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MALFORMATION VARIABILITY ASSOCIATED TO CHROMOSOME TRISOMIES. CLINICAL AND PHENOTIPICAL IMPLICATIONS IN SEVERAL PATIENTS AT A PEDIATRIC HOSPITAL IN MEXICO

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ABSTRACT

Chromosome trisomies are considered alterations in the chromosome number or structure. A trisomy is therefore a type of polysomy in which there are three chromosome copies, instead of the normal two. A trisomy is considered an aneuploidy or abnormal number of chromosomes. There are two different trisomy types; Full trisomy" where an entire extra chromosome has been copied. "Partial trisomy" means that there is an extra copy of part of a chromosome. Depending on the chromosome, a trisomy is named as "Autosomal trisomies" (trisomies of the non-sex chromosomes) and "Sex-chromosome trisomies." In this study both Autosomal and Sex-chromosome trisomies are described in differents patients, depending on the affected chromosome. Among 4617 chromosomal studies performed during 19 years (from 1992 to 2011), at Hospital Para el Niño Poblano in México, 34.6% (1596 patients) had chromosomal alterations. Among these studies population, a male and female pediatric patients are described, with different chromosome trisomies, were chromosome changes are classified as structural or numeric alterations. All trisomies patients were described in this study analyzing their phonotypical and clinical features, medical treatments and prognosis.

Keywords: Chromosome trisomy, Karyotype, Numeric and structural chromosome.

INTRODUCTION

Trisomies can be seen at any chromosome, but often result in miscarriage as Trisomy 16 reported one of the most common trisomy in human pregnancies, occurring in more than 1% of pregnancies;

only those where there are a number of cells with a normal complement of chromosomes called mosaic trisomy 16 survive.Hassold *et al.* (1995) This chromosome event, however, usually results in spontaneous miscarriage in the first trimester.

The most common types of autosomal and sex chromosome trisomy found in this study are: trisomy 21 (Down syndrome), Trisomy 18 (Edwards syndrome), Trisomy 13 (Patau syndrome), Trisomy 6, Trisomy 10, Trisomy 22, XXX (Triple X syndrome), XXY (Klinefelter syndrome). Of these, Trisomy 21 and Trisomy 18 are the most common. In rare cases, a fetus with Trisomy 13 or Patau syndrome can survive. Autosomal trisomy can be associated with birth defects, mental retardation and shortened life expectancy.

A chromosome is an organized structure of DNA and protein found inside cells. It is a single piece of coiled DNA with many genes, regulatory elements and other nucleotide sequences. Chromosomes also contain DNA-bound proteins, which serve to package the DNA and control its functions Thanbichler *et al.* (2005) ; Sandman *et al.* (1998); Sandman (2000); Pereira *et al.* (1997). 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 cellsWhite (1973) have large linear chromosomes and prokaryotic cells Thanbichler and Shapiro (2006); Nakabachi *et al.* (2006); (Pradella *et al.*, 2002), have smaller circular chromosomes.

Chromosome recombination plays a vital role in evolution and genetic diversity, Hinnebusch and Tilly (1993). If these structures begin through processes known as chromosomal instability and mutation, the cell may die, or it may avoid apoptosis leading to initiation to cell malignization. Human's chromosomes are divided into two known types; autosomes, and sex chromosomes. Certain genetic traits are linked to a person's sex, and are passed on through the sex chromosomes. The autosomes contain all the genetic hereditary information. Both chromosome types act in the same way during cell division. Human cells have 23 pairs of large linear nuclear chromosomes. The karyotype is the characteristic chromosome complement of eukaryote organisms. White (1973) the preparation and study of karyotypes is part of a science called cytogenetics.

A female patient in relation to chromosome 6 was studied, with trisomy 6 Figures 1 A, B and C. In relation to Chromosome 6, total Geraedts and Haak (1976); Moormeier *et al.* (1991); Jonveaux *et al.* (1994); La Starza *et al.* (1998); Mohamed *et al.* (1998); Onodera *et al.* (1998); (Wong, 2004) and Dellacasa *et al.* (1993); (Brondum *et al.*, 1993); Uhrich *et al.* (1991); Bartalena *et al.* (1990); (Chase *et al.*, 1983). Trisomy 6q is an extremely rare chromosomal disorder. Associated symptoms may vary depending of the case. However, in this study a total trisomy is reported where slow physical development (growth retardation); mental retardation; no malformations of the skull and

facial (craniofacial) region with short, webbed neck; joint contractures were observed and normal hematological results.

Partial trisomy 6q, all or a portion of the end (distal) region of the long arm (q) of chromosome 6 is due to duplication portion at various points (i.e., breakpoints) and the range and severity of associated symptoms may depend on the specific length Turleau and de Grouchy (1981); Schmid *et al.* (1979) or total duplication of the entire chromosome as in this study.

In most reported cases, Chromosome 6, Partial Trisomy 6 has resulted from a balanced chromosomal rearrangement in one of the parents Chase *et al.* (1983), usually of maternal origin. However, paternal chromosomal rearrangements are rare and such a chromosomal rearrangement may be associated with an increased risk of abnormal chromosomal development in one of the parents. There have also been cases in which Chromosome 6, partial trisomy 6 has appeared to result from spontaneous (de novo) changes very early in embryonic development Bartalena *et al.* (1990);Neu *et al.* (1981) . In such de novo cases, the parents of the affected child usually have normal chromosomes and a relatively low risk of having another child with the chromosomal abnormality.

Chromosomal analysis and genetic counseling are often recommended for parents of an affected child to help confirm or exclude the presence of a balanced translocation or other chromosomal rearrangement. In relation to complete trisomy 6 as the patient in this study, it has been associated to acute myeloid leukemia (AML) and myelodysplastic syndrome. Benedict *et al.* (1979); Panani *et al.* (1980); Testa *et al.* (1985); Mecucci *et al.* (1986). Several patients with total or partial trisomy in this study as number 6 showed AML-M1 morphology and expression of stem cell antigen CD34 on the leukemic blasts, suggesting that trisomy 6 may be associated with a different form of AML. Nevertheless, a phonotypical or clinical malformation as mental retardation was observed in several of the studied patients. Some trisomies associated to female miscarried pregnancy. It is interesting to analyze how partial or total trisomy can modify a normal life patient.

MATERIALS AND METHODS

From 4617 karyotypes Figure 16 performed at Hospital Para el Niño Poblano, Mexico in 19 years period of time, only 1596 patients (34.6%) showed chromosomal alterations, among the studies population, different chromosome trisomies were reported during this period of time**.** Male and female patients were evaluated at the Department of Genetics in a multidisciplinary manner. Chromosomal studies (karyotypes) where performed for all patients by using GTG banding. Cells were locked part-way through division (in metaphase) in vitro (in a reaction vial) with colchicine. These cells were then stained, photographed, and them arranged and evaluated for chromosomal analysis and diagnosis. Hematological studies were also performed.

DISCUSION

Where chromosome trisomy is observed, an additional chromosome is present over and above the usual pair. The aberration is usually caused by either the sperm or the egg containing a pair of chromosomes (rather than a single chromosome). This arises from a failure of the normal separation of a pair of chromosomes during cell division, if it occurs during meiosis the resulting gamete will have 24 chromosomes and the complementary gamete with 22 chromosomes will be non-viable. Taking in consideration that human cells normally contain 46 chromosomes which carry the estimated 70,000 genes needed for normal growth and development. There are 23 pairs: 22 pairs of autosomes, and two sex chromosomes, X and Y (XX in females, XY in males). Normal female and male karyotypes are abbreviated to 46XX and 46XY respectively.

Autosomal trisomies are associated to maternal age. This probably reflects the differences between male and female gametogenesis. In particular the primary oocyte ages while in "suspended animation" for up to 50 years within the ovary. Trisomies of any chromosome can occur during gametogenesis, but the majority of resulting pregnancies are not viable and result in early miscarriage.

