

## Phenotype variability in thirteen 16p11.2 deletion patients<sup>☆</sup>



### Variabilidad fenotípica en 13 casos de delección 16p11.2

Dear Editor:

In the past 10 years, comparative genomic hybridization array (aCGH) methods have allowed the identification and characterization of numerous syndromes caused by copy-number variations. The deletion of approximately 600 kb in chromosome 16p11.2 is one of the most frequent disorders of this type.<sup>1</sup> It was initially associated with autism, but at present there is evidence of its association with a wide phenotypic spectrum with incomplete penetrance and variable expression, manifesting most frequently with language disorders, obesity and psychiatric disorders.<sup>2-4</sup>

Chromosome 16p11.2 deletion syndrome (OMIM 611913) has an autosomal dominant pattern of inheritance. Most

cases correspond to *de novo* mutations, but the deletion can be inherited from a symptomatic or asymptomatic parent.

We present 6 index cases (Table 1) and the cases of 7 relatives with chromosome 16p11.2 deletion syndrome diagnosed by means of aCGH.

We obtained the informed consent of all the patients or their legal guardians.

**Case 1.** Boy aged 7 years presenting with psychomotor retardation (PMR), social impairment and nasal flaring. In the past few months, the patient had exhibited spells during which he was unaware of his surroundings during the evaluation. The mother was a carrier of the deletion and reported having had problems in school and dropping out of compulsory secondary education.

**Case 2.** Boy aged 6 years with language delay, mainly in expressive language, and difficulty performing logical or sequential tasks. The mother, grandmother and 3 maternal uncles had the deletion.

The grandmother, aged 53 years, had epilepsy and overweight. The mother, aged 33 years, had anxiety and depression. A maternal aunt aged 27 years dropped out of

**Table 1** Clinical characteristics of index cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex, age	M, 7 y	M, 6 y	M, 8 y	F, 11 y	F, 15 y	F, 26 y
Size of deletion (number of contained genes)	596 kb (29)	598 kb (29)	448 kb (26)	516 kb (28)	514 kb (27)	552 kb (29)
Inheritance	Maternal	Maternal	<i>de novo</i>	<i>de novo</i>	Maternal	Undetermined <sup>a</sup>
Perinatal history	Delivery at 36 weeks	IUGR	TTN	—	—	—
Anthropometry	Wt: 33 (82th PCTL)	Wt: 32.5 (97th PCTL)	Wt: 46.5 (98th PCTL)	Wt: 41.5 (42th PCTL)	Wt: 63 (74th PCTL)	Wt: >100 (>99th PCTL)
Ht and HC (cm)	Ht: 124 (15th PCTL)	Ht: 120 (45th PCTL)	Ht: 130 (31th PCTL)	Ht: 149 (47th PCTL)	Ht: 158 (26th PCTL)	Ht: 159 (20th PCTL)
BMI	HC: 54 (83th PCTL)	HC: 54 (92th PCTL)	HC: 55 (94th PCTL)	HC: 55 (70th PCTL)	HC: 55 (88th PCTL)	HC: 58 (>98th PCTL)
	BMI: 21.5 (96th PCTL)	BMI: 22.6 (>99th PCTL)	BMI: 27.5 (>99th PCTL)	BMI: 18.9 (43th PCTL)	BMI: 25.3 (88th PCTL)	BMI >39.6 (>99th PCTL)
Dysmorphic features	Cupid's bow upper lip, macroglossia	—	Cupid's bow upper lip, single palmar crease	High-arched palate, clinodactyly in 5th finger	Cupid's bow upper lip, high-arched palate, short neck	High-arched palate, short neck
Psychomotor retardation	+ (mild)	—	+ (mild)	+ (mild)	—	—
Cognitive impairment	+ (mild)	+ (borderline)	+ (mild)	+ (mild)	+ (mild)	+ (mild)
Social impairment	+	—	—	—	+	—
Language disorder	+	+	+	+	NR	+
Behavioural/psychiatric disorder	—	ADHD	—	—	NR	Depression
Epilepsy	+	—	—	+	+	Bulimia
Macrocephaly	—	—	—	—	—	+ (resolved)
Obesity (years of age at onset)	+ (6)	+ (5)	+ (6)	—	Overweight	+ (6)
Other	Strabismus	SAHS AT Submucous cleft palate	Hypotonia	Spina bifida occulta Pes cavus	VOUS at 14q11.2	HPS Hydrocephalus SAHS AT

