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Dual diagnoses in 152 patients with Turner syndrome: Knowledge of the second condition may lead to modification of treatment and/or surveillance

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Abstract

Turner syndrome is a sex chromosome abnormality in which a female has a single X chromosome or structurally deficient second sex chromosome. The phenotypic spectrum is broad, and atypical features prompt discussion of whether the known features of Turner syndrome should be further expanded. With the advent of clinical whole exome sequencing, there has been increased realization that some patients with genetic disorders carry a second genetic disorder, leading us to

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ADDENDUM

After this manuscript was reviewed, a series of nine patients with pathogenic *RERE* variants were reported to expand the genotype–phenotype correlations (Jordan et al., 2018).

CONFLICTS OF INTEREST

None.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

hypothesize that a “dual diagnosis” may be more common than suspected for Turner syndrome. We report five new patients with Turner syndrome and a co-occurring genetic disorder including one patient with Li-Fraumeni syndrome, Li-Fraumeni and Noonan syndrome, mosaic trisomy 8, pathogenic variant in *RERE*, and blepharophimosis-ptosis-epicanthus inversus syndrome. We also undertook an extensive literature review of 147 reports of patients with Turner syndrome and a second genetic condition. A total of 47 patients (31%) had trisomy 21, followed by 36 patients (24%) had one of 11 X-linked disorders. Notably, 80% of the 147 reported patients with a dual diagnosis had mosaicism for Turner syndrome, approximately twice the frequency in the general Turner syndrome population. This article demonstrates the potential for co-occurring syndromes in patients with Turner syndrome, prompting us to recommend a search for an additional genetic disorder in Turner patients with unusual features. Knowledge of the second condition may lead to modification of treatment and/or surveillance. We anticipate that increased awareness and improved diagnostic technologies will lead to the identification of more cases of Turner syndrome with a co-occurring genetic syndrome.

Keywords

blepharophimosis-ptosis-epicanthus inversus; dual diagnosis; Li-Fraumeni syndrome; Noonan syndrome; *RERE* gene; sex chromosome abnormality syndrome; trisomy 8; Turner syndrome; whole exome sequencing

1 | INTRODUCTION

Turner syndrome is a genetic disorder characterized by an absent or structurally abnormal X chromosome (Bondy et al., 2007; Davenport, 2010; Gravholt et al., 2017; Sybert & McCauley, 2004). Mosaicism, in which there is a combination of 45,X and other karyotypes, occurs in over half of the affected individuals (Hook & Warburton, 1983). Various cardiovascular, thyroid, gastrointestinal, neuropsychologic, mental health, social, skeletal, cutaneous, endocrine, gastrointestinal, immune, and reproductive issues are frequently associated with this condition. Atypical features are usually interpreted as extensions of the Turner phenotype or as coincidental. However, it is increasingly clear that a second co-occurring genetic disorder should be considered in patients with unusual or unexpected phenotypes (Kurolap et al., 2016; Posey et al., 2017).

We report five new patients with Turner syndrome and a co-occurring genetic diagnosis as well as an extensive literature review comparing the frequency of complete and mosaic forms of Turner syndrome and the inheritance patterns of the additional disorders.

2 | CLINICAL REPORTS

Patient 1.

A 9-month-old African American girl presented to another genetics clinic with global developmental delays and noted to have a prominent forehead, high anterior hairline, mildly down-slanted palpebral fissures, hypertelorism, mild epicanthi, nystagmus, low-set ears with increased posterior angulation, overfolded superior helices, hypoplastic fifth fingernails, lymphedema of hands and feet, and hypotonia. Chromosome analysis of lymphocytes

showed non-mosaic 45,X, and FISH probes were negative for the presence of *SRY* and the Y centromere. The patient's appearance was not typical for Turner syndrome. Developmental delays improved with the assistance of physical and speech therapies. An echocardiogram and a renal ultrasound were normal.

At 2 years of age (Figure 1a,b), she presented to the University of Mississippi Medical Center with a 1-month history of difficulty walking. Subsequent magnetic resonance imaging showed a large (6 × 7 cm) peritoneal mass arising from the right adrenal gland that encased multiple major blood vessels and a left paraspinal mass (4 × 2 cm) resulting in severe spinal canal stenosis. Metastases to the bone marrow, right pelvis, and right distal femur were also present. A biopsy of the retroperitoneal mass was performed and the pathology revealed poorly differentiated neuroblastoma with unfavorable histology and no *MYCN*(*N-myc*) amplification. She was treated with four cycles of induction chemotherapy per the Children's Oncology Group protocol ANBL12P1, which consisted of cyclophosphamide, topotecan, cisplatin, etoposide, vincristine, and doxorubicin. Because her tumor was deemed unresectable, she received two additional cycles of chemotherapy and was referred to a surgeon at Memorial Sloan-Kettering Cancer Center (MSKCC) for tumor resection. Following surgery, she received four additional cycles of chemotherapy and radiation therapy and two cycles of immunotherapy with m3f8, a murine antibody under study at MSKCC. Because she developed human anti-mouse antibodies to m3f8, she was unable to proceed with further immunotherapy. Her last oncologic evaluation performed 11 months off therapy at age 4 years and 1 month showed no radiographic or laboratory evidence of active disease.

A targeted next-generation sequencing panel on the tumor revealed the pathogenic variants of *PTPN11* c.922A>G (p.Asn308Asp) and *TP53* c. 844C>T (p.Arg282Trp). Targeted germline testing revealed that the patient had both *TP53* and *PTPN11* variants in her blood, leading to the additional diagnoses of Noonan syndrome and Li-Fraumeni syndrome (LFS). Subsequent familial testing showed that the patient's mother and brother did not carry either the *TP53* or *PTPN11* variants; the patient's father was unavailable for testing.

Patient 2.

A 3-year-old Caucasian girl with dysmorphic features was diagnosed with Turner syndrome at 2 months of age; chromosome analysis on lymphocytes showed 45,X[18]/46,X,idic(X)(p11.2) [2]. She subsequently presented to the University of Mississippi genetics clinic with bilateral blepharophimosis, ptosis, and epicanthus inversus as well as mild micrognathia, mild redundant posterior nuchal skin, protruding ears with mild cupping, mild lymphedema of hands and feet, and dysplastic nails (Figure 1c,d). She was diagnosed with blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) and molecular studies revealed *FOXL2* c.843_859dup17 (p. Pro287Argfs*75).

The patient has undergone multiple ophthalmologic procedures, including bilateral medial rectus recession and a blepharophimosis medial canthus repair at 2 years of age and a subsequent re-recess of the lateral medial rectus at 3 years of age. She had a normal audiological evaluation, normal echocardiogram, and normal renal ultrasound although she

developed high blood pressure at three and a half years of age. She was developmentally appropriate without any history of interventional therapies.

Patient 3.

A 25-year-old Caucasian woman initially presented with short stature to a major Boston pediatric hospital at approximately 6 years of age and was diagnosed with Turner syndrome based on chromosome analysis of lymphocytes showing 45,X. Short stature, ovarian insufficiency, and pigmented nevi were consistent with Turner syndrome; however, dysmorphic facial features, neck webbing, cubitus valgus, and lymphedema were not present. Echocardiography was normal. Growth hormone was administered between ages 6 and 16 years. She began hormone replacement at age 16 years and is currently being treated with a conjugated estrogen.

In addition to Turner syndrome, she was counseled at a major cancer center about the maternal family history of LFS by the same oncologist who had cared for her mother when she was diagnosed with liposarcoma at age 23 years and breast cancer at age 32 years, ultimately dying at age 45 years of complications. The patient's two brothers were also diagnosed with LFS. The younger brother carried the familial *TP53* mutation and died of a brain tumor at age 4 years; the older brother has been treated for a sarcoma of his arm and at age 15 years has not had genetic testing. There were also various cancer diagnoses (breast, colon, stomach, and lung) in numerous members of her extended maternal family, many of whom have undergone genetic testing. The patient was found to have a pathogenic p.Tyr220Cys variant in the *TP53* gene. The breast MRI was negative, and at the last evaluation she had not yet had endoscopy or colonoscopy for gastrointestinal cancers. She continued her estrogen replacement as it is not contraindicated in LFS patients (Bösze, Tóth, & Török, 2006), and is contemplating risk-reducing bilateral mastectomies.

Patient 4.

A 10-year-old Caucasian girl who had been diagnosed prenatally with Turner syndrome (45,X) by amniocentesis has been followed since birth at the University of Iowa genetics clinic (Figure 1e,f). She was briefly evaluated by A.E.L at the 2015 National Turner Syndrome Conference, with subsequent review of relevant medical records. She was born at 37 weeks gestational age to a 34-year-old G4P3SAB1 mother by vaginal vertex delivery. Prenatal ultrasonography at 18 weeks gestational age had shown short femurs, nuchal thickening, intrauterine growth restriction, single umbilical artery, and fetal echocardiography detected coarctation of the aorta. Postnatal echocardiography confirmed coarctation of the aorta (repaired after birth), hypoplastic aortic arch, persistent left superior vena cava, and bicuspid aortic valve. Renal and head ultrasonography was normal.