Scientists have been studying trisomies since chromosomes were first seen under a microscope. While trisomies have been studied and described for decades, there is still a lot that we don't understand about the cause of trisomies. This article is going to cover some of the facts about what we do know, and provide some information about other common human trisomies. Therefore these 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, such as Down syndrome, considered as the more frequent chromosomal trisomy. Investigation into the human karyotype took many years to settle the most basic question. How many chromosomes does a normal diploid human cell contain? In 1912, von Winiwarter reported 47 chromosomes in spermatogonia and 48 in oogonia, concluding an XX/XO sex determination mechanism.Von (1912). and Painter (1922) was not certain whether the diploid number of man is 46 or 48, at first favoring 46. He revised his opinion later from 46 to 48, and he correctly insisted on humans having an XX/XY system, Tjio and Levan (1956); Ford and Hamerton (1956). Considering the techniques of Von (1912) and Painter (1922), their results were quite remarkable.Hsu (1979) showed in chimpanzees (the closest living relatives to modern humans) have 48 chromosomes. Some chromosome abnormalities do not cause disease in carriers as it was found in some patient´s parents in this study.

From a total of 4617 karyotypes (100%) performed in this study Aparicio *et al.* (2011), 33.6% (1553 patients) Table 1 and Figure 17 were diagnosed as chromosomal trisomy, were 32.8% (1511 patients) diagnosed as Down syndrome (trisomy 21) Aparicio *et al.* (2009). Moreover, 0.93% with

different trisomies Table 1, as the case of a female patient in this study with a rare trisomy 6 Figure 1C, without any phenotypical malformations nor cranio-facial dimorphism Figure 1 A and B, taking in consideration that trisomy 6 is an extremely rare chromosomal disorder and has been associated to aplastic anemia Geraedts and Haak (1976). Rare instances of trisomy 6 may be encountered in childhood acute mixed lineage leukemia, lymphoblastic transformation of chronic myeloid leukemia, and chronic myeloproliferative disorder. Trisomy 6 may define a distinctive subtype of aplastic anaemia with mild dysplastic changes, Geraedts and Haak (1976); (Moormeier *et al.*, 1991); Jonveaux *et al.* (1994); La Starza *et al.* (1998); Mohamed *et al.* (1998); Onodera *et al.* (1998); Wong (2004), poor response to steroids and ATG therapy, and propensity for AML transformation. More cases need to be collected to substantiate this contention.

Partial trisomy 6, however, may be variable. The disorder is characterized by growth delays before and after birth, severe to profound mental retardation, a delay in the acquisition of skills requiring coordination of muscular and mental activity (psychomotor retardation), with malformations of the skull and facial (craniofacial) region as microcephaly, ocular hypertelorism, micrognathia and cleft palate, musculoskeletal abnormalities, and/or additional physical features. Chromosome 6, Partial Trisomy 6q is an extremely rare chromosomal disorder that appears to affect males and females equally. Dellacasa *et al.* (1993); Brondum *et al.* (1993); (Uhrich *et al.*, 1991); (Bartalena *et al.*, 1990); (Chase *et al.*, 1983).

Two healthy carriers parents were observed in this study, one of them Figure 2 A and B, a healthy carrier mother with translocation 46XX, ins (10; 7) (q21; q23q35) Figure 2 C.D**.** However her mentally retarded son revealed a translocation from long arm of chromosome 10 t(10q+), giving rise to partial trisomy 7. Aparicio *et al.* (2010). Similar case as the Healthy carrier father Figure 3 A and B. with a balanced translocation 46XY,ins(10;9 and his son Figure 3 A, B, C and D, presented plagiocephaly and facial hemiatrophy wide nose and hipoplasic jaw with chromosomal translocation t(9;10) giving rise to partial trisomy 9.

Several patients were diagnosed with bilateral cleft lip and palate and cranio-facial dimorphism like the male patient that revealed a partial trisomy of chromosome 14, (14q24 leads to qter) due to a balance malformation translocation t(11;14) (q25;q24.1) Figure 4. A and B where chromosome 11 is associated to several syndromes, Grossfeld *et al.* (2004). Similar case as the new born female patient with cleft palate and displasic ears with a balanced chromosomal translocation 21;14 due to a 14 trisomy Figure 5 A, B and C**.**

From a total of 4617 karyotypes (100%) performed, 33.6% (1553 patients) Table 1 were diagnosed as chromosomal trisomy, were 32.8% (1511 patients) Figure 6 diagnosed as Down syndrome (trisomy 21). This alteration is usually caused by an extra copy of chromosome 21 (trisomy 21). Characteristics include decreased muscle tone, stockier build, asymmetrical skull, slanting eyes and

mild to moderate developmental disability, Aparicio *et al.* (2009). 1127 patients have regular trisomy (47XX+21 or 47XY+21) in this study, caused by a meiotic nodisjunction event Table 1 Figure 7. A, B and C, also chromosomal translocations were observed; 260 patients 46XYt(14;21) or 46XXt(14;21q) were the long arm of chromosome 21 is attached to chromosome 14**,** Figure 8 A, B and C**,** 43 patients 46XY t(21;21) or 46XX t(21;21), and 81 patients with mosaicism. Moreover, 0.90% have other kind of trisomies in different chromosomes Table 1 Partial trisomy of chromosome 7, 46XY, $7q^+$ was diagnosed in a male patient with facial hypoplasia, narrow set eyes, sinofris, hipoplasic jaw with restricted motion and limited mouth opening Figure 9 A, B and C if compared to a female patient with a facial hypoplasia and oblicua desviation of both eyes, small mouth hipoplasic jaw and facial with a partial trisomy of chromosome 7, 46XX, $7q^+$. Figure 10 A, B and C.

Edwards and Patau syndromes rarely found among pediatric patients. Both syndromes share similar symptoms. Figure 11 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, 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, Figure 12 A, B, C and D. and only one male patient with mental retardation, epileptic seizures microcephaly, and hypoplasia was diagnosed as trisomy 22, (47 XY + 22) Figure 13 A, B and C.

In relation to sexual chromosomes, some studies aims to assess prevalence and pregnancy outcome for sex chromosome trisomies (SCTs) diagnosed prenatally or in the first year of life, with a prevalence of XXX, XXY and XYY were 0.54 (95% CI 0.46-0.64), 1.04 (95% CI 0.92-1.17) and 0.30 (95% CI 0.24-0.38), respectively, Boyd PA et al. (2011). However, in this study several phenotypical malformations associated to polyploidy as XXX and Kllinefelter, were observed. Figure 14 A and B where a male patient was diagnosed with Opitz G/B.B.B. syndrome, hypertelorism and cleft lip and palate, cranio-facial dismorphism. However the karyotype reveals an X sexual chromosome duplication 46,XXY (Klinefelter syndrome). Male with this syndrome are usually sterile and have a higher incidence of speech delay and dyslexia. During puberty, without testosterone treatment, some of them may develop gynecomastia. This patient must be evaluated periodically by endocrinology and pediatric surgery.

A female with cranio-facial dimorphism, small eyes with hypotelorism, turricefalia and hypoplasia was associated to trisomy of X sexual chromosomes 47,XXX (triple-X syndrome) Figure 15 A, B

and C. XXX females tend to be tall and thin. They have a higher incidence of dyslexia and they are somewhat more likely to have learning difficulties.

Abnormal numbers of chromosomes or chromosome sets, aneuploidy, may be lethal or give rise to genetic disorders. Some of the main chromosomal alterations in this study can be seen in Table 1 and Figure 6. Genetic counseling was offered for carrier families Figures 2 A, B,C and D; 3 A, B, C, D and 8 A, B, C, D with important 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. 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 for the patient and the entire family.

