We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Double Aneuploidy in Down Syndrome

Fatma Soylemez

Additional information is available at the end of the chapter

Abstract

Aneuploidy is the second most important category of chromosome mutations relating to abnormal chromosome number. It generally arises by nondisjunction at either the first or second meiotic division. However, the existence of two chromosomal abnormalities involving both autosomal and sex chromosomes in the same individual is relatively a rare phenomenon. The underlying mechanism involved in the formation of double aneuploidy is not well understood. Parental origin is studied only in a small number of cases and both nondisjunctions occurring in a single parent is an extremely rare event. This chapter reviews the characteristics of double aneuploidies in Down syndrome have been discussed in the light of the published reports.

Keywords: Double aneuploidy, Down Syndrome, Klinefelter Syndrome, Chromosome abnormalities

1. Introduction

With the discovery in 1956 that the correct chromosome number in humans is 46, the new area of clinical cytogenetic began its rapid growth. Several major chromosomal syndromes with altered numbers of chromosomes were reported, such as Down syndrome (trisomy 21), Turner syndrome (45,X) and Klinefelter syndrome (47,XXY). Since then it has been well established that chromosome abnormalities contribute significantly to genetic disease resulting in reproductive loss, infertility, stillbirths, congenital anomalies, abnormal sexual development, mental retardation and pathogenesis of malignancy [1]. Clinical features of patients with common autosomal or sex chromosome aneuploidy is shown in Table 1.

INTECH
open science | open minds

Trisomy 21 or Down syndrome is one of the best-recognized and most common chromosome disorders caused by the presence of all or part of a third copy of chromosome 21 (Figure 1). It is the single most common genetic cause for mental retardation. The incidence of Down syndrome is approximately 1/800 newborns [2]. The risk for having a child with Down syndrome increases with maternal age. Clinical features include mental and growth retardation, characteristic faces and other abnormalities described in Table 1. Approximately 94% of Down syndrome patients have trisomy 21 resulting from meiotic nondisjunction, the failure of homologous chromosomes or sister chromatids to separate during cell division. The generally exponential increase in the frequency of nondisjunction with increasing maternal age is correlated with a decline in genetic recombination frequency, for example, for chromosomes 21 [3].
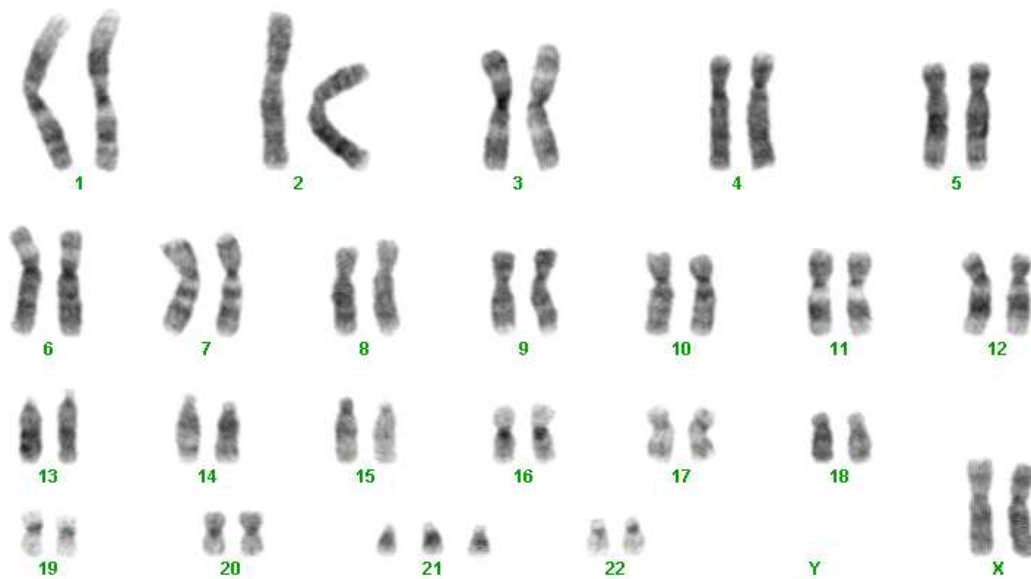

Figure 1. XX,+21 female Down syndrome karyotype demonstrating trisomy 21. (Karyotype prepared by Fatma Soylemez)

Aneuploidy is the second major category of chromosome mutations in which chromosome number is abnormal. An aneuploid is an individual organism whose chromosome number differs from the wild type by part of a chromosome set. Double aneuploidy that leads to trisomy of the two different chromosomes occurs due to accidentally meiotic nondisjunction events; both could have a same or different parental origin. The first case of double aneuploidy (48,XXY,+21) was reported in 1959 by Ford et al [4]. Other double aneuploidy that are found frequently are 48,XXX,+21, 48,XXY,+18 and 48,XXX,+18.

In this chapter, we will discuss double aneuploidies in Down syndrome in the light of the published reports. We will also examine possible underlying mechanism involved in the double aneuploidy.

Syndrome	Karyotype	Main clinical features
Down	Trisomy 21	Short, broad hands with single palmar crease, decreased muscle tone, mental retardation, broad head with characteristic features, open mouth with large tongue, up-slanting eyes
Edwards	Trisomy 18	Multiple congenital malformations of many organs, low-set malformed ears, receding mandible, small eyes, mouth and nose with general elfin appearance, severe mental deficiency, congenital heart defects, horseshoe or double kidney, short sternum, posterior heel prominence
Patau	Trisomy 13	Severe mental deficiency, small eyes, cleft lip and/or palate, extra fingers and toes, cardiac anomalies, midline brain anomalies, genitourinary abnormalities
Turner	45,X	Female with retarded sexual development, usually sterile, short stature, webbing of skin in neck region, cardiovascular abnormalities, hearing impairment, normal intelligence
Klinefelter	47,XXY	Male, infertile with small testes, may have some breast development, tall, mild mental deficiency, long limbs, at risk for educational problems
Triple X	47,XXX	Female with normal genitalia and fertility, at risk for educational and emotional problems, early menopause

Table 1. Clinical features of patients with common autosomal or sex chromosome aneuploidy.

2. Common double aneuploidies involving chromosome 21 and autosomal chromosomes

The simultaneous occurrence of two independent chromosomal anomalies in a given individual has been reported for various combinations of aberrations. Such associations most frequently involve aneuploidy of a sex chromosome and trisomy of an autosome, while double autosomal trisomies are less frequent. The reported cases involving autosome and/or sex chromosome aneuploidy, such as double autosomal trisomy are extremely rare in live newborns.

The data of fourteen previously reported cases with double autosomal trisomy, twelve of them mosaics, may be summarized as follows: The distribution of the maternal ages at birth of the patients was striking: six mothers were younger than 21 years, seven mothers were older than 34 years. In those patients with prevalence of one of the two extra chromosomes in their karyotypes, the corresponding trisomy syndrome also predominated clinically. In those cases with an equal proportion of both additional chromosomes there were as many patients with clinical predominance of the one as of the other trisomy syndrome. Survival beyond the second

half of the first year of life was seen only in those patients who showed the clinical picture of mongolism.

