Journal of Asian Scientific Research, 2014, 4(6): 280-291

Journal of Asian Scientific Research

journal homepage: http://www.aessweb.com/journals/5003

CHROMOSOME ABERRATIONS IN A MEXICAN PEDIATRIC HOSPITAL. RING CHROMOSOMES 4, 13 AND 18

Aparicio Rodríguez Juan Manuel

Medical Genetics Hospital para el Niño Poblano Estomatology Benemérita Universidad Autónoma de Puebla

Barrientos Pérez Margarita

Endocrinology Hospital para el Niño Poblano, México

Sergio Chatelain Mercado

Department of Biotechnology, Universidad Autónoma Metropolitana, Mexico City

ABSTRACT

The chromosome alteration due to a ring formation, is a rare event of chromosomes 4, 13 and 18 which is in relation to changes in the phenotypic development, neurologic and genital abnormalities. It was also observed clinical variations as treboliform skull with early seizures and malformed genitals with micropenis. Looking at chromosome alterations, the ring of autosomic chromosome 4, 13 and 18 are not frequent, the main clinical alterations in this study are in relation to neurological, genital and craniofacial malformations. Taking in consideration that mutations are considered alterations in the chromosome number or structure. Since all these genetic changes are seen when a human being is starting to get cell maturation, considered the first three months old of development the most important for the cell and DNA. Due to the different repair processes inside the cell. Almost 5000 chromosomal studies were performed at a Pediatric Hospital in Mexico during a long period of time were more than 1500 patients showed various chromosomal alterations including ring chromosome aberrations. All the chromosome changes five rise to different genetic diseases. And are described in this study analyzing their clinical characteristics, medical or surgical treatments in multidisciplinary manner.

Keywords: Chromosome 4, Chromosome 13, Chromosome 18, Ring chromosome, Cariotype, Mosaics, Malformations.

1. INTRODUCTION

This study is one of very few studies which have investigated some of the rare chromosome aberration in humans as ring structure changes. Some pediatric patients with several clinical malformations are diagnosed in a wrong manner. It is therefore to important to perform chromosome studies for a better clinical and surgical treatment.

Thought the protein production the cells are controlled. Thanbichler, et al. [1]; Sandman, et al. [2]; Sandman and Reeve [3]; Pereira, et al. [4]. Chromosomes have variability processes according to the specific organisms [5]. Where, eukaryotic cells have linear chromosomes Pradella et al. [6], if compared to smaller structural basic animals. Chen, et al. [7].

Ring syndrome is caused by an autosomal chromosome ring formation. Main clinical manifestations includes failure extreme growth and normal appearance, some with normal intelligence or variable mental retardation. This study presents patients with chromosome 4, 13 and 18 ring mosaic and their clinical features are analyzed.

Ring chromosome 4 FIGURES 5 A, B AND C is a rare disorder that is typically characterized by loss (deletion) of genetic material from both ends of the 4th chromosome and joining of the chromosomal ends to form a ring. Related symptoms may vary, depending on the location of lost genetic material. Some affected pediatric patients may have a low birth weight; growth retardation; delays in the acquisition of skills requiring the coordination of mental and physical activities (psychomotor retardation); an abnormally small head (microcephaly); a broad, "beaked" nose; and/or various additional physical abnormalities that are present at birth (congenital anomalies). It has also been reported that ring chromosome 4 is primarily associated with growth retardation, with no major physical anomalies and normal psychomotor development. Chromosome 4 as a ring is usually caused by spontaneous (de novo) errors very early in the development of the embryo that appear to occur randomly for unknown reasons (sporadically) which we believed is similar to the case in this study.

With respect to alterations chromosomal pairs number 4, 13 and 18 formations in ring of the chromosomal material with DNA losses have been reported as mental retardation, hypotonic and craniofacial malformations, which vary depending on the degree of chromosome alteration [8-10].

In relation to monosomy of chromosome 18, it could be monosomy 18p and 18q; Although stature has been observed in both monosomíes, there is also mental retardation and skeletal abnormalities.

Alteration in ring chromosome 18 (r18), however, is a rare genetic form and the clinical feature is less severe than monosomy 18, although some clinical alterations occur in both syndromes. It has been observed hypotonia, microcephaly, epicanthus and hypertelorism, strabismus, ptosis, nystagmus, partial aniridia and microphthalmia; low ears implantation, low oral commissure, microglosia and micrognathia. Autism has also been reported by Fryns and Kleczkowska [11], epilepsy and arthrogryposis multiplex congenital [12], skeletal abnormalities of the lower limbs [13], clinodactyly of the fifth finger, and overlapping of the toes as malformation in genitals. The difference of clinical disorders may be due to a mosaic situation, as the patient in this study.