Postnatal lymphocyte karyotype at age 21 months showed she was, in fact, mosaic for a second cell line with trisomy 8 (45,X[5]/47, XX,+8[15]). Her phenotype included typical Turner syndrome features, such as short stature, low posterior hairline, neck webbing, low-set ears, mild hearing loss, hypertelorism, epicanthi, and melanocytic nevi. Features which were atypical for Turner syndrome, but consistent with trisomy 8 mosaicism included deep palmar and plantar creases, hypoplastic distal phalanx of the fifth finger of the right hand

with absent fingernail, less so on the left hand, and flexion contractures of the fifth fingers. She had developmental delay, otitis media, feeding difficulties, restricted growth, fever with recurrent infections, gastroesophageal reflux, and dental caries. Growth hormone therapy was initiated at age three and a half years and continues to present.

The family was counseled about increased risk of myelodysplasia and malignancy associated with Trisomy 8 mosaicism and that the role of annual monitoring. At age 5 years, she was diagnosed with bilateral pars planitis, a form of uveitis. Treatment has been mainly infliximab supplemented with low-dose methotrexate. She is doing well in fifth grade and in regular classes with minimal accommodations mainly for visual and hearing needs. At eight and a half years, she had a formal cognitive and neuropsychologic evaluation, which showed the Full Scale IQ at the 34th percentile (average) and average range verbal, visual-perceptual, fluid reasoning, working memory, learning of complex auditory-verbal information, and learning and long-term memory of visual content, but borderline-low long-term memory recall and visual-spatial information. No behaviors suggested ADHD. At age 10 years, there was mild aortic root dilation (2.91 cm, Z-score 2.91).

Patient 5.

A 3-week-old biracial (Jamaican-Mexican) girl who had been prenatally diagnosed with mosaic Turner syndrome was evaluated in the MGH Turner syndrome clinic (Figure 1g). Noninvasive prenatal testing showed underrepresentation of X chromosome material suggesting Turner syndrome; maternal karyotype was normal (46,XX). Subsequent chorionic villus sampling showed very low level (2.2%) mosaicism for Turner syndrome (45,X[2]/46,XX[88]). Prenatal ultrasound and fetal echocardiogram were normal. She was born at 39 weeks gestation to a 37-year-old G4P1-2 mother and 39-year-old father. On physical examination, there was macrocephaly without typical features of Turner syndrome, such as neck webbing, pedal edema, or abnormal pinnae. Postnatal peripheral blood (lymphocyte) karyotype at 12 days of age showed mosaicism with a greater fraction of 45,X (60%), that is, 45,X[12]/46,XX[8]. At 20 months, she also had a buccal FISH analysis which showed a slightly lower level of 45,X (29%) Postnatal echocardiography showed a left upper pulmonary venous connection.

When re-evaluated at age 14 months, she had developed premature thelarche and was being treated for myoclonic seizures. There was progressive macrocephaly (occipitofrontal circumference (OFC 49.5 cm, >97th centile), atypical facial features for Turner syndrome (frontal bossing, straight eyebrows), hypotonia and developmental delay. The initial MRI scan of the brain (at 13 months of age) showed T2 hyperintensity in the left anterior temporal lobe, possible low-grade glioma versus cortical dysplasia. A second MRI (at 14 months of age) noted similar size and configuration of nonspecific T2 hyperintense/FLAIR hypointense abnormality within the left anterior temporal lobe, with an apparent small (3 mm) focus of cortical enhancement along the anterior aspect of the juxtacortical T2 hyperintense abnormality. The leading interpretation was focal cortical dysplasia/meningiomatosis, although neoplastic conditions were considered such as dysembryoplastic neuroepithelial tumor, ganglioglioma, pilocytic astrocytoma, and other low-grade gliomas. At age 17 months, craniotomy was performed to resect the site of epileptogenesis.

Pathologic examination showed gliosis with some disorganization of neurons as well as a focus of some prominent vessels, suggestive of remote ischemia and/or developmental anomaly.

Because of her atypical phenotype, clinical whole exome sequencing (WES) was performed which showed a de novo heterozygous pathogenic mutation in the *RERE* gene (p.Leu1517Gln [CTG>CAG]: c.4550T>A in exon 23), which is associated with neuro-development disorder with or without anomalies of the brain, eye or heart (MIM # 616975). Her seizures are treated with oxacarbazepine and levetiracetam.

At age 20 months, her height was 82.6 cm (50th centile), weight was 11.4 kg (70th centile), and OFC remained much greater than the 97th centile (51.5 cm, Z score 3.54). She was receiving physical therapy for gross motor delays and making progress crawling, climbing, and walking backwards. Sound field audiogram performed at 21 months was normal. At the most recent (22 months) speech and language evaluation, gestures and pragmatics were age appropriate, play and language comprehension were mildly delayed (15–18 months), and expressive language showed scatter (12–21 months). Her social skills are age-appropriate.

3 | LITERATURE REVIEW

We performed a literature review in PubMed (NCBI) (www.ncbi.nlm.nih.gov/pubmed/) (MeSH: D014424) from January 1951 to January 2018. Only cases with karyotype confirmation of Turner syndrome and at least one additional inherited genetic condition with either clinical or molecular confirmation were included. The cases were divided into the following categories: X-linked disorders, aneuploidies, structural chromosomal rearrangements, autosomal dominant disorders, autosomal recessive disorders, imprinting disorders, and mitochondrial disorders (Supporting Information Tables 1–7).

4 | RESULTS

4.1 | MGH Turner syndrome clinic

From March 5, 2010 until November 30, 2017, we evaluated 172 patients (30% were 45,X, and the remaining 70% had either mosaicism with 46,XX or another cell line, or a structural abnormality of the X chromosome) with a karyotype-proven diagnosis of Turner syndrome followed in the MGH Turner Syndrome Clinic. Of these 172 patients, two (1.1%) are considered to have a “dual diagnosis” either because of a known genetic disorder (patient 3 had LFS) or because clinical suspicion prompted additional genetic testing (patient 5). Patient 4 with Turner syndrome and trisomy 8 is not enrolled into the MGH study and therefore not included in this calculation.

4.2 | Literature

A total of 147 individuals with a dual diagnosis are described in published reports. Of those individuals, 36 had a co-occurring X-linked conditions, including Fragile X syndrome [MIM #300624], Duchenne muscular dystrophy [#310200], Becker muscular dystrophy [#300376], hemophilia A [#306700] and B [#306900], X-linked juvenile retinoschisis [#312700], X-linked retinitis pigmentosa [#304020], Fabry disease [#301500], X-linked dystonia-

parkinsonism [#314250], X-linked hypophosphatemic rickets [#307800], and Aicardi syndrome [#304050]. X-linked (XL) conditions were diagnosed in both mosaic and non-mosaic Turner syndrome cases with approximately equal frequency.

We observed that autosomal dominant, autosomal recessive, mitochondrial and imprinting disorders were also described in individuals with Turner syndrome, listed in Tables 1 and 2. As population-based studies are not available, it is impossible to determine whether they occurred at a higher rate than expected. However, aneuploidies with complex mosaic and non-mosaic karyotypes appear more common in Turner syndrome individuals than if they occurred as independent events. Among reported patients, Down syndrome (47 patients, 32%), trisomy 18 (12 patients, 8%), trisomy 13 (4 patients, 4%), and trisomy 8 (4 patients, 4%) were the most common findings. Whereas most co-occurring conditions were equally distributed between mosaic and non-mosaic patients, aneuploidies of autosomes were largely associated with non-mosaic karyotypes, raising the suspicion that the same meiotic error led to both events. However, further mechanistic studies may be warranted to substantiate this hypothesis.

5 | DISCUSSION

Historically, the predominant diagnostic principle in medicine is that the simplest explanation is the most likely (also known as Occam's razor). Consequently, many closely associated and seemingly unrelated features have been connected with a single underlying etiology (e.g., lymphedema, coarctation of the aorta, and horseshoe kidney in Turner syndrome). Improved diagnostic technologies have challenged this principle by using Hickam's dictum, which counters that patients can have more than one disease (Miller, 1998).