2.1. Down and trisomy 18 (Edwards) syndrome

The trisomy 18 syndrome, also known as Edwards syndrome, is a common chromosomal disorder due to the presence of an extra chromosome 18, either full, mosaic trisomy, or partial trisomy 18q. The condition is the second most common autosomal trisomy syndrome after trisomy 21 [5].

The syndrome pattern comprises a recognizable pattern of major and minor anomalies, an increased risk of neonatal and infant mortality, and significant psychomotor and cognitive disability. The main clinical features represent the clues for the diagnosis in the perinatal period and include prenatal growth deficiency, characteristic craniofacial features, distinctive hand posture, nail hypoplasia, short hallux, short sternum, and major malformations (Table 1).

Most authorities have suggested that the extra chromosome is present because of nondisjunction. In parent of origin analyses the extra chromosome is most often of maternal origin, the result of an error during the segregation of chromosomes in meiosis or post zygotic mitosis. About 50% of the nondisjunction errors in oogenesis occur in meiosis II, unlike other human trisomies where the malsegregation is more frequent in meiosis I. In the minority of cases in which the extra chromosome has a paternal origin, the error is the result of a post zygotic error. The cause of nondisjunction is unknown.

Most reported cases of double aneuploidy of Edwards syndrome are Edwards-Turner, Edwards-XXX, Edwards-Klinefelter and Edwards-XYY. However, double aneuploidy involving Down and Edwards syndromes is very rare occurrence because most of them probably are miscarriages (Table 2). Interestingly, the existence of double autosomal trisomy was reported in a newborn child: Down syndrome-trisomy 18 and Down syndrome and trisomy 13 [6].

Karyotype	Phenotype	Reference
48,XX,+18,+21	Edwards/Down Syndrome	Hsu et al, 1965 [7]
48,XX,+18,+21	Edwards/Down Syndrome	Grosse et al, 1977 [8]
48,XX,+18,+21	Edwards/Down Syndrome	Castel et al, 1983 [6]
48,XX,+18,+21	Edwards/Down Syndrome	Reddy et al, 1997 [9]

Table 2. Some examples of double aneuploidy in patients affected with Down and Edwards Syndrome.

2.2. Down and trisomy 13 (Patau) syndrome

Trisomy 13, also called Patau syndrome, is the least common of the major autosomal trisomies with an estimated incidence of 1 in 20 000 live births. Trisomy 13 is associated with advanced maternal age. The extra 13 usually results from a maternal meiotic nondisjunctional error.

Trisomy 13 is a chromosomal condition associated with severe intellectual disability and physical abnormalities in many parts of the body. Individuals with trisomy 13 often have heart defects, brain or spinal cord abnormalities, very small or poorly developed eyes (microphthal-mia), extra fingers or toes, an opening in the lip (a cleft lip) with or without an opening in the roof of the mouth (a cleft palate), and weak muscle tone (hypotonia) (Table 1). Owing to severe clinical abnormalities including central nervous system malformations, heart defects, growth retardation and numerous other congenital anomalies, trisomy 13 patients rarely survive the newborn period.

Due to the presence of several life-threatening medical problems, many infants with trisomy 13 die within their first days or weeks of life. Only five percent to 10 percent of children with this condition live past their first year. Like Edwards syndrome many affected pregnancies do not survive to delivery and therefore the incidence in mid pregnancy is higher. Double aneuploidy involving Down and Patau syndromes is very rare occurrence because most of them probably are miscarriages as well as Edwards syndrome (Table 3).

Karyotype	Phenotype	Reference
48,XX,+13,+21	Patau/Down Syndrome	Castel et al, 1983 [6]
48,XX,+13,+21/47,XX,+21	Patau/Down Syndrome mosaic Down Syndrome	Barnett et al, 1987 [10]
48,XX,+13,+21	Patau/Down Syndrome	Reddy et al, 1997 [9]
48,XY,+13,+21	Patau/Down Syndrome	Jenderny, 2014 [11]

Table 3. Some examples of double aneuploidy in patients affected with Down and Patau Syndrome.

3. Common double aneuploidies involving chromosome 21 and sex chromosomes

Sex chromosome abnormalities have less severe clinical anomalies than those associated with comparable autosomal imbalances. This difference can be attributed to genetic inactivation of all but one X-chromosome in those cases where multiple copies are present, and the relatively low gene content of the Y-chromosome. Sex chromosome aneuploidy is relatively common, with overall frequency of about 1 in 500 live births. Some (XXX, XXY, XYY) are relatively frequent in newborns but rare in spontaneous abortions. Monosomy X (Turner syndrome), in contrast, is one of the most common chromosome abnormalities seen in spontaneous abortions but relatively rare in newborns.

3.1. Down and Turner syndrome (45,X)

Turner syndrome, a disorder in females characterized by the absence of all or part of a normal second sex chromosome, leads to a constellation of physical findings that often includes congenital lymphedema, short stature, and gonadal dysgenesis (Table 1). Turner's syndrome

occurs in 1 in 2500 to 1 in 3000 live-born girls. Approximately half have monosomy X (45,X), and 5 to 10 percent have a duplication (isochromosome) of the long arm of one X (46,X,i(Xq)). Most of the rest have mosaicism for 45,X, with one or more additional cell lineages.

The clinical features range from a severe phenotypic character with short stature, gonadal dysgenesis and different malformations to an isolated mild reduction in final height or premature ovarian failure. The most visible phenotype is the short stature, which has been reported in up to 98 % of all Turner syndrome patients. Peripheral lymphedema dorsally of the hands and feet may be the initial presenting sign of Turner syndrome and is found in approximately one-third of affected infants. Turner's syndrome should be suspected in any newborn girl with edema or hypoplastic left heart or coarctation of the aorta, since the frequency of both conditions is increased among children with Turner's syndrome. In the last decade, the association between aortic dissection and Turner syndrome has been increasingly recognized with several reports of sudden death. In most other patients with Turner's syndrome, the condition is diagnosed either in adolescence when they fail to enter puberty or in adulthood because of recurrent pregnancy loss.

Most of Turner syndrome cases have mosaicism with Down syndrome. However, double aneuploidy involving Down and Turner syndromes is a rare occurrence (Table 4). The patients reported to have combined Down and Turner syndromes, fundamentally usually different forms of chromosome mosaicism have been noted and all have been mosaic with respect to monosomy X. Townes et al reported the first example of a Turner-Down patient in whom there was no X mosaicism [12].

Karyotype	Phenotype	Reference
46,X,+21	Turner/Down Syndrome	Townes et al, 1975 [12]
46,X,+21/47,XX,+21	Turner/Down Syndrome mosaic Down Syndrome	MacFaul, 1981 [14]
46,X,+21	Turner/Down Syndrome	Ruangdaraganon, 1993 [16]
46,X,+21	Turner/Down Syndrome	Jaruratanasirikul et al, 1995 [13]
46,X,+21/47,XX,+21	Turner/Down Syndrome mosaic Down Syndrome	Zaki et al, 2005 [15]
46,X,+21	Turner/Down Syndrome	Jenderny, 2014 [11]

Table 4. Some examples of double aneuploidy in patients affected with Down and Turner Syndrome

One of the first reports with double aneuploidy (Turner-Down) was reported that the first example of a Turner-Down patient in whom there is no X mosaicism [12]. The case of an 8 month-old female infant with non-mosaic Down-Turner double aneuploidy was reported by Jaruratanasirikul et al [13]. She had Down faces without stigmata of Turner syndrome.

