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RING CHROMOSOMES ABERRATIONS AT A PEDIATRIC MEXICAN HOSPITAL. TWO CASES WITH MOSAISISM OF CHROMOSOME 13, 46XY / 46, XY, r (13) AND CHROMOSOME 18, 46, XY / 46, XY, r (18).

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ABSTRACT

The autosomic alteration due to a ring formation is a rare aberration of either chromosome 13 and 18 which is in relation with phenotipic malformations, neurologic problems and genital abnormalities. Two clinical polymalformed cases with skull treboliform dismorfies with early seizures and malformed genitals with micropenis is presented from four of the total patients found in this study. Among chromosomic alterations, the ring of autosomic chromosome 13 and 18 are not frequent, the main phenotipical alterations in this study are in relation to neurological, genital and craniofacial malformations. Taking in consideration that mutations or chromosome aberrations are alterations in the chromosome number or structure. They are mainly considered due to gametogenesis inborn error (meiosis) or during the zygote first cellular divisions. All these alterations might be observed during metaphase from the cellular cycle, where DNA loses are seen due to DNA repair processes deficiency o total absence, among others. 4617 chromosomal studies were performed at Hospital Para El Nino Poblano (Pediatric Hospital) in Mexico (from 1992 to 2011) were 34.6% (1596 patients) showed different chromosomal alterations and only two patients showed ring chromosome aberrations. These chromosome changes are classified as structural alterations. Both pediatric patients with these genetic diseases are described in this study analyzing their clinical characteristics, medical or surgical treatments according to the phenotypic alterations.

Keywords: Chromosome 13, Chromosome 18, Ring chromosome, Trisomy, Karyotype, mosaisism, Malformations.

INTRODUCTION

Chromosomes contain DNA-bound proteins, which serve to package the DNA and control its functions Thanbichler and Shapiro (2006); (Pereira *et al.*, 1997; Sandman and Reeve, 2000). Chromosomes are different according to a variety of organisms. The DNA molecule may be circular or linear, and can be composed of 100,000 to 10,000,000,000 Paux *et al.* (2008) nucleotides in a long chain. Normally, eukaryotic cells (cells with nuclei) White (1973) have large linear chromosomes and prokaryotic cells (cells without defined nuclei) Thanbichler and Shapiro (2006); Nakabachi *et al.* (2006); Pradella *et al.* (2002), have smaller circular chromosomes. Also, cells may contain more than one type of chromosome.

With respect to alterations chromosomal pairs number 13 and 18, monosomíes, trisomíes **FIGURES 2 and 4**, deletions, translocations, and formations in ring **FIGURES 1 and 3** of the chromosomal material with variable losses and similar phenotypic characteristics, have been described as mental retardation, hypotonia and craniofacial malformations, which vary depending on the degree of deletion (Vivarelli *et al.*, 1992; mj. *et al.*, 1993; khalifa *et al.*, 1996).

Within the monosomy of chromosome 18, there are two variants: monosomy 18p and 18q; Although stature, of 70 patients with this chromosomal disorder 18p has been observed in both monosomíes, there is also mental retardation, rounded walls connective and skeletal abnormalities. While 50 patients reported with monosomy 18q, there are craneofacials alterations such as microcephaly and prognathism as well as vertebral alterations.

Alteration in ring chromosome 18 (r18), as the patient in this study FIGURE **3** however, is a rare genetic entity and the clinical picture is less severe than the one presented by the monosomy 18, although some clinical alterations occur in both syndromes. It has been observed hypotonia (90%), microcephaly (75-90%), more than two-thirds present epicanthus and hypertelorism, ocular disorders such as strabismus (50%), ptosis, nystagmus, partial aniridia and microphthalmia; malformations of auditory structures, low ears implantation, low oral commissure, microglosia and micrognathia. In addition, neurological disorders such as Autism (Fryns *et al.*, 1992), epilepsy and arthrogryposis multiplex congenital (Sheridan *et al.*, 1994). Some other clinical manifestations that have arisen are: skeletal abnormalities of the lower limbs and above (Andersen, 1992), clinodactyly of the fifth finger, and overlapping of the toes. Abnormalities of the genitalia have been observed. The decrease of clinical disorders may be the result of a chromosomal alteration in mosaic as the patient in this study. Other associated findings have been documented renal and cardiovascular disorders, body hemiatrophy with hyperpigmentation of the skin (woods *et al.*, 1994) e hypomelanosis (Bocian *et al.*, 1993) in patients with mosaic of r18; growth hormone deficiency (Meloni *et al.*, 1994) by a neurosecretory dysfunction (Eiben *et al.*, 1992; Aritaki *et al.*, 1996), as well as hypothyroidism and hypoparathyroidism. More than 70 r18-affected cases have been

