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Review article

7q31.32 partial duplication: First report of a child with dysmorphism, autistic spectrum disorder, moderate intellectual disability and, epilepsy. Literature review

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ABSTRACT

Introduction: Duplication of long arm of chromosome 7(q) is uncommon. It may occur as "pure", isolated anomaly or in association with other mutations involving the same or other chromosomes. "Pure" chromosome 7q duplication has recently been classified by segment involved: the interstitial, proximal, or distal segment of the arm. Attempts to correlate genotype with phenotype in each group has yielded questionable results even though intellective disability and minor dysmorphic features of variable types are typically seen.

Material and Methods: In a young boy showing minor facial dysmorphism, language delay, autistic spectrum disorder, epileptic seizures, behavioral disturbances and irritability an array-CGH analysis was carried out.

Results: Array-CGH analysis found in the proband a de novo variant of partial duplication of 7q31.32 (122.254.792–122.376.908).

Discussion: A very few cases of partial 7q duplication have been reported thus far mainly presenting with clinical signs of dysmorphic features, large head, developmental delay, epileptic seizures and skeletal anomalies. To our knowledge, this is the first report of a case of a de novo variant of 7q31.32 duplication, showing dysmorphic anomalies and neurologic impairment including ASD and seizures. In the 7q31.32 region is located the gene *CADPS2*, which has been associated to autistic spectrum disorder and other neurologic disorders. In the child, a genotype-phenotype correlation may be hypothesized. Further similar reports may be useful to confirm this observation.

1. Introduction

In children with developmental delay, neurologic impairment, behavior disturbances and malformation anomalies, the use of array-Comparative Genomic Hybridization (array-CGH) has become routine technology offering a great contribution to the diagnostic issue. Microdeletions and microduplications detected using this technology have allowed to distinguish and clinically define patients with congenital anomalies. There is a wide clinical variability in the setting of individuals diagnosed by Array-CGH ranging from normal to others with moderate or severe disabilities and complex anomalies. Among the numerous copy-number variants (CNVs), duplications of long arm of chromosome 7 are uncommon. Pure duplication of chromosome 7 affects either the entire arm or interstitial, proximal, or distal portions of the segments. In some cases, chromosome 7 duplication might be associated with additional deletions involving other chromosomes with overlapping clinical manifestations (Paspaliaris et al., 2017; Ruiz-Botero and Pachajoa, 2016; Forabosco et al., 1988; Pavone et al., 2010; Chen et al., 2015; Tüysüz et al., 2008; Isidor et al., 2012).

Herewith we report on a 4-year-old boy with minor facial dysmorphism, language delay, moderate intellectual disability, Autistic Spectrum Disorder (ASD), epileptic seizures, and behavioral disturbances. The array-CGH analysis disclosed a microduplication of 122 Kb on ch.7q31.32. At our knowledge, this is the first case of de novo variant duplication involving the 7q31.32 region and presenting clinical signs of dysmorphic features, ASD, moderate intellectual

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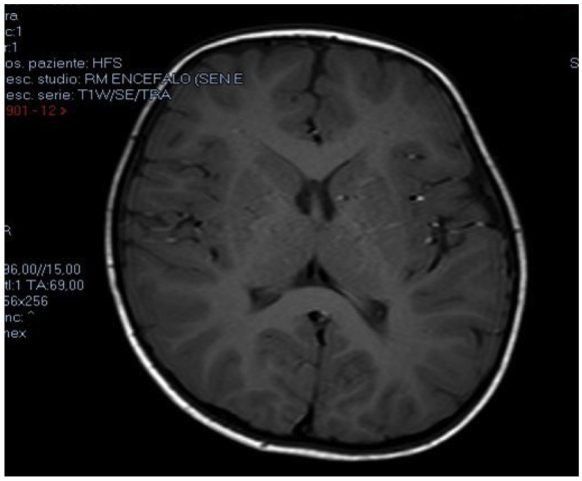


Fig. 1. Two-year-old child. Brain MRI showing hypotrophy of the temporal left pole with a mild widening of liquor spaces.

disability, epileptic seizures and, behavioral disturbances with notable irritability. In the child, a genotype-phenotype correlation is supposed.

