



## THE IMPORTANCE OF CLINICAL GENOTYPE IN PATIENTS WITH KLINEFELTER SYNDROME. A GENETIC DISORDER ASSOCIATED TO TAURODONTISM

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### ABSTRACT

*Taurodontism is a clinical condition found in the molar teeth of humans whereby the body of the tooth and pulp chamber is enlarged vertically at the expense of the roots. As a result, the floor of the pulp and the furcation of the tooth is moved apically down the root. It is due to the failure or late invagination of Hertwig's epithelial root sheath, which is responsible for root formation and shaping causing an apical shift of the root furcation. The constriction at the amelocemental junction is abnormally formed. Taurodontism is most commonly found in permanent dentition although the term is traditionally applied to molar teeth. It has been reported that taurodontism follows an autosomal dominant type of inheritance. Meanwhile, Mutations or chromosome aberrations are considered alterations in the chromosome number or structure. They are mainly considered due to gametogenesis inborn error at meiosis, where DNA losses are seen due to DNA repair processes deficiency. Some chromosome studies were performed were 34.6% (1596 patients) showed different chromosome alterations. Among the studies population, male and female pediatric patients with sexual genetic diseases were chosen. These chromosome changes are classified as numeric or structural alterations, respectively. A wide variety of pediatric patients with genetic diseases chromosome alterations are described in this study analyzing their clinical characteristics, medical, surgical treatments and their clinical evolution according to the genetic disease.*

**Keywords:** Chromosomes, Syndromes, Inheritance, Mutations, Numerical and structural changes, Karyotype, taurodontism and DNA.

## Contribution/ Originality

This study contributes in the existing literature the relation of a well known genetic syndrome as klinefelter, a sexual chromosome alteration (47, XXY) and pediatric patients with taurodontism, an oral situation with teeth roots that grow crookedly with very huge teeth, likened to a bull.

## 1. INTRODUCTION

Taurodontism is found to be associated to amelogenesis imperfecta, ectodermal dysplasia, some chromosomal aberrations and tricho-dento-osseous syndrome. The term means "bull like" teeth derived from similarity of these teeth to those of ungulate or cud-chewing animals. According to Shaw [1].

These can be classified as hypotaurodont, hypertaurodont and mesotaurodont. Kahn Michael [2]; Richard [3].

**Taurodontism** is classified into three main types, namely:

- Hypotyrodont – It exhibits mild traits of Taurodontism.
- Mesotyrodont – It is marked by moderate characteristics of the syndrome.
- Hypertyrodont – It is characterized by severe traits of the disorder.

The main symptoms in Children suffering from this condition have teeth roots that grow crookedly with very huge teeth, likened to a bull. In an X-ray machine, its roots look like the horns of a bull. The condition is exhibited by vertically enlarged pulp chamber and tooth that cause complications in the root area of the tooth. This results in an apically downward sloping floor of the pulp and furcating of the tooth.

### 1.2. Chromosome Alterations

Mutations and chromosome alterations are considered to be alterations in the number and structure and secondary to errors of the birth. In order to investigate chromosome alterations a study was carried out Figure 1.

The 34.6% (1596 patients) of the studied patients, showed different chromosome alterations. Clinical features as dental, nutritional, medical or surgical procedures are analyzed and their evolution according to the genetic condition evaluating its relationship in the health area. Chromosomes are found attached to proteins, which serve as packages of DNA and controls its function [4]; [5]; [6]. The chromosomes are different according to each variety of organisms. The DNA molecule may be circular or linear, and consist of 100,000 to 10,000,000,000 [7]. Nucleotides in a long chain. Eucariotes [8] cells usually have linear chromosomes and cells procariotes [9]; [10]; [11] it has small groups of circular chromosomes. In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure called chromatin. This allows the complete DNA molecule is found inside the nucleus. Chromosome recombination plays a vital role in the evolution and genetic diversity. If these structures initiated through processes known

as chromosome instability and mutation, cells may die or avoid the onset of apoptosis, initiating a risk for the onset of cancer.

Human chromosomes are divided into two types; autosomes and sex chromosomes where taurodontism has been reported.

