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Case Report

Live-Born Double Aneuploidy at the Johns Hopkins Cytogenomics Laboratory: Case Report and Review of the Literature

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Abstract

Double aneuploidy is the co-occurrence of aneuploidy of two different chromosomes within the same individual. Genomic imbalance associated with two aneuploidies in humans is associated with early lethality, and observation in live-born humans is rare. In isolation, trisomy of chromosomes 13, 18, 21, X, and Y may be better tolerated, whereas monosomy of X is the only such type of aberration that may be compatible with life. It is hypothesized that two successive malsegregation events must occur in early development to be observed constitutionally. Mechanisms like trisomy rescue or selection against aneuploidies may result in mosaicism and promote subsequent survival in live-born individuals, depending on the chromosomes involved. From the literature, double aneuploidy in the live-born is rare, with (acrocentric) autosomal with gonosomal aneuploidy more common than double autosomal aneuploidy. A retrospective case study of patients who underwent routine postnatal cytogenetic testing at The Johns Hopkins Hospital (JHH) Cytogenomics Laboratory (from its inception in the early 1960s-present) was carried out to identify mosaic and/or non-mosaic

forms of double aneuploidy. One case each of non-mosaic [Klinefelter with Edwards Syndrome] and non-mosaic [Klinefelter with Down Syndrome] is identified. No gonosomal and autosomal cases in females nor double autosomal trisomies were identified in live-born individuals at the JHH Cytogenomics Laboratory. Given the advancements in non-invasive prenatal screening for common aneuploidies, the need for diagnostic confirmation studies persists. Providers should be aware of the possibility of early detection of pregnancies bearing double aneuploidy (common or rare) when maternal malignancy is not suspected. Additionally, clinicians should consider the possibility of double aneuploidy in rare situations of atypical or blended phenotypes reminiscent of dual diagnoses. Further work is needed to identify and compile these and even rarer double aneuploidy cases to improve genotype-phenotype correlations.

Keywords
Non-mosaic double aneuploidy; Klinefelter and Edwards syndrome; Klinefelter and Down syndrome

1. Introduction

Aneuploidy is a major category of chromosomal aberrations present in humans and is defined as any chromosome number that is not an exact multiple of the haploid number [1]. Constitutional genetic disorders affect the entire body, and much of our understanding of these disorders is based on observations of development and phenotypes. Historically, conventional cytogenetics and now array-based chromosomal microarray technologies have identified trisomies as well as other abnormalities (unbalanced structural anomalies, monosomies, polyploidies, and multiple aneuploidies) in products of conception and early human embryos. Whether the aneuploidy is compatible with life depends on the chromosome (dosage sensitivity of the genomic content) involved and the level of involvement, whether mosaic or non-mosaic. Additionally, aneuploidy may also be observed as part of normal aging and neoplasia. Examples of aneuploidy encountered in humans are described below.

Nullisomy (2N - 2) is defined as the state of loss of a pair of homologous chromosomes and is generally not compatible with life in diploid organisms, whereas monosomy (2N - 1) for a particular chromosome indicates the loss of one copy of an entire chromosome. A monosomy scenario that may be compatible with life is the loss of an X chromosome, which may be observed in individuals with Turner syndrome. Loss of the Y chromosome can also be observed as a mosaic finding in a second line with a normal male chromosomal complement. Mosaic loss of one copy of either of the sex chromosomes can also be observed as an age-related finding, whereas loss of autosomal chromosomes is less frequently described [2]. Acquired loss of the sex chromosomes may also be observed in association with neoplasia. An additional concern for individuals bearing the monosomic chromosome is the possibility that the subsequent hemizygous status may unmask recessive disease by allowing the condition to be directly expressed.

Trisomy (2N + 1) is the state of bearing an extra chromosomal copy (n = 47). The types of simple trisomies that can be observed across the human lifespan vary greatly from early conception to the live-born and as a consequence of aging. Overall, the type of common autosomal chromosomes

more frequently involved in viable aneuploidies like trisomies are smaller chromosomes, likely corresponding to lesser genomic content involvement and greater tolerance for dosage of involved genes therein (chromosomes 13, 18, and 21). Generally, trisomies involving the sex chromosomes can be observed in live births (XXX, XXY, XYY, etc.). Rare autosomal trisomies (RATs) are those chromosomal trisomies that are infrequently seen at birth and may be associated with poor obstetric outcomes [3]. Polysomy is the state of having at least one more copy of a particular chromosome than normal and can include trisomy and tetrasomy. Due to the gross genomic imbalance, tetrasomy (2N + 2) with only partial chromosomal arm involvement may be compatible with life, and observation in live births is rare. The single exception being 48,XXXX or tetrasomy X which can be observed in female live-born children [4] due to X-inactivation. In the excess of the normal sex chromosomal complement, cellular processes accommodate this imbalance via inactivation of any additional X chromosomes, resulting in a highly variable phenotype as some loci are not subject to inactivation [5]. In this example, complete tetrasomy of the X chromosome is attributed to two incidences of nondisjunction, most likely due to successive maternal meiotic nondisjunction events [6].

