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Case Report

Mosaic Potocki-Lupski Syndrome Due to a Supernumerary Marker Chromosome Containing *RAI1*

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Abstract

Potocki-Lupski syndrome (PTLS) is a recurrent microduplication syndrome characterized by developmental delay, behavioral abnormalities, mildly dysmorphic facial features, hypotonia, and sleep disorders. We report here a 3-year-old girl diagnosed with mosaic PTLS harboring a supernumerary marker chromosome containing the *RAI1* (retinoic acid induced 1) gene. Cytogenetic testing, including chromosomal microarray, karyotype, and FISH analysis, identified a ring chromosome containing portions of chromosomes 14 and 17 in 85% of cells. Clinical features of this individual included atypical facies with frontal bossing, bitemporal narrowing, prominent cupped ears, and mild speech delay. Presented here is a novel case of PTLS associated with mosaic gains of chromosomes 14 and 17. As small supernumerary marker chromosomes (sSMCs) involving non-acrocentric chromosomes are rare, this case contributes to our understanding of phenotypic spectrum associated with sSMC(17).

Keywords

Small supernumerary marker chromosome (sSMC); Potocki-Lupski syndrome (PTLS); mosaic duplication

1. Introduction

Potocki-Lupski syndrome (PTLS) (OMIM #610883) is an autosomal dominant genetic disorder caused by duplication of the chromosome 17p11.2 region encompassing the *RAI1* (retinoic acid inducible 1) gene [1-3]. The estimated prevalence of PTLS is 1 in 25,000 births [1] with most cases arising due to *de novo* microduplications [1-4]. Individuals with PTLS are characterized by developmental delay, behavioral disorders, mildly dysmorphic facial features; congenital anomalies, hypoglycemia associated with growth hormone deficiency, infantile hypotonia, sleep disorders, and oropharyngeal dysphagia leading to failure to thrive [1, 3-5]. A wide range of cognitive impairments such as intellectual disability, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder, gross motor skill deficits, and speech delay are also observed in majority of individuals with PTLS [1, 3, 4, 6]. Common craniofacial dysmorphisms associated with PTLS include triangular facies, prominent zygomatic arch, high-arched palate, frontal eminences, broad forehead, prominent ears, down-slanting palpebral fissures and mandibular hypoplasia [1, 3, 7, 8]. In addition, PTLS-related cardiovascular malformations include hypoplastic left heart syndrome, septal defects, bicuspid aortic valve, and dilated aortic root [1, 9, 10]. Mild skeletal defects and congenital anomalies of kidney are also frequently described in individuals with PTLS [1, 4, 8, 10, 11]. Notably, not all individuals with PTLS develop the above-mentioned clinical features, thus symptoms related to neurodevelopmental, behavioral, and anatomical abnormalities present on a spectrum ranging from mild to severe.

The chromosome 17p11.2p12 region contains multiple clusters of low-copy repeats (LCRs) that predispose the region to non-allelic homologous recombination (NAHR). LCRs are typically 10-500 kb long and share greater than 95% sequence identity [12]. The proximal 17p11.2 cluster, termed Smith-Magenis syndrome low-copy repeats (SMS-REPs), contains a proximal, middle, and distal LCR which share approximately 98% homology [13]. The proximal and distal SMS-REPs are in direct orientation and mediate NAHR leading to recurrent deletions and duplications [1, 3, 13]. Approximately 65-75% of individuals with PTLS harbor a recurrent 3.7-Mb microduplication mediated by the proximal and distal SMS-REPs [11].

The reciprocal deletion of the 17p11.2 region is associated with Smith-Magenis Syndrome (SMS). SMS is characterized by developmental delay, intellectual disability, sleep disturbances, and behavior abnormalities [14]. Although the SMS/PTLS region contains many genes, it is believed that dosage of the *RAI1* gene underlies many of the common features associated with these syndromes. Rare, non-recurrent duplications as small as 0.41 Mb in size have been reported in individuals with PTLS. The smallest region of overlap of reported non-recurrent duplications is a 125 kb region that includes only the gene *RAI1*, implicating *RAI1* as the critical gene for PTLS [11]. Studies also suggest that *RAI1* overexpression impairs the expression of genes involved in circadian rhythm and may account for the sleep disturbances that are associated with PTLS [15]. Furthermore, multiple individuals with a clinical diagnosis of SMS, but without a 17p11.2 deletion, have been found to carry *RAI1* loss-of-function variants [16, 17]. Comparison of the phenotypes observed in individuals harboring loss-of-functions sequence variants and recurrent deletions demonstrated that many of the features associated with SMS are due to *RAI1* haploinsufficiency [18]. Taken together, PTLS and

SMS implicate dosage sensitive of the *RAI1* gene; however, additional genes in the region likely contribute some of phenotypic variability observed in those syndromes.

