defect, and limb anomalies has not been reported in cases with 16p13.11 deletion. We feel that the contribution of the 16p13.11–p12.3 deletion to our patient's phenotype would be only neurological if any; however, the possibility that 16p13.11 deletion serves as a risk factor for multiple congenital anomalies remains, as suggested by Hannes et al. [2009].

Unfortunately, our proposita died during the neonatal period, and we were not able to monitor her neurological development. Therefore, it remains to be determined whether the duplicated regions in our proposita are responsible for the neurological phenotype in 12p duplication/PKS. The critical genomic region responsible for the neurological phenotype could be located outside of 12p13.31. In the previous case series, Segel et al. [2006] reported that development was less delayed (but not statistically significantly so) in patients with shorter duplicated segments, suggesting the possibility of the involvement of multiple genes on 12p in the pathogenesis of the neurological phenotype in PKS.

Among the frequently seen features of PKS, it is worth mentioning the absence of diaphragmatic hernia in the previously reported patients with 12p duplication. Also, coarse facial feature was not mentioned in any cases with 12p duplication, and congenital heart disease and hearing loss were reported rarely in association with 12p duplication, while present in 40 and 77% of cases in PKS, respectively [Wilkins et al. submitted]. Such phenotypic differences could be attributable to the mosaic chromosomal abnormality seen in PKS rather than a dosage effect of the genes located on chromosome

12p. Another possibility is that four copies of the 12p genes are required to develop the full PKS phenotype, while three copies, as seen in 12p duplication, result in a milder phenotype with some features not being seen due to a threshold effect. The documented poorer growth of tetrasomy 12p cells compared to non-tetrasomic cells may also contribute to the PKS phenotype [Tang and Wenger, 2005]. Further analyses are required to deepen the understanding of the molecular and cellular etiology contributing to the 12p duplication and PKS phenotypic similarities and differences.

In conclusion, we describe an infant with a microduplication of 12p13.31, who manifested with a striking phenotypic resemblance to PKS. This case enabled us to define a putative minimal critical region for the core phenotype of PKS containing 26 genes. The literature review of previously described cases with 12p duplication supports our conclusion of the presence of PKS critical region within 12p13.31. This case suggests the possibility that the PKS phenotype could result from the duplication or triplication of a very small number of developmentally critical genes.

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