The process of diagnosing and characterizing phenotypes in co-occurring genetic syndromes has arisen recently with the advent of whole genome and exome sequencing. Large cohort studies of families undergoing whole exome sequencing have found that co-occurring genetic syndromes have occurred in 4.3% of their solved cases and 1% of the total WES cohort (Balci et al., 2017; Posey et al., 2017). While the majority of reported co-occurring genetic diagnoses with Turner syndrome are individual case reports, the percentage of dual diagnosis in the MGH Turner syndrome clinic was 1%. This is consistent with the frequency reported in the reported in the total WES cohorts, suggesting that Turner syndrome may need to be considered in patients with atypical features. Reports from WES cohorts have shown that some patients had phenotypes that were a blend of the two molecular diagnoses and the delineation of the features was not elucidated until after molecular testing. Given that Turner syndrome was diagnosed with a karyotype prior to molecular testing, we show evidence in our cohort that atypical findings in Turner syndrome patients could be due to a second underlying molecular diagnosis in some cases. Some patients may be easily distinguished because of very atypical features, such as our patients with BPES and the *RERE* mutation, but other patients may have more subtle differences that may be difficult for the clinician to distinguish. For example, a Turner syndrome patient with significant intellectual disability could have a pathogenic variant in a non-syndromic X-linked intellectual disability gene or another disorder like Noonan syndrome (like our first patient).

In our literature review, it was surprising that additional aneu-ploidies were the most common finding. One potential explanation for this finding is that some women may have a predisposition to multiple aneuploidies. It has been previously established that some women who have at least one aneuploidic conception are at a higher risk for a subsequent conception with aneuploidy or mosaicism (Munné et al., 2004; Vialard, Boitrelle, Molina-Gomes, & Selva, 2011; Warburton et al., 2004). While these reports have primarily focused on trisomic aneuploidies, it is possible that a predisposition to aneuploidic conceptions may explain some of the patients with Turner syndrome and a co-occurring aneuploidy. Another possibility is that increased aneuploidies are an artifact of the timeline of genetic testing with some of these reports dating to the 1960s when only cytogenetic testing was available. As molecular testing continues to improve, we anticipate that the prevalence of the different types of co-occurring genetic syndromes may be affected with an increase in single-gene disorders (including X-linked disorders) are being diagnosed concurrently with Turner syndrome.

Additionally, we observed an increased number of reported patients with mosaicism of the X chromosome with a co-occurring syndrome as compared to the karyotypes of the general Turner syndrome population (80 vs. 50%). It is unclear if the increased prevalence is due to increased survival of the patients with mosaic Turner syndrome with a co-occurring genetic syndrome or if the patients with mosaic Turner syndrome are more likely to be suspected of having a second genetic disorder. With increased awareness of co-occurring genetic syndromes, more patients with Turner syndrome may be found with other co-occurring syndromes.

Unmasking of recessive alleles in the context of monosomy X is an accepted mechanism leading to the high prevalence of XL conditions in individuals with Turner syndrome. Determining if a Turner syndrome patient has a co-occurring genetic syndrome may have significant implications for medical management, prognosis, and reproductive counseling for the patients as well as their family members. Potential examples of this may be the co-occurrence Turner syndrome with Noonan syndrome (similar to patient 1) or an X-linked disorder which may recur in the brothers of affected patients. Likewise, the women with Turner syndrome mosaicism who have the greatest potential to become pregnant may also miscalculate the recurrence risk of certain features in their children.

In conclusion, this article demonstrates that a search for a second disorder should be conducted in a patient with Turner syndrome and unexpected features, rather than to assume the phenotype is atypical for Turner syndrome. There are important implications for the management, prognosis, and reproductive counseling for the patients as well as their family members.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- Abdalla EM, & Nabil KM (2012). Axenfeld-Rieger spectrum in a patient with 45,X Turner syndrome. *Ophthalmic Genetics*, 33, 111–115. [PubMed: 22229795]
- Afonso Lopes L, Benador D, Wacker P, Wyss M, & Sizonenko PC (1995). Turner's syndrome and hypogonadotrophic hypogonadism: Thalassemia major and hemochromatosis. *Journal of Pediatric Endocrinology and Metabolism*, 8, 73–77. [PubMed: 7584702]
- Aver'ianov IN, Bogomazov EA, & Logunova LV (1977). Duchenne's muscular dystrophy in a girl with 45,X/46,XX chromosomal mosaicism. *Zhurnal Nevropatologii I Psikhiatrii Imeni S. S. Korsakova*, 77, 1449–1452.
- Baguena Candela R, Forteza Bover G, & Amat Aguirre E (1965). Un nuevo tipo de aberracion cromosomica: El mosaico normal/trisomia G-monosomia XO. *Medicina Espanola*, 54, 256–262.
- Baguena Candela R, Forteza Bover G, Ortiz Hernandez MD, & Comin Ferrer J (1966). Un caso con estigmas del síndrome de Bonnevie-Ullrich y del mongolismo y cariotipo 45, XO-trisomia G. *Medicina Espanola*, 55, 454–461.
- Bajnóczy K, & Méhes K (1979). Down syndrome with XO/XX mosaicism. *Acta Paediatrica Academiae Scientiarum Hungaricae*, 20, 237–239. [PubMed: 161847]
- Balci TB, Hartley T, Xi Y, Dymont DA, Beaulieu CL, Bernier FP, ... Boycott KM (2017). Debunking Occam's razor: Diagnosing multiple genetic diseases in families by whole-exome sequencing. *Clinical Genetics*, 92, 281–289. [PubMed: 28170084]
- Banes SL, Begleiter ML, & Butler MG (2003). 45,X/46,XY mosaicism and fragile X syndrome. *American Journal of Medical Genetics. Part A*, 116, 99–100.
- Barakat BY & Der Kaloustian VM (1973). Combined autosomal-sex chromosomal mosaicism in a newborn female with mongolism. 4th International Conference on Birth Defects, Vienna, Austria, p. 73.
- Becerra-Solano LE, Arnaud-Lopez L, Diaz-Rodriguez M, Mantilla-Capacho JM, Nastasi-Catanese JA, Ortiz-Aranda M Figuera LE (2008). First case reported of Turner syndrome and trisomy 14 chromosomal mosaicism in a patient. *Clinical Dysmorphology*, 17, 27–30. [PubMed: 18049077]
- Beck B, & Mikkelsen M (1981). Chromosomes in the Cornelia de Lange syndrome. *Human Genetics*, 59, 271–276. [PubMed: 7333580]
- Blaise P, Fumal A, Janin N, Verloes A, Moonen G, & Andris C (2005). Diffuse cortical atrophy in a patient with Turner syndrome and Leber hereditary optic neuropathy. *Journal of Neurology*, 252, 232–233. [PubMed: 15729534]
- Bondy CA, & Turner Syndrome Study Group. (2007). Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. *Journal of Clinical Endocrinology and Metabolism*, 92, 10–25. [PubMed: 17047017]
- Bösze P, Tóth A, & Török M (2006). Hormone replacement and the risk of breast cancer in Turner's syndrome. *New England Journal of Medicine*, 355, 2599–2600. [PubMed: 17167149]
- Brouns R, Eyskens F, De Boeck K, Ceuterick-de Groote C, Van den Broeck M, Van Broeckhoven C, & De Deyn PP (2009). Fabry disease in a patient with Turner syndrome. *Journal of Inherited Metabolic Disease*, 32(Suppl 1), S45–S48. [PubMed: 19343533]
- Chelly J, Marlhens F, Le Marec B, Jeanpierre M, Lambert M, Hamard G, ... De Kaplan JC (1986). Novo DNA microdeletion in a girl with Turner syndrome and Duchenne muscular dystrophy. *Human Genetics*, 74, 193–196. [PubMed: 2876949]
- Chen H, Tyrkus M, & Woolley PV (1978). Double aneuploidy: Partial trisomy 21 and XO/XXX in a family with 12/21 translocation. *Annales de Génétique*, 21, 177–180. [PubMed: 315194]

