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# POTOCKI-LUPSKI SYNDROME DUP17P11.2 IN A GIRL WITH HYPOTONIA AND EARLY BEHAVIOURAL DISTURBANCES

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## ABSTRACT

Potocki-Lupski syndrome (PTLS) is a contiguous gene syndrome caused by duplication of chromosome 17p11.2. PTLS is characterized by hypotonia, failure to thrive, congenital anomalies (particularly of the cardiovascular system), intellectual disability, and behavioural disturbances.

The patient was a full-term baby girl, 2,750 grams at birth, delivered via an uncomplicated vaginal delivery with pronounced hypotonia at birth. Nevertheless, there was failure to thrive (weight 7.6 kg; 2.8 SD). Micrognathia, epicanthal skin folds, and megalocornea were noticeable. There was a harsh continuous systolic murmur, and the ultrasound of the heart revealed a persistent arteriosus duct which was surgically closed. At the age of 18 months, the girl could not sit without support, and she could not utter simple words. The girl is often moody, angry, and aggressive. She is hyperactive and unable to establish contacts with family members. A 17p12-p11.2 microduplication was identified via MLPA.

Muscle hypotonia, congenital heart malformation, failure to thrive, developmental delay, behavioural disturbances (or autism spectrum disorder), and intellectual disability are early signs of PTLS. The presence of PTLS was proven by an MLPA analysis.

**Keywords**: Potocki–Lupski syndrome, hypotonia, cognitive delay, behavioural disturbances, congenital heart malformation

## INTRODUCTION

Potocki-Lupski syndrome (PTLS) has a frequency of approximately 1 in 25,000 births (Potocki et al 2017). The syndrome is characterised by infantile hypotonia, poor feeding, cognitive impairment, cardiovascular abnormalities, speech impairment, and behavioural disturbances [1, 2, 3, 4, 5].

PTLS is caused by a genetic duplication in the 17p11.2 region [6, 7, 8]. It is inherited in an autosomal dominant manner, with most subjects having de novo duplication [1]. It is of note that PTLS is most frequently associated with a ~3.7-Mb duplication, larger and smaller duplications were observed (Potocki et al 2000). Large duplications that encompass the PTLS region at 17p11.2 and PMP22 result in Yuan-Harel-Lupski syndrome (YUHAL)[1].

The chromosome 17p12 is prone to rearrangements and is associated with Charcot-Marie-Tooth disease type 1A, the peripheral neurop-

athies and hereditary neuropathy with liability to pressure palsies (HNPP)[1].

Our patient is a toddler with a surgically corrected persistent arteriolar duct and early and pronounced aggressive behavioural manifestations with autistic spectrum disorders traits.

## PATIENT REPORT AND METHODS

The patient is an 18-month-old girl with speech delay and muscle hypotonia. She was a full-term baby girl, 2,750 grams at birth, delivered via an uncomplicated vaginal delivery. There was no sign of short stature (76cm at 18 months; -1SD). Nevertheless, she persisted with a failure to thrive (weight 7.6 kg; 2.8SD). Micrognathia, epicanthal skin folds and megalocornea were noticeable (fig.1). She had a history of a newborn inflammation of the lacrimal glands. There are two 0.5 cm skin haemangiomas on the chest. There was a continuous systolic murmur, normal ECG and the ultrasound of the heart revealed a persistent arteriosus duct, which was surgically closed. An ultrasound of the kidneys was uneventful. The child cannot sit without support. Her hearing was unchanged. There was no anaemia, and liver and kidney biochemistry were uneventful. T4/TSH, IGF1 were within normal ranges. The girl is often hyperactive, moody, angry, and verbally and physically aggressive.

### Methods

DNA was extracted using the standard phenol-chloroform extraction method, followed byethanol precipitation. The Multiplex Ligation Probe-dependent Amplification (MLPA) methodwas applied, using P245 Microdeletion syndromes probemix and P374 Microdeletion 8 probemix (International Centre for Genetic Engineering and Biotechnology at Macedonian Academy of Sciences and Arts).

The products of MLPA reaction were analysed by capillary electrophoresis on an ABI3500 Genetic Analyzer. Coffalyzer software (MRC-Holland) was used for the analysis andinterpretation of the results.

