# Double Aneuploidy of Down Syndrome (Trisomy 21) and Jacobs Syndrome (Trisomy XYY) with Complete Tracheal Rings Deformity: Case Report and Literature Review

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## Abstract

Down syndrome (DS, trisomy 21) with an extra copy of chromosome 21 is one of the most common aneuploidies in humans. Jacobs syndrome or XYY syndrome (trisomy XYY) with an extra copy of sex chromosome Y is a rare sex chromosome trisomy in males. Double aneuploidy (DA) with an extra copy of chromosome 21 and sex chromosome Y is an extremely rare occurrence. Most trisomy 21 results from nondisjunction during maternal oocyte meiosis-I, whereas trisomy XYY is results from nondisjunction during paternal spermatocyte meiosis-I. We present a case of natural conception premature newborn of 30.4 weeks gestational age who had a DS facial phenotype with extensive syndactyly on both hands and feet. Other multisystem congenital anomalies were discovered, including mal-aligned perimembranous ventricular septal defect, bicuspid aortic valve, Dandy–Walker malformation's tetraventriculomegaly, and a rare complete tracheal rings deformity (CTRD) with trachea stenosis. Prenatal amniocentesis and postnatal chromosomal karyotyping analysis detected 48, XYY, +21 nontranslocation trisomy 21, and free-lying Y chromosome without translocation. The existence of DA is rarely reported in literature reviews. In this review, we will discuss the characteristics of DS and Jacobs syndrome as well as the associated multiorgan malformation including the rare lethal CTRD.

**Keywords**
- aneuploidy
- complete tracheal rings defect
- double aneuploidy
- Down syndrome
- extra chromosome
- Jacobs syndrome
- trisomy 21
- trisomy XYY
- XYY syndrome

Aneuploidy is one of the most common causes of chromosomal abnormalities in humans. Aneuploidy pregnancies are frequently nonviable in-utero.[1] Cytogenetic studies of pregnancy losses estimated that around 80% of pregnancy losses were due to aneuploidies.[1–3] Trisomy (extra copy of a chromosome) is one of the most frequent chromosomal aneuploidies.[1] Double aneuploidy (DA) in a live-birth newborn is a rare occurrence. Majority of DA embryos are incompatible with life.[4] We presented a rare DA preterm live-birth male from a natural conception pregnancy with extra copy of autosome

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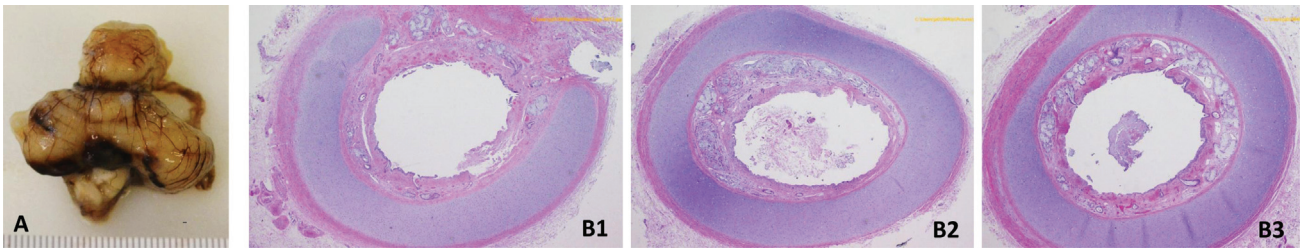


**Fig. 1** (**A**) Cerebellar hypoplasia, H&E, × 20. (**B**) Tracheal stenosis. Tracheal cartilage plate (**B1**) and complete tracheal cartilage ring (**B2**, **B3**), H&E, × 20.

chromosome 21 (trisomy 21) and extra copy of sex chromosome Y (trisomy XYY) which was detected through pre- and postnatal chromosomal analysis using high-resolution GTW banding (650 banding; G-bands by Trypsin using Wright stain). Our literature searches (PubMed) of Down syndrome (DS) with trisomy XYY (T-XYY) revealed that there were only 14 published cases from 1965 to 2000, 2 cases of mosaicisms, and only 1 case published after 2000 where advanced cytogenetic test becomes more widely available.

Case presentation: this is a case report of a neonate with DS features weighing 1,140 grams delivered by urgent repeat cesarian section due to maternal severe preeclampsia at $30^{4/7}$ weeks of gestation after completing two full courses of prenatal steroid (Betamethasone) within 2 weeks apart and prenatal magnesium sulfate for fetal neuroprotection. Mother was a 31-year-old G6P3. Father was a healthy 24-year-old. There was no family history of congenital malformations or consanguinity. Pregnancy was complicated by polyhydramnios, preterm labor, and preeclampsia (treated with hydralazine, magnesium sulfate, labetalol, and procardia). Fetal ultrasound detected congenital heart defect, nuchal thickening, and intrauterine growth retardation (third percentile by Hadlock) with abnormal umbilical Doppler flow. Amniocentesis cytogenetic test resulted in 48, XYY, +21.