Chromosomal trisomy or translocation give rise to loss or DNA alterations which can lead to a variety of genetic disorders as it was found in both patients presented in his study. It is important whether these chromosomal aberrations can be diagnosed early for a better rehabilitation therapy and the best quality of life for the patient. Early intervention may be important in ensuring that affected children reach their potential. Special services that may be beneficial include special education and/or other medical, social, and/or vocational services. Genetic counseling will also be of benefit for the families of affected individuals. Other treatment for this disorder is symptomatic and supportive.

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FIGURE LEYENDS

Figure 1. Female patient diagnosed with none neither phenotypical malformations nor **A. B.** craneo-facial dimorphism **C.** karyotype revealed complete trisomy of chromosome 6.

Figure 2 A. Healthy carrier mother **B.** of a chromosomal translocation 46XX,ins(10;7) (q21;q23q35) **C.** however her mentally retarded son **D**. revealed a balanced chromosomal translocation from long arm of chromosome 10 t(10q+), giving a rise to a partial trisomy 7.

Figure 3 A. Healthy carrier father **B**. of a chromosomal translocation 46XY,ins(10;9) B. And his son with plagiocephaly and facial hemiatrophy **C**. wide nose and hipoplasic jaw However her physically retarded son **D**. revealed a balanced chromosomal translocation t(9;10) giving a rise to a partial trisomy 9

Figure 4. A. Male patient with bilateral cleft lip and palate and cranio-facial dimorphism **B**. karyotype revealed a partial trisomy of chromosome 14, (14q24 leads to qter) due to a balance translocation t(11;14) (q25;q24.1).

Figure 5 A. New born female patient with cleft palate **B**. and displasic ears **C.** karyotype revealed a balanced chromosomal translocation 21;14 due to a 14 trisomy.

Figure 6 From all chromosomal trisomies 1553 (33.6%), It can be seen that 1511 (32.7%) were different kind of trisomy 21.

Figure 7 A. B. A 6 years old male patient with Down syndrome and mental retardation **C.** karyotype reveals a trisomy 21 (47,XX,+21) caused by a meiotic nondisjunction event.

Figure 8 A. B. An 8 years old female patient with Down syndrome, mental retardation, and epilepsy. **C**. karyotype reveals a Robertsonian translocation. The long arm of chromosome 21 is attached to chromosome 14 (46,XX,t(14;21q).

Figure 9. Male patient **A**. with a facial hypoplasia, have narow set eyes and sinofris **B.** hipoplasic jaw with restricted motion and limited mouth opening **C.** karyotype revealed a partial trisomy of chromosome 7, 46XY, $7q^{+}$.

Figure 10. Female patient **A**. with a facial hypoplasia and oblicua desviation of both eyes, small mouth **B.** hipoplasic jaw and facial hypoplasia **C**. karyotype revealed a partial trisomy of chromosome 7, 46XX, $7q^{+}$.

Figure 11 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 12 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 13 A. A 2 months old male patient with mental retardation, epileptic seizures microcephaly, and **B**. hypoplasia **C.** karyotype reveals a trisomy 22, 47 XY + 22.

Figure 14 A. Male patient diagnosed with Opitz G/B.B.B. síndrome, hypertelorism and cleft lip and palate, cranio-facial dimorphism B. karyotype reveals an X sexual chromosome duplication (Klinefelter syndrome).

Figure **15 A.** Female patient with cranio-facial dimorphism, small eyes with hypotelorism **B.** turricefalia and hypoplasia **C.** karyotype reveals a trisomy of X sexual chromosomes (47, XXX).

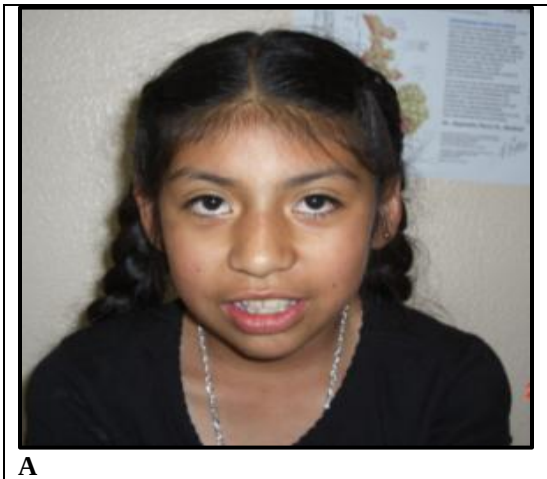
Figure 16. From a total of 4617 chromosome studies, 34.6% were observed to have chromosome alterations.

Figure 17. Chromosomal alterations in 19 years, shows 1596 patients (34.6%) , trisomy 21 (1511 patients) and various trisomies (43 patients)

TABLES

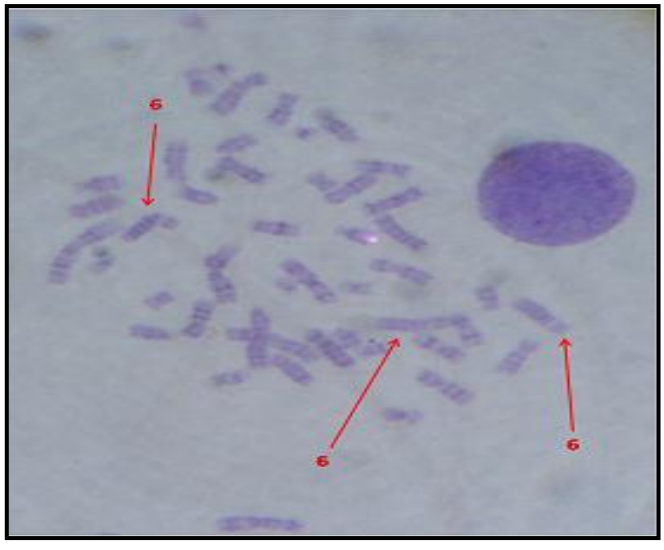
Table-1. Different chromosomal alterations as trisomies (33.6%) observed in 19 years at the Hospital parael Nino Poblano, Mexico.

