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Brief Clinical Report

Mild Phenotype Due to Tandem Duplication of l7p11.2

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We present a mildly affected girl with de novo dup(17)(p11.2p11.2). The patient was evaluated because of minor anomalies noted during a hospitalization for nonrecurrent tonic-clonic seizures associated with transient hypoglycemia. She also had unilateral renal hypoplasia and relative short stature, but at 2 years of age, she scored within the low normal range on neurodevelopmental examinations. Compared with other similar duplications, this patient represents the milder range of the spectrum for this karyotypic abnormality. Am. J. Med. Genet. 94:296–299, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: duplication; chromosome; band 17p11.2, dup(17) (p11.211.2)

INTRODUCTION

Deletions of the 17p11.2 segment are common and recognized as the Smith-Magenis syndrome. As expected, clinically they are more severe and more commonly reported than duplications of the same segment. The phenotypic abnormalities of patients with duplication of l7p11.2 have been reported [Magenis et al., 1986; Kozma et al., 1991; Roa et al., 1996; Upadhyaya et al., 1993; Brown et al., 1996], but these studies often include fairly severely delayed patients. We report on a girl with de novo dup(17)(p11.2p11.2) with surprisingly mild phenotype.

CLINICAL REPORT

A 17-month-old white girl hospitalized for seizures was referred for evaluation of minor facial anomalies. She was a product of a 20-year-old G2P1 mother, whose pregnancy was notable for a low maternal serum alpha fetal protein and ultrasonographic findings suggesting poor fetal growth. Other parameters of fetal well-being, including activity, were normal. Delivery was uncomplicated, and birth weight was 2.82 kg (25th centile) while length was 49.53 cm (50th centile). Initial motor development was fairly normal: she sat at 6 months, crawled at 8 months, and began walking at 14 months. At 17 months, her vocabulary consists of 6–7 words.

The family history is notable for congenital bilateral hip dislocations in her father and uncharacterized seizures in the maternal great-grandfather and first cousins.

At 17 months, the infant was admitted with 2 recurrent brief afebrile tonic-clonic seizures that occurred after 4 days of an upper respiratory infection. Initial evaluation showed both hypoglycemia (33 mg/dL) and hyponatremia (125 mEq/L). On examination, the child's length measured 78.74 cm (25–50th centile), weight 9.18 kg (10th centile), and head circumference 45.4 cm (25th centile). She had a triangular face, mild frontal bossing, and epicanthal folds. Interpupillary distance was 4.6 cm (50th centile) and inner canthal distance was 2.8 cm (90th centile) (Fig. 1). Palpebral fissures were slightly downslanting and measured 2.0 cm (<30th centile). The left ear measured 4.8 cm (50th centile); the pinnae were pointed and lobes, hypoplastic. The nose had a prominent columella. Philtrum was smooth and measured 1 cm (25th centile). The palate was high and narrowly arched. She had mild malar hypoplasia and a down-turned mouth. There was mild retrognathia, and she had dental caries of the two upper incisors. She also had a prominent cowlick. Creases of the hands and feet were normal, and there was mild bilateral clinodactyly. Tone and deep tendon reflexes were normal. Urinalysis detected no glucose, but abundant ketones. On admission, the child had elevated liver enzymes including LDH 318 (0–222 U/L), SGOT 209 (normal 0–30 U/L), SGPT 162 (normal 0–35 U/L), and GGT 87 (normal 0–30 U/L).

