17p13.1 Microduplication Syndrome in a Child, Familial Short Stature, and Growth Hormone Deficiency: A Case Report and Review of the Literature

Sofia Leka-Emiri^a Vassilios Petrou^a Emmanouil Manolakos^d
Loretta Thomaidis^c Aspasia Fotinou^b Elpis Vlachopapadopoulou^a
Stefanos Michalacos^a

Departments of ^aEndocrinology, Growth and Development, ^bBiochemistry and Hormonology, and ^cDevelopmental Assessment Unit, Department of Pediatrics, P&A Kyriakou Children's Hospital, School of Medicine, National and Kapodistrian University of Athens, and ^dAccess to Genome (ATG P.C.), Clinical Laboratory Genetics, Athens, Greece

Established Facts

- Familial short stature is considered a “normal” variation of growth and is the most common cause of short stature with a prevalence of 40% among children growing beyond <-2 SD for the same sex and age.
- The prevalence of growth hormone deficiency is reported to occur in 1:4,000 to 1:10,000 among children.

Novel Insights

- Growth hormone deficiency should be investigated in familial short stature.
- Developmental disabilities and short stature should prompt CGH analysis.
- The 17p13.1 microduplication syndrome may be associated with growth hormone deficiency.

Keywords

Comparative genomic analysis · Familial short stature · Growth hormone deficiency · Microduplication syndrome 17p13.1

Abstract

To date, 6 cases of 17p13.1 microduplications have been described in the literature. Intellectual disability is the core fea-

ture, together with minor facial dysmorphisms and obesity. We describe the first case of a young patient with a maternally inherited microduplication in 17p13.1 presenting with growth hormone deficiency. The boy was addressed to the endocrine division for growth retardation (weight and height <3 rd percentile). Besides minor facial dysmorphisms, physical and neurological examinations were normal except for motor dyspraxia. Basic blood tests and endocrinological investigations were normal, but IGF1 levels were low for his

age. Growth hormone deficiency was confirmed. Hypothalamic pituitary MRI was normal. His karyotype was 46XY. Array-CGH analysis detected a 422-kb copy number gain in the spanning region 17p13.1 inherited from his mother. Although familial short stature is considered a “normal” variation of growth retardation, hormonal and genetic investigation is essential in the etiological diagnosis.

© 2018 S. Karger AG, Basel

The short arm of chromosome 17 is associated with a large variety of copy number losses and gains, resulting from nonallelic homologous recombinations between low copy repeats that lead to several well-characterized genomic disorders. While the 17p13.1 microdeletion syndrome is well described [Komoike et al., 2010; Carvalho et al., 2014], to date only few cases of 17p13.1 microduplication have been reported [Belligni et al., 2012; Coutton et al., 2012; Kuroda et al., 2014; Mooneyham et al., 2014; Maini et al., 2016], and a distinct phenotype has not yet been defined. Intellectual disability was observed in all patients as the hallmark feature. In addition, a wide range of clinical signs has been reported, such as behavioral abnormalities, growth retardation, dysmorphisms, obesity, and other endocrinological abnormalities such as insulin resistance and diabetes as well as dyslipidemia and hypothyroidism (Understanding Rare Chromosome and Gene Disorders [UNIQUE]): <https://www.rarechromo.org>. Here, we report a 7-year-old boy with a 17p13.1 microduplication who, along with intellectual disability and mild facial dysmorphism, presented with growth retardation due to growth hormone (GH) deficiency.

Case Report

The boy was first examined at the age of 3.5 years for growth retardation: his weight was 12.8 kg (3rd percentile) and his height was 89.1 cm (<3rd percentile). He is the only child of healthy unrelated parents of Caucasian ancestry. His mother is short (height: 148.5 cm, <3rd percentile) and was diagnosed with learning difficulties at school. His father is also short (height: 154.5 cm, <3rd percentile) with normal intelligence, and no other family history of intellectual disability or endocrine disorder was reported. The child was born by normal spontaneous vaginal delivery at 40 weeks' gestation after an uneventful pregnancy (weight: 3,070 g, 25th percentile; length: 47 cm, 3rd percentile, and head circumference: 34 cm, 25th percentile). During infancy and early childhood, the boy showed mild developmental delay. At 7 years of age, he was underweight (18 kg, –2 SD), but his height was more severely compromised (105 cm, –3.2 SD). Apart from minor facial dysmorphic features such as moderate micrognathia, low-set ears, and a long philtrum, no other abnormalities, asymmetries, or skeletal deformities were found (Fig. 1).