described in the literature; Fukushima (1984) noted an association between ring and autoimmune thyroiditis. There have been defects in the middle line ranging from an incomplete closure of the palate to serious problems of holoprosencephaly (Sheridan *et al.*, 1994). The legacy of chromosome 18 ring is rare, being in particular chromosomal formations in ring of novo, the most frequent. Some authors mention that the deletion occurs at 18p11 and 18q23.

In relation to chromosome 13, more than 60 cases have been published, in which the long arm of chromosome D is missing, and chromosome of this group has been replaced by a ring. Although these cases may represent heterogeneity, there is evidence to suggest that the affected chromosome is the number 13. The average survival is variable and 39 months for cases 13q and 89 months for cases 13r **FIGURE 1.**

The loss of the long arm of one of the chromosomes of Group D, was described in a patient with growth deficiency which arose from the prenatal age. Subsequently, more than 50 cases have been described and the chromosome with partial loss has been considered to be number 13. The phenotype varies, but the pattern of malformations allows to suspect the existence of this disorder. It has been observed a phenotype, where missing part of the short arm and part of the long arm of chromosome 13 **FIGURES 1 and 2.** The following features have been observed in the patient's 13q-; central nervous system, short and redundant neck, all patients presented somatic and mental retardation and many have been hypotonic microcephaly (with a tendency to hydrocephalus, trigonocephaly, aprosencephaly, arrinencefalia and holoprosencephaly. Agenesis of the Corpus Callosum and alopecia. Although the degree of mental impairment has been variable, the majority of patients have severe mental retardation.

Other defects as microphthalmia, coloboma of the iris, optic nerve dysplasia and hypertelorism, folds epicanthal, telecantus and apparent ptosis and prominent nasal bridge (Coffin and wilson, 1970). Cleft palates (Cagianut. and theiler, 1970), micrognathia, high palate have been described in several cases of 13q syndromes. The phenotypic alterations associated with different degrees of deletion and hypoplasia of the thumb that were missing have been mentioned with 13q- approximately and in less than 30% of the cases 13r, clinodactyly of the fifth finger, talipes, Simian creases, synostosis of the fourth and fifth metacarpals and equinovarus was also observed Pigmentation changes. Congenital cardiovascular anomalies (defect in the ventricular septum or aortic malformation), have been described in about 50% of both groups.

Within the abnormalities reported musculoskeletal bilateral dislocation of the hip, inguinal hernia and coxa valga. The Genitourinary anomalies are represented by hypospadias, cryptorchidism, cleft scrotum or hypoplastic, small penis and pelvic kidney (Sparkes, 1967) and anal atresia. Most notorious was unilateral or bilateral retinoblastoma, which has been documented in more than half

of the cases 13q- (Taylor, 1970), as well as in several patients with chromosome 13 ring (Grace, 1971).

Compaction of the duplicated chromosomes during mitosis and meiosis results in the classic known four-arm structure. Chromosome recombination plays a vital role in evolution and genetic diversity. If these structures begin through processes known as chromosomal instability and mutation, the cell may die, or it may avoid apoptosis leading to initiation of cancer.

MATERIALS AND METHODS

Chromosomal studies (karyotypes) where performed for all patients in this study by using GTG banding **FIGURES 1,2,3 C and 4 D**. 4617 karyotypes were performed at Hospital Para el Niño Poblano, Mexico in 19 years period of time (from 1992 to 2011). However, only 1596 patients (34.6%) showed chromosomal alterations, among the studies population, male and female pediatric patients with different genetic diseases were analyzed.

For r18 patient **FIGURE 4 D**., study of karyotype, 80 metaphases analyzed with two cell lines, of which 12 metaphases showed a normal formula male 46 XY and 68 remaining metaphases a chromosome 18 ring with chromosomal formula 46 XY/46 XY, r (18). The karyotype of the mother, in 100 metaphases, also found two cell lines, of which 92 metaphases showed a normal female formula 46 XX and the 8 remaining metaphases a chromosome 18 ring with chromosomal formula 46 XX/46 XX, r (18). However the father presented among 100 metaphases a chromosomal formula, 46 normal male XY.

