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CROMOSOME 4 DELETIONS AND TRANSLOCATIONS AMONG 4617 CARIOTYPE STUDIES AT A THIRD LEVEL PEDIATRIC MEXICAN HOSPITAL. 4P-, 4Q-, T (1; 4), T (3; 4), SIX CASES REPORT

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ABSTRACT

Chromosome aberrations are considered changes in the chromosome number or structure. The etiology factor is due to gametogenesis inborn error (meiosis) or during the zygote first cellular divisions. It might occurs during metaphase from the cellular cycle, where DNA loses are seen (clastogenic processes) due to DNA repair processes deficiency o total absence, among others. Six genetic patients associated to chromosome 4 aberration were analyzed; three Wolf-Hirschhorn

syndrome patients, a deletion of long arm 4 chromosome and two 1;4 and 3;4 chromosome translocations among 4617 Karyotype studies performed during 19 years period of time (from 1992 to 2011) at a Pediatric Hospital in Mexico.

These chromosome changes are classified as structural alterations where these six patients from different families were chosen to evaluate their clinical characteristics, medical or surgical treatments according to their different genetic aberration.

Key Word: Chromosome, Translocation, Deletion, Chromosome aberration, Structural changes, Karyotype.

INTRODUCTION

Human beings have 46 chromosomes in each cell, divided into 23 pairs. Where two copies of chromosome 4, should have. Chromosome 4 spans more than 191 million DNA base pairs and represents more than 6 percent of the total DNA in cells. Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 4 aproximatelly contains between 1,300 and 1,600 genes among the estimated 20,000 to 25,000 total genes in the human genome

Chromosome 4 was chosen in this study since it is known that changes in the number or structure of chromosome 4 might have clinical effects including delayed growth and development, intellectual disability, distinctive facial features, heart defects among others.

It is therefore important know that 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 and Reeve (2000). Pereira *et al.* (1997). The word chromosome comes from the Greek (chroma, color) and (soma, body) due to their property of being strongly stained by particular dyes. 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 10,000,000,00 Paux *et al.* (2008) nucleotides in a long chain. Normally, eukaryotic cells (cells with nuclei) White MJD. (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; for example, mitochondria in most eukaryotes and chloroplasts in plants have their own small chromosomes.

In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure known as chromatin. This allows the entire DNA molecules to fit into the cell nucleus. The structure of chromosomes and chromatin varies through the cell cycle. Chromosomes are the essential unit for

cellular division and must have replication, division, and passed successfully to their daughter cells so as to ensure the genetic diversity and survival of their progeny. Chromosomes may exist as either duplicated or unduplicated. Unduplicated chromosomes are single linear strands, whereas duplicated chromosomes (copied during synthesis phase) contain two copies joined by a centromere. 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, (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 of cancer.

Human's chromosomes are divided into two known types; autosomes, and sex chromosomes and 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 (22 pairs of autosomes and one pair of sex chromosomes), giving a total of 46 per cell. In addition to these, human cells have many hundreds of copies of the mitochondrial genome. The 23 human chromosome during prometaphase in fibroblast cells.

Asexually reproducing species have one set of chromosomes, which are the same in all body cells. However, asexual species can be either haploid or diploid. Sexually reproducing species have somatic cells (body cells), which are diploid [2n] having two sets of chromosomes, one from the mother and one from the father. Gametes, reproductive cells, are haploid [n]: They have one set of chromosomes. Gametes are produced by meiosis of a diploid germ line cell (Kelman and Kelman, 2004). During meiosis, the matching chromosomes of father and mother can exchange small parts of themselves (crossover), and thus create new chromosomes that are not inherited solely from either parent. When a male and a female gamete is produced (fertilization), a new diploid organism is then made.

Some animal and plant species are polyploid [Xn]: They have more than two sets of homologous chromosomes. Plants important in agriculture such as tobacco or wheat are often polyploid, compared to their ancestral species. Wheat has a haploid number of seven chromosomes, still seen in some cultivars as well as the wild progenitors. The more-common pasta and bread wheats are polyploid, having 28 (tetraploid) and 42 (hexaploid) chromosomes, compared to the 14 (diploid) chromosomes in the wild wheat (Sakamura, 1918). Therefore, the karyotype is the characteristic chromosome complement of eukaryote organisms. (White MJD., 1973) the preparation and study of karyotypes is part of a science called cytogenetics.

MATERIALS AND METHODS

Among 4617 karyotypes performed at Hospital Para el Niño Poblano, (Aparicio RJM. *et al*., 2011), only six patients had 4 chromosome aberrations; Wolf-Hirshornn syndrome (three patients), deletion of chromosome 4 long arm (one patient) and chromosome 4 translocations 1;4 and 3;4 (two patients), in a 19 years period of time. Chromosomal studies (karyotypes) where performed for all patients in this study by using GTG banding. three male and female Wolf-Hirshornn pediatric patients Figures 1 A, 2 A and 3 A with the same genetic diseases were analyzed, same as the male and female translocated patients Figures 5 A and 6 A and the long arm 4 chromosome deletion patient Figure 4 A.

Replication and transcription of DNA is highly standardized in eukaryotes, confirmed with the patient's karyotype, which showed not variability. There was no significant variation between the patients in this study, in chromosome deletions and in detailed organization, reported variation in karyotype occurred according to the technique of karyotyping Figures 1 B, 2 B, 3 B, 4 B, 5 B, and 6 B. 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.

DISCUSION

It is already known that chromosome 4 contains between 1,300 and 1,600 genes. These genes perform a variety of different roles in the body and control cell proliferation. Therefore, changes in chromosome 4 have been associated to human cancer. These genetic changes are somatic, which means they are acquired during the patient´s life and might be only in certain cells. For example, rearrangements (translocations) of genetic material between chromosome 4 and several other chromosomes have been associated with leukemias, which are cancers of blood-forming cells or solid tumors as the patient in this study with 1;4 translocation Figure 5 A.

A specific translocation involving chromosome 4 and chromosome 14 is commonly found in multiple myeloma, which is a cancer that starts in cells of the bone marrow. The translocation, t(4;14)(p16;q32), abnormally fuses the *WHSC1* gene on chromosome 4 with part of another gene on chromosome 14. The fusion of these genes activates *WHSC1*, which appears to promote the uncontrolled growth and division of cancer cells, which should be considered an important chromosome test for patients with cancer family background.