## 2. DISCUSSION

Taurodontism is found in association with amelogenesis imperfecta, ectodermal dysplasia and tricho-dento-osseous syndrome. The term means "bull like" teeth derived from similarity of these teeth to those of ungulate or cud-chewing animals. According to Shaw these can be classified as hypotaurodont, hypertaurodont and mesotaurodont [2]; [3].

According to Mangion taurodontism may be:

- A retrograde character
- A primitive pattern
- Mendelian recessive character
- Atavistic feature
- A mutation

Taurodontism has also been reported in Klinefelter's syndrome, XXYY and Down's syndrome. A different chromosome aberrations are presented in this study where teeth involved are invariably molars, sometimes single and at the other times multiple teeth may be involved. The teeth themselves may look normal and do not have any particular anatomical character on clinical examination. On a dental radiograph, the involved tooth looks rectangular in shape without apical taper. The pulp chamber is extremely large and the furcations may be only a few millimeters long at times. Chromosome aberrations are disruptions in the normal chromosome structures and is considered a major cause of genetic human conditions, known as genetic disease that can have or not a pattern of inheritance, such as Down syndrome, considered as the most frequent chromosome Trisomy observed in this study, Table 1 y figure 2.

Table-1. Different chromosome alterations found in this study.

Chromosome Aberrations	(%) patients
1. Trisomy	1553
2. Deletions	9
3. Inversions	1
4. Rings	4
5. Duplications	2
6. Translocations	11
7. Monosomies	15
8. Chimeras	1
Chromosome Aberrations	(34.6%) 1596
Total of Trisomies	(33.6%) 1553
Trisomy 21	(32.8%) 1511
1. T21	1127
2. T21;14	260
3. T21;21	43
4. Mosaic	81
	<i>Continúe</i>

Various Trisomies	(0.90%) 42
Different Chromosome Aberrations:	(0.93%) 43
Total (karyotypes)	(100%) 5000
Total normal karyotypes	(65.4%) 3021
Total Chromosome Aberrations	(34.6%) 1596

Research on the human karyotype took many years [12]; [13] sex determination mechanism was not sure whether the diploid number of man was 46 or 48 and subsequently insisted on humans have a XX/XY [13]; [14] system. Taking into account the reported techniques [12]; [15] chromosome disorder were found in this study Table 1.

Patients as mentioned in Figure 1, showed different chromosome alterations 33.6% (1553) showed a chromosome Trisomy. Of these 33.6% of the population, trisomic, 32.8% (1511 patients) were diagnosed as Down syndrome (trisomy 21) Figure 2 and 0.90% have other Trisomy table 1. Similar to the rest of the chromosome aberrations 0.93% (43 patients) Table 1 y figure 1.

Several malformations of the central nervous system associated with changes in the structure were observed with regard to the sex chromosomes, Craniofacial, as it is the case of monosomy as Turner syndrome, chimera, polyploidy XXX and Klinefelter, among others. This study shows one of the patients, male diagnosed as syndrome of Opitz, et al. [16] hypertelorism and lip and cleft palate and craniofacial dimorphism.

However the karyotype reveals a duplication of the sex chromosomes X 46, XXY (Klinefelter's syndrome). Men with this syndrome are usually sterile and has a higher incidence of retardation and dyslexia. This patient is evaluated periodically by dentistry, maxillofacial surgery, endocrinology, nutriology and pediatric surgery.

On the other hand few oral alterations were observed, in a female patient diagnosed as syndrome of Turner, with wide neck and short stature. Their karyotype revealed only one chromosome X (45XO) Turner syndrome (X instead of XX). In Turner syndrome, female sexual characteristics are present but underdeveloped, unlike this patient, another female patient with small eyes, Craniofacial dimorphism with hypotelorism, turricefalia and hypoplasia associated had a sex chromosomes trisomy 47, XXX (triple X syndrome). The patient with XXX tends to be tall and thin. They have a higher incidence of dyslexia and it is more likely to have learning problems and bad nutrition.