Figure 1



A

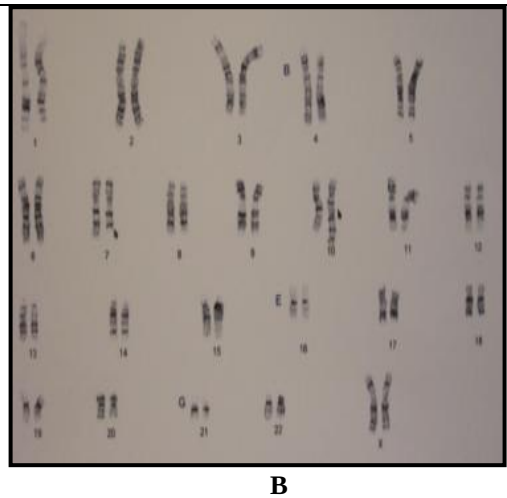
B



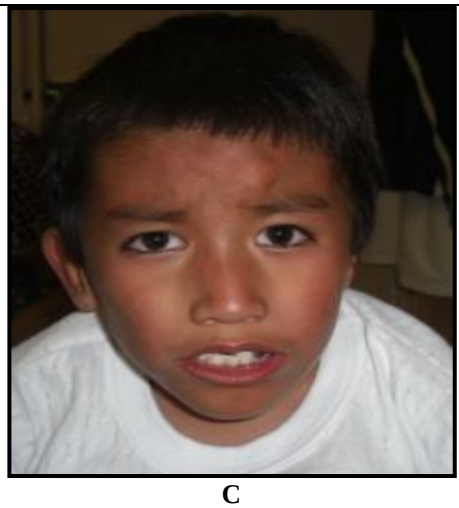
C

Figure 2

A



B



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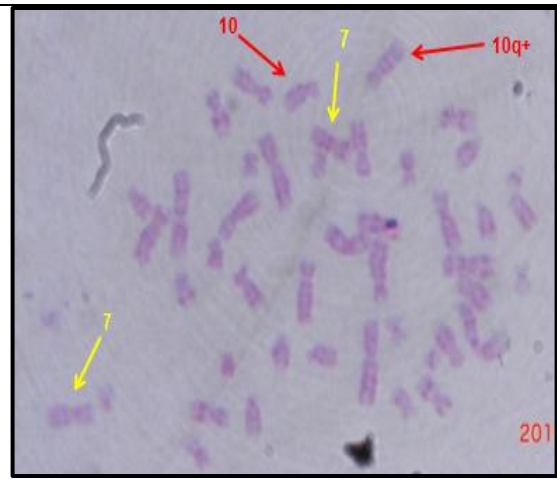
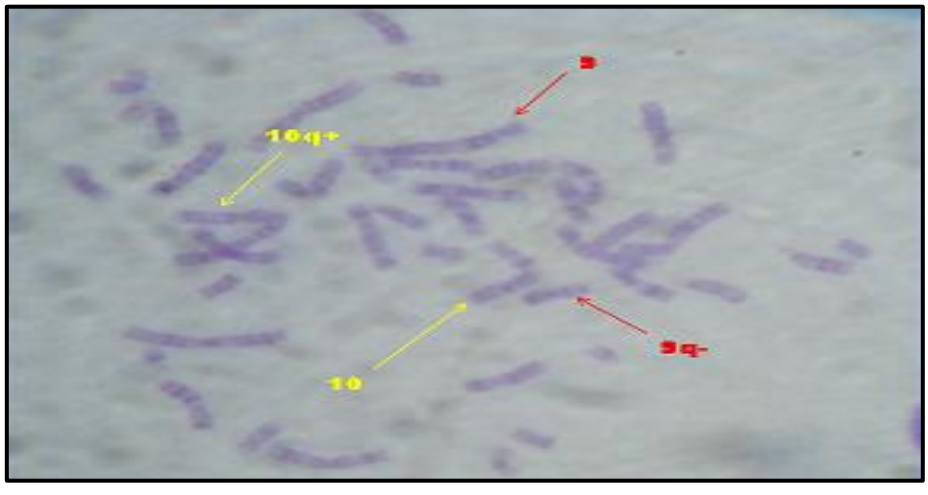


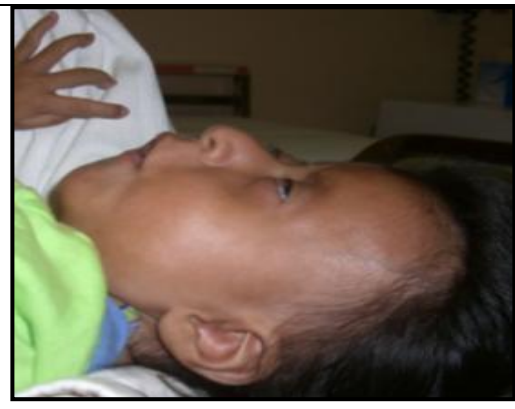
D

Figure 3



A

B



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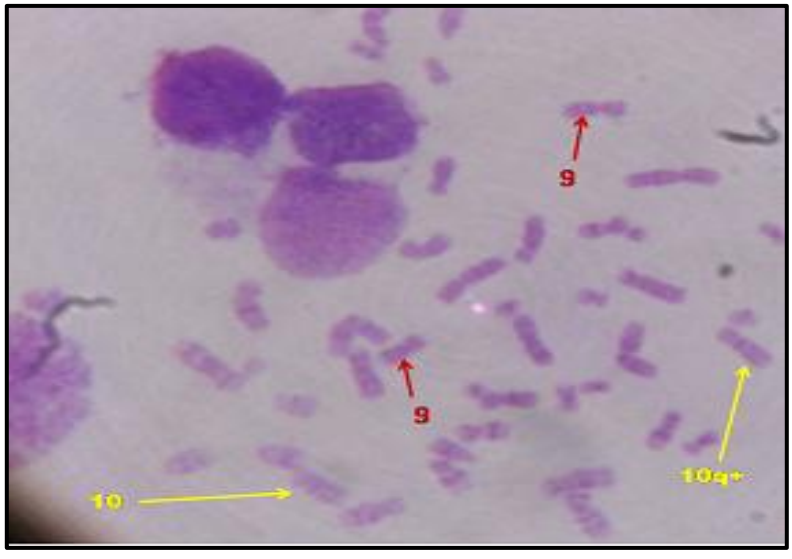
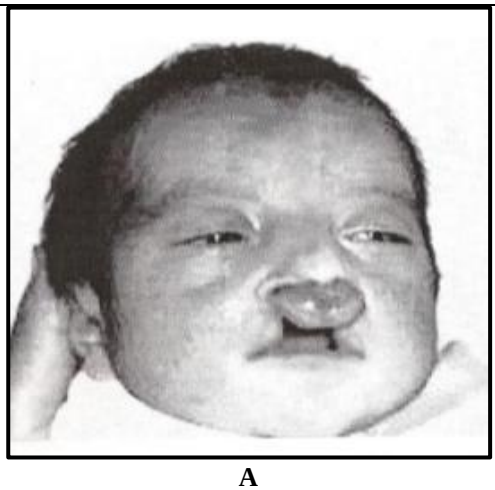


D

Figure 4



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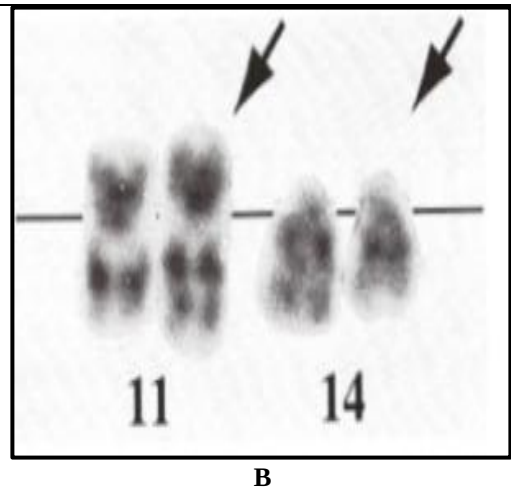
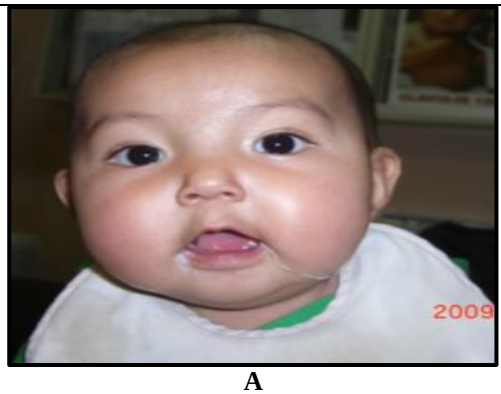


B

Figure 5



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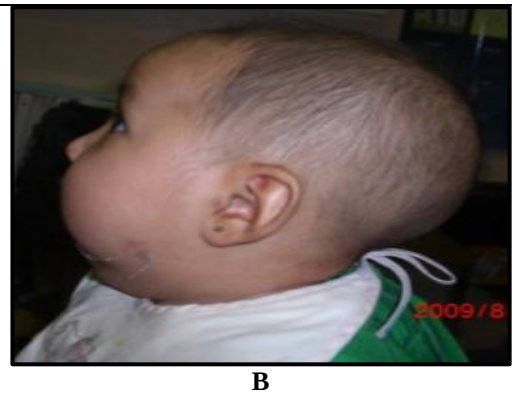