Other associated findings have been documented renal and cardiovascular disorders, body hemiatrophy with hyperpigmentation of the skin [14] and hypomelanosis [15] in patients with mosaic of r18; growth hormone deficiency [16] by a neurosecretory dysfunction [17, 18], as well as hypothyroidism and hypoparathyroidism, Fukushima in 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 [19]. Some cases might be due to de novo presentation.

Chromosome 13, is more rare to be observed, as a ring strucutre. The average survival is variable.

More than 50 cases have been described and the chromosome with partial loss has been considered to be number 13 with a phenotype variability, but the presentation of malformations allows to suspect the existence of this aberration. It has been observed a phenotype, where missing part of the short arm and part of the long arm of chromosome 13. Patients with some deletions; have some diseases as central nervous system, short and redundant neck, with mental retardation and hypotonic, microcephaly, Agenesis of the Corpus Callosum and alopecia. Although the degree of mental impairment has been variable, most of patients have severe mental retardation, microphthalmia, coloboma of the iris, optic nerve dysplasia and hypertelorism and apparent ptosis. Cleft palate, micrognathia and high palate.

It has been discussed the phenotypic alterations associated with different ring chromosome aberrations where congenital cardiovascular anomalies have been observed.

Genitourinary anomalies are usually represented by hypospadias, cryptorchidism, cleft scrotum or hypoplastic, small penis and pelvic kidney [20] and anal atresia; renal, and pelvic abnormalities. Also unilateral or bilateral retinoblastoma, which has been documented in cases with 13q- [21], as ring chromosome 13 [22].

Chromosome recombination plays an important role in evolution and genetic diversity, Hinnebusch and Tilly [23]. 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.

2. MATERIALS AND METHODS

Karyotypes where performed among all patients in this study. 4500 karyotypes were performed during a long period of time. However, only 4 patients were positive for ring chromosome, among the studies population FIGURE 6, male and female pediatric patients with this genetic disease were analyzed.

For r4 patient, study of karyotype, 60 metaphases analysed with one cell line, all metaphases showed a chromosome 4 ring with chromosomal formula 46 XY, r (4) FIGURES 5 A, B AND C. Both parents did not wanted to have chromosome studies.

For r18 patient FIGURES 4 A, B AND C, study of karyotype, 80 metaphases analysed with two cell lines, of which 12 metaphases showed a normal formula male 46 XY and 68 metaphases a chromosome 18 ring 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 resulting 46 XX/46 XX, r (18). However the father presented among 100 metaphases a chromosomal formula, 46 normal male XY.

For r13 patient FIGURES 1 A, B AND C, study of karyotype, 100 metaphases analysed with two cell lines, of which 20 metaphases showed a normal formula male 46 XY and 80 remaining metaphases a chromosome 18 ring 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 was normal among 100 metaphases 46 XY.

Different studies 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.

3. DISCUSION

It has been observed that some major chromosome changes are due to climatic changes, food and differences of life style, the r4, r13 or r18 syndromes are rare and clinically have similar patterns. Most of these patients were reported with cranial disorders, mental retardation, microcephaly or with treboliform skull as in this study. In approximately 50% of patients with this chromosome abnormalities, there is low weight at birth, data not observed in this work. However facial alterations as hypertelorism, epicanthal folds and low-set ears in some cases has been observed.

In relation to r4, the symptoms and physical findings are quite variable from case to case. Some infants with ring chromosome 4 are associated to low birth weight, feeding difficulties, failure to grow and gain weight with developmental delays, malformations of the skull and facial (craniofacial) region FIGURES 5 A, B AND C and cardiovascular malformations. Some clinical features are similar to patients with Wolf-Hirschhorn syndrome, which is a chromosomal disorder characterized by partial deletion (monosomy) of the short arm (p) of chromosome 4 (partial monosomy 4p) Balci, et al. [24]; Del Mazo [25]; Perez-Castillo [26].

The ring chromosome 4 has been associated with mental retardation and delays in the development of physical, mental, and behavioral skills, as delays in language and speech development. However, other patients may have normal intelligence and normal psychomotor development.