At birth, the neonate responded to routine neonatal resuscitative measures. Apgar scores were 7 and 9 at 1 and 5 minutes of life, respectively. Respiratory status began to worsen at approximately 6 minutes of life. The patient eventually required intubation with ventilator support. During intubation, it was unable to pass the 2.5-mm endotracheal tube (ET-tube) below the clavicle level. Direct laryngobronchoscopy conducted by pediatric ENT (ear, nose, and throat) revealed severe tracheal stenosis from vocal cords to carina for suspected complete tracheal rings deformity (CTRD), and tracheal balloon dilatation was performed (►**Fig. 1**). The patient was intubated with uncuffed ET tube 2.5 mm in size as a temporary tracheal stent and kept under the sedated–paralyzed condition to prevent accidental extubation of the critical airway.

The newborn had DS facial features of low-set ears, slanted palpebra fissure, brachycephaly, redundant posterior neck skin, and wide, flat nasal bridge. Extensive syndactyly was seen in both hands' fingers and feet's toes (►**Fig. 2**). Postnatal cranial ultrasound, complete abdominal ultrasound, and echocardiography revealed Dandy–Walker malformation with tetraventriculomegaly, malaligned perimembranous ventricular septal defect, bicuspid aortic valve, and severe pulmonary hypertension (►**Table 1**). Postnatal chromosomal karyotyping analysis detected 48, XYY, +21 nontranslocation trisomy 21 (T-21) and extra free-lying Y chromosome without translocation (►**Fig. 3**). Placenta pathology demonstrated small size placenta (< 10th % weight) with features of decidual vasculopathy exhibiting hypoplastic and hypovascular of the distal villi.

The complexity of the patient's medical condition including severe trachea stenosis, severe pulmonary hypertension, congenital heart defect, and prematurity, the medical team recommended a palliative care approach to parents. Multisubspecialty teams (ENT, cardiology, genetic, neonatal intensive care unit) discussed with parents the extremely poor prognosis regardless of any intervention. Parents decided to discontinue medical care. The patient died at 8 days old, and parents consented for a complete autopsy. Both parents declined further genetic testing.

## Discussion

### Aneuploidy

Aneuploidy is abnormal chromosome numbers in each cell. Normal human karyotype contains 22 pairs of autosome chromosomes plus a pair of sex chromosome. Abnormal numerical arrangement of the chromosomes in each cell

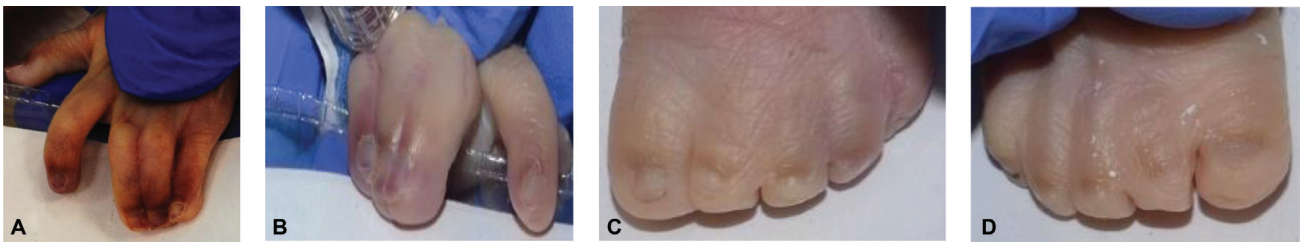


**Fig. 2** Digit malformations. Syndactyly of finger 3–5 in the left hand (**A**) and right hand (**B**). Syndactyly of toe 1–5 in the left foot (**C**) and right foot (**D**). Clinodactyly of fifth toes in the left foot (**C**) and right foot (**D**), H&E, × 20.