- Chuansumrit A, Sasanakul W, Goodeve A, Treratravirapong T, Parinayok R, Pintadit P, & Hathirat P (1999). Inversion of intron 22 of the factor VIII gene in a girl with severe hemophilia A and Turner's syndrome. *Thrombosis and Haemostasis*, 82, 1379. [PubMed: 10544944]
- Co ulu O, Tirpan C, Ozkinay F, Gündüz C, & Ozkinay C (2002). The second case with 47, XY, + 8 [38]/45, X0 [12] karyotype. *The Turkish Journal of Pediatrics*, 44, 86–89. [PubMed: 11858390]
- Cohen MM, & Davidson RG (1972). Double aneuploidy (47,XX,21 +–45,X) arising through simultaneous double non-disjunction. *Journal of Medical Genetics*, 9, 242–244. [PubMed: 4261629]
- Davenport ML (2010). Approach to the patient with Turner syndrome. *Journal of Clinical Endocrinology and Metabolism*, 95, 1487–1495. [PubMed: 20375216]
- DeBrasi D, Genardi M, D'Agostino A, Calvieri F, Tozzi C, Varrone S, & Neri G (1995). Double autosomal/gonosomal mosaic aneuploidy: Study of nondisjunction in two cases with trisomy of chromosome 8. *Human Genetics*, 95, 519–525. [PubMed: 7759072]
- Digilio MC, Mingarelli R, Giannotti A, Melchionda S, & Dallapiccola B (1994). Congenital cardiac defect in a patient with 45,X/46, XX, i(21q) karyotype. *Clinical Genetics*, 46, 268–270. [PubMed: 7820944]
- Dobkin C, Radu G, Ding XH, Brown WT, & Nolin SL (2009). Fragile X prenatal analyses show full mutation females at high risk for mosaic Turner syndrome: Fragile X leads to chromosome loss. *American Journal of Medical Genetics Part A*, 149, 2152–2157.
- Edgren J, de la Chapelle A, & Kääriäinen R (1966). Cytogenetic study of seventy-three patients with Down's syndrome. *Journal of Intellectual Disability Research*, 10, 47–62.
- Eiben B, Hansen S, Goebel R, & Hammans W (1989). Tissue-specific 45,X0/47,XY,+13 mosaicism in an 18-year-old woman. *Human Genetics*, 82, 391–392. [PubMed: 2737672]
- Feiertag-Koppen CC, Anders GJ, Stronk MG, & Boevé HJ (1966). Mosaicism of X and G chromosomes. *The Lancet*, 287, 1271.
- Ferrier P, Bamatter F, & Klein D (1965). Muscular dystrophy (Duchenne) in a girl with Turner's syndrome. *Journal of Medical Genetics*, 2, 38–46. [PubMed: 14296923]
- Fontenele R, Costa-Santos M, & Kater CE (2018). 17 α -hydroxylase deficiency is an underdiagnosed disease. High frequency of misdiagnoses in a large cohort of Brazilian patients. *Endocrine Practice*, 24, 170–178. <https://doi.org/10.4158/EP171987.OR> [PubMed: 29144824]
- Franceschini P, Guala A, Camerano P, Franceschini D, Vardeu MP, & Signorile F (1996). Ullrich-Turner phenotype with unusual manifestation in a patient with mosaicism 45,X/47,XX,+18. *American Journal of Medical Genetics*, 62, 26–28. [PubMed: 8779320]
- Freedenberg DL, Gane LW, Richard s. C. S., Lampe M, Hills J, O'Connor R, ... Patil SR (1999). Fragile X syndrome and an isodicentric X chromosome in a woman with multiple anomalies, developmental delay, and normal pubertal development. *American Journal of Medical Genetics*, 85, 197–201. [PubMed: 10398226]
- Gafer U, Shabtal F, Kahn Y, Halbrecht I, & Djaldetti M (1976). Aplastic anemia followed by leukemia in congenital trisomy 8 mosaicism. Ultrastructural studies of polymorphonuclear cells in peripheral blood. *Clinical Genetics*, 9, 134–142.
- Gatrad AR (1981). Congenital dislocation of the knees in a child with Down-mosaic Turner syndrome. *Journal of Medical Genetics*, 18, 148–151. [PubMed: 6453997]
- Gengel N, & Marshall I (2017). Rare presentation of neurofibromatosis and Turner syndrome in a pediatric patient. *Pediatric Reports*, 9, 6810. [PubMed: 28706617]
- Genuardi M, Pomponi MG, Torrisi L, Neri G, Stagni ML, & Tozzi C (1999). 45,X/47,XX, + 18 constitutional mosaicism: Clinical presentation and evidence for a somatic origin of the aneuploid cell lines. *Journal of Medical Genetics*, 36, 496–498. [PubMed: 10874643]
- Gilchrist GS, Hammond D, & Melnyk J (1965). Hemophilia A in a phenotypically normal female with XX-XO mosaicism. *New England Journal of Medicine*, 273, 1402–1406. [PubMed: 5850038]
- Gilgenkrantz S, Briquel ME, Mandel JL, & Oberle I (1986). A case of female hemophilia with a 46,XXr karyotype studied with X-chromosome DNA probes. *Human Genetics*, 72, 157–159. [PubMed: 3455922]
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, ... Backeljauw PF (2017). International Turner Syndrome Consensus Group (2017). Clinical practice guidelines for

- the care of girls and women with Turner Syndrome. *European Journal of Endocrinology*, 177(3), G1–G170. [PubMed: 28705803]
- Grosse KP, Hopfengärtner F, & Schwanitz G (1971). Doppelte aneu-ploidie: 46, XX/45, XO/47, XX, G+. Kasuistische mitteilung. *Humangenetik*, 13, 333–337.
- Guenego A, Morel Y, Ionesco O, Mallet D, & Priou-Guesdon M (2015). A late 17 α -hydroxylase deficiency diagnosis that leads to the discovery of a new CYP17 gene mutation. *Annales d'Endocrinologie*, 76, 71–74.
- Gutmann DH, Brooks ML, Emanuel BS, McDonald-McGinn DM, & Zackai EH (1991). Congenital nystagmus in a (46,XX/45,X) mosaic woman from a family with X-linked congenital nystagmus. *American Journal of Medical Genetics*, 39,167–169. [PubMed: 2063919]
- Harada N, Abe K, Nishimura T, Sasaki K, Ishikawa M, ... Fujimoto M Niikawa M (1998). Origin and mechanism of formation of 45,X/47, XX, +21 mosaicism in a fetus. *American Journal of Medical Genetics*, 75, 432–437. [PubMed: 9482654]
- Hatipoglu N, Kurtoglu S, Kendirci M, Keskin M, & Per H (2010). Neurofibromatosis type 1 with overlap Turner syndrome and Klinefelter syndrome. *Journal of Tropical Pediatrics*, 56, 69–72. [PubMed: 19578129]
- Hook EB, & Warburton D (1983). The distribution of chromosomal genotypes associated with Turner's syndrome: Livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Human Genetics*, 64, 24–27. [PubMed: 6683706]
- Hoppman-Chaney N, Jang JS, Jen J, Babovic-Vuksanovic D, & Hodge JC (2012). In-frame multi-exon deletion of *SMC1A* in a severely affected female with Cornelia de Lange Syndrome. *American Journal of Medical Genetics. Part A*, 158, 193–198.
- Hunter AG (2017). Learning the importance of double diagnosis. *American Journal of Medical Genetics. Part A*, 173, 568. [PubMed: 27748056]
- Hustinx TW, Haar BG, Scheres JM, & Rutten RJ (1974). Autosomal/heterosomal mixoploids: A report on two patients, a female with a 45, Z/47,XX plus 21 and a male with A 45,X/47,XY, plus 21 chromosome constitution. *Annales de Génétique*, 17, 225–234. [PubMed: 4281287]
- Igarashi M, Tsukahara M, Sugio Y, Katayama K, & Kajii T (1985). 46,X, i(Xq)/47,XX,+13 mosaicism. *Annales de Génétique*, 28, 241–244. [PubMed: 3879438]
- Ikonen RS, Lindlöf M, Janas MO, Simola KO, Millington-Ward A, & de la Chapelle A (1989). Coincident maternal meiotic nondisjunction of chromosomes X and 21 without evidence of autosomal asynapsis. *Human Genetics*, 83, 235–238. [PubMed: 2571561]
- Jansen S, Kruger AJ, & Liebenberg G (1991). Turner/Down mosaicism: A case report. *South African Medical Journal*, 79, 731–732. [PubMed: 1828633]
- Jaruratanasirikul S, & Jinorose U (1995). An infant with Down-Turner double aneuploidy: A case report and literature review. *Journal of the Medical Association of Thailand*, 78, 108–112. [PubMed: 7629445]
- Jordan VK, Fregeau B, Ge X, Giordano J, Wapner RJ, Balci TB, ... Scott DA (2018). Genotype-phenotype correlations in individuals with pathogenic RERE variants. *Human Mutation*, 39, 666–675. [PubMed: 29330883]
- Kaczorowska E, Zimowski J, Cicho -Kotek M, Mrozi ska A, Purzycka J, Wierzba J, ... Lipska-Zi tkiewicz BS (2016). Co-incidence of Turner syndrome and Duchenne muscular dystrophy—An important problem for the clinician. *Developmental Period Medicine*, 20, 273–278. [PubMed: 28216480]
- Kan K, Fujita T, Sato S, Okajima S, & Fukui T (1976). A case of pseudo-pseudo hypoparathyroidism associated with sex chromosomal abnormality (45, XO/46, XX mosaic). *Nihon Naika Gakkai Zasshi*, 65, 269–275. [PubMed: 987136]
- Klosovskiĭ BN, Iankova MF, Fateeva EM, & Damanskaia L (1968). On the problem of the De Lange's syndrome. *Pediatrics*, 47, 33–39.
- Knudtson J, Ledaal P, Middelthon-Moe M, & Aarskog D (1988). 45,X/47,XY,+13 mosaicism and Crohn's disease. *Acta Paediatrica Scandinavica*, 77, 922–924. [PubMed: 3207028]

