



## Phenotypic variations in X chromosome mutations: Two case reports

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### ABSTRACT

Turner syndrome (TS) affects 1 in 2500 females. Monosomy X is the most common etiology, classically presenting with hypogonadism and short stature. We present two cases of partial X chromosome deletions that do not reflect the typical phenotype of TS.

Patient 1 presented at age 17 with primary amenorrhea, cognitive delay and tall stature. Patient 2 presented at age 16 with primary amenorrhea, normal intelligence and average stature.

Patient 1's karyotype revealed isodicentric X chromosome [46 X, idic(X)(q21)]. Patient 2's karyotype revealed [46 X, del(X)(q13.3)]. The stature of these patients was not affected. Estrogen therapy was required to provide secondary sexual changes promote bone health.

Advances in technology and reproductive health provide an opportunity to make more specific recommendations for patients previously mistakenly diagnosed with TS.

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### 1. Introduction

There is wide variation in the phenotypic presentation of patients with X chromosome mutations and deletions. Turner syndrome, first described in 1938 and explicated by cytogenetic chromosomal analysis in 1959, is one of the most common sex chromosome disorders [1,2]. The most common etiology is monosomy X, which accounts for 50–60% of cases. Mosaicism with aberrant X chromosomes, primarily isochromosomes, has also been described. Although the reported incidence of Turner syndrome has been quoted as 1:2500, the true incidence in the developed world is likely now significantly lower (1:4000) due to ultrasound screening and elective terminations [3]. The syndrome may be identified through the characteristic finding of cystic hygroma on ultrasound or with non-invasive prenatal testing (NIPT). However, in cases of X chromosome mosaicism, cystic hygroma and other soft-tissue ultrasound markers may not be reliably identified [4]. Evaluation for fetal aneuploidy by examining maternal plasma derived cell free fetal DNA (cfDNA) has now become the most sensitive screening method for the detection of Turner syndrome. Abnormal findings are confirmed either by chorionic villus sampling or amniocentesis [5].

Prior to NIPT and ultrasound, the stereotypical patient with Turner syndrome was diagnosed clinically. Classically, the affected newborn has increased nuchal skin, edema of the distal extremities, a shield-shaped thorax with widely spaced nipples and facial dysmorphism such as low-set ears and a low hairline [6]. Cardiac defects such as coarctation of the aorta and hypoplastic left heart may present with cyanosis in the

newborn, while musculoskeletal abnormalities such as cubitus valgus, short stature, and shortened 4th metacarpal with abnormal finger nails become more evident in childhood and adolescence. Other clinical findings, including hypothyroidism, urological abnormalities, and metabolic dysfunction may also become apparent later in life. Sybert and McCauley reported that approximately two-thirds of patients with Turner syndrome are diagnosed after birth or during childhood. Only one-third of patients were diagnosed in adolescence or in young adulthood after failing to undergo puberty [7]. The classic presentation is with low estrogen, short stature, and cardiac anomalies [6,7].

Patients with one or more of the above findings may have a karyotype determination as part of their evaluation. If they are found to have an abnormal X chromosome, they are often labeled as “Turner variants” or “atypical Turner syndrome”. However, many of them do not meet the classical picture of Turner syndrome and may even violate the putative phenotype. We present two patients with X chromosome partial deletions that do not reflect Turner syndrome. With newer technologies, the phenotype and exact karyotype can be better correlated. Given the genetic diagnosis, we purport that these patients should no longer be classified as “Turner variants” but should instead be separately classified as having X chromosome mutations and partial deletions.

