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

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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 postnatal 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

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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.¹⁻⁵ 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.

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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 × 180 K Microarray) revealed a 108-kb deletion in the p1.2 region of chromosome 2 within the intron 7 of the \textit{CTNNA2} gene arr 2p11.2-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, \textit{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, \textit{REEP1}, \textit{CTNNA2} and \textit{LRRTM1} that is located within \textit{CTNNA2} intron 7. In our patient, only a part of intron 7 of the \textit{CTNNA2} was included in the deletion. \textit{CTNNA2} (OMIM*114025) encodes for a catenin implied in cell adhesion, axon intracellular trafficking, synaptogenesis and stabilization of dendritic spines in hippocampal neurons.\(^1\) 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.6 | Tzschach et al.3 | Writzl et al.7 | Rocca et al.4 | Stevens et al.8 | Silipigni et al.5 | Present case |
|------------------------|----------------|------------------|---------------|---------------|-----------------|-----------------|--------------|
| **Position of deletion in 2p** | 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 | 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 | Vesico-ureteral reflux | Incomplete myelination of white matter | Hyperreflexia lower limbs, clumsy gait | Hypermobile 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 \textit{LRRTM1} gene (Figure 3) and might be involved in the expression regulation of this gene. \textit{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.\(^9\) Moreover, Francks et al.\(^{10}\) showed that \textit{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 \textit{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.

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Informed consent

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