**Table 1** Autopsy findings

| Organ system | Complete autopsy finding |
|---|---|
| Facial phenotype | • Craniofacial dysmorphism: brachycephaly, flat occiput, frontal bossing, triangle face, short midface, bilateral mild up slanted palpebral fissures, mild hypertelorism and epicanthal folds. Bulbous nose, low-set ears, absent philtrum, thin lips. Short slightly webbed neck. |
| Central nervous system | • Brain: weighed 184 grams (reference range for 31 weeks' gestation 180 ± 34 g). The cerebral hemispheres were approximately equal in volume and generally symmetrical. Dandy–Walker malformation with mildly dilated fourth ventricle and cerebellar hypoplasia.<br>• Cranial nerve: absence of bilateral olfactory nerves.<br>(►**Fig. 1A**) |
| Airway-esophagus | • Larynx, Thyroid and Esophagus: normal.<br>• Thymus: small weighed 1.0 g (reference range for 31 weeks' gestation 4.0 ± 3.4 g).<br>• Trachea: normally positioned and showed hourglass-like stenosis of a portion of the middle segment. Tracheal lumen measured 0.5 cm in the proximal, 0.35 cm in the mid and 0.2 cm in the narrowest segments in diameter. The cutting surface demonstrated ring tracheal cartilage segmentally, the narrowest segment (0.2 cm in diameter) had complete tracheal cartilage rings. Tracheal epithelial erosion, immature squamous metaplasia was also noted.<br>(►**Fig. 1B**) |
| Cardiovascular pulmonary | • Thoracic organs: were in normal anatomic location.<br>• Ribs: elastic rib cage with bifid left third and fifth ribs.<br>• Lungs: normal lobation of the right lung, while the left lung had two incomplete separated lobes. The right lung weighed 13 g and the left 10 g, with combined weight of 23 g (reference range for 31 weeks' gestation, total lungs' weight: 28.5 ± 13.2 g).<br>• Heart: weighed 9.0 g (reference range for 31 weeks' gestation 9.0 ± 2.8 g), with bifid apex. Dissection of the heart revealed a patent ductus arteriosus, small 0.3 cm central perimembranous ventricular septal defect. Redundant and irregularly thickened tricuspid valve leaflets, bicuspid aortic valve. |
| Abdomen | • Abdominal organs: were in normal anatomic location.<br>• Liver, gallbladder, adrenal glands: normal.<br>• Spleen: weighed 1.0 g (reference range for 31 weeks' gestation 4.0 ± 1.2 g). 0.3 cm in diameter accessory spleen was noted around the pancreatic tail.<br>• Intestine: An ileal (Meckel's) diverticulum was noted at 13.5 cm from ileocecal valve. NO stenosis, dilation or exudates observed. Normal mesentery, with mesenteric root taking a normal diagonal course.<br>• Kidneys: normally positioned. The right and the left kidney each weighed 4.0 and 3.0 g (reference range for 31 weeks' gestation, combined: 13.7 ± 5.2 g) and lobation is normal, benign small renal cortical cysts noted. |
| Extremities | • Hands-Fingers: Bilateral five nail-covered fingers showed symmetrically cutaneous syndactyly in finger 3–5 with both first finger clinodactyly and right single palmar crease.<br>• Feet–Toes: All toes were nail-covered and cutaneous syndactyly and prominent heels.<br>(►**Fig. 2**). |
| Genitalia | • Genitalia: external and internal genitalia of male phenotype with both testes in proximal inguinal canal. |

can cause multiorgan maldevelopment, multiorgan dysfunction, and death. Aneuploidy is one of the leading causes of chromosomal abnormalities that is associated with embryo implantation failure, miscarriages, birth defects, and intellectual disabilities.[5] Majority of miscarriages are associated with aneuploidy pregnancies (approximately 70%) with only approximately 0.5% progressing to live birth.[1,2,6] Pregnancy with autosomal chromosome aneuploidy is more likely to perish in-utero compared with sex chromosome aneuploidy.[1] Monosomy (missing chromosome) embryos are more likely incompatible with life compared with trisomy (extra chromosome) except for monosomy of sex chromosomes.[1] However, few trisomy embryos involving certain chromosomes (13, 18, 21, X, and Y) may potentially survive to live birth.[6] Aneuploidy is caused by chromosome nondisjunction (c-NDJ).

c-NDJ is the improper separation of homologous chromosomes or sister chromatids during cell division resulting in aneuploid chromosomes. There are three forms of c-NDJ: (1) meiosis-1 (M-I): missegregation of homologous chromosomes, (2) meiosis-II (M-II): missegregation of sister chromatids, and (3) mitosis: missegregation of sister chromatids. Abnormal cell division can occur in germ cells (meiosis), somatic cells (mitosis), or stem cells (mitosis). Chromosome missegregation can happen during preconception, conception, postconception, and in cancer cells.[5,7,8] Birth defect aneuploidies arise from c-NDJ during (1) maternal oogenesis M-I or M-II (approximately 90%), (2) paternal spermatogenesis M-1 or M-II (approximately 4%), and (3) zygotic mitosis (rare).[6,9] Majority of birth defect aneuploidies are from maternal oogenesis c-NDJ M-I.[6,9] In oogenesis, first meiotic division begins in fetal ovary, enters prolonged arrest phase,

