

Cryptic t(1;12)(q44;p13.3) Translocation in a Previously Described Syndrome With Polymicrogyria, Segregating as an Apparently X-Linked Trait

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We report on the multistep progression to the correct genetic diagnosis in an apparently new syndrome of mental retardation and multiple congenital anomalies, including hypogenitalism and polymicrogyria. We had previously reported it as an X-linked condition affecting four members (three males and one female) of a family [Zollino et al., 1992: *Am J Med Genet* 43:452–457]. Two of the four patients, both males, presented with a brain abnormality that was initially described as pachygyria, while the remaining two (one male and one female) did not. Our present study includes a clinical follow-up on the patients, neuroradiological re-examination of one patient, X linkage studies and X inactivation analyses, and finally molecular cytogenetics, which allowed us to establish definitely the genetic causes of the condition. After the detection of a subtle t(1;12)(q44;p13.3) balanced translocation in healthy carriers, two unbalanced segregation products were observed in different patients, resulting in 1q44qter monosomy and 12p13.3pter trisomy in patients with polymicrogyria and severe psychomotor delay, 12p13.3pter monosomy and 1q44qter trisomy in the other two patients without polymicrogyria, with less severe mental

retardation and less distinctive physical anomalies. Thus, this condition is no longer to be considered X-linked, but the result of cryptic autosomal imbalance. Furthermore, this study identified an approximately 14 Mb interval in 1q44qter pathogenetically related to polymicrogyria. © 2003 Wiley-Liss, Inc.

KEY WORDS: cryptic chromosome imbalance in MR/MCA syndrome; 1q44qter and polymicrogyria; brain cortical dysplasia; neuronal migration disorder

INTRODUCTION

An apparently new syndrome with mental retardation and multiple congenital anomalies, including pachygyria, was previously reported in four individuals, three males and one female, born to three healthy sisters [Zollino et al., 1992]. This condition, sometimes referred to as Zollino syndrome, was initially considered to be X-linked, based on the characteristic of the pedigree, which led us to search for a locus on the X chromosome involved in neuronal cortical migration. On a subsequent brain MRI, the cerebral cortex anomaly was diagnosed as polymicrogyria. After the demonstration of a cryptic chromosome imbalance, described herein, this syndrome is no longer considered an X-linked condition.

The present observation teaches two important lessons. First, caution is to be exerted in predicting a monogenic pattern of inheritance of a familial condition, even in apparent absence of chromosome alterations. Cryptic unbalanced rearrangements have been diagnosed in many cases of idiopathic mental retardation, mostly in association with physical anomalies [Knight et al., 1999; Colleaux et al., 2001].

Second, a new gene for polymicrogyria is inferred to reside within an approximately 14 Mb region on 1qter.

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Several genes/loci involved in disorders of neuronal migration/cortical dysplasia have been identified in recent years: the *LIS1* gene in 17p13.3 causing type I lissencephaly [Dobyns et al., 1993]; *doublecortin* in Xq22.3-23, causing human X-linked lissencephaly and double cortex syndrome [Gleeson et al., 1998]; *EMX2* causing schizencephaly [Brunelli et al., 1996]; *RELN* gene in autosomal recessive lissencephaly with cerebellar hypoplasia [Hong et al., 2000]; and a gene for bilateral periventricular nodular heterotopia in Xq28 [Eksioglu et al., 1996]. Autosomal imbalances have also been reported in association with polymicrogyria, such as 22q11.2 microdeletion [Bingham et al., 1998; Kawame et al., 2000]. The new locus on 1q44 herein reported most likely causes polymicrogyria through haploinsufficiency.

MATERIALS AND METHODS

Pedigree and detailed clinical descriptions of each patient were reported previously by Zollino et al. [1992]. Briefly, two of four affected subjects (III-1 and III-3 in Fig. 1), who are first cousins born to three healthy sisters, presented with severe mental retardation, severe congenital hypotonia, normal growth, short nose with depressed nasal bridge and anteverted nostrils, prominent cheeks, hypogenitalism, seizures, and apparent pachygyria on an initial brain MRI assessment. The

remaining two patients, one male and one female, presented with moderate to mild mental retardation, microcephaly, a narrow face, and a long nose with prominent tip. Brain MRI was normal in both of them.

