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Clinical Findings in a Patient Mosaic for a Supernumerary Ring Chromosome 20

Enrique Daniel Austin-Ward,[1]* Silvia Castillo,[1] Yuri Dragnic,[2] Patricia Sanz,[1] Samuel Salazar,[1] and Joan H. M. Knoll[3]

[1]Servicio de Genética, Departamento de Medicina, Hospital Clínico Universidad de Chile, Santiago, Chile
[2]Neurología Infantil, Centro de Diagnóstico, Hospital Clínico Universidad de Chile, Santiago, Chile
[3]Division of Genetics, Children's Hospital and Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Marker chromosomes present a problem in genetic counseling because there are often no clear phenotype-karyotype correlations. We present the clinical findings in a patient who is mosaic for a supernumerary marker chromosome 20 determined by fluorescence in situ hybridization (FISH) and compare these findings to others reported in the literature. Am. J. Med. Genet. 91:171–174, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

There is interest in clinical genetics to elucidate the phenotypic effects of marker chromosomes because of their implications in prognosis and genetic counseling. Chromosomal markers are now often identified by molecular cytogenetic methods, but limited data currently do not permit consistent phenotype-genotype correlations to be made. In addition, variations in the size and parental origin of the marker can influence outcome. The best known example of such influences exist for pseudo-dicentric chromosome 15s where a normal phenotype often results when the marker is devoid of the Angelman/Prader-Willi (AS/PWS) region and an abnormal phenotype when the marker has two maternally derived copies of the AS/PWS region [Cheng et al., 1994; Leana-Cox et al., 1994; Mignon et al., 1996]. We present the clinical findings in a child who is mosaic for a supernumerary ring chromosome derived from chromosome 20.

CLINICAL REPORT

Mother and father are a healthy nonconsanguineous couple, age 19 and 20 years, respectively. Family history was unremarkable. The patient has a healthy maternal half sister, aged 4 years. This pregnancy was normal, and a boy was born at 39 weeks gestation. His weight was 3.76 kg (50th centile), length 50 cm (50th centile) and occipitofrontal circumference (OFC) 35 cm (50th centile). The Apgar score were 9 at 1 and 5 min. At 2 years 8 months, the patient was evaluated by a geneticist because of psychomotor retardation, facial anomalies, and speech delay. His weight was 16.1 kg (50th centile), length 91 cm (50th centile) and OFC 50

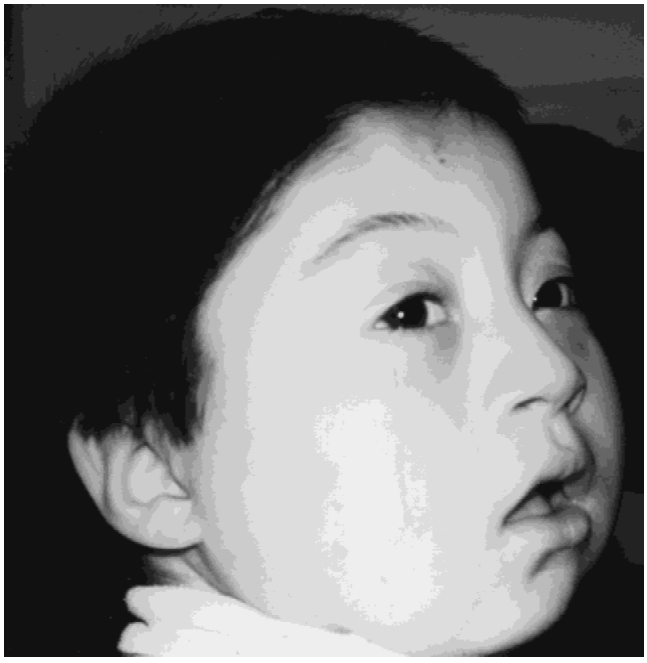

Fig. 1. Facial dysmorphism in a patient with a ring marker chromosome 20.

Current address: Joan H. M. Knoll, Section of Medical Genetics and Molecular Medicine, Children's Mercy Hospital, University of Missouri School of Medicine, Kansas City, Missouri.