Whole-organism aneuploidy or complete aneuploidy is more frequently caused by meiotic nondisjunction. Full aneuploidies are often encountered in early pregnancy losses due to the gross chromosomal imbalance being incompatible with life. The prevailing mechanism favors a two step process [7]. The first event occurring at meiosis I, involves a less well-tethered bivalent at meiosis I, and the second at meiotic metaphase II, results in a consequential aberrant distribution [5]. Reproductive-age females may more frequently experience whole-chromosome nondisjunction events associated with increased aneuploidy at a younger age, which is in contrast with the centromeric and more extensive chromatid cohesion protein deterioration in older females [8], though theoretically, this error could occur at any parental age [5].

Considered a rare cause of full aneuploidy, gonadal mosaicism may also be present in the pre-meiotic germ cells of the parent, conferring an increased risk for a single aneuploidy [9]. Another potential rare cause of full aneuploidy could be a very early post-zygotic mitotic nondisjunction event occurring in a normal conceptus. Short tandem repeat (STR) testing of the proband and parents could be employed to clarify the parental origin of nondisjunction, though this is not performed routinely in the clinical setting. Historically, some banding techniques could be considered to identify the parental origin of the chromosome if available polymorphisms were informative.

Aneuploidy viability may also improve when observed as a mosaic karyotype in conjunction with a euploid line. The mechanism for the more commonly encountered aneuploidies is better understood, with certain aneuploidies being more frequently associated with maternal or paternal meiotic nondisjunction errors. Mosaicism, known as partial aneuploidies, can be caused by post-zygotic mitotic nondisjunction and may be associated with a less severe presentation, depending on the chromosome involved and the extent of cells affected presenting as a mosaic euploid/aneuploid line. Human implantation embryos in early development can present mosaic aneuploidies at a high frequency, with potential consequences for implantation and loss, and reconciling this finding with the embryo's ability to self-correct may pose a challenge in determining the clinical significance of the genomic imbalance [10].

Double aneuploidy is the presence of two chromosomal abnormalities in the same organism and is more frequently described in products of conception when all cells and lineages are involved. It is

estimated that 15% of clinically recognized pregnancies experience spontaneous miscarriages, and half (7.5%) of these are attributed to chromosome abnormalities [11]. For spontaneous abortions, double and multiple aneuploidy are observed at 4.6 and 0.4%, respectively [11]. There is a constraint against genomic imbalances such as single aneuploidy, with the exception of smaller autosomes and sex chromosomes. From analyses of products of conception, double aneuploidies [X/+21; +21/+22; +16/+21; and +7/+16] are described in decreasing order and multiple aneuploidies [+X/+5/+8; +8/+20/+22; +16/+20/+22; +14/+21/+22; −X/+21/+21; −X/+7/+21] are also noted [11], and an increased incidence may be associated with advanced maternal age [11]. In descending frequency order, observed double aneuploidy events consist of chromosomes 21, 16, X, 22, 18, 13, and 15 [11]. Autosomal and gonosomal chromosomes may co-occur in double aneuploidy as an infrequent postnatal finding.

Mosaic double aneuploidy likely arises from two successive malsegregation events involving different chromosomes and co-occurring in a single individual, resulting in the creation of at least two cell lines. If two different chromosomal anomalies co-occur in the same cell line by chance, then presumably, there are also subsets carrying each abnormality independently, along with the two euploid complements in isolation. To observe double aneuploidy (mosaic or non-mosaic) in live-born humans is rare. To answer whether historical cases were present in a single-site Cytogenomics laboratory dating back to the early 1960s, a retrospective postnatal abnormal case review from the Johns Hopkins Hospital (JHH) Cytogenomics Laboratory was undertaken with the intent to include mosaic and non-mosaic forms of this finding. This case report adds one case each of complete or non-mosaic Klinefelter (XXY) with Edwards Syndrome (trisomy 18) (KS + T18) and Klinefelter (XXY) with Down Syndrome (trisomy 21) (KS + T21) to the literature. The rarer autosomal double aneuploidy and more common combinations of double aneuploidy autosomal with X chromosome aneuploidy (polysomy X or monosomy X) described in the literature, were absent in available laboratory records. In conjunction with the identified postnatal cases, a PubMed review of relevant literature, from 1960 to the present, communicated in English and accessible, was carried out to clarify the significance of the identified clinical JHH cases.