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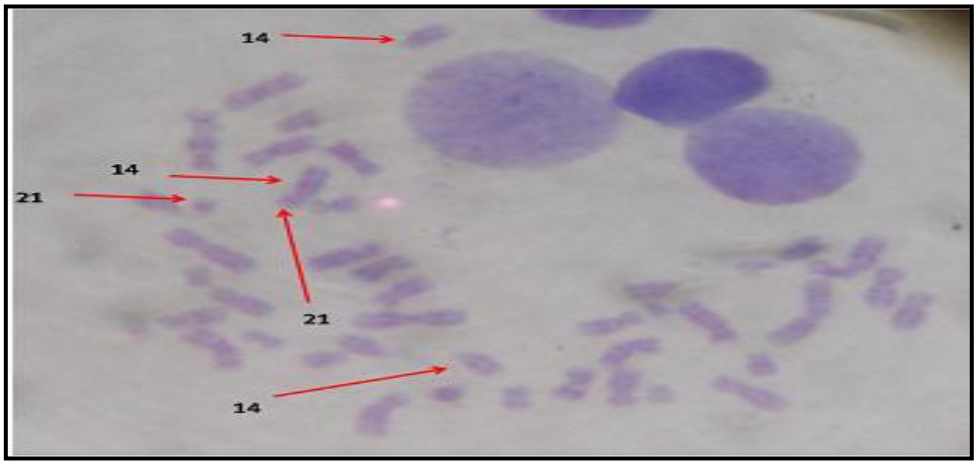

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Figure 6

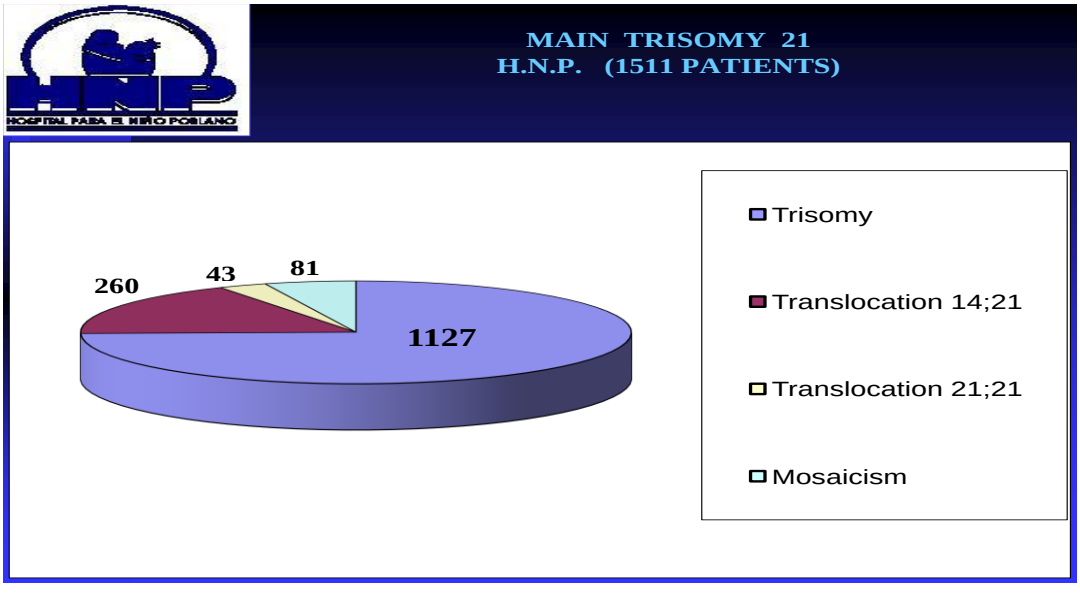
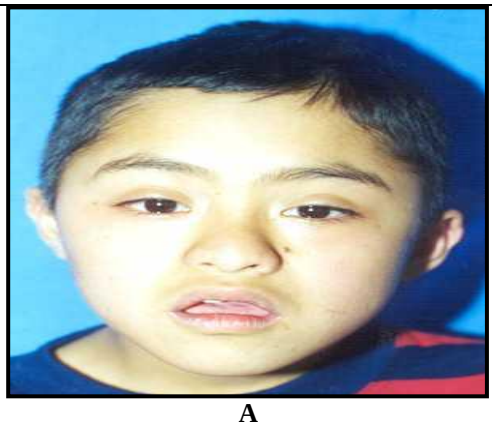


Figure 7



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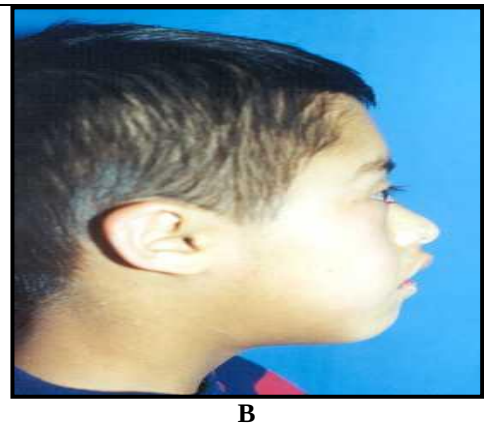

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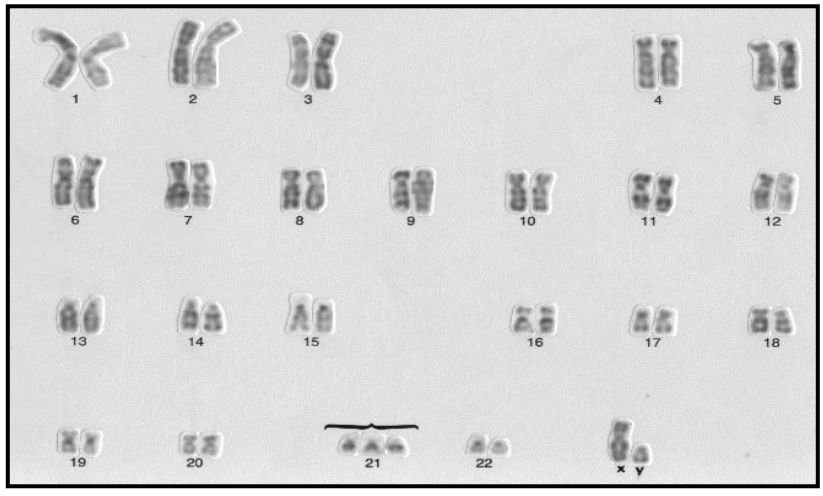

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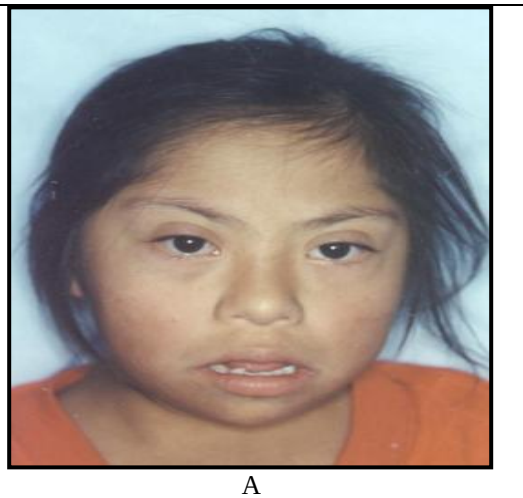
Figure 8



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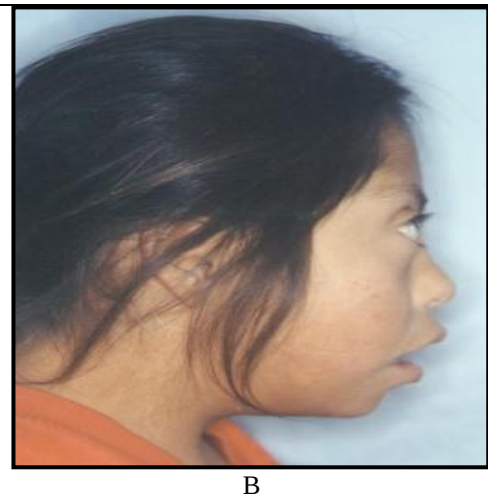

