Ring Chromosome 13 in a Filipino Child– A new category with new features?

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ABSTRACT

We report on a child with ring chromosome 13 syndrome whose main clinical manifestations coincide with those of previously described cases. However, additional features such as marked hypotonia and joint laxity were noted in this child, anomalies which have not been previously reported in individuals with ring 13.

Key Words: ring 13 chromosome, developmental delay, facial dysmorphism, genital abnormality, vertebral abnormalities, hypotonia and joint laxity

Introduction

Ring chromosomes are quite rare, but have been detected for every human chromosome. The usual ring phenotype involves mental retardation and mild dysmorphisms but several investigators suggest that different patients with rings of a particular chromosome would display distinct clinical features.

Ring chromosome 13 syndrome involves the deletion of both ends of chromosome 13 with 2 broken ends reuniting to form a ring-shaped figure. Phenotypic expression varies according to breakpoint locations and length of deleted segments. Some patients exhibit only minor dysmorphic features, but most are severely affected by a wide range of abnormalities.

We present the clinical features of a patient with ring chromosome 13 and compare our findings with those of previously described individuals with similar cytogenetic rearrangement.

Clinical Report

The patient was a 16 month old boy who was the first child of a non-consanguineous Filipino couple. He was born full term by vaginal delivery after an uncomplicated pregnancy with a low birth weight at 2.2 kg (<5th percentile). Spine deformity, ambiguous genitalia and marked hypotonia were noted at birth.

His psychomotor development was delayed, with a 3 month old level for gross motor skills. Fine motor, language and personal and social functions were at the fourth month level.

His height, weight and head circumference were below the 5th percentile for age. Pertinent physical findings showed prominent metopic suture, flat occiput, hypertelorism with median epicanthal folds, esotropia, horizontal nystagmus, prominent and broad nasal bridge, micrognathia, high arched palate, irregularly placed teeth, prominent antihelices with anterior indentation of the earlobes, short neck, short penile structure with hypospadia, cryptorchidism and a sacral pit. There were no murmurs appreciated. Limb and spine anomalies included levoscoliosis, clinodactyly of the 5th digits, somewhat long, flattened and overlapping toes, proximally inserted 4th toes, broad distal phalanges of the toes, hypotonia and joint laxity. Scalp hair was fine and sparse (Figure 1A-C).

Skeletal survey showed the following findings: brachycephalic skull, narrowed intercostal spaces, thoracic and lumbar levoscoliosis, spina bifida at the 1st and 2nd vertebrae, hemivertebra of the 4th –6th thoracic vertebrae and hypoplastic 5th middle phalanges (Figure1D). Bone aging was compatible with that of a 0-3 month old infant.

2-D echocardiography was normal. No cranial imaging or formal eye evaluation was done.

The chromosomal analysis of our patient revealed a 46, XY karyotype with a ring chromosome 13 on all 15 banded metaphase spreads (Figure 2).

Discussion

There is a wide variation in the phenotypic expression of the recorded ring chromosome 13 cases, however, there are sufficient common features that could lead to a possible diagnosis. (Table 1)

In a review of reported cases[1-3] of patients with r13, microcephaly, low birth weight and mental retardation were the most consistent findings occurring in almost 80 % of cases. Occurring in more than 50% of cases were brain anomalies (arrhinencephaly, agenesis of corpus callosum), ear anomalies (large, low-set or malrotated auricles), broad prominent nasal bridge, epicanthal folds, hypertelorism and various hand and foot deformities (brachydactyly, syndactyly, polydactyly, dysplastic or absent thumbs,