2. Case Report

Per the institution guidelines, a case report includes a qualitative and retrospective analysis of three or fewer clinical cases that were de-identified. As deemed by the institution, this retrospective review was carried out as a medical/educational activity that does not meet the DHHS definition of "research" and confers no more than minimal risk. This study does not require written consent by IRB policies.

2.1 Cytogenetic Testing

2.1.1 Patient 1

Chromosome analysis confirms an abnormal male karyotype 48,XXY,+21 in peripheral blood (50 metaphases examined and six fully analyzed) taken at two days old; no evidence of mosaicism was observed (see Figure 1). These findings are interpreted as a male with Klinefelter syndrome and trisomy 21 or Down syndrome (KS + T21). The indication for testing was ruling out trisomy 21 and XXY, based on a prenatal amniotic fluid karyotype result. Additionally, one fragile X site was seen at

Xq27.3 in one metaphase cell. Prominent features at birth included tetralogy of Fallot and a complete common atrioventricular canal defect. After this diagnosis, he underwent repair of these defects.

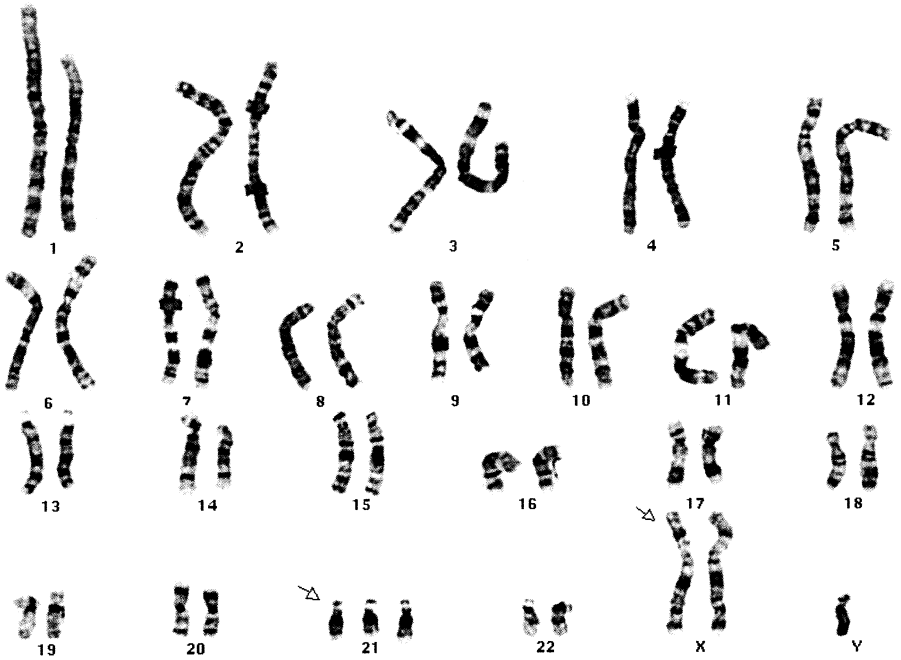

Figure 1 G-banded karyotype at two days old showing trisomy 21 and XXY.

At 5 years of age, he demonstrated a residual primum atrial septal defect (ASD), which was repaired along with partial re-closure of a residual mitral valve cleft. He was also known to have a probable broken sternal wire, which initially protruded from the lower aspect of his sternum, but spontaneously stabilized without intervention. He was asymptomatic, active, and has had no changes in his exertional tolerance, no obvious problems with chest pain or palpitations, severe respiratory infections or other issues and otherwise was in excellent medical health. His sterum had not been tender or painful. He was generally alert, well-developed, well-nourished appearing, and in no distress. Cardiac examination, electrocardiogram, and echocardiogram were unremarkable. A possible mild left lower pulmonary vein stenosis was noted without hemodynamic significance at this time. Given his excellent repair with no hemodynamic issues, the patient was recommended to return in three years with an electrocardiogram, echocardiogram, and chest-xray, with no restrictions on activities or cardiac medications.

At his last visit at 8 years of age, again, cardiac examination, electrocardiogram, and echocardiogram were unremarkable. A possible mild left lower pulmonary vein stenosis was again noted without hemodynamic significance at this time. He was still asymptomatic, according to his mother. He was active and had no obvious problems with chest pain or palpitations. His mother was questioning whether there was any need for further concern about the sternal wires. The patient was recommended to return in three years with an electrocardiogram, echocardiogram, and chest-x-ray, with no restrictions on activities or cardiac medications, but was subsequently lost to follow-up. As the subject was ascertained prior to the advent of molecular cytogenetics methods and no remnant material exists, neither the exclusion of mosaicism in other tissues nor the inheritance of the extra chromosomes could be confirmed.