Down's/Turner's mosaic is a rare chromosomal abnormality, occurring in about 1 in 2 000 000 births. Two babies with Down's/Turner's mosaic karyotype was reported that 2 babies born with this disorder in each of whom chromosomal analysis of amniotic fluid had mistakenly identified the fetus as a normal male [14]. The infant had the facial appearance of a Down

syndrome. She was markedly hypotonic with a low hairline, and had pronounced webbing of the neck. The heart was normal. Karyotype was 46,X+21/47XX+21. The 46,X+21 was present in 12% of the cultured cells. At age 11 months she had the appearance typical of Down syndrome together with some webbing of the neck. Mother was 36 years old. Same investigators reported another patient who had a baby with Down/Turner aneuploidy. Mother was 38 years old. The amniotic fluid karyotype was thought to be 46,XY. A girl weighing 1750 g was delivered at 36 weeks' gestation by caesarean section performed for intrauterine growth retardation. The infant had the facial appearance of Down's syndrome, a large clitoris, puffy hands and feet, and for a few days was cyanosed in air, and had a cardiac murmur. There was a single palmar crease and talipes on the right. She died from bronchopneumonia aged 15 weeks. The karyotype obtained in the neonatal period was 47,XX+21/46,X+21. Zaki and colleagues recently represented a female, mosaic (46,X,+21/47,XX,+21) where monosomy X was detected only by FISH in 15 percentages of cells, nevertheless, stigmata of Turner syndrome was more obvious in this patient [15].

3.2. Down and Klinefelter syndrome (47,XXY)

Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development. Its signs and symptoms vary among affected individuals. The incidence of 48,XXY,+21 in the general population is 0.4 to 0.9 per 10,000 male births. Unlike Turner syndrome, males with Klinefelter syndrome are not usually detected in the newborn period. These individuals are generally normal in appearance before puberty. After puberty they are frequently ascertained in infertility clinics or identified by their small testes, breast enlargement and tall stature. Affected individuals typically have small testes that do not produce as much testosterone as usual. Some affected individuals also have genital differences including undescended testes, the opening of the urethra on the underside of the penis (hypospadias), or an unusually micropenis (Table 1). Significant mental retardation is not part of this syndrome but patients have a higher incidence of educational and emotional problems.

Klinefelter and his colleagues (1942) described a characteristic syndrome in nine male patients who had gynecomastia and a specific form of hypogonadism comprising small testes with hyalinized seminiferous tubules and absent spermatogenesis but with intact Leyding cells. This syndrome is now well established in clinical practice and contributes significantly to infertility in the male.

Most Klinefelter patients have a 47,XXY karyotype (Figure 2). At least 10% have mosaicism involving normal 46,XY cells plus another population of cells with two or more X chromosomes. Mosaic patients have more variable clinical features and occasionally may have relatively normal testicular development. Cytogenetic and molecular data have indicated that 47,XXY is equally likely to result from a maternal or paternal meiotic nondisjunctional error. Maternally derived cases are associated with maternal age. Variants of Klinefelter syndrome include those patients with more than two X-chromosomes, multiple X-chromosome mosaicism and multiple Y-chromosomes. The presence of additional X-chromosomes is associated with increasing severity of clinical abnormalities including mental retardation, sexual development and skeletal anomalies.
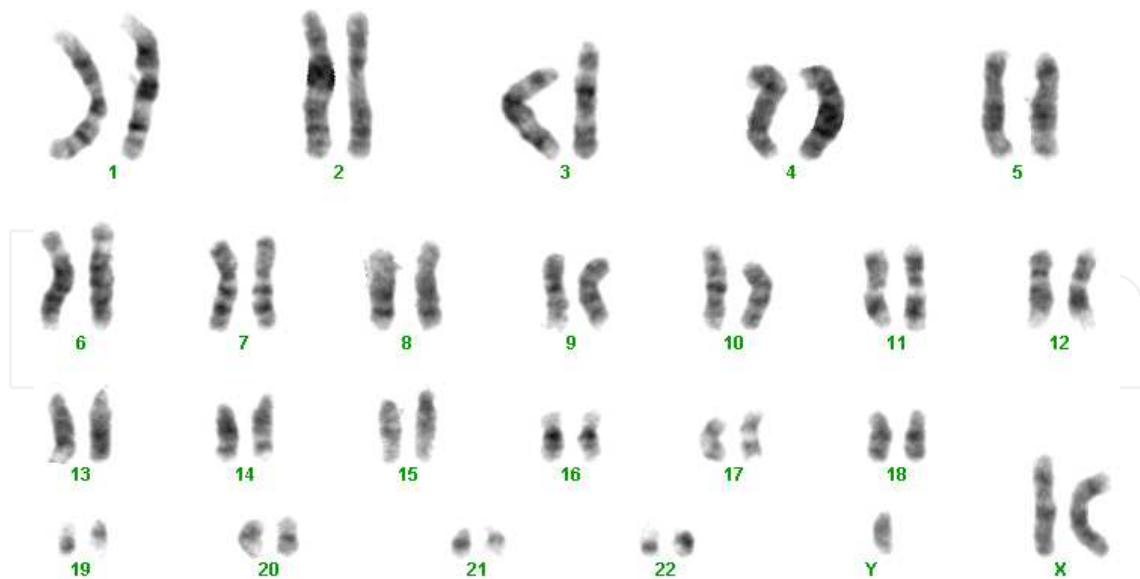
Figure 2. XXY Klinefelter syndrome karyotype (Karyotype prepared by Fatma Soylemez).

Trisomy 21 and numerical sex chromosome anomalies are common chromosome disorders. Down syndrome is the most common chromosomal abnormality in humans with an incidence of one in 770 live births. Although it is the most intensively studied human chromosomal abnormality, little is known about its cause and only advanced maternal age is confirmed as a risk factor [17]. On the other hand, Klinefelter syndrome is the most common disorder of sex chromosomes in humans, with prevalence of one in 500 males. The classic form is the most common chromosomal disorder, in which there is one extra X chromosome resulting in the karyotype of 47,XXY [18]. Double aneuploidy was first described in a patient with both Down and Klinefelter (48, XXY,+21) syndromes. This is also the most commonly described double aneuploidy. The karyotype is shown on Figure 3 [19].

The coincidence rate of both Down and Klinefelter syndromes in the same individual is estimated to lie in the range 0.27 to $0.7 \times 10\text{-}5$ [20]. On the other hand, lower values of XXY pattern recorded in older boys and men with Down syndrome suggest that there might be an increased selection against these individuals after birth [21]. Several cases of double aneuploidy of XXY and trisomy 21 have been published since the first report by Ford et al. (Table 5).