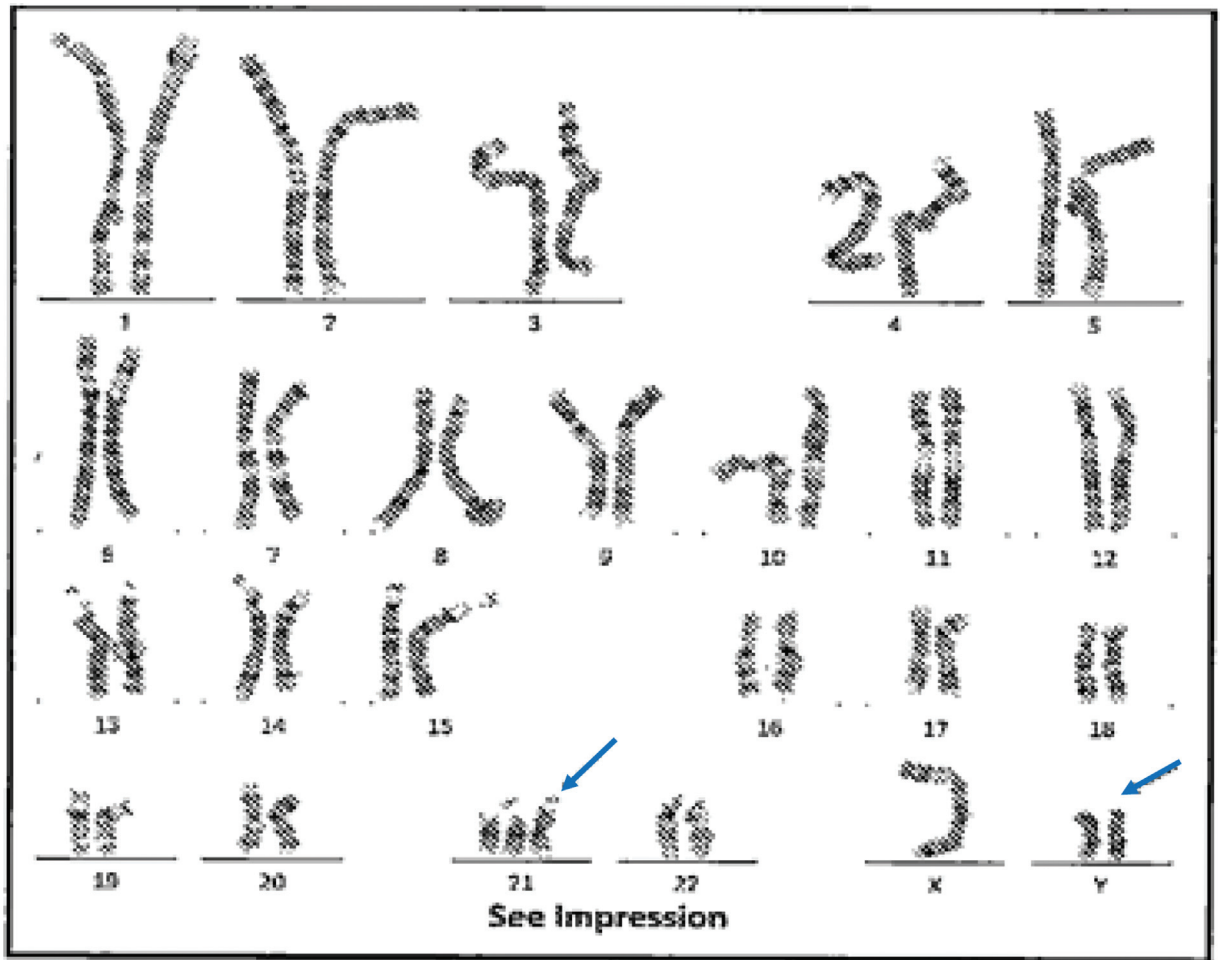


**Fig. 3** Double Aneuploidy: extra copy of chromosome 21 and extra copy of chromosome Y. (GTW banding; high resolution 650 banding).

and completes the cell division cycle during ovulation which occurs at approximately 15 to 50 years later.[9,10] Risk factors for c-NDJ are advanced age, chemical exposure, and environmental exposure.[6,9] The exact molecular mechanisms of c-NDJ are still evolving; however, multifactorial causes involving cell-cycle division have been suggested, which includes susceptible chromosome (acrocentric chromosome), genetic predisposition, kinetochore failure, spindle assembly checkpoint failure, oogenesis propensity to missegregate, failure in homologous recombination, cohesion loss, aging, and exposure to aneugens.[5,7–9,11–14]

## Double Aneuploidy

DA is a coexistence of two chromosome aberrations within the same individual. The first case of DA was reported by Ford et al[15] in 1959, with a case of T-21 (DS) and T-XXY (Klinefelter syndrome).[15] The exact mechanism of DA is not clearly understood. Hypothetically, DA is an aneuploidy of two different chromosomes from two c-NDJ events during meiosis or a single event in a trisomy zygote (mitosis) which can originate from one or both parents. Karyotyping studies of spontaneous abortions showed that DA incidence is around 0.21 to 4.6% of miscarried fetuses.[16–18] DA conceptions tend to be associated with advanced maternal age, fetal anomalies, and increased risk of miscarriages.[1,17] Live-birth DA cases tend to involve trisomy of chromosomes 13, 18, 21, X, and Y.[16] DA with the combination of an autosome chromosome and a sex chromosome is more frequently reported in live birth DA cases than the combination of both autosome chromosomes.[4,17] Lethality of DA depends on the involving chromosomes and the severity of the congenital malformations associated with the affected chromosomes. DA phenotype depends on dominant features from both affected chromosomes except for sex chromosome aneuploidy in which the phenotype features will present later at around puberty age.

## Down Syndrome (Trisomy 21)

T-21 or DS, an extra copy of chromosome 21 (Hsa21), is one of the most common autosomal aneuploidies with incidence estimated around 1 in 700 live births.[19] Genetically, there are four types of DS: (1) complete or nontranslocation T-21 (95%), (2) translocation T-21 (approximately 3% with 1/4 inherited from parent), (3) mosaic T-21 (approximately 2%), and (4) partial T-21 (< 1%; rare).[20] Triplication of Hsa21 occurs from random error that can originate from: (1) maternal oogenesis c-NDJ (95%): at M-I (70%) or M-II (30%), (2) paternal spermatogenesis c-NDJ (5%): at M-I

(20%) or M-II (80%), (3) zygotic mitosis or embryo development (1–2%), and (4) duplication of only a delimited segment of Hsa21 associated with DS phenotype (rare).[21] All DS individuals have specific physical or facial features and intellectual disability.

