

# An intragenic deletion within CTNNA2 intron 7 in a boy with short stature and speech delay: A case report

SAGE Open Medical Case Reports  
Volume 5: 1–4  
© The Author(s) 2017  
Reprints and permissions:  
sagepub.co.uk/journalsPermissions.nav  
DOI: 10.1177/2050313X17693967  
journals.sagepub.com/home/sco



Valeria Paganelli<sup>1</sup>, Mara Giordano<sup>2</sup>, Cristina Meazza<sup>3</sup>,  
Lucia Schena<sup>1</sup> and Mauro Bozzola<sup>3</sup>

## Abstract

**Background/Objectives:** Deletions on the short arm of chromosome 2 at bands p11 and p12 have been detected in association with short stature, mild mental retardation and speech delay.

**Results:** We describe a 4 year-old boy with some facial dysmorphic traits, congenital malformations and pre- and post-natal growth failure. He also presented marked expressive language problems. The molecular karyotype revealed a 108 Kb deletion within the seventh intron of the CTNNA2 gene at 2p11.2-p12. We observed that some features (short stature, facial dysmorphisms and speech delay) were present in our patient and in patients carrying much larger overlapping deletions.

**Conclusions:** The description of this small intragenic rearrangement might help to elucidate the role of the single genes included in the 2p11.2-p12 critical region.

## Keywords

2p11.2 deletion, short stature, facial dysmorphisms, speech delay

Date received: 15 November 2016; accepted: 23 January 2017

## Introduction

Interstitial deletions of the short arm of chromosome 2 at band p11 and p12 are uncommon chromosomal abnormalities. So far, few cases have been reported with deletions larger than 7.5 MB with the minimally commonly deleted region including three candidate genes, *CTNNA2*, *LRRTM1* and *REEP1*, highly expressed in brain.<sup>1–5</sup> Patients with these microdeletions show intellectual disability, growth retardation, speech delay, minor facial anomalies (high forehead, frontal bossing, broad nasal bridge, abnormal ears) and congenital defects.

Here, we describe a boy with short stature, facial dysmorphism and congenital malformations and a chromosomal unbalance that might contribute to his phenotype.

## Clinical report

The patient is the only child of healthy, non-consanguineous parents; he was born at 36.1 weeks of gestational age, by caesarean section. At the 16th week of gestational age, amniocentesis was performed and the karyotype was normal. The ultrasound examination at the 30th week revealed

diaphragmatic hernia and dextrocardia and intra-uterine growth retardation (IUGR). At birth, weight was 1480 g (below third centile), and length was 44 cm (below third centile). Apgar score was 9 and 10, at first and fifth minutes, respectively. The diaphragmatic hernia was surgically corrected on the second day of life. The patient remained hospitalized for 100 days because of several complications including patent arterial duct, jaundice, cholestasis, pulmonary hypertension and sepsis from *Staphylococcus epidermidis*.

<sup>1</sup>University of Pavia—Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

<sup>2</sup>Laboratory of Genetics, Department of Health Sciences, University of Eastern Piedmont, Novara, Italy

<sup>3</sup>Internal Medicine and Therapeutics Department, Paediatric and Adolescent Unit, University of Pavia—Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

## Corresponding Author:

Mauro Bozzola, Internal Medicine and Therapeutics Department, Paediatric and Adolescent Unit, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Piazzale C. Golgi 2, 27100 Pavia, Italy.  
Email: mauro.bozzola@unipv.it





**Figure 1.** Facial features of the patient. High forehead, long face, horizontal palpebral fissures, right palpebral ptosis, broad high nasal bridge, bulbous tip nose, thin upper lip border, low-set and protruding ears are shown.

Cerebral ultrasound showed a modest lateral ventricular dilatation, electroencephalogram showed a path with immaturity aspects and auditory evoked potential were normal. Cardiac ultrasound, electrocardiogram and renal ultrasound were normal.