## RESULTS

The MLPA analyses revealed duplication in the 17p11.2 chromosomal region, with a minimal length of ~1 Mb, involving the COPS3, RAI1, TOM122, DRC3 and LLGL1 genes. The duplication was not present in the parents; thus, it has arisen as a de novo event.

17p11.2 duplication was detected by MLPA analysis using probemix P245 and probemix P374.

## DISCUSSION

There are two reciprocal contiguous gene syndromes within the 17p11.2 region: Smith-Magenis syndrome (SMS) and PTLS [1]. The retinoic acid-inducible 1 gene (RAI1) is the dosage-sensitive gene responsible for the major phenotypic features of both syndromes.

PTLS has a plethora of neurodevelopmental disturbances [1, 11]. Infantile hypotonia and failure to thrive can dominate clinical manifestations of PTLS. In addition, there is developmental delay (our patient did not walk or speak at the age of 18 months), usually moderate intellectual disability. It is of note that patients with PTLS may have features of autism spectrum disorder and hyperactivity [9]. Upon completing sleep studies there was sleep-disordered breathing.

Congenital heart disease and surgically closed persistent arterial duct are common. Jefferies et al. (2012; 3) found cardiovascular anom-

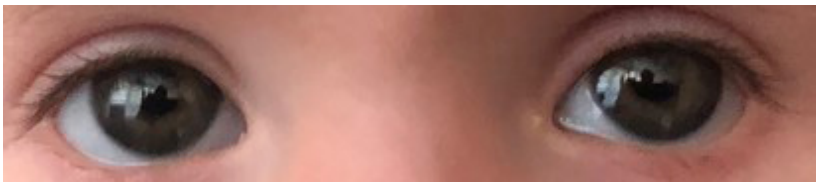

**Figure 1.** *Epicanthus and megalocornea.*

alies in 10 of 25 (40%) of PTLS subjects. The most frequent abnormality was a dilated aortic root (20% of total cohort). They also observed bicommissural aortic valve (2/25), atrial (3/25) and ventricular (2/25), septal defects, and patent foramen ovale (4/25). A hypoplastic left heart syndrome was also reported [13].

The common facial features are micrognathia and down slanting palpebral fissures [5, 9]. We also observed epicanthal folds and macrocornea. Our patient had a low weight but her height was in the 25th percentile, which, together with normal serum concentrations of IGF1, were signs that there was no growth hormone deficiency, something which can also be found in PTLS.

In conclusion, muscle hypotonia, congenital heart malformation, failure to thrive, developmental delay, behavioural disturbances (or autism spectrum disorder), and intellectual disability are early signs of PTLS syndrome. The PTLS was proven by MLPA analysis.