Slightly distal to the SMS-REP LCRs is a second cluster of LCRs at 17p12, referred to as CMT1A-REPs. Recurrent deletions and duplications of this region that include the gene *PMP22* are associated with hereditary neuropathy with liability to pressure palsies (HNPP) and Charcot-Marie-Tooth type 1A (CMT1A), respectively, which are both characterized as adult-onset neuropathies [19]. The PTLS/SMS LCRs and HNPP/CMT1A LCRs do not share homology with each other and therefore mediate separate genomic events [13, 20]. However, some individuals with non-recurrent duplications containing *RAI1* and *PMP22* have been reported [21]. Additionally, larger, rare recurrent deletions and duplications of the SMS/PTLS region have been identified. These 5 Mb copy number variants have been shown to utilize yet another family of LCRs in the 17p11.2p12 region, termed LCR17p. The larger recurrent duplications identified in individuals with PTLS are mediated by NAHR between LCR17pA, which is located near the proximal CMT1A-REP, and LCR17pD, located adjacent to the proximal SMS-REP (Figure 1F) [11, 22]. The larger region of rare duplications mediated by LCR17pA and LCR17pD completely contains the common 3.7 Mb interval, and no significant difference in phenotypes associated with the two duplications has been observed [22].

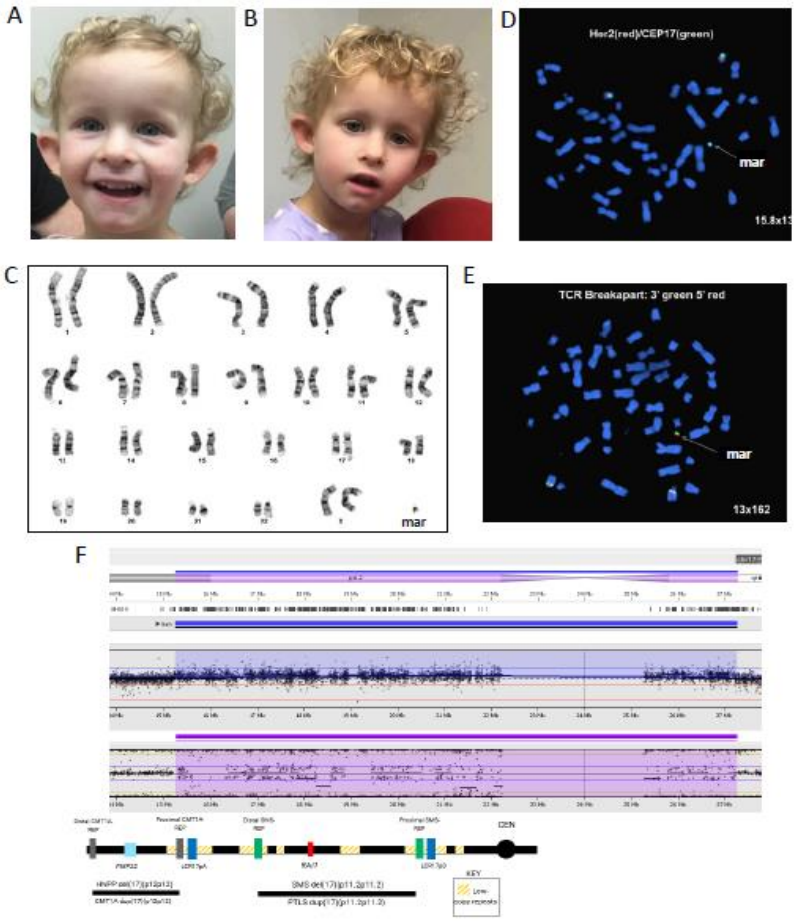

Figure 1 Clinical and Cytogenetic Findings. A. Frontal facial appearance of patient at age of 22-months and B. at 3 years 4 months. C. G-banded karyotype of patient showing supernumerary marker chromosome [47,XX,+mar]. D. Metaphase FISH showing the presence of CEP17 (green; chr 17 centromere) on both chromosome 17 and the marker chromosome; however, Her2 (red; 17q12) is present only on chromosome 17 and

absent in the marker chromosome. The arrow indicates the sSMC(17) E. Metaphase FISH showing the presence of TCR (red and green; 14q11.2) on both chromosomes 14 and the marker chromosome. F. CMA data showing the mosaic duplication on chromosome 17 and a schematic representation of the genomic region including the position of LCRs.