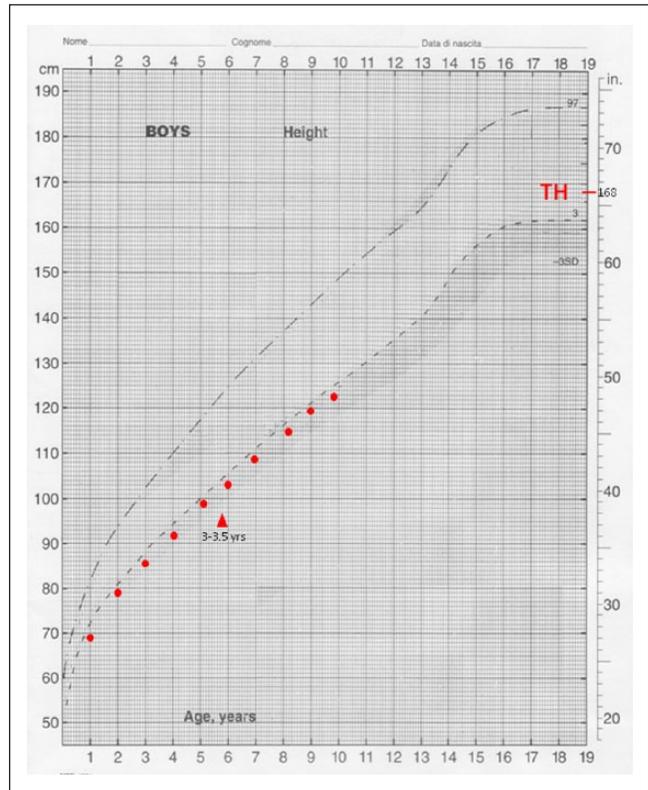
Psychomotor development was retarded (standing upright at 17 months, walking at 18 months and sphincter control at 3 years). He also needed logotherapy because of remarkable expressive language problems.

He was referred to our Department at the age of 4. His height was 92 cm (below third centile,  $-2.24$  standard deviation score (SDS)), his weight was 11.8 kg (below third centile), and he had some peculiar facial features including high forehead, long face, horizontal palpebral fissures, right palpebral ptosis, broad high nasal bridge, bulbous tip nose, thin upper lip border, low-set and protruding ears (Figure 1). His mother's height was 149 cm and his father's height was 174 cm (target height: 168 cm). His genitalia were normal, with prepubertal testes. His bone age was 3–3.5 years when he was 5 years and 8 months old.

From a psychomotor point of view, he made good eye contact, he developed good eye-hand coordination, he was able to walk normally and he attended a regular school with some external support, because of mild cognitive impairment with speech difficulties.

We excluded hypothyroidism, skeletal dwarfism and malabsorption, in particular celiac disease. By a careful endocrine evaluation, we excluded growth hormone (GH) deficiency (GH peak: 12.8 ng/mL; normal values  $>8$  ng/mL; insulin-like growth factor-I: 74.9 ng/mL;  $-0.73$  SDS (normal values between  $-1$  and  $+1$  SDS)). Then, we followed the patient at least once a year to check his growth. As shown in Figure 2, till the age of 10 years, his height was just below the third centile.

The array comparative genomic hybridization (aCGH, performed using the Agilent Human Genome G3 SurePrint 4  $\times$  180 K Microarray) revealed a 108-kb deletion in the p1.2