Methods and Results

Neurological examination showed oral motor dyspraxia without focal neurological signs. EEG recordings revealed slow background activity without paroxysmal features. Basic hematologic and biochemistry tests as well as endocrinological investigation revealed normal thyroid and cortisol levels, but IGF1 levels were low for his age. GH response to 2 different stimulation tests was <10 ng/mL, consistent with GH deficiency (Table 1). Hypothalamic pituitary MRI was normal.

Taking the familial pattern of short stature and intellectual disability into consideration, genetic investigation was prompted. A chromosome analysis revealed a normal male karyotype. Further investigation with array CGH was performed by hybridizing the sample against a male human reference commercial DNA sample (Promega Biotech) using an array-CGH platform which includes 60,000 oligonucleotides distributed across the entire genome (Agilent Technologies). Only those copy number changes that affect at least 5 consecutive probes with identically oriented change were considered as CNVs. For the majority of the genome, the average genomic power of resolution of this analysis was 200 kb. Array-CGH analysis detected a 422-kb copy number gain in the spanning region 17p13.1. The breakpoint was mapped between genomic coordinates chr17:6,902,072–7,324,005 (genomic coordinates are listed according to genomic build GRCh37/hg19) (Fig. 2). No additional aberrations were detected. Both parents were found to have normal karyotypes, but the mother's and son's array-CGH results were identical, indicating that the boy had inherited the duplication from his mother. The father's array-CGH analysis was normal.

Discussion

In the literature, 6 cases with 17p13.1 microduplications have been described so far, and duplications ranged between 62.50 and 788 kb [Belligni et al., 2012; Coutton et al., 2012; Maini et al., 2016; Kuroda et al., 2014; Mooneyham et al., 2014]. Detailed clinical information of all cases regarding the 17p13.1 duplication syndrome is reported in Table 2. The de novo 586-kb duplication (6,690,620–7,276,764) in 17p13.1 described by Coutton et al. [2012] and the de novo 788-kb duplication (6,610,939–7,399,323) in 17p13.1 described by Mooneyham et al. [2014] share a large duplicated region with our case presenting with a 422-kb duplication (6,902,072–7,324,005).

Fig. 1. Growth curves and physical appearance of the patient at the age of 7 years.

Table 1. Hormone levels

	Levels
IGF1	57 (17–248) ng/mL
Clonidine stimulation test	GH peak max: 7.6 ng/mL (>10 ng/mL)
Glucagon stimulation test	GH peak max: 6.06 ng/mL (>10 ng/mL)
TSH	2.4 μ IU/mL (0.5–6)
FT4	1.19 ng/dL (0.9–1.9)
Cortisol (8 a.m.)	15.1 μ g/dL (6.2–18)

FT4, free thyroxine; GH, growth hormone; IGF1, insulin-like growth factor 1; TSH, thyroid-stimulating hormone.

To our knowledge, our case is the second described so far, with growth retardation and the first with a detected GH deficiency. The only child described in the literature with growth retardation and 17p13.1 microduplication was a boy with Russel-Silver syndrome [Coutton et al., 2012].

In that case, although serum GH levels were normal, GH therapy was initiated at 4.5 years of age, due to small for gestational age. At 15 years, he achieved puberty, his height was 158 cm (5–10th centile), and his weight 48 kg (10–25th centile). In our case, rhGH was initiated at 7 years with consistent growth acceleration since then (Fig. 1).

Children born with duplication of different regions of chromosome 17 are often, but not always, small and underweight at birth. Feeding difficulties are a major area of concern for families, and infants may have failure to thrive. The hypotonia that is common in babies with a 17p duplication (regardless of the region duplicated in 17p) can lead to difficulties with sucking and swallowing. Children with a duplication of 17p often have short stature. Among the 36 genes located in the duplicated region, 2 genes (*GABARAP* and *SLC2A4*) have been reported to be related to growth retardation, but their exact role remains uncertain. *GABARAP* is a GABA_A receptor-asso-

