Trisomy 8 Mosaicism in Two Filipino Children

Mary Anne D. Chiong[1,2], Edsel Allan G. Salonga[2]
Eva Maria C. Cutiongco-de la Paz[1,2]

[1]*Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila;*
[2]*Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila*

ABSTRACT

We describe two Filipino patients with Trisomy 8 mosaicism syndrome. Both had global developmental delay, mental deficiency, facial dysmorphism, skeletal deformities and the characteristic deep plantar and palmar creases. Their phenotype and radiologic features were consistent with the previously reported cases. Hematologic malignancies have recently been found to be associated with this chromosomal abnormality, emphasizing the importance of monitoring for cancer risks.

Key Words: trisomy 8 mosaicism, deep palmar and plantar creases, skeletal abnormalities, hematologic malignancy

Introduction

Chromosomal mosaicism is defined as the presence in an individual or a tissue of two or more cell lines which differ genetically but are derived from a single zygote. A common cause of mosaicism is nondisjunction during early postzygotic mitotic division. The effects of mosaicism on development vary with the timing of the nondisjunctional event, the nature of the chromosome abnormality, the proportion of the different chromosome complements present, as well as the tissues affected.[1]

Chromosome 8 is one of the largest autosomes found to be trisomic among humans. Trisomy 8 mosaicism syndrome (T8mS) consists primarily of individuals whose chromosome complement is mosaic for chromosome 8, i.e. patients with a chromosomally normal cell line in addition to the trisomic cell line.

It has been previously proposed to be a distinct clinical entity based on the constellation of abnormalities associated with it, including mild to moderate psychomotor retardation, osseous and soft tissue abnormalities, characteristic dermatoglyphics and other craniofacial and visceral anomalies.

We present 2 patients with clinical and cytogenetic findings compatible with this syndrome.

Corresponding author: Mary Anne D. Chiong, MD
Institute of Human Genetics, National Institutes of Health,
University of the Philippines Manila
625 Pedro Gil Street, Ermita Manila 1000, Philippines
Telephone: +632 536 7002
E-mail: madchiong@post.upm.edu.ph

Clinical Reports

Patient 1

This female patient was first seen at 7 years and 3 months of age for skeletal anomalies and mental retardation. She was born full term by spontaneous vaginal delivery to a 34 year old G5P4 (4004) whose pregnancy had been uneventful. She had good cry and activity at birth with a weight of 4.5 kg. Except for congenital bilateral talipes equinovarus deformity which were corrected with metal braces in infancy, her past medical history was unremarkable.

Developmental milestones have been normal with the exception of speech delay. She has remained very poorly articulated. Her performance was below average compared to the rest of her classmates in school. Her disposition was reported to be agreeable despite bouts of "hyperactivity".

Physical examination revealed that her height and weight were at the 75th percentile for age. Her head was plagiocephalic with a circumference at the 50th percentile for age. Other pertinent physical findings showed prominent forehead, supraorbital hypoplasia, upslanted palpebral fissures with hypertelorism, flat nasal bridge with broad nasal tip, anteverted nares, full lips with downturned corners of the mouth, narrow palate, low set ears with preauricular pits, short neck with torticollis tilted to the right, narrow shoulders, short clavicles and hypoplastic nipples. Limb and spine anomalies included a long slender trunk, exaggerated lumbar lordosis, dislocated radial head on the right, camptodactyly of the distal interphalangeal joints, clinodactyly of the 5th digits, broad feet with widely spaced toes and deep plantar creases. Palmar creases were normal. There was no abnormal pigmentation. The rest of the physical and neurologic examinations were normal (Figures 1 A-E).