All patients were clinically evaluated 7 years later (Fig. 2). Patient III-1, age 15 years, presented with microcephaly (OFC 50 cm), profound mental retardation, and severe hypotonia. He was unable to walk, language was absent, occasional seizures responded to successful anticonvulsivant treatment. A quite warm disposition toward the environment was evident. He died at the age of 17 years of pneumonia *ab ingestis*. Patient III-2, age 20 years, presented with microcephaly (OFC 51 cm) and mild mental retardation. She could write and read, was able to count money and to attend to housework efficiently. Patient III-3, age 7.5 years, was short (height 106 cm; <3rd centile) and had an OFC of 50 cm (2nd centile). He started to walk at 6 years, language was absent, and he had seizures about once a week. He appeared to be a severely retarded boy. A new brain MRI was also performed in this patient, making it possible to define the cortical dysgenesis as polymicrogyria (Fig. 3). Patient III-4, age 10 years, presented with normal height (129 cm) and microcephaly (OFC 49 cm). He was mildly mentally retarded, and at a level quite similar to that of patient III-2. Updated clinical manifestations are summarized in Table I.

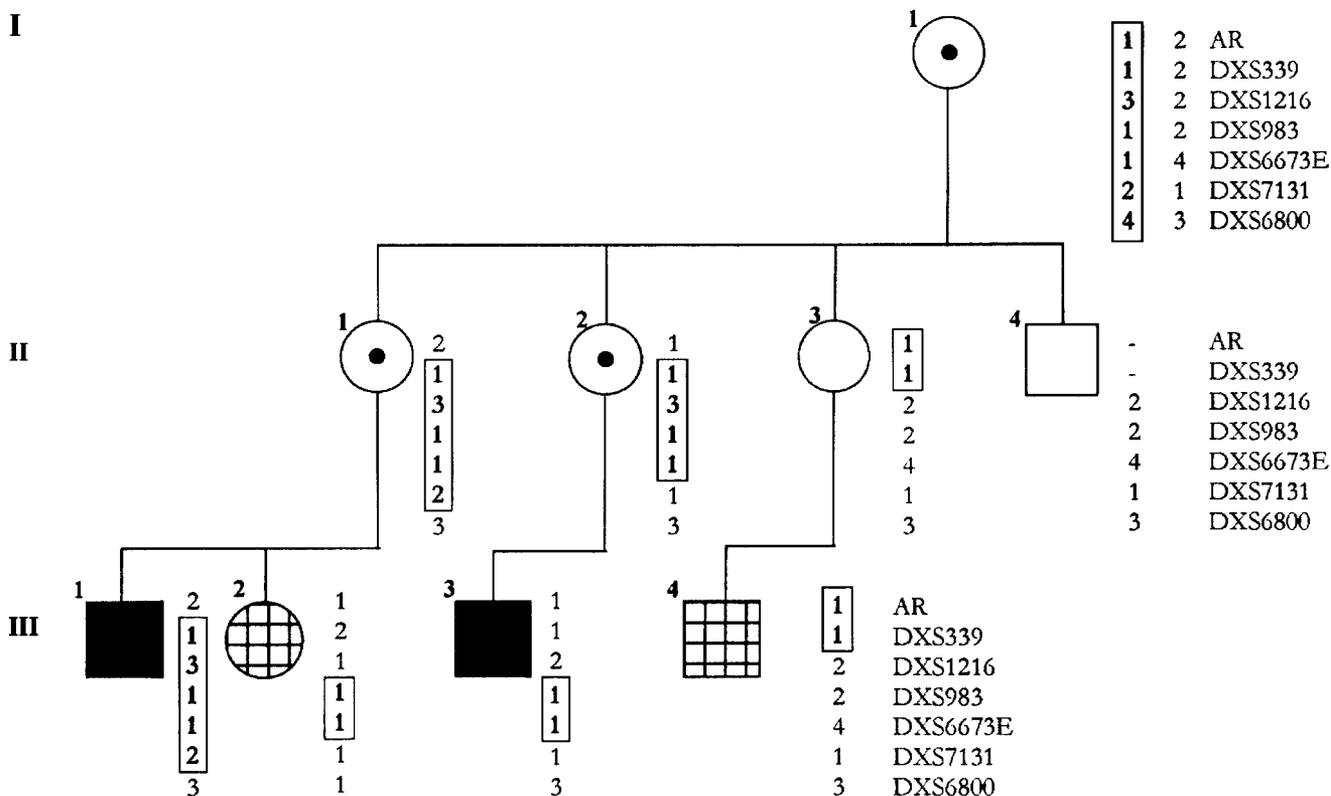


Fig. 1. Family pedigree. Closed symbols are used to designate individuals with severe mental retardation, polymicrogyria, and similar facial appearance. Hatched symbols are used to designate individuals without polymicrogyria, who presented with slight mental retardation and similar facial appearance. The only shared alleles include DXS983 and DXS6673E loci, but on condition that patient III-4, lacking polymicrogyria, is considered affected by a different genetic condition.



Fig. 2. Previously reported patients, 7 years later. In patients 1 (III-1) and 2 (III-3), note high forehead, full cheeks, short nose with depressed nasal bridge and anteverted nostrils, long and hypoplastic philtrum, large and downturned mouth with thin vermillion borders. They were trisomic for 1qter and monosomic for 12pter. In patients 3 (III-2) and 4 (III-4), note long

face, bitemporal narrowing of the skull, short palpebral fissures, long nose with high nasal bridge, micrognathia, and abnormally modeled ears. They were trisomic for 1qter and monosomic for 12pter. Image of patient III-2 refers to the age of 13 years (first report).