For r13 patient karyotype **FIGURE 1 C** , 100 metaphases analyzed with two cell lines, of which 20 metaphases showed a normal formula male 46 XY and 80 remaining metaphases a chromosome 18 ring with chromosomal formula 46 XY/46 XY, r (18). The karyotype of the mother, in 100 metaphases, also found two cell lines, of which 90 metaphases showed a normal female formula 46 XX and the 10 remaining metaphases a chromosome 18 ring with chromosomal formula 46 XX/46 XX, r (18). However the father presented among 100 metaphases a normal chromosomal formula, 46 XY.

Different studies were performed for both r18 and r13 patients; hormonal determinations (17-oh-progesterone, dehidroepiandros-cations and serum cortisol) and pelvic ultrasound was performed. Also, echocardiogram and because of the Association of these chromosomal anomalies with renal alterations, urology service request study of image for kidneys, bladder, and pelvis.

DISCUSION

Chromosomal aberrations are disruptions in the normal chromosomal structures of a cell and are a major cause of genetic conditions in humans, known as genetic disease which might have or not an inheritance pattern, the r13 or r18 syndromes **FIGURES 1,2 A B** are rare and clinically have similar patterns. The majority of these patients were reported with cranial disorders and mental retardation microcephaly or with skull treboliform as in this study. In approximately 50% of patients with these chromosome abnormalities, there is a history of low weight at birth (Grouchy, 1969) data not observed in this work. However facial alterations are represented by hypertelorism, epicanthal folds and low-set ears in some cases has been observed.

the molecular mechanism of carcinogenesis, at stomach level is in direct relation to a loss of genetic heterozygosity, coupled with alterations on chromosome 18 (Tahara, 1993), as well as type myeloid disorders in patients with structural malformation of chromosome 7 and 18 ring formations. It is possible to think that there is significant causal relationship between genetic imbalance and the possibility of developing this type of tumor. The loss of the long arm of chromosome 13 band q-14 has been the specific region, implicated as a cause in this case in particular for retinoblastoma. It would be convenient to conduct chromosomal studies in patients who have retinoblastoma with mental deficiency and growth, as well as other abnormalities mentioned above.

Patients affected with r18 and r13, as in this study (**FIGURES 1 and 3)** are in relation to similar clinical manifestations skeletal abnormalities of the lower limbs (Andersen, 1992), neurological disorders such as Autism (fryns and kleczkowska, 1992), epilepsy, arthrogryposis multiplex congenital and neurological disorders, corporal hemiatrophy with hyperpigmentation of the skin (woods *et al.*, 1994) e hypomelanosis (Bocian *et al.*, 1993) in patients with mosaic of r18, origin hypothalamic growth hormone deficiency which was not confirmed in this study (Meloni *et al.*, 1994) by a neurosecretory dysfunction (Aritaki *et al.*, 1996). The decrease of abnormalities at genitalia in a fifth of the patients were reported. The difference in this study might be due to the result of a chromosomal alteration 13 or 18 in mosaisism **FIGURES 2 and 3.** Body hemiatrophy with hyperpigmentation of the skin (woods *et al.*, 1994) hypomelanosis (Bocian *et al.*, 1993) in patients with mosaic of r18, due to hypothalamic growth hormone deficiency (Meloni *et al.*, 1994) by a neurosecretory dysfunction (Eiben *et al.*, 1992; Aritaki *et al.*, 1996). As well as hypothyroidism and hypoparathyroidism, more of seventy affected r18 cases have been described by (Fukushima, 1984). There is also an association between ring and autoimmune thyroiditis and cleft palate.