Pediatric cardiologists are familiar with screening of babies with Down syndrome for congenital heart defects, expecting in approximately 50% to find a heart defect, typically atrioventricular septal defect. However, in children diagnosed with Klinefelter syndrome, a chronic heart disease has only rarely been reported. Shen et al reported one case of 48,XXY,+21 karyotype with chronic heart disease. The phenotypic characteristics of the 4-month-old child had showed the presence of features typical of mongoloid slant. Also, Doppler echocardiogram detection has been showed atrial septal and ventricular septal defects with patent ductus arteriosus, pulmonary hypertension and mild tricuspid regurgitation [22]. Similarly, a 14-month-old boy was reported with double aneuploidy and a double aortic arch suffered from frequently recurrent severe feeding and respiratory problems [23].

Figure 3. GTG-banded karyotype of the case showing double aneuploidy - 48,XXY,+21. (Karyotype prepared by Fatma Soylemez.)

Karyotype	Phenotype	Reference
48,XXY,+21	Klinefelter/Down Syndrome	Ford et al, 1959 [4]
48,XXY,+21	Klinefelter/Down Syndrome	Harnden et al, 1960 [33]
48,XXY,+21	Klinefelter/Down Syndrome	Lanman et al, 1960 [34]
48,XXY,+21	Klinefelter/Down Syndrome	Hustinx et al, 1961 [35]
48,XXY,+21	Klinefelter/Down Syndrome	Gelderen and Hustinx, 1961 [36]
48,XXY,+21	Klinefelter/Down Syndrome	Hamerton et al, 1961 [26]
48,XXY,+21	Klinefelter/Down Syndrome	Milcou and Mainanesco, 1963 [37]
48,XXY,+21	Klinefelter/Down Syndrome	Court Brown et al, 1964 [38]
48,XXY,+21	Klinefelter/Down Syndrome	Pfeiffer, 1964 [39]
48,XXY,+21	Klinefelter/Down Syndrome	Taylor and Moores, 1967 [27]
47,XXY/48,XXY,+21	Klinefelter/Down Syndrome-Mosaic	Yamaguchi et al, 1989 [20]
48,XXY,+21	Klinefelter/Down Syndrome	Al Awadi et al, 1998 [25]
48,XXY,+21	Klinefelter/Down Syndrome	Iliopoulus et al, 2004 [24]
48,XXY,+21	Klinefelter/Down Syndrome	Cyril et al, 2005 [40]
48,XXY,+21	Klinefelter/Down Syndrome	Glass et al, 2006 [17]
48,XXY,+21	Klinefelter/Down Syndrome	Akbas, Soylemez et al, 2008 [19]
48,XXY,+21	Klinefelter/Down Syndrome	Karaman and Kabalar, 2008 [41]
48,XXY,+21	Klinefelter/Down Syndrome	Biselli et al, 2009 [42]
48,XXY,+21	Klinefelter/Down Syndrome	Jeanty and Turner, 2009 [43]
48,XXY,+21	Klinefelter/Down Syndrome	Gerretsen et al, 2009 [23]
48,XXY,+21	Klinefelter/Down Syndrome	Shen et al, 2012 [22]
48,XXY,+21	Klinefelter/Down Syndrome	Shu et al, 2013 [24]
48,XXY,+21	Klinefelter/Down Syndrome	Mishra et al, 2014 [44]

Table 5. Some examples of double aneuploidy in patients affected with Down and Klinefelter Syndrome.

Shu et al recently presented a neonate with a double aneuploidy associated with congenital heart defect suffered from cyanosis after birth. The patient had typical features of Down syndrome including hypertelorism, slightly lowest ears with protruding pinna (Figure 4). Doppler echocardiography has been indicated complex congenital heart disease with an ostium secundum atrial septal defect, enlarged right ventricle, and mild tricuspid valve regurgitation. Until now, only eight cases of double aneuploidy associated with CHD defect has been reported [24].

Figure 4. Facial dysmorphic features of the children with karyotype 48,XXY,+21, reveals signs of Down syndrome. a) [19], b) [22], c) [23]

This abnormality has also been described in a pair of monozygotic twins [25]. Further, both the sibs of the proband showing 48,XXY,+21 were found to exhibit trisomy 21 in yet another study [26]. Hamerton et al have summarized the data on the frequency of 48,XXY,+21 males and concluded that the expected incidence of double trisomics based on chance association should be about 0.31×10^{-5} live-born males [27]. In six sex chromatin surveys of the newborn 23.229 live-born males were studied; 47 of these were chromatin positive and two were double

trisomics (48,XXY,+21), an incidence of 8.62x10^{-5} [28]. This was 18 times higher than the indirect estimate for the general population and 30 times higher than the expected frequency based on chance association. These figures suggested that there was a much higher incidence of double trisomics at birth than would be expected by chance; the most satisfactory explanation for the reduced incidence among older groups was that double trisomics had a much higher mortality during the early years of life than the primary trisomics.

The association of Klinefelter Syndrome and Down syndrome in the same siblings has already been referred to and would be expected by chance although this is more difficult to establish. In particular, three of them, trisomy 21, trisomy 18 and trisomy 13 are the most frequently seen autosomal aneuploidies. Other commonly seen gonosomal aneuploidies are Turner syndrome, Klinefelter syndrome and its variants, poly X syndromes and poly Y syndromes. However, neonatal survey data has revealed that the incidence of XXY and trisomy 21 double trisomy at birth is higher than expected from the incidence of either alone [28].

The prenatal mortality rate of Downs-Klinefelter syndrome has not been extensively studied. Mutton et al found that 35% (6 of 17) of double aneuploidy cases that included an additional chromosome 21 died in utero [29]. Kovaleva and Mutton reported 2 miscarriages in 10 cases of prenatally diagnosed 48,XXY,+21, giving a mortality rate of 20%. Compared with either condition alone, the survival rate for the combination of XXY and trisomy 21 appears to be intermediary [30]. Forrester and Merz reported 1 death in utero (3.5%) in 28 cases of Klinefelter syndrome [31]. Bojesen et al reported no intrauterine deaths in 49 fetuses with prenatally diagnosed Klinefelter syndrome [32]. These data excluded terminations of pregnancies. Since the first reported cases of double aneuploidy with 48, XXY,+21 karyotype [20, 28, 33-40], many cases with Down and Klinefelter syndrome in the same individual has been reported in the literature, some of them very new [17,19, 22-26,41-44] (Table 5).

3.3. Down and Triple X syndrome (47,XXX)

Triple X syndrome, also called trisomy X or 47,XXX, is characterized by the presence of an additional X chromosome in each of a female's cells. The frequency of 47,XXX in newborn females is about 1 in 1000 and is associated with maternal age. Most XXX females are clinically normal with normal gonadal function and fertility. Although females with this condition may be taller than average, this chromosomal change typically causes no unusual physical features. Most females with triple X syndrome have normal sexual development and are able to conceive children. However, there is an increased risk for learning disabilities, reduction in performance IQ, menstrual problems and early menopause (Table 1). Triple X syndrome is associated with an increased risk of learning disabilities and delayed development of speech and language skills. Delayed development of motor skills such as sitting and walking, weak muscle tone (hypotonia), and behavioral and emotional difficulties are also possible, but these characteristics vary widely among affected girls and women (Figure 5). Seizures or kidney abnormalities occur in about 10 percent of affected females. Thus, the clinical manifestations are of trisomy 21 alone in many cases reported that Triple X syndrome/Down syndrome double aneuploidy. Trisomy-21 and triple-X in the same individual has been reported earlier [45, 46] and more recently [47-52] and phenotypic features of classical Down syndrome were only seen. However, strabismus, periorbital swelling, scanty eyebrows and microganthia have not been observed in these reports (Table 6).