Neuroradiological Findings

Patient III-3 was studied by MRI for the first time at 8 months. A second MRI was performed when he was 7 years old, using a superconducting MR unit and obtaining multiplanar Spin-Echo and Turbo Spin-Echo T1- and T2-weighted as well Inversion-Recovery T1-weighted imaging sequences. The new MRI study showed a diffuse increase of the cortical gray matter thickness more severe of the right frontal lobe, without the normal interdigitations of the subcortical white matter. The increased thickness was associated with an abnormal pattern of gyri and sulci. The right Sylvian fissure had an abnormal posterior extension to the hemispheric surface. Moreover, the right hemisphere and the right hemicranium demonstrated a definite reduction of the transverse diameter, with enlarged subarachnoid spaces, containing prominent vessels, and dilated perivascular spaces. The left cerebral hemisphere was completely normal. The ventricles appeared slightly dilated. The corpus callosum appeared normal.

The unilateral thickening of the cortex, its more severe extension along the abnormal Sylvian fissure, the associated findings indicating loss of substance (reduced

diameter of the hemicranium, dilated subarachnoid spaces and vessels) strongly suggest the diagnosis of polymicrogyria (Fig. 3).

Genetic Studies

Linkage analysis. Segregation analysis of 54 polymorphic X markers in a total of nine individuals from this family failed to identify a shared haplotype among patients. A positive LOD score (1.701, $\theta = 0.01$) was only found for DXS6673E mapping in Xq13.1, but on condition that the male patient lacking cortical dysplasia was considered affected by a different condition. This unlikely event represents the first observed inconsistency in our initial study.

X inactivation analysis. To determine whether the healthy carrier females or the only affected female showed skewed X inactivation, we performed a PCR-based assay for X inactivation by using the androgen-receptor gene [Allen et al., 1992]. The pattern of X inactivation was random in each case. This is the second observed inconsistency.