Renal and bladder ultrasound, and 2D echocardiography revealed normal results. Radiologic findings showed that the clavicles were sharply curved and with a cephalad convexity laterally giving the characteristic "handle bar" configuration. There were 13 ribs and 13 dorsal vertebrae. There was fusion of the C2-C3 vertebral bodies and posterior elements, consistent with Klippel – Feil sequence. Coxa valga deformity of both hip joints were also noted and the pelvis was described as narrow. Based on Greulich and Pyle method, the patient's wrist most closely resembled a

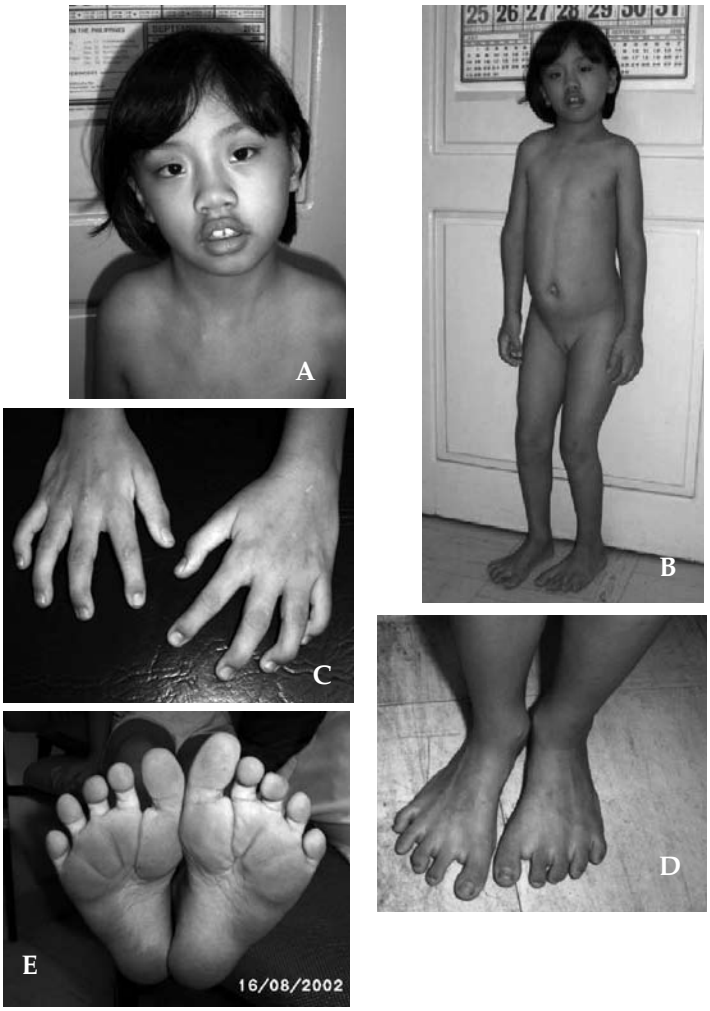


Figure 1. A) Upslanted palpebral fissures, hypertelorism, flat nasal bridge, anteverted nares, full lips and torticollis. B) Exaggerated lumbar lordosis and dislocated radial head. C) Camptodactyly. D) Broad feet with widely spaced toes. E) Deep plantar creases (with permission).

standard 7 yr 10 mo old female (Figures 2A-B).

Cytogenetic studies from peripheral blood showed that out of 20 cells studied, 12 had normal 46,XX karyotype while 8 were trisomic for chromosome 8 (47,XX +8). Ideally, cytogenetic studies on fibroblasts should have been done to detect mosaicism in other tissues (Figure 3).

Patient 2

This male patient was second in a sibship of two, born to a non-consanguineous, healthy couple. The full term gestation was complicated by a urinary tract infection at the beginning of the 2nd trimester. Labor and delivery were uneventful. The following physical findings were noted at birth: head circumference of 39.5 cm (>97th percentile), length of 56.5 cm (97th percentile), weight of 2.9 kg (50th percentile), micrognathia, ankyloglossia, overlapping fingers, clinodactyly and rocker bottom feet.

He was noted to have stridolous breathing at 1 month of age and was assessed to have laryngotracheomalacia at 8 months of age. He had occasional regurgitation during feeding. He had global developmental delay. A diagnosis of cerebral palsy was given by a neurologist at 7 months.

On examination at 9 months of age, his weight was less than the 5th percentile for age, and head circumference was below 2 SD for age. His length was within the 75th-90th percentile with a high upper to lower segment ratio. Pertinent physical findings showed plagiocephaly with a flattened occiput, bitemporal narrowing, small anterior fontanelle, low anterior hairline with a nevus flammeus on the glabellar area, supraorbital hypoplasia with bilateral median epicanthal folds, flat nasal bridge with bulbous nasal tip, anteverted nares, ankyloglossia, micrognathia and low set ears that were posteriorly rotated with prominent antihelices and broad helical roots (Figures 4A- B).