This type of sex chromosomes alteration is important in medical areas as nutrition, stomatology, psychology also important in chromosome events such as the chimera chromosome where two different cells that there are lines 46, XX/46, XY in the same patient associated with ambiguous genitalia. In relation to this patient it has been discussed among a medical group, if the patient should keep their sexual identity as a male or female, since half the information of the sex chromosomes are XX and half XY. It is important to decide the future sexual behavior, psychological, physical function, and external and internal genital structure of the patient. A decision shall be taken by the multidisciplinary group of physicians [17].

Therefore, international associations and institutions such as the Institute de Vega offer information in relation to the human genome data. This Wilming, et al. [18] is information obtained from 2008 to 2011 and the structures of genes are presented in Table 2.

**Table-2.** (<http://www.ncbi.nlm.nih.gov/genome/seq/>) sequencing of the human genome has provided a lot of information about each of the chromosomes. This table contains statistics for the chromosomes, based on information about the human genome of the Sanger Institute in the annotation of vertebrate genome (VEGA) database [18].

<b>Chromosome</b>	<b>Genes</b>	<b>Total of bases</b>	<b>Secuence of bases</b>
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 (cromosoma sexual)	1,846	154,913,754	151,058 ,754
Y (cromosoma sexual)	454	57,741,652	25,121 ,652
Total	32,185	3,079,843,747	2,857,698,560

An abnormal number of chromosomes, euploidy, may be lethal [19]; [20]; [21]; [22] some chromosome alterations in this study are seen in table 1 and Figure 1. Genetic counseling can be provided in multidisciplinary form with the necessary knowledge, which is important for families carrying this type of chromosome rearrangements, including patients with taurodontism. The gain or loss of DNA from chromosomes can lead to a variety of other genetic diseases, as it is possible to be observed in this study. It could be important if chromosome aberrations could be diagnosed, not only in the practice of genetics but also nutrition, dentistry and pediatrics, providing to the patient an early management, which will contribute to an accurate diagnosis, early treatment and a better genetic counseling and a better quality of life for the patient and family. In this study different sexual chromosome disorders will be compared according to their different clinical manifestations.

### 3.1. Sexual Chromosomes

**Turner (45X0).** The Turner syndrome also known as: gonadal dysgenesis; monosomy X is a genetic disorder that occurs only in women. The cells of women typically have two X chromosomes, but only Turner syndrome have a chromosome X or part of an X chromosome. This causes different clinical features or signs, as it is low and the lack of development of ovaries and infertility consistent size. Taking into account the causes, incidence and risk factors, humans have 46 chromosomes containing all the genes and DNA as mentioned in previous studies. Two of these chromosomes, the sex chromosomes, determine the gender of a person. These female sex chromosomes are chromosomes X (XX), the opposite of the male X and Y (XY). These sex chromosomes helps the person develop fertility and sexual characteristics of their gender. In Turner syndrome, the girl does not have the normal pair of two complete X chromosomes. It is more common that the female patient has only one X chromosome in their cells figure 3 B. Some affected patients by this syndrome have two X chromosomes, but one of them is incomplete. In other cases, there is the process of the cellular mosaicism where some cells are normal, however others have only one X chromosome. Turner syndrome occurs in nearly 1 per every 2,000 newborns, giving very specific clinical features as you can see in figure 3 A.

Symptomatology in female patients with turner syndrome affects; size, with some degree of malnutrition, wide neck, blepharophimosis, flat chest, broad shaped "shield", delay in the development of the mammary glands and sparse pubic hair. Infertility, amenorrhea, lack of normal moisture in the vagina. Taking into account the exams and tests, it can be diagnosed at the time of the birth or during childhood, puberty or adulthood and also it can be diagnosed by amniocentesis before birth performing a karyotype as part of a prenatal exam. Infants with Turner Syndrome often have swelling of feet and hands (lymphedema), which probably comes from changes in the drainage of the lymphatic system, since sometimes the pediatrician or neonatologist may think of a renal alteration.

The expectations of patients with this syndrome of Turner may have a normal life span and a normal productive life provided a careful medical control occurs and no taurodontism has been reported. However, estomatologic procedures, must be performed in multidisciplinary form with nutrition, endocrinology, cardiology, offering better handling and a more favourable for the patient.