Cytogenetics. By conventional cytogenetics, prometaphase chromosomes were apparently normal in all

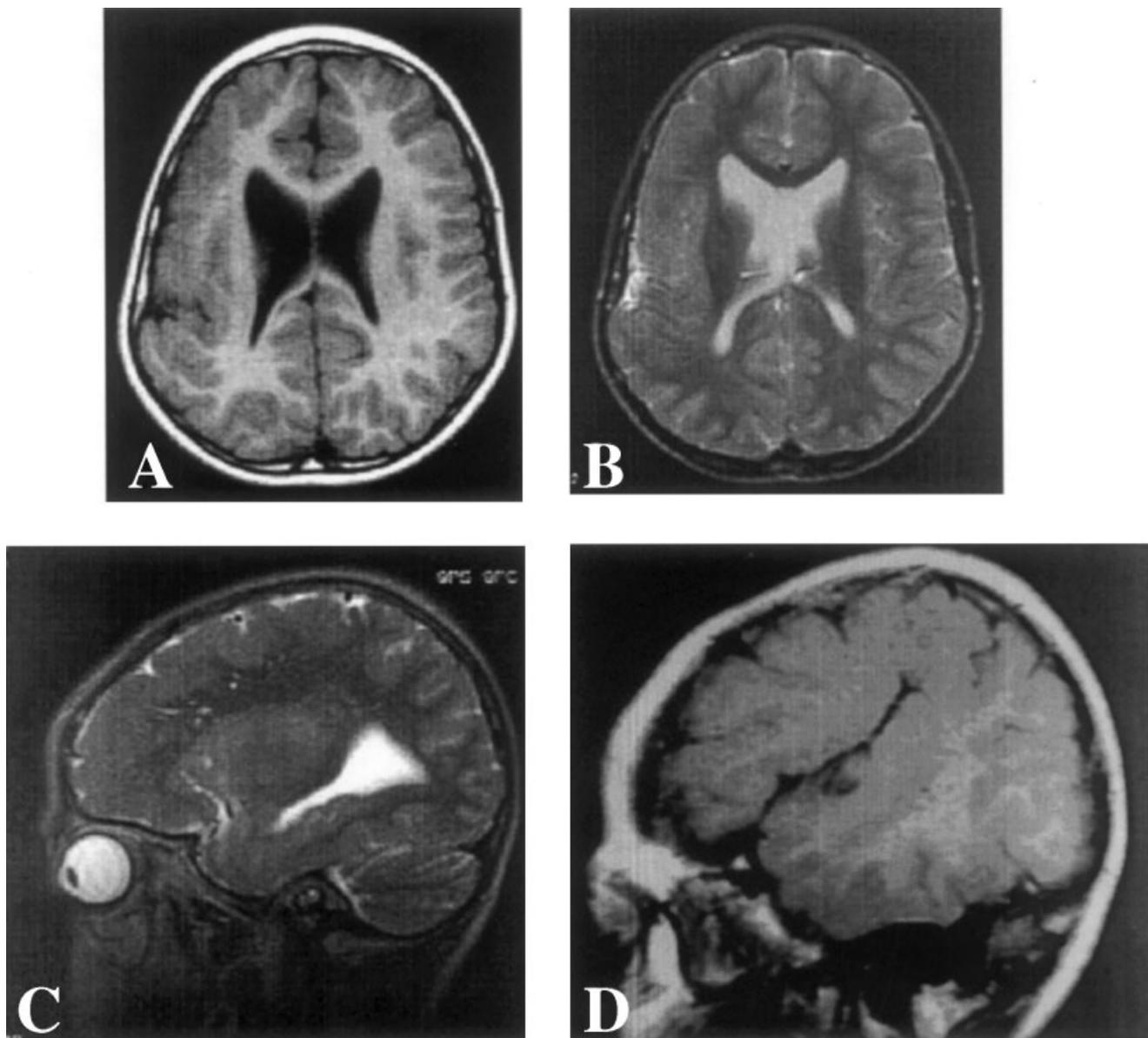


Fig. 3. Brain MRI demonstrating polymicrogyria in the right cerebral hemisphere in patient III.3. **A:** Axial T1-weighted (IR) image. **B:** Axial T2-weighted image (SE). **C:** Sagittal T2-weighted image (TSE). **D:** Sagittal T1-weighted image (SE). Note the abnormal increased thickness of the cortical gray matter of the right cerebral hemisphere especially in the frontal lobe; the lack of digitating subcortical white matter in the affected areas; the