## REFERENCES


1. Potocki L, Neira-Fresneda J, Yuan B.Potocki-Lupski Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2017 Aug 24.
2. Campbell IM, Shaw CA, Stankiewicz P, Lupski JR. Somatic mosaicism: implications for disease and transmission genetics. Trends Genet. 2015;31:382–92.
3. Jefferies JL, Pignatelli RH, Martinez HR, Robbins-Furman PJ, Liu P, Gu W, Lupski JR, Potocki L. Cardiovascular findings in duplication 17p11.2 syndrome. Genet Med. 2012;14:90–4.
4. Magoulas PL, Liu P, Gelowani V, Soler-Alfonso C, Kivuva EC, Lupski JR, Potocki L. Inherited dup(17)(p11.2p11.2): expanding the phenotype of the Potocki-Lupski syndrome. Am J Med Genet A. 2014;164A:500–4.
5. Neira-Fresneda J, Potocki L. Neurodevelopmental disorders associated with abnormal gene dosage: Smith-Magenis and Potocki-Lupski Syndromes. J Pediatr Genet. 2015;4:159–67.
6. Walz K, Paylor R, Yan J, Bi W, Lupski JR. Rai1 duplication causes physical and behavioural phenotypes in a mouse model of dup(17)(p11.2p11.2). J Clin Invest. 2006;116:3035–41.
7. Walz K, Spencer C, Kaasik K, Lee CC, Lupski JR, Paylor R. Behavioral characterization of mouse models for Smith-Magenis syndrome and dup(17)(p11.2p11.2). Hum Mol Genet. 2004;13:367–78.
8. Yuan B, Harel T, Gu S, Liu P, Burglen L, Chantot-Bastaraud S, Gelowani V, Beck CR, Carvalho CMB, Cheung SW, Coe A, Malan V, Munnich A, Magoulas PL, Potocki L, Lupski JR. Nonrecurrent 17p11.2p12 rearrangement events that result in two concomitant genomic disorders: the PMP22-RAI1 contiguous gene duplication syndrome. Am J Hum Genet. 2015;97:691–707.
9. Potocki L, Bi W, Treadwell-Deering D, Carvalho CMB, Eifert A, Friedman EM, Glaze D, Krull K, Lee JA, Lewis RA, Mendoza-Londono R, Robbins-Furman P, Shaw C, Shi X, Weissenberger G, Withers M, Yatsenko SA, Zackai EH, Stankiewicz P, Lupski JR. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism Phenotype. Am J Hum Genet. 2007;80:633–49.
10. Potocki L, Chen K-S, Park S-S, Osterholm DE, Withers MA, Kimonis V, Summers AM, Meschino WS, Anyane-Yeboa K, Kashork CD, Shaffer LG, Lupski JR. Molecular mechanism for duplication 17p11.2 - the homologous recombination reciprocal of the Smith-Magenis microdeletion. Nat Genet. 2000;24:84–7.
11. Soler-Alfonso C, Motil KJ, Turk CL, Robbins-Furman P, Friedman EM, Zhang F, Lupski JR, Fraley JK, Potocki L. Potocki-Lupski syndrome: A microduplication syndrome associated with oropharyngeal dysphagia and failure to thrive. J Pediatr. 2011;158:655–9.e2.
12. Treadwell-Deering DE, Powell MP, Potocki L. Cognitive and behavioural characterization of the Potocki-Lupski syndrome (duplication 17p11.2). J Dev Behav Pediatr. 2010;31:137–43.
13. Yusupov R, Roberts AE, Lacro RV, Sandstrom M, Ligon AH. Potocki-Lupski syndrome: An inherited dup(17)(p11.2p11.2) with hypoplastic left heart. Am J Med Genet A. 2011;155A:367–71.

**Резиме**

## СИНДРОМОТ ПОТОЦКИ-ЛУПСКИ ((DUP(17) (P11.2P11.2)) КАЈ ДЕВОЈЧЕ СО ХИПОТОНИЈА И РАНО НАРУШУВАЊЕ ВО ОДНЕСУВАЊЕТО

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Синдромот Поточки-Лупски (PTLS) е синдром на соседен ген предизвикан од дуплирање на хромозомот 17p11.2. PTLS се карактеризира со хипотонија, неуспех за напредување, вродени аномалии (особено на кардиоваскуларниот систем), интелектуална попреченост и нарушувања во однесувањето.

Пациентот беше доносено девојче, 2.750 грама при раѓање, со вагинално породување без компликации со изразена хипотонија при раѓање. Како и да е, имаше неуспех за напредување (тежина 7,6 кг; 2,8 СД).

Беа забележливи микрогнатија, епикантални набори на кожата и мегалокорнеа. Имаше остар континуиран систолен шум, а ултразвукот на срцето откри постојан артериозус канал кој беше хируршки затворен. На возраст од 18 месеци, девојчето не можеше да седи без поддршка и не може да изговори едноставни зборови. Девојчето е често нерасположено, луто и агресивно. Таа е хиперактивна и не може да воспостави контакти со членовите на семејството. Микродупликација на 17p12-p11.2 беше идентификувана преку MLPA.

Мускулна хипотонија, вродена срцева малформација, неуспех во напредување, одложување на развојот, нарушувања во однесувањето (или нарушување на спектарот на аутизам) и интелектуалната попреченост се рани знаци на PTLS. Присуството на PTLS беше докажано со MLPA анализа..

**Клучни зборови**: синдром Потоцки-Лупски, хипотонија, когнитивно доцнење, нарушувања во однесувањето, вродена малформација на срцето