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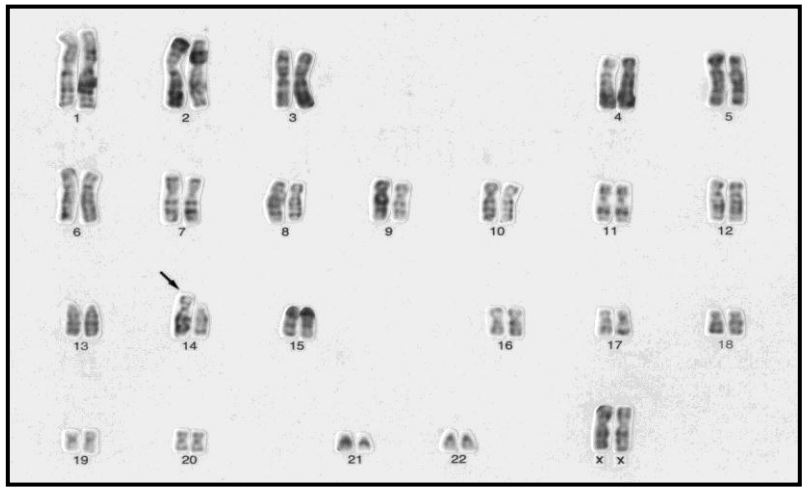
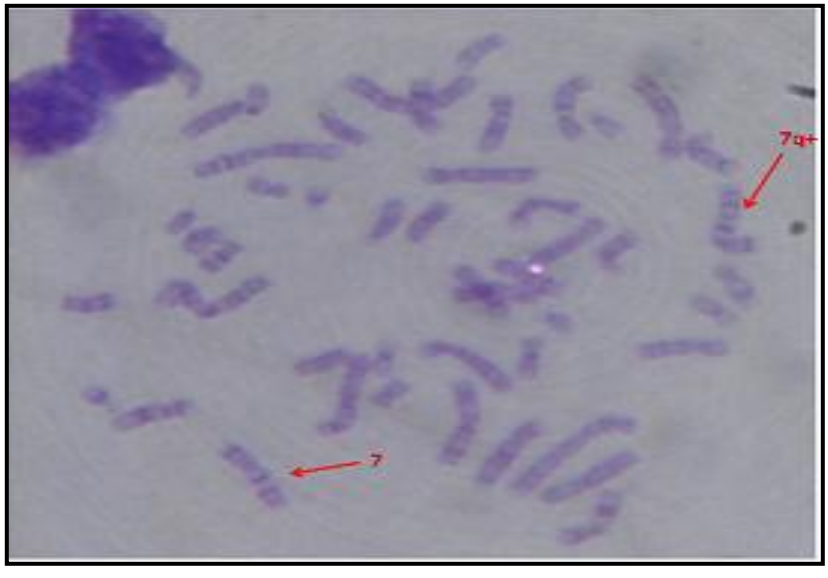


C

Figure 9

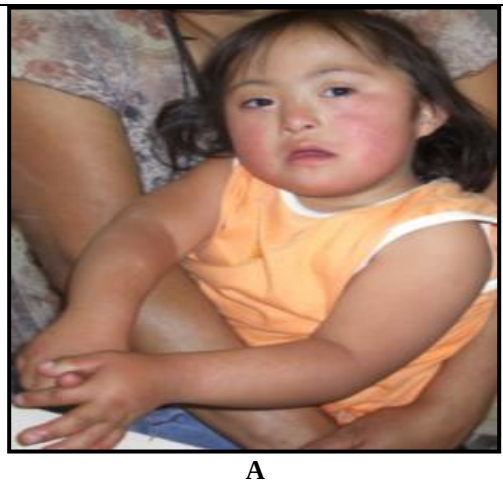
A

B



C

Figure 10



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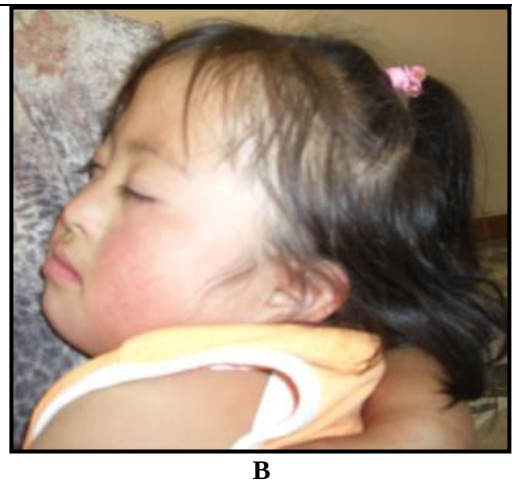

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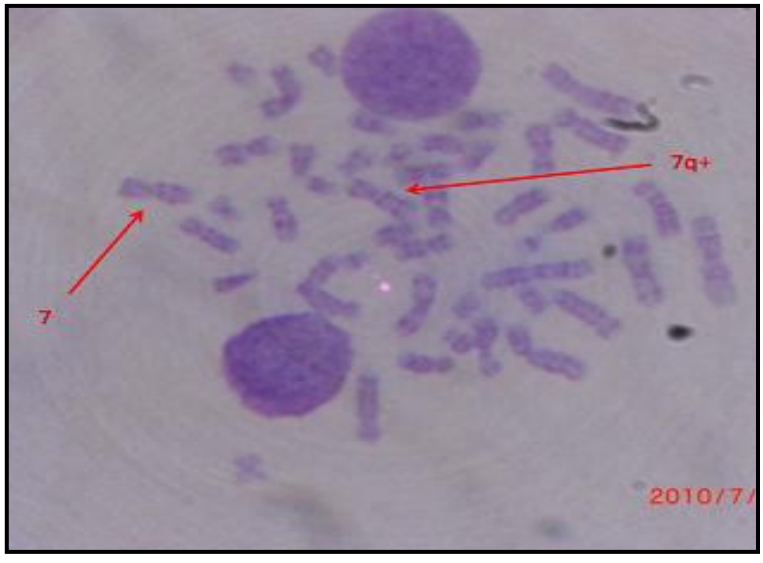
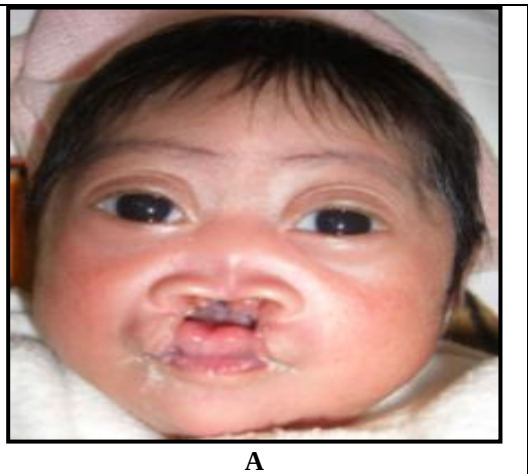


C

Figure 11



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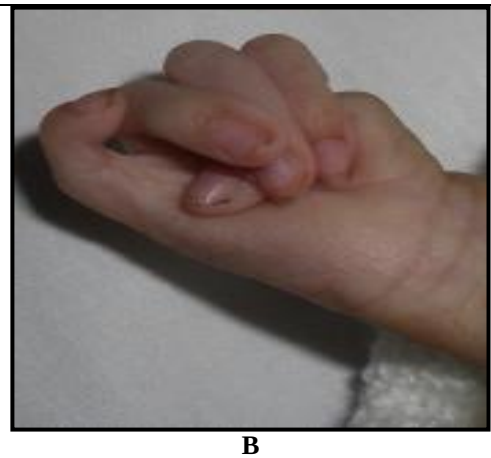