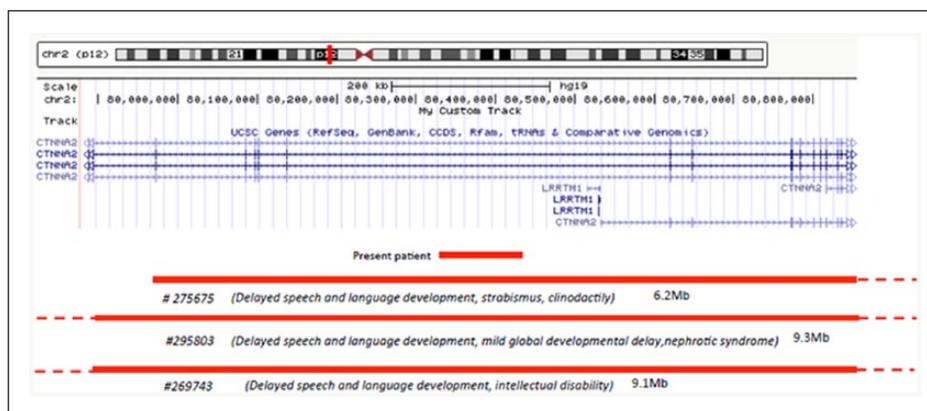


**Figure 2.** Height curve of the subject. The triangle indicates the bone age. TH: target height.

region of chromosome 2 within the intron 7 of the *CTNNA2* gene arr2p11.2-p12 (80,296,005x2; 80,314,156–80,422,635x1; 80,437,276x2, Genome Assembly hg19, build 37). This intron also includes another coding gene, *LRRTM1*, and the deletion is located just downstream. The presence of this rearrangement was confirmed through quantitative polymerase chain reaction (PCR) in the patient, and the extension of the assay to the parents revealed that it was transmitted by the mother. The mother showed a mild speech defect.

## Discussion

Although all the previously described patients carried larger deletions at 2p11.2-p12 than that in the present patient (Figure 3), he shared some common features with the other cases: mild mental retardation with speech delay, short stature and facial dysmorphisms (Table 1). In many of the previously reported cases, the minimal commonly deleted region included three OMIM genes, hypothesized to be responsible for the patients' phenotype, namely, *REEP1*, *CTNNA2* and *LRRTM1* that is located within *CTNNA2* intron 7. In our patient, only a part of intron 7 of the *CTNNA2* was included in the deletion. *CTNNA2* (OMIM\*114025) encodes for a catenin implied in cell adhesion, axon intracellular trafficking, synaptogenesis and stabilization of dendritic spines in hippocampal neurons.<sup>1</sup> The gene transcript is highly expressed



**Figure 3.** Graphic representation of part of the CTNNA2 gene. The 108.5-kB deletion detected in our patient at 2p12 (80,314,156–80,422,635x1) is reported along with other three larger deletions (larger than 6.2 MB) reported in DECIPHER (<https://decipher.sanger.ac.uk/>). The ID of each patient and the length of the deletions are reported. The clinical features of the patients are in parentheses, below the corresponding deletion as described in DECIPHER.

**Table 1.** Clinical manifestations of 2p11.2-p12 deletion in seven patients previously reported and in this case.

	Barber et al. <sup>6</sup>	Tzschach et al. <sup>3</sup>	Writzl et al. <sup>7</sup>	Rocca et al. <sup>4</sup>	Stevens et al. <sup>8</sup>		Silipigni et al. <sup>5</sup>	Present case
					Patient 1	Patient 2		
Position of deletion in 2p	p11.2-p12	p11.2-p12	p11.2-p12	p11.2-p12	p11.2-p12	p11.2-p12	p11.2-p12	p12
Deletion size	7.5 MB	11.4 MB	10.4 MB	9.2 MB	9.4 MB	9.4 MB	9.4 MB	108 kB
Sex	M	F	M	F	M	M	F	M
Inheritance	Maternal	De novo	De novo	De novo	De novo	De novo	De novo	Maternal
Age of evaluation	4 years	5 years	5 years and 9 months	9 years	15 years and 8 months	5 years and 4 months	12 months	4 years
Microcephaly	+	–	–	–	–	–	–	–
High forehead	+	+	+	+	+	+	+	+
Broad high nasal bridge	+	+	+	+	+	+	+	+
Low-set ears	+	+	+	+	+	+	+	+
Large ears	+	+	+	+	+	+	+	+
Foot anomalies	–	+	+	–	+	–	–	–
Growth retardation	NA	+	+	+	–	–	–	+
Speech delay	+	+	+	+	+	+	+	NA
Delayed motor development	+	+	+	+	+	+	+	+
Hypertonia	–	–	+	–	–	–	–	–
Ataxia	–	–	+	+	–	–	–	–
Intellectual disability	+	+	Mild	Mild	Moderate	Border-line	Mild	Mild
Happy disposition	+	+	+	+	+	+	+	+
Digital abnormalities	–	+	+	–	–	–	–	–
Other problems	Wilm's tumor	Single umbilical artery	Vesicoureteral reflux	Incomplete myelination of white matter	Hyperreflexia lower limbs, clumsy gait	Hypermobility hands	Bilateral coanal atresia, atrial septal defects	Left diaphragmatic hernia, dextrocardia

+: present; -: absent; F: female; M: male; NA: not available.

mainly in human brain, while it is not significantly expressed in other tissues. However, in the absence of a functional assay we cannot predict if the intronic deletion here identified might influence the correct splicing process as it does not affect any canonical splicing sequence.