### 3.2. Klinefelter (47 XXY)

Klinefelter syndrome is a condition that occurs in male patients as a result of the presence of an extra X chromosome and whose most common symptom is high size, change in the distribution of body fat and infertility. Taking into account the causes, incidence and risk factors, males have one X chromosome and one and which is written as XY. The two sex chromosomes help a person develop fertility and sexual gender

Characteristics, as mentioned previously. In Klinefelter Syndrome, male patients have one or more of one X-extra (written as XXY figure 4 B).

In this case specific note that the patient presents two genetic alterations, a syndrome of [Opitz, et al. \[16\]](#) and perform a chromosome study, it was observed a doubling of their sexual X chromosomes (47 XXY) Figure 4 A, and you can see that the patient presents as part of its clinical features, cleft lip and palate (CLP) bilateral and hypertelorism. It is important to mention that although CLP is known in genetics to be non-hereditary, multifactorial entity 90% about could be valued at CLP clinic in the Dentistry area, like a line defect only and treated as such.

This should be well thought for the professionals in dentistry, nutrition, pediatrics and genetics that a patient with cleft palate should be investigated through a good clinical history, anamnesis and laboratory studies before considering a single diagnosis in the patient, such as serious in this case, where the patient presents CLP, however is part of a syndrome (Klinefelter). This syndrome occurs in one of every 500 to 1000 newborn males. Women with pregnancies after age 35 are likely to slightly greater than having a child with this syndrome.

Within the most commonly observed signs are as follows: small penis, testicles small and firm, little facial, axillary and pubic hair, sexual dysfunction, gynecomastia and carving high abnormal body ratio (long legs, short trunk). Adults can go to the doctor because of infertility, and school-age children, psychomotor retardation in some of them, who should be treated as such to assess whether they should be handled in the area of dentistry under general anesthesia supported by the area of nutrition. Of the tests that were carried out to patients, the following results can be found: karyotyping that shows 47 XXY, count low semen, low serum testosterone level, level of hormone serum luteinizing and follicle serum estradiol (a type of estrogen) high.

The treatment will consist of therapy with testosterone, which will result: improve the strength, the appearance of muscles, self-esteem and mood, energy and sex drive. Most of the patients are infertile. However, there are some cases of men with an extra X chromosome having offspring. In relation to taurodontism prevalence [\[3\]](#) the condition affects less than 200,000 individuals or 1 out of every 2000 people in the United States. The Office of Rare Diseases (ORD), supervised by the National Institutes of Health, lists this as a rare disorder.

As mentioned before the main causes of taurodontism remain a mystery to those in the medical and dental field [\[2\]](#); [\[3\]](#). figures 5 A,B.

. However, some possible causes of this condition are said to be:

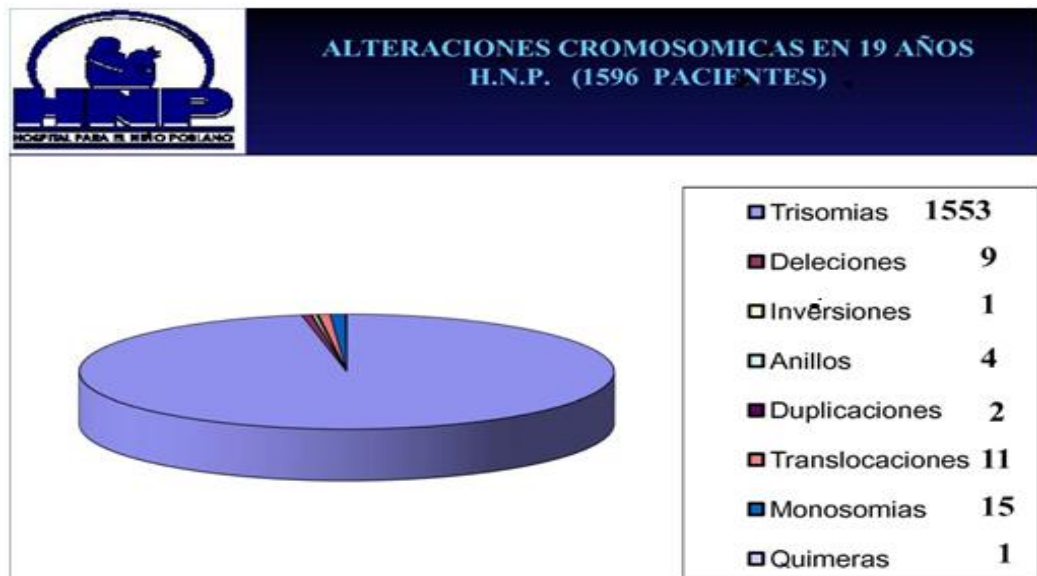
- Unusual development pattern
- Odontoblastic deficiency
- Delay in calcification of the pulpal chamber
- Alteration of Hertwig's Epithelial Root Sheat
- Disrupted developmental homeostasis