Chromosomal mutations are considered then, 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 among affected families. Deletion of 4 chromosomes long or short

arm, such as Wolf-Hirshornn syndromes, considered a rare chromosomal event if compared to trisomy 21 observed in here with 1511 patients, Table 1 and Figure 6. Investigation into the human karyotype took many years to settle 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. (Painter, 1922) doubted whether the diploid number of man was 46 or 48. (Painter, 1923), (Tjio and Levan, 1956). (Ford and Hamerton, 1956). Considering the techniques of (Von, 1912) and (Painter, 1922). (Hsu, 1979) showed in chimpanzees have 48 chromosomes.

Some chromosome abnormalities do not cause disease in carriers, such as translocations, chromosomal inversions nor deletions as the patients in this study, although they may lead to a higher chance of birthing a child with a chromosome disorder as was found in this study Table 1 Figure 4. Among the studies population, male and female pediatric patients with different genetic diseases were evaluated at the department of genetics.

Chromosome deletions in this study were analyzed at chromosomes 4 among 4617 karyotypes performed from 1992 to 2011. 34.6% (1596 patients) Table 1 Figure 7 showed chromosomal aberrations. Where invertions, duplications, translocations, monosomies, chimeras, deletions and ring formations were analyzed in 43 patients (0.93%), (not including trisomies) Table 1 and Figure 8. Only 0.33% (4 patients) have chromosome specific deletions same as (0.17%) 2 patients with translocation at chromosome 4, which is considered a rare mutation if compared Table 1 and Figure 8 to 33.6% (1553 patients) with chromosome trisomy where 32.8% (1511 patients) diagnosed as Down syndrome (trisomy 21) Table 1 Figure 9.

Chromosome 4 deletions or translocation were then analyzed. Figures 1 A and 2A show a male and female patients diagnosed as Wolf-Hirshhorn syndrome, with typical phenotype, facial dimorphism like "greek helmet": prominent glabella, ocular hypertelorism, epicanthic folds and marked broad-beaked nose, microphtalmia and mental retardation with a loss of genetic material at chromosome 4 short arm Figures 1 B, 2B and 3B. however the male patient had major malformations including cleft lip and palate, facial asymmetry, and renal alterations; with nephrological assessment data meets prerenal acute renal failure and metabolic acidosis secondary, presenting BUN 53 mg / dL, urea 13 mg / dL and creatinine 1.0 mg / dL with controls at 48 hrs with BUN 39 mg / dL and creatinine of 1.2 mg / dL. By renal ultrasound study, left kidney was reported with hypoechoic images about 9 and 11 mm in length, without further apparently systemic involvement, determining renal cysts. The patient is expected to gradually improve renal function. Therefore he will be evaluated for control and monitoring. All patients were a de novo mutation with deletion of gene WHSC1 and other linked contiguous genes (Aparicio RJM. *et al.*, 1997), (Aviña *et al.*, 2008).

Wolf-Hirschhorn syndrome is then caused by a deletion of genetic material near the end of the short (p) arm of chromosome 4 at a position described as 4p16.3. The signs and symptoms of this condition are related to the loss of multiple genes from this part of the chromosome. The size of the deletion varies among affected individuals; studies suggest that larger deletions tend to result in more severe intellectual disability and physical abnormalities than smaller deletions.

The region of chromosome 4 that is deleted most often in people with Wolf-Hirschhorn syndrome is known as Wolf-Hirschhorn syndrome critical region 2 (WHSCR-2). This region contains several genes, some of which are known to play important roles in early development. A loss of these genes leads to developmental delay, a distinctive facial appearance, as mentioned before and other characteristic clinical features of the condition. Scientists are working to identify additional genes at the end of the short arm of chromosome 4 that contribute to the characteristic features of Wolf-Hirschhorn syndrome.

A four female patient showed a deletion of chromosome 4 long arm Figure 4 A and 4 B, which is different from the wolf hirshornn syndrome mentioned before. There is not any clinical malformation. However the patient was evaluated by nephrology and audiology;

She was evaluated at nephrology to analyze renal malformation, with Wolf-Hirschhorn syndrome diagnosis. By nephrologic evaluation was determined kidney failure by presenting renal BUN 33 mg / dL, Urea 7112 mg / dL, creatinine 0.7 mg / dL, with pH 6.0 urinalysis, urine specific gravity 1.025, protein 340 mg / dL, and leukocytes 13 per field. Renal ultrasound showed cortex-medulla loss and cystourethrography with important postvoid residual urine. It is not necessary replacement therapy at the moment.

Audiology also evaluated this patient due to bilateral hearing loss, failure to phonemic discrimination voice normal intensity, lack of response to sounds and language development alterations, at the level of babbling, of insidious onset of steady evolution. It is important to mention the patient antecedents, where a sister presented bilateral congenital hearing loss with hearing aid use bilaterally with adequate gain and comfort, denied debris. Psychomotor development; support head at 7 months, sitting 1 year, 1 year 2 months crawling, standing 1 year 4 months, 1 year 6 months up, toilet training at 2 years 6 months. Physical examination; Conscious, quiet, cooperative, with profound hearing loss hearing behavior, high-pitched voice, clear timbre, intensity adequate level language babbling, understanding age-adecauda sign support head without pathological data without exostosis or subsidence, normal pupils, with normal ears canals permeable intact tympanic membranes unaltered rhinoscopy functional, with the presence of hyaline mucus bridges, oral cavity proper seal lip, palate full, adequate mobility of the soft palate, with presence of slurred tongue movements, uvula central mobile. Audiometric study is performed, obtaining irregular profile curves of bilateral profound hearing loss, sensory type, Tympanometry curves with adequate compliance

and pressure for age (Jerger type A bilateral), ipsilateral stapedial reflexes absent bilaterally maximum intensities, otoacoustic emissions without distortion product reproducibility bilaterally, auditory evoked potentials in brainstem response wave V at 105 dB bilaterally, testing is performed auditory evoked potentials stable, which show an audiogram support profound bilateral hearing loss In relation to chromosomal translocations; a male patient with several oral tumors, diagnosed by oral hystopatological studies as Cementoma Gigantiforme (and been evaluated every 6 months by oncology to avoid cellular metastasis) had unexpected balance translocation 46,XY,t(1;4) (q11q11). Figure 5 A and B, (Aparicio RJM. *et al.*, 2002; Aparicio RJM. *et al.*, 2006; Aviña JF. *et al.*, 2008)This case is different from a female patient diagnosed as Opitz G/B.B.B. syndrome Figure 6 A and B. with hypertelorism, unilateral cleft lip and palate and facial asymmetry had unexpected translocation between long arms of chromosomes 3 and 4, 46XX t(3q;4q). (Aparicio-Rodríguez *et al.*, 2011).