- Ko JH, Lee HS, Hong J, & Hwang JS (2010). Virilizing adrenocortical carcinoma in a child with Turner syndrome and somatic TP53 gene mutation. *European Journal of Pediatrics*, 169, 501–504. [PubMed: 19701813]
- Koçak-Midillioglu I, Karadeniz N, Yalvaç I, Kooçak-Altintas AG, & Duman S (2003). Eight-year follow-up of Axenfeld-Rieger syndrome *with Turner syndrome*. *European Journal of Ophthalmology*, 13, 580–583. [PubMed: 12948319]
- Krutilkova V, Trkova M, Fleitz J, Gregor V, Novotna K, Krepelova A, ... Sedlacek Z (2005). Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline TP53 mutations. *European Journal of Cancer*, 41, 1597–1603. [PubMed: 15925506]
- Kumar M, Lal V, Chapadgaonkar S, & Bhattacharya SK (2014). A rare case of mosaic 45,X/47,XX,+13 in 28-year-old women with secondary amenorrhoea: A case report and literature review. *Meta Gene*, 3, 8–13. [PubMed: 26925371]
- Kurolap A, Orenstein N, Weisz Hubshman M, Tiosano D, Mory A, Levi Z, ... Baris HN (2016). Is one diagnosis the whole story? *Patients with double diagnoses*. *American Journal of Medical Genetics. Part A*, 170, 2338–2348. [PubMed: 27271787]
- Lee KA, Han SH, Choi JR, Chung JS, & Choi YC (2008). Becker muscular dystrophy with r(X) carrying an out-of-frame DMD deletion. *Pediatric Neurology*, 39, 129–132. [PubMed: 18639760]
- Lee MN, Choi KH, Kim DK, & Kim SH (2014). Mosaic double aneuploidy (45,X/47,XX,+8) with aortic dissection. *Genetic Counseling*, 25, 177–182. [PubMed: 25059016]
- Lishner M, Confino-Cohen R, Mekori YA, Feigin M, Manor Y, Goldberg A, ... Amiel A (1996). Trisomies 9 and 8 detected by fluorescence in situ hybridization in patients with systemic mastocytosis. *The Journal of Allergy and Clinical Immunology*, 98, 199–204. [PubMed: 8765835]
- Lorda-Sanchez I, Trujillo MJ, Gomez-Garre P, de Alba MR, Gonzalez-Gonzalez C, García-Hoyos M, ... Ramos C (2003). Turner phenotype in a girl with a 45,X/46,XX/47,XX,+18 mosaicism. *American Journal of Medical Genetics. Part A*, 121, 20–24.
- Los E, Baines H, & Guttmann-Bauman I (2017). Concurrent van der Woude syndrome and Turner syndrome: A case report. *SAGE Open Medical Case Reports*, 5, 1–3.
- Lowry RB, & Wood BJ (1977). Multiple epiphyseal dysplasia and Turner syndrome variant (45,XO/46,X ring) associated with advanced maternal age. *Birth Defects Original Article Series*, 13, 211–220.
- Luthardt RW, & Palmer CG (1971). X chromosome long arm deletion in a patient with Down's syndrome. *Journal of Medical Genetics*, 8, 387–391. [PubMed: 4255466]
- MacFaul R, Turner T, & Mason MK (1981). Down's/Turner's mosaicism. Double aneuploidy as a rare cause of missed prenatal diagnosis of chromosomal abnormality. *Archives of Disease in Childhood*, 56, 962–963. [PubMed: 6460476]
- MacMahon JM, O'Sullivan MJ, McDermott M, Quinn F, Morris T, Green AJ, ... O'Connell SM (2017). Early bilateral gonadoblastoma in a young child with mosaicism for Turner syndrome and trisomy 18 with Y chromosome. *Hormone Research in Paediatrics*, 87, 130–135.
- Manassero-Morales G, Alvarez-Manassero D, & Merino-Luna A (2016). Down-Turner syndrome: A case with double monoclonal chromosomal abnormality. *Case Reports in Pediatrics*, 2016, 8760504. [PubMed: 27672470]
- Marshall I, Betensky BP, Goseco A, Vogiatzi MV, & Flieder D (2004). Fragile X and mosaic 45,X/46,XY mixed gonadal dysgenesis in a girl with ambiguous genitalia. *American Journal of Medical Genetics. Part A*, 124, 213–215.
- Martolf JT, Ray M, Bauder F, Boychuk R, & Armstrong JD (1977). Down and Turner syndromes in a female infant with 47,X,del(X)(p11), +21. *Human Genetics*, 39, 103–108. [PubMed: 144697]
- McCorquodale MM, Cummins T, & Furlong J (1985). Prenatal diagnosis of trisomy 21 and X/XX sex chromosome mosaicism. *Prenatal Diagnosis*, 5, 295–298. [PubMed: 2931678]
- McGoey RR, Jackson K, & Marble M (2009). 45,X/47,XX,+18 and ring (18) mosaicism with mild phenotypic features including normal stature: Clinical report and review of the literature. *Clinical Dysmorphology*, 18, 59–61. [PubMed: 19002012]
- Medenis R, Forbes A, & Rosenthal IM (1962). Mosaicism associated with mongolism, abstracted. *Society for Pediatric Research*, 32, 75.

- Meng X, Li Z, Liu T, & Wen Z (2013). Turner syndrome and monosomy 1p36 deletion syndrome misdiagnosed as thyrophenia: Report of one case. *Journal of Southern Medical University*, 33, 1861–1863. [PubMed: 24369264]
- Mielke G, Enders H, Goelz R, Klein-Vogler U, Ulmer R, & Trautmann U (1997). Prenatal detection of double aneuploidy trisomy 10/monosomy X in a liveborn twin with exclusively monosomy X in blood. *Clinical Genetics*, 51, 275–277. [PubMed: 9184253]
- Mikel'saar AV, Blyumina MG, Kuznetsova LI, Mikel'saar RV, & Lur'e IV (1971). A double chromosomal aberration of the 47, XX, 21 +/47, XXp-q-, 21+ type in a girl with features of Down's and Turner's syndromes. *Soviet Genetics*, 7, 675–679. [PubMed: 4272425]
- Miller WT (1998). Occam versus Hickam. *Seminars in Roentgenology*, 33, 213.
- Monzavi R, Fefferman RA, & Pitukcheewanont P (2005). Prader-Willi syndrome and mosaic Turner's syndrome. *Journal of Pediatric Endocrinology & Metabolism*, 18, 711–717. [PubMed: 16128248]
- Munné S, Sandalinas M, Magli C, Gianaroli L, Cohen J, & Warburton D (2004). Increase rate of aneuploid embryos in young women with previous aneuploid conceptions. *Prenatal Diagnosis*, 24, 638–643. [PubMed: 15305354]
- Musarella MA, & Verma RS (2001). An infant with Turner-Down aneuploidy and massive capillary hemangioma of the orbit: A case report with review. *Annales de Génétique*, 44, 67–70. [PubMed: 11522243]
- Neuschatz J, & Necheles TF (1973). Hemophilia B in a phenotypically normal girl with XX (ring) XO mosaicism. *Acta Haematologica*, 49, 108–113. [PubMed: 4196476]
- Niessen RC, Jonkman MF, Muis N, Hordijk R, & van Essen AJ (2005). Pigmentary mosaicism following the lines of Blaschko in a girl with a double aneuploidy mosaicism: (47,XX,+7/45,X). *American Journal of Medical Genetics. Part A*, 137, 313–322.
- Ornek D, Aydin GB, Kahveci K, Çiçek F, & Dikmen B (2012). Anesthetic management of a child with both Marfan syndrome and Turner syndrome. *Journal of Anesthesia*, 26, 442–444. [PubMed: 22349745]
- Osborne RA, Hennigar GR, & Barnett CD (1975). Mosaic double aneuploidy of X and G chromosomes. *American Journal of Mental Deficiency*, 79, 644–647. [PubMed: 125038]
- Ou Z, Li S, Li Q, Chen X, Liu W, & Sun X (2010). Duchenne muscular dystrophy in a female patient with a karyotype of 46,X,i(X)(q10). *The Tohoku Journal of Experimental Medicine*, 222, 149–153. [PubMed: 20944443]
- Panarello C, Aquila M, Caprino D, Gimelli G, Pecorara M, & Mori PG (1992). Concomitant Turner syndrome and hemophilia A in a female with an idic(X)(p11) heterozygous at locus DXS52. *Cytogenetics and Cell Genetics*, 59, 241–242. [PubMed: 1544315]
- Pfeiffer RA, Scharfenberg W, Büchner T, & Stolecke H (1968). Ringchromosomen und zentrische Fragmente bei Turner-Syndrom. *Geburtsch und Frauenheilk*, 28, 12–26.
- Picone O, Hirt R, Brisset S, Frydman R, Senat MV, & Tachdjian G (2006). Double aneuploid mosaicism 45,X/46,XX/47,XX,+18 in a fetus with cerebral malformations. *Prenatal Diagnosis*, 26, 755–757. [PubMed: 16865741]
- Pié J, Puisac B, Hernández-Marcos M, Teresa-Rodrigo ME, Gil-Rodríguez M, Baquero-Montoya C, ... Ramos FJ (2016). Special cases in Cornelia de Lange syndrome: The Spanish experience. *American Journal of Medical Genetics Part C*, 172, 198–205.
- Pinto MR, Leite RP, & Areias A (1989). Features of Turner's and DiGeorge's syndromes in a child with an X;22 translocation. *Journal of Medical Genetics*, 26, 778–780. [PubMed: 2614798]
- Pivnick EK, Furman WL, Velagaleti GV, Jenkins JJ, Chase NA, & Ribeiro RC (1998). Simultaneous adrenocortical carcinoma and ganglioneuroblastoma in a child with Turner syndrome and germline p53 mutation. *Journal of Medical Genetics*, 35, 328–332. [PubMed: 9598730]
- Posey JE, Harel T, Liu P, Rosenfeld JA, James RA, Coban Akdemir ZH, ... Lupski JR (2017). Resolution of disease phenotypes resulting from multilocus genomic variation. *New England Journal of Medicine*, 376, 21–31. [PubMed: 27959697]
- Prieur M, Dutrillaux B, Carpentier S, Berger R, Raoul O, Rethoré M-O, & Lejeune J (1972). Mosaïque 45,X/47, XY, +21. *Annales de Génétique*, 15, 195–196. [PubMed: 4539770]
- Prieur M, Dutrillaux B, Lafourcade J, Roy C, & Lejeune J (1976). 45, X/47, XY, +13 mosaicism in a 19-year-old girl. *Annales de Génétique*, 19, 199–202. [PubMed: 1086629]

- Reddy KS, Smith DL, & Ball CS (1999). Cri du chat and Turner syndrome features in a newborn girl with an unbalanced 45,X,psu dic(5,X) (p15.2;p22.1) karyotype: FISH and replication banding studies. *Annales de Genetique*, 42, 105–108. [PubMed: 10434125]
- Robertson M, Curren J, Warwick L, Jammu V, Ellwood DA, & Dahlstrom JE (2006). A rare abnormal karyotype (45,X/47,XY + 18) associated with increased nuchal translucency thickness. *Ultrasound in Obstetrics & Gynecology*, 27, 229–231. [PubMed: 16302283]
- Root AW, Bongiovanni AM, Breibart S, & Mellman WJ (1964). Double aneuploidy: Trisomy 21 and X0/XX sex chromosome mosaicism. *Journal of Pediatrics*, 65, 937–939. [PubMed: 14244103]
- Ruangdaraganon N, Kotchabhakdi N, & Mekanandha V (1993). Double aneuploidy: 46,X, +21 a combination of Down syndrome and Turner syndrome. *Journal of the Medical Association of Thailand*, 76(Suppl 2), S215–S217.
- Ryu S-W, Lee G, Baik CS, Shim SH, Kim J-T, Lee J-S, & Lee K-A (2010). Down-Turner syndrome (45,X/47, XY, +21): Case report and review. *Korean Journal of Laboratory Medicine*, 30, 195–200.
- Sano M, Saito F, Yamamoto K, Tonomura A, & Tsukagoshi H (1987). Duchenne muscular dystrophy in a female with 45,X/46,XX chromosome constitution. *Jinrui Idengaku Zasshi*, 32, 257–262. [PubMed: 3448308]
- Santos Mello R, Souza OA, Santos Mello EM, & Pimentel EC (1974). Patient with Down's syndrome and male pseudohermaphroditism with a 47, XY, +21/46, X, +21 karyotype. *Clinical Genetics*, 5, 259–262. [PubMed: 4275956]
- Sato M, Oshika T, Kaji Y, & Nose H (2003). Three novel mutations in the X-linked juvenile retinoschisis (XLR51) gene in 6 Japanese patients, 1 of whom had Turner's syndrome. *Ophthalmic Research*, 35, 295–300. [PubMed: 12920343]
- Satre V, Monnier N, Devillard F, Amblard F, & Lunardi J (2004). Prenatal diagnosis of DMD in a female foetus affected by Turner syndrome. *Prenatal Diagnosis*, 24, 913–917. [PubMed: 15565644]
- Schinzel A, Schmid W, & Prader A (1974). Turner phenotype: Mosaic 45,X/47,XY, +18. *Journal of Medical Genetics*, 11, 101–104. [PubMed: 4135076]
- Schluth-Bolard C, Sanlaville D, Labalme A, Till M, Michel-Calemard L, Rafat A, ... Edery P (2009). Unexpected diagnosis of 45,X/47,XX,+18 mosaicism in a girl with mild phenotype. *American Journal of Medical Genetics. Part A*, 149, 2584–2587.
- Schofield B, Babu A, Pinales-Morejon D, Popescu S, Leiter E, Franklin B, & Penchaszadeh VB (1992). Double mosaic aneuploidy: 45,X/47,XY,+8 in a male infant. *American Journal of Medical Genetics*, 44, 7–10. [PubMed: 1519655]
- Schorry EK, Lovell AM, Milatovich A, & Saal HM (1996). Ullrich-Turner syndrome and neurofibromatosis-1. *American Journal of Medical Genetics*, 66, 423–425. [PubMed: 8989459]
- Schubert R, Eggermann T, Hofstaetter C, von Netzer B, Knöpfle G, & Schwanz G (2002). Clinical, cytogenetic, and molecular findings in X/47,XX,+18 mosaicism: Clinical report and review of the literature. *American Journal of Medical Genetics*, 110, 278–282. [PubMed: 12116238]
- Serville F, Fontan D, Laurent C, Cazauran JM, & Verger P (1977). Mosaic 45,X/47,XY,+18. *Human Genetics*, 36, 351–353. [PubMed: 852877]
- Shahiari M, Bazrafashan A, Moghadam M, & Karimi M (2016). Severe hemophilia in a girl infant with mosaic Turner syndrome and persistent hyperplastic primary vitreous. *Blood Coagulation & Fibrinolysis*, 27, 352–353. [PubMed: 26484646]
- Shapiro LR, Simensen RJ, Wilmot PL, Fisch GS, Vibert BK, Fenwick RG, ... Phelan MC (1994). Asymmetry of methylation with FMR-1 full mutation in two 45,X/46,XX mosaic females associated with normal intellect. *American Journal of Medical Genetics*, 51, 507–508. [PubMed: 7943030]
- Skórka A, Ciara E, Gieruszczak-Biatek D, Pelc M, Kugaudo M, Chrzanowska K, & Krajewska-Walasek M (2012). A girl with two syndromes: Turner syndrome and Costello syndrome: A case history. *American Journal of Medical Genetics. Part A*, 158, 1486–1488.
- Sparagana M, Wong PW, Dorsch TR, Casten C, Rauer M, & Szego K (1980). 45,X/46,XY/47,XY, +21 mosaicism in a hypogonadal phenotypic male. *Journal of Medical Genetics*, 17, 319–321. [PubMed: 6451705]