Craniofacial malformations associated with ring chromosome 4 may include an unusually small head (microcephaly); as the case in this study with craneosinostosis, with a surgical treatment FIGURES 5 A, B AND C. Micrognathia and malformed (dysplastic) ears. In some cases, other craniofacial abnormalities may also be present, such as incomplete closure of the roof of the mouth (cleft palate) and ptosis, clinodactyly) and affected males with hypospadias.

There have also been a few reports in which ring chromosome 4 is associated with congenital renal hypoplasia or renal agenesis. Important feature for kidney development for its normal function and normal patient condition.

Carcinogenesis is in relation to genetic homeostasis due to chromosome 18 [27], as well myeloid disorders in patients with chromosome 7 and 18 ring malformations. It is possible to believe that there is relationship between genetic imbalance the tumor development. The loss of the long arm of chromosome 13 band q-14 has been associate to retinoblastoma.

Patients with r18 and r13, in this study (FIGURES 1 AND 4 A,B,C) are in relation as reported previously to skeletal abnormalities of the lower limbs [13], Autism [11], epilepsy, arthrogryposis multiplex congenital and neurological disorders, corporal hemiatrophy with hyperpigmentation of

the skin [14] and hypomelanosis [15] in patients with mosaic of r18, origin growth hormone deficiency which was not confirmed in this study [16] by a neurosecretory dysfunction [17]. The decrease of genital anormalities in a fifth of the patients was reported. The difference in this study might be due to the result of a chromosomal alteration 13 or 18 in mosaisism.

Body hemiatrophy with hyperpigmentation of the skin [14] hypomelanosis [15] due to neurosecretory dysfunction . Eiben et al [18]. as well as hypothyroidism and hypoparathyroidism, described by Fukushima [28] and cleft palate [29]

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 4 ABC, if compared to the mothers reported with a single cell line [30]. the midline defects have been observed ranging from an incomplete closure of the palate to serious problems of holoprosencephaly [12]. An investigation of the gene defect on both 13 and 18 chromosome has been studied with specific genetic markers.

Genetic counseling at prenatal diagnosis is possible for early detection of the both r13 or r18. There are studies of amniocentesis already described in the first trimester of pregnancy [18].

Reported trisomies, deletions, duplications or rings 13 and 18, related to mental retardation, hypotonia and Craniofacial malformations which varies depending on the degree of chromosome aberration [8], Mcginniss, et al. [9], Khalifa, et al. [10].

This paper reported the case of two male patient with ring syndrome 13 18 respectively, which presents some of the typical clinical malformations of this abnormal chromosomes as mentioned above; it is interesting to compare both 13 and 18 ring with 13 and 18 trisomies due to their similar clinical features.

Both trisomies, Edwards and Patau syndromes rarely found among pediatric patients. Both syndromes share similar symptoms and share some clinical manifestations as r13 and r18 chromosome aberrations. FIGURES 1 AND 4 A, B AND C 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 FIGURES 2 A, B AND C, is the least common of the autosomal trisomies, after Down syndrome (Trisomy 21) and Edwards syndrome (Trisomy 18) FIGURES 3 A, B AND C. 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 shows a18 trisomy, FIGURE 3 A, B, C AND D.

A human chromosomal aberrations, change the patient's life and it has a great role in evolution.

As mentioned before ring alterations in this study both chromosomal 13 and 18 ring aberrations; FIGURES 1 AND 4 A, B AND C shows a female patient with bilateral cleft lip and palate and craniofacial dimorphism and hypertelorism characterized by progressive deformity of spine and 13 chromosome ring malformation Aparicio, et al. [31], 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. [32].

In relation to r4 referred to as "ring syndrome," a general term used to describe the presence of growth retardation in the absence of major malformations due to a ring chromosome. It has been suggested that such ring chromosomes originate with abnormal fusion of the chromosome ends and this results due to instability of the ring chromosome during subsequent cellular divisions. Lee, et al. [33]; Sigurdardottir [34], Anderson [35], Park [36];

When the parents of the affected child usually have normal chromosomes, it could be possible to be a “de novo” event as we believed the case in this study since both parents did not wanted to performed chromosome analysis. Pezzolo [37]; Giuffre [38]; Gutkowska [39].

Abnormal numbers of chromosomes or chromosome sets, aneuploidy, may be lethal or give rise to genetic disorders Huret, et al. [40]. Some of the main chromosomal alterations in this study can been seen in Table 1 and Figure 6. Genetic counseling was offered for carrier in this study, that carry these chromosome rearrangements. The gain or loss of DNA from chromosomes can lead to a variety of genetic disorders as it was found in this study.

