IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
March 2024 Vol.:30, Issue:3

An Overview of Turner Syndrome

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Jyothika Vemulapalli[1*], Yenkathala Shivani[1], Mukesh Choudhary[2], Ishu[2], Aashutosh Sinwal[2], Yashika Sapre[2]

[1]Malla Reddy College Of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100

[2]Pharm D, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India- 302017

Submitted: 20 February 2024
Accepted: 25 February 2024
Published: 30 March 2024

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Turner syndrome, Chromosome, Short stature homeobox, Hormone replacement therapy, Karyotype

ABSTRACT

Henri Turner, a doctor from Oklahoma, initially defined Turner syndrome in 1938. The partial or whole absence of an X chromosome in females can cause this condition. There are two main types of TS: classical and mosaic. Epidemiological and neonatal genetic screening data from the US, Europe, and Japan indicate that it occurs in around 1% to 3% of live female births. Physical characteristics of TS are a webbed neck, swollen hands and feet, low hairline, shield-shaped chest, droopy eyelids, hearing loss, high-arched palate, and increased elbow carrying angle. Turner syndrome can be verified by standard karyotyping, which examines the chromosomes of 30 peripheral cells. Complications of TS include Cardiovascular abnormality, hypogonadotropic hypogonadism, infertility, Skeletal abnormalities, and autoimmune diseases. Growth hormone therapy is the primary treatment for TS, with various treatments depending on the organ affected.

INTRODUCTION

Henri Turner, a doctor from Oklahoma, initially defined Turner syndrome in 1938. The condition is also known as congenital ovarian hypoplasia syndrome. When it comes to female chromosome abnormalities, this one is by far the most frequent. [1] The partial or whole absence of an X chromosome causes this condition. The anomalies and characteristics observed in women with Turner's syndrome are caused by the missing genes. Some other names for Turner's syndrome are Ullrich-Turner syndrome, 45X, and monosomy X. The degree of chromosomal aberration determines the consequences and severity of the illness, which can vary greatly. About 1% of all female infants are born with Turner's syndrome. Nonetheless, this anomaly may be more prevalent than initially believed due to its prenatal prevalence. Only around 1% of fetuses with this chromosomal anomaly make it to term, and it's associated with 10% of miscarriages. [2] There are two main types of TS: classical and mosaic. In mosaic Turner, two cell lines coexist, while in classical TS, one X chromosome is completely absent. A karyotype can validate a clinical diagnosis of TS. People with short height have a haploinsufficiency in the short stature homeobox (SHOX) gene, which is located on the distal portion of the short arm of chromosome 10. Remember that these females do not exhibit any abnormalities in the growth hormone (GH)/insulin-like growth factor axis. In terms of physical characteristics, TS is characterized by a small height, a webbed neck, heart problems, reduced glucose tolerance, thyroid illness, hearing loss, and ovarian failure. The most common phenotypic characteristics are low height and gonadal dysgenesis, however, there is a great deal of variation among these traits. Hormone replacement therapy (HRT) and growth hormone (GH) are the main treatments for TS in females. [2,3]

INCIDENCE AND PREVALENCE

In a 1938 article, Henri Turner, a physician from Oklahoma, described seven women who had cubitus valgus, small height, sexual immaturity, neck webbing, and neck webbing as a clinical condition, before the availability of karyotyping. Nevertheless, several years ago, Otto Ulrich had detailed a girl of the same age who had the same phenotypic. The majority of female sex chromosomal abnormalities are associated with Turner syndrome. Epidemiological and neonatal genetic screening data from the US, Europe, and Japan indicate that it occurs in around 1% to 3% of live female births. It is challenging to determine the actual frequency of Turner syndrome since some individuals may go untreated due to a

milder phenotype. [4] If a patient's phenotypic is mild, a diagnosis may not be made until late in life. The incidence of Turner syndrome is relatively constant across all racial and ethnic groups and nations. However, it seems like certain nations are seeing a decrease in the prevalence at birth. Some pregnant women who are carrying fetuses with Turner syndrome opt to end the pregnancy, and there has been an uptick in prenatal ultrasonographic screening as a result. Conversely, X chromosomal monosomy (45, X) is associated with a very high rate of stillbirth. At least 10% of spontaneous abortions have the 45, X genotype. [3,4]

CLINICAL FEATURES OF TURNER'S SYNDROME

In addition to partial deletions of the long (Xq) or short (Xp) arms, TS characteristics are also linked to total monosomy X. Certain characteristics within the clinical spectrum of TS may be linked to the deletion of particular regions of the X chromosome. [5] Gonadal dysgenesis, also known as ovarian failure, is one of the most prevalent characteristics. It causes infertility, inadequate pubertal development, and low levels of circulating estrogen. Short stature and any of several specific somatic abnormalities, such as the webbed neck, swollen hands and feet, low hairline, shield-shaped chest, droopy eyelids, hearing loss, high-arched palate, increased elbow carrying angle (cubitus valgus), short fourth or fifth metacarpals, renal malformations, multiple pigmented nevi, lymphedema, impaired glucose tolerance, autoimmune thyroid disease, and hypertension, are additional physical characteristics of TS. In early childhood, short stature is usually noticeable. TS women who did not receive growth hormone treatment had adult height measures ranging from 146 to 148.5 cm. Growth hormone therapy promotes better growth. Some physical characteristics (edema, short metacarpals, and cubitus valgus) manifest in childhood and continue into adulthood, whereas other physical characteristics (nevi) manifest in adolescence and adulthood. [5,6] Hypertension and poor glucose tolerance are two examples of complex multifactorial characteristics that typically manifest in youth or are diagnosed in maturity. Because TS involves multiple systems, treating this patient population necessitates a multidisciplinary team of healthcare professionals. A clinical practice guideline for the treatment of women and girls with Turner's syndrome was recently released by the Turner Syndrome Consensus Study Group. Comprehensive care, including prenatal and postnatal diagnosis and monitoring for related issues in the areas of cardiovascular, vision, hearing, dental, renal, skeletal, endocrine, immune system, and psychosocial adjustment, is the focus of this recommendation. The time-tested procedures for administering growth hormone to maximize height and estrogen therapy to induce puberty are well-designed. [7]

PATHOPHYSIOLOGY OF TS

Karyotypes

The clinical condition of Turner syndrome can arise in women with a variety of karyotypes, all of which are characterized by a paucity of X-chromosomal material. Some examples of karyotypes include 45, X (full loss of one X chromosome), mosaics of these chromosomes (e.g., 45, X/46, XX; 45, X/47, XXX), ring chromosomes, Y-chromosomal material, isochromosomes of the p or q arm, and many more. Forty to fifty percent of women with Turner syndrome have the 45, X karyotype; fifteen to twenty-five percent have 45, X/46, XX mosaicism; twenty percent of women have an isochromosome; and a small number of women have ring X chromosomes. Furthermore, around 3% of women with varying levels of Y chromosomal material (45, X/46, XY) are among the 10-12% that exhibit this trait. [8]

Associated genes

So far, just one X and Y chromosomal pseudo autosomal region gene, called short stature homeobox protein (SHOX), has been connected to the Turner syndrome phenotype. [4] Turner syndrome growth loss may be explained by the fact that SHOX can avoid X-inactivation and that the disorder is exacerbated by its decreased expression. SHOX haploinsufficiency is also frequently characterized by scoliosis, micrognathia, a high-arched mouth, Madelung deformity, and short legs (but normal sitting height). The SHOX gene product not only regulates the expression of fibroblast growth factor receptor 3 (FGFR3) and natriuretic peptides B (NPPB), but it also interacts with genes that encode members of the SRY-related high mobility group box family of transcription factors involved in cell fate determination, such as SOX5, SOX6, and SOX9. [3,7]