Figure 5. Phenotype of the child with karyotype 48,XXX,+21 showing characteristic faces with low set ears and short neck. a) [51], b) [52]

Sheth et al reported a case of double aneuploidy showing trisomy 21 and triple-X chromosome in a case of Down syndrome born to young non-consanguineous parents. The child presented with strabismus, periorbital swelling, scanty eyebrows and microganthia in addition to Down features. Molecular characterization had shown the maternal origin of double aneuploidy with trisomy 21 at meiosis-II and triple-X at meiosis-I [51].

Karyotype	Phenotype	Reference
48,XXX,+21	Double chromatin positive female with Down Syndrome	Day et al, 1963 [45]
48,XXX,+21	Double chromatin positive female with Down Syndrome	Yunis et al, 1964 [46]
48,XXX,+21	Triple X/Down Syndrome	Park et al, 1995 [47]
48,XXX,+21	Triple X/Down Syndrome	Devlin and Morrison, 2004 [48]
48,XXX,+21	Triple X/Down Syndrome	Balwan et al, 2008 [49]
48,XXX,+21	Triple X/Down Syndrome	Guzel et al, 2009 [50]
48,XXX,+21	Triple X/Down Syndrome	Sheth et al, 2011 [51]
48,XXX,+21	Triple X/Down Syndrome	Uwineza et al, 2012 [52]

Table 6. Some examples of double aneuploidy in patients affected with Down and Triple X Syndrome

3.4. Down and 47,XYY syndrome

47,XYY syndrome is characterized by an extra copy of the Y chromosome in each of a male's cells. Approximately 1 in 1000 newborn males have a 47,XYY karyotype. Although most 47,XYY patients are clinically normal, they tend to be taller than normal and have an increased tendency for behavioral and learning problems as children and young adults. Y-chromosome aneuploidy results from paternal meiotic nondisjunction and is not associated with maternal age. Although males with this condition may be taller than average, this chromosomal change typically causes no unusual physical features. Most males with 47,XYY syndrome have normal sexual development and are able to father children. 47,XYY syndrome is associated with an increased risk of learning disabilities and delayed development of speech and language skills. Delayed development of motor skills such as sitting and walking, weak muscle tone (hypotonia), hand tremors or other involuntary movements (motor tics), and behavioral and emotional difficulties are also possible (Table 1). These characteristics vary widely among affected boys and men. A small percentage of males with 47,XYY syndrome are diagnosed with autistic spectrum disorders, which are developmental conditions that affect communication and social interaction.

Most cases of 47,XYY syndrome are not inherited. The chromosomal change usually occurs as a random event during the formation of sperm cells. An error in cell division called nondisjunction can result in sperm cells with an extra copy of the Y chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra Y chromosome in each of the body's cells. The XYY occurs when 24YY spermatozoa are formed due to nondisjunction either at paternal meiosis II or mitosis. Unlike Down syndrome, the XYY is not associated with increased parental age. The only consistent phenotypic feature associated with the XYY syndrome is tall stature, which becomes evident at about 5-6 years of age. These children may have learning difficulties, attention deficits, hyperactivity and increased aggressiveness. However, the behavioral changes appear to be variable and may be modified by the environment in which these children live. Therefore, it is important to recognize the XYY abnormality at the earliest so that these children can be evaluated periodically and given appropriate care and interventions for learning and behavioral needs.

Karyotype	Phenotype	Reference
48,XYY,+21	47,XYY/Down Syndrome	Verresen et al, 1965 [53]
48,XYY,+21	47,XYY/Down Syndrome	Migeon, 1965 [54]
48,XYY,+21	47,XYY/Down Syndrome	Uchida et al, 1966 [55]
47,XYY,+21	47,XYY/Down Syndrome	Al-Aish MS et al, 1971 [56]
47,XYY,+21/47,XY,+21	47,XYY /Down Syndrome mosaic Down Syndrome	Schwanitz et al, 1978 [57]
47,XYY,+21	47,XYY/Down Syndrome	Reddy, 1997 [58]
47,XYY,+21	47,XYY/Down Syndrome	Parmar et al, 2002 [59]
47,XYY,+21	47,XYY /Down Syndrome	Koken et al, 2011 [60]
47,XYY,+21/47,XY,+21	47,XYY/Down Syndrome mosaic Down Syndrome	Parihar et al, 2013 [61]

Table 7. Some examples of double aneuploidy in patients affected with Down and 47,XYY Syndrome

Although etiological predisposing factor for 48,XYY,+21 is not known, there are reported several cases of karyotype with 48,XYY,+21 since 1970's [53-57] (Table 7). Fewer than 40 cases of Down syndrome with XYY have been reported until date, only one of which has mosaicism for XYY. Reddy observed only 22 cases of double aneuploidy, such as XXY and 21 trisomy among 3024 spontaneous abortuses that the frequency even less than expected if the two aneuploidy events were independent of each other. They also occurred at an older mean maternal age [58]. Koken et al presented the patient had typical features of Down syndrome, however, phenotypic features of XYY was not present (Figure 6). In addition, the patient also had atrial septal defect, multiple trabecular small ventricular septal defect, and moderate degree of pulmonary hypertension [60]. Parihar et al reported a 5-year-old boy with the clinical features of Down syndrome. Cytogenetic analysis has been showed a mosaicism for a double aneuploidy, Down syndrome and XYY. The karyotype was 47, XY,+21(19)/48, XYY,+21(6),ish XYY (DXZ1 × 1, DYZ1 × 2) [61].

Figure 6. Phenotype of the child with karyotype 48,XYY,+21, reveals signs of Down syndrome [60-Koken et al, 2011].

4. Results

It has been over 50 years since trisomy 21 was identified as the cause of Down's syndrome, providing the first link between a clinical disorder and a chromosome abnormality. In the intervening half-century, the importance of numerical chromosome abnormalities to human disease pathology has been well-documented. Taken together, these studies established aneuploidy as the leading known cause of congenital birth defects and miscarriage and demonstrated that most aneuploid conceptuses perish in utero.

The occurrence of double aneuploidy i.e. the existence of two chromosomal abnormalities in the same individual is an uncommon phenomenon. Although aneuploidies are common

structural chromosomal abnormalities, double aneuploidies involving chromosomes 21 and sex and autosomal chromosomes are very rare. Trisomy 21 and numerical sex chromosome anomalies are common chromosomal disorders, with a birth incidence of 1:700 to 1:2,500 respectively [30]. The chances of two chromosomal anomalies occurring in a single conceptus are a rare event and the reported incidence varies from 0.21% to 2.8% in spontaneous miscarriages subjected to cytogenetic study [50]. In 1959, the first case with autosomal and sex chromosomal anomalies, 48,XXY,+21, was presented by Ford et al [4].

