UNIVERSIDAD DE GUADALAJARA

Centro Universitario de Ciencias Biológicas y Agropecuarias

División de Ciencias Biológicas y Ambientales

"DUPLICACIÓN CONSTITUCIONAL 11q23 *DE NOVO* QUE INCLUYE AL GEN *MLL*"

ARTÍCULO CIENTÍFICO PUBLICADO

PARA OBTENER EL TÍTULO DE

LICENCIADO EN BIOLOGÍA

PRESENTA:

MIRIAM PARTIDA PÉREZ

DIRECTOR:

DRA. EN C. MA GUADALUPE DOMÍNGUEZ QUEZADA

LAS AGUJAS, ZAPOPAN, JALISCO. NOVIEMBRE 2005

Universidad de Guadalajara

Centro Universitario de Ciencias Biológicas y Agropecuarias

Coordinación de Titulación y Carrera de Licenciatura en Biología

312/ C. C. BIOLOGÍA

C. MIRIAM PARTIDA PÉREZ
PRESENTE

Manifestamos a usted que con esta fecha ha sido aprobado su tema de titulación en la modalidad de: **Investigación y Estudios de posgrado** opción **Articulo Científico** con el titulo : **" CONSTITUTIONAL DUPLICATION 11q23 DE NOVO INVOLVING THE MILL GENE"** para obtener la Licenciatura en Biología.

Al mismo tiempo le informamos que ha sido aceptado como Director / a de dicho trabajo al **DRA. MA. GUADALUPE DOMÍNGUEZ QUEZADA.**

Sin más por el momento, le envío un caluroso saludo.

ATENTAMENTE
"PIENSA Y TRABAJA"
Las Agujas, Zapopan., 1 de Noviembre del 2005.

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P R E S E N T E.

Por medio de la presente comunicamos a usted que ha sido designado como sinodal para el proyecto: **"CONSTITUTIONAL DUPLICATION 11q23 DE NOVO INVOLVING THE MILL GENE"** elaborado por el alumno: **C. MIRIAM PARTIDA PÉREZ** con la **MODALIDAD:** Investigación y estudios de posgrado **OPCIÓN:** Articulo científico publicado

El Director del Trabajo es el/la: **DRA. MA. GUADALUPE DOMÍNGUEZ QUEZADA.**

Le reiteramos que como sinodal, le corresponde evaluar la viabilidad (si/no) de este proyecto y, en su caso de aprobarlo. Se requiere que su respuesta no exceda el plazo de una semana a partir de la fecha en que lo reciba.

Sin más por el momento, aprovechamos para enviarle un cordial saludo.

ATENTAMENTE
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October 17, 2005

Dear Dr. Domínguez Quezada,

I am pleased to let you know that your manuscript "Constitutional duplication 11q23 *de novo* involving the *MLL* gene" is accepted for publication in Genetic Counseling.

With best regards,

Prof. Dr. J.P. FRYNS

JPF/rl

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"El hombre encuentra a Dios detrás de cada puerta que la ciencia logra abrir."

A. Einstein

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Al **Dr. Horacio** por creer en mi.

CONSTITUTIONAL DUPLICATION 11q23 DE NOVO INVOLVING THE *MLL* GENE

BY M. PARTIDA-PÉREZ[c], M. G. DOMÍNGUEZ[c*], J. SÁNCHEZ-CORONA[b], G. CASTAÑEDA-CISNEROS[a,b], C.L. GARCÍA-GONZÁLEZ[a,b], M.G. LÓPEZ-CARDONA[a,b] AND H. RIVERA[c]*

Running title: Constitutional duplication 11q23

Summary:
We report a child with mental retardation, brain anomalies and congenital heart defect. His karyotype, after G-banding and FISH with a whole chromosome probe for chromosome 11 and a locus-specific probe for the *MLL* gene, was 46,XY,dup(11)(q23q23).ish dup(11)(q23q23)(wcp11+,MLL++) de novo; i.e., he had a pure partial 11q23 duplication. Clinical and cytogenetic findings of the present case were compared with the 7 previously reported cases with pure partial trisomy 11q; in 6/8 cases the region 11q23 was involved. We conclude that the scarce number of cases and their heterogeneity do not allow to establish a reliable genotype-phenotype correlation.

Key-words: Duplication 11q23 - *MLL* gene.