While in hospital, subsequent tests showed glucose, electrolytes, and liver enzyme levels returning to normal. Cerebrospinal fluid was hypocellular and culture-negative. Imaging of brain by both MRI and CT were normal. Postictal EEG was normal. Cardiac echocardiogram was normal. Free and total carnitine, acylcarnitine profiles and a metabolic screen were normal. A 12-hr fast in hospital did not induce hypoglycemia. Nerve conduction velocities showed no evidence of peripheral neuropathy; the peroneal, sural, and median velocities of 42, 30, and 48 m/sec were nor-

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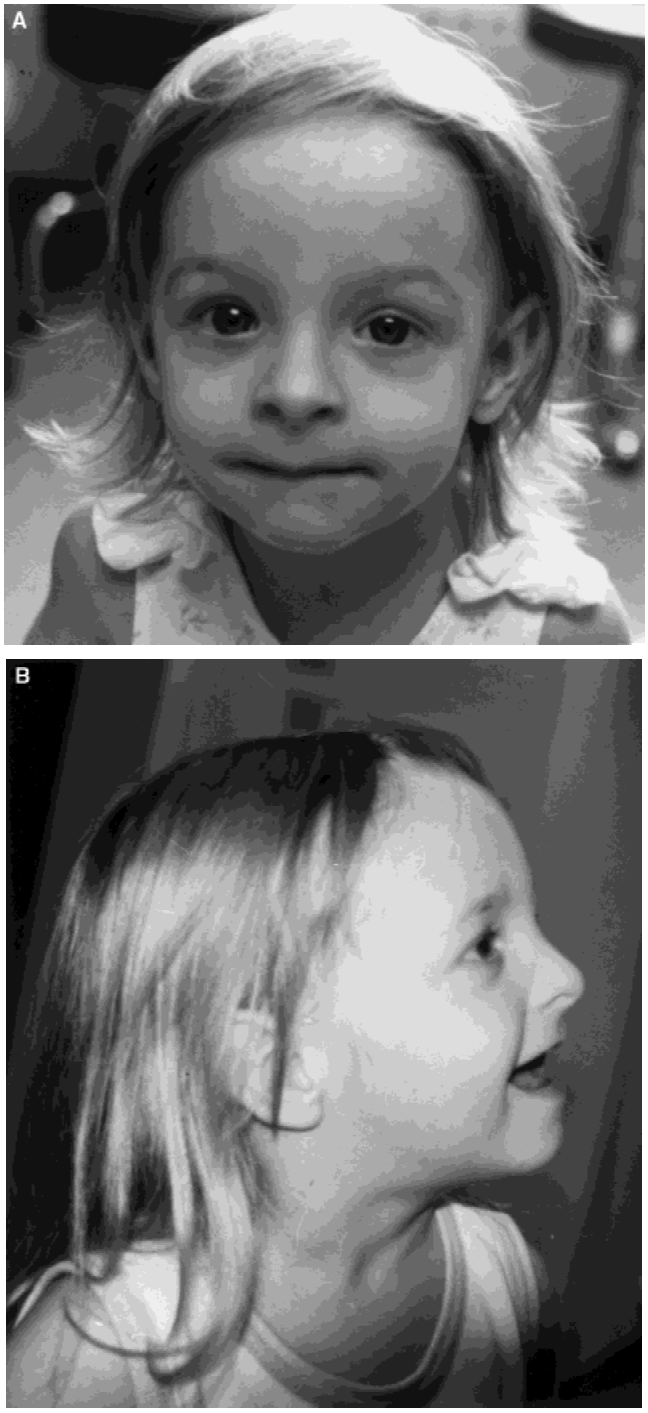

Fig. 1. Front and side view of patient.

mal for age. Renal ultrasonography showed that the left kidney was slightly hypoplastic at 4.9 cm in length.

Posthospitalization psychological evaluations found that the child was functioning in a low average range with a mental developmental index of 83, a psychomotor developmental index of 80 on the BSID-II, and a composite score of 83 on the Vineland adaptive behavior scales.

Karyotype showed an unbalanced duplication of bands p11.1- p11.2 of chromosome 17 (see Fig. 2A). Fluorescence in situ hybridization (FISH) using wcp7 and D17S258 (17p11.2- Smith Magenis region) showed only the D17S258 probe signal was duplicated (see Fig. 2B). Parental karyotypes were normal. Further analysis has shown a tandem paternal duplication with the characteristic junctional fragments of 17p11.2 (Smith-Magenis region) involving the D17S805 to D17S1794 interval (Fig. 1e [patient 1251], Potocki et al. [1999]).