Due to the genomic structure of the 17p11.2p12 region, some duplications are part of complex genomic rearrangements, including chromothripsis, supernumerary marker chromosomes, and ring chromosomes [9, 21, 23, 24]. Herein, we report a young female with a diagnosis of mosaic PTLS due to a supernumerary marker chromosome containing large duplications of 14q11.1q12 (7.1 Mb) and 17p12q11.2 (12 Mb) involving the critical region of PTLS.

2. Materials and Methods

2.1 Chromosomal Microarray Analysis (CMA)

Extracted DNA from a peripheral blood specimen was labeled and hybridized to an Illumina Global Diversity + Cyto hg19 (NCBI build 37) whole genome array consisting of 1.8 million markers, with mean probe spacing of about 1.5kb. Data was processed and analyzed using NxClinical software (Bionano).

2.2 Karyotype Analysis

Lymphocytes from a peripheral blood specimen were stimulated with phytohemagglutinin and cultured for 72 h. Cells were arrested in metaphase by Colcemid treatment for 30 min followed by incubation for 30 min at room temperature with hypotonic solution (0.075 molar potassium chloride). Cells were then fixed three times with 3:1 methanol/acetic acid. Chromosomes were banded using the G-band method. Metaphase images were captured in CytoVision computerized imaging system (Leica Biosystems). G-banded metaphases were analyzed and karyograms were prepared from computer-assisted digital images of these metaphases.

2.3 Metaphase FISH

Metaphases FISH analysis was performed on PHA-stimulated lymphocytes using HER2/CEP17 and TCR probes (Abbott). Probes were hybridized overnight, and metaphase cells were analyzed using fluorescence microscopy and CytoVision Software (Leica Biosystems).

Written informed consent for participation and publication was obtained from this individual's parents.

3. Results

3.1 Case Presentation

This individual initially presented to medical genetics at an outside institution at 9 months of age for medical evaluation due to a history of failure to thrive, poor feeding, malnutrition, and severe dermatitis. Her prenatal history was complicated by late presentation to prenatal care at 26 weeks. She was born at 39 weeks via an induced vaginal delivery. Apgar scores following birth were 7 and 8, and her birthweight was 6 lb. 4 oz. She had no known family history of poor growth, speech delay,

or genetic disorders. Previous workup including a brain MRI, echocardiogram, chest and abdominal X-rays, and upper GI endoscopies and swallow studies were all unremarkable. Exome sequencing was performed at this time which showed a paternally inherited *FLG* c.2282_2285delCAGT pathogenic variant associated with ichthyosis vulgaris. No other variants were reported.

She was next evaluated in medical genetics at our institution at 23 months old. A developmental history was taken and noted that she had begun walking at 13 months, but at 23 months she was only speaking an estimated five single words, thus raising concern for a mild speech delay. Growth curves were reviewed, showing a weight <1%ile (Z-score around -2.5), length 7%ile, and head circumference measured around 30%ile. Physical exam at this time was notable for atypical facies which included frontal bossing and bitemporal narrowing, prominent ears that were simplified/cupped, bilateral shoulder dimples, and a hyperpigmented streak on her left shoulder (Figure 1A). She additionally had some skin concerns consistent with eczema and/or ichthyosis vulgaris.

A follow-up visits to the clinic at the age of 3 years 4 months showed some speech progress, speaking about 30 single words and some two-word phrases after occupational therapy and speech therapy. Her physical examination remained consistent with no newly noted significant findings (Figure 1B). Growth parameters at this time showed weight < 1%ile and height at 16%ile.