Chromosomal analysis and genetic counseling are typically recommended for parents of an affected child to help confirm or exclude the presence of certain chromosomal abnormalities in one of the parents, such as ring chromosome, potential mosaics’, or a "balanced translocation" involving chromosome 4, 13 or 18.

It should be diagnosed n a correct manner for the best into the future of the patient future. It might be also 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 for the patient ant his family.

REFERENCES

[1] M. Thanbichler, S. Wang, and L. Shapiro, "The bacterial nucleoid: A highly organized and dynamic structure," *J. Cell. Biochem,* vol. 96, pp. 506–21, 2005.

[2] K. Sandman, S. Pereira, and J. Reeve, "Diversity of prokaryotic chromosomal proteins and the origin of the nucleosome," *Cell. Mol. Life Sci.*, vol. 54, pp. 1350–64, 1998.

[3] K. Sandman and J. Reeve, "Structure and functional relationships of archaeal and eukaryal histones and nucleosomes," *Arch. Microbiol*, vol. 173, pp. 165–9, 2000.

[4] S. Pereira, R. Grayling, R. Lurz, and J. Reeve, "Archaeal nucleosomes," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 94, pp. 12633–7, 1997.

[5] E. Paux, P. Sourdille, and J. Salse, "A physical map of the 1-gigabase bread wheat chromosome 3B," *Science*, vol. 322, pp. 101–104, 2008.

[6] S. Pradella, A. Hans, C. Sproer, H. Reichenbach, K. Gerth, and S. Beyer, "Characterisation, genome size and genetic manipulation of the myxobacterium sorangium cellulosum so ce56," *Arch Microbiol*, vol. 178, pp. 484–92, 2002.

[7] C. Chen, C. Hsu, and C. Tzen, "Prenatal diagnosis of mosaic ring chromosome 4," *Prenat Diagn,* vol. 27, pp. 485-7, 2007.

[8] Vivarelli, M. Paolieri, C. Anichini, R. Scarinci, R. Berardi, l. Rosaia, and l. Pucci, "Correlations between karyotype and phenotype in structural and numerical abnormalities of chromosome 18," *Boll Soc Ital Biol Sper.*, vol. 68, pp. 263-9, 1992.

[9] M. Mcginniss, C. Rosenberg, S. G. Sattion, A. schinzel, and F. Binkert, "unbalanced translocation, t (18; 21), detected by fluorescence in situ hybridization (Fish) in a child with 18q-syndrome and a ring chromosome 21," *Am J Med Genet.*, vol. 46, pp. 647-51, 1993.

[10] M. Khalifa, H. Yamashiro, A. Duncan, M. Hefferon, and A. Martin, "A famele with monosomy 18 mosaicism; a previously undescribed chromosome abnormality," *Clin Genet,* vol. 49, pp. 318-20, 1996.

[11] J. Fryns and A. Kleczkowska, "Autism and ring chromosome 18 mosaicism (Letter)," *Clin Genet,* vol. 42, pp. 55-57, 1992.

[12] E. Sheridan, T. Torbergsen, K. Nakken, R. Gimse, and O. Sjaastand, "Epileptic seizures, arthogryposis, and migratorial brain disorders: A syndrome," *ACTA Neurol Scand,* vol. 90, pp. 232-40, 1994.

[13] U. Andersen, "Ringkromosom 18," *Ugeskrift for Laeger,* vol. 154, pp. 3250-3251, 1992.

[14] C. Woods, A. Bankier, J. Curry, l. Sheffield, S. slaney, K. Smith, l. Voullaire, and D. Wellwsley, "Asimmetry and skyn pigmentary anomalies in chromosome mosaicism," *J Med Genet,* vol. 31, pp. 694-701, 1994.

[15] E. Bocian, T. limiters, E. Bulawa, H. Stanczak, and G. Rowicka, "Triple structural mosaicism of chromosome 18 in a child with mr/mca syndrome and abnormal skin pigmentation," *J Med Genet.,* vol. 30, pp. 614-5, 1993.

[16] A. Meloni, l. Bocoone, l. Angius, S. loche, A. Falchi, and A. Cao, "Hypothalamic growth hormone deficiency in a patient with ring chromosome 18," *EUR J Pediatr,* vol. 153, pp. 110-2, 1994.

[17] S. Aritaki, Takagi, H. Someya, and l. Jun, "Growth hormone neurosecretory dysfunction associated with ring chromosome 18," *ACTA Paediatr JPN.,* vol. 38, pp. 544-8, 1996.

