CLINICAL REPORT

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A Rare Case of Trisomy 15pter-q21.2 Due to a De Novo Marker Chromosome

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Supernumerary marker chromosomes (sSMC) may or may not be associated with an abnormal phenotype, depending on the presence of euchromatin, on their chromosomal origin and whether they are inherited. Over 80% of sSMCs are derived from acrocentric chromosomes and half of them include the short arm of chromosome 15. Generally, they appear as bisatellited isodicentric marker chromosomes, most of them are symmetric. These chromosomes are normally originated de novo and are associated with mild to severe intellectual disability but not with physical abnormalities. We report on a patient with an SMC studied using classical and molecular cytogenetic procedures (G and C banding, NOR staining, painting and centromeric fluorescent in situ hybridization (FISH), BAC-FISH, and SKY). The MLPA technique and DNA polymorphic markers were used in order to identify its parental origin. The marker chromosome, monosatellited and monocentric, was found to be derived from a maternal chromosome 15 and was defined as 15pter-q21.2. This is the report of the largest de novo monosatellited 15q marker chromosome ever published presenting detailed cytogenetic and clinical data. It was associated with a phenotype including cardiac defect, absence of septum pellucidum, and dysplasia of the corpus callosum.

Key words: chromosome 15; duplication 15pter-q21.2; marker chromosome; partial trisomy; trisomy 15q

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INTRODUCTION

A marker chromosome is a structurally abnormal chromosome in which no part can be identified [Shaffer et al., 2009]. Marker chromosomes have been described derived from all human chromosomes, with different sizes and shapes, appearing as small, ring, and large chromosomes, with or without centromeres and satellites. Their clinical manifestations are variable and depend on the size of the marker, presence of euchromatic material, degree of mosaicism, and/or uniparental disomy [Eggermann et al., 2002; Rodríguez et al., 2007]. The marker chromosomes most frequently observed are the small supernumerary marker chromosomes (sSMC). sSMCs are found in 0.14–0.72/1,000 newborns [Gardner and Sutherland, 1996] and in 3.27/1,000 mentally disabled patients [Buckton et al., 1985]. An increased frequency of sSMC has been observed amongst infertile males [Liehr and

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Weise, 2007]. Approximately 30% of all sSMC are familial and may not be associated with an abnormal phenotype, depending on the presence of euchromatin and on the chromosomal origin [Liehr and Weise, 2007]. Over 80% of sSMCs are derived from the short arm and pericentric regions of acrocentric chromosomes, half of them including the short arm of chromosome 15 [Friedrich and Nielsen, 1974; Buckton et al., 1985; Maraschio et al., 1988]. Marker chromosomes involving structural rearrangements of the 15q11-q13 region (Prader–Willi/Angelman Syndrome critical region—PWACR), a region known to be imprinted in humans, have been extensively reported in the literature [Hall, 1990]. Generally, they appear as bisatellited isodicentric marker chromosomes, most of them with a symmetric shape [Schinzel, 2001]. These chromosomes usually occur de novo and are associated with mild to severe intellectual disability but rarely with physical abnormalities. There are only few cases in the literature with marker chromosomes larger than those with breakpoint at 15q13 and none with a complete cytogenetic and clinical evaluation. We report here on a patient with many clinical findings who presents an SMC derived from chromosome 15 (15pter-q21.2). This is the largest de novo monosatellited 15q marker chromosome ever reported, with breakpoint at 15q21.2. We compare the phenotypic features of our patient with similar cases described in the literature.