3.2 Cytogenetic Results

Based on the patient's history of poor growth, speech delay, and mildly dysmorphic facial features, a chromosomal microarray testing was sent. Chromosomal microarray analysis identified large chromosomal gains at 14q11.1q12 (7.1 Mb) and at 17p12q11.2 (12 Mb) which appeared to be mosaic with an estimated aberrant fraction of 70%. In addition, a non-mosaic duplication of unclear clinical significance was detected at 2q14.3 (1.3 Mb) which included 3 protein-coding genes. Only one gene in this region, *BIN1*, has been associated with human disease. *BIN1* is associated with autosomal recessive centronuclear myopathy and there is no evidence that duplication results in a clinical phenotype. This may represent a benign variant; however, parents were unavailable for testing, so the inheritance is unknown. The mosaic gain detected at 17p12q11.2 involved 192 genes and completely overlapped the chromosomal region associated with PTLS but did not include *PMP22* (Figure 1F). The mosaic gain detected at 14q11.1q12 appeared to be complex based on the B-allele frequency with the distal portion of the region having potentially four copies. Overall, the identification of mosaic chromosomal gains, with the 17p12q11.2 region spanning the centromere of chromosome 17, was suspicious for a small supernumerary marker chromosome (sSMC), prompting further investigation with a karyotype analysis. Karyotype analysis performed on peripheral blood ultimately revealed the presence of a mosaic marker chromosome. Based on morphology the morphology the marker appeared to be a ring chromosome; however, the exact structure could not be determined. (Figure 1C). Out of 20 cells analyzed, 12 cells (60%) contained a small marker chromosome, 5 cells (25%) contained two copies of the marker chromosome, and 3 cells (15%) were normal. Metaphase FISH demonstrated the presence of chromosome 17 centromere (CEP17) and 14q11 (TCR) on the marker chromosome further establishing that the additional genetic material identified by chromosomal microarray was present as a small supernumerary marker chromosome (mos 47,XX,+mar[12]/48,XX,+marx2[5]/46,XX[3].ish der(17)(TCR+,D17Z1+).arr[GRCh37]

2q14.3(126679224_127927990)x3,14q11.1q11.2(19011627_22414797)x3[0.7],14q11.2q12(22494430_26120779)x3,17p12q11.2(15236321_27274903)x3[0.7]) (Figure 1C and Figure 1D). As mosaicism level can vary in different tissue, the high level of mosaicism for the marker chromosome that was detected in the blood may not be representative of other tissues. However, other tissue sources were not available for testing.

4. Discussion

In this case report, we present a 3 -year-old girl harboring large chromosomal gains of 14q11.1q12 (7.1 Mb) and 17p12q11.2 (12 Mb) contained on a mosaic supernumerary marker chromosome. The pathogenic mosaic gain detected at 17p12q11.2 encompasses the *RAI1* gene and completely overlaps the recurrent PTLS duplication region [11, 25]. Small and constitutional supernumerary marker chromosomes (sSMCs), including ring chromosomes, are detected with a frequency of 0.24/1000 in newborn surveys, of 0.4-1.5/1000 in prenatal studies, and in 0.5/1000 in the general population [26-29]. The incidence of *de novo* sSMCs increases with maternal age suggesting nondisjunction is a major driver of sSMC formation [30]. Complex sSMC, contain material two or more chromosomes. Similar to the case presented here, complex sSMC often involve acrocentric chromosomes (chromosomes 13, 14, 15, 21, 22) [30-32]. Recurrent complex sSMCs have been reported which are derived from parental balanced rearrangements. In some cases, with recurrent breakpoints, complex sSMCs have been shown to be mediated by palindromes, gene clusters such as the olfactory receptor gene cluses, or fragile sites [33-36]**.** However, the mechanism for formation of complex sSMC with unique breakpoints is unclear. Some sSMCs involving non-acrocentric chromosomes may be associated with unstable LCRs [30-32, 37, 38]. sSMC(17) has only been reported in a small number of cases. Phenotypic findings in those individuals included growth delay, variable degree of developmental delay and intellectual disability, hypotonia, scoliosis, and seizures [9, 23, 38-40]. The highly variable phenotypes reported in individuals with sSMC(17) is likely due to differences in size and level of mosaicism of the duplicated material. Three other cases of molecularly defined sSMC(17) containing a region of chromosome 17 similar to the one reported here have been described [9, 23, 41]. Common phenotypes in these individuals included mild developmental delay, speech delay, hypotonia, feeding difficulties, and mild dysmorphic facial features. One individual also had seizures [9, 23, 41]. Although our patient also had a region of chromosome 14 contained on the marker chromosome, her clinical features are consistent with those seen in previously reported similar cases of sSMC(17). This suggests the mosaic duplication of chromosome 17 is primarily responsible for her phenotypic findings.

As discussed previously, the chromosomal region of 17p11p12 is particularly rich (LCRs) and frequently involved in interchromosomal and intrachromosomal recombination, thereby resulting in *de novo* interstitial deletions, duplications, triplications, translocations and other structural abnormalities [2, 3, 11, 42, 43]. In addition to the SMS-REP LCRs that mediate the vast majority of PTLS duplications, rare recurrent 5 Mb duplications mediated by additional LCRs in the region, termed LCR17pA and LCR17pD, have been reported [11, 22]. LCR17pA is located near the proximal CMT1A-REP LCR which overlaps the distal 17p duplication breakpoint in our case (Figure 1F). Interestingly, a previously reported case of sSMC(17) was also found to have a breakpoint at LCR17pA [23] consistent with LCR-mediated complex genomic rearrangements involved in marker chromosome formation.