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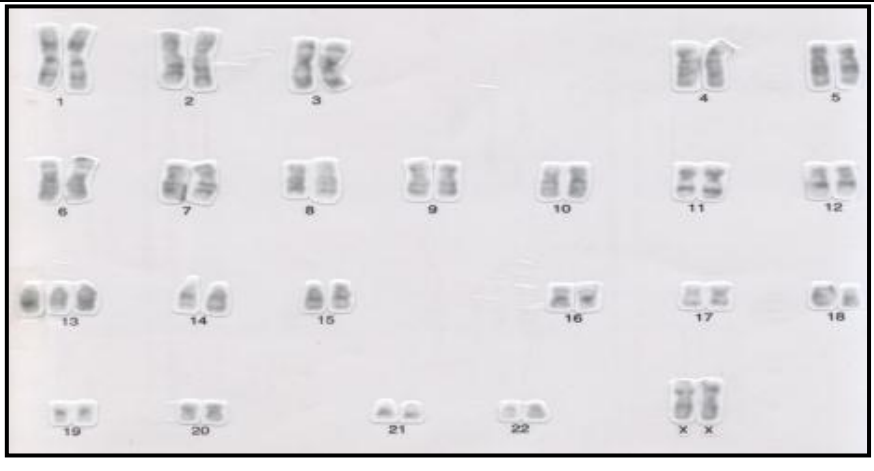
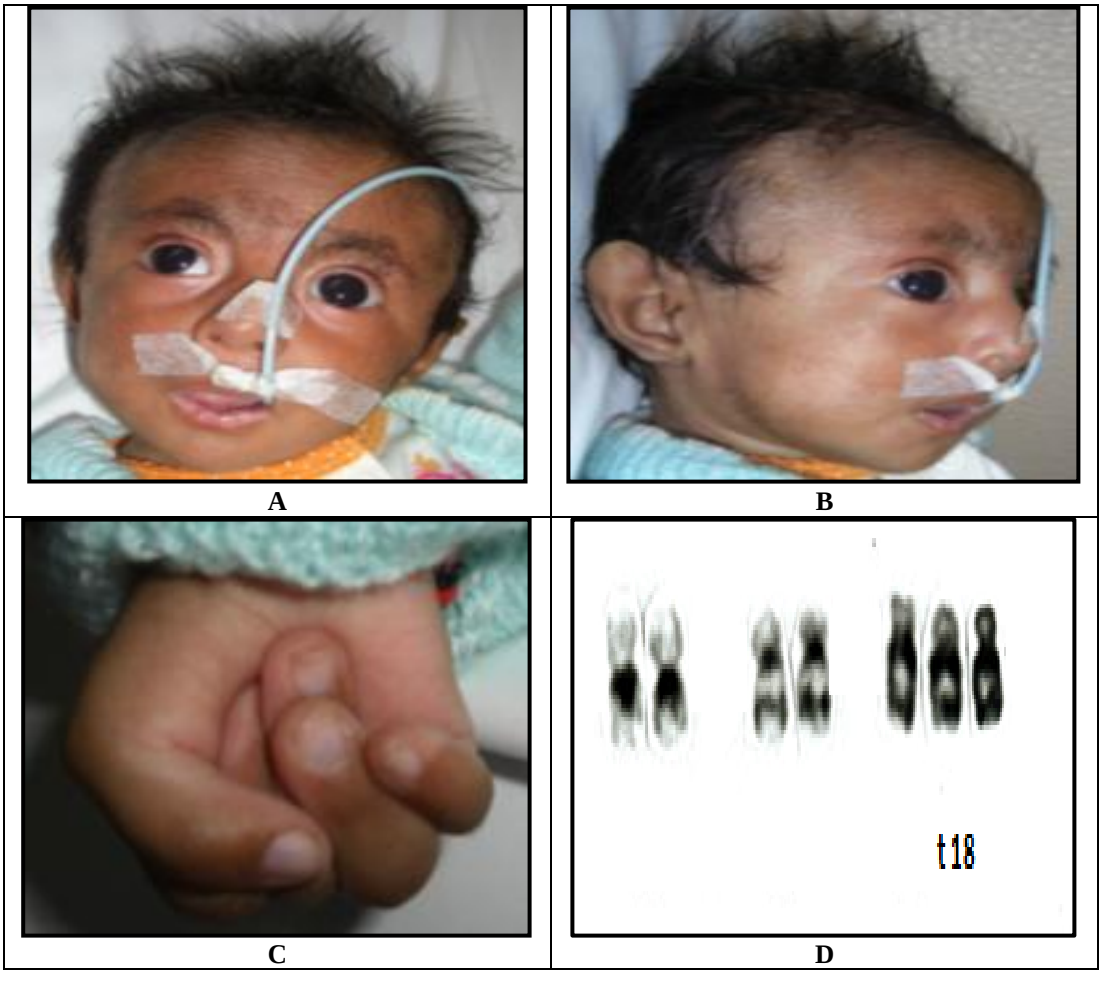