Stridor was remarkable with evident suprasternal, intercostals and subcostal retractions. Cardiac and abdominal findings were normal. The examination of the genitalia revealed bilaterally descended testes with shawl scrotum and hypospadia. A deep pit over the sacral bone was present and limb and spine anomalies included a long slender trunk with narrowed shoulders, overlapping fingers (2nd and 4th over 3rd), camptodactyly of the 3rd digits, clinodactyly of the 2nd and 5th digits, prominent calcaneal bones with proximally inserted 2nd toes and deep palmar and plantar creases. Hirsutism was present over the face and back. Neurologic examination showed esotropia on primary gaze (Figures 4 C-D).

Abdominal ultrasound, 2D echocardiography, and

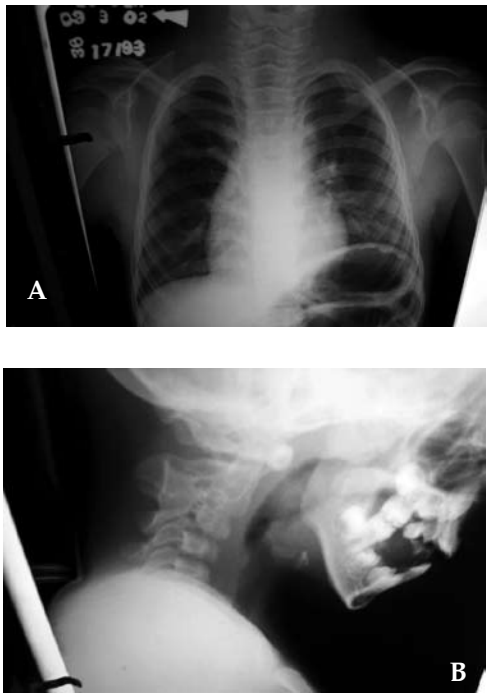
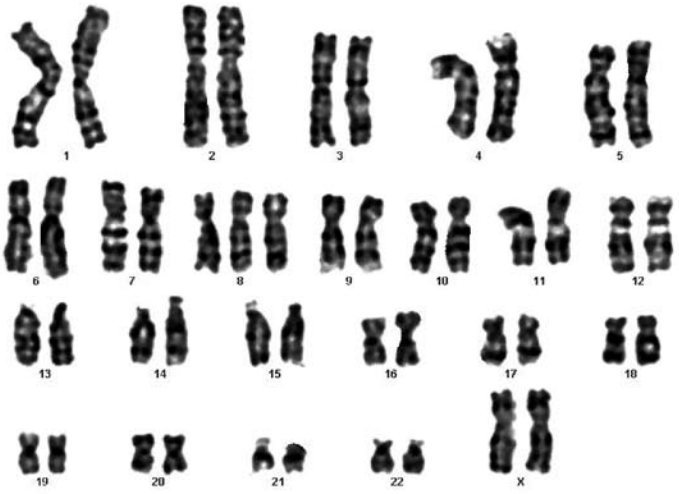


Figure 2. A) Handle bar deformity. B) C2-C3 fusion of the clavicles.

a routine complete blood count (CBC) were all normal. Ophthalmologic examination was likewise normal.