### 2. Cases

#### 2.1. Patient 1

Patient 1 presented to an outside provider at age 17 with primary amenorrhea, failure to undergo puberty, cognitive delay and low-set ears. Karyotype determination revealed isodicentric X chromosome

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[46 X, idic(X)(q21)] with deletion of most of the long arm (q), and with duplication of the centromere, proximal long arm and short arm (p) (Fig. 1). She was labeled as a Turner variant and was placed on combined oral contraceptive pills for hormone replacement therapy. Her medical history included depression, migraines, left hydronephrosis and reconstructive mammoplasty. Her physical examination was otherwise unremarkable, and she was noted to be six feet three inches tall, which was appropriate given the height of her parents. Oral contraceptive pills controlled her vasomotor symptoms for 15 years, but subsequently these worsened. Evaluation at this time revealed low serum estradiol of <5 mIU/mL and decreased bone mineral density on dual energy x-ray absorptiometry (DEXA) with a Z score of  $-2.0$  at the distal forearm and  $-0.4$  to  $-0.8$  in the spine, femoral neck and hip. An estrogen patch was added to her regimen to improve her vasomotor symptoms and bone mineral density.

The patient then took a long air flight and developed a significant pulmonary embolism with right heart strain, which required thrombolytics and management in the intensive care unit. Hormonal therapy was discontinued and she was placed on rivaroxaban (Xarelto®) for anticoagulation. She subsequently developed disordered sleep patterns and mood changes, and her vasomotor symptoms worsened. It was at this time that she was referred to our clinic, at the age of 32. Sertraline hydrochloride (Zoloft®) was started in an attempt to treat her vasomotor symptoms and mood symptoms. However, no improvement was seen. Her estradiol level was <5 pg/mL, FSH 28 mIU/mL, LH 21 mIU/mL and an antimullerian hormone (AMH) < 0.015 ng/mL. She was referred to hematology, where her thrombophilia workup was negative. At the suggestion of hematology, her Xarelto was continued and she was restarted on an estradiol 0.1 mg patch twice weekly. Since restarting HRT, the patient's vasomotor symptoms have been controlled and her mood disturbances have significantly improved.

## 2.2. Patient 2

Patient 2 was referred at age 16 for primary amenorrhea, delayed breast development and disordered sleep. She denied hot flashes and had no other complaints. Physical examination revealed normal height (five feet three inches) and weight, with a BMI of 23.6 (kg/m<sup>2</sup>), mild acne, normal external female genitalia, vaginal atrophy of the introitus, Tanner stage I-II breasts and Tanner stage IV pubic hair. Her FSH level was 97mIU/mL, LH 29 mIU/mL, AMH 0.054 ng/mL, prolactin 17 ng/dL, free T4 1.35 ng/dL, and TSH 5.32 mU/L. Thyroid peroxidase antibodies and thyroglobulin antibodies were both positive and 21 hydroxylase antibodies were negative. Her DEXA scan showed decreased bone mineral density with a T score of  $-2.2$  at the lumbar spine and

femoral neck. Pelvic MRI demonstrated absent ovaries and small uterus (4.0 × 1.3 × 1.7 cm) without an identifiable endometrium. An echocardiogram was normal and her fragile X testing was normal. Karyotype determination revealed partial deletion of the long arm [46 X, del(X)(q13.3)] (Fig. 1). She was started on Synthroid and hormone replacement with estradiol tablets (Estrace®) 2 mg daily. Six months later, she reported breast development. She was counseled on future fertility with use of donor eggs and continues to do well.

## 3. Discussion

These two cases demonstrate the variations in genetic and phenotypic presentations of patients with X chromosome mutations. While they have some phenotypic similarities to those with Turner syndrome, these patients do not fit the classic presentation and do not have the same medical considerations.

The diagnosis of X chromosome mutations is critical in patients with short stature and ovarian insufficiency so that recombinant growth hormone and hormonal replacement may be initiated in a timely manner. Patients who do not receive growth hormone therapy are shorter than their adult counterparts due to failure of the growth spurt with puberty as well as deletion of the Xp [8]. The SHOX homeobox gene located on Xp22.23 is involved in skeletal growth and development. Additionally, short stature resulting from disordered growth occurs in various parts of the life cycle, including in utero, during childhood and at puberty [9]. Maximal height is achieved when recombinant growth hormone is combined with estrogen therapy, which is usually initiated at 12–14 years of age. Neither of our patients required growth hormone therapy. Both patients had preservation of the Xp, which likely played a role in their tall and average heights [10].