INTRODUCTION

Most cases of partial trisomy 11q result from a 3:1 meiotic segregation of a familial t(11;22)(q23.3;q11.2) and are therefore impure (9, 11). Pure 11q trisomies are rare and may be due to an intrachromosomal duplication or an interchromosomal insertion (2, 10). In fact, six out of seven patients with pure partial trisomy 11q have had intrachromosomal duplications including two instances inherited from a mother with the same duplication (1, 2, 5, 6, 10, 11); the remaining patient had a recombinant from an intrachromosomal insertion carrier (4). We report a further patient with pure 11q23 duplication and compare the clinical and cytogenetic findings with similar cases.

CASE REPORT

The proband was the fourth child born to 25-year-old and unrelated parents. He was delivered at the 40th week of gestation by caesarean section prompted by fetal distress. At birth, weight was 3.090 kg, and lenght 51 cm. At 6 months of age, he underwent surgery for right cryptorchidism and inguinal hernia. He had head control at 8 months. At the age of 18 months, his growth parameters were delayed: weight 9.100 kg (10^{th} centile), height 72 cm (3^{rd} centile), and head circumference 45 cm (3^{rd} centile). The patient (*Fig.* 1) had microtrigonocephaly, triangular face, inner canthal distance of 2.4 cm (25^{th} centile), bitemporal narrowing with fullness of lateral orbits, left palpebral ptosis, short and beaked nose, shotgun nostrils, posteriorly

angulated and anteverted ears, prominent left ear, cupid's bow mouth, micrognathia, short neck, trunk hypotonia, scoliosis, short penis, shallow scrotum, limb hypertonicity, and moderate psychomotor retardation with speech delay (he only used a few simple words). A brain CT scan revealed corpus callosum hypoplasia while a heart examination disclosed a persistent ductus arteriosus.

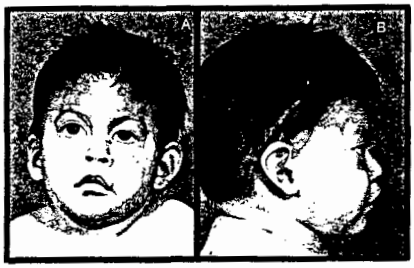

Figure 1. Facial appearance of the propositus at 18 months. Note the trigonocephaly, bitemporal narrowing with fullness of lateral orbits, relative hypotelorism, posteriorly angulated and anteverted ears, short and beaked nose, shotgun nostrils, cupid's bow mouth, thick and everted lower lip, micrognathia and short neck.

CHROMOSOMAL ANALYSIS

Peripheral blood lymphocytes from the patient and his parents were cultured for 72 h and chromosome preparations were stained for GTG bands. Moreover, the patient's chromosomes were hybridized *in situ* with a WCP for chromosome 11 and a locus-specific probe for the *MLL* gene (Vysis) located on the 11q23 band. This dual color probe consists of a 350 kb portion centromeric to the breakpoint cluster region (bcr) labeled in Spectrum Green and another largely telomeric portion of 190 kb labeled in Spectrum Orange

RESULTS

The initial G-banding evaluation (n=20 cells) of the proband revealed, as the sole abnormality, an 11q+ whose extra material apparently corresponded to a direct duplication of 11q23. The whole chromosome 11 probe painted entirely the 11q+, thus confirming that the extra material was derived from chromosome 11 without involvement of any other chromosome. The 11q23 duplication was further characterized by the *MLL* probe which showed a dual large signal on the 11q+ as compared with the normal homologue. The patient's karyotype was 46,XY,dup(11)(q23q23).ish dup(11)(q23q23)(wcp11+,*MLL*++) (Fig. 2). In 1/30 metaphases scored after hybridization with the *MLL* probe, the 11q+ apparently had a fragile site in q23 that split the red and green signals into two parts. Parental karyotypes were normal.

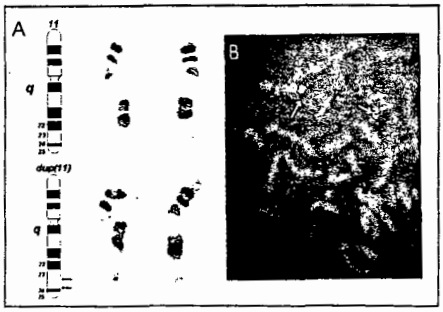

Figure 2. A) Partial G-banded karyotype from two cells showing the pure duplication 11q23 (*lower row*). B) FISH analysis with a locus specific probe for the *MLL* gene; arrows point to both the normal homologue and the 11q+ with the dual large signal.

Table I: Clinical and cytogenetic findings of the 8 patients with pure trisomy 11q.