Alteration in both 13 and 18 ring chromosomes reported in healthy carriers mothers with mosaicism 46XX/46XX r(18) and r(13) children with multiple malformations phenotypic as in this

study (**FIGURES 1 and 3)**, if compared to the mothers reported with a single cell line ((Fryns *et al.*, 1992). The midline defects have been observed ranging from an incomplete closure of the palate to serious problems of holoprosencephaly (Sheridan *et al.*, 1994). An investigation of the gene defect on chromosome 13 and 18 has been performed (bruyn. *et al.*, 1996) by using specific markers in comparative studies (Esmer *et al.*, 1996). In relation to genetic counseling at prenatal diagnosis is possible early detection of the both r13 or r18 (The fj. *et al.*, 1996). There are studies of amniocentesis already described in the first trimester of pregnancy (Eiben *et al.*, 1992), subsequently confirming malformations in the study of fetus necropsy (The fj. *et al.*, 1996). Reported trisomies, deletions, duplications or rings 13 and 18, related to mental retardation, hypotonia and Craniofacial malformations which varies depending on the degree of deletion or type of trisomy (Vivarelli *et al.*, 1992; mj. *et al.*, 1993), (khalifa *et al.*, 1996). This paper reported the case of two male patient with ring syndrome 13 18 respectively, treated at a Pediatric hospital, which presents some of the typical clinical malformations of this abnormal chromosomes as mentioned before; it is interesting to compared both 13 and 18 ring **FIGURES 1 and 3**.with 13 and 18 trisomies **FIGURES 2 and 4** since both chromosome aberrations have specific clinical alterations.

Both trisomies, Edwards and Patau syndromes **FIGURES 2 and 4, A, B** rarely found among pediatric patients. Both syndromes share similar symptoms and share some clinical manifestations as r13 and r18 chromosome aberrations **FIGURES 1 and 3** shows a female patient with 13 chromosome trisomy or Patau syndrome with hypoplasic face, bilateral cleft lip and palate and cranio-facial dimorphism, absent or malformed nose especial flexion of the fingers on both hands. Trisomy 13, is the least common of the autosomal trisomies, after Down syndrome (Trisomy 21) and Edwards syndrome (Trisomy 18). The extra copy of chromosome 13 in Patau syndrome causes severe neurological and heart defects which make it difficult for infants to survive. In relation to Edwards's syndrome, a male patient with hirsutism, microcephaly, sinofris, jaw hypoplasia and especial flexion of the fingers on both hands was observed, which karyotype reveals an 18 trisomy, **FIGURES 2 A, B, C and D.** As mentioned ring alterations in this study both chromosomal 13 and 18 ring aberrations; FIGURES 1 and 3 A, B shows a female patient with bilateral cleft lip and palate and cranio-facial dimorphism and hypertelorism characterized by progressive deformity of spine with hemivertebrae and 13 chromosome ring malformation Aparicio *et al.* (2000), different clinical features from a male patient with an 18 ring chromosome aberration with general hypoplasia and hipotonía, ambiguous genitalia, hypertelorism and small hands with especial flexion of the fingers (Aparicio *et al.*, 1998)

Abnormal numbers of chromosomes or chromosome sets, aneuploidy, may be lethal or give rise to genetic disorders (Huret *et al.*, 2000). Some of the main chromosomal alterations in this study can been seen in **TABLE 1, FIGURES 5 and 6.** Genetic counseling was offered for carrier in this study that carries these chromosome rearrangements. Some mutations are neutral and have little or

no effect. However, another chromosomal aberrations, change the patient's life and it has a great role in evolution. Therefore, international associations and institutions as the Vega Institute present data from the manual annotation of the human genome. The annotation shown in this release of Vega is from a data freeze taken from 2008 to 2011 and the gene structures, presented in

Table-2.

The gain or loss of DNA from chromosomes can lead to a variety of genetic disorders as it was found in this study. It might be important if chromosomal aberrations can be diagnosed early, which will contribute for a precise diagnosis, an early treatment, a better genetic counseling and a better quality of life.

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FIGURE LEYENDS

Figure 1 A. Female patient with bilateral cleft lip and palate and cranio-facial dimorphism and hypertelorism **B.** characterized by progressive deformity of spine with hemivertebrae. **C.** karyotype revealed a 13 chromosome ring malformation.

Figure 2 A. Female patient with Patau syndrome with hypoplasic face, bilateral cleft lip and palate and cranio-facial dimorphism, absent or malformed nose **B.** especial flexion of the fingers on both hands **C.** karyotype revealed a 13 chromosome trisomy.

Figure 3 A. Male patient with general hypoplasia and hipotonía, ambiguos genital and hypertelorism **B.** Small hands with especial flexion of the fingers **C.** karyotype reveal an 18 ring chromosome aberration.