*Correspondence to: Enrique Daniel Austin-Ward, M.D., Apto. 10378, Zona 4, Panama, Republic of Panama.
E-mail: Austin_Ward@yahoo.com

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cm (50th centile). He had brachyturricephaly, normal set ears with lobe creases, ocular proptosis, flat brow ridges, full cheeks and a high arched palate (Fig. 1). He had a short neck, and his chest was normal without heart murmurs. The abdomen and lower limbs were normal. Bilateral clinodactyly of the fifth finger was observed. Examination of external genitalia showed that both testes were in the inguinal canal. Electroencephalograph (EEG), skull radiographs, and results of metabolic screening were normal. A computed tomography (CT) scan was essentially normal, with a slight increase in the sella turcica size noted. A clinical diagnosis of craniosynostosis type 2 (Boston type [Warman et al., 1993]) was suggested due to the frontal orbital recession.

CYTOGENETICS

Lymphocytes from a peripheral blood sample were phytohemagglutinin (PHA)-stimulated, cultured by standard methods and analyzed by Giemsa banding technique (GTG). This analysis showed a ring chromosome in most cells with the karyotype 47, XY, +r[25]/46,XY[6] (Fig. 2). Centromere (C)-banding and nucleolar organizer region (NOR)-banding were positive and negative, respectively, suggesting the chromosome had

TABLE I. Clinical Findings in Patients With Supernumerary Ring/Marker Chromosome 20s

Patient	Age	Karyotype (% cells with de novo ring[r]/ marker[m] chromosome)	Clinical findings
This study	2y 8m	47,XY,+r/46,XY (80% lymphocytes)	Psychomotor retardation (PMR), brachiturricephaly, posteriorly rotated ears with lobe creases, occular proptosis and flat brow ridge, full cheeks, high arched palate, micrognathia, short neck, clinodactyly of 5th fingers.
Callen et al., 1991 (case 10)	7y 10m	47,XY,+m/48,XY,+2m (72 and 28% of lymphocytes)	Normal intelligence, <3rd centile for height and weight, scaphocephaly, low set ears, high palate with high-pitched voice, micrognathia, hyperextensible elbows and fingers, clinodactyly of fingers 2, 4 and 5, syndactyly of fingers 2–5; mild scoliosis.
Blennow et al., 1993 (case E)	4y	47,XY,+r/46,XY (48% lymphocytes)	PMR, slight growth retardation, low set ears; limited hip mobility as a newborn; abnormal behavior
Batista et al., 1995	1y 4m	47,XY,+r/46,XY (86% cord blood) Note: +20 and 2r(20)s also observed in fibroblast and prenatally	PMR, < 3rd centile for height and weight, asymmetric face, micrognathia, high palate, short philtrum, abnormal ears, hypotonia, hyperextensible joints, clinodactyly.
van Langen et al., 1996	1y 2m	47,XY,+r/46,XY (60% lymphocytes)	PMR, 25th centile for height, 75th centile for weight, coarse facies with full cheeks, deep set eyes, slightly upslanted palpebral fissures, strabismus, normal ears, short nose with anteverted nares, micrognathia, normal philtrum and palate; broad neck and thorax, widely space nipples, broad and short hands and feet, clinodactyly of 5th fingers, slight hyperextensible elbows and knees.
Viersbach et al., 1997 (case 1)	1y 8m	47,XY,+r/46,XY (80% amniocytes; 9% cord blood)	Normal development, syndactyly of 2nd and 3rd toes.
Viersbach et al., 1997 (case 3)	4y 2m	47,XY,+(29)/48,XY,+2r/46,XY (1 and 2 rings in 25 and 71% of lymphocytes)	PMR, <3rd centile for height and weight, cardiac anomalies, hypertelorism, low set ears, clubbed fingers, depressed root of nose, bilateral plantar furrow.
Crolla et al., 1998 (case 24)	1y 9m	47,XY,+r/46,XY (57% lymphocytes)	PMR, hypoplastic alae nasi, long filtrum, micrognathia, pectus excavatum; hypotonia.
LeChien et al., 1994 Grammatico et al., 1992		Trisomy 20p resulting from unbalanced translocations	PMR, normal growth, coarse facies with full cheeks, short philtrum, epicanthal folds, short upturned nose and micrognathia, normal palate.
Herens et al., 1990		Trisomy 20q resulting from unbalanced translocations	Prominent forehead, small eyes, large ears, anteverted nares, short neck, heart defect, dimpled chin.