DISCUSSION

Our patient has a de novo duplication of chromosomal region 17p11.2 and findings similar but milder than previously described cases (Table I). Kozma et al. [1991] described a 6.5-year-old boy with a triangular face, downslanting palpebral fissures, dental malocclusion, posteriorly angulated ears with hypoplastic landmarks, and clubfeet. Prenatal and postnatal growth retardation occurred. He had generalized hypotonia with exaggerated deep tendon reflexes and "poor" posture and coordination. Magenis et al. [1986] described a 32-month-old girl with similar face, left calcaneovalgus deformity, and mild developmental delay. Brown et al. [1996] recently described 2 patients with a duplication of 17p11.2 including a 5-year-old boy with developmental delay, mild growth retardation, a flat nasal bridge, epicanthal folds, and narrow palpebral fissures. A second unrelated infant, who died 10 days after surgery for pulmonary atresia, did not have abnormal facial features. Unlike the previous cases, our patient has neither significant developmental delay, clubfeet, nor growth retardation. In addition, as expected from the exclusion of the PMP22 gene from the duplication (J.R. Lupski, personal communication), the child does not have Charcot-Marie-Tooth disease or abnormal nerve conduction velocities.

The cause of seizures is not apparent in our case. They could be due to the hypoglycemia; however, the hypoglycemia did not recur after a hospital observed fast. At present, we do not know the etiology for her seizures or whether they are related to her karyotypic abnormality; seizures have not been observed in patients with this small duplication. Her family history of seizures may be significant.

Larger duplications of 17p have been reported. Martsolf et al. [1988] described a child with complete trisomy 17p who had severe growth and motor retardation, heart defects, and facial anomalies including a round and flat midface, small palpebral fissures, hypertelorism, microcephaly, and low set prominent ears. Docherty et al. [1983] described a case of a tandem duplication of 17p11-cen who had pointed ears, narrow palpebral fissures, downward slant of palpebral fissures, high arched palate, micrognathia, and congenital hypotonia. At 2 ½ years she was observed to have seizures. In addition, she had both growth retardation and severe mental deficits.

In addition, duplications that extend distally into the17p12 peripheral myelin protein PMP22, the 17p11.2-p12 gene mutated (most often duplicated) in Charcot-Marie-Tooth disease locus type 1A, show the expected signs of the disorder. For example, Upadhyaya et al. [1992] observed a duplication of 17p11.2-p12 in a boy with developmental delay, reduced motor

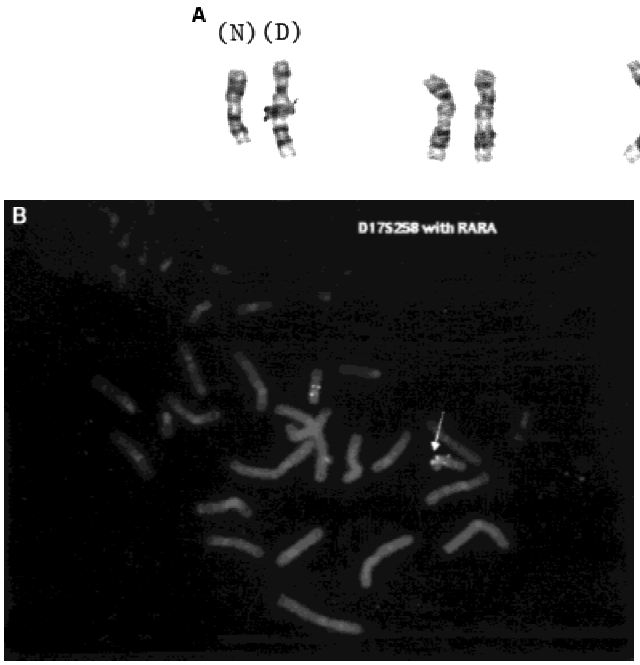

Fig. 2. **A:** Pairing of the chromosome 17s from the patient with the normal chromosome on the left (N) and the duplication chromosome on the right (D). **B:** Fluorescent in situ hybridization of patient karyotype with probes for D17S258 and a control probe at RARA 17q11 (Oncor). The arrow designates the duplication chromosome wherein 2 tandem signals for the D17S28 probe can be detected. In both chromosomes the 17q11 RARA hybridization is recognizable as two separate signals at the same locus (right and upper, respectively).