Figure 4 A. Male patient with hirsutism, microcephaly, sinofris and general hypoplasia **B.** hypoplasia of the jaw **C**. especial flexion of the fingers on both hands **D.** Karyotype reveals an 18 trisomy.

Figure 5. 4617 karyotypes were performed **f**rom 1992 to 2011, where 1596 patients (34.6%) showed chromosomal alterations.

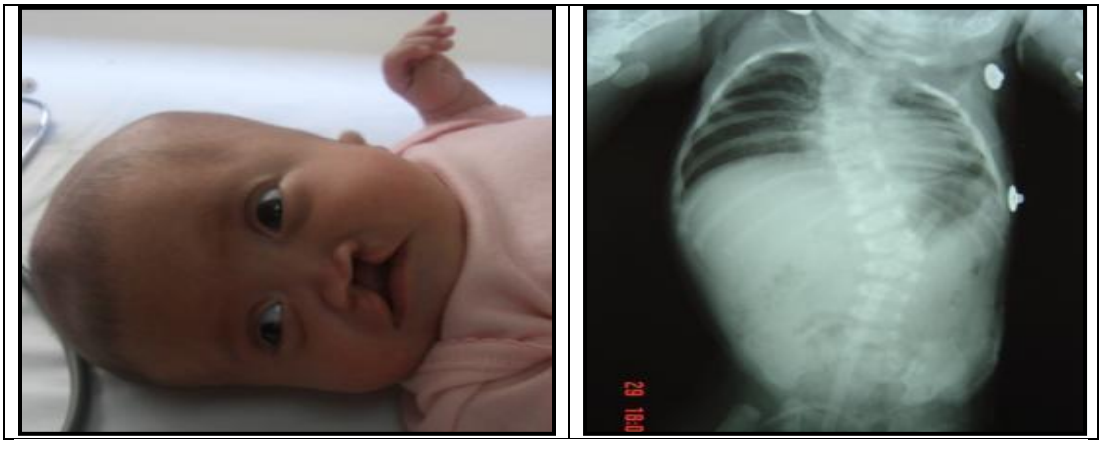
Figure 6. Chromosomal alterations in 19 years, shows 1596 patients (34.6%) with different aberrations. From these, 4 (0.087%) were ring chromosome malformations.

TABLES

Table 1. Different chromosomal alteration in 19 years at the Hospital Para el Nino Poblano, Mexico.

Table 2. Sequencing (http://www.ncbi.nlm.nih.gov/genome/seq/) of the human genome has provided a great deal of information about each of the chromosomes. This table is compiling statistics for the chromosomes, based on the Sanger Institute's human genome information in the Vertebrate Genome Annotation (VEGA) database. (Vega, 2011)