Advanced maternal age: major risk of DS birth is advanced maternal age (> 35 years old) with the majority of the cases involving M-I errors from the prolonged oocyte dictyotene (arrest) phase during oogenesis.[1,10] However, other associated risks have been proposed which include genetic predisposition, chemical exposure, environmental exposure, diet, hormonal balance, grand-maternal effect, and parental aging.[22]

Diagnosis of DS: prenatal screening test: (1) quad screen at 15 to 22 weeks (β-human chorionic gonadotropin, unconjugated estriol, inhibin A, and pregnancy-associated plasma protein A), (2) fetal ultrasound: nuchal translucency and DS associated anomalies, and (3) cell-free DNA test (as early as 10 weeks). Prenatal DS confirmatory diagnostic test is a complete karyotyping analysis conducted via chorionic villus sampling at 10 to 12 weeks or amniocentesis at 15 to 18 weeks.[20,23] Postnatal diagnostic test on individuals with DS physical/facial features: (1) complete karyotyping analysis is the test of choice to detect any type of DS but requires longer turnover time, and (2) fluorescent in situ hybridization (FISH) of T-21 or quantitative-fluorescent polymerase chain reaction of T-21 with rapid turnover time (24–48 hours); however, if the result is positive, it requires complete karyotyping analysis to confirm the type of DS.[20,23] In translocation DS, complete karyotyping of both parents is necessary to delineate the inherited cause. In our case, both prenatal and postnatal complete karyotyping analyses were conducted. However, we did not test both parents; therefore, we did not have both parents' DNA polymorphic analysis or polymerase chain reaction (PCR) amplification to trace whether the T-21 is of maternal or paternal origin.[21]

Phenotype variation and severity of DS: DS genotype–phenotype molecular pathophysiology is an ongoing research area to correlate various intensities of clinical conditions and/or congenital defects seen in DS individuals. Besides the role of epigenetic factors, currently, there are 200 to 300 protein-coding genes on the triplicated Hsa21 which encode for genes that involve directly or indirectly in regulating multiorgan formation, development, and function (OMIM; https://www.omim.org).[22,23] Gene dosage, gene sensitivity, and chromosome instability hypotheses have been proposed as the mechanisms in DS phenotype–genotype variation and severity.[23] All DS individuals have a common core phenotype of DS craniofacial-physical characteristics, hypotonia, and intelligence disability. The core phenotype of DS characteristics are up-slanted palpebra fissures, small low-set ears, flat nasal bridge, brachycephaly, flat occiput, redundant posterior neck skin, short neck, macroglossia, micrognathia, simian crease, sandal toes, and brachydactyly.[20] Our case had all the core phenotype characteristics of DS. Besides core phenotype, DS individuals can have variable congenital defects and medical conditions that affect multiorgan systems, whereas mosaic DS individuals may or may not have milder clinical conditions as well.[20,23,24]

Common associated congenital anomalies and medical conditions in DS individuals are congenital heart defect (50%), hearing deficits (80%), vision problems (60%), feeding problems (60%), obstructive sleep apnea (60%), laryngomalacia (50%), autoimmune hypothyroidism (50%), dermatologic problems (50%), immune deficiencies (40%), obesity (50%), autism (20%), orthopedic problems (20%), epilepsy (10%), transient myeloproliferative disorder (10%), gastrointestinal anomalies (10%), pulmonary hypertension (5%), congenital hyperthyroidism (5%), tracheomalacia, bronchomalacia, tracheal bronchus, early onset Alzheimer, and male infertility.[20,24] Other less common congenital anomalies and medical conditions are trachea stenosis, cerebellar hypoplasia, Dandy–Walker malformation, syndactyly, autoimmune diabetic mellitus, leukemia, Moya–Moya syndrome, autoimmune arthropathy, celiac disease, and kidney-genitourinary tract anomalies.[20,23–25] Our case had Dandy–Walker malformation, cerebellar hypoplasia (►**Fig. 1A**), small kidneys, small thymus, ileal Meckel's diverticulum, small spleen, and extensive syndactyly (►**Fig. 2**). Advanced in medical care has improved the life expectancy of DS individuals; however, early mortality can increase with the presence of congenital heart defect, congenital airway malformation, and/or pulmonary hypertension.[20]

## Jacob Syndrome or XYY Syndrome or Double-Y Syndrome (Trisomy XYY)

T-XYY, an extra copy of sex chromosome Y, is a rare sex chromosome trisomy in males with a reported incidence estimated around 1 in 1,000 male live births.[26,27] Nearly 85% of T-XYY males have never been actually diagnosed.[26] Majority of T-XYY cases were diagnosed accidentally at adulthood when genetic screening was conducted for other medical conditions such as infertility, behavioral or psychiatry disorder, speech-language delay, or learning difficulty.[27] Contrary to DS, the extra copy of Y chromosome in T-XYY occurs from random error that originates from (1) paternal spermatogenesis NDJ at M-I or M-II (more common at M-II) and (2) zygotic mitosis.[27] Unlike DS, T-XYY is not associated with increased paternal age.

Diagnosis of T-XYY: fetal ultrasound screening abnormalities such as increased nuchal translucency, cystic hygroma, and fetal hydrops tend to be presented in the fetus with trisomy XYY.[28] Prenatal diagnostic test includes (1) cell-free DNA test (noninvasive) or (2) complete karyotyping via CVS or amniocentesis. The postnatal diagnostic test is complete karyotyping.

The phenotype of T-XYY: T-XYY individuals have close to normal features at birth. Physical and clinical features are presented at later age or adulthood. Although phenotype and clinical presentations are mild, a wide range of variety and severity can be seen as well. Core phenotype or characteristics of T-XYY individuals are tall statue (manifested at around 6 years old), behavioral or psychiatric problems (aggressive behavior, attention deficit hyperactive disorder,

autistic spectrum disorder, and bipolar disorder), mild motor developmental delay (hypotonia), speech-language delay, learning difficulty, slightly lower-to-normal IQ, macrocephaly, hypertelorism, and fertility issues.[29] Other physical and clinical presentations that have been reported are cystic acne, thin body habitus, clinodactyly, flat feet, prognathic jaw, macrodontia, mild resting/intention tremor, genitourinary anomalies (hypospadias, microphallus, cryptorchidism, and macroorchidism), risk of asthma, and risk of seizure.[27,29] Despite subtle phenotype and clinical condition, early detection will have a significant role in modifying the outcome.

### Double Aneuploidy in Down Syndrome: with Trisomy XYY (DS-XYY)

An epidemiology study of live birth and miscarriage cases of DS with DA of sex chromosome trisomies estimated the proportion of DS-XYY to be approximately 0.012%, DS-XXX approximately 0.018%, and DS-XXY approximately 0.098%.[4] The lower proportion of DS cases with XYY DA are unclear; however, genetic predisposition and selective fertilization of disomic ovum or disomic sperm have been speculated.[4] DA of DS-XYY arises from two c-NDJ events from paternal and/or maternal origin. In contrast to advanced parental age dependence in the majority of the DA cases, thus far the reported cases of DS-XYY tend to be associated with younger paternal and maternal age.[4] In DS-XYY (►**Fig. 3**), the DS phenotype features will predominate at neonatal age and T-XYY phenotype features will present later. As sexual development depends on the existence of Y chromosome, male phenotypic will be expected in DS-XYY individuals. In our case, the newborn had DS features with normal male gonads. With extensive malformation of multiorgan systems, we offered further genetic tests (exome or genome studies) to both parents which were declined.

### Complete Tracheal Rings Defect: In Down Syndrome with Trisomy XYY

Tracheal stenosis is considered one of the rare congenital features of DS. The prevalence of symptomatic congenital tracheal stenosis in DS is around 0.4%.[30] Congenital tracheal stenosis secondary to CTRD is one of the rare congenital tracheal malformations ($< 1\%$).[31,32] CTRD is excessive growth of the tracheal cartilages at around 8th to 10th week of tracheal embryologic development, which results in circumferentially continuous or nearly continuous cartilaginous tracheal rings without the posterior membranous portion of the trachea or O-shaped tracheal cartilage.[33] Normal tracheal cartilage consists of 15 to 20 C-shaped tracheal cartilages with a normal cartilage-to-posterior membrane wall ratio of 4:1 to 5:1.[32–34] There are several types of CTRD[34–36]: (1) entire tracheal length with similar diameter, (2) long segment ($> 50\%$ tracheal length), (3) short segment stenosis in mid-trachea, (4) funnel-shaped with patent proximal but very small distal rings near the carina, and (5) extended to the bronchus. Majority of the CTRD are associated with congenital heart defects (70%), pulmonary artery anomalies (50%), vascular ring, trachea shortening, reduced mucociliary clearance, lung agenesis, and/or genetic syndromes.[33,34] Isolated CTRD is only approximately 10 to 25%.[33] CTRD is associated with very high mortality (approximately 80–100%) in neonates or infants who presented with severe symptoms and cardiovascular anomalies.[31,36] Our case autopsy demonstrated hourglass or mid-trachea CTRD (►**Fig. 1B**) with pulmonary hypertension, incomplete separation of the left lung lobes, patent ductus arteriosus, perimembranous ventricular septal defect, and bicuspid aortic valve.