Taurodontism is supposed to be closely related to developmental syndromes as well as anomalies as:

- Klinefelter syndrome XXY figures 4 A,B.
- Cleft lip and palate figures 4 A,B.
- Mohr syndrome
- Tricho-dento-osseous syndrome
- Wolf-Hirschhorn syndrome
- Ectodermal Dysplasia
- Lowe syndrome
- Thalassemia major
- Ectodermal dysplasia
- McCune-Albright syndrome
- Williams Syndrome
- Van der Woude Syndrome

Since this dental condition has been then reported associated to various chromosome conditions. It was interesting to be analyzed in this study the facial and dental distortions together with impaired cognitive ability and physical growth.

To conclude, taurodontism is an extreme challenge for doctors who provide dental treatment. The complexity of the root canal anatomy and its proximity to the buccal orifices for the complete filling of the root canal system is a very challenging feat to fulfill. Nevertheless, dentists have devised a modified filling technique to proceed with the treatment comprised of lateral compaction in the apical region followed by vertical compaction on the elongated pulp chamber. This has been the most prominent proposal of many dentists, but its approval remains on the discretion of the dentist-in-charge and the patient



**Figure-1.** Chromosome alterations, shows 1596 (34.6%) patients with different aberrations. Of these, 1553 (33.6%) patients with Trisomy.