2.1.2 Patient 2

Chromosome analysis confirms an abnormal male karyotype 48,XXY,+18 in peripheral blood (30 metaphases counted and five fully analyzed) taken at four days old (see Figure 2); the patient was receiving care at an outside hospital. These findings are interpreted as a male with Klinefelter syndrome and trisomy 18 or Edwards syndrome (KS + T18). Indications for testing included multiple congenital anomalies (skeletal system, heart, hypotonia), which created concern for trisomy 18 or 13. Birth history included polyhydramnios and an otherwise normal delivery at 38 weeks. Noted features upon physical examination included hypotonia, a hairy mole, thin ribs, short forearms, and an absent sacrum on x-ray. An increased spleen was noted on physical exam, along with hand contracture, ulnar wrist deviation, and medial deviation of the big toe. As the subject was ascertained via an outside hospital, no additional clinical information could be obtained beyond the provided testing indication on the testing requisition. Since the subject was ascertained prior to the advent of molecular cytogenetics methods and no remnant material exists, neither the exclusion of mosaicism in other tissues nor the inheritance of the extra chromosomes could be confirmed.

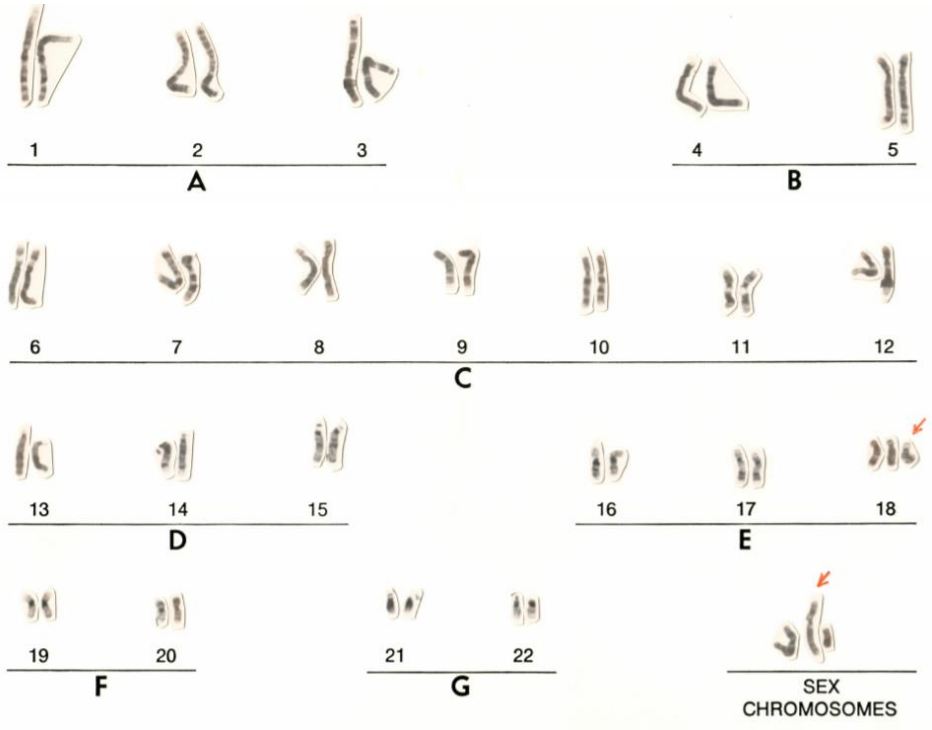

Figure 2 G-banded karyotype at four days old showing trisomy 18 and XXY.

3. Discussion

From the literature, at least five live-born cases bearing double autosomal trisomy [+8/+14; +8/+21; +13/+18; +13/+21; and two instances of +18/+21] [12] are described. In the latter case, a combined phenotype of both trisomy 21 and trisomy 18 was noted [12]. Mosaic autosomal double aneuploidy is incredibly rare in live-born individuals [12]. Notably, no such cases bearing double autosomal trisomy (non-mosaic or mosaic) were present in a historical review of live-born cases from the JHH Cytogenomics Laboratory (from the early 1960s to the present), consistent with its noted rarity in the literature.

As acrocentric (autosomal) with gonosomal double aneuploidy comprises a majority of historical constitutional cytogenetic reports, an internal case review identifies two additional cases of full autosomal [trisomy 21 or trisomy 18] with gonosomal (XXY) double aneuploidy in all cells examined from peripheral blood. Notably, no instances of Turner (monosomy X) or polysomy X (XXX or XXXX) were observed with an autosomal aneuploidy in our laboratory, a karyotype previously described in the literature.