[18] B. Eiben, M. Unger, G. Stoltenberg, G. Rutt, R. Goebel, Meyer, U. Gamerdinger, W. Hammams, S. Hansen, and H. Hauss, "Prenatal diagnosis of monosomy 18 and ring chromosome 18 mosaicism," *Prenat Diagn,* vol. 12, pp. 945-50, 1992.

[19] E. Sheridan, T. Torbergsen, K. Nakken, K. Andersen, R. Gimse, and O. Bjaastad, "Epileptic seizures, arthogryposis, and migrational brain disorders: A syndrome?," *ACTA Neurol Scand,* vol. 90, pp. 232-40, 1994.

[20] R. S. Sparkes, "Absent tumbs with a ring chromosome D2: A new deletion syndrome," *Am J. Hum Genet,* vol. 19, pp. 644-659, 1967.

[21] A. I. Taylor, "DQ, DR. and retinoblastoma," *Human Genetic,* vol. 10, pp. 209-217, 1970.

[22] E. Grace, "The 13q-deletion syndrome," *J Med Genet,* vol. 8, pp. 351-357, 1971.

[23] J. Hinnebusch and K. Tilly, "Linear plasmids and chromosomes in bacteria," *Mol Microbiol,* vol. 10, pp. 917–22, 1993.

[24] S. Balci, O. Engiz, and D. Akta, "Ring chromosome 4 and wolf-hirschhorn syndrome (WHS) in a child with multiple anomalies," *Am J Med Genet.,* vol. 140, pp. 628-32, 2006.

[25] J. Del Mazo, "Partial deletion of 4p16 band in a ring chromosome and wolf syndrome," *Hum Genet,* vol. 44, pp. 105-08, 1978.

[26] A. Perez-Castillo, "Ring chromosome 4 and wolf syndrome," *Hum Genet,* vol. 37, pp. 87-91, 1977.

[27] E. Tahara, "Molecular mechanism of stomach carcinogenesis (Editorial)," *J Cancer Res Clin Oncol,* vol. 119, pp. 265-72, 1993.

[28] F. Fukushima, "Predisposition to autoimmune thyroiditis as part of chromosome 18 syndrome," *JPN J Hum Genet,* vol. 29, pp. 127-132, 1984.

[29] R. Gorlin, "Facial clefting syndromes," *Birth Defect,* vol. 7, pp. 3-49, 1971.

[30] Fryns, A. Kleczkowska, S. Smeets, and H. Van Den Berghe, "Transmission of ring chromosome 18 46, XX/46, XX, R (18) mosaicism in a mother and ring chrosome 18 syndrome in her are," *Ann Genet,* vol. 35, pp. 121-3, 1992.

[31] R. Aparicio, P. Barrientos, S. Walter, H. Hurtado, J. Enciso, and M. Huitzil, "Estudio comparativo de una aberración cromosómica anular. Reporte de un caso con mosaisismo del cromosoma 13, 46, XY/46, XY, R(13)," *ORAL.,* vol. 2, pp. 36-39, 2000.

[32] R. Aparicio, P. Barrientos, G. Camacho, A. Maldonado, H. Hurtado, M. Huitzil, V. Frías, and V. García, "Anillo del cromosoma 18 en un lactante con cariotipo 46,XY/46,XY, R(18), hijo de madre con mosaicismo para el anillo cromosómico," *Bol Med Hosp Infant Mex.,* vol. 55, pp. 505-510, 1998.

[33] M. Lee, S. Park, and Y. Kim, "Molecular cytogenetic characterization of ring chromosome 4 in a female having a chromosomally normal child," *Cytogenet Genome Res.,* vol. 111, pp. 175-8, 2005.

[34] S. Sigurdardottir, "Clinical, cytogenetic, and fluorescence in situ hybridization findings in two cases of complete ring syndrome," *Am J Med Genet,* vol. 87, pp. 384-90, 1999.

[35] C. Anderson, "Ring chromosome 4 mosaicism coincidence of oligomeganephronia and signs of seckel syndrome," *Am J Med Genet.,* vol. 72, pp. 281-85, 1997.

[36] S. Park, "Oligomeganephronia associated with 4p deletion type chromosomal anomaly," *Pediatr Pathol,* vol. 13, pp. 731-40, 1993.

[37] A. Pezzolo, "Presence of telomeric and subtelomeric sequences at the fusion points of ring chromosomes indicates that the ring syndrome is caused by ring instability," *Hum Genet,* vol. 92, pp. 23-27, 1993.