Diagnosis of CTRD: computer tomography scan with angiogram of neck and chest or magnetic resonance imaging with angiography of neck and chest. Echocardiogram is recommended to evaluate for any associated congenital heart defect. The gold standard of diagnosis is direct laryngoscopy and bronchoscopy.[30,34,36]

Symptom variation of CTRD: symptoms of CTRD can be variable, which include asymptomatic, stridor, wheezing, subcostal or suprasternal retraction, obstructive apnea, cyanotic spell, chest congestion, recurrent pneumonia, respiratory distress, or fatal respiratory failure.[30,37] However, it is commonly presented as respiratory distress in the newborn period.[36] Symptoms usually will not be significant until tracheal stenosis greater than 50%.[32,34] Severity of the clinical symptoms depends on the degree of the trachea stenosis such as the involved tracheal length, the tracheal diameter, as well as the associated cardiac, regional vascular, and pulmonary anomalies.[35–37] In asymptomatic individuals, respiratory illness may trigger the symptoms or accidentally discover during elective intubation.[30]

Management of CTRD: most CTRD cases with neonatal onset symptoms require surgical intervention due to the small tracheal diameter and the severity of the respiratory insufficiency symptoms.[36] The severity of the respiratory insufficiency may require the use of steroids, humidification, intubation, ventilator, or extracorporeal membrane oxygenation for ventilation-oxygenation support until definitive surgical repair can be performed. Conservative nonsurgical management with close observation for potential tracheal diameter growth can be done for mild respiratory complaints, CTRD length less than 50%, and tracheal stenosis diameter less than 60% of the normal tracheal diameter.[36,37] Current surgical technique options[30,36]: (1) resection and primary anastomosis for short-segment CTRD, (2) slide tracheoplasty (most preferable), (3) patch tracheoplasty with nontracheal autologous tissue from costal cartilage or pericardium, and (4) tracheal transplant with cadaveric tracheal homograft. Tracheoplasty is performed significantly more often in children with DS than in non-DS children.[30] Simultaneous repair of congenital heart defects is advocated; however, complex cardiac defects are associated with an increased mortality rate. Long-term surgical complications are persistent granulation tissue and recurrent stenosis.[38] Although surgical repair of CTRD often leads to a patent tracheal lumen, extensive comorbidity in DS may worsen survival.[30]

## Conclusion

DA pregnancies are highly associated with miscarriages. DA of DS-XYY may not be associated with advanced parental age

and may originate from paternal and/or maternal origin. Live-birth DA of DS-XYY presented with CTRD has never been reported. Extensive syndactyly, Dandy–Walker malformation, and cerebellum hypoplasia which were rarely reported congenital anomalies in DS individuals also presented in this case. DA phenotype depends on the dominant features from both affected chromosomes except for sex chromosome aneuploidy in which the phenotype features will exhibit around puberty. CTRD is commonly associated with congenital heart defect, regional vascular anomaly, and pulmonary anomaly. Mortality of symptomatic CTRD with cardiopulmonary-vascular anomalies in newborn is approximately 80 to 100%. Surgical repair of CTRD with congenital heart defects poses a high mortality risk. Parental consultation regarding high mortality and complexity of DA is important. Ongoing advances in molecular genetic research including exome or genome sequencing as well as the affordability and accuracy of these tests will provide more future insight into the causes and severities of aneuploidies.

### Informed Consent

The case report study, which included the photographs, has received IRB approval from the University of Tennessee Health Science Center and LeBonheur Children's Hospital to conduct the study. Patient's personal information was deidentified in the manuscript article and pictures.

### Authors' Contributions

O.A. was involved in diagnosing, patient care, literature review, obtaining IRB approval, writing the manuscript first draft, manuscript revision, manuscript edition, and approval of the final manuscript as submitted. H.E. was involved in the manuscript edition and approval of the final manuscript as submitted. J.Z. was involved in literature review, pathologic exam, pathologic photograph (autopsy), manuscript edition, and approval of the final manuscript as submitted. B.J was involved in diagnosing, patient care, literature review, and approval of the final manuscript as submitted. M.H. was involved in diagnosing, patient care, literature review, critical review, obtaining IRB approval, manuscript revision, manuscript edition, and approval of the final manuscript as submitted.

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### Conflict of Interest

None declared.