MATERIALS AND METHODS

Clinical Report

The patient, a female, is the first child of healthy, nonconsanguineous parents. Family history was unremarkable. Prenatal history showed increased first-trimester nuchal translucency, and at the third trimester a complex cardiopathy was detected. Intrauterine growth retardation led to early delivery, by cesarean, at 32 weeks of gestation. At birth, the Apgar score was 7, weight was 1,585 g (<5th centile), length 38 cm (<5th centile), and head circumference 29 cm (mean for GA 32 weeks: 30.1 cm). The proposita presented a triangular face, telecanthus, bilateral epicanthic folds, low nasal bridge, narrow palate, low-set ears, preauricular sinus, preauricular skin tags, short neck, and multiple hemangiomas on head, neck, back, and arms, short hands with hypoplastic nails and bilateral clinodactyly of fifth fingers. One *café-au-lait* spot with 1.0 cm diameter was observed on the left arm. Ocular and mammary hypertelorism, sparse eyebrows, micrognathia, short columella, down turned corners of the mouth, spasticity, and dysregulation of muscular tonus were also observed (Fig. 1). The results of postnatal cardiac and renal ultrasonography showed atrial septal defect, ventricular septal defect, and patent ductus arteriosus and hyperecogenicity of the renal parenchyma. Brain ultrasonography showed mild ventricular enlargement without hemorrhagic areas. Nuclear magnetic resonance examination showed absent septum pellucidum and dysplastic corpus callosum. The patient presented developmental delay since birth. When referred, at the age of 5 months, she presented with short stature (46.0 cm, <5th centile), low weight (2,480 g, <5th centile), and microcephaly (HC: 35.5 cm). At 1 year and 7 months, she was still short in stature (60.0 cm, <5th centile), low-weight (5,750 g, <5th centile), and microcephalic (HC: 42.0 cm, <5th centile). X-rays of hands and feet showed no abnormality, except for a severely retarded bone age (6 months). She was admitted to the local hospital several times, due to recurrent pulmonary and gastrointestinal infections. She died at 1 year and 10 months, after cardiac

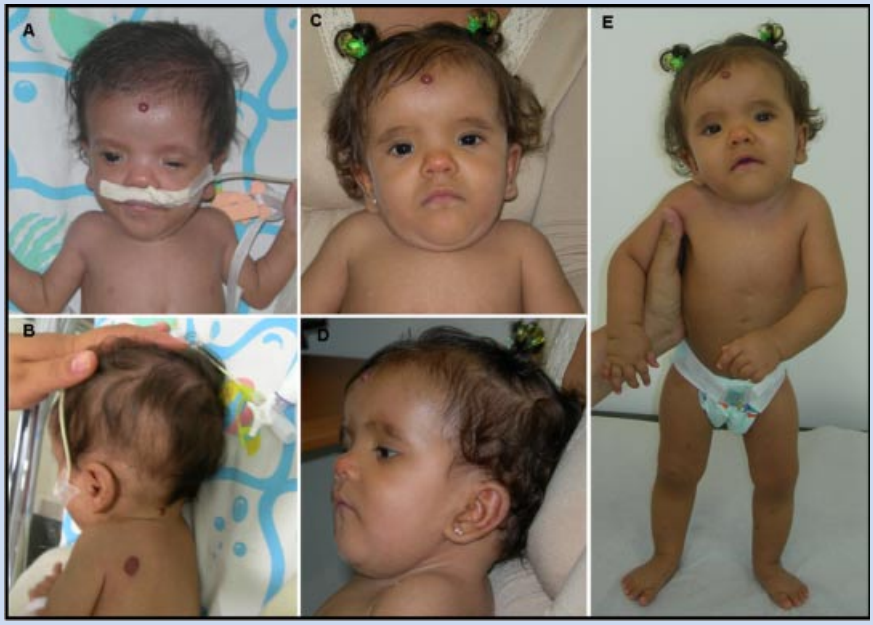

FIG. 1. Patient at the age of 5 months (A,B) and of 17 months (C,D,E). [Color figure can be viewed in the online issue, available at: www.interscience.wiley.com.]

surgery for sustained arrhythmia. Autopsy was not performed. Informed consent for this study was obtained from the patient's parents.

Cytogenetic Analysis

Blood samples from the proband and her parents were processed by standard cytogenetic and FISH procedures. Cytogenetic analyses were performed using the standard phytohemagglutinin-stimulated lymphocyte culture method followed by G-banding. Twenty metaphase cells each were analyzed for the patient and her parents. In the proposita, additional analyses by C-banding and NOR staining were also performed.