Epigenetics & RNA expression

Other autosomal genes that were not previously linked to Turner syndrome are implicated in the research on epigenetics and RNA expression in blood from individuals with the illness that was carried out in 2015 and 2016. [2] These findings may have implications for our knowledge of Turner syndrome's genetic makeup. Comparing the genomes of women with 46, XX, and RNA expression abnormalities affecting X chromosomal genes and autosomal genes, the Turner syndrome genome has fewer areas of hypermethylation. Furthermore, the whole genome exhibits hypomethylation. Remember that women with 45, X only have one X chromosome, therefore escape genes X-chromosome genes that are known to elude X-

inactivation may contribute to the explanation of any symptom associated with Turner syndrome. [8]

DIAGNOSIS OF TS

Turner syndrome can be verified by standard karyotyping, which examines the chromosomes of 30 peripheral cells. Either a mixture of normal cells with one extra X chromosome (45, X/46, XX; mosaic Turner syndrome) or normal cells with one extra X chromosome (45, X) will be present in half or more of the people. As karyotyping focuses on lymphocytes rather than relevant organs (such as the brain, heart, or ovaries), a mosaic result cannot always accurately reflect severity. [7,9]

A karyotype can be obtained by sending the complete volume of blood in a green-top sodium heparin tube, at room temperature, to a laboratory for analysis. Over a week, karyotyping takes place. When a timely diagnosis is needed, like in situations where parents are worried or a critical clinical crisis occurs, X-specific fluorescence in situ hybridization can confirm monosomy X in less than a day.[10]

Although the X chromosome is most frequently linked to Turner syndrome, other sex chromosome defects such as ring X, deletion Xp, or an aberrant Y chromosome can also cause it. Individuals with Y chromosomal material should have imaging tests done as well as a laparoscopic gonadectomy for the removal of testicular tissue—because they have a 12% chance of developing gonadoblastoma.[11]

For girls who are short in stature, Turner syndrome is frequently not identified until much later in life. One study found that it takes an average of seven years from the time a woman's low height becomes clinically evident on her development curves to the time a diagnosis is made. In a case study, it was discovered that, regardless of their family's history of height, 4% of girls with isolated short stature who were referred for genetic testing had Turner syndrome. Nearly 30% of the girls who were sent for therapy had Turner syndrome, which was identified by amenorrhoea or other questionable phenotypic traits. Girls should be karyotyped if their height is more than two standard deviations below the average for their age. [7,10,11]

COMPLICATIONS OF TS

Disorders associated with Turner syndrome hypogonadotropic hypogonadism, infertility, and sexual function

Almost all individuals with Turner syndrome also have hypogonadotropic hypogonadism, which causes either primary or secondary amenorrhoea and, eventually, infertility; only a small percentage of women can sustain spontaneous fertility. While the specific causes of this phenotype remain a mystery, Turner syndrome46 is characterized by an early and rapid oocyte loss from the ovaries. In 21-50% of teenagers with Turner syndrome, breast growth occurs naturally at the start of puberty. [11,12]

Cardiovascular abnormality

The total death rate for TS patients was three times higher than the usual population, according to epidemiological research. For 41% of patients, cardiovascular events pose a significant risk. There is an increased prevalence of congenital cardiovascular anomalies in TS patients compared to the general population. Aortic bicuspid deformity is more common in TS individuals, and heart valve dysfunction is a common anomaly overall. [12] Aneurysms caused by aortic dissection account for the majority of TS-related deaths; the aortic diameter is smaller in TS youth compared to the general population; and aortic surgery is necessary to prevent aortic dissection in TS patients older than 18 years with an ascending aortic size index greater than 2.5 cm/m2. Further research is required to determine the precise incidence of cardiovascular illness in TS patients because of the small sample size and ethnic variations. [13]

Skeletal abnormalities

As far as TS problems go, fractures are among the most serious. Women with TS have around a 25% greater risk of fracture, most often forearm fractures, however, there is no evidence that TS increases the risk of fracture in children and adolescents. Studies of older individuals without estrogen or with delayed or inadequate treatment have cast doubt on tomographic data from TS patients; as a result, the reported frequency of fractures may be exaggerated. [8,13]