2. Clinical findings

This 4-year-old boy is the second of three children of healthy, unrelated Italian parents. The two brothers aged 1 and 6 years are healthy. At the time of gestation, the mother was 29 years old and the father 36 years old. The mother felt normal fetal movements during gestation and, intrauterine ultrasound did not show anomalies. The mother referred having smoked several cigarettes (20–30 daily) and denied having had complications during the gestation. The child was born at 38 weeks of gestation by cesarean section because of internal podalic version. His birth weight was 3200 g, birth length 50 cm and, occipito-frontal circumference (OFC) 36 cm. The Apgar scores were 7 at one minute and 9 at five minutes. Dysmorphic features were not impressive and initially unnoticed. The child was discharged by the hospital in good condition. During the first months, he exhibited delayed developmental milestones. In the following months, delay was more evident, involving speech in particular which started at the age of 20 months with the pronunciation of a single word. Two tonic-clonic afebrile seizures were recorded at the age of 16 and 21 months. Treatment with valproate at dosage 10 mg/Kg/day was started.

He first came at our observation at the age of 2 years. His weight was 13 Kg (50–75th percentile), length 92 cm (75–90th percentile), and head circumference 51 cm (90th percentile). The parents complained that he was particularly irritable and showed stereotyped movements such as flitting of the hands and pedaling. At physical examination the child showed facial dysmorphism but not impressive. The child

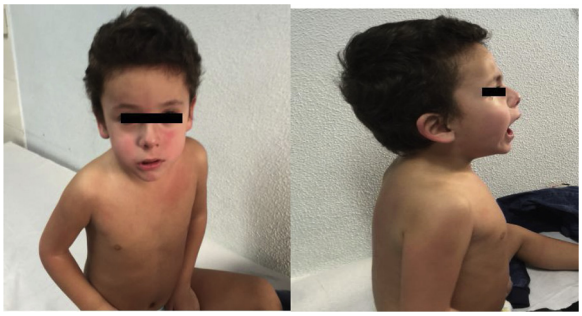
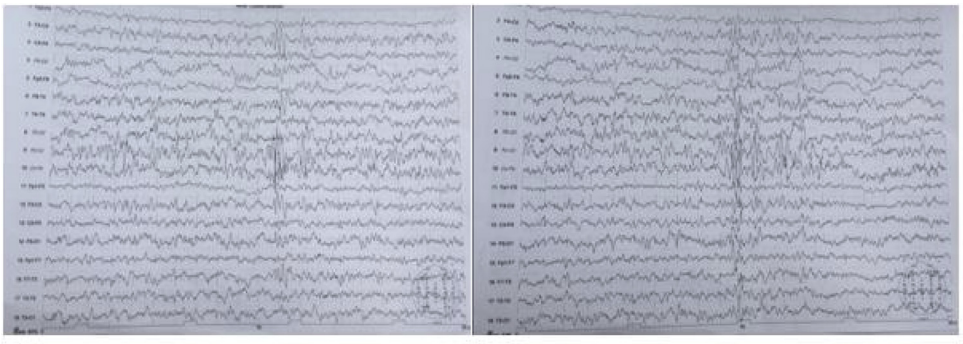


Fig. 3. a -b: 4-year-old child. To note facial dysmorphism with brachycephaly, high forehead, middle sparse eyebrow, protruding upper jaw, short nose, small mouth, thin upper lip, short neck.

