17p13.1 Microduplication Syndrome in a child with familial short stature and growth hormone deficiency: A short case report and review of the literature

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Introduction and objectives

- 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 < -2SDS 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
- We describe a young patient with a microduplication maternally inherited in 17p13.1 who is the first case reported presenting growth hormone deficiency

Case report

A toddler boy age 7 was addressed to the endocrine division for growth retardation (weight and height <3rd percentile).

On **physical examination** besides minor facial dysmorphism, physical and neurological examination were normal except for motor dyspraxia (fig.1).

Laboratory investigations:

- Basic blood tests and endocrine investigations were normal
- IGF1 levels were low for his age.
- Growth hormone deficiency was confirmed (table 1).
- Hypothalamic pituitary MRI was normal. Karyotype was 46 XY, normal male.
- **Array-CGH analysis** detected a 422 Kb gain of copy in the spanning region 17p13.1 inherited from his mother (fig.2).

Results

- In the literature 6 cases with 17p13.1 microduplications have been described so far and duplications ranged between 62,50kb and 788kb (table 2).
- Our case is the second one described so far, with growth retardation and the first one presenting growth hormone deficiency.
- Among the 36 genes described to be present in the duplicated region 2 genes (GABARAP and SLC2A4) have been reported to be related to growth retardation but their exact role remains uncertain.
- In addition, 4 genes that are present 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 abnormalities so far.
- Minor abnormalities of the genitals are reported, in male infants with 17p.13.1 microduplication syndrome, such as hypospadias, micropenis and cryptorchidism. Our patient did not present genital abnormalities.

Conclusions

- The patient presented here illustrates the necessity to investigate not only hormonally but genetically as well, children with familial short stature.
- 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.
- Etiological investigation of familial short stature is of great importance not only for precise diagnosis but even more importantly for the future life-long health surveillance and guidance.

[Maini et al., 2012; Mooneyham et al., 2014; Kuroda et al., 2014; Belligni et al., 2012; Coutton et al., 2012].

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

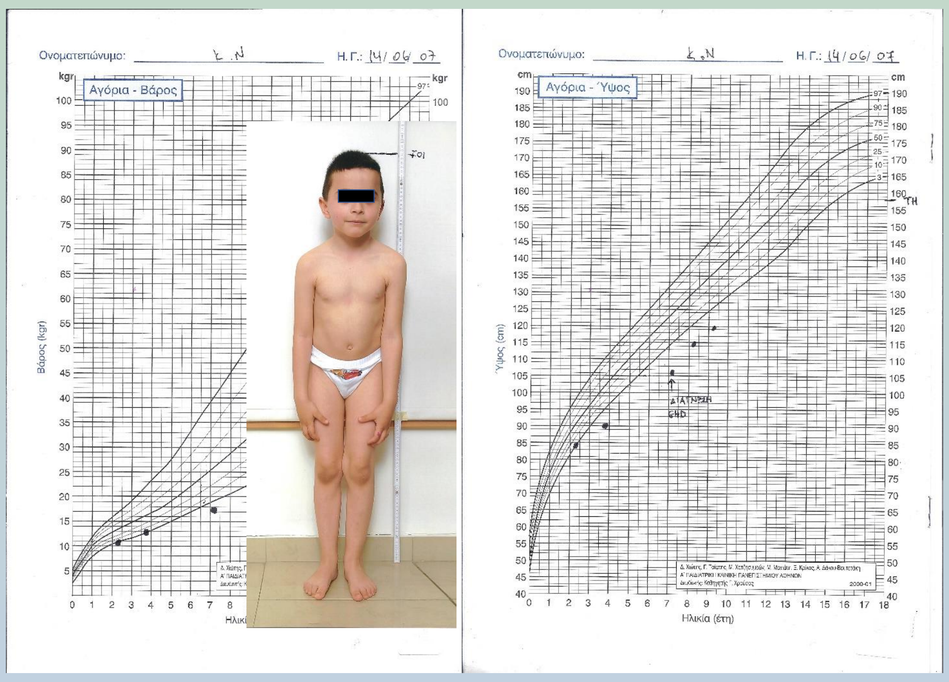

Table 1. Hormonal levels

IGF1:57 (17-248)ng/ml
Clonidine stimulation test: GH peak max: 7.6 ng/ml (>10ng/ml)
Glucagon stimulation test: GH peak max: 6.06ng/ml (>10ng/ml)
TSH: 2.4μIU/ml (0.5-6), FT4:1.19ng/dl(0.9-1.9)
Cortisol (8am): 15.1μg/dl (6.2-18)

Fig. 2. Array-CGH analysis detected a 422 Kb gain of the copy numbers in the spanning region 17p13.1. The breakpoint was mapped between genomic coordinates chr17: 6,902,072-7,324,005. Genes and gene predictions located in the duplicated region taken from http://genome.ucsc.edu. The red box indicates the duplicated region of 17p13.1 chromosome band.