[38] L. Giuffre, "Ring chromosome 4 in twins," *Pediatr Med Chir.,* vol. 9, pp. 349-50, 1987.

[39] A. Gutkowska, "Ring chromosome 4: 46,XY, R(4) (p16q35) in a boy," *Klin Padiatr,* vol. 197, pp. 294-96, 1985.

[40] J. Huret, C. Leonard, and J. Savage, "Cromosomas, anomalias cromosómicas," *Atlas Genet Cytogenet Oncol Haematol,* vol. 2, pp. 100-140, 2000.

FIGURE LEYENDS

Figure 1 A. Female patient with bilateral cleft lip and palate and cranio-facial dimorphism and hypertelorism B. scoliosis and hemivertebrae. C. karyotype shows r13.

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. chromosome studies showed a t13 formula.

Figure 3 A. Male patient with microcephaly, sinofris small size B. micrognacia C. especial flexion of the fingers on hands D. Karyotype reveals a t18.

Figure 4 A. Male patient with general hypoplasia and hipotonía, ambiguos genital and hypertelorism B. fingers with over position C. chromosome studies showed r18.

Figure 5 A. B. Male patient with general hipotonía, mental retardation and hypertelorism **C**. karyotype reveal an 4 ring chromosome alteration.

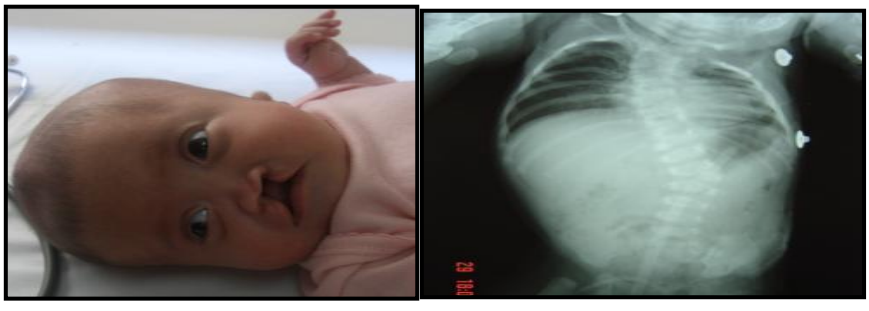
Figure 6. more than 4500 chromosome studies were performed. Only four patients shows ring malformation.

TABLES

Table-1. Only four ring chromosome aberrations were observed.

FIGURE-1.

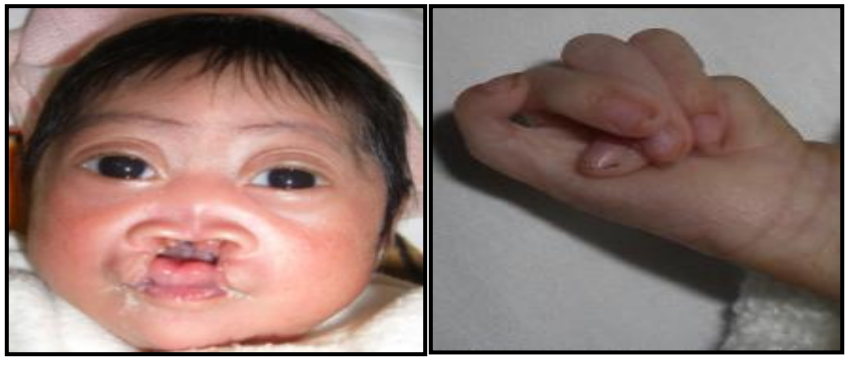
A B



C

FIGURE-2.