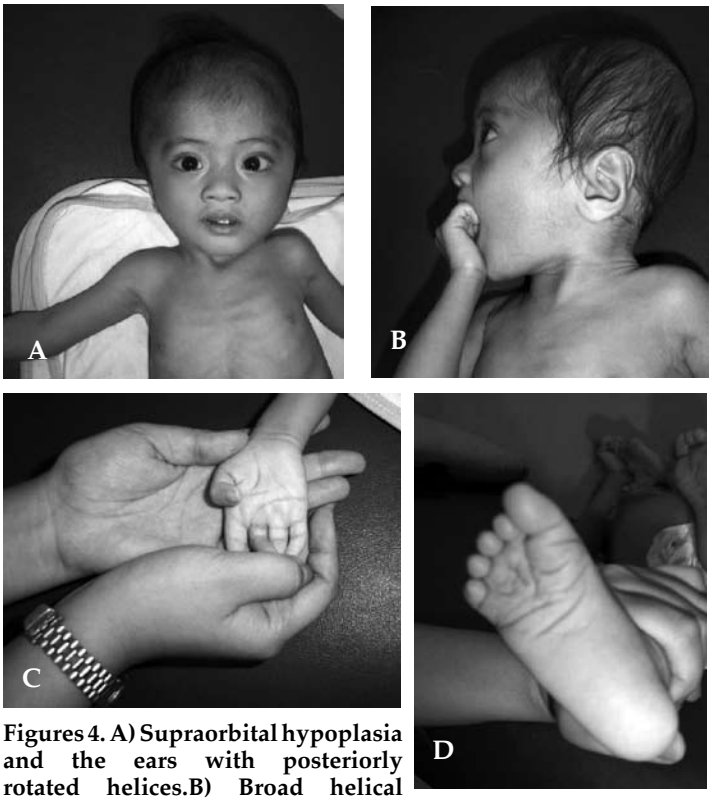
Radiographic studies showed the characteristic "handle bar" configuration of the clavicles. There was Sprengel's deformity on the right scapula and he had 12 ribs with wavy contour which were slightly thickened. Slight leftward curvature of the thoracic spine and coxa valga deformity of both hip joints were also observed. Bone age was compatible with that of a 9 month old male infant (Figures 5A- B).

Chromosomal analysis on peripheral blood showed 2 cell lines. Of the 40 cells studied, 3 cell lines showed an additional chromosome 8 (47,XY, +8) while the other cell lines showed a normal male karyotype (46,XY). Cytogenetic studies on fibroblast cells were not done (Figure 6).



47, XX+8
Source: Cytogenetics Laboratory, Institute of Human Genetics

Figure 3. Chromosomal analysis showing an extra chromosome 8 on 8 cell lines.



Figures 4. A) Supraorbital hypoplasia and the ears with posteriorly rotated helices.B) Broad helical roots and prominent antihelices. C) Camptodactyly. D) Deep palmar and plantar creases (with permission).

Discussion

More than 100 cases have already been reported since it was first recognized in 1963 by Stalder et al.[2] Reported cases have shown sufficient uniformity of signs, symptoms and anomalies, and thus have helped delineate this clinical syndrome. These common features are summarized below and those that were observed in our 2 patients are presented[2,3,4,5] (Table1).

In conjunction with the clinical features found to be common in Trisomy 8 mosaicism syndrome, there are also characteristic radiographic features[2,3,4,5,6] (Table 2).

In general, our patients presented with features consistent with previously reported cases of Trisomy 8 mosaicism syndrome. Both of them shared the following: developmental delay, mental deficiency, characteristic dysmorphic facies and limb anomalies. Growth is variable from small to tall and both our patients' heights were along the 75th percentile for age. However, Patient 1 had more remarkable skeletal deformities compared to Patient 2 which included Klippel Feil sequence, 13 pairs of ribs, narrow iliac wings and absent patellar bones.

In recent years, several conditions have been associated with Trisomy 8 mosaicism; hematologic and other forms of malignancies were most noteworthy among these. Trisomy 8 mosaicism was seen in a range of disorders, both acquired and constitutional. Trisomy 8 mosaicism as an acquired condition is found in hematological disorders notably in myelodysplastic (MDS) and acute myeloid leukemia (AML), and is restricted to the malignant cells. The full constitutional condition presents with the physical stigmata, skeletal abnormalities and a mild to moderate mental retardation in addition to the malignancies.[7] A report on three patients with CT8m who developed refractory anemia, acute lymphoblastic anemia and idiopathic myelofibrosis led to the postulate that CT8m could be regarded as the first mutation in a multistep carcinogenetic process.[8] Indeed, this view was supported by a more recent finding that the frequency of constitutional Trisomy 8 in hematologic dysplastic and neoplastic disorders was approximately 15-20%.[9]

The other hematologic and neoplastic abnormalities reported in patients with Trisomy 8 mosaicism were hypereosinophilic syndrome,[10] paroxysmal nocturnal hemoglobinuria,[11] clotting factor defects,[3] leiomyosarcoma,[2] gestational trophoblastic diseases, germ cell tumors and cystic nephroblastoma. This predisposition to neoplasms in general, may all be secondary to the cytogenetic changes which presumably enhance proto-oncogene expression.