Molecular Cytogenetic Analysis

Fluorescence spectral karyotyping (SKY) was performed on the metaphase cells according to the probe manufacturer's instructions (ASI, Carlsbad, CA) and as previously published [Bayani et al., 2003]. Spectral images were acquired with an SD200 spectral bioimaging system (Applied Spectral Imaging [ASI], Migdal Ha'Emek, Israel) and analyzed using the ASI SkyView software (version 1.2).

FISH was performed with centromeric chromosome painting for chromosome 15 and pantelomeric probes (Cambio Ltd, Cambridge, UK) according to the manufacturer's instructions. To estimate the size of the SMC, FISH was performed with BAC probes according to the technique of Pinkel et al. [1988], with modifications [Sullivan et al., 1996]. The BAC probes were obtained from a human BAC filter library at the Roswell Park Cancer Institute (http://genomics.roswellpark.org/human/overview.html) and selected using the UCSC Genome Browser from the University of California at Santa Cruz (http://genome.ucsc.edu—Build 35). BAC DNAs were isolated using a Plasmid Purification Kit (Qiagen, Valencia, CA), and labeled using a Nick Translation Labeling Kit (Vysis, Downers Grove, IL) with either Spectrum Orange or Spectrum Green. FISH images were captured on an Axioplan 2 imaging fluorescence microscope (Zeiss, Göttingen, Germany) and analyzed with ISIS software (MetaSystems, Altlussheim, Germany).

Molecular Analysis

Genomic DNA was extracted from peripheral blood leukocytes of the patient and her parents according to standard procedures. A Multiplex Ligation-dependent Probe Amplification (MLPA) reaction was performed for the patient using the SALSA MLPA Kit 070-Subtelomeric (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's instructions. The results were analyzed with the GeneMarker software (Softgenetics, LLC, State College, PA).

Polymorphism analysis using three microsatellite markers within the region 15q11-q13 (D15S11, D15S113, and GABRB3) was performed in the patient and her parents, in order to investigate the parental origin of the SMC. The methylation status of the PWACR was investigated by SNURF–SNRPN exon 1 methylation analysis after PCR amplification of bisulfite-modified DNA [Zeschnigk

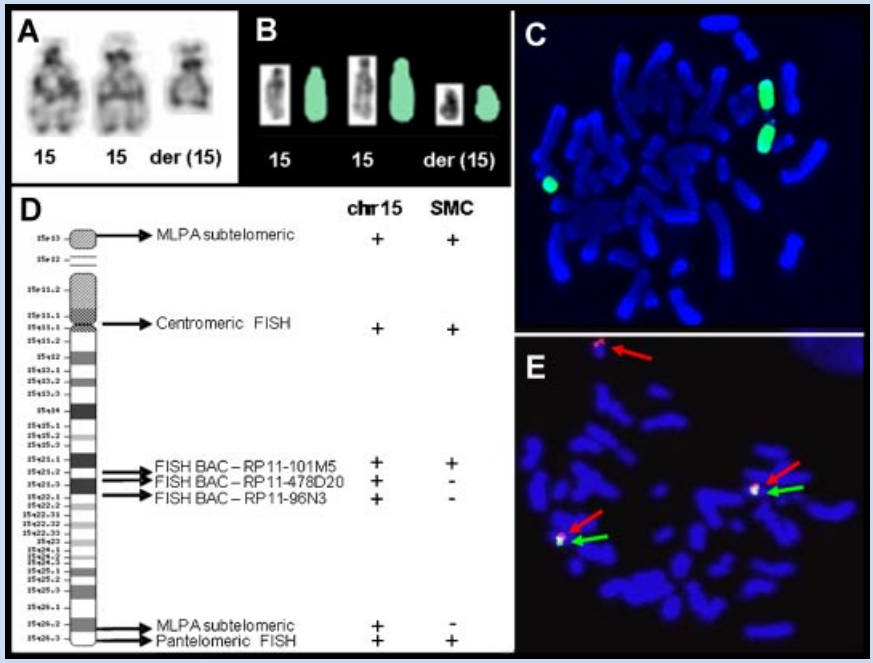

FIG. 2. A: G-banding showing the SMC; (B) SKY showing a derived chromosome 15; (C) FISH with chromosome painting probes; (D) chromosome 15 ideogram showing the localization of all techniques and probes; (E) BAC-FISH using probes RP11-101M5 (red) and RP11-478D20 (green), indicating the breakpoint at 15q21.2. [Color figure can be viewed in the online issue, available at: www.interscience.wiley.com.]

et al., 1997]. This methodology is based on primers specific to paternal and maternal alleles that amplify fragments of 221 and 313 bp, respectively.