A B



C

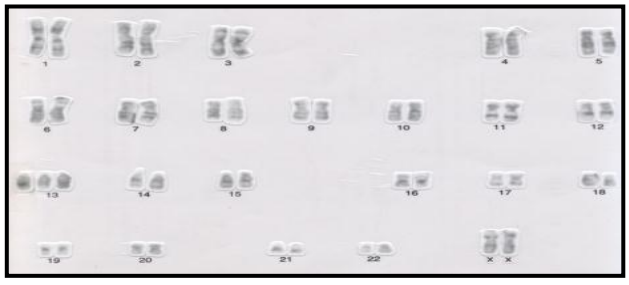
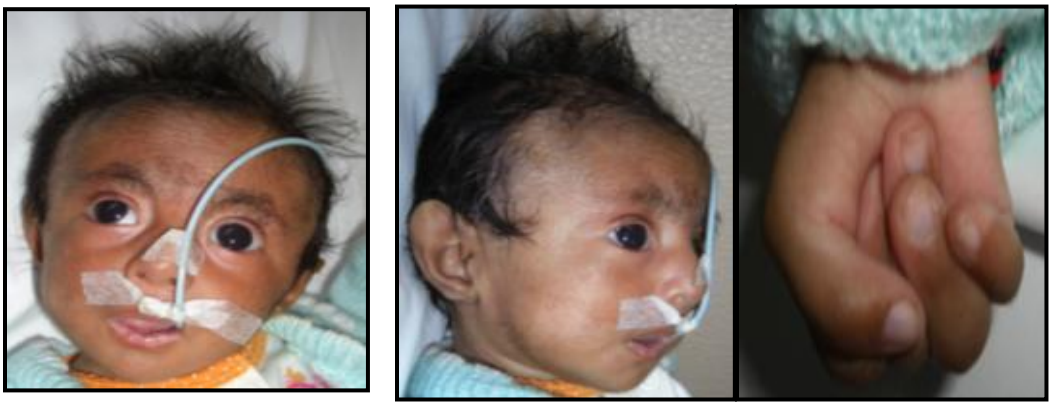


FIGURE-3.

A B C



D

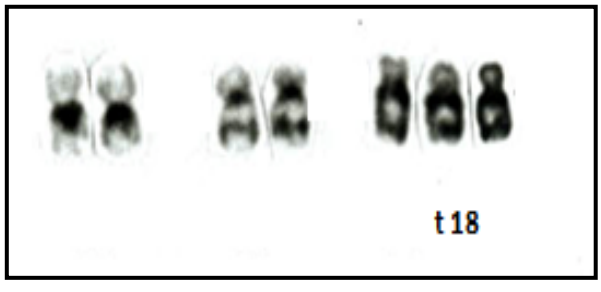
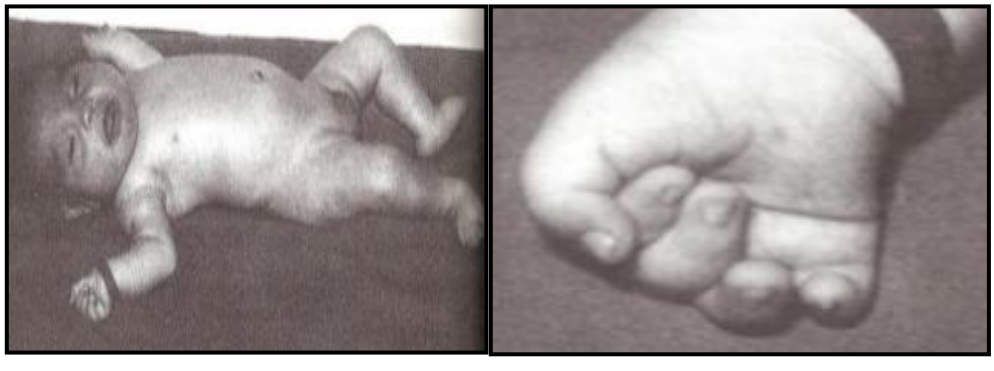


FIGURE-4.

A **B**



C

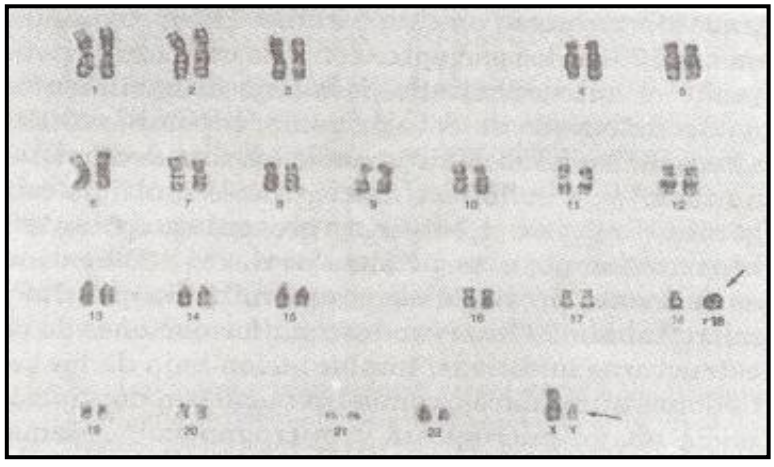
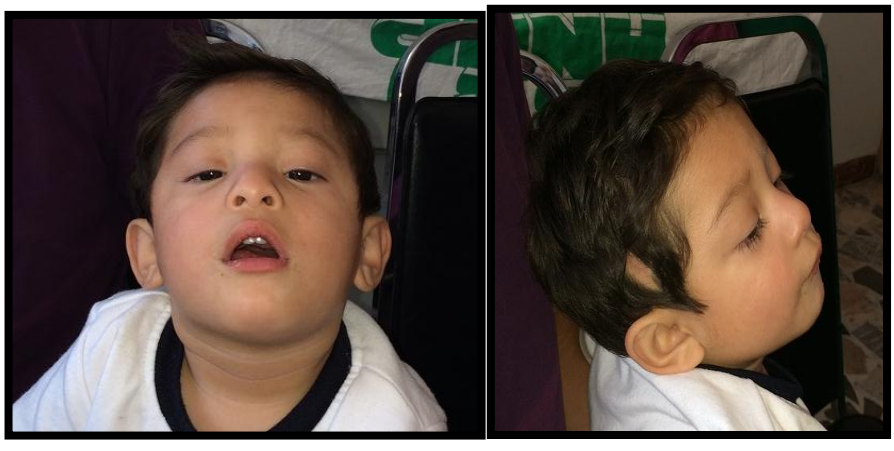