Various double aneuploidy associations are summarized in Tables above. The most frequently reported type of double aneuploidy is the 48,XXY,+21; other types include 48,XYY,+21. In general, the double aneuploidies which involve the sex chromosomes as well as 21-trisomy have phenotypic features representative of both aneuploidy conditions. These usually have the features of both conditions although the more serious condition usually masks the less serious. The presence of an associated sex chromosome abnormality in children with Down syndrome may not be clinically evident until puberty.

The existence of two chromosomal abnormalities in the same individual is relatively a rare phenomenon. Double aneuploidy leading to trisomy and/or monosomy of two different chromosomes arises because of two meiotic nondisjunctional events. Both these aneuploidies could have the same or different parental origin [62]. Double aneuploidy leading to trisomy and / or monosomy of two different chromosomes arises because of two meiotic nondisjunctional events. Both aneuploidies arise as a result of nondisjunction in maternal meiosis II [47] and these results support the hypothesis that a segregation defect at the cellular level may cause nondisjunction involving more than one chromosome. Most reported cases of double aneuploidy are presented in the form of spontaneous abortions. The reported cases involving autosome and/or sex chromosome aneuploidy, such as double autosomal trisomy and autosomal trisomy with sex chromosome monosomy or trisomy, are extremely rare in live newborns. These syndromes include Edwards-Down, Down-Klinefelter, Down-Turner mosaicism, Down-XYY, Patau-Klinefelter, Edwards-Turner mosaicism, Edwards-XXX, Edwards-Klinefelter, and Edwards-XYY. A rare case of double chromosome aneuploidy including Edwards syndrome (trisomy 18) and Klinefelter syndrome was described highlighting the patient's longer life span. Most cases of double aneuploidies in live births involve the sex chromosomes combined with either trisomy 13, 18 or 21, i.e. XXX/18, XXX/21, XXY/13, XXY/18, XXY/21, XYY/13, XYY/18 and XYY/21.

Double aneuploidies are observed in 0.21-2.8% of the aborted fetuses [63]. For women 35 years and older, the rate of trisomy 21 is increased to 1 per 120 pregnancies when data from 2 sources are combined. The rate of Klinefelter syndrome in pregnancies carried by women 35 years or older is 1 per 787.41 By multiplying the individual frequencies, the expected frequency of 48,XXY,+21 would be 1 per 94,440 pregnancies. Caron et al found 1 case of 48,XXY,+21 in 24,901 amniocentesis performed for advanced maternal age (≥35 years), which is a 3.8-fold increase over the expected rate [64]. The nonrandom aspect of double aneuploidy provides evidence that a hereditary predisposition to nondisjunction exists, with one chromosomal imbalance increasing the risk of another to occur, which suggests that both events arise from the same parent. Nondisjunction in cases of double trisomy has been found to be entirely maternal in

origin, entirely paternal in origin, and both maternal and paternal in origin. In such cases in which the additional chromosomes originate from different parents, the two errors may be coincidental and unrelated to a genetically determined nondisjunction. Abnormal separation of chromosomes may occur in older individuals because of dysfunction of structures related to chromosome separation, such as the spindle apparatus and kinetochore. Among 28 reports of 48,XXY,+21, which include 36 cases with known parental ages, Kovaleva and Mutton found that the risk for 48,XXY,+21 was age dependent, with a mean maternal age of 33 years and a mean paternal age of 38 years [30].

Trisomy 21, resulting in Down Syndrome (DS), is the most common autosomal trisomy among live-born infants and is caused mainly by nondisjunction of chromosome 21 within oocytes. Risk factors for nondisjunction depend on the parental origin and type of meiotic error. For errors in the oocyte, increased maternal age and altered patterns of recombination are highly associated with nondisjunction. Studies of normal meiotic events in humans have shown that recombination clusters in regions referred to as hotspots. In addition, GC content, CpG fraction, Poly(A)/Poly(T) fraction and gene density have been found to be significant predictors of the placement of sex-averaged recombination in the human genome. The results from early studies demonstrated that most aneuploidies are due to errors in maternal meiosis and that increasing maternal age is a powerful contributor to the occurrence of aneuploidy. However, studies during the past 10-15 years have also implicated events that occur at the onset of female meiosis in the fetal ovary and during the protracted dictyate arrest. The duration of the division (10 to 50 years and beyond) provides ample opportunity for errors to occur and to accumulate, which is a feature that has been the basis of a number of hypotheses to explain the maternal age effect. Indeed, the emerging picture indicates that aneuploidy is not due to a single causal factor but involves a complex constellation of effects that begins in utero, continues throughout the reproductive lifespan of the woman, is exacerbated by age and is facilitated by the unique features of cell cycle control in the oocyte.

Trisomics and monosomic (aneuploid) embryos account for at least 10% of human pregnancies and, for women nearing the end of their reproductive lifespan, the incidence may exceed 50%. The errors that lead to aneuploidy almost always occur in the oocyte but, despite intensive investigation, the underlying molecular basis has remained elusive. Increased maternal age and altered number and location of recombination events have been found to be associated with maternal meiotic errors involving chromosome 21 [65]. The overwhelming majority of trisomy 21, or Down syndrome, is caused by the failure of chromosomes to separate properly during meiosis, also known as chromosome nondisjunction. As nondisjunction is the leading cause of pregnancy loss, mental retardation and birth defects, it is imperative that we under-stand the biology underlying this phenomenon. Characteristics of chromosome 21 nondis-junction are typical of many of the other human autosomes. That is, the overwhelming majority is due to errors during oogenesis: at least 90% of cases have chromosome 21 nondisjunction are due to maternal meiotic errors.

Whereas there was no obvious maternal age association with recombination patterns among normally disjoining chromosomes 21, there was a significant one among maternal MI and ''MII'' errors. One set of observations provides evidence for specific recombination patterns being the proximal cause of nondisjunction, while the others suggest an interaction between

specific recombination patterns and maternal age-related risk factors. Specifically, the absence of recombination or the presence of a single recombinant event near the telomere of 21q are associated with maternal meiosis I (MI) errors and these associations appear to be independent of the age of the oocyte (i.e., maternal age at the time of birth of the infant with trisomy 21). Meiosis II (MII) errors appear to be driven by different age and recombination traits: MII errors are associated with the placement of a recombinant event near the centromere of 21q and this association increases with increasing age of the oocyte.

Nondisjunction could be possibly attributed to genetic, environmental or combined factors. Theoretically genes predisposing to increased nondisjunction can be classified in several different ways: a) Gene(s) producing nondisjunction of a specific chromosome (e.g. chromosome 21), b) Gene(s) that can predispose to nondisjunction of different autosome/sex chromosomes in the same individual, or in sibs, due to, parental and/or post zygotic or post systic nondisjunction "double aneuploidy" (such as, 48,XX, or XY,+21; 48,XXY,+21; 46,X,+21). The occurrence of double aneuploidy would not prove the existence of predisposition gene(s). Such outcome resulting from parental mosaicism has been demonstrated in some families with >2 trisomy 21 sibs. Familial double aneuploidy is very rare. However, the occurrence of aneuploidy for different chromosomes is better evidence for genetic predisposition although environmental factors could also be invoked as a possible cause. Amniocentesis and live birth data provide little evidence for a strong double aneuploidy effect although a weak effect cannot be excluded. Studies in abortions are suggestive of genetic mosaicism in double aneuploidy.