presented large head, brachycephalic, high forehead with frontal bossing, sparse eyebrows, epicanthus, short nose with depressed nasal bridge and rounded tip. Protruding upper jaw, long flat phyltrum, small mouth, thin upper lip, microretrognathia were noted. The ears were low set and normally-structured, and the neck was short. At the neurological examination, the child showed hypotonia and mild joint hyperlaxity. Speech delay with the use of a single word was noted. The patellar tendon reflexes tapped briskly. Heart, thorax, abdomen and genital organs were normal. Brain MRI showed no signal alterations at cerebral, cerebellar and encephalic trunk levels; hypotrophy of the temporal left pole with a mild widening of liquor spaces was noted (Fig. 1). The EEGs while awake and during sleep showed spike and wave discharges bilaterally in frontal regions (Fig. 2a–b). Fundus examination and hearing exploration were normal. At routine laboratory analysis, electrolytes, plasma and urinary amino acids, thyroid markers, organic acids, plasma purine, and total cholesterol were within the normal limits. At the follow up three episodes of epileptic seizures recorded as secondary generalized tonic-clonic were reported. At the present age of 4 years, his weight is 16 kg (50th percentile), height is 102 cm (75th percentile), and head circumference is 53 cm (90th percentile). Cognitive evaluation indicates a moderate delay, particularly in the speech being able to refer only a few words even if in a clear way. Neuropsychiatric evaluation resulted in a spoken skill score of 56, IQ of 64 and performance skill score of 76. He is hyperactive with poor social contact and stereotyped movements suggestive of a diagnosis of Autistic Spectrum Disorder (ASD). Dysmorphic features are unchanged (Fig. 3a–b).

3. Genetic testing

After extraction of genomic DNA from whole blood lymphocytes, molecular karyotyping by high-resolution 8 × 60 K Human Genome CGH microarray (Agilent Technologies, Santa Clara, CA) was performed using DNA proband labeled by Cy5 and hybridized against a Cy3



a b

Fig. 2. a–b Two-year-old child. The EEG while awake and during sleep showing spike and wave discharges bilaterally in frontal regions.

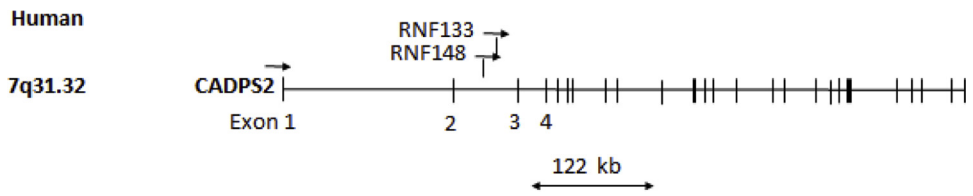


Fig. 4. Exon-intronic structure of the Human *CADPS2* gene localized on 7q31.32 and the approximate location of 122 Kb mutation.

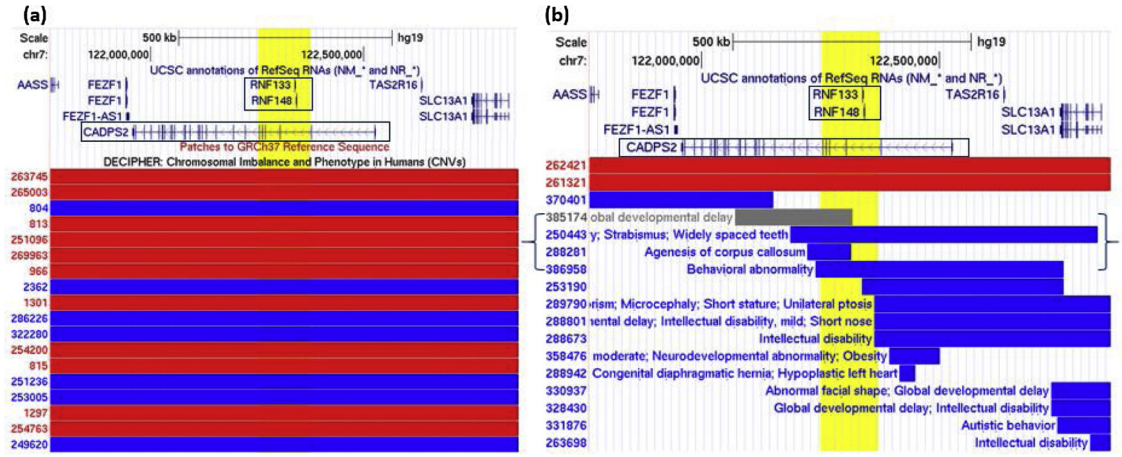


Fig. 5. a–b Image modified from UCSC with Deciper Database tracks showing annotated patient CNV. CNV *loss* (*red*) and *gain* (*blue*). In blue squares are indicated *RNF133*, *RNF148* and *CADPS2* genes contained in the duplicated region of clinical interest highlighted in yellow (7:122.254.792–122.376.908). (b) in curly brackets are indicated overlapping CNV variants with the probe's size region.

labeled reference DNA (human DNA Promega). Protocol provided by Agilent for purification, hybridization and washing steps has been followed with no modifications. The array was analyzed with the Agilent Scanner Control (v7.0) and the Feature Extraction software (v9.5.1). Data visualization was obtained using Agilent Cytogenomics Software Edition 2.5.

4. Results

Array-CGH revealed a 120 kb duplication of the long arm of chromosome 7: arr[hg19] 7q31.32(122.254.792–122.376.908)x3 (Fig. 4). A corresponding copy number variant (CNV) was not observed in either parent by array-CGH analysis, who were clinically normal.

5. Discussion

In the present study, we report a child with minor facial dysmorphism, moderate intellectual disability, poor speech, poor social interaction and stereotyped movements ranging in autistic spectrum disorders, epileptic seizures and, behavioral disturbances, carrying a de novo variant duplication (122 kb) in 7q31.32.

In this re-arranged genomic region, referred as AUTS1 locus in SFARI gene database (https://gene.sfari.org/), CNVs include *CADPS2, RNF133* and *RFN14*8 genes involved in synaptic plasticity and autistic signaling mechanisms. *CADPS2* gene encodes a member of the calcium-dependent activator of secretion (CAPS) protein family, which regulates vesicle release during exocytosis and dense core vesicles in neurons and brain structures (Sadakata et al., 2010; Shinoda et al., 2011; Berwin et al., 1998). This gene has been shown to interact with brain derived neurotrophic factor (*BDNF*) and regulate cell differentiation survival during cerebellar development (Sadakata et al., 2010; Shinoda et al., 2011; Berwin et al., 1998; Speidel et al., 2003; Sadakata et al., 2004). Presence of several microdeletions within 7q31.32 including the *CADPS2* locus were identified in single alleles of autistic patients and in mouse with autistic-like behavioral phenotypes (Sadakata and Furuichi, 2009; Christian et al., 2008; Szatmari et al., 2007; Sadakata et al., 2013). Sadakata et al. (2013) support on the basis of study reported in autistic patients that *CADPS2* may be recognized as a candidate autism susceptibility gene. More recently, a male patient with ASD and recurrent psychotic syndrome has been reported presenting with deletion involving the 7q31.32 band at the *CADPS2* gene locus (Grabowski et al., 2017). Interestingly, the predominant CNV associated with ASD in the CADPS2 locus is a deletion, unlike the variant we report.

Both RING proteins, Rnf133 and Rnf148, coded by genes located in AUTS1 locus, characterized by a structural domain of zinc finger type, play a notable role in the ubiquitination pathway in neurodevelopmental and post-neurodevelopmental processes (Louros and Osterwell, 2016; Maab and Ehlers, 2010; Hillier et al., 2003; Scherer et al., 2003). Their association with ASD individuals and other neurologic manifestations is poorly known, although there is evidence of a co-occurring mutation in CNVs of RNF family genes and *CADPS2* in the pathogenesis of ASD (Sadakata et al., 2013).

To our knowledge, the detected CNV and clinical signs to which is related has not previously reported in literature. According to Decipher data (https://decipher.sanger.ac.uk/), individuals with duplication of this region may be found. Probably most of the reported cases have larger CNVs or very small, or the duplication involves an intronic region. Following the Decipher data, 7q31.32 is susceptible to different structural rearrangements, the majority of which are deletions containing at least part of *CADPS2*, *RF133* and *RFN148* genes involved in functions that are sensitive to neurodevelopmental delay (Fig. 5a–b).

However in Decipher, there is a clinical case affected by abnormality of the nervous system with a copy number gain of 97 kb [patient 288281] approximately similar to phenotype and the duplication size of our proband (Fig. 3a–b; Table 1). This variant including only the genetic sequence of *CADPS2* is reported as likely benign and inherited from healthy parents. In our case a possible correlation between the dup7q31.32 and the clinical manifestations by the child, including ASD and epilepsy may be linked to the action of modifying factors. More suggestive is the hypothesis that the CNV within 7q31.32 including *CADPS2* locus may have interfered with the normal cerebral development creating an upsetting, which have caused the clinical pattern

Table 1
View of patient gain variants reported on DECIPHER overlapping the probe's CNV site.

Decipher	Position	Genomic size(bp)	Phenotypes	Inheritance	Pathogenecity	Contribution
385174	122072866–122320449	247584	Mild global developmental delay	Maternally inherited, constitutive in mother	Uncertain	Uncertain
250443	122190032–122838147	648116	Broad nasal tip; Congenital nystagmus; Depressed nasal bridge; Epicanthus; Intellectual disability; Strabismus; Widely spaced teeth.	Inherited from normal parent	Unknown	Unknown
288281	122225549–122317305	91757	Agenesis of corpus callosum	Likely benign	Unknown	Unknown
386958	122242786–122765721	522936	Behavioral abnormality	Unknown	Uncertain	Uncertain

showed by the child.

Actually, partial duplication of the long arm of Ch. 7 is uncommon. It can be isolated or manifested in association with deletions involving other chromosomes interfering each other and causing various clinical manifestations (Paspaliaris et al., 2017; Ruiz-Botero and Pachajoa, 2016; Forabosco et al., 1988; Pavone et al., 2010; Chen et al., 2015; Tüysüz et al., 2008; Isidor et al., 2012). In patients with "pure" 7q duplication, recent attempts have been made trying to link the entire arm and/or each segment involved to a specific clinical manifestations. The results obtained were inconclusive and a direct correlation between genotype and phenotype has not been established (Scelsa et al., 2008; Alfonsi et al., 2011). Novales et al. (1982), grouped patients according to duplication location. Those patients with interstitial duplication from 7q22 to 7q31 showed facial dysmorphism such as frontal bossing, long eyelashes, narrow palpebral fissures, epicanthus, hypertelorism, small nose, long upper lip and ocular manifestations. Neither skeletal anomalies nor cleft palate, microretrognathia or early deaths were observed among these patients. Those with the duplication in the region 7q31 to 7qter, showed large fontanelle, narrow palpebral fissures, hypertelorism, small nose, cleft palate, micrognathia, low-set and malformed ears along with developmental delay, poor sucking and feeding difficulties. Among this group, skeletal anomalies and precocious deaths were observed. Finally, those with duplication of 7q32 to 7qter showed small nose, low-set ears, skeletal anomalies and neurologic symptoms including hypotonia, feeding difficulties, developmental delay, and early death. Among this group, microretrognathia and cleft palate were not presenting anomalies.