RESULTS

The patient showed a 47,XX,+mar karyotype (Fig. 2). The parents' cytogenetic analysis showed normal karyotypes. C-banding and NOR-staining characterized the marker as a monocentric and monosatellited chromosome; SKY and chromosome painting showed it to be derived from chromosome 15, with no other associated chromosome rearrangement. FISH with centromeric and painting probes confirmed these results. FISH with BAC probes mapped the breakpoint to the distal region of band 15q21.2, between RP11-101M5 (~50.0–50.2 Mb from 15pter) and RP11-478D20 (~51.1–51.3 Mb from 15pter). MLPA analysis confirmed the presence of three copies of the NDN gene mapped at 15q11.2 and two copies of the subtelomeric region of the long arm (FLJ22604 gene). No subtelomeric region of any other chromosome was detected. FISH using a pantelomeric probe showed the presence of telomeric sequences in the marker chromosome. The final karyotype was defined as 47,XX,+mar.ish der(15)(wcp15+,RP11-101M5+,RP11-478D20−). Maternal origin of the extra chromosome was demonstrated by the presence of three alleles of the GABRB3 microsatellite marker, one paternal and two different maternal alleles. The D15S11 and D15S113 markers showed uninformative results. SNURF–SNRPN methylation pattern analysis showed the presence of both paternal and maternal bands.

DISCUSSION

The most common class of marker chromosomes are derived from acrocentric chromosomes and have a satellited or bisatellited structure, with chromosome 15 accounting for the highest percentage in this group [Liehr et al., 2006]. The size of the marker, the presence of PWACR and the parental origin of the SMC seem to be important to the phenotype. Small markers derived from chromosome 15 are frequently associated with normal phenotype, but in some rare cases these markers have been associated with the Prader–Willi syndrome and Angelman syndrome (PWS/AS) [Eggermann et al., 2002; Crolla et al., 2005]. About 100 cases with extra inv dup(15) chromosomes were reported [Webb, 1994; Webb et al., 1998; Schinzel, 2001]. Most of the markers described are triplications of the region 15pter-q13. The phenotypic characteristics associated with these cases are unspecific and include facial dysmorphism, cardiac alterations, seizures, and intellectual disability. In patients with phenotypic alterations, the duplication is usually maternally derived, as in our case, while paternal origin of the duplication has been associated with a normal phenotype [Mohandas et al., 1999]. The fact that the majority of dup15 and sSMCs including the PWACR are maternal in origin suggests that duplications of paternal origin may be either lethal or with no phenotypic effect [Browne et al., 1997]. Eggermann et al. [2002] studied 32 carriers of 15q sSMC and showed that only those with larger chromosomes, comprising at least chromosomal band 15q12, presented abnormal phenotypes. Patients with a breakpoint different from 15q13 are rarely described. Castel et al. [1976], Herwijer et al. [1988] and Schroer et al. [1998] described cases of dup(15)(pter-q14). The case described by Castel et al. [1976] presented with short stature and severe intellectual handicap, but no gross dysmorphic features. The case described by Herwijer et al. [1988] showed some features found in trip(15)(pter-q13) and, in addition, ptosis, deafness, and anterior placement of the a.u.. Schroer et al. [1998] described a 4-year-old male with seizures and no dysmorphic phenotype. Akahoshi et al. [2001] described a case with an interstitial duplication of 15q11.2-q14 who had clinical manifestations of proximal 15q trisomy and hyperpigmentation. Crolla et al. [1995] reported on a patient with an inv dup(15) with breakpoints at 15q11 and 15q15 whose clinical features were similar to the ones found in trip(15)(pter-q13) with few minor anomalies, but with seizures and profound mental deficiency. Annerén and Gustavson [1982] reported on a 13-year-old patient with severe intellectual disability, congenital hip luxation, cleft palate, microcephaly, and other minor features. This patient had an extra chromosome derived from a maternal 13;15 translocation and consequent distal trisomy 15 involving the region 15pter-q21.