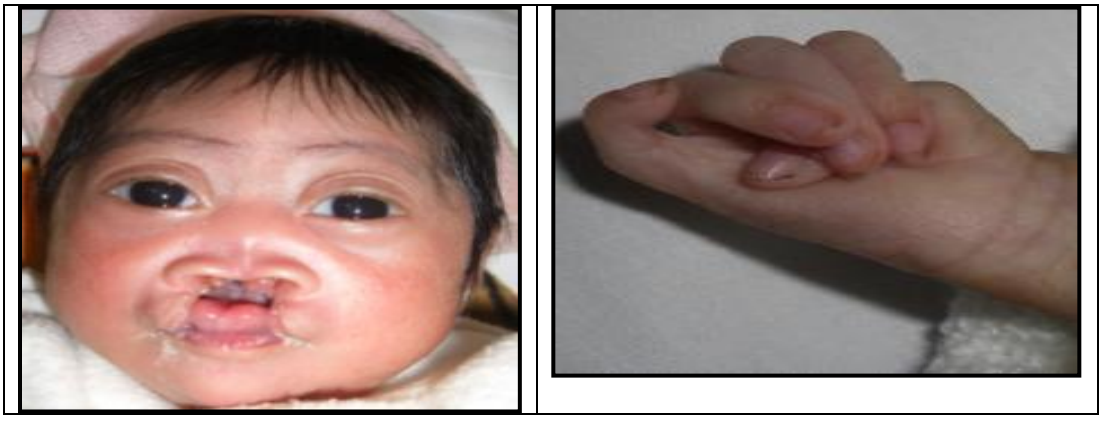
Figure 1



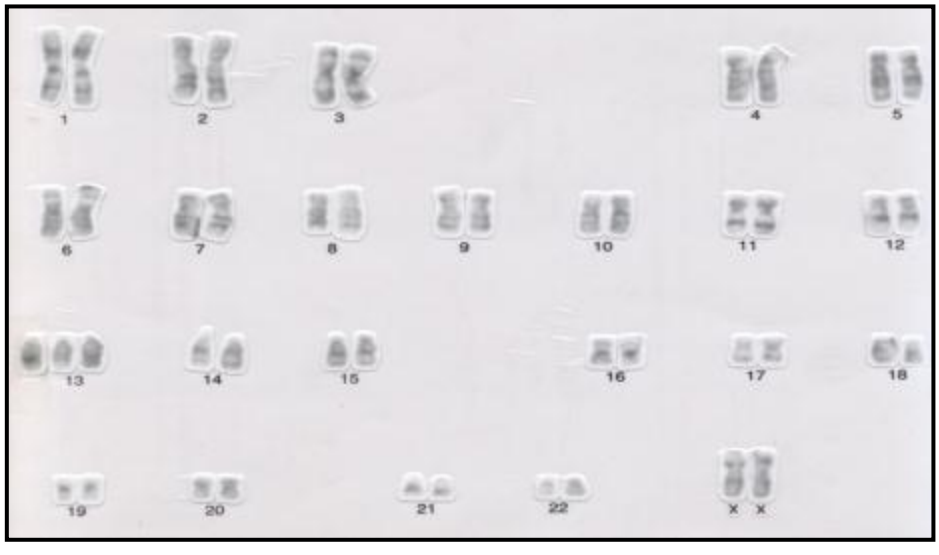
A **B**

C

Figure 2

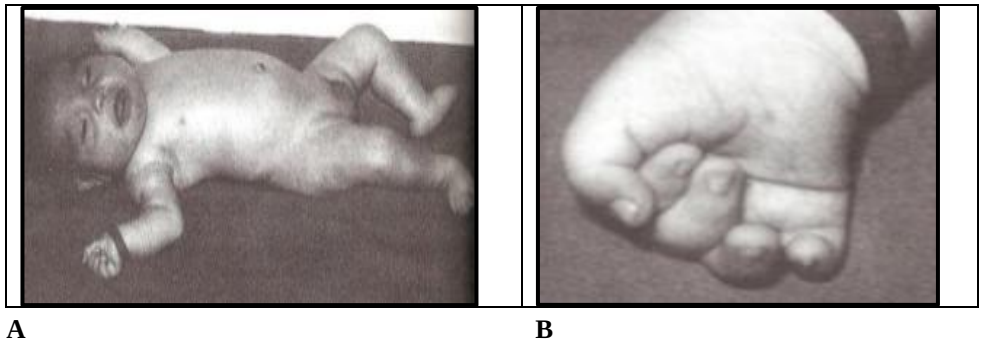


A **B**

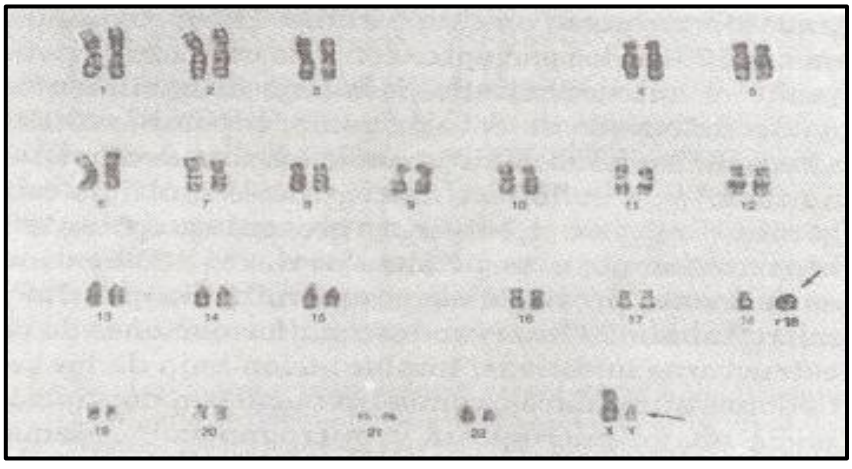