Some mutations are neutral and have little or no effect. However, we decided to analyze these specific chromosomal aberrations at chromosomes 4 due to craniofacial malformations, congenital hearing loss, mental retardation and cell proliferation which change the patient's life and it has a great role in evolution. Furthermore, 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 were gene structures are important to be analyzed.

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 and Figure 5. The five patients presented in this study were all "the novo". However, genetic counseling should be offered, if necessarily for carrier families for these chromosome rearrangements. The loss of DNA from chromosomes deletions 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 earlier, which will contribute for a better diagnosis an early treatment, a better genetic counseling and a better quality of life for the patient and his (her) family.

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FIGURE LEYENDS

Figure-1. A. Male patient diagnosed as Wolf-Hirshhorn syndrome, with typical phenotype, facial dysmorphism like "greek helmet": prominent glabela, ocular hypertelorism, epicanthal folds and marked broad-beaked nose and microphtalmia karyotypes revealed loss of genetic material at chromosome 4 short arm; **B**. A case of probable de novo mutation with deletion of gene WHSC1 and other linked contiguous genes located on the short arm.

Figure -2. A. Female patient diagnosed as Wolf-Hirshhorn syndrome, with typical phenotype, facial dysmorphism like "greek helmet": prominent glabela, ocular hypertelorism, epicanthal folds and marked broad-beaked nose and microphtalmia karyotypes revealed loss of genetic material at chromosome 4 short arm; with a chromosome formula, 46 XX del (4) (p16).

Figure- 3. A. A male patient with renal, generalized dysplasia, microcefaly bilateral cleft lip palate, with ambiguous genitalia. **B.The** karyotype revealed a chromosome deletion of the short arm of chromosome 4 (46, XY,del (4) (p15).

Figure -4 .A. A female patient was diagnosed with bilateral hypoacusia, being a patient for surgical cochlear restoration, with minor dimorphic symptoms and low mental retardation. **B.** karyotype revealed loss of genetic material at chromosome 4 long arm 46XX, del (4) (q25 q27).

Figure -5. A. Male patient diagnosed hystopatology as Cementoma Gigantiforme. **B.** Karyotype shows a balance translocation 46,XY,t(1;4)(q11q11).

Figure- 6. A. Female patient diagnosed as OpitzG/B.B.B. syndrome, with hypertelorism, unilateral cleft lip and palate and cranio-facial dimorphism **B.** Karyotype shows a chromosomal translocation between long arms of chromosomes 3 and 4, 46XX t(3q;4q).

Figure -7. 4617 karyotypes were performed from 1992 to 2011, where 1596 patients (34.6%) showed chromosomal alterations.

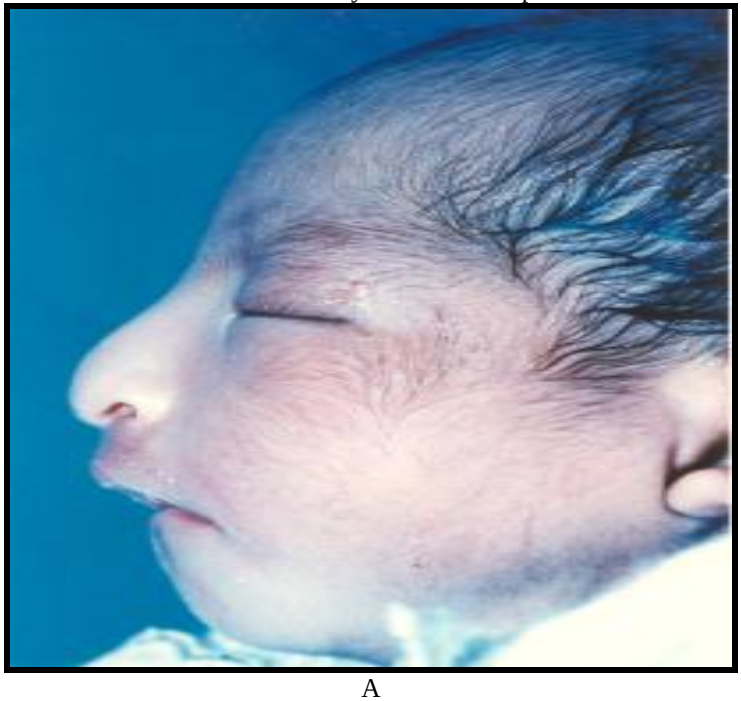
Figure- 8. Chromosomal alterations in 19 years, shows 1596 patients (34.6%) with different aberrations. From nine deletions, four deletions at chromosome 4 were analyzed and from eleven translocations, two specific translocation including chromosome 4 were analyzed: 1; 4 and 3; 4.

Figure -9. From all chromosomal trisomies 1553 (33.6%), It can be seen that 1511 (32.7%) were different kind of trisomy 21.

Figure- 10. it is a diagram called ideogram as a standard representation for chromosome 4. Ideograms show a chromosome's relative size and its banding pattern. A banding pattern is the characteristic pattern of dark and light bands that appears when a chromosome is stained with a chemical solution and then viewed under a microscope. These bands are used to describe the location of genes on each chromosome. **U.S. National Library of Medicine®**. http://ghr.nlm.nih.gov/chromosome/4.