C

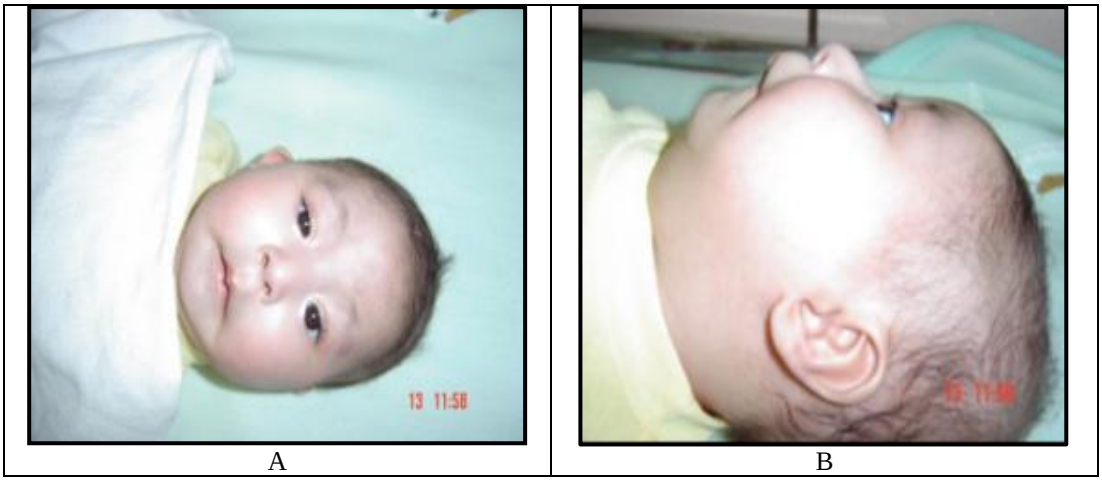
Figure 12



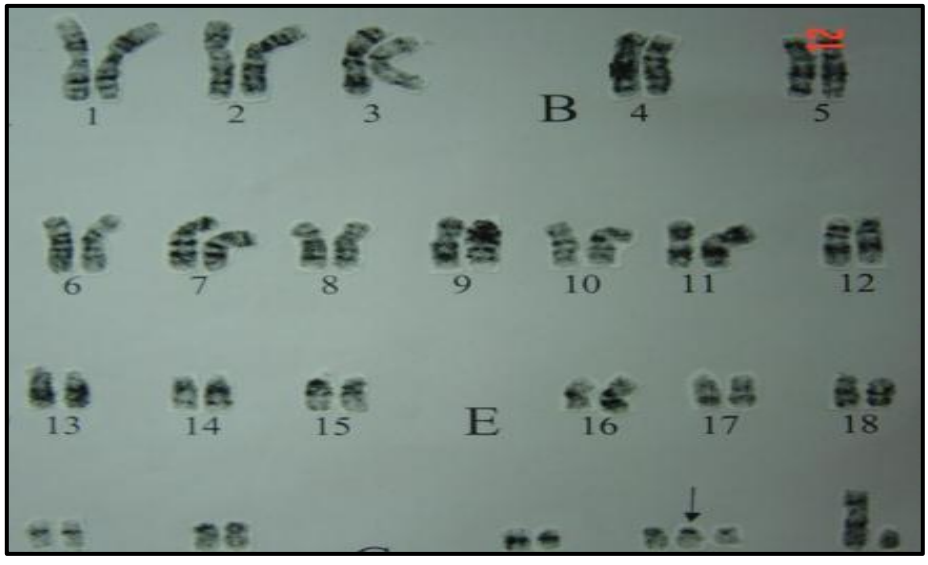
A **B**

C **D**

Figure 13

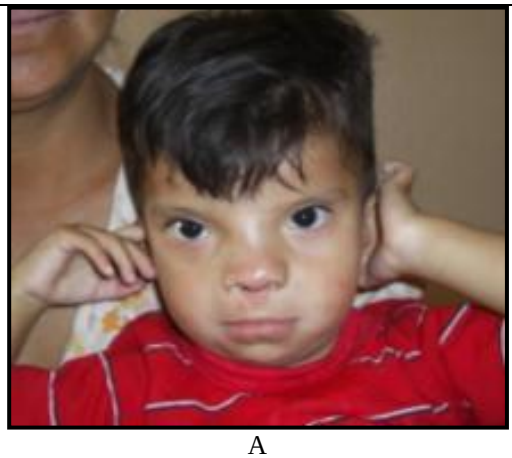


A B



C

Figure 14



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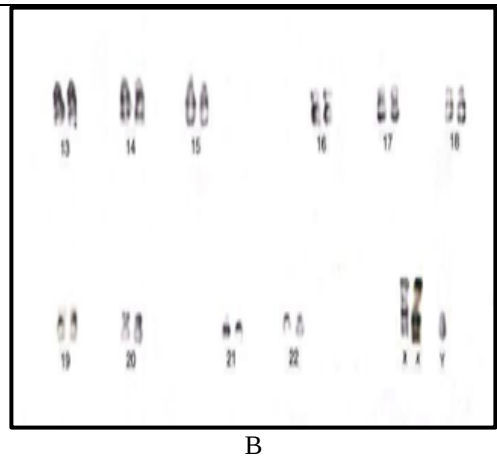

B

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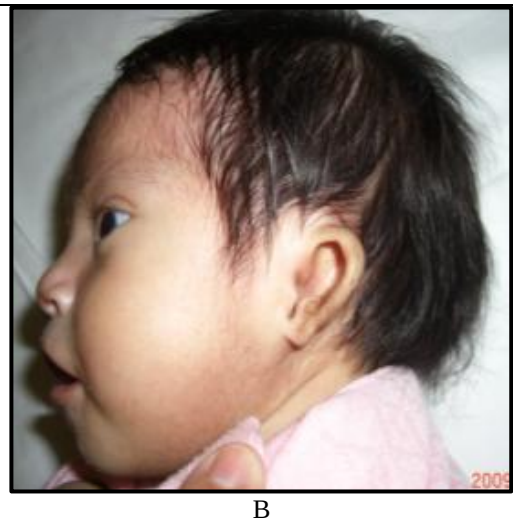

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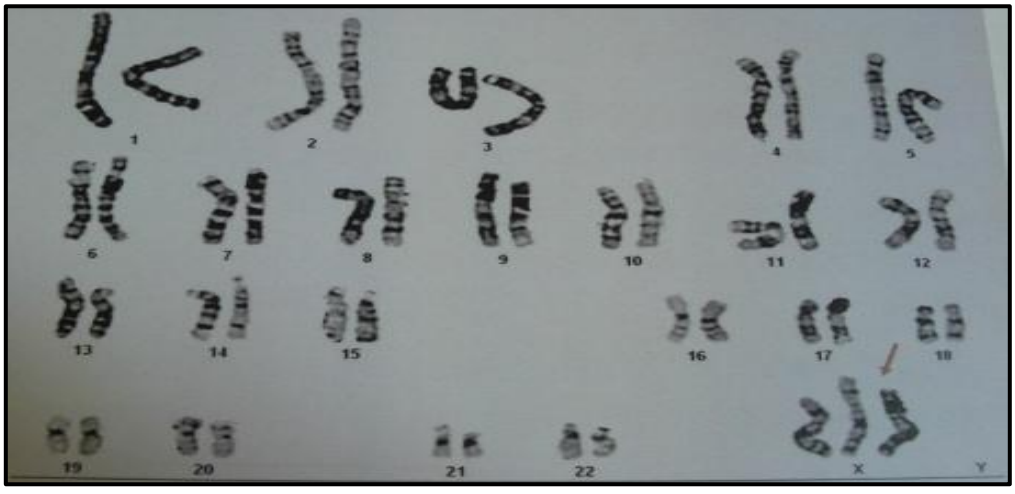

C

Figure 15

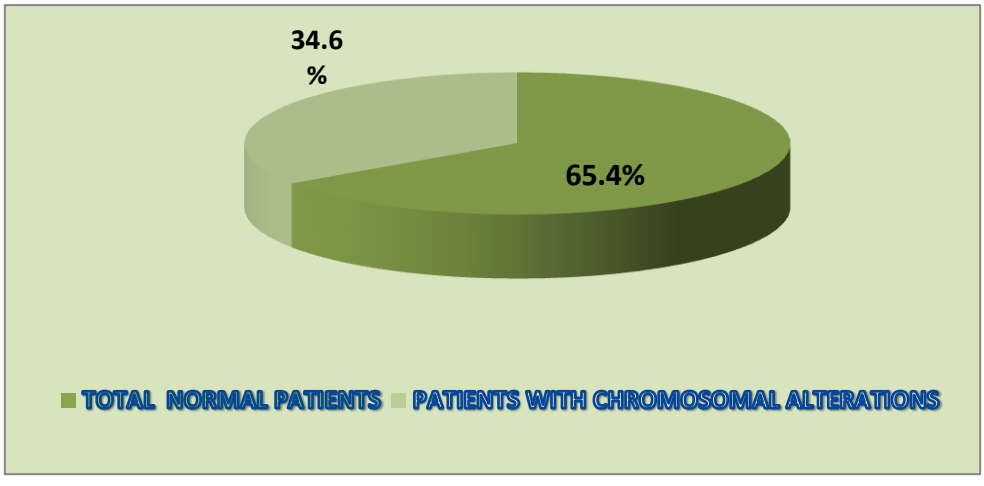

Figure 16

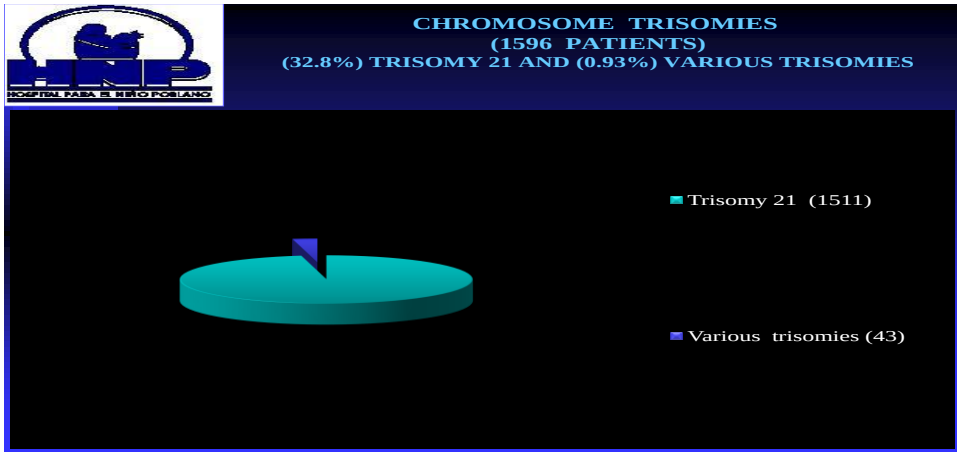

Figure 17

Table-1.

Chromosome aberration patients	**(%)**
1. Trisomies	1553
Chromosome aberrations	(34.6%) 1596
Total Trisomies	(33.6%) 1553
A-Trisomy 21	(32.8%) 1511
B-Various Trisomies:	(0.93%) 43
Total (karyotype studies in 19 years)	(100%) 4617
Total normal karyotypes	(65.4%) 3021
Total chromosome aberrations	(34.6%) 1596