nerve conduction velocity, and minor anomalies. When Roa et al. [1996] examined 4 patients with the same duplicated regions, 2 of which were the patients previously described by Kozma et al. [1991] and Magenis et al. [1986], 2 had nerve conduction abnormalities compatible with CMT1A, whereas the other 2 were normal. The patients with normal NCVs had a smaller portion of band p12 duplicated, confirming visible duplications encompassing the PMP22 correlate with abnormal NCVs. Our patient did not have a duplication of 17p12,

TABLE I. Clinical and Cytogenetic Characteristics in Patients With dup(17)(p11.2p11.2)

	Current case	Kozma et al. [1991]	Magenis et al. [1986]	Upadyaya et al. [1992]	Brown et al. [1996]	Brown et al. [1996]	Lupski et al. [1996]	Lupski et al. [1996]
Karyotype dup	17p11.1 p11.2	17p11.2-p12	17p11.2-p12	17p11.1-p12	17p11.2 (JM)	17p11.2 (HG)	17p11.2-p12 (621)	17p11.2-p13.3 (527)
Sex	F	M	F	M	M	M	M	M
Age	17 mo	6.5 yr	32 mo	?	5 yr	3 mo	19 mo	3 yr
Decreased birth weight	–	+	+	?	?	?	–	+
Small stature	–	+	+	?	–	?	–	+
Microcephaly	–	–	+	?	+	–	+	–
Triangular face	+	+	–	?	?	–	–	–
Downslanted palpebral fissures	+	+	+	?	?	–	+	–
Narrow palpebral fissures	–	+	+	?	+	–	–	–
Maxillary hypoplasia	+	+	–	?	?	–	+	–
High arched palate	+	+	–	?	?	–	+	–
Dental malocclusion	–	+	–	?	?	–	–	–
Micrognathia	+	–	–	?	?	–	–	–
Abnormal ears	+	+	+	?	?	–	–	–
Short sternum	–	+	–	?	?	–	–	–
Café-au lait spots	–	+	–	?	?	–	–	–
Clinodactyly	+	+	–	?	?	–	–	–
Club foot	–	+	+	?	?	–	–	–
Seizures	+	–	–	?	?	–	–	–
Feeding difficulty	–	+	–	?	?	+	+	–
Failure to thrive	–	+	–	?	+	+	+	–
Mild developmental deficits	?	+	+	+	+	?	+	+
Hyperactivity	–	+	–	?	?	?	–	
Reduced nerve conduction velocity	?	–	–	+	?	?	+	+

has normal NCVs, and is not expected to develop CMT1A.

Recently, in a series of articles Chen et al. [1997] and Potocki et al. [1999] proposed a mechanism by which gene deletion/duplication of 17p11.2 syndrome occurs. They suggest that unequal crossovers at homologous flanking repeat gene clusters cause the deletions of the 17p11.2 region deleted in Smith-Magenis syndrome (SMS). They go on to speculate that one of the mechanisms that may explain this deletion is an inter- or intra-chromosomal rearrangement leading to a reciprocal duplication/deletion. CMT1A is one example in which such a mechanism has been found [Chen et al., 1997]. The duplication event observed here is the reciprocal event observed from an SMS deletion.

This case reinforces that the duplication of 17p11.2 may present with only mild developmental delay and nonspecific minor anomalies. Clinical descriptions of milder cases are useful for clinicians to better counsel patients with the associated karyotypic abnormalities.

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