Trisomy 15pter-q22 associated with another chromosome imbalance was previously reported in patients with derivative chromosomes due to maternal translocations [Bannister and Engel, 1975; Cohen et al., 1975; Geneix et al., 1979]. The translocations found in their mothers, as determined by classical cytogenetics, were D/E translocations: t(4;15)(p16;q22) and t(5;15), respectively. These three patients had in common growth and mental delay, microcephaly, dysplastic and low-set ears, micrognathia, high palate, and club feet. The common features our patient had with the previously described cases are: microcephaly, epicanthal folds, low nasal bridge, low-set ears, micrognathia, short neck, clinodactyly of fifth fingers, ventricular septal defect, hypotonia, epilepsy, seizures, spasms, growth, and neuromotor delay. Apart from these, there are some features that are exclusive to her, such as the triangular face, sparse eyebrows, telecanthus, short columella, preauricular skin tags, downslanting mouth, narrow palate, *café-au-lait* spots, hemangiomas, mammary hypertelorism, and hypoplastic nails. The most important are: dysplastic corpus callosum, ventricular septal defect, atrial septal defect, and patent ductus arteriosus.

Concerning chromosome 15 anomalies and heart defects, Lalani et al. [2006] described a patient with a 15q21.1-q22.2 deletion who presented coarctation of the aorta, partial agenesis of the corpus callosum and mild to moderate developmental delay, among other features. Two additional cases with interstitial deletion 15q15-q21 were described with, respectively, atrial and ventricular septal defects and Fallot's tetralogy with septal hypertrophy [Koivisto et al., 1999; Shur et al., 2003]. These findings suggest that there is a gene responsible for the cardiac defects mapped to 15q21. Within this region there are a few genes that are known to be expressed in the heart, including *ARPP-19* [Girault et al., 1990], *RAB27A* [Ramalho et al., 2001], and *ADAM10* [Arndt et al., 2002]. Partial agenesis of the corpus callosum has been reported in patients with 15q21.1-q22.2 deletion [Lalani et al., 2006], a feature also found in our patient. Partial agenesis of the rostral corpus callosum was also described by Mohandas et al. [1999] in a patient with duplication of the PWACR.

The chromosome 15 is one of the seven human chromosomes with a highly unstable region (15q proximal) and a high rate of low-copy repeats (LCR) that can be prone to misalignment during meiosis and can be involved in the genesis of these chromosomal abnormalities [Wandstrat and Schwartz, 2000; Zody et al., 2006]. These duplications are largely clustered in two regions with extensive ancient similarity [Pujana et al., 2001], on proximal and distal 15q; the proximal region is nonstable because recombination among the segmental duplications can result in deletions causing the PWS/AS [Zody et al., 2006]. Wandstrat and Schwartz [2000] suggested that sSMCs derived from chromosome 15 are the result of an aberrant recombination event between homologous chromosomes and that exchange may occur between either sister chromatids or homologous chromosomes, pre or postrecombination. This is consistent with reports stating that deletions of chromosome 15 associated with PWS/AS are also the result of inter- and intrachromosomal rearrangements [Carrozzo et al., 1997; Robinson et al., 1998]. In our patient, the breakpoint is located in a region containing no known LCR. Chromosomal rearrangement studies with breakpoints, which include no known LCR may contribute to the discovery of other mechanisms of origin, different from LCR [Nogueira et al., 2008]. The SMC studied here has no subtelomeric sequence from any other chromosome, as observed by MLPA. The pantelomeric FISH analysis showed the presence of telomeric sequences on the long arm of the marker chromosome. These data indicate that this marker chromosome actually presents an interstitial deletion or a terminal deletion stabilized by a telomere capture mechanism. The present article emphasizes the importance of using molecular cytogenetic techniques in determining chromosome breakpoints and understanding the mechanisms that predispose to chromosomal rearrangements.

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