TABLE

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



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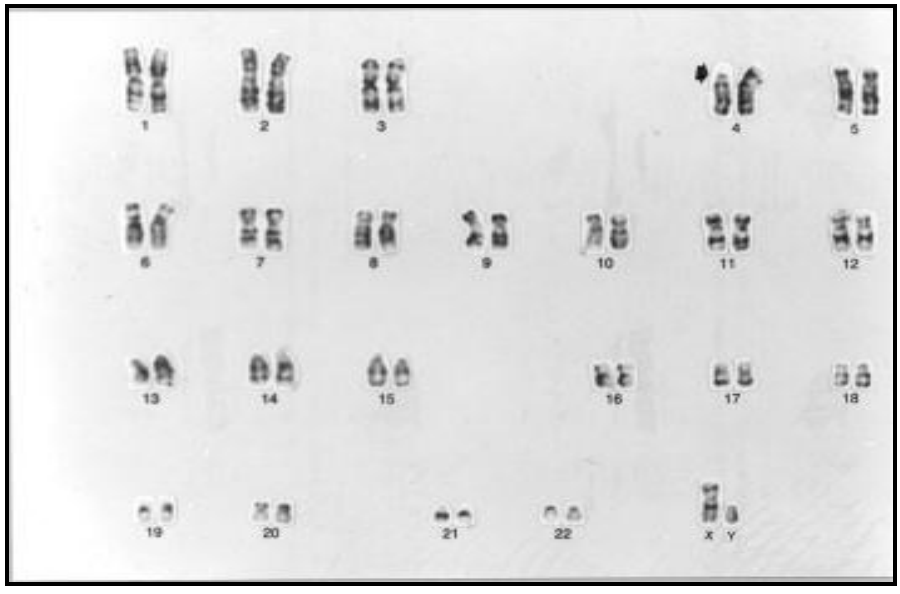

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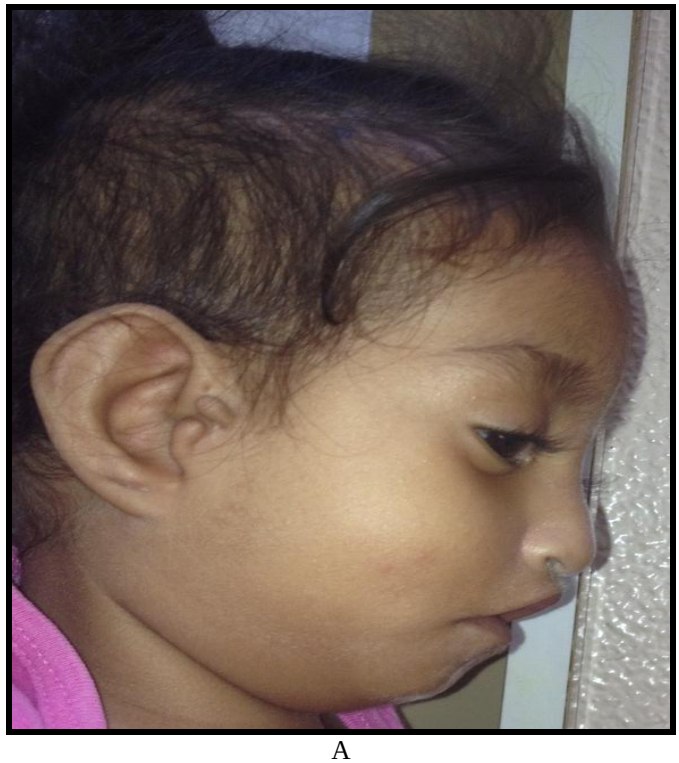

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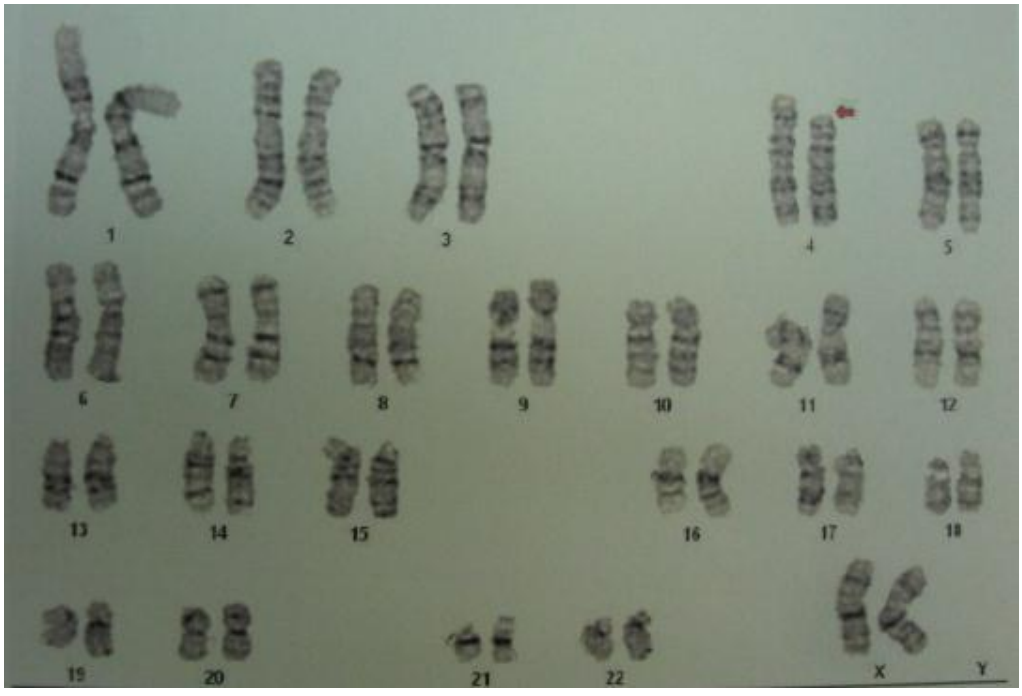