Autoimmune diseases

One of the most noticeable aspects of TS, caused by X chromosomal aneuploidy, is secondary autoimmune illness. Thyroiditis is the most frequent autoimmune illness caused by TS, however, it can also cause colitis, celiac disease, psoriasis, type 1 diabetes, and other autoimmune conditions. According to studies that followed up on patients with TS, 3.2% of those patients developed autoimmune thyroiditis. [14] The risk of Hashimoto's thyroiditis is higher in Chinese individuals with TS compared to the general population in China, where the prevalence ranges from 0.4% to 1.5%. Children with TS have a far greater risk of developing Hashimoto's thyroiditis compared to children in other parts of the world. Celiac disease is more common in TS patients compared to the general population; the frequency of the illness ranges from 2.2% to 8.1% among the patients evaluated. Celiac illness can worsen symptoms of hypogonadism, osteoporosis, and short stature. Patients with TS are somewhat affected by the prevalence of other autoimmune illnesses. [15]

TREATMENT

Short Stature

Turner syndrome is characterized by stunted development in girls, who are often somewhat low in stature. A lack of growth hormone is not a symptom of Turner syndrome. Patients, on the other hand, benefit greatly from growth hormone treatment, which should begin as soon as their height drops below 5% of their chronological age. [16] The projected adult height is 20 centimetres less than the typical adult female's height if the condition is not adequately addressed. It is recommended that patients continue taking growth hormone therapy until they attain their adult height and are no longer capable of further development. Sometimes, underlying scoliosis becomes apparent once the patient begins growth hormone medication. Therefore, it is crucial to regularly evaluate the patients' spines as they undergo therapy. Orthopaedic surgery should be consulted when patients develop scoliosis to discuss bracing or corrective surgical options. Additional potential side effects of growth hormone administration include pancreatitis, slipping capital femoral epiphyses, and intracranial hypertension. Growth hormone, oxandrolone, or delayed pubertal induction are options for patients who need additional growth support. [16,17]

Cardiac

An abnormal heartbeat is frequently associated with Turner syndrome. When diagnosing a patient, a cardiologist should look for a prolonged QT interval on the electrocardiogram (ECG). Blood pressure checks should be performed on both the upper and lower limbs and cardiac magnetic resonance imaging (MRI) or echocardiogram should be performed to identify any cardiac abnormalities. If you wish to maintain a long QT interval, avoid using any psychiatric, macrolide, fluoroquinolone, metronidazole, antifungals, antiretroviral, or antiarrhythmic medications. If aortic coarctation is present, surgery is required to rectify it. [18] Throughout their lives, patients should have cardiac MRIs or echocardiograms examined for aortic dilatation frequently. Maintain a normal blood pressure range to reduce the risk of aortic dilatation and dissection. Beta-blockers should be administered initially, followed by ACE inhibitors, to control blood pressure. [15]

Cognitive function/learning disabilities

Despite having average intellect, many girls with Turner syndrome struggle academically and may benefit from individualized testing and instruction. [18]

Hearing loss

It is suggested to regularly evaluate hearing throughout life, with adults having an audiology evaluation every five years and children every three years. [18]

Renal

When making a diagnosis, a renal ultrasound is essential. Collection system anomalies, positional/horseshoe kidneys, and mal-rotated kidneys are common renal abnormalities in Turner syndrome. Hydronephrosis and an increased risk of pyelonephritis can result from obstruction caused by anomalies in the ureteropelvic junction. Referral to nephrology should be made if any irregularities are detected. [17]

Ovarian Failure

Primary amenorrhoea or delayed puberty due to early ovarian failure are common symptoms in girls with Turner syndrome. The recommended ages to test serum FSH and AMH are 10–11. Individuals whose serum AMH levels are measurable are more likely to have spontaneous puberty, which can be used as a predictor of ovarian function. If breast growth does not