+: present; —: absent; ADHD, attention-deficit hyperactivity disorder; AT, adenotonsillectomy; BMI, body mass index; F, female; HC, head circumference; HPS, hypertrophic pyloric stenosis; Ht, height; IUGR, intrauterine growth restriction; M, male; NR, not reported; PCTL, percentile; SAHS, sleep apnoea hypopnoea syndrome; TTN, transitory tachypnoea of the newborn; Wt, weight; VOUS, variant of unknown significance.

<sup>a</sup> Father not available.

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compulsory education due to school failure. She had a history of morbid obesity but had lost weight as a result of anxiety and depression. A maternal uncle aged 16 years was obese and had no problems in school. The other uncle, aged 12 years, was receiving treatment for ADHD, had unilateral duplex kidney, 2 hemivertebrae, and academic difficulties on account of which he required adaptations to the regular curriculum. All family members had undergone adenotonsillectomy.

**Case 3.** Boy aged 8 years that presented with PMR and difficulties with expressive language and writing.

**Case 4.** Girl aged 11 years that presented with PMR, absence seizures with onset at age 18 months, expressive language disorder and polyphagia requiring monitoring to maintain an adequate weight.

**Case 5.** Girl aged 15 years with intellectual disability (ID), epilepsy and obesity. The aCGH evaluation also detected a 1 Mb deletion in chromosome 14q11.2 classified as a variant of unknown significance. Her mother carried the 16p11.2 deletion and was overweight.

**Case 6.** Woman aged 26 years. She had been evaluated as early as age 4 months for assessment of macrocephaly with a head circumference of 46 cm (z-score, +4.4). She had moderate hydrocephalus that resolved spontaneously by age 4 years. From age 5 months to 3 years she had partial epilepsy of infancy, with no seizures after that age. She exhibited clear problems with language starting at age 3 years. The patient has had depression and bulimia as an adult. She was unable to graduate from high school. Her mother and siblings did not carry the deletion, and the father was not available for assessment.

The typical 16p11.2 deletion was first described in 2007 and encompasses 29 genes. The main reasons that lead to evaluation are ID, PMR and autism. In our series, the most frequent reason for evaluation was ID.

The clinical picture is variable. This deletion should be suspected in children with delayed language development with abnormal speech articulation, ID, social impairments, macrocephaly, seizures, vertebral malformations and/or Chiari malformation and obesity in the context of PMR.<sup>4</sup>

Intellectual disability is usually mild (iq. 82.7), but with IQ scores nearly 2 SDs below those of non-carrier familial controls.<sup>2</sup> Twenty-four percent have autism spectrum disorder (ASD), but up to 70% present with autism traits, such as repetitive behaviours. Cases 1, 2 and 5 in our series had autistic traits, but did not fulfil the criteria for diagnosis of ASD. Language disorders are present in 70% of affected individuals, and there seem to be anatomical abnormalities associated to problems in different areas of language development.<sup>5,6</sup> In our case series, language disorders were the most frequent feature along with mild ID.

Ninety-three percent of adults with 16p11.2 deletion syndrome have at least one diagnosed psychiatric disorder; in our series, 3 out of 5 adults with the deletion had psychiatric disorders.

Seizures, described in 20% of patients in the literature, occurred in 4 of the index cases. Only one patient had macrocephaly, and only one relative of an index case had a vertebral malformation.

The management of chromosome 16p11.2 deletion syndrome should focus on the specific clinical manifestations presented by the patient. Early diagnosis helps identify the potential needs of patients, such as early stimulation, speech therapy and dietary management, thus leading to improved outcomes. It also makes genetic counselling possible.

In conclusion, chromosome 16p11.2 deletion syndrome is characterized by a wide phenotypic variability between individuals and within families, and the most frequent manifestations are language disorders, mild ID, mild dysmorphic features and obesity. Considering that this microdeletion can be inherited, we recommend genetic testing of individuals with compatible manifestations for the purpose of early intervention and genetic counselling.

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