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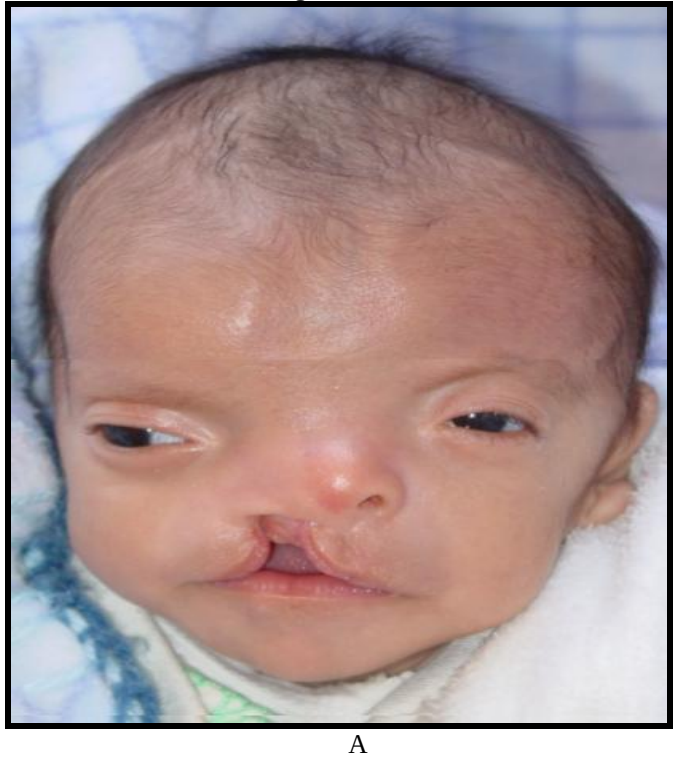

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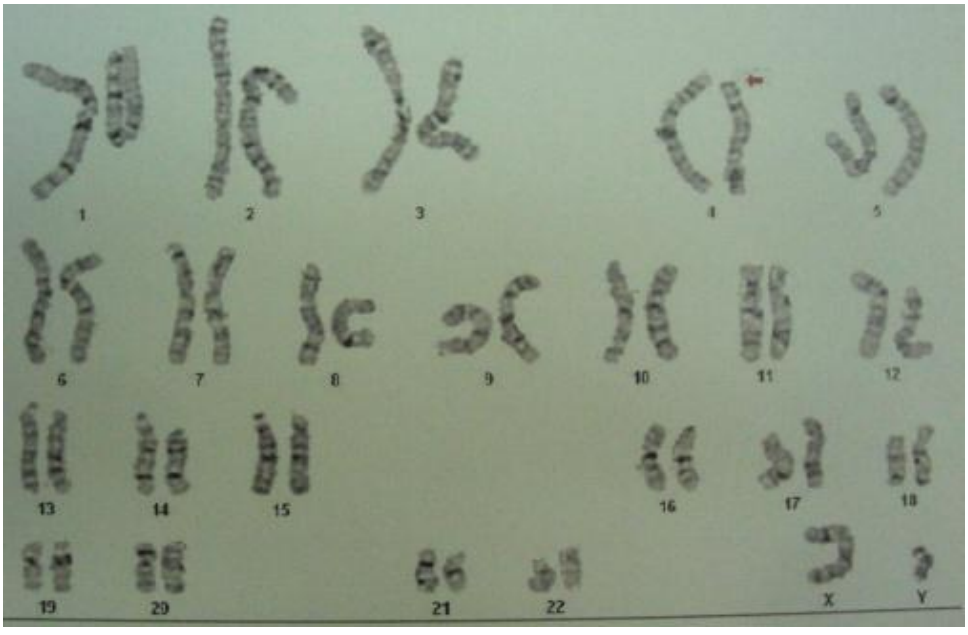

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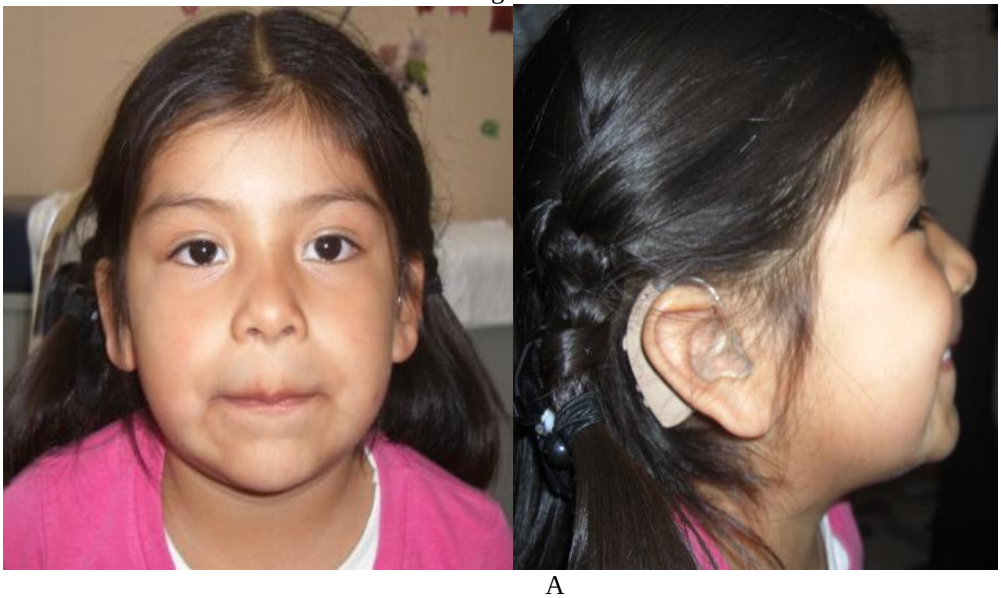