commence by the time a girl is 11 or 12 years old, she should begin estrogen replacement treatment. [19] For almost all girls with Turner syndrome, estrogen medication is still required even if they have spontaneous puberty, which can last for a while but is usually followed by primary ovarian insufficiency. Cyclic progestins are subsequently added to the regimen to induce cyclic uterine bleeding and prevent endometrial hyperplasia. Between the ages of 11 and 12, estrogen therapy should be started in cases where gonadotropin levels are high or AMH levels are low. Therapy can begin at dosages between a tenth and an eighteenth of the adult replacement dose, and it can be increased every six months until the patient reaches the adult dosage to replicate the normal process of puberty. One popular treatment for individuals with Turner syndrome is cryopreservation of ovarian tissue or oocytes. This option is not recommended for children under the age of twelve, and ovarian function must be established before it can be explored. [11,20] The majority of women with Turner syndrome are unable to become pregnant due to insufficient egg production from their ovaries. One method of beginning a family is through in vitro fertilization with donor oocytes. [16,20]

Osteoporosis/Bone Health

Those who have Turner syndrome are more likely to fracture and have low bone mineral density. Their risk is decreased by estrogen replacement therapy in addition to calcium and vitamin D supplementation. Because Turner syndrome increases the risk for scoliosis, patients with this condition should have screening for the condition once a year and every six months when on growth hormone treatment. [20]

Screening for other comorbidities

The recommended starting point for measuring tissue transglutaminase immunoglobulin A antibodies in children with celiac disease is about two years of age, with further repeat testing every two years thereafter. [18] Measurements of TSH and free or total T4 should be taken yearly, starting at around four years of age, for autoimmune thyroiditis. When a child reaches the age of 10, yearly testing for liver disease should include ALT, AST, GGT, and alkaline phosphatase. Although these labs tend to be increased in Turner syndrome, a hepatologist should be seen for additional assessment if the abnormal levels continue and are more than twice the normal range. [19] To screen for hyperglycaemia and metabolic syndrome, hemoglobin A1c should be evaluated yearly starting at the age of 10. All patients with a history of cardiovascular disease or any risk factor for cardiovascular disease should have yearly lipid panel testing to detect dyslipidemia. Prevention of vitamin D insufficiency:

Measure serum 25-hydroxyvitamin D levels every two to three years beginning at the age of nine or eleven and continuing afterwards. [20] Patients with Turner syndrome, virilization, or marker chromosomal elements on karyotype should have Y chromosome screening for gonadoblastoma. It is recommended to remove the gonads if the Y chromosome is present, as this lowers the chance of gonadoblastoma. [21]

CHILDREN

Cardiovascular monitoring and treatment of congenital heart disease are crucial components of Turner syndrome management in children. Growth hormone therapy, which can be started as early as 12 to 24 months of age, augments linear growth. Supplemental estrogen therapy, which is usually initiated in the preteen years, promotes sexual development and preserves bone mineral density. The average adult height in patients with Turner syndrome is 4 ft, 8 in (140 cm), but with growth hormone and oestrogen therapy, the average height increases to 5 ft (150 cm). Contrarily to sex hormone therapy, which is sometimes continued throughout life, growth hormone therapy is usually stopped after the patient achieves the bone age of fourteen. [21] Blood pressure readings in all four limbs, audiometry to detect sensorineural or conductive hearing loss due to recurrent otitis media, and ongoing monitoring of thyroid function, liver enzymes, fasting lipids, and glucose levels are all necessary for patients with Turner syndrome. Turner syndrome should be carefully evaluated for congenital hip dislocation in infants and young children using the Barlow/Ortolani maneuvers. If the child is older than one year, a pediatric ophthalmologist should be consulted to check for hyperopia and strabismus. To detect congenital renal abnormalities, ultrasonography should be done throughout the diagnostic process. To screen for celiac disease, girls over the age of four should undergo a tissue transglutaminase immunoglobulin A test every two to four years. To detect malocclusion and other dental abnormalities, patients seven years of age and up should undergo orthodontic assessment. Checking for kyphosis and scoliosis in teenagers should be a top priority. [21,22]

ADULTS

Many people with Turner syndrome worry a lot about their fertility and how their sexuality will develop. Usually, the ovaries degenerate while still developing, either during the fetal period or early childhood years. Patients with Turner syndrome should be counselled about birth control if they are sexually active, as spontaneous menstruation and childbirth occur in 2

to 5 percent of cases. This may be explained by substantial 46, XX/45, X mosaicism, with normal cell populations existing in the ovaries.

[23] Patients with Turner syndrome often seek advice from their primary care physicians regarding their fertility, and age-appropriate counseling regarding infertility treatments can significantly lessen the emotional toll of the diagnosis. Studying young women with Turner syndrome involves doing in vitro fertilization procedures, which include harvesting and freezing oocytes before ovarian regression is complete. Because of the high dangers of both natural and aided pregnancies, it is crucial to have a cardiac echocardiogram or magnetic resonance imaging (MRI) before trying to conceive. As an integral element of a multidisciplinary team that includes specialists in reproductive endocrinology, cardiology, and high-risk obstetrics, primary care physicians should oversee the pregnancy. [24] Treatment for Turner syndrome in adults includes continuing sex hormone medication, managing atherogenic cardiovascular risk factors (such as hypertension, diabetes, and hyperlipidemia), and providing reproductive counselling. Other measures include taking calcium and vitamin D supplements to avoid osteoporosis. On the initial visit, adults should get a bone mineral density scan using dual-energy x-ray absorption technology. If a woman is an adult, she should get an MRI or echocardiogram of her aorta every five to ten years to see if she needs surgery to fix significant aortic root dilatation, which develops in 8 to 42% of patients over time. [24,25]

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Wolff DJ, Van Dyke DL, Powell CM. Working Group of the ACMG Laboratory Quality Assurance Committee. Laboratory guideline for Turner syndrome. Genet Med. 2010;12:52–5.
2. Wang H, He Y, Shao X, Ding Y. Clinical characteristics and chromosome analysis of 67 children with Turner syndrome in Suzhou. Chinese Journal of Birth Health & Heredity. 2009;17:52–3.
3. Zhang F, Zhang Z. Advances in the study of the diagnosis and treatment of Turner syndrome. Journal of China-Japan Friendship Hospital. 2015;29:192–4.
4. Li J, Zi G, Mei X, Li J. Cytogenetic analysis of 18 cases of Turner syndrome in Zhengzhou. Chinese Journal of Birth Health & Heredity. 2011;19:44–44.

5. Wang Z, Zou P, Lu L, Mao Q, Chen T. Cytogenetic analysis of 44 patients with Turner syndrome in Ningbo. Chinese Journal of Birth Health & Heredity. 2011;19:49–49.
6. Su Q. Cytogenetic analysis of 73 patients with Turner syndrome in Beihai. Chinese Journal of Birth Health & Heredity. 2014;22:59–60.
7. Knickmeyer RC, Davenport M. Turner syndrome and sexual differentiation of the brain: implications for understanding male-biased neurodevelopmental disorders. J Neurodev Disord [Internet]. 2011;3(4):293–306. Available from: http://dx.doi.org/10.1007/s11689-011-9089-0
8. Gravholt CH, Lauridsen AL, Brixen K, Mosekilde L, Heickendorff L, Christiansen JS. Marked disproportionality in bone size and mineral, and distinct abnormalities in bone markers and calcitropic hormones in adult Turner syndrome: a cross-sectional study. J Clin Endocrinol Metab [Internet]. 2002;87(6):2798–808. Available from: http://dx.doi.org/10.1210/jcem.87.6.8598
9. Menke LA, Sas TCJ, de Muinck Keizer-Schrama SMPF, Zandwijken GRJ, de Ridder MAJ, Odink RJ, et al. Efficacy and safety of oxandrolone in growth hormone-treated girls with turner syndrome. J Clin Endocrinol Metab [Internet]. 2010;95(3):1151–60. Available from: http://dx.doi.org/10.1210/jc.2009-1821
10. Ross JL, Quigley CA, Feuilian P, Chipman JJ, Cutler GB. Effects of childhood low-dose estrogen on pubertal development in patients with Turner syndrome (TS): Results of a double-blind, randomized, placebo-controlled clinical trial. Hormone Research. 2008;70:43–43.
11. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol [Internet]. 2017; 177(3):G1–70. Available from: http://dx.doi.org/10.1530/EJE-17-0430
12. El-Mansoury M, Barrenäs M-L, Bryman I, Hanson C, Larsson C, Wilhelmsen L, et al. Chromosomal mosaicism mitigates stigmata and cardiovascular risk factors in Turner syndrome. Clin Endocrinol (Oxf) [Internet]. 2007;66(5):744–51. Available from: http://dx.doi.org/10.1111/j.1365-2265.2007.02807.x
13. Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet [Internet]. 1997;16(1):54–63. Available from: http://dx.doi.org/10.1038/ng0597-54
14. Rajpathak SN, Vellarikkal SK, Patowary A, Scaria V, Sivasubbu S, Deobagkar DD. Human 45,X fibroblast transcriptome reveals distinct differentially expressed genes including long noncoding RNAs potentially associated with the pathophysiology of Turner syndrome. PLoS One [Internet]. 2014; 9(6):e100076. Available from: http://dx.doi.org/10.1371/journal.pone.0100076
15. Saenger P. Turner's syndrome. N Engl J Med [Internet]. 1996;335(23):1749–54. Available from: http://dx.doi.org/10.1056/nejm199612053352307
16. Ford C. A sex-chromosome anomaly in a case of gonadal dysgenesis (turner's syndrome). Lancet [Internet]. 1959;273(7075):711–3. Available from: http://dx.doi.org/10.1016/s0140-6736(59)91893-8
17. Gravholt CH, Viuff M, Just J, Sandahl K, Brun S, van der Velden J, et al. The changing face of turner syndrome. Endocr Rev [Internet]. 2023;44(1):33–69. Available from: http://dx.doi.org/10.1210/endrev/bnac016
18 Huang AC, Olson SB, Maslen CL. A review of recent developments in Turner syndrome research. J Cardiovasc Dev Dis [Internet]. 2021;8(11):138. Available from: http://dx.doi.org/10.3390/jcdd8110138
19. Brown CJ, Lafreniere RG, Powers VE, Sebastio G, Ballabio A, Pettigrew AL, et al. Localization of the X inactivation center on the human X chromosome in Xq13. Nature [Internet]. 1991;349(6304):82–4. Available from: http://dx.doi.org/10.1038/349082a0
20. Davies W. The contribution of Xp22.31 gene dosage to Turner and Klinefelter syndromes and sex-biased phenotypes. Eur J Med Genet [Internet]. 2021;64(4):104169. Available from: http://dx.doi.org/10.1016/j.ejmg.2021.104169
21. Urbach A, Benvenisty N. Studying early lethality of 45,XO (turner's syndrome) embryos using human embryonic stem cells. PLoS One [Internet]. 2009;4(1):e4175. Available from: http://dx.doi.org/10.1371/journal.pone.0004175
22. Qi X, Wang Q, Yu M, Kong Y, Shi F, Wang S. Bioinformatic analysis identifies the immunological profile of turner syndrome with different X chromosome origins. Front Endocrinol (Lausanne) [Internet]. 2023;14. Available from: http://dx.doi.org/10.3389/fendo.2023.1024244

23. Cameron- Pimblett A, La Rosa C, King TFJ, Davies MC, Conway GS. The Turner syndrome life course project: Karyotype-phenotype analyses across the lifespan. Clin Endocrinol (Oxf) [Internet]. 2017;87(5):532–8. Available from: http://dx.doi.org/10.1111/cen.13394
24. Sybert VP. Phenotypic effects of mosaicism for a 47, XXX cell line in Turner syndrome. J Med Genet [Internet]. 2002;39(3):217–20. Available from: http://dx.doi.org/10.1136/jmg.39.3.217
25. Prakash SK, Crenshaw ML, Backeljauw PF, Silberbach M, Scurlock C, Culin DD, et al. 45,X mosaicism in a population-based biobank: implications for Turner syndrome. Genet Med [Internet]. 2019;21(8):1882–3. Available from: http://dx.doi.org/10.1038/s41436-018-0411-z