- Spennato P, La Porta A, Varone A, Ruggiero C, Buono S, & Cinalli G (2013). Aicardi and Turner syndrome in a 45,X0/46,XX female. *Clinical Neurology and Neurosurgery*, 115, 820–822. [PubMed: 22898088]
- Spiro R, Rita D, Jazmines L, Jones C, & Booth CW (1996). Trisomy 12/monosomy X/normal female mosaicism: Prenatal detection and confirmation in a liveborn. *Prenatal Diagnosis*, 16, 734–740. [PubMed: 8878284]
- Suttur MS, Mysore SR, Krishnamurthy B, & Nallur RB (2009). Rare association of Turner syndrome with neurofibromatosis type 1 and tuberous sclerosis complex. *Indian Journal of Human Genetics*, 15, 75–77. [PubMed: 20680156]
- Sybert VP, & McCauley E (2004). Turner's syndrome. *New England Journal of Medicine*, 351, 1227–1238. [PubMed: 15371580]
- Tang HW, Liao SF, & Li JS (2014). Development of patients with 47,XX,+13/45,X mosaics: Case report and review of the literature. *European Journal of Pediatrics*, 173, 251–255. [PubMed: 23666113]
- Taylor AI (1970). Further observations of cell selection in vivo in normal-G trisomic mosaics. *Nature*, 227, 163–164. [PubMed: 4246764]
- Tegenkamp T, Gobrail M, Goodwin C, Swedlund S, Labidi F, & Tegenkamp I (1980). Sex selection in a 45, X, -X, /48, XY, +X, +8 mosaic pseudo true hermaphrodite with multiple anomalies. *American Journal of Human Genetics*, 32, 133A.
- Tejada MI, Mornet E, Tizzano E, Molina M, Baiget M, & Boue A (1994). Identification by molecular diagnosis of mosaic Turner's syndrome in an obligate carrier female for fragile X syndrome. *Journal of Medical Genetics*, 31, 76–78. [PubMed: 8151646]
- Thauvin-Robinet C, De Monlon JV, Nivelon-Chevallier A, Petit A, & Huet F (2001). Association of Marfan's syndrome and Turner's syndrome. *Journal of Pediatric Endocrinology & Metabolism*, 14, 1661–1663. [PubMed: 11795658]
- Tolksdorf M, Kunze J, Rossius H, & Chiyo H (1980). Male infant with cat cry syndrome and apparent absence of the Y chromosome. *European Journal of Pediatrics*, 133, 293–296. [PubMed: 7389744]
- Townes PL, White MR, Stiffler SJ, & Goh K (1975). Double aneuploidy. Turner-Down syndrome. *American Journal of Diseases of Children*, 129, 1062–1065. [PubMed: 127528]
- Trolle C, Mortensen KH, Pedersen LN, Berglund A, Jensen HK, Andersen NH, & Gravholt CH (2013). Long QT interval in Turner syndrome—A high prevalence of LQTS gene mutations. *PLoS One*, 8, e69614. [PubMed: 23936059]
- Tyler CT, Rice GM, Grady M, & Raca G (2009). Mild clinical presentation in a child with prenatally diagnosed 45,X/47,XX,+18 mosaicism. *American Journal of Medical Genetics. Part A*, 149, 2588–2592.
- Van Buggenhout GJ, Hamel BC, Trommelen JC, Meiloo H, & Smeets DF (1994). Down-Turner syndrome: Case report and review. *Journal of Medical Genetics*, 31, 807–810. [PubMed: 7837259]
- Van Gelderen HH, Gaillard JL, & Schaberg A (1967). Trisomy G/-normal mosaics in non-mongoloid mentally deficient children. *Acta Paediatrica Scandinavica*, 56, 517–525. [PubMed: 4227851]
- Van Wijck JAM, Blankenborg GJ, & Stolte LAM (1964). XO/XX mosaicism and mongolism in the same person. *The Lancet*, 283, 171.
- Verma S, Goyal P, Beam C, & Shah D (2017). Turner syndrome and Duchenne muscular dystrophy. *Muscle & Nerve*, 56, E12–E15. [PubMed: 28214339]
- Vialard F, Boitrelle F, Molina-Gomes D, & Selva J (2011). Predisposition to aneuploidy in the oocyte. *Cytogenetic and Genome Research*, 133, 127–135. [PubMed: 21335956]
- Vidmar AP, Miyazaki B, Sanchez-Lara PA, & Pitukcheewanont P (2017). X-linked Hypophosphatemic rickets, del(2)(q37.1;q37.3) deletion syndrome and mosaic Turner syndrome, mos 45,X/46,X, del(2)(q37.1;q37.3) in a 3-year-old female. *Journal of Bone Metabolism*, 24, 257–261. [PubMed: 29259966]
- Villaverde MM, & Da Silva JA (1975). Turner-mongolism polysyndrom. Review of the first eight known cases. *JAMA*, 234, 844–847. [PubMed: 127053]

- Warburton D, Daillaire L, Thangavelu M, Ross L, Levin B, & Kline J (2004). Trisomy recurrence: A reconsideration based on North American data. *American Journal of Human Genetics*, 75, 376–385. [PubMed: 15248154]
- Weinspach S, Siepermann M, Schaper J, Sarikaya-Seiwert S, Rieder H, Gerigk M, ... Laws HJ (2009). Intracranial hemorrhage in a female leading to the diagnosis of severe hemophilia A and Turner syndrome. *Klinische Pädiatrie*, 221, 167–171. [PubMed: 19437365]
- Westenburger A, Rosales RL, Heinitz S, Freimann S, Lee LV, Jamora RD, ... Klein C (2013). X-linked dystonia-parkinsonism manifesting in a female patient due to atypical Turner syndrome. *Movement Disorders*, 28, 675–678. [PubMed: 23389859]
- Wierzbica J, Gil-Rodríguez MC, Polucha A, Puisac B, Arnedo M, Teresa-Rodrigo ME, ... Pié J (2012). Cornelia de Lange syndrome with *NIPBL* mutation and mosaic Turner syndrome in the same individual. *BMC Medical Genetics*, 13, 43. [PubMed: 22676896]
- Wilkin H, Tuohy J, & Theewis W (2000). Prenatal diagnosis of fragile X and Turner mosaicism in a 12-week fetus. *Prenatal Diagnosis*, 20, 854–855. [PubMed: 11038471]
- Yeung CY, & Yang L (1976). Down's syndrome with X0/XY mosaicism. *Acta Paediatrica Scandinavica*, 65, 391–395. [PubMed: 5841]
- Zaki MS, Kamel AA, & El-Ruby M (2005). Down syndrome in three Egyptian patients: Down-Turner and Down-Klinefelter syndromes. *Genetic Counseling*, 16, 393–402. [PubMed: 16440882]
- Zergollern L, & Hoefnagel D (1964). X-chromosome mosaicism with trisomy-21. *The Lancet*, 283, 1108–1109.
- Zhou Q, Yao F, Wang F, Li H, Chen R, & Sui R (2017). A heterozygous mutation in *RPGR* associated with X-linked retinitis pigmentosa in a patient with Turner syndrome mosaicism (45,X/46,XX). *American Journal of Medical Genetics. Part A*, 176, 1–5.
- Zhu J, Wang D, Ren A, Xing Y, Zhang D, Wei J, ... Ye S (2015). Abnormal methylation status of the *GNAS* exon 1A region in Pseudohypoparathyroidism combined with Turner syndrome. *The American Journal of Medical Sciences*, 350, 458–462.

FIGURE 1.

The composite shows four patients with Turner syndrome and a co-occurring diagnosis proven by karyotype or molecular analysis. (a and b) At ages 2 and 3 years, patient 1's appearance is not typical for either Turner syndrome or Noonan syndrome; (c and d) at 29 and 42 months patient 2 has typical facial features of blepharophimosis-ptosis-epicanthus inversus syndrome; (e and f) at 3 years of age, patient 4 with trisomy 8 mosaicism has classic craniofacial features of Turner syndrome (low-set ears with increased posterior angulation, hypertelorism, downslanted palpebral fissures, and neck webbing), but at age 10, these features are less apparent; (g) patient 5 with additional de novo mutation of *RERE* at 18 months of age. Although parents did not permit photograph without black bar, the forehead bossing is apparent

TABLE 1

Categories of genetic syndromes in patients with Turner syndrome

Category of co-occurring genetic diagnoses	Total number	Percentage of total patients (<i>n</i> = 152*) ^{a,b}
X-linked disorders	36	24
Aneuploidy syndromes	77	51
Chromosomal rearrangements	5	3
Autosomal dominant disorders	26	17
Autosomal recessive disorders	4	3
Imprinting disorders	3	2
Mitochondrial disorders	1	<1

^a Asterisk indicates a new patient included in total.