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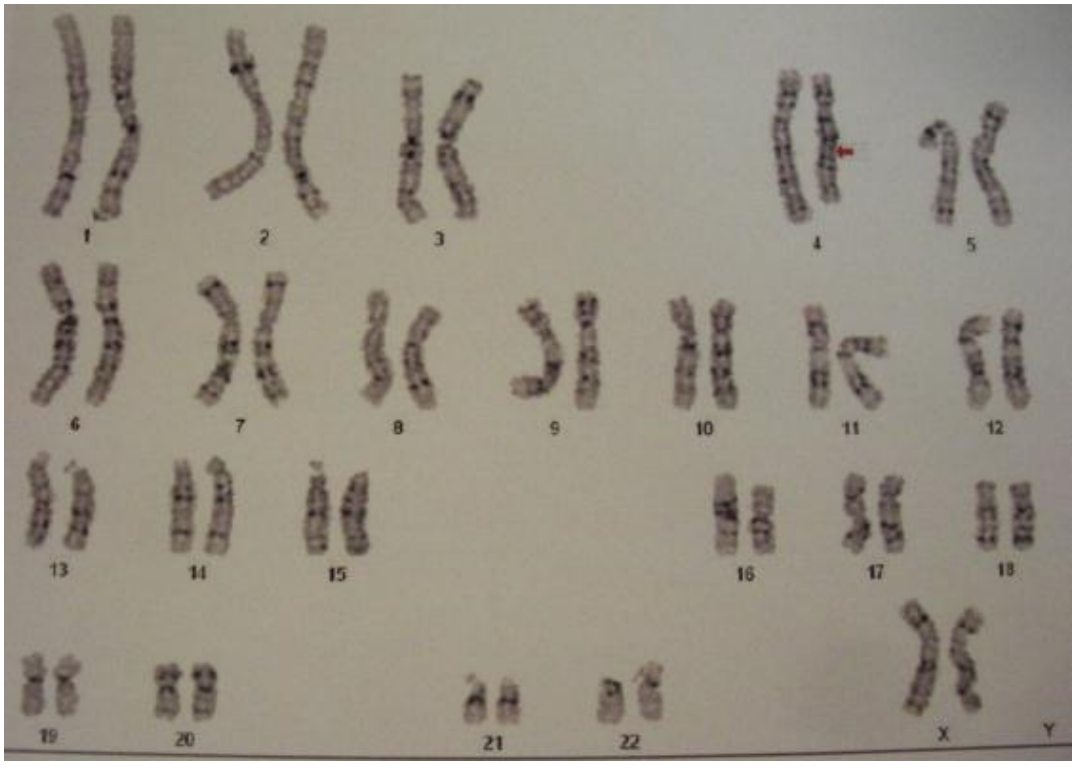

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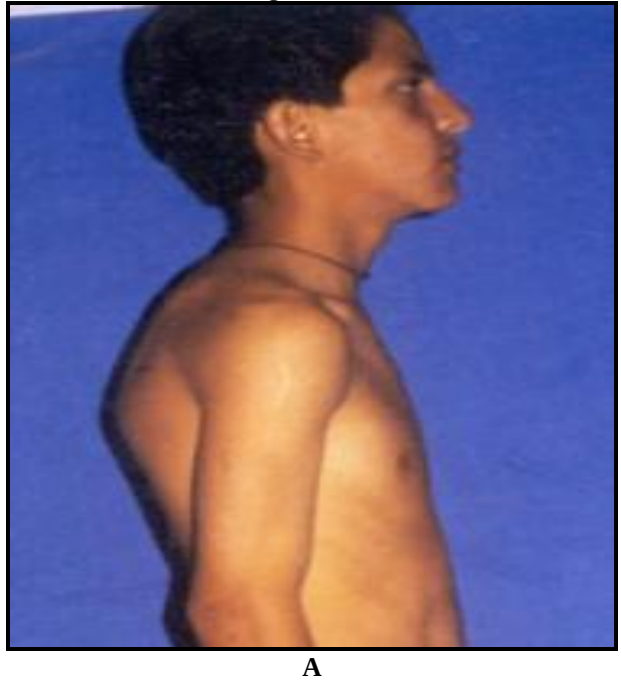

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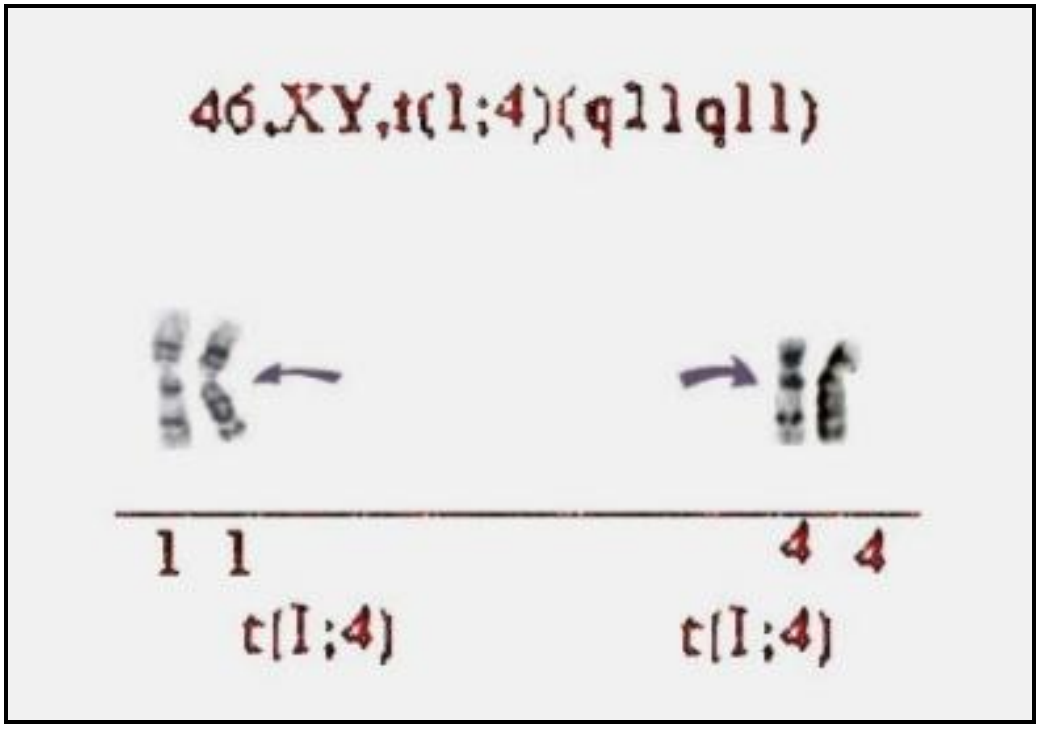