3.1 Patient 1: Klinefelter-Down

Patient 1 has an XXY complement along with trisomy 21. Independently, Down syndrome (DS) and Klinefelter syndrome (KS) are the most common chromosomal aneuploidies in humans, with an incidence of one in 700 live births for trisomy 21 and one in 1,000 for Klinefelter [13]. The first instance of this double trisomy was described by Ford et al. in 1959 [14]. Prior reports suggest that double (autosomal with a gonosomal) aneuploidy may be more frequent than simply multiplying the frequencies of each of the aneuploidies. The possibility of increased frequency might be explained by an individual predisposition to nondisjunction [15]. Some estimates for KS and DS suggest it is a relatively frequent finding (co-incidence 0.098%) [16]. Given the frequency in the population (and presence in the literature) taken together, the combination may generally be better tolerated than either condition alone. Trisomy 21 is associated with advanced maternal age. However, the occurrence of the paternal or maternal meiotic nondisjunction of the extra X chromosome is equally distributed. If the extra X is maternal in origin, then nondisjunction occurred in either the first or second meiotic division. In contrast, a paternally inherited extra X can only derive from nondisjunction in the first meiotic division [17]. The parent of origin of the extra chromosomes and the step at which meiotic nondisjunction occurred were not assessed in this older historical case as no remnant material exists. One report approximates that at least 67 such cases exist in the literature [18], while others have estimated at least 82 postnatal cases of KS + DS are described [19]. At least one instance of presumably monozygotic twins bearing this double trisomy and presenting with typical features of DS is described [13]. A 1963 case report describes two independent sibling duos with one child having KS and the other having DS [20], raising the possibility of increased predisposition for nondisjunction events in some rare cases.

As a common aneuploidy syndrome, individuals with KS are not generally considered at increased risk for major structural malformations like congenital heart defects (CHD). However, slight increases in morbidity/mortality linked with CHD and other congenital anomalies have been described [21, 22]. In contrast, there is an abundance of literature regarding the frequency and types of CHDs in DS. The American Academy of Pediatrics (APA) endorses that all patients with DS have a postnatal echocardiogram to evaluate for complex CHDs [22]. Into adolescence and adulthood, concern for a valvar disease may warrant echocardiography with Doppler for symptomatic DS patients [22]. Specific phenotypes for non-mosaic (KS + DS) may include congenital heart defects such as atrial and atrioventricular septal defects [23]. At least 15 such individuals with congenital heart disease are described worldwide, of which at least 14 individuals were live-born [18, 23]. At birth or in early postnatal life, a presentation of DS may be observed, with KS symptoms manifesting at puberty. Potential phenotypic indicators may include genitalia developmental abnormalities, delayed or absence of puberty, and features of hypergonadotropic hypogonadism [19, 23]. A taller stature and epileptic seizures and behavioral issues have also been described in association with the

KS component in KS + DS cases [24]. At birth, the primary concern for the single KS + DS Hopkins patient was the management of his cardiac features, which required surgical repair (see Table 1). While the sole case identified at JHH case was non-mosaic, at least one mosaic case of double aneuploidy with KS and DS is described. The individual had a 47,XXY/48,XXY,+21 (4%/96%) karyotype, conferring milder stigmata of DS and development of normal height and a micropenis [25]. This adds to the literature one more additional live-born double aneuploidy case associated with CHD defect and who was ultimately given a good prognosis following surgical repair.

Table 1 Klinefelter + Down Syndrome Clinical Features.

Clinical findings of reported cases with Klinefelter and Down syndromes (48,XXY,+21) and Congenital Heart Disease.					
Authors	Karyotype	Comment	Down syndrome features	Potential Klinefelter syndrome features	Congenital Heart Disease
Hustinix et al. (Twins) [26]	48,XXY,+21	Monozygotic Twins: Second twin passed away due to heart defect.	Brachycephaly, epicanthus, fissured tongue, short, thick fingers and toes, transverse palmar crease and hypermobility of the joints. (7 month old twin pair)	None	First twin, cardiac anomalies; second twin, an open ductus and a septum anomaly.
De Grouchy et al. (Case) [27]	48,XXY,+21		Bilateral epicanthic folds, hypertelorism, transverse palmar crease, microcephaly, thick fissured tongue, bilateral clinodactyly of the 5th digits, undescended testis, small scrotum, and phallus, brachydactyly and brachycephaly. (6 years old)	None	Cardiac anomalies.
Hecht et al. (Case) [28]	48,XXY,+21	Maternal age = 26 yrs; Paternal age = 29 yrs.	Muscular hypotonia, intellectual disability, growth retardation, epicanthic folds, umbilical hernia, spina bifida occulta, brachycephaly, slight nystagmus, Brushfield spots, hypoplasia of the middle phalanx of the 5th digit, furrowed tongue, absence of right 12th rib, small down-folded pinnae, sandal gap, and an upward slant to the palpebral fissures. (8 years old)	Absence of spermatogonia in the tubules characteristic of preadolescent boys with XXY (testicular biopsy).	Mild aortic stenosis and chance of having pulmonary stenosis.
Erdtmann et al. (Case) [29]			Brachycephalic head, hypoplastic nasal bone, loose skin, cone-shaped incisors and slight micrognathia, implanted low and	None	A surcharge of the right auricle. Ventricle compatible.