Table 2. Clinical information for all cases carrying a 17p13.1 duplication

	Present case male, 7 yrs	Maini et al. [2016] male, 12 yrs	Mooneyham et al. [2014] male, 2 yrs	Mooneyham et al. [2014] female, 29 yrs	Kuroda et al. [2014] female, 9 yrs	Belligni et al. [2012] male, 15 yrs	Couton et al. [2012] male, 4.5 yrs	Total
Intellectual disability	+	+		+	+	+	+	6/7
Developmental delay	+		+					2/7
Sociable		+				+	+	3/7
Hyperactive		+		+		+	+	4/7
Food hoarding		+		+		+	+	4/7
Afebrile seizures				+		+		2/7
Hypotonia			+		+	+		3/7
Nystagmus			+					1/7
Motor dyspraxia	+	+						2/7
Strabismus	+	+		+				3/7
Dysmorphic features								7/7
Macrocephaly			+, A	+, R			+, R	3/7
Broad forehead	+		+				+	3/7
High anterior line	+		+	+			+	4/7
Flat occiput	+	+	+					3/7
Triangular face	+		+				+	3/7
Round face	+	+			+	+		4/7
Synophrys		+						1/7
Upslanting palpebral fissures	+	+		+	+			3/7
Broad nasal tip	+		+	+	+	+		5/7
Upturned nostrils	+	+			+			3/7
Micrognathia	+	+	+	+		+	+	6/7
Full lips			+	+	+			3/7
Clinodactyly	+			+			+	3/7
Short hyperconvex nails		+						1/7
Obesity		+		+	+	+		4/7
Endocrinological abnormalities								
Hypothyroidism						+		1/7
Dyslipidemia		+		+	+	+		4/7
Insulin resistance		+		+	+	+		4/7
Diabetes		+		+		+		3/7
Growth retardation	+						+	2/7
	Ht: -3.2 SD Wt: -2 SD	Ht: +0.5 SD Wt: +1.3 SD	Ht: -0.8 SD Wt: -0.2 SD	Ht: +0.6 SD Wt: +1.8 SD	Ht: -0.2 SD Wt: +2.1 SD	Ht: -0.8 SD Wt: +1.8 SD	Ht: -3 SD	
Brain MRI				n.d.	n.d.		n.d.	
Enlarged extra-axial spaces			+					1/7
Hippocampal anomalies		+						1/7
Reduced cortical gyration		+						1/7
Choroid plexus cysts						+		1/7

A, absolute; Ht, height; n.d., not done; R, relative; Wt, weight; yrs, years; +, present.

delayed bone age [Blassnig-Ezeh et al., 2013]. In short children, microdeletions (in contrast to microduplications) are encountered more frequently than in controls [Dauber et al., 2011]. The 17q21q25 duplication syndrome (17q2125dup) includes developmental delay, distal arthrogyrosis, GH insensitivity, disturbed STAT5B, PI3K, and NF-kappaB signaling with a possible role of PRKCA mRNA overexpression [Lukusa and Fryns, 2010; Mul et al., 2012]. Distal 14q duplication syndrome (14q32.2qter) presents with short stature, mild developmental delay, a high forehead, hypertelorism, dysplastic ear helices, short

philtrum and cupid bow upper lip, a broad mouth, and micrognathia [Thiel et al., 2008]. Short stature with microcephaly and speech delay is also described in the 5q35.2q35.3 duplication syndrome (5q35.2q35.3dup) [Franco et al., 2010]. However, for these individual cases, it often remains uncertain if their growth failure is due to the encountered CNV, and which of the genes is responsible for growth delay. Comparison of index cases with previously reported patients and databases such as DECIPHER (<http://decipher.sanger.uk>) and ECARUCA (<http://www.ecaruca.net>) may give hints for candidate genes.

In addition, 4 genes that are located in the duplicated region (*SLC16A11*, *SLC16A13*, *CLEC10A*, and *PLSCR3*) have been associated to insulin resistance and glucose intolerance. Our patient has not developed glucose metabolism disorders so far. Minor abnormalities of the genitals are reported in male infants with 17p.13.1 microduplication syndrome, such as hypospadias and cryptorchidism. Micropenis has been seen in a boy with 17p13 microduplication syndrome [Roos et al., 2009]. Our patient showed no genital abnormalities.

In conclusion, we describe a patient with familial short stature, GH deficiency, and mild developmental delay in association with 17p13.1 microduplication. For children with familial short stature, endocrinological testing belongs to standard procedures. The patient reported here illustrates the necessity to additionally prompt genetic investigation in these cases. It is noteworthy that GH deficiency is reported to account for up to 1–2% in children with short stature; in 30% of the cases it is a familial trait. Familial short stature is considered a “normal” variation of growth and is the most common cause of short stature

with a prevalence of 40% among children growing beyond <-2 SD for the same sex and age [Murray et al., 2016; Wit et al., 2016]. The improvement of molecular techniques in association with careful medical history and physical examination can elucidate the etiology for patients with short stature that previously could be characterized as normal variants. Familial heritability of short stature is of great significance, not only for precise diagnosis, but even more importantly for the future life-long health surveillance and guidance.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that there is no financial interest or any conflicts of interest.