## References

1 Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001;2(04):280–291
2 Brosens JJ, Bennett PR, Abrahams VM, et al. Maternal selection of human embryos in early gestation: insights from recurrent miscarriage. Semin Cell Dev Biol 2022;131:14–24
3 Menasha J, Levy B, Hirschhorn K, Kardon NB. Incidence and spectrum of chromosome abnormalities in spontaneous abortions: new insights from a 12-year study. Genet Med 2005;7(04): 251–263
4 Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. Am J Med Genet A 2005;134A(01):24–32
5 Nagaoka SI, Hassold TJ, Hunt PA. Human aneuploidy: mechanisms and new insights into an age-old problem. Nat Rev Genet 2012;13 (07):493–504
6 Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 2007;16 Spec No. 2((02):R203–R208
7 Levine MS, Holland AJ. The impact of mitotic errors on cell proliferation and tumorigenesis. Genes Dev 2018;32(09):(10):620–638
8 Vázquez-Diez C, FitzHarris G. Causes and consequences of chromosome segregation error in preimplantation embryos. Reproduction 2018;155(01):R63–R76
9 Gruhn JR, Zielinska AP, Shukla V, et al. Chromosome errors in human eggs shape natural fertility over reproductive life span. Science 2019;365(6460):1466–1469
10 MacLennan M, Crichton JH, Playfoot CJ, Adams IR. Oocyte development, meiosis and aneuploidy. Semin Cell Dev Biol 2015;45:68–76
11 Lane S, Kauppi L. Meiotic spindle assembly checkpoint and aneuploidy in males versus females. Cell Mol Life Sci 2019;76 (06):1135–1150
12 Klaasen SJ, Kops GJPL. Chromosome inequality: causes and consequences of non-random segregation errors in mitosis and meiosis. Cells 2022;11(22):3564
13 Potapova T, Gorbsky GJ. The consequences of chromosome segregation errors in mitosis and meiosis. Biology (Basel) 2017;6(01):12
14 More SJ, Bampidis V, Bragard C, et al; EFSA Scientific Committee (SC) Guidance on aneugenicity assessment. EFSA J 2021;19(08): e06770
15 Ford CE, Jones KW, Miller OJ, et al. The chromosomes in a patient showing both mongolism and the Klinefelter syndrome. Lancet 1959;1(7075):709–710
16 Diego-Alvarez D, Ramos-Corrales C, Garcia-Hoyos M, et al. Double trisomy in spontaneous miscarriages: cytogenetic and molecular approach. Hum Reprod 2006;21(04):958–966
17 Reddy KS. Double trisomy in spontaneous abortions. Hum Genet 1997;101(03):339–345
18 Subramaniyam S, Pulijaal VR, Mathew S. Double and multiple chromosomal aneuploidies in spontaneous abortions: a single institutional experience. J Hum Reprod Sci 2014;7(04):262–268
19 Mai CT, Isenburg JL, Canfield MA, et al; National Birth Defects Prevention Network. National population-based estimates for major birth defects, 2010-2014. Birth Defects Res 2019;111 (18):1420–1435
20 Bull MJ. Down syndrome. N Engl J Med 2020;382(24):2344–2352
21 Antonarakis SEDown Syndrome Collaborative Group. Parental origin of the extra chromosome in trisomy 21 as indicated by analysis of DNA polymorphisms. N Engl J Med 1991;324(13):872–876
22 Coppedè F Risk factors for Down syndrome. Arch Toxicol 2016;90 (12):2917–2929
23 Antonarakis SE, Skotko BG, Rafii MS, et al. Down syndrome. Nat Rev Dis Primers 2020;6(01):9
24 Lagan N, Huggard D, Mc Grane F, et al. Multiorgan involvement and management in children with Down syndrome. Acta Paediatr 2020;109(06):1096–1111
25 Lin AE, Santoro S, High FA, Goldenberg P, Gutmark-Little I. Congenital heart defects associated with aneuploidy syndromes: new insights into familiar associations. Am J Med Genet C Semin Med Genet 2020;184(01):53–63
26 Stochholm K, Juul S, Gravholt CH. Diagnosis and mortality in 47, XYY persons: a registry study. Orphanet J Rare Dis 2010;5:15
27 Sood B, Fuentes RWC. Jacobs syndrome. Treasure Island, FL: StatPearls Publishing; 2022
28 Vaknin Z, Reish O, Ben-Ami I, Heyman E, Herman A, Maymon R. Prenatal diagnosis of sex chromosome abnormalities: the 8-year experience of a single medical center. Fetal Diagn Ther 2008;23 (01):76–81

29 Bardsley MZ, Kowal K, Levy C, et al. 47,XYY syndrome: clinical phenotype and timing of ascertainment. J Pediatr 2013;163(04): 1085–1094
30 Fockens MM, Hölscher M, Limpens J, Dikkers FG. Tracheal anomalies associated with Down syndrome: a systematic review. Pediatr Pulmonol 2021;56(05):814–822
31 Bravo MN, Kaul A, Rutter MJ, Elluru RG. Down syndrome and complete tracheal rings. J Pediatr 2006;148(03):392–395
32 Ho AS, Koltai PJ. Pediatric tracheal stenosis. Otolaryngol Clin North Am 2008;41(05):999–1021, x
33 Sinner DI, Carey B, Zgherea D, et al. Complete tracheal ring deformity. A translational genomics approach to pathogenesis. Am J Respir Crit Care Med 2019;200(10):1267–1281
34 Javia L, Harris MA, Fuller S. Rings, slings, and other tracheal disorders in the neonate. Semin Fetal Neonatal Med 2016;21 (04):277–284
35 Schweiger C, Cohen AP, Rutter MJ. Tracheal and bronchial stenoses and other obstructive conditions. J Thorac Dis 2016;8(11): 3369–3378
36 Hofferberth SC, Watters K, Rahbar R, Fynn-Thompson F. Management of congenital tracheal stenosis. Pediatrics 2015;136(03): e660–e669
37 Landry AM, Rutter MJ. Airway anomalies. Clin Perinatol 2018;45 (04):597–607
38 Hewitt RJ, Butler CR, Maughan EF, Elliott MJ. Congenital tracheobronchial stenosis. Semin Pediatr Surg 2016;25(03):144–149