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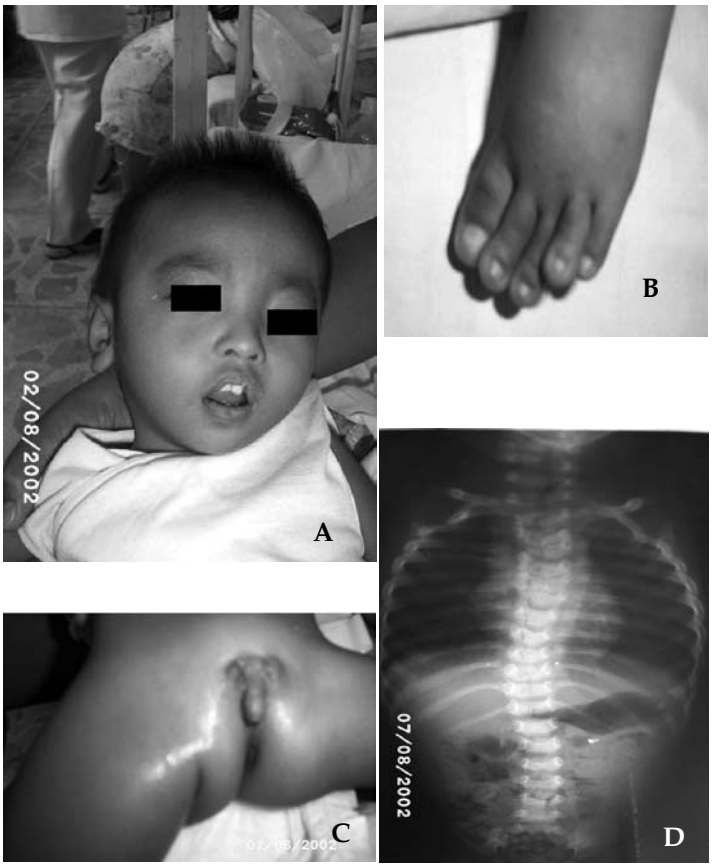
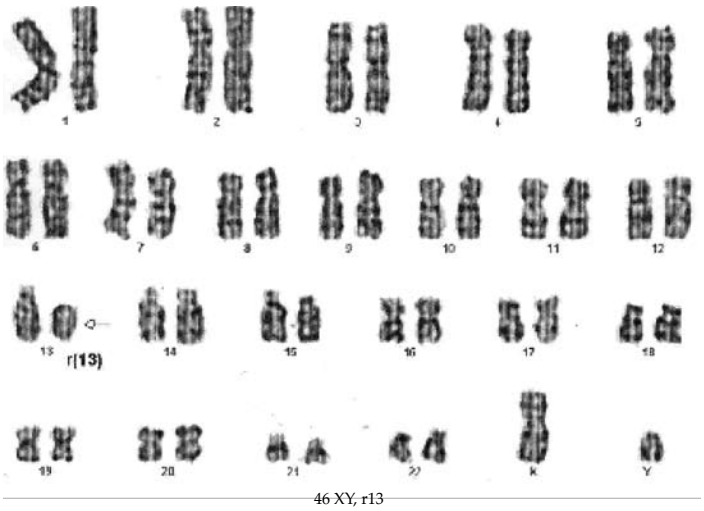


Figure 1. A) Prominent metopic suture and mild micrognathia. B) Proximally inserted fourth toe and broad distal phalanges of toes. C) Short penile structure and cryptorchidism. D) Levoscoliosis and hemivertebrae of the 4th-6th thoracic vertebrae (with permission).



46 XY, r13
Source: Cytogenetics Laboratory, Institute of Human Genetics

Figure 2. There was breakage in both arms of one chromosome 13 with fusion of the points of fracture and loss of the distal segments leading to ring formation. The breakage and reunion have occurred at bands 13p13 and 13q33 . The segments distal to these breakpoints have been deleted.

overlapping fingers, simian creases and clubfeet). The next most common group of features appearing in more than 30% of cases were cardiac defects, high arched palate, genital defects (ambiguous genitalia , hypospadias, micropenis, cryptorchidism, bifid scrotum, dysplasia of labia majora and clitoris), and anorectal anomalies (imperforate anus,deep sacral dimple). Occasional features were eye defects (microphthalmia, hypertelorism, colobomas, strabismus), micrognathia, tooth anomalies, renal defects, vertebral defects, hair and skin abnormalities and trigonocephaly.