Despite its small size, this unbalance is located just downstream of the *LRRTM1* gene (Figure 3) and might be involved in the expression regulation of this gene. *LRRTM1* encodes for a leucine-rich repeat transmembrane protein which is involved in the modulation of cell adhesion in neurons. It is highly expressed in brain and is thought to be related to autism.<sup>9</sup> Moreover, Francks et al.<sup>10</sup> showed that *LRRTM1* is involved in the maintenance of lateralized cerebral function. They also showed an association with left handedness and schizophrenia. As language represents a lateralized cerebral function and a common feature of some of the patients carrying deletions of *LRRTM1* is speech delay, we can hypothesize that this gene might be involved in difficulties in developing speech abilities.

Due to the presence of rare similar overlapping variants in the “UCSC Genome Browser” (<https://genome.ucsc.edu/>) detected in the control population, the pathogenicity of the deletion remains of uncertain significance for the molecular diagnosis of the patient. Moreover, the severe clinical features of the patient are not present in the mother, who transmitted the deletion. In general, the phenotype variability of individuals with the same unbalances, ranging from severe disorders to healthy phenotype, might be explained with the presence of so far unidentified co-occurring genetic alterations. Thus, our patient might carry some other variants such as a deletion or duplication under the resolution of the used aCGH platform or point mutations that contribute to the clinical phenotype.

### Acknowledgements

The authors are grateful to Susan West for revising the English of the paper.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

### Informed consent

Written informed consent was obtained from the patient’s parents and a legally authorized representative(s) for anonymized patient information and image to be published in this article.

### References

1. Abe K, Chisaka O, Van Roy F, et al. Stability of dendritic spines and synaptic contacts is controlled by alpha N-catenin. *Nat Neurosci* 2004; 7: 357–363.
2. Anthoni H, Zucchelli M, Matsson H, et al. A locus on 2p12 containing the co-regulated MRPL19 and C2ORF3 genes is associated to dyslexia. *Hum Mol Genet* 2007; 16: 667–677.
3. Tzschach A, Graul-Neumann LM, Konrat K, et al. Interstitial deletion 2p11.2-p12: report of a patient with mental retardation and review of the literature. *Am J Med Genet A* 2009; 149: 242–245.
4. Rocca MS, Fabretto A, Faletta F, et al. Contribution of SNP arrays in diagnosis of deletion 2p11.2-p12. *Gene* 2012; 492: 315–318.
5. Silipigni R, Cattaneo E, Baccarin M, et al. Rare interstitial deletion of chromosome 2p11.2p12. Report of a new patient with developmental delay and unusual clinical features. *Eur J Med Genet* 2016; 59: 39–42.
6. Barber JC, Thomas NS, Collinson MN, et al. Segmental haplo-sufficiency: transmitted deletions of 2p12 include a pancreatic regeneration gene cluster and have no apparent phenotypic consequences. *Eur J Hum Genet* 2005; 13: 283–291.
7. Writzl K, Lovrečić L and Peterlin B. Interstitial deletion 2p11.2-p12: further delineation. *Am J Med Genet A* 2009; 149: 2324–2326.
8. Stevens SJ, Blom EW, Siegelae IT, et al. A recurrent deletion syndrome at chromosome bands 2p11.2-2p12 flanked by segmental duplications at the breakpoints and including REEP1. *Eur J Hum Genet* 2015; 23: 543–546.
9. Reissner C, Runkel F and Missler M. Neurexins. *Genome Biol* 2013; 14: 213.
10. Francks C, Maegawa S, Laurén J, et al. *LRRTM1* on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Mol Psychiatry* 2007; 12: 1129–1139.