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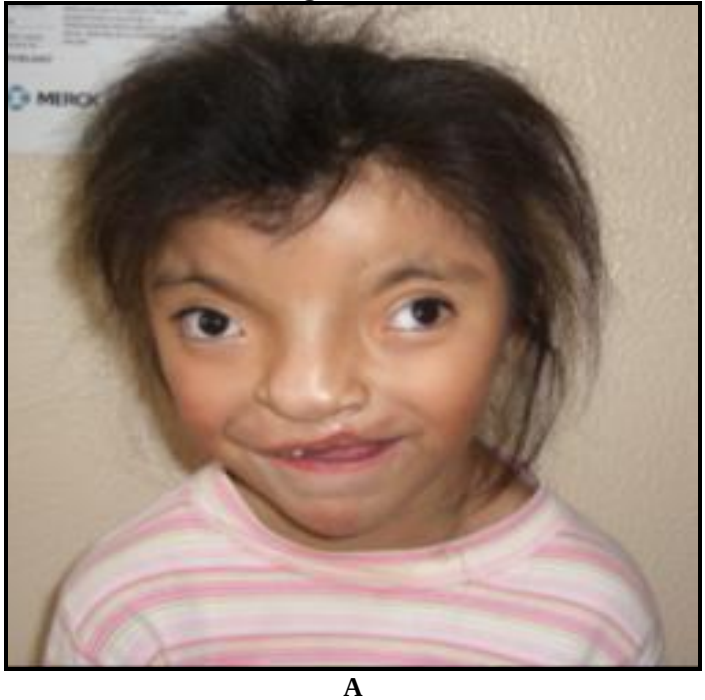

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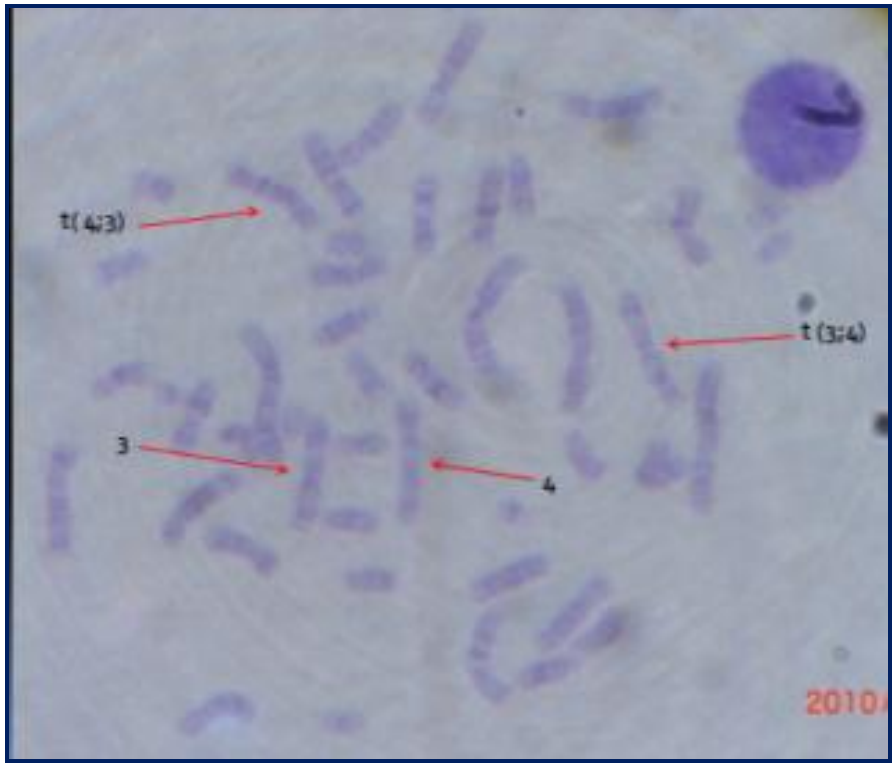

Figure-6. B

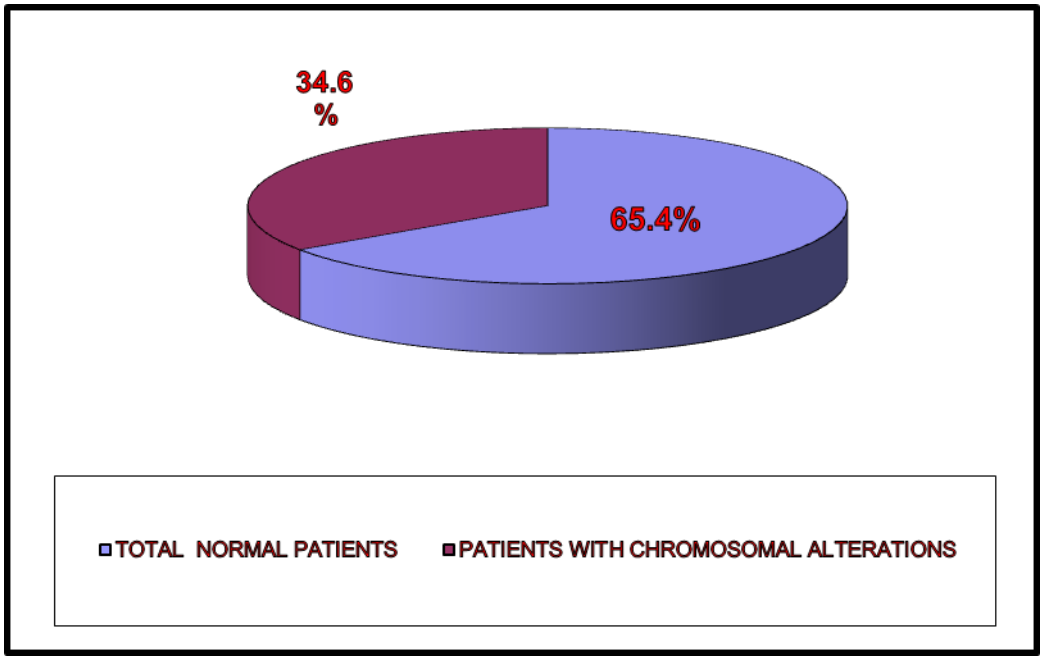

Figure-7.