	Leglus *et al.* (5)	Yelavarthi and Zunich (10)	De Die-Smulders and Engelen (1)	Pfeiffer and Shütz (6)	Delobel *et al.* (2)	Fortsythe *et al.* (4)	Zhao *et al.* (11)	Present case
Duplicated segment	q13.3 to q14.2	q13.5 to q21	q22 to q23	q23 to qter	q23.3 to q24?	q23.3 to q24.2	q25 to q13	q23
Familial/*de novo*	*de novo*	Familial*	?	Familial*	*de novo*	Familial	*de novo*	*de novo*
Age/sex	31 years/F	2 1/2 years/ M	50 years/F	7 months/M	19 years/F	11 years/F	5 years/F	1 1/2years/M
Mental retardation	+	+	++	+	++	+	+	+
Trigonocephaly	Nr	+	-	+	-	-	-	+
Microcephaly	+		+	+	+	+	+	+
Triangular facies	-	+	-	-	+	-	Round face	+
Ocular defects	Strabismus	-	Hypertelorism	Hypotelorism	-	Strabismus	Myopia and bilateral coloboma of the iris	Relative hypotelorism
Abnormal ears	Small ears whit prominent antihelix	Low set protruding ears	Large and protuding ears	Large and prominent ears	Posteriorly angulated anteverted ears	-	Right cupped ear	Posteriorly angulated anteverted ears and prominent left ear
Short nose	-	-	+	+	-	-	+	+
Beaked nose	Nr	+	Nr	Nr	Nr	+	-	+
Small mouth	-	-	-	+	-	-	+	-
High–arched palate	-	+	-	-	-	Nr	+	-
Thick and everted lower lip	Nr	-	Everted	Nr	Thick	+	-	+
Pointed chin	-	+	-	Nr	-	-	Nr	-

Retrognathia/ micrognathia/ prognathia	Retrognathia	Nr	Prognathia	Microretrognathia	Nr	Retrognathia	Micrognathia	Micrognathia
Short limbs	-	-	-	-	+ (clinodactyly)	-	+ (brachydactyly)	-
Scoliosis	-	-	Kyphoscoliosis	-	+	+	Nr	+
Congenital heart defects	VSD/PVS	-	-	ASD II	-	-	ASD	PDA/PVS
Seizures	+	-	-	-	+	Nr	+	-
Brain anomalies	-	-	-	+	-	Nr	Nr	+
Hypertonicity	-	-	+	-	+	Nr	-	+ (Limbs)
Hypotonia	+	+	-	-	+	Nr	+	+ (Trunck)

-Absent, + Present, Severe mental retardation (++), VSD ventricular septal defect, PVS pulmonar valve stenosis, ASD atrial septal defect, PDA persistent ductus arteriosus, Nr not reported, *Duplication inherited from the mildly affected nonmosaic (10) or mosaic (6) mother.

DISCUSSION

The clinical features in eight patients with pure partial trisomy 11q are heterogenous (Table I). The present infant compares with the 19-year-old girl described by Delobel et al. (2) who had a similar interstitial duplication involving 11q23 and also exhibited limb hypertonicity, posteriorly angulated and anteverted ears, mental retardation, microcephaly, triangular face, scoliosis and thick lower lip. In addition, he shares with the other patients some mostly nonspecific phenotypical features that could hardly be used to delineate the 11q pure trisomy syndrome. Altogether, the phenotypical repercussion of this chromosomal imbalance seems to be rather benign as demonstrated by survival into adulthood of 3/8 patients and the mother-to-child transmission of different 11q duplications in two instances (6, 10). This finding is remarkable because 11q23 is a G-negative band with many active genes whose imbalance may lead to a severe phenotype. Since this band is involved in 5/8 cases with pure trisomy 11q, the underlying breakpoint may also occur in the AT-rich segment of 190 pb commonly involved in the t(11;22)(q23;q11.2) translocation (9). These findings suggest that AT-rich regions are prone to recombination events that lead to diverse rearrangements (9). A factor that could influence the frequency of this rearrangement is the 11q23.3 rare fragile site induced by BrdU (6). Thus, the finding of a single cell with a fragile site-like defect in 11q23, although likely fortuitous, is intriguing.

The duplicated region on 11q23 contains, among others, the *MLL* gene. The *MLL* amplification is a recurrent defect associated with adverse prognosis in acute myeloid leukemia (AML), acute lymphocytic leukemia, and myelodysplastic syndrome (3). Nevertheless, Schnittger et al. reported that in AML a tandem duplication of the *MLL* gene is not restricted to malignant cells (either karyotypically normal or abnormal) but may also occur in a subset of normal hematopoietic cells (7, 8). Accordingly, it is not unexpected to ascertain that the constitutional 11q23 duplication has not resulted in leukemia.

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