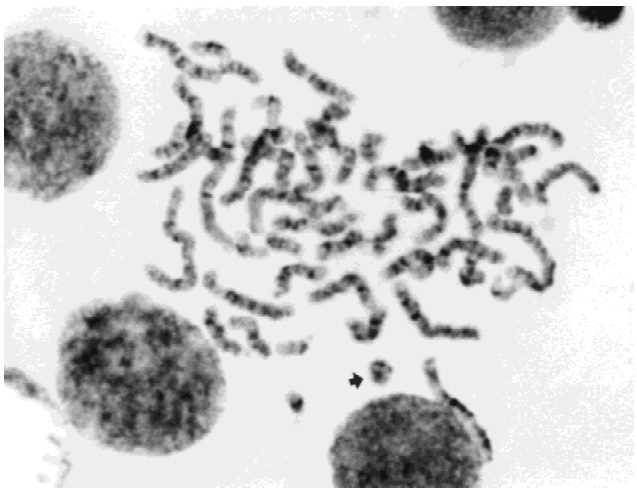

Fig 2. High resolution G-banded karyotype showing the marker chromosome.

a centromere but no nucleolar organizer region. Fluorescence in situ hybridization (FISH) with probes for all centromeres (Oncor, Gaithersburg, MD), chromosome specific centromeres (Vysis) (Oncor) and whole chromosome paints (WCP) Gibco BRL, Gaithersburg, MD), was performed to detect the chromosomal origin of the ring. FISH was performed according to the manufacturers specifications. Chromosomes were counterstained with 4′,6-diamidino-2-phenyl indole (DAPI). The ring generally had a single centromere and hybridized in its entirely with the chromosome 20 paint probe. Occasionally, larger sized rings with two centromeres were observed. Parental chromosomes were normal in peripheral blood.

DISCUSSION

Complete trisomy 20 mosaicism, the most common autosomal mosaicism identified prenatally, poses a genetic counseling dilemma since it can be associated with either poorly defined phenotypic abnormality or with normality [Hsu et al., 1991; Micale et al., 1996]. Supernumerary ring or marker chromosome 20s, resulting in partial trisomy for chromosome 20, have been identified in several children. Table I compares the clinical and cytogenetic findings in these patients and compares them to our case. The supernumerary ring was de novo in all cases, but variation in the level of mosaicism was identified. In the case reported by Viersbach et al. [1997], the level of mosaicism was 9% in cord blood, and the patient was reported as normal with only syndactyly of second and third toes observed. In most other cases in which the trisomy was present in higher frequency in lymphocytes (approximately 80% of lymphocytes in the case presented here), the children were observed to have psychomotor retardation, craniofacial abnormalities and some growth abnormalities. There was a striking similarity between our case and others [Bastista et al., 1995; Callen et al., 1991; Van Langen et al., 1996] whose ring chromosomes appeared similar in size by routine cytogenetics. We were not able to perform a more detailed molecular characterization of the ring chromosome but the G-banding pattern and the phenotype of the patient resembles that of chromosome 20p trisomy (Table I: LeChien et al. [1994] and Grammatico et al. [1992]) not 20q trisomy (Table 1: Herens et al. [1990]). The case reported by Callen et al. [1991] had many of the features in common with trisomy 20p but had normal intelligence with no psychomotor retardation. This child had a cytogenetically smaller marker chromosome (slightly larger than the centromeric heterochromatin), and presumably its size contributed to this difference.

Currently, it appears that mosaicism involving chromosome 20p trisomy in approximately 50% or greater of lymphocytes results in psychomotor retardation, craniofacial abnormalities, and clinodactyly. The effects on clinical outcome are presumably dependent on tissue distribution and genetic content of the supernumerary chromosome, although parental origin (i.e., imprinting) may also play a role for chromosome 20 [Juppner et al., 1998]. The spectrum of effects will be defined as more detailed clinical and molecular evaluations of supernumerary chromosomes are performed.

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