C

Figure 3

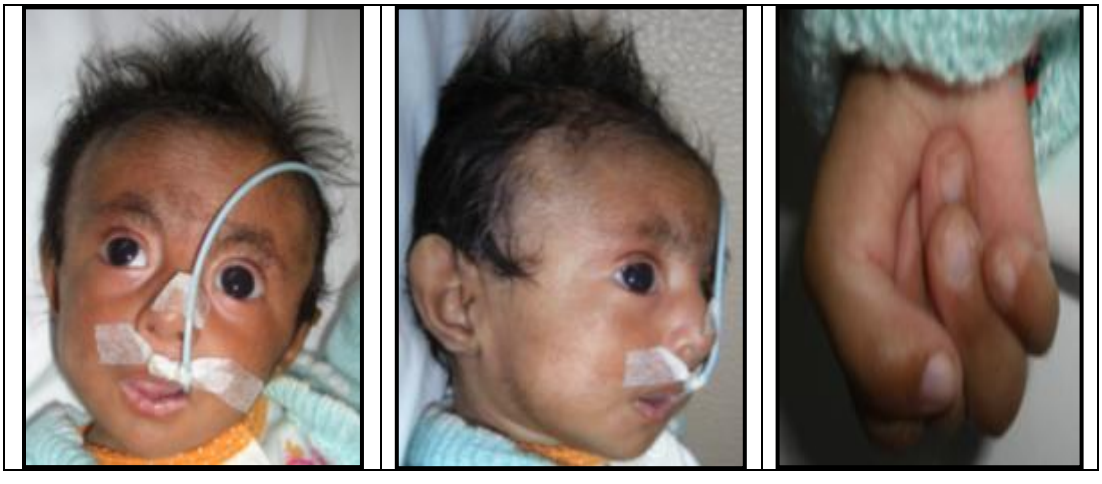


A **B**

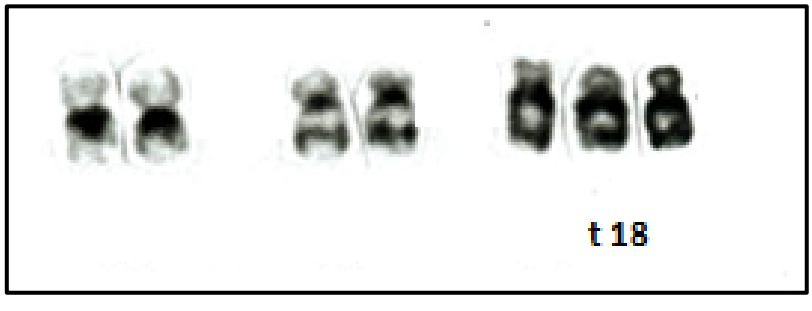


C

Figure 4



A B C



D

Figure 5.

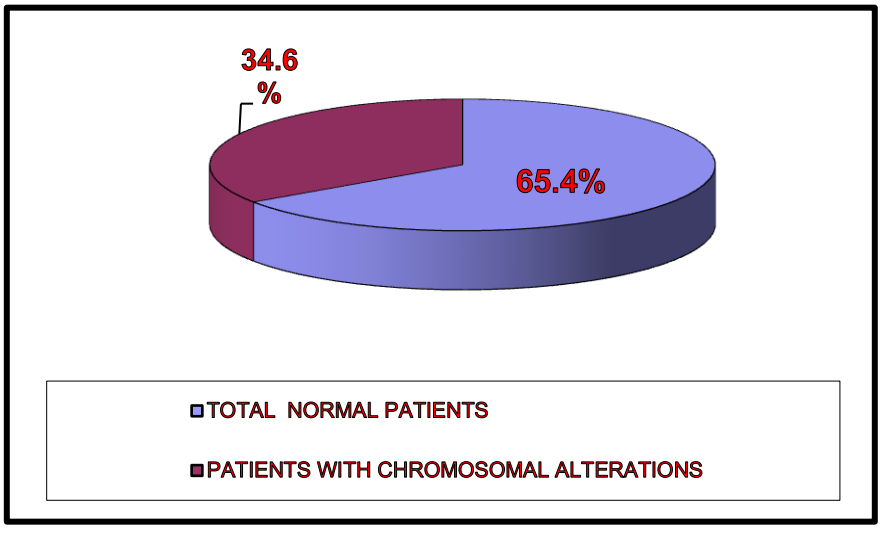


Figure 6.