			malformed ears, bilateral epicanthus and small eyes, hypotrophic and slightly hypotonic muscles, asymmetrical face, short neck with pterygium colli, and narrow palatal arch. (2 years old)		
Efinski et al. (Case) [30]	48,XXY,+21		Low-set ears, muscular hypotonia, eyes slanted downward and inward, saddle nose, narrow shoulders, fissured large tongue, short neck, narrow palatal arch, small penis, and hypertelorism. (15 years old)	Epilepsy seizures and antisocial behavior. Mild gynecomastia in adolescence.	Generalized cyanosis developed during exercise. A systolic murmur.
Akbas et al. (Case) [31]	48,XXY,+21	Maternal age = 25 yrs.; Paternal age = 28 yrs.	Flat nasal bridge, extra skin on the neck, flat face, high palate, hypertelorism, low hair line, epicanthic folds, transverse palmar crease, micropenis and bilateral cryptorchidism, and macrognathia. (2 years old)	None	Atrioventricular septal defect. Pulmonary valve stenosis.
Jeanty and Turner et al. (Case) [24]	48,XXY,+21	Fetus	Short, thick neck, oblique palpebral fissures, and low nasal bridge. (Fetus)	None	Atrioventricular canal defect.
Gerretsen et al. (Case) [32]	48,XXY,+21	Severe feeding and respiratory problems.	Not described (14 months old)	None	Double aortic arch. Small atrial septal defect, ostium secundum type.
Biselli et al. (Case) [33]	48,XXY,+21	Maternal age = 13 yrs; Paternal age = 24 yrs.	Low weight and stature, flat nasal bridge, sandal gap sign, muscular hypotonia, brachycephaly, hypertelorism, epicanthic	None	Interatrial communication.

			folds, slanted palpebral fissures, and transverse palmar crease. (3 months old)		
Shen et al. (Case) [34]	48,XXY,+21	Maternal age = 30 yrs; Paternal age = 32 yrs.	Transverse palmar crease, brachycephaly, flattened against the head, low-set ears, flat facial profile, short, thick neck, low hair line, sandal gap sign, high palate, macrognathia, flat nasal bridge, hypertelorism, micropenis, slanted palpebral fissures. (4 months old)	None	Ventricular septal defect with ductus arteriosus and large atrial septal defect. Tricuspid regurgitation and pulmonary hypertension.
Shu et al. (Case) [35]	48,XXY,+21	Maternal age = 21 yrs.; Paternal age = 23 yrs.	Anterior fontanelle and flat without broadening cranial suture, normal genitalia. On admission, showed hypertonia, tachypnea, and cyanosis. Hypertelorism and low set ears. Exudative lesions present in the lungs. (1 day old)	None	Atrial septal defect (ostium secundum), enlarged right ventricle, and mild tricuspid valve regurgitation.
Bozdogan et al. (Case) [36]	48,XXY,+21	Maternal age = 36 yrs; Paternal age = 35 yrs.	Hypothyroidism, including flat face, upslanting palpebral fissures, a flat nasal bridge with epicanthal folds, small nose, micrognathia, microcephaly, low set ears with overfolded ear lobes, brachydactyly, bilateral single palmar creases, and sandal gap deformity, 3rd percentile for height, 3 to 10th percentile for weight, and	None	Atrial septal defect, ventricular septal defect, and patent ductus arteriosus.