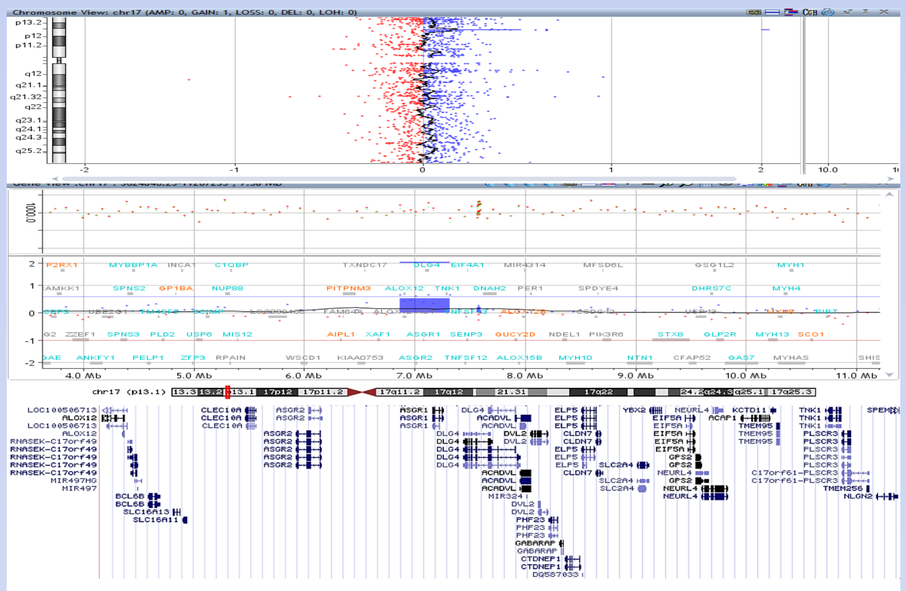

Table 2. Clinical information for all cases carrying the 17p13.1 duplication

	Present case male, 7yrs	Maini et al [2016] male, 12yrs	Mooneyham et al. [2014] male, 2yrs	Mooneyham et al. [2014] female, 29yrs	Kuroda et al. [2014] female, 9yrs	Belligni et al. [2012] male, 15yrs	Couton et al. [2012] male, 4.5yrs	Total
Intelectual disability	+	+		+	+	+	+	6/7
Developmental delay	+		+					2/7
Sociable		+				+	+	3/7
Hyperactive		+		+		+	+	4/7
Food hording		+		+		+	+	4/7
Afebrile seizures				+		+		2/7
Hypotonia			+		+	+		3/7
Nystagmus			+					1/7
Motor dyspraxia	+	+						2/7
Strabism	+	+		+				3/7
Dysmprphic features								7/7
Macrocephaly			+ (A)	+ (R)			+ (R)	3/7
Broad forehead	+		+				+	3/7
High anterior line	+		+	+			+	4/7
Flat occiput	+	+	+					3/7
Triangular face	+		+				+	37
Rounded face	+	+			+	+		4/7
Synophris		+						1/7
Upslantig 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	+ Ht: <-3.2SD Wt: <-2SD	Ht: +0.5SD Wt: +1.3SD	Ht: -0.8SD Wt: -0.2SD	Ht: +0.6SD Wt: +1.8SD	Ht: -0.2SDS Wt: +2.1SD	Ht: -0.8SD Wt: +1.8SD	+ Ht: -3SD	2/7
Brain MRI				n.d.	n.d		n.d	
Enlarged extra-axial spaces			+					1/7
Hippocampal dysmorphisms		+						1/7
Reduced cortical gyration		+						1/7
Choroid plexus cysts						+		1/7

A= absolute; R= relative; n.d.=not done; + = present

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Growth and syndromes (to include Turner syndrome)

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