In conclusion, since the first description of a case of double aneuploidy with 48, XXY,+21 karyotype, approximately 385 cases with double aneuploidy are reported in the literature. Autosomal double trisomies are observed in spontaneous abortions but are rarely reported in live born infants. Most double aneuploidies are associated with an increased maternal age, abnormal sonogram, and pregnancy loss at a very early gestational age. However, sex chromosome aneuploidy and trisomies involving chromosomes 16, 18, and 21 can survive for longer gestation. The mechanism underlying the origin of double aneuploidy is unclear. It is hypothesized that double aneuploidy results either from two nondisjunctional events in gametogenesis or a single nondisjunctional event in a trisomics zygote. The published literature shows that there is no specific chromosome association in double aneuploidy formation; however, the most frequently involved chromosomes are the sex chromosomes and acrocentric chromosomes.

Author details

Fatma Soylemez

Address all correspondence to: soylemez_fatma@yahoo.com

University of Avrasya, Department of Molecular Biology and Genetics, Trabzon, Turkey

References

[1] Luthardt F, Keitges E. Chromosomal Syndromes and Genetic Disease. The Quarterly Review of Biology 2001; 79 (1): 69-70.

[2] Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down sydrome. Mental Retardation and Developmental Disabilities Research Reviews 2007; 13: 221-227.

[3] Sherman SL, Petersen MB, Freeman SB. Nondisjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. Hum Mol Genet 1994; 3: 1529-1535.

[4] Ford CE, Jones KW, Miller OJ, Mittwoch U, Penrose LS, Ridler M et al. The chromosomes in a patient showing both mongolism and the Klinefelter syndrome. Lancet 1959; 1: 709-710.

[5] Carey JC. Trisomy 18 and trisomy 13 syndromes. Management of Genetic Syndromes, Second Edition 2005; 555-568.

[6] Castel Y, Le Marec B, Toudic L, Lemarchand M, Cosson JP. Association of trisomy 21 and gonosomal trisomy. Apropos of 2 cases. Pediatrie. 1983; 38 (4): 235-41.

[7] Hsu LY, Schwanger AJ, Nemhauser I, Sobel EH. A case of double autosomal trisomy with mosaicism: 48/XX (Trisomy 18+21) and 46/XX. J Pediatr. 1965 ;66: 1055-60.

[8] Grosse KP, Schwanitz G. Double autosomal trisomy: case report (48, XX, +18, +21) and review of the literature. J Ment Defic Res 1977; 21: 299-308.

[9] Reddy KS. Double trisomy and spontaneous abortions. Hum Genet 1997; 101: 339-345.

[10] Barnett SH, Jhaveri M, Gertner M. Double autosomal trisomy mosaicism: 47,XY, +21/48,XY,+13,+21. Am J Med Genet. 1987; 28 (2): 501-502.

[11] Jenderny J. Chromosome aberrations in a large series of spontaneous miscarriages in the German population and review of the literature. Mol Cytogenet. 2014; 5 ;7-38.

[12] Townes PL, White MR, Stiffler SJ, Goh K. Double aneuploidy. Turner-Down syndrome. Am J Dis Child. 1975; 129 (9): 1062-5.

[13] Jaruratanasirikul S, Jinorose U. An infant with Down-Turner double aneuploidy: a case report and literature review. J Med Assoc Thai. 1995; 78 (2): 108-12.

[14] MacFaul R, Turner T, Mason MK. Down's/Turner's mosaicism. Double aneuploidy as a rare cause of missed prenatal diagnosis of chromosomal abnormality. Arch Dis Child. 1981; 56 (12): 962-963.

[15] Zaki MS, Kamel AA, El-Ruby M. Double aneuploidy in three Egyptian patients: Down-Turner and Down-Klinefelter syndromes. Genet Couns. 2005; 16 (4): 393-402.

[16] Ruangdaraganon N, Kotchabhakdi N, Mekanandha V. Double aneuploidy: 46,X, +21 a combination of Down syndrome and Turner syndrome. J Med Assoc Thai. 1993; 76 (2): 215-217.

[17] Glass IA, Li L, Cotter PD. Double aneuploidy (48,XXY,+21): molecular analysis demonstrates a maternal origin. Eur. J. Med. Genet 2006; 49: 346–348.

[18] Visootsak J, Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. Orphanet. J. Rare Dis 2006; 1: 42.

[19] Akbas E, Soylemez F, Savasoglu K, Halliogluand O, Balci S. A male case with double aneuploidy (48,XXY,+21). Genet Couns. 2008;19 (1): 59-63.

[20] Yamaguchi T, Hamasuna R, Hasui Y, Kitada S, Osada Y. 47,XXY/ 48,XXY,+21 chromosomal mosaicism presenting as hypospadias with scrotal transposition. J Urol 1989; 142: 797-798.

[21] Hecht F, Nievaard JE, Duncanson N, Miller JR, Higgins JV, Kimberling WJ et al. Double aneuploidy: The frequency of XXY in males with Down syndrome. Am J Hum Genet 1969; 21: 352-359.

[22] Shen Z, Zou CC, Shang SQ and Jiang KW. Down-Klinefelter syndrome (48,XXY,+21) in a Child with Congenital Heart Disease: Case Report and Literature Review. Intern Med 2012; 51: 1371-1374.

[23] Gerretsen MF, Peelen W, Rammeloo LA, Koolbergen DR, Hruda J. Double aortic arch with double aneuploidy--rare anomaly in combined Down and Klinefelter syndrome. Eur J Pediatr. 2009; 168 (12): 1479-81.

[24] Shu X, Zou C, Shen Z. Double aneuploidy 48,XXY,+21 associated with a congenital heart defect in a neonate. BJMG 2013; 16 (2): 85-90.

[25] Iliopoulos D, Poultsides G, Peristeri V, Kouri G, Andreou A, Voyiatzis N. A Double trisomy (48,XXY,+21) in monozygotic twins: Case report and review of the literature. Ann de Genet 2004; 47: 95-98.

[26] Al Awadi SA, Naguib KK, Bastaki L, Gouda S, Mohammed F M, Abulhasan SJ et al. Down syndrome in Kuwait: Recurrent familial trisomy 21 in siblings. Downs Syndr Res Pract 1998; 5: 131-137.

[27] Hamerton J, Brigges S, Gianelli F, Carter C. Chromosomal studies in detection of parents with high risk of second child with Down's syndrome. Lancet 1961; 2: 788.

[28] Taylor AI, Moores EC. A sex chromatin survey of newborn children in two London hospitals. J Med Genet 1967; 4: 258.

[29] Mutton D, Alberman E, Hook EB. Cytogenetic and epidemiological findings in Down syndrome, England and Wales 1989 to 1993. National Down Syndrome Cytogenetic Register and the Association of Clinical Cytogeneticists. J Med Genet 1996; 33: 387–394.