Our case is unique, however, as the marker chromosome also contained a region of proximal 14q. Although most sSMCs involve acrocentric chromosomes, some small bi-satellited marker chromosomes are not associated with a clinical phenotype [44-46]. Delineating the phenotype associated with sSMC(14) is further complicated by multiple factors. First, sSMC(14) is sometimes associated with uniparental disomy (UPD)14, presumably due to a trisomy rescue event [47, 48]. Maternal and paternal UPD(14) are associated with Temple Syndrome and Kagami-Ogata syndrome, respectively. Individuals with maternal UPD(14) typically have poor growth, small hands and feet, hypotonia, developmental delay, and precocious puberty. Paternal UPD(14) is commonly associated respiratory distress due to a small bell-shaped thorax and narrow chest wall, abdominal wall defects, and mildly dysmorphic facial features. Some individuals may also have speech and motor delays [49]. Therefore, in cases with UPD(14) it is difficult to determine the contribution of sSMC(14) to the clinical findings. Additionally, chromosomes 14 and 22 share alphoid sequences used for common FISH centromere probes (i.e D14/22Z1). Due to the cross hybridization, some SMCs characterized by FISH cannot be definitively determined to be derived from chromosome 14 or 22. One study further characterized D14/22Z1 positive SMC cases to determine the frequency and phenotype associated with sSMC(14) and sSMC(22) [50]. In this study it was found that 40% of the characterized markers were derived from chromosome 14. Furthermore, in cases with clinical information available, 80% of individuals with sSMC(14) had a normal phenotype.

Duplications of chromosome 14 similar to the one detected in our current case have not been reported. Individuals with duplications of chromosome 14 including *FOXG1*, located at 14q12 but not included in the duplicated region in our case, appear to have a more severe phenotype with severe speech delay and seizures [51]. Smaller duplications of 14q11.2 including the genes *CHD8* and *SUPT16H*, which are contained in our patient's duplication, have been reported in a few individuals. These individuals had variable phenotypes that commonly included developmental delay, speech delay, and hypotonia [52-54]. Although the clinical significance of duplication of the proximal 14q region contained on the marker chromosome presented here is not well understood, the mosaic gain of 14q11.2-q12 may also be contributing to the phenotype in this individual. Overlapping phenotypes reported in PTLS and duplications of 14q11.2 include developmental delay, speech delay, hypotonia. As these phenotypes are relatively non-specific it is difficult to delineate the relative contribution of the detected gains of chromosomes 14 and 17 to the observed phenotype in this individual. Individuals with PTLS often have additional findings including behavioral disorders, mildly dysmorphic facial features, congenital anomalies, hypoglycemia associated with growth hormone deficiency, sleep disorders, and oropharyngeal dysphagia leading to failure to thrive [4-8]. As our patient did not present with all findings associated with PTLS, the mosaic nature of the chromosomal gain may be resulting in a milder phenotype. Additionally, the level of mosaicism was not assessed in other tissues and may affect phenotypic expression.

In summary, we report a novel case of an individual with mosaic PTLS harboring combined gains of 14q and 17p presenting as a supernumerary marker chromosome. Our patient shares many clinical features commonly seen in PTLS such as a triangular face with point chin, frontal bossing, prominent cupped ears, speech delay, and mild growth delay. As mosaic PTLS is rare, our case adds to the phenotypic spectrum associated with supernumerary marker chromosomes containing the Potocki-Lupski critical region.

Abbreviation

ADHD	Attention-Deficit/Hyperactivity Disorder
CMT1A	Charcot-Marie-Tooth type 1A
HNPP	hereditary neuropathy with liability to pressure palsies
LCRs	low-copy repeats
NAHR	non-allelic homologous recombination
PTLS	Potocki-Lupski syndrome
RAI1	retinoic acid inducible
sSMC	small supernumerary marker chromosome
SMS	Smith-Magenis Syndrome
SMS-REPs	Smith-Magenis syndrome low-copy repeats

Acknowledgments

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Author Contributions

Khaliunaa Bayanbold wrote initial draft of the case report; Noel N. Tolvanen BS created figures and contributed to revisions of the final draft; John A. Bernat first consulted with patient, did physical examination, wrote notes, sent genetic testing and evaluated a final diagnosis; Jaime Nagy performed karyotype, FISH and CMA testing, and analysis, revised and wrote final draft.

Competing Interests

The authors have declared that no competing interests exist.

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