To our knowledge, hypotonia and joint laxity have not yet been described in individuals with r13 syndrome. The hypotonia may be central in origin. Regarding joint laxity, it is interesting to note that the genes COL4A1 and COL4A2 which code for the alpha 1 and alpha 2 chains respectively are located on the long arm of chromosome 13 (13q33-q34).[4] This may verify the possibility that a deleted gene on chromosome 13 may have a role in the maintenance of joint integrity. The delayed bone age in this patient may indicate overall delay in physical maturation along with the short stature and penile abnormality. Possible causes may include hormone deficiencies or pituitary abnormalities; however, no further investigations were done along this line. There were no reports in literature regarding endocrine abnormalities in ring 13 syndrome.

Phenotypic expression varies according to the location of the breakpoints. The severity of clinical consequences would depend on the size of the deleted segment and on the number and function of genes that it contains.

Another contributing factor for the variability of phenotype in patients with r13 chromosome is mitotic instability. In general, rings are prone to secondary rearrangements and undergo difficulties at mitosis, especially when the 2 sister chromatids of the ring chromosome attempt to disjoin at anaphase. There may be breakage, fusion and generation of larger and smaller rings and there is the consequence of rings becoming entangled, broken, doubled or otherwise disrupted following sister chromatid exchange.[5] Some of the rings in mosaic state may die, however, survival may be related to losing the ring in some tissues. This could result to uniparental disomy of the normal chromosome 13 as a conversion event if the ring is lost and may make an unfavorable contribution to the phenotype.[6,7]

Based on the variable chromosomal rearrangements that resulted to loss of genetic material from the long arm of chromosome 13, Lorentz et al identified 4 main categories of cytogenetic and clinical syndromes[3] (Table 2).

We could not readily categorize our patient into any of the groups reported because his chromosomal rearrangement was not consistent with the corresponding phenotype and vice versa. His cytogenetic analysis was compatible with those belonging to the second category but he did not present with severe and lethal birth defects. His phenotype on the other hand, most likely belonged to the third category because of the prominent genitourinary and skeletal defects, although, he did not

Table 1. Comparison of Clinical Features of our Patient with the Previously Reported Cases of Ring 13 Syndromes

Clinical Features	Features of Patient
Microcephaly[1-3]	+
MR/ Developmental delay[1-3]	+
LBW/SGA[2-3]	+
Brain anomaly[1-3]	?
Ear Anomalies[1-3]	+
Broad prominent nasal bridge[1-3]	+
Epicanthal folds[1-3]	+
Hypertelorism[1-3]	+
Hand / foot anomalies[1-3]	+
Genital defects[1,3]	+
Anorectal anomaly[1,3]	-
Heart murmur[1-3]	-
High arched palate[1-3]	+
Micrognathia[1-2]	+
Tooth anomalies[1-2]	+
Microphthalmia/other eye defects[1]	+
Renal defects[1-3]	-
Alopecia/Sparse hair[2]	+
Scattered pigmentation[2]	--
Trigonocephaly[2]	+
Vertebral defects[1,3]	+
	Hypotonia Joint Laxity

Table 2. Categories of cytogenetic and clinical syndromes involving deletion of 13q

Categories	Types of deletion on the long arm of chromosome 13	Clinical features
I	Mosaic deletion of 13q	Digital anomalies, abnormal facies, microcephaly, intrauterine growth retardation, anomalies of anus and CNS
II	Nonmosaic deletion of 13q including ring formation	Lethal birth defects such as anencephaly, encephalocoele, severe microcephaly
III	Mosaic for distal 13q deletion	Genitourinary and skeletal defects
IV	Partial duplication and deletion of chr13 as part of a complex chromosome rearrangement	Reports of facial dysmorphisms

show a mosaic cell line. These findings uphold the fact that in ring 13 syndrome, whether mosaicism is present or not, phenotypic expression still greatly depends on the location of the breakpoints and the length of the deleted segments.

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