			3rdpercentile for head circumference, and hypotonia. (4 months old)		
Rodrigues et al. (Case) [23]	48,XXY,+21	Maternal age = 23 yrs; Paternal age = 24 hrs.	Epicanthic folds, muscle hypotonia, excess nuchal fluid, small ear and nose, flat nasal bridge, brachycephaly, and hydrocele. (28 days old)	None	Complete atrioventricular septal defect with Rastelli type B and significant left ventricular failure, moderate atrioventricular valve regurgitation, right-sided heart failure, and preserved systolic function.
Alallah et al. (Case) [18]	48,XXY,+21	Maternal age: 42 yrs; Paternal age: 50 yrs.	Broad forehead, upward slanting eyes, infraorbital crease, hypertelorism, depressed nasal bridge, flat philtrum, low-set malformed ears with attached ear pinnae, and micrognathia with a large tongue and high arched palate, and a short and webbed neck, mild hypotonia, hypothyroidism, and recurrent chest infection. (discharged after 38 days old)	None	Moderate, patent ductus arteriosus, two ventricular septal defects (anterior and posterior), and coarctation of the aorta.
Current Case	48,XXY,+21	Known prenatally	Unavailable; successful heart repair otherwise asymptomatic; (Alive and well as of 8 years old)	None	Tetralogy of Fallot, a complete common atrioventricular canal defect; pulmonary vein stenosis was again noted without hemodynamic significance; residual primum atrial septal defect that was repaired along with partial re-closure of residual mitral valve cleft.

Modified from Rodrigues et al. [23] and Alallah et al. [18].

3.2 Patient 2: Klinefelter-Edwards

Patient 2 has an XXY complement (KS) with trisomy 18 or Edwards (KS + T18). KS is one of the most common chromosomal aneuploidies in humans, as stated above. While T18 is observed in about 1 in 5,000 live-born infants, it can be more common in pregnancy with affected fetuses frequently not surviving to term. The first documented non-mosaic livebirth for this double trisomy combination was reported in 1968 [37]. While each trisomy independently may be common, the number of clinical reports describing both in the same individual is limited. Given the T18 and associated features, and its poor prognosis, genetic counseling focuses on the T18 phenotypes in early life [38], compared to the better prognosis associated with the KS finding. Prevalence for T18 is associated with increased maternal age, whereas 47,XXY (KS) incidence is not [39]. The parent of origin of the extra chromosomes and the step at which meiotic nondisjunction occurred were not assessed in this older historical case as no material exists. To date, at least eleven non-mosaic cases are reported worldwide [38]. Features of this double aneuploidy combination can include micrognathia, clenched hands, and congenital heart defects reflective of T18 and cryptorchidism, which is seen in KS [40]. This adds to the literature one additional live-born case with KS + T18 presenting with multiple congenital anomalies, including cardiac with no known genitourinary involvement in early life (see Table 2).

Table 2 Klinefelter + Edwards Syndrome Clinical Features.

Clinical findings of reported live-born cases with Klinefelter and Edwards syndromes (48,XXY,+18).				
Authors	Karyotype	Comment	Edwards syndrome features	Potential Klinefelter syndrome features
Haylock et al. (Case 2) [41]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 45 yrs; Paternal age = 47 yrs.	Ventricular septal defect, patent foramen ovale, left chylous pleural effusion, horseshoe kidney, facial dysmorphism, micrognathia, absent corpus callosum, clenched hands, neonatal death. (16 days old)	None
Cohen and Bumbalo (Case) [42]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 21 yrs; Paternal age = 35 yrs.	Delivery at 40 weeks, 2,670 g, facial dysmorphism, micrognathia, clenched hands, rocker-bottom feet, normal male genitalia, clinodactyly, total anomalous venous drainage, single atrium, signal ventricle, right ventricular hypertrophy, neonatal death. (16 weeks old)	Undescended testes.
Zellweger and Abbo (Case 1) [43]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 23 yrs; Paternal age = 29 yrs.	Delivery at 43 weeks, 2,070 g, high-arched palate, ventricular septal defect, patent ductus arteriosus, facial dysmorphism, micrognathia, clenched hands, neonatal death. (10 weeks old)	None
Henchman et al. (Case) [44]	47,XXY/48, XXY,+18	Mosaic; Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 23 yrs; Paternal age = 26 yrs.	Delivery at 40 weeks, 2,140 g, clinodactyly, ventricular septal defect, patent ductus arteriosus, enlargement of right kidney, facial dysmorphism, micrognathia, clenched hands, neonatal death. (3 months old)	None