Bone mineral density was affected in both patients due to estrogen deficiency. Although the normal range of T scores has not been clearly delineated for adolescents, a Z score of less than  $-2.0$  is considered low bone density for chronological age [11]. Estrogen therapy, calcium and vitamin D are paramount for establishment of normal bone mineralization.

Both patients presented with delayed puberty and were found to have ovarian insufficiency in mid-adolescence. Ovarian failure is associated with deletion of the q arm, and there was at least partial deletion in both of our patients [12]. Our patients required exogenous estrogen to provide secondary sexual development, promote bone health and cardiovascular protection. Patient 1 was able to achieve normal breasts using augmentation mammoplasty while patient 2 utilized pharmacologic therapy for breast development. Estrogen is also useful for the maturation of the infantile uterus, which may be useful to support a pregnancy later in life. The use of exogenous estrogens, however, is not without consequences. Venous thromboembolism (VTE) is a serious complication in any patient on exogenous estrogen and may increase the risk 2–4 times above baseline, particularly in those with additional risk factors. Patient 1 developed a provoked VTE after prolonged air travel. Although her estrogen therapy was paused during the period of critical health and shortly afterwards, hormonal replacement therapy was subsequently restarted with anticoagulation treatment. Based on current evidence, it is appropriate to continue much-needed hormonal replacement therapy in patients after a provoked VTE who are appropriately anticoagulated [13].

Cardiac defects such as aortic coarctation, hypoplastic left heart, bicuspid valves, and vasculopathy affect up to 30% of patients with Turner syndrome [14]. However, both our patients were without cardiac abnormalities. This is important information for future reproductive counseling. Cardiovascular risks associated with Turner syndrome increase in pregnancy and some infertility centers choose not to allow such patients to conceive, even with donor egg [15]. Evidence is lacking that partial X chromosome deletions are associated with the same cardiovascular risk profile.

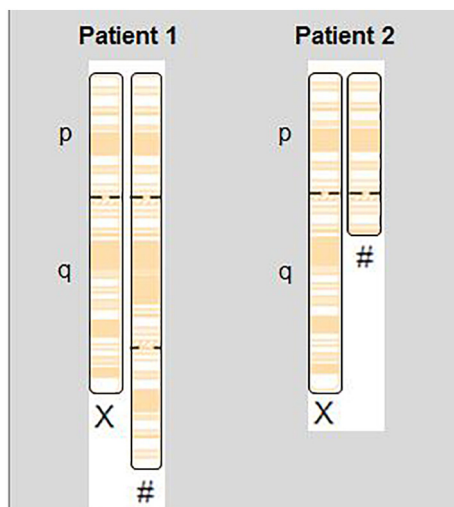


Fig. 1. Karyotype for patient 1 and 2.

In addition to correctly identifying the specific X chromosome mutations, determination of the karyotype is also useful to exclude an abnormal Y chromosome. Findings of a partial Y chromosome would necessitate the removal of the non-functional streak gonads due to risk of malignancy [16].

Finally, it is important to appropriately classify patients with X chromosome mutations and deletions, for both medical and psychosocial reasons. For instance, both patients would likely have felt out of place in a support group for patients with Turner syndrome given their normal to tall stature. Additionally, the majority of patients and their carers now seek information online. An improper search term may leave parents confused and frustrated if the available information is not pertinent to their own child.

With technological advances, the wide genetic variations in patients with X chromosome mutations and partial deletions can now be correlated to their clinical presentation. Such patients should no longer be classified as "Turner variants" but should instead be separately classified as having X chromosome mutations and deletions.

### Contributors

All authors contributed to the preparation of this case report and saw and approved the final manuscript.

### Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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### Patient Consent

Obtained.

### Provenance and Peer Review

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