abnormal pattern of the gyri and sulci in comparison with controlateral side; the abnormal upward extension of the right Sylvian fissure; the reduced diameter of both the right hemisphere and hemicranium; the dilated perivascular spaces and the dilated subarachnoid spaces between the abnormal cortex and the inner aspect of the skull.

affected individuals and in their respective carrier mothers. However, a cryptic t(1;12)(q44;p13.3) balanced translocation was detected by FISH analysis initially with subtelomeric probes (Cytocell, U.K.), and then with chromosome 1- and 12-specific painting probes (Oncor, Gaithersburg, MD) in all carrier mothers. The translocated segments from 1q and 12p did span about 14 Mb and 15 Mb, respectively [Rossi et al., 2001].

Reciprocal unbalanced segregation products were demonstrated in different patients. A 1q44qter monosomy in association with 12p13.3pter trisomy was detected

in both of the patients with cortical dysgenesis. A 12p13.3pter monosomy in association with 1q44qter trisomy was observed in the two patients lacking polymicrogyria. Relevant FISH results are shown in Figure 4.

DISCUSSION

A new syndrome with mental retardation and multiple congenital anomalies, including cerebral cortex dysplasia, was reported previously in four cousins, three

TABLE I. Clinical Manifestations of Patients

Sign	Patient			
	III-1	III-3	III-2	III-4
Microcephaly	+	-	+	+
Prenatal growth retardation	-	-	-	-
Postnatal growth retardation	+	+	-	-
Congenital hypotonia	+	+	-	-
Mental retardation	+	+	+	+
Long face, long nose with bulbous tip, short palpebral fessures	-	-	+	+
Round face, full cheeks, short nose with anteverted nostrils	+	+	-	-
Hypogenitalism	+	+	-	-
Polymicrogyria and agenesis of corpus callosum	+	+	-	-

males and one female, born to three healthy sisters [Zollino et al., 1992]. Familial segregation was highly suggestive of X-linked recessive inheritance, with variable penetrance in males. The different clinical outcome among five female carriers, four of whom were healthy (three sisters and their mother), with only one presenting with partial clinical manifestations of the condition, was considered most likely due to a different pattern of X inactivation. However, linkage analysis with a total of 54 polymorphic markers spanning the entire X chromosome at intervals of about 20 cM failed to identify any X locus shared by all affected individuals. The pattern of X inactivation was random in all carrier females. Despite the apparent normality of prometaphase chromosomes, a familial cryptic translocation, resulting in reciprocal chromosome imbalances, was the only reasonable explanation for the many clinical and molecular discrepancies observed in the family. Indeed, a balanced $t(1;12)(q44;p13.3)$ cryptic translocation was