Scelsa et al. (2008) report a young boy presenting with clinical manifestations linked to a pure partial trisomy of the long arm of Ch. 7q32-qter. The patient showed mild facial dysmorphic features consisting of frontal bossing, hypertelorism, narrow palpebral fissures, down slanting eyes, small nose, depressed nasal bridge, microretrognathia, cleft palate, low-set and malformed ears, strabismus and short neck. Congenital heart and genital urinary defects were also reported. Neurologic manifestations included macrocephaly, severe developmental delay, epileptic seizures, hypotonia and poor interaction with the environment. The same authors (Scelsa et al., 2008) report a review of 16 cases of the literature at the aim to correlate clinical manifestations with specific chromosome segments duplication. Four groups were distinguished on the basis of the involved region: duplication of the entire arm and duplication involving the interstitial, proximal and distal segments. Despite this, there are no established correlations between chromosomal rearrangement and the phenotype observed. More recently, Alfonsi et al. (2011) describe a young patient affected by a pure partial 7q duplication involving the region q21.1-q22.3. This boy presented with frontal bossing, strabismus, malformed ears, short neck, microcephaly, hypotonia, and developmental delay. The authors (Alfonsi et al., 2011) compare the clinical features of their patient with six patients reported by the literature with similar 7q duplications. Psychomotor delay and low-set malformed ears were found in all patients including their own; strabismus and frontal bossing was found in 6; skeletal anomalies in five, and genital urinary defects, hypotonia, macrocephaly, hypertelorism, small upturned nose, microretrognathia, cleft palate, high arched palate in three. In this report, other types of anomalies were reported in one or two patients. The results obtained at the aim to recognize a direct correlation between each segment duplicated and specific clinical expression were inconclusive and the authors draw the conclusion that a genotype-phenotype correlation among the 7q segments involved in the duplication is presently not feasible.

Comparing our patient's phenotype to those previously published cases with a pure partial 7q duplication, we report a new case of a de novo duplication variant on 7q31.32 with unique clinical presentation consisting of facial dysmorphism and complex neurologic impairment.

Some clinical correlations of our case have been found in several studies involving the distal segment of the long arm of Ch. 7 (Couzin

Table 2
List of clinical manifestations of reported cases of pure distal duplication 7q.

	Couzin et al (1986)	Keith et al (1988)	Romain et al (1990) Case n2	Romain et al (1990) Case n 3	Bartsch et al (1990)	Verma et al. (1992)	Scelsa et al. (2008)	Present case
Gender	M	M	M	F	M	M	M	M
Segment Ch. 7	7q32-qter	7q32→34	7q34-qter	7q34-qter	7q33-qter	7q36-qter	7q32-qter	q31.32→qter
Facial dysmorphim	+	+	+	+	+	+	+	+
Large head	+	n.r	n.r	n.r	+	+	+	+
Development delay	+	+	+	+	+	+	+	+
ASD	n.r.	n.r	n.r	n.r	n.r	+	n.r	+
Epileptic seizures	Absence epilepsy	n.r	n.r	n.r	n.r	n.r	+	+
Skeletal anomaly	kyphoscoliosis	n.r	Kyphoscoliosis	Knock knees	–	n.r	scoliosis	–
Genitourinary anomaly	n.r.	n.r	Left testis absent	n.r	n.r	n.r	Bilateral criptorchidism	–
Others	Spastic tetraplegia -peripheral lymphedema	Lateral rectus muscle absent	myopia	–	CT scan: enlarged subarachnoid spaces and cisterns-hypodense areas in the occipital region	–	Pulmonary valve dysplasia- MRI brain-stem hypotrophy and nodular heterotopia	–

et al., 1986; Keith et al., 1988; Romain et al., 1990; Bartsch et al., 1990; Verma et al., 1992; Scelsa et al., 2008). Among these, consistent reported features are minor, not typical facial dysmorphism (8/8), developmental delay (8/8), large head (5/8), epileptic seizures (3/8), ASD (2/8) and skeletal anomalies (4/8). To note male gender was clearly prevalent (7/8) (see Table 2). Gender disproportion (M:F) as found in this condition is high and not easy to explain. It might be casual. A protective genetic role of the X chromosome could be a possible alternative hypothesis.

In conclusion, duplication of the distal segment of the 7q chromosome may display wide clinical variability, but the cognitive involvement, minor dysmorphic features, large head are frequently reported and, thereby this set of clinical features matched with a distinct cytogenomic abnormality can be useful to reach a correct diagnosis. The present case is the first report of a de novo 7q31.32 duplication presenting with dysmorphic features and complex neurologic involvement including ASD and epileptic seizures. Findings of similar observations will help to better establish the cause and to define the clinical features of the affected patients and the mechanisms that underlie their clinical manifestations.

Statement of ethics

The authors have no ethical conflicts to disclose.

Declaration of Competing Interest

Authors have not conflicts of interest to declare.

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