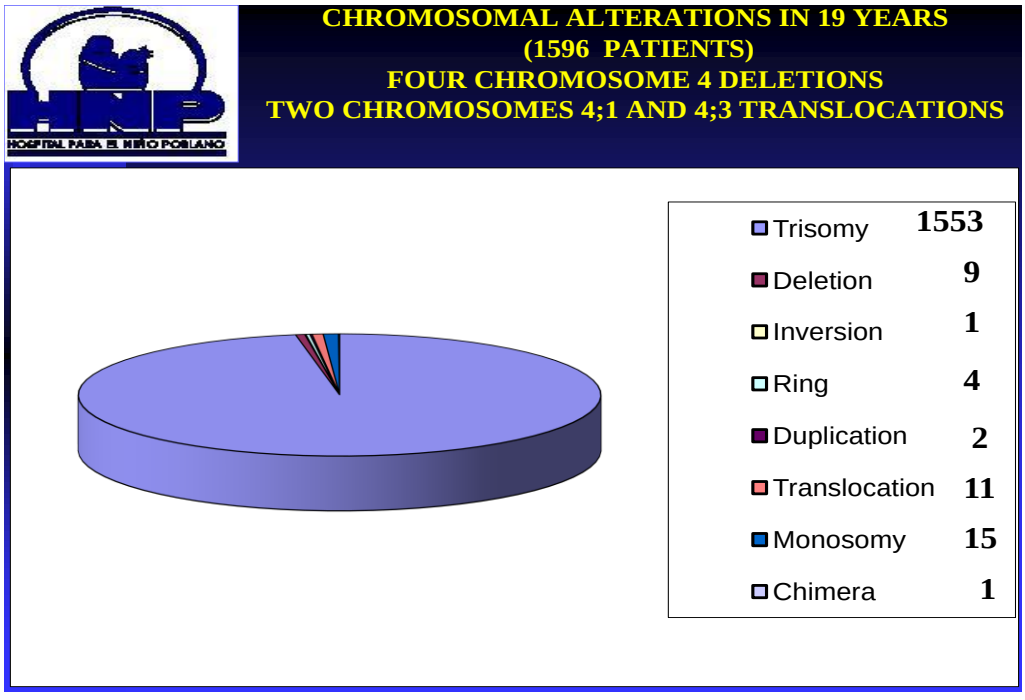

Figure-8.

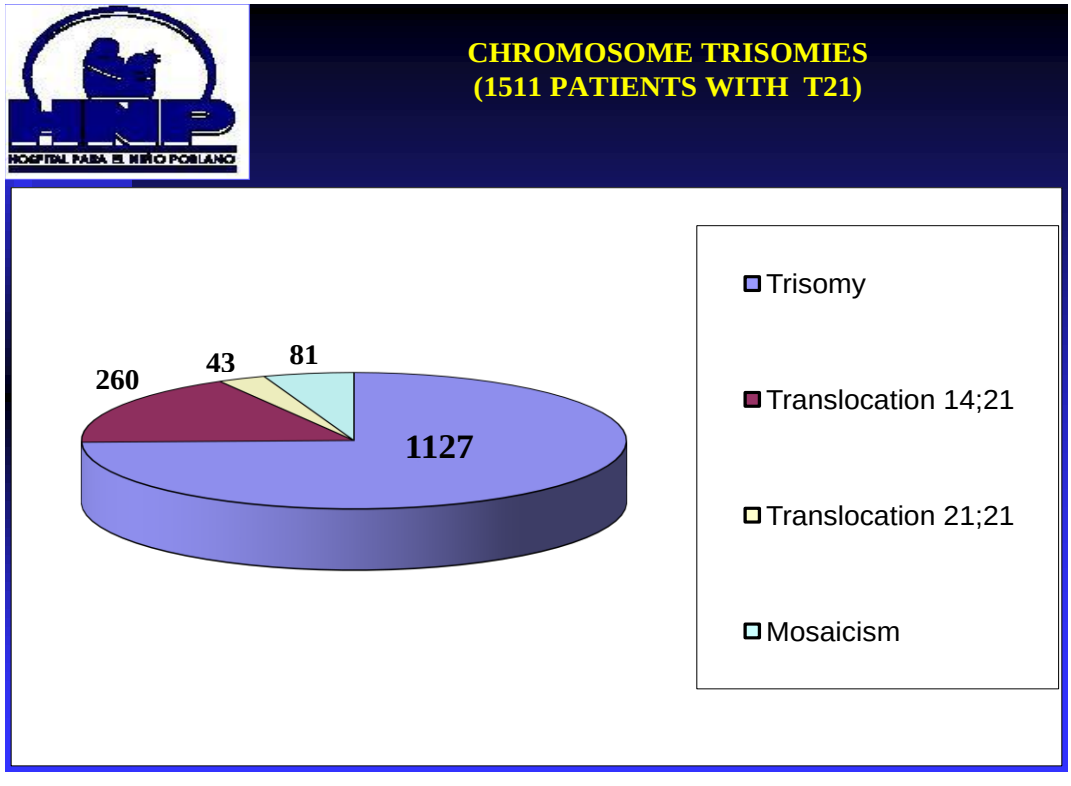

Figure-9.

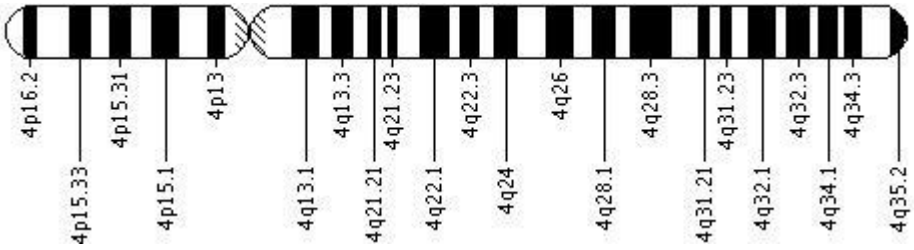

Figure-10.

Table- 1.

Chromosomal aberration		(%) patients	
1. Trisomy		1553	
2.Deletions (chromosome 4)		***(0.33%)4***	
Other deletions (chromosomes 6, 7, 9 and 10)		***(0.41%)5***	
3. Invertion		1	
4. Ring			4
5. Duplication			2
6. Translocation (1;4 and 3;4)		***(0.17%)2***	
Other translocations (7,10, 21, 22, etc)		***(0.76%)9***	
7. Monosomy			15
8. Chimera			1
Chromosomal aberrations		(34.6%) 1596	
Total Trisomies		(33.6%) 1553	
A-Trisomy 21		(32.8%) 1511	
1. 1127	T		21
2. 260	T21;14		
3. 43	T21;21		
4. 81	Mosaicism		
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	