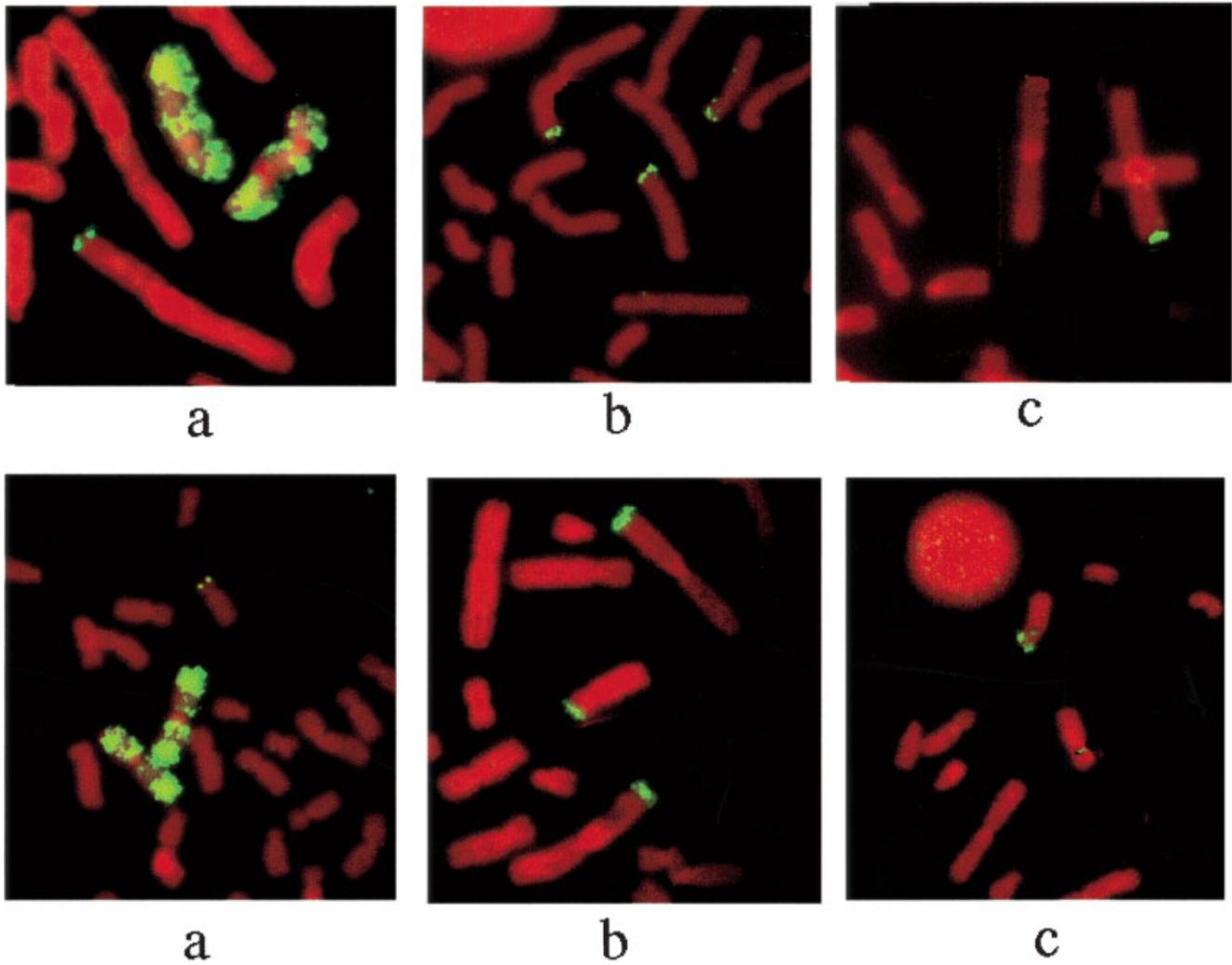


Fig. 4. Relevant FISH results in patients. **Top:** Partial 12p trisomy and partial 1q monosomy, as demonstrated by 12-specific chromosome painting (a), 12p subteleric probe (b), and 1q subteleric probe (c). **Bottom:** Partial 1q trisomy and partial 12p monosomy, as demonstrated by 1-specific chromosome painting (a), 1q subteleric probe (b), and 12p subteleric probe; a centromeric probe was also used for chromosome 12 identification (c).

demonstrated in normal carriers initially using subtelomeric probes and subsequently chromosome 1- and 12-specific painting probes. The similar size of the translocated segments, as evident on FISH analyses with chromosome 1- and 12-specific painting probes (Fig. 4), in addition to their similar G(GTG) and R(RBG) banding pattern, made this rearrangement undetectable on conventional cytogenetics.