Figure-5.

A B



C

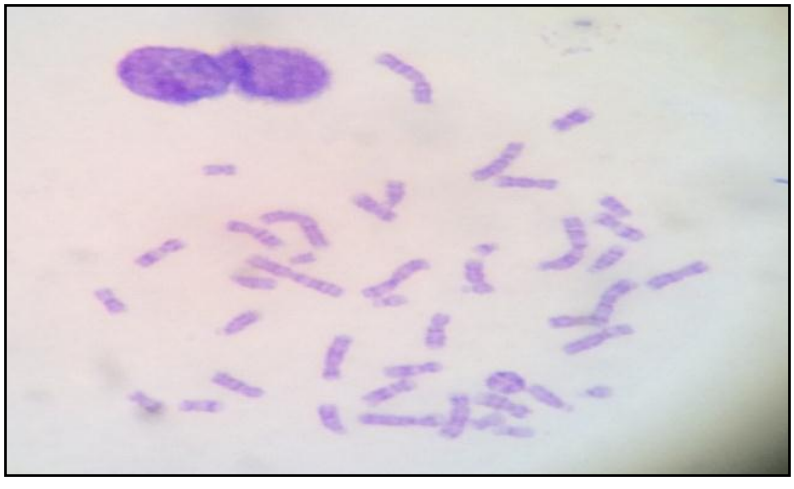


Figure-6.

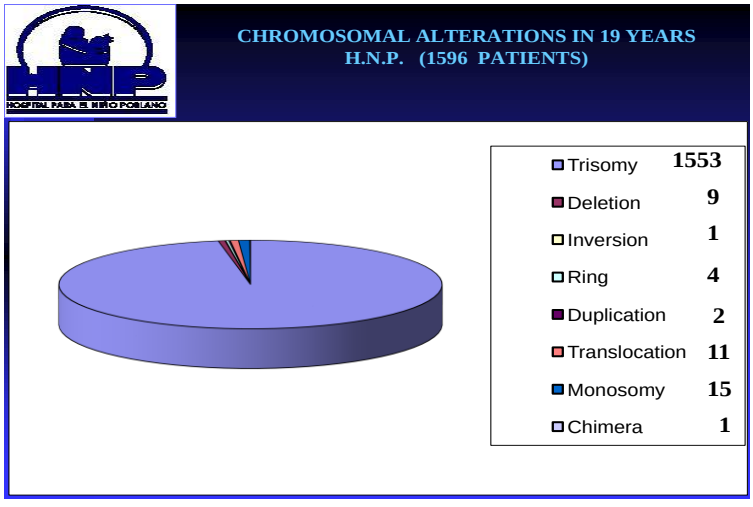


Table-1.

Alterations	**(percentage) patients**
1. Trisomy	1553
2.Deletions(chromosomes 4,6,9)	6
Other deletions	3
3. Invertion	1
4. Ring	4
5. Duplication	2
6. Translocation	11
7. Monosomy	15
8. Chimera	1
Chromosomal aberrations	**(34.6%) 1596**
Trisomies	**(33.6%) 1553**
A-Trisomy 21	**(32.8%) 1511**
1. T 21	1127
2. T21;14	260
3. T21;21	43
4. Mosaicism	81
B-Various Trisomies:	**(0.90%) 42**
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