[30] Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. Am J Med Genet A 2005; 134:24–32.

[31] Forrester MB, Merz RD. Pregnancy outcome and prenatal diagnosis of sex chromosome abnormalities in Hawaii,1986–1999. Am J Med Genet A 2003; 119:305–310.

[32] Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003; 88: 622–626.

[33] Harnden DG, Miller OJ, Penrose LS. The Klinefeltermongolism type of double aneuploidy. Ann Hum Genet. 1960; 24: 165-169.

[34] Lanman JL, Shlarin B, Cooper H, Hirschhorn K. Klinifelter's syndrome in a ten months old mongolism idiot. N Eng J Med 1960; 263: 887.

[35] Hustinx TWJ, Eberle P, Geerts SJ, Brink JT, Woltring LM. Mongoloid twins with 48 chromosomes (AA A21XXY). Annals of Human Genetics 1961; 25: 111-113.

[36] Gelderen V and Hustinx TWJ. Combination of Klinifelter's syndrome and mongolism. Ned Tij Genetic 1961; 105: 1925-1928.

[37] Milcou M and Maianesco M. Klinifelter's syndrome associated with mongolism and bilateral testicular ectopy. Pathol Biol 1963; 11: 1247-1250.

[38] Court Brown WM, Harnden DG, Jacobs PA, Maclean N, Mantle DJ. Abnormalities of the Sex Chromosome Complement in Man. Medical Research Council 1964, Special Report No. 305. HMSO, London.

[39] Pfeiffer RA. Double aneuploidy (Trisomy 21 and XXY) in an infant. Arch Kinderheilkd. 1964;171: 69-79.

[40] Cyril C, Jagatheesan CN, Chandralekha T, Gopinath PM and Marimuthu KM. Down syndrome child with 48,XXY, +21 karyotype, Ind. J. Human. Genet 2005; 11: 47-48.

[41] Karaman A, Kabalar E. Double aneuploidy in a Turkish child: Down-Klinefelter syndrome. Congenit Anom (Kyoto). 2008; 48 (1): 45-47.

[42] Biselli JM, Machado FB, Zampieri BL, Alves da Silva AF, Goloni-Bertollo EM, Haddad R, Eberlin MN, Vannucchi H, Carvalho VM, Medina-Acosta E, Pavarino-Bertelli EC. Double aneuploidy (48,XXY,+21) of maternal origin in a child born to a 13-year-old mother: evaluation of the maternal folate metabolism. Genet Couns. 2009; 20 (3): 225-34.

[43] Jeanty C, Turner C. Prenatal Diagnosis of Double Aneuploidy, 48,XXY,+21, and Review of the Literature. Ultrasound Med 2009; 28: 673–681.

[44] Mishra SR, Bisht JS, Kumar M, Kumar S, Gaur K, Kumar R, Lal V, Bhattacharya SK. Double aneuploidy 48,XXY,+21 in a fetus with congenital abnormalities. Der Pharmacia Letter 2014; 6 (3): 351-354.

[45] Day, R. W., Wright, S. W., Koons, A., and Quigley, M. XXX 21-trisomy and retinoblastoma. Lancet 1963; 2: 154-155.

[46] Yunis JJ, Hook EB, Mayer M. DNA. replication analysis in identifying the cytogenetic defect in Down's syndrome (mongolism). Lancet. 1965; 27 (1): 465–466.

[47] Park VM, Bravo RR, Shulman LP. Double non-disjunction in maternal meiosis II giving rise to a fetus with 48,XXX,+21. J Med Genet 1995; 32: 650- 653.

[48] Devlin L, Morrison PJ. Mosaic Down's syndrome prevalence in a complete population study. Arch Dis Child. 2004; 89 (12): 1177-8.

[49] Balwan WK, Kumar P, Raina TR, Gupta S. Double trisomy with 48, XXX+21 karyotype in a Down's syndrome child from Jammu and Kashmir. Ind J Genet, 2008; 87(3): 257-259.

[50] Guzel AI, Demirhan O, Pazarbasi A, Ozgunen FT et al. Detection of parental origin and cell stage errors of a double non-disjunction in a fetus by QF-PCR. Genet Test Mol Biomarkers 2009; 13(1): 73-77.

[51] Sheth HJ, Munoz A, Sergi C, Pani J, Blouin JL, Sheth JJ, Sheth FJ. Triple-X Syndrome in a Trisomic Down Syndrome Child: Both Aneuploidies Originated from the Mother. Int J Hum Genet 2011; 11(1): 51-53.

[52] Uwineza A, Hitayezu J, Murorunkwere S, Ndinkabandi J, Mutesa L. An unusual case of double aneuploidy of down syndrome associated with triple X syndrome: 48,XXX, +21. Rwanda Medical Journal 2012; 69 (4): 27-29.

[53] Verresen, H. and van den Berghe, H. 21-trisomy and XYY. Lancet 1965; 1: 609.

[54] Migeon BR. G trisomy in an XYY male. Human Chromosome Newsletter 1965; 17: 16.

[55] Uchida, I. A., Ray, M., and Duncan, B. P. 21 Trisomy with an XYY sex chromosome complement. Journal of Pediatrics 1966; 69: 295-298.

[56] Al-Aish MS, Dodson WE, Plato CC. Down's syndrome with XYY: 48,XYY, G+. Am J Dis Child. 1971; 121 (5): 444-446.

[57] Schwanitz G, Hagner M. Double trisomy as a mosaic. Case history (48, XYY, +21/47, XY, +21) and survey of the literature of mixed autosomal-gonosomal trisomies. Acta Genet Med Gemellol (Roma) 1978; 27: 67–74.

[58] Reddy KS. Double trisomy in spontaneous abortions. Hum Genet. 1997;101 (3): 339-45.

[59] Parmar RC, Muranjan MN, Swami S. Trisomy 21 with XYY. Indian J Pediatr. 2002; 69 (11): 979-981.

[60] Koken R, Bukulmez A. Double Aneuploidy: A Case of Trisomy 21 with XYY. Eur J Gen Med 2011; 8 (4): 338-341.

[61] Parihar M, Koshy B, Srivastava VM. Mosaic double aneuploidy: Down syndrome and XYY. Indian J Hum Genet. 2013; 19(3): 346–348.

[62] Lorda-Sanchez I, Petersen MB, Binkert F, Maechler M, Schmid W, Adelsberger PA et al. A 48,XXY,+21 Down syndrome patient with additional paternal X and maternal 21. Hum Genet 1991; 87: 54-56.

[63] Subramaniyam S, Pulijaal VR, Mathew S. Double and multiple chromosomal aneuploidies in spontaneous abortions: A single institutional experience. Journal of Human Reproductive Sciences 2014; 7 (4): 262-268.

[64] Caron L, Tihy F, Dallaire L. Frequencies of chromosomal abnormalities at amniocentesis: over 20 years of cytogenetic analyses in one laboratory. Am J Med Genet 1999; 82: 149–154.

[65] Oliver TR, Feingold E, Yu K, Cheung V, Tinker S, et al. New insights into human nondisjunction of chromosome 21 in oocytes. PLoS Genet 2008; 4 (3): 1-9.