Postzygotic mitotic nondisjunction has been deduced to be the most likely mechanism underlying the origin of the mosaicism trisomy 8 cell line.[8,12,13] The clinical and

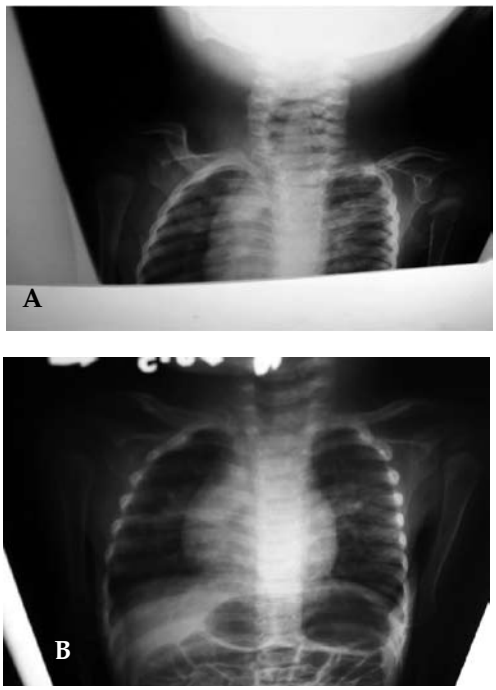


Figure 5. A) Sprengel deformity of the right scapula. B) 12 pairs of ribs.

Table1. Clinical Features of Reported Cases of Trisomy 8 Mosaicism and Those of Our Patients

Clinical Features	Patient 1	Patient 2
Mental Retardation	+	-
Delayed Motor Development	+	+
Delayed and/or Poor Speech	+	+
Craniofacial Abnormalities:		
Skull Deformity	+	+
Prominent forehead	+	-
Strabismus	-	+
Hypertelorism	+	-
Low set and/or Dysplastic Ears	+	+
Broad upturned nose	+	+
Prominent Lips or Everted	+	-
Micro/retrognathia	-	+
Palatal Deformity	+	-
Cardiovascular abnormality	-	-
Urinary tract Abnormality	-	-
Genital Abnormality	-	+
Limbs/Skeleton:		
Narrow Shoulders	+	+
Short neck	+	-
Camptodactyly and flexion Contractures of Peripheral Joints	+	+
Congenital Luxation of Several Joints	+	-
Palmar and/or Deep Plantar Skin Furrows	+	+
Abnormalities of the Hands and Feet	+	+
Long Slender Trunk	+	+

47, XX+8
Source: Cytogenetics Laboratory, Institute of Human Genetics

Figure 6. Chromosomal analysis showing an extra chromosome 8 on 3 cell lines.

Table 2. Radiographic Findings in Trisomy 8 Mosaicism Syndrome

Radiologic Features	Patient 1	Patient 2
Handle bar configuration	+	+
Sprengel's deformity of the scapula	-	+
>12 pairs of ribs	+	-
Narrow iliac wings	+	-
Vertebral anomaly (bifid vertebra, extra lumbar vertebra, spina bifida occulta, scoliosis)	-	+
Narrow diaphysis of long bones	-	-
Absent patella	+	-
Advanced bone age	-	-

cytogenetic variability in Trisomy 8 mosaicism syndrome demonstrated that cytogenetic variation both in the proportion of mosaicism and in the extent of chromosome 8 duplicated were not predictive of clinical severity.[14]

In conclusion, this paper presented 2 Filipino patients with trisomy 8 mosaicism syndrome, whose clinical and radiologic features are similar to previously described cases. Recent studies showed a striking association between this syndrome and hematologic malignancies, further supporting the hypothesis that tissues with constitutional genomic imbalance such as structural or numerical chromosomal abnormalities increase predisposition to cancer. Thus, aside from directing the management towards the specific medical problems and towards special education and therapy programs that will help maximize their own potentials, these patients should be accurately observed and monitored for cancer risks.

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