^b Abdalla and Nabil (2012); Afonso Lopes, Benador, Wacker, Wyss, and Sizonenko (1995); Aver'ianov, Bogomazov, and Logunova (1977); Baguena Candela, Forteza Bover, and Amat Aguirre (1965); Baguena Candela, Forteza Bover, Ortiz Hernandez, and Comin Ferrer (1966); Bajnóczky and Méhes (1979); Banes, Begleiter, and Butler (2003); Barakat and Der Kaloustian (1973); Becerra-Solano et al. (2008); Beck and Mikkelsen (1981); Blaise et al. (2005); Brouns et al. (2009); Chelly et al. (1986); Chen, Tyrkus, and Woolley (1978); Chuansumrit et al. (1999); Co ulu, Tirpan, Ozkinay, Gündüz, and Ozkinay (2002); Cohen and Davidson (1972); DeBrasi et al. (1995); Digilio, Mingarelli, Giannotti, Melchionda, and Dallapiccola (1994); Dobkin, Radu, Ding, Brown, and Nolin (2009); Edgren, de la Chapelle, and Kääriäinen (1966); Eiben, Hansen, Goebel, and Hammans (1989); Feiertag-Koppen, Anders, Stronk, and Boevé (1966); Ferrier, Bamatter, and Klein (1965); Fontenele, Costa-Santos, and Kater (2018); Franceschini et al. (1996); Freedenberg et al. (1999); Gafter, Shabtal, Kahn, Halbrecht, and Djaldetti (1976); Gatrad (1981); Gengel and Marshall (2017); Genuardi et al. (1999); Gilchrist, Hammond, and Melnyk (1965); Gilgenkrantz, Briquel, Mandel, and Oberle (1986); Grosse, Hopfengärtner, and Schwanitz (1971); Guenego, Morel, Ionesco, Mallet, and Priou-Guesdon (2015); Gutmann, Brooks, Emanuel, McDonald-McGinn, and Zackai (1991); Harada et al. (1998); Hatipoglu, Kurtoglu, Kendirci, Keskin, and Per (2010); Hoppman-Chaney, Jang, Jen, Babovic-Vuksanovic, and Hodge (2012); Hunter (2017); Hustinx, Haar, Scheres, and Rutten (1974); Igarashi, Tsukahara, Sugio, Katayama, and Kajii (1985); Ikonen et al. (1989); Jansen, Kruger, and Liebenberg (1991); Jaruratanasirikul and Jinorose (1995); Kaczorowska et al. (2016); Kan, Fujita, Sato, Okajima, and Fukui (1976); Klosovskiĭ, Iankova, Fateeva, and Damanskaia (1968); Knudtson, Ledaal, Middelthorpe-Moe, and Aarskog (1988); Ko, Lee, Hong, and Hwang (2010); Koçak-Midillioglu, Karadeniz, Yalvaç, Koçak-Altintas, and Duman (2003); Krutikova et al. (2005); Kumar, Lal, Chapadgaonkar, and Bhattacharya (2014); Lee, Choi, Kim, and Kim (2014); Lee, Han, Choi, Chung, and Choi (2008); Lishner et al. (1996); Lorda-Sanchez et al. (2003); Los, Baines, and Guttmann-Bauman (2017); Lowry and Wood (1977); Luthardt and Palmer (1971); MacFaul, Turner, and Mason (1981); MacMahon et al. (2017); Manassero-Morales, Alvarez-Manassero, and Merino-Luna (2016); Marshall, Betensky, Goseco, Vogiatzi, and Flieder (2004); Martsolf, Ray, Bauder, Boychuk, and Armstrong (1977); McCorquodale, Cummins, and Furlong (1985); McGoey, Jackson, and Marble (2009); Medenis, Forbes, and Rosenthal (1962); Meng, Li, Liu, and Wen (2013); Mielke et al. (1997); Mikel'saar, Blyumina, Kuznetsova, Mikel'saar, and Lur'e (1971); Monzavi, Fefferman, and Pitukcheewanont (2005); Musarella and Verma (2001); Neuschatz and Necheles (1973); Niessen, Jonkman, Muis, Hordijk, and van Essen (2005); Ornek, Aydin, Kahveci, Ciqek, and Dikmen (2012); Osborne, Hennigar, and Barnett (1975); Ou et al. (2010); Panarello et al. (1992); Pfeiffer, Scharfenberg, Büchner, and Stolecke (1968); Picone et al. (2006); Pié et al. (2016); Pinto, Leite, and Areias (1989); Pivnick et al. (1998); Prieur, Dutrillaux, Lafourcade, Roy, and Lejeune (1976); Prieur et al. (1972); Reddy, Smith, and Ball (1999); Robertson et al. (2006); Root, Bongiovanni, Breibart, and Mellman (1964); Ruangdaraganon, Kotchabhakdi, and Mekanandha (1993); Ryu et al. (2010); Sano, Saito, Yamamoto, Tonomura, and Tsukagoshi (1987); Santos Mello, Souza, Santos Mello, and Pimentel (1974); Sato, Oshika, Kaji, and Nose (2003); Satre, Monnier, Devillard, Amblard, and Lunardi (2004); Schinzel, Schmid, and Prader (1974); Schluth-Bolard et al. (2009); Schofield et al. (1992); Schorry, Lovell, Milatovich, and Saal (1996); Schubert et al. (2002); Serville, Fontan, Laurent, Cazauran, and Verger (1977); Shahiari, Bazrafashan, Moghadam, and Karimi (2016); Shapiro et al. (1994); Skórka et al. (2012); Sparagana et al. (1980); Spennato et al. (2013); Spiro, Rita, Jazmines, Jones, and Booth (1996); Suttur, Mysore, Krishnamurthy, and Nallur (2009); Tang, Liao, and Li (2014); Taylor (1970); Tegenkamp et al. (1980); Tejada et al. (1994); Thauvin-Robinet, De Monléon, Nivelon-Chevallier, Petit, and Huet (2001); Tolksdorf, Kunze, Rossius, and Chiyo (1980); Townes, White, Stiffler, and Goh (1975); Trolle et al. (2013); Tyler, Rice, Grady, and Raca (2009); Van Buggenhout, Hamel, Trommelen, Meiloo, and Smeets (1994); Van Gelderen, Gaillard, and Schaberg (1967); Van Wijck, Blankenborg, and Stolte (1964); Verma, Goyal, Beam, and Shah (2017); Vidmar, Miyazaki, Sanchez-Lara, and Pitukcheewanont (2017); Villaverde and Da Silva (1975); Weinspach et al. (2009); Westenburger et al. (2013); Wierzbza et al. (2012); Wilkin, Tuohy, and Theewis (2000); Yeung and Yang (1976); Zaki, Kamel, and El-Ruby (2005); Zergollern and Hoefnagal (1964); Zhou et al. (2017); Zhu et al. (2015).

TABLE 2

Summary of patients with Turner syndrome and co-occurring disorders (see Supporting Information tables for complete listing)

Co-occurring genetic diagnoses	Patients ^a	Patients with mosaic karyotypes (% of total patients in that category)
X-linked disorders		
Fragile X	13	12
Duchenne muscular dystrophy/Becker muscular dystrophy	9	6
Hemophilia A	5	3
Hemophilia A with persistent hyperplastic primary vitreous	1	1
Hemophilia B	1	1
X-linked juvenile retinoschisis	1	0
X-linked retinitis pigmentosa	1	1
Fabry disease	1	1
X-linked dystonia-parkinsonism	1	1
X-linked congenital nystagmus	1	1
X-linked hypophosphatemic rickets and deletion of 2q37	1	1
Alcadi syndrome	1	1
Total X-linked conditions	36	29(81)
Aneuploidy syndromes		
Down syndrome	47	42
Trisomy 18	12	12
Trisomy 14	1	1
Trisomy 13	6	6
Trisomy 12	1	1
Trisomy 10	1	1
Trisomy 9	1	1
Trisomy 8 mosaicism*	6 + 1	6 + 1
Trisomy 7	1	1
Total aneuploidy syndromes*	77	72 (94)
Chromosomal rearrangements		

Co-occurring genetic diagnoses	Patients ^a	Patients with mosaic karyotypes (% of total patients in that category)
Cri du chat syndrome	2	1
Deletion of 1p36 syndrome	1	0
Williams syndrome	1	0
Deletion of 22q11	1	0
Total chromosomal rearrangements	5	1 (20)
Autosomal dominant disorders		
Neurofibromatosis Type 1	4	1
Neurofibromatosis Type 1 with tuberous sclerosis complex	1	0
Cornelia de Lange syndrome	4	3
Long QT syndrome	3	1
Marfan syndrome	2	1
Axenfeld-Rieger syndrome	2	1
Costello syndrome	1	1
Van der Woude syndrome	1	1
Noonan syndrome (with Li-Fraumeni syndrome)*	1	0
Li-Fraumeni syndrome*	3 + 1	0
<i>RERE</i> -related disorder*	1	1
Blepharophimosis-ptosis-epicanthus inversus*	1	1
Total autosomal dominant disorders*	26	11 (42)
Autosomal recessive disorders		
Thalassemia major	1	1
Multiple epiphyseal dysplasia	1	1
17 α hydroxylase deficiency	2	2
Total autosomal recessive disorders	4	4 (100)
Imprinting disorders		
Prader-Willi syndrome	1	1
Pseudohypoparathyroidism	1	1
Pseudopseudohypoparathyroidism	1	1
Total imprinting disorders	3	3 (100)

Co-occurring genetic diagnoses	Patients ^a	Patients with mosaic karyotypes (% of total patients in that category)
Mitochondrial disorders		
Leber hereditary optic neuropathy	1	1
Total mitochondrial disorders	1	1 (100)
Total reported Turner syndrome cases	147 + 5 new = 152	121 (80%)

^a Asterisk indicates a new patient included in total.