The two different phenotypes observed in this family, with and without polymicrogyria, were caused by reciprocal unbalanced segregation of the maternal balanced translocation; thus, both patients with severe mental retardation and polymicrogyria were monosomic for 1q44qter and trisomic for 12p13.3pter.

The two 12p13.3pter monosomic-1q44qter trisomic patients presented with mild mental retardation, microcephaly, long face, and bulbous nasal tip. Few physical anomalies were noted, consistent with 1qter trisomy [Verschuuren-Bemelmans et al., 1995; Villa et al., 2000] and 12pter monosomy [Romain et al., 1987] syndromes.

Clinical manifestations in patients monosomic for 1q44qter and trisomic for 12p13.3pter were rather consistent with the trisomy 12p syndrome phenotype [Hansteen et al., 1978; Allen et al., 1996; Rauch et al., 1996]. They presented with a round face with prominent cheeks, short nose with depressed nasal bridge and anteverted nostrils, prominent everted lower lip, short neck, foot deformity, and hypogenitalism. Birth weight was normal in both cases, postnatal growth and head circumference were also initially normal in one patient (III-3). However, at 7 years, he was short, with relatively normal OFC. Both had seizures. Distal deletions of chromosome 1 usually result in significant neurological involvement [Murayama et al., 1991] and minor phenotypic abnormalities [Ioan et al., 1992; Villa et al., 2000].

Polymicrogyria is a brain dysgenesis with a complex nosology. Although it is currently included within disorders of neuronal migration [Golden, 2001], controversy exists as to whether polymicrogyria is a malformation, secondary to arrest of neuronal migration, or a postmigrational disruption of development, perhaps due to vascular injuries [Van Bogaert et al., 1998]. An ischemic mechanism is likely to act in the few reported cases of polymicrogyria associated with chromosome 22 microdeletion [Bingham et al., 1998; Kawame et al., 2000], as postulated by Bingham et al. [1998]. Most individuals with del 22q11 syndrome, as a matter of fact, do not have cortical lesions on brain MRI.

On the other hand, polymicrogyria appears to be causally heterogeneous. Its familial occurrence [Miller et al., 1998; Bartolomei et al., 1999; Borgatti et al., 1999; Caraballo et al., 2000; Guerriero et al., 2000] makes it evident that gene mutations cause this brain anomaly in many instances.

Disorders of neuronal migration or cortical dysgenesis have been detected by means of brain CT scan or MRI in 25% of recurrent childhood seizures [Kuzniecky and Jackson, 1995]. Autosomal and X-linked genes were recently demonstrated to be involved in neuron migration, the first being *LIS1* gene on 17p13.3, responsible for the Miller-Dieker syndrome and for isolated

lissencephaly, through haploinsufficiency [Dobyns et al., 1993].

In reviewing a total of 20 patients with del(1q) syndrome [Murayama et al., 1991; Ioan et al., 1992; Villa et al., 2000], we found that 80% (16/20) had seizures. Recurrent seizures are also described in 27% of patients with pure trisomy 12p syndrome [Biederman et al., 1977; Hansteen et al., 1978; Suerinck et al., 1978; Kondo et al., 1979; Parslow et al., 1979; Arnaud et al., 1984; Ray et al., 1985; Rivera et al., 1987; Tayel et al., 1989; Allen et al., 1996; Rauch et al., 1996]. Unfortunately, information on brain CT scan or MRI is not provided in these cases.

Neuroradiologically, polymicrogyria in the present patients shows the following main characteristics: unilateral perisylvian location, lack of normal digitated subcortical white matter, reduced size of the affected hemisphere and hemicranium, and dilated subarachnoid spaces and vessels. These observations allowed us to identify an approximately 14 Mb interval on 1qter, containing gene(s) whose haploinsufficiency most likely causes disorders of cerebral cortex development.

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