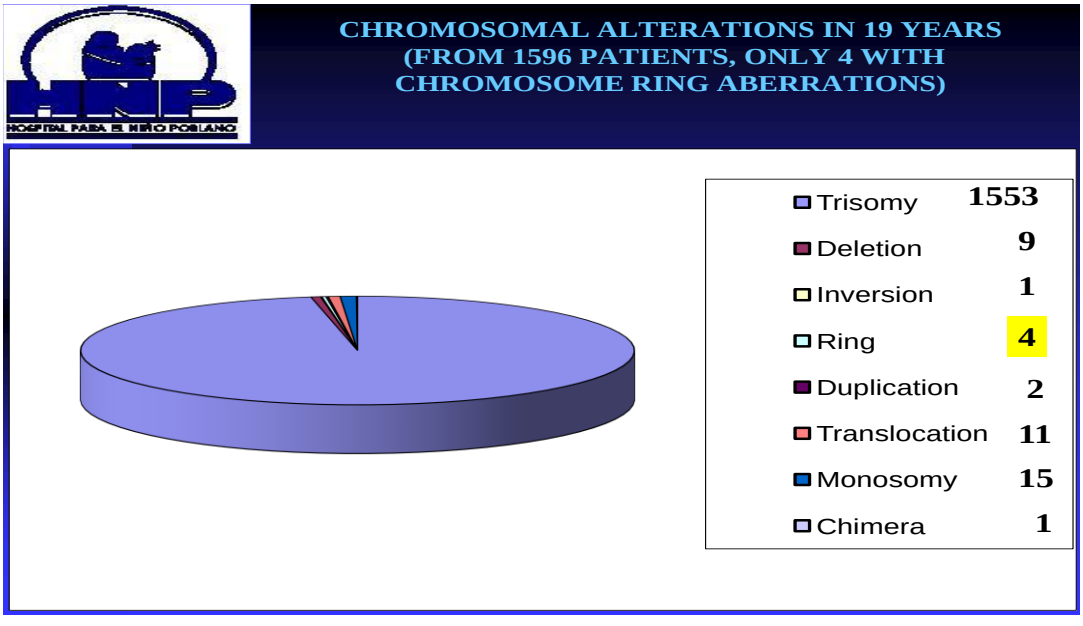


Table-1.

Chromosomal aberration	(%) patients	
1.Trisomy		1553
2.Deletions(chromosomes 4,6,9)		6
Other deletions		3
3.Invertion		1
4. Ring		4
	r13	2
	r18	2
5. Duplication		2

6. Translocation	11
7. Monosomy	15
8. Chimera	1
Chromosomal aberrations	**(34.6%) 1596**
Total ring chromosomes	**(0.087%) 4**
	r18 (0.043%) 2
	r13 (0.043%) 2
Different chromosomal aberrations:	**(0.93%) 43**
Total (karyotype studies in 19 years)	**(100%) 4617**
Total normal karyotypes	**(65.4%) 3021**
Total chromosomal aberrations	**(34.6%) 1596**

Table-2.

Chromosome	Genes	Total bases	Sequenced bases
1	4,220	247,199,719	224,999,719
2	1,491	242,751,149	237,712,649
3	1,550	199,446,827	194,704,827
4	446	191,263,063	187,297,063
5	609	180,837,866	177,702,766
6	2,281	170,896,993	167,273,993
7	2,135	158,821,424	154,952,424
8	1,106	146,274,826	142,612,826
9	1,920	140,442,298	120,312,298
10	1,793	135,374,737	131,624,737
11	379	134,452,384	131,130,853
12	1,430	132,289,534	130,303,534
13	924	114,127,980	95,559,980
14	1,347	106,360,585	88,290,585
15	921	100,338,915	81,341,915
16	909	88,822,254	78,884,754
17	1,672	78,654,742	77,800,220
18	519	76,117,153	74,656,155
19	1,555	63,806,651	55,785,651
20	1,008	62,435,965	59,505,254
21	578	46,944,323	34,171,998
22	1,092	49,528,953	34,893,953
X (sex chromosome)	1,846	154,913,754	151,058,754
Y (sex chromosome)	454	57,741,652	25,121,652
Total	**32,185**	**3,079,843,747**	**2,857,698,560**