References

- Belligni EF, Di Gregorio E, Biamino E, Calcia A, Molinatto C, et al: 790 Kb microduplication in chromosome band 17p13.1 associated with intellectual disability, afebrile seizures, dysmorphic features, diabetes, and hypothyroidism. *Eur J Med Genet* 55:222–224 (2012).
- Blassnig-Ezeh A, Bandelier C, Frühmesser A, Revencu N, Krabichler B, et al: Severe growth retardation, delayed bone age, and facial dysmorphism in two patients with microduplications in 2p16→p22. *Am J Med Genet* 161:3176–3181 (2013).
- Carvalho CM, Vasanth S, Shinawi M, Russell C, Ramocki MB, et al: Dosage changes of a segment at 17p13.1 lead to intellectual disability and microcephaly as a result of complex genetic interaction of multiple genes. *Am J Hum Genet* 95:565–578 (2014).
- Coutton C, Devillard F, Vieville G, Amblard F, Lopez G, et al: 17p13.1 microduplication in a boy with Silver-Russell syndrome features and intellectual disability. *Am J Med Genet A* 158A:2564–2570 (2012).
- Dauber A, Yu Y, Turchin MC, Chiang CW, Meng YA, et al: Genome-wide association of copy-number variation reveals an association between short stature and the presence of low-frequency genomic deletions. *Am J Hum Genet* 89:751–759 (2011).
- Franco LM, de Ravel T, Graham BH, Frenkel SM, Van Driessche J, et al: A syndrome of short stature, microcephaly and speech delay is associated with duplications reciprocal to the common Sotos syndrome deletion. *Eur J Hum Genet* 18:258–261 (2010).
- Komoike Y, Shimojima K, Liang JS, Fujii H, Mae-gaki Y, et al: A functional analysis of GABARAP on 17p13.1 by knockdown zebrafish. *J Hum Genet* 55:155–162 (2010).
- Kuroda Y, Ohashi I, Tominaga M, Saito T, Nagai J, et al: De novo duplication of 17p13.1-p13.2 in a patient with intellectual disability and obesity. *Am J Med Genet A* 164:1550–1554 (2014).
- Lukusa T, Fryns JP: Pure de novo 17q25.3 microduplication characterized by micro array CGH in a dysmorphic infant with growth retardation, developmental delay and distal arthrogryposis. *Genet Couns* 21:25–34 (2010).
- Maini I, Ivanovski I, Iodice A, Rosato S, Pollazzon M, et al: Endocrinological abnormalities are a main feature of 17p13.1 microduplication syndrome: a new case and literature review. *Mol Syndromol* 7:337–343 (2016).
- Mooneyham KA, Holden KR, Cathey S, Dwivedi A, Dupont BR, Lyons MJ: Neurodevelopmental delays and macrocephaly in 17p13.1 microduplication syndrome. *Am J Med Genet A* 164:2887–2891 (2014).
- Mul D, Wu S, de Paus RA, Oostdijk W, Lankester AC, et al: A mosaic de novo duplication of 17q21–25 is associated with GH insensitivity, disturbed in vitro CD28-mediated signaling, and decreased STAT5B, PI3K, and NFkB activation. *Eur J Endocrinol* 166:743–752 (2012).
- Murray PG, Dattani MT, Clayton PE: Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child* 101:96–100 (2016).
- Roos L, Jönch AE, Kjaergaard S, Taudorf K, Simonsen H, et al: A new microduplication syndrome encompassing the region of the Miller-Dieker (17p13 deletion) syndrome. *J Med Genet* 46:703–710 (2009).
- Thiel CT, Dörr HG, Trautmann U, Hoyer J, Hofmann K, et al: A de novo 7.6 Mb tandem duplication of 14q32.2-qter associated with primordial short stature with neurosecretory growth hormone dysfunction, distinct facial anomalies and mild developmental delay. *Eur J Med Genet* 51:362–367 (2008).
- Wit JM, Oostdijk W, Losekoot M, van Duyvenvoorde HA, Ruivenkamp CA, Kant SG: Mechanisms in endocrinology: novel genetic causes of short stature. *Eur J Endocrinol* 174:R145–173 (2016).