Bach et al. (Case) [45]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 23 yrs; Paternal age = 23 yrs.	Delivery at 42 weeks, 2,700 g, facial dysmorphism, micrognathia, clenched hands, neonatal death. (6 weeks old)	None
Nielsen et al. (Case) [46]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 42; Paternal age = 50 yrs.	Delivery at 41 weeks, 2,000 g, ventricular septal defect, syndactyly, facial dysmorphism, micrognathia, clenched hands, congenital diaphragmatic hernia, dilated renal tubules, neonatal death. (21 hours old)	None
Rogers et al. (Case) [47]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 24 yrs; Paternal age = NA.	Delivery at 30 weeks, 640 g, micrognathia, bilateral cataracts, contracture of left wrist, generalized hirsutism, facial dysmorphism, clenched hands, neonatal death. (4 hours old)	None
Hanna et al. (Case) [48]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal and Paternal ages = NA.	Gastroschisis, facial dysmorphism, clenched hands.	None
Van Ravenswaaij-Arts et al. (Case) [49]	48,XXY,+18	The child proper had a 46,XY/47,XY,+3/48,XXY,+18 mosaicism with the clinical symptoms of trisomy 18; Parental Origin of Aneuploidy unknown; PZM (suspected for Chrs. 18 and X); Maternal age = 26 yrs; Paternal age = NA.	Prenatal ultrasound at 31 weeks: intrauterine growth restriction, polyhydramnios, bilateral cleft lip. Amniocentesis: 47,XY,+3/48,XXY,+18. Delivery at 38 weeks, 1,746 g, bilateral cleft lip and palate, ventriculomegaly, camptodactyly, an atrioventricular septal defect, hypoplasia of cerebellar vermis, facial dysmorphism, clenched hands, micropenis, cryptorchidism, neonatal death. (10 days old)	None

Komwilaisak et al. (Case) [50]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 21 yrs; Paternal age = NA.	Prenatal ultrasound at 33 weeks: intrauterine growth restriction, polyhydramnios, single umbilical artery, micrognathia, bilateral club hands, clenched hands, rocker-bottom feet. Cordocentesis: 48,XXY,+18. Delivery at 38 weeks, 2,200 g, microcephaly, bilateral cataracts, microtia, two-vessel cord, facial dysmorphism, micropenis, neonatal death. (18 days old)	Undescended testes.
Li et al. (Case) [51]	48,XXY,+18	Parental Origin of Aneuploidy (Maternal)/Cell stage of nondisjunction MI (Chrs 18 and X); Maternal and Paternal ages = NA.	NA	None
Hou (Case) [52]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal age = 21 yrs; Paternal age = NA.	Intrauterine growth restriction, polyhydramnios in late gestation. Delivery at 39 weeks, 2,040 g, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, facial dysmorphism, micrognathia, microcephaly, single umbilical artery, congenital diaphragmatic hernia, left renal hypoplasia, right hydronephrosis, clenched hands, clinodactyly,high-arched palate, a normal penis, inguinal hernia, cryptorchidism. (alive at 15 months old)	None

Begam et al. (Case) [53]	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal and paternal ages = NA.	Prenatal ultrasound at 34 weeks: intrauterine growth restriction, choroid plexus cysts, cerebellar hypoplasia, ventricular septal defect, club feet, clinodactyly, pectus excavatum. Amniocentesis: 48,XXY,+18. Facial dysmorphism,clenched hands, neonatal death. (2 days old)	None
Current case	48,XXY,+18	Parental Origin of Aneuploidy/Cell stage of nondisjunction unknown; Maternal and Paternal ages = NA.	Birth history included polyhydramnios. Delivery at 38 weeks. Multiple congenital anomalies (skeletal system, heart, hypotonia), hypotonia, a hairy mole, thin ribs, short forearms, and an absent sacrum on x-ray, increased spleen, hand contracture, ulnar wrist deviation, and medial deviation of the big toe. Concern for trisomy 18 or 13. (Alive and well at 4 days old)	None

Chr = chromosome; MI = meiosis I nondisjunction error; MII = meiosis II nondisjunction error; PZM = postzygotic mitotic error; NA = not available; Yrs = years old.

Modified from Chen et al. [54].

4. Conclusion

Currently, the availability of non-invasive prenatal screening (NIPS) has resulted in the identification of fetal aneuploidies [55], among other findings. In comparing the performance of different NIPS platforms for the common trisomies, the SNP-based method has a higher detection rate and lower false positive rate than massively parallel shotgun sequencing [56]. While NIPS is considered to have a high positive predictive value (PPV) for the detection of trisomy 21 or trisomy 18 in singleton pregnancies (99%, 97.7%, respectively) [57], the detection rate for 47,XXY is lower (93%) [58]. Invasive confirmation testing is still recommended to rule out a false positive. While both cases identified at JHH predated NIPS testing, future cases of double and multiple aneuploidy may be identified prenatally [55]. It is anticipated that most pregnancies with double and multiple aneuploidy will result in spontaneous abortion [55]. While a rare possibility, clinicians may encounter the scenario of double aneuploidy in rare situations of atypical or blended phenotypes reminiscent of these syndromes in the prenatal and neonatal setting. It also raises the possibility that not all associated features may present within the neonatal period, as with KS. Further work is needed to identify and compile rare double aneuploidy cases, both mosaic and complete forms, to improve genotype-phenotype correlations [59, 60].

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Author Contributions

J. Murry conceived the topic and wrote the manuscript. Y. Zou contributed to the intellectual content through the review and edits to this body of work.

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Competing Interests

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