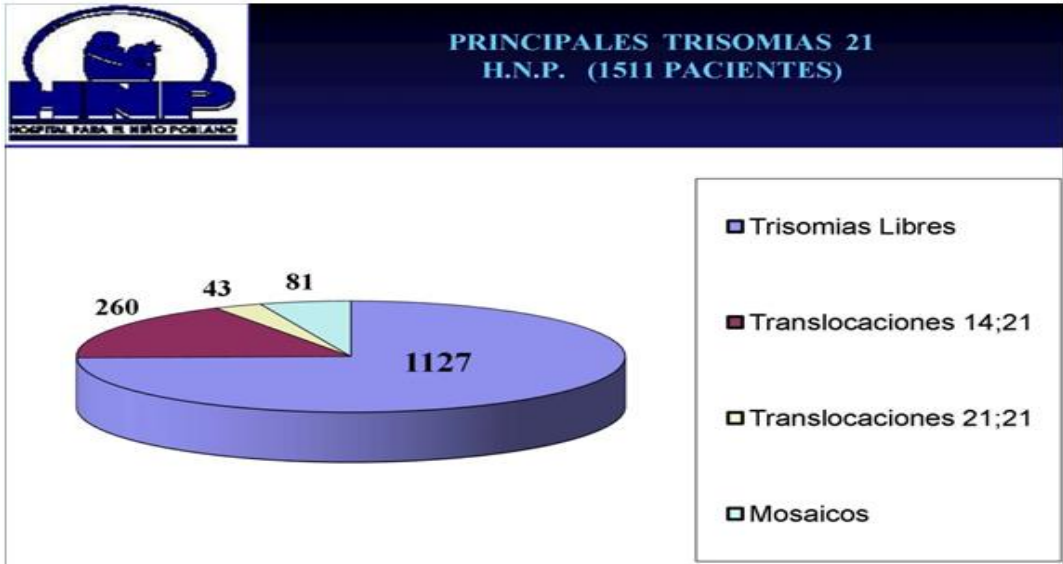
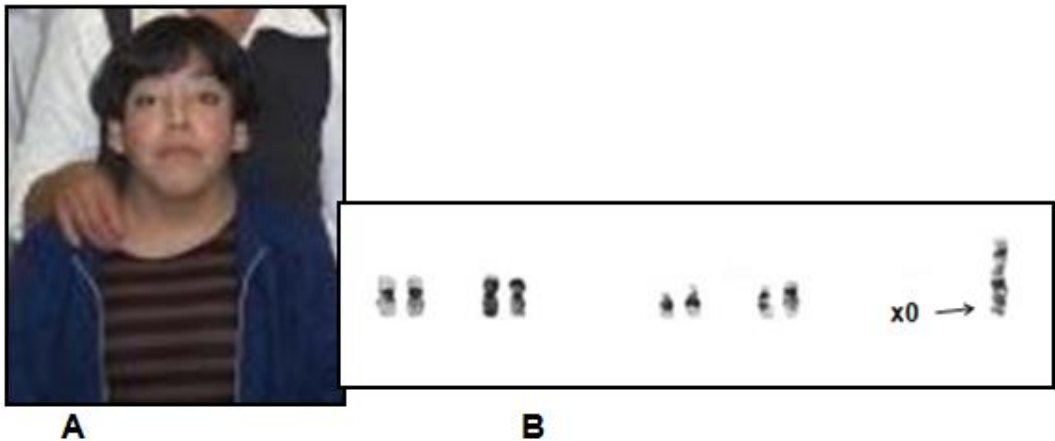
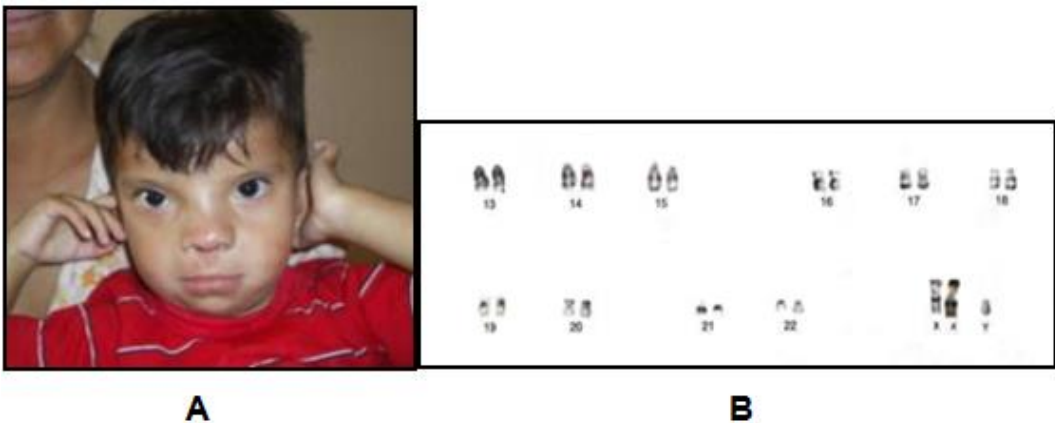


Figure-2. Of all the trisomy chromosomes, 1553 (33.6%), are observed 1511 (32.7%) were different types if compared to trisomy 21.



Figures-3A. Patient with Turner syndrome, short stature and pterigium coli B. The karyotype reveals a chromosome X (45XO).



Figures-4A. Male patient diagnosed as syndrome of Opitz G/B.B.B. hypertelorism, lip and cleft palate with B. craniofacial dimorphism The karyotype reveals a doubling of sex chromosome X (Klinefelter's syndrome).



**A**  
**B**  
**Figures-5A.** Male patient with a taurodontic phenotype **B.** molar teeth whereby the body of the tooth and pulp chamber is enlarged vertically at the expense of the roots. The floor of the pulp and the furcation of the tooth is moved apically down the root

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