Published in final edited form as:
Fertil Steril. 2012 October ; 98(4): 775–779. doi:10.1016/j.fertnstert.2012.08.021.

Genetic Considerations in the Patient with Turner Syndrome—45,X with or without Mosaicism

Quincy Zhong, B.S. and **Lawrence C. Layman, M.D.**
Section of Reproductive Endocrinology, Infertility, & Genetics, Department of Obstetrics & Gynecology; Institute of Molecular Medicine and Genetics; Neuroscience Program; Georgia Health Sciences University, Augusta, GA 30912

Abstract

Turner syndrome (TS) is a complex developmental disorder in individuals with short stature who possess a 45,X cell line, with or without mosaicism. Since the single X chromosome is maternally derived in 80%, the genesis of the 45,X karyotype is due to instability of the Y chromosome leading to its loss during meiosis. Phenotypic features vary depending upon the mode of ascertainment, with postnatal presentation usually generating a more severe phenotype than a prenatal one. Although patients with pure 45,X present with delayed puberty more often than those with 46,XX or 47,XXX cell lines, the chromosomal complement cannot reliably predict the clinical presentation. Most living TS patients are mosaics, while nearly all first trimester TS fetuses have single 45,X cell line. Exclusion of a Ycell line, the presence of which increases the risk of gonadoblastomas and subsequent gonadal germ cell tumors, is best accomplished by karyotype, fluorescent in situ hybridization, and DNA analysis if necessary. The precise genetic etiology of TS has not been elucidated, but it does appear that deletion of the short arm of the X chromosome is sufficient to result in the TS phenotype, thereby implicating haploinsufficiency of multiple genes including *SHOX*.

Turner Syndrome and the 45,X Karyotype

Turner syndrome (TS), as originally described by Henry Turner in 1938 prior to the advent of chromosome analysis, consisted of a constellation of phenotypic findings—short stature, sexual infantilism, webbed neck, and cubitus valgus.[1] Only later, did Ford et al[2] identify that TS was due to a missing X chromosome. Nowadays, Turner syndrome (TS), also called gonadal dysgenesis, usually applies to females with short stature and 45,X cell line, either singly or in combination with another mosaic cell line. Here we will review genetic aspects of this important multisystem, reproductive developmental disorder and address some common notions about Turner syndrome and the supportive evidence for this.

Correspondence should be addressed to: Lawrence C. Layman, M.D., Robert B. Greenblatt, M.D. Chair in Endocrinology, Section of Reproductive Endocrinology, Infertility, & Genetics, Department of Obstetrics & Gynecology, Georgia Health Sciences University, 1120 15th Street, Augusta, GA 30912, USA., Phone: (706) 721-7591; Fax: (706) 721-0340; llayman@georgiahealth.edu.

Disclosure: The authors have nothing to disclose.

What is the Phenotype of Turner Syndrome—Is There a Karyotype/Phenotype Correlation?

The classic phenotypic presentation of TS includes short stature most commonly (with nearly all patients being less than 5 feet in stature) and delayed puberty in 60–90%.[1,3–8] Additional features are quite variable but include edema of hands or feet, webbed neck, low posterior hairline, nail dysplasia, rotated ears, small mandible, nail hypoplasia, hyperconvex nails, multiple pigmented nevi, characteristic facies, broad shield chest, cubitus valgus, short fourth metacarpal, and high arched palate. [9–10] However, it is the left-sided cardiac anomalies (including coarctation, bicuspid aortic valve, dilated aortic root), which occur in about 50%,[11–12] and renal anomalies (horseshoe kidney, double or cleft renal pelvis, or others), seen in one-third,[13] that may have the greatest impact upon health. There may also be an increased risk of Hashimoto's thyroiditis and hypothyroidism, [10] particularly if an isochromosome of X is present.[10] These somatic features may be present regardless of the presence or absence of mosaicism or the degree of mosaicism.

Approximately 45% of postnatal TS patients have a pure 45,X cell line without any detectable mosaicism.[9] Other karyotypes that may be mosaic with 45,X most commonly include: 46,X,i(Xq), 46,XX, 47,XXX, 46,X,del(Xp), or 46,XY (Table 1). Typically the isochromosome of the X, consisting of two long arms of X and designated 46,X,i(Xq), is the most frequent of the mosaic cell lines.[9–10,14] The presence of a 46,XY cell line may occur in 5–10% and has clinical significance because of the risk of gonadoblastomas and subsequent germ cell tumors, which necessitates removal of the gonads.[15] Any marker chromosomes also need to have proper identification to exclude a Y. Some 45,X/46,XY mosaics may be detected by molecular techniques (see below).[16]

Short stature is the only consistent phenotypic finding (Table 1). However, available evidence indicates that a higher probability of menstruation and pregnancy occurs in mosaic TS patients. Sybert et al[7] reviewed the literature and found that 13/123 (11%) of 45,X patients had spontaneous menses compared to 11/32 (34%) 45,X/46,XX and 30/44 (68%) 45,X/46,XX/47,XXX patients.[7] Eleven of 13 (84%) of 45,X/47,XXX patients also had spontaneous menses. The length of time that menstrual function persisted was highly variable, but not quantified in this review. [7] Fertility rates were lower in the patients with non-mosaic 45,X (1/123 = 0.8%) compared with 6/32 (19%) for 45,X/46,XX, 20/44 (45%) for 45,X/46,XX/47,XXX, and 9/13 (69%) 45,X/47,XXX.[7] When TS patients conceive spontaneously, there is an increased risk of spontaneous abortion, stillborn, congenital anomalies, and aneuploidy.[17–19] Interestingly, the risk of Down syndrome approximates 5% and the recurrence risk of a 45,X fetus is about 10%.[17–19]

Lippe et al[8] studied 141 TS patients and found that 7/79 (8.8%) 45,X patients had ovarian function, which was less than any of the mosaic TS patients—8/10 (80%) in 45,X/46,XX, 7/22 (32%) in 45,X/46,X,i(Xq), and 3/10 (30%) in 46,X,i(Xq). Other categories were too small to make meaningful comparisons, but of note, none of four with a 46,XXp- had puberty. However, in this publication, clinical evidence of ovarian function was defined as breast development and menses, whether it was transient or longer term.[8] In fact, all 29 patients with ovarian function in the study by Lippe et al[8] had at least Tanner III breasts, with menses occurring at least once in all 25/29 (86%). However, regular menstruation only persisted into adulthood in 15/29 (52%). So although it may be more likely that patients who are 45,X mosaics have ovarian function, a 45,X cell line does not preclude spontaneous menstruation and fertility. [3,6] In both mosaic and nonmosaic forms, however, the presence of ovarian function does not necessarily indicate persistent ovarian function. There also does not seem to be any correlation of somatic TS anomalies with the presence or absence of ovarian function. However, differences in ascertainment probably contribute to the

prevalence of detectable somatic anomalies and reproductive dysfunction in these patients (see below).

If a Y cell line is present in combination with 45,X (45,X/46,XY), the patient may have a variable, unpredictable phenotype (Table 1).[20] In addition to the above mentioned phenotypic features, a phenotypic female may have no evidence of any androgen effect (if she has bilateral intra-abdominal streak gonads). Therefore, she will present as a phenotypic female with sexual infantilism. However, if there is an intra-abdominal testis and contralateral streak, clitoromegaly may be present, but if there is an intra-abdominal streak and descended testis, frank ambiguity will be observed.[20] Some patients with a 45,X/46,XY karyotype will have bilaterally descended testes and be phenotypic males, with even the presence of sperm.[21] Therefore, the TS phenotype cannot predict the presence of a Y cell line. Indeed, phenotypic females without any signs of masculinization may have a 46,XY cell line and gonadoblastomas, which predisposes to germ cell tumors.[20] Cools et al[15] have summarized the literature and found the overall prevalence of germ cell tumors in 45,X/46,XY patients to be 18/119 (15%). Although a gonadoblastomas locus has been proposed to reside in the pericentromeric region of Y,[22–23] evidence for a causative gene remains elusive.

Does the Age at Diagnosis Influence the Phenotypic Findings?

It is very likely that the ascertainment bias of TS plays a considerable role in how clinicians view the diagnosis. The pediatrician, pediatric endocrinologist, or pediatric geneticist is more likely to see the child with short stature with or without somatic anomalies—lymphedema, cystic hygroma/webbed neck, cubitus valgus, shield chest, etc.[7] The gynecologist or reproductive endocrinologist is much more likely to first see the adolescent with normal phenotypic features, but absent pubertal development—although short stature will invariably be present.[5–6,10]

A 45,X karyotype has been observed in 1–2% of human conceptions, 10% of first trimester pregnancy losses, 1% of stillbirths, and 1/2500 liveborns.[24] Interestingly, more than 99% of 45,X fetuses abort, typically by 28 weeks gestation. This has led to the long-held hypothesis that all living 45,X individuals must have mosaicism for another cell line.[24] If a 45,X cell line is ascertained by amniocentesis at the time of prenatal diagnosis, the eventual postnatal phenotype may not be easy to predict.[25–26] In fact, in a study by Chang et al[26] in which 76 fetuses identified as 45,X/46,XY prenatally, ~ 95% of the fetuses delivered had normal male external genitalia. However, 5% demonstrated some degree of sexual ambiguity and 27% of the small number evaluated (3 of 11) had abnormal gonadal histology.[26] Hsu[27] reviewed 54 cases of 45,X/46,XY ascertained at the time of prenatal diagnosis. The phenotype postnatally was known for 47 cases and was found to be that of a normal male in 42 cases (89%), while three (6%) had mixed gonadal dysgenesis and two were questionably abnormal. Follow up postnatal cytogenetic studies of the fetus or placenta indicated confirmation of 45,X/46,XY in 70% of 40 cases.[27] If no somatic anomalies are seen by ultrasound, the majority of fetuses will appear normal at birth. However, a postnatal karyotype should be done and long-term follow up is necessary into adulthood to identify somatic anomalies and to determine gonadal function.

More frequently a 45,X/46,XX karyotype may be identified at the time of amniocentesis (estimated at 1/3,000).[28] In a small study of 12 such amniocentesis cases compared with 41 postnatal 45,X/46,XX cases, the phenotype was much milder in the prenatally diagnosed group.[28] Nine of 12 appeared normal at birth and most did not have elevated gonadotropins in the neonatal period.[28] Certainly, long-term studies are necessary, but it appears that the prenatal diagnosis of 45,X/46,XX portends a potentially milder phenotype.

How is Mosaicism Appropriately Detected?

Prenatal Diagnosis

When a 45,X cell is identified in amniotic fluid or at the time of chorionic villus sampling, there are guidelines published by the American College of Medical Genetics,[9] which were largely based upon the work of Hsu and Ben.[29] Briefly, if a 45,X cell line is identified, 20 additional cells from a different cell culture or 12 colonies from coverslips other than the one with the abnormality should be evaluated. If a structurally abnormal X chromosome or marker chromosome is identified, additional cultures should also be assessed.[9,29] If a marker chromosome is found, additional FISH testing with X and Y centromere probes is recommended.[9]

Postnatal Diagnosis

In the patients with suspected TS, a karyotype should be obtained from peripheral leukocytes, but additional cells should have the total number of chromosomes counted. As reported by Hook,[30] to detect 10% mosaicism with 95% confidence, ≥ 29 metaphases are needed to exclude a mosaic cell line (such as 45,X). To detect 5% and 1% mosaicism with 95% confidence, ≥ 59 and ≥299 metaphases, respectively, are needed.[30] Additionally, interphase FISH for X and Y probes may be useful to determine low level mosaicism. If there is low-level mosaicism, it is important to take the phenotype into account—short stature in particular, and recognize that there is an age-related loss of the X chromosome, which can complicate the analysis.[31]

In the patient with an apparent nonmosaic 45,X karyotype, it is prudent to exclude a Y cell line utilizing FISH. Normal male and normal female controls should be studied to set the cutoff for the limits of detection. As reported by Wiktor et al,[32] at the 95% confidence level, if 500 nuclei are scored, the presence of five or more cells with two X signals is required to establish the presence of an XX cell line, whereas three or more Y signals are needed to document a 46,XY cell line.[32] It is possible that these exact cutoffs could vary somewhat from laboratory to laboratory, but the important concept is that validated control guidelines should be established by the laboratory.

The role of Y chromosome detection by PCR has been reported in a number of studies, but there have been concerns of false positives,[33] which would result in unnecessary surgery. When Cools et al[15] reviewed 11 studies containing 541 TS patients without a Y by karyotype, 27 (5%) had Y chromosome mosaicism by PCR. If a marker chromosome (mar) was present in the original karyotype, nearly all had Y DNA. Including patients from these 11 studies who had cytogenetic evidence of a Y, 43/557 (11.6%) TS patients had gonadoblastomas.[15] McDonough and Tho[34] recommend that a karyotype analyzing 30–50 metaphases should be the first step to detect Y DNA in 45,X patients. If a marker chromosome of unknown origin is identified, reflex metaphase FISH should be performed with centromeric X (DXZ1) and Y (DYZ3) centromeric probes to confirm the marker identity.[34] If nonmosaic 45,X, nonmosaic 46,XY, or nonmosaic 47,XYY cell lines are identified, reflex interphase FISH should be done on 500 nuclei to search for a Y (or 45,X) cell line. FISH results, whether positive or negative, should be confirmed with PCR analysis for DYZ3, SRY, DYZ4 A, and DYZ4 B using sequence tagged sites (STS) if DNA is still available.[34]

Sex chromosome mosaicism is very variable in TS patients and depends upon the methodology and the criteria used for its determination. The number of cells that are counted; the number of tissues that are tested (blood, skin, etc.); the technique (karyotype, FISH), and the standards that are used for its interpretation all affect the presence of mosaicism. Most living TS patients have documented mosaicism if cytogenetics and

interphase FISH are utilized. Held et al[35] studied lymphocyte and fibroblast cultures in 87 TS patients and found mosaicism in 58/87 (67%), no mosaicism in 18/87 (21%), and nonmosaic structural abnormalities of the X chromosome in 11/87 (13%). Fernandez-Garcia et al[36] detected mosaicism in 37/41 (90%) of TS patients using the combination of cytogenetics, extensive FISH analysis, PCR, and sequencing for SRY.

What is the Genetic Basis of Turner Syndrome?

Turner syndrome is normally a sporadic condition that is unrelated to advanced maternal age. In fact, the missing X chromosome more typically is paternal in origin for ~75% of liveborns who are 45,X, as repeatedly determined using a number of different methods—Xg blood grouping, restriction-fragment length polymorphism (RFLP) and single nucleotide polymorphism (SNP) in parents.[37] Hassold et al[38] first studied 35 nonmosaic 45,X patients and found that 80% of patients had a maternal X chromosome. Uematsu et al[37] studied 50 unselected TS without regard to karyotype and found that 76.2% of pure 45,X and 72.4% of 45,X/mosaic patients had a maternal X chromosome. They also summarized the literature, which has been remarkably consistent for 45,X—227/303 (74.9%) had a maternal X chromosome. Although the numbers were smaller, similar findings were found for the origin of ring chromosomes, marker chromosomes, or Xp deletions.[37]

The one exception seems to be the 46,X,i(Xq) mosaic cell line. First reported by Callen et al[39] in five patients with X isochromosomes, and studied in larger sample sizes by other investigators, the likelihood of a maternal or paternal i(Xq) was similar. Jacobs et al[14] studied the most 45,X/46,X,i(Xq) patients and found that 15 had a maternal X and 20 had a paternal X. This is a fairly consistent observation in the literature as reported by Uematsu et al[37] who summarized a number of studies and found that of 131 45,X/46,X,i(Xq) patients, the i(Xq) was maternal in 46% and paternal in 54%.

The observation that 45,X does not increase with maternal age argues against a maternal meiotic error, and the finding that 75% of TS patients have a maternal X suggest that a paternal meiotic error generates abnormal sex chromosomes.[37] These in turn predispose to mitotic loss by anaphase lag for a pure 45,X cell line or nondisjunction if a mosaic cell line is present (such as a 47,XXX). This seems true for nonmosaic 45,X, or 45,X with other mosaic cell lines such as 46,X,del(Xp), 46,X,r(X), and 46,X,mar(X).[37] Certainly, the presence of a Y cell line is paternal in origin as well. However, the etiology may be different for 45,X/46,X,i(Xq). Since there is an equal likelihood of a maternal or paternal i(Xq), this indicates a gametogenic error could occur with equal frequency. It is also possible that 45,X/46,Xi(Xq) occurs postzygotically, and if so, it should be at the first mitotic division. In fact, 45,X/46,XX/46,Xi(Xq) mosaics, which would occur at later cell divisions, are extremely uncommon.[14] As mentioned above, ~99% of pure 45,X are lost in the first trimester and that most living TS patients are mosaics.[24]

What Genes Cause Turner Syndrome?

Turner syndrome with a pure 45,X cell line is thought to result from haploinsufficiency of multiple genes on the X chromosome (or loss of the Y chromosome) that affect embryologic development, stature, and gonadal function. The short stature, and perhaps the bony abnormalities (at least in part), likely result from the deletion of one allele of *SHOX* (short stature homeobox gene), a transcription factor on Xp22 that is primarily expressed in osteogenic cells.[40] Interestingly, patients with idiopathic short stature (without Turner syndrome) may harbor mutations in *SHOX*, of which the type of mutation may affect the phenotype. Langer mesomelic dysplasia results from *SHOX* deletions, while Leri-Weill dyschondrosteosis, a skeletal dysplasia with disproportionate short stature, mesomelic limbs,

and the Madelung deformity (a radial bone anomaly), results from *SHOX* nonsense mutations. [40–41] The Madelung deformity may sometimes be seen in Turner syndrome.

Structural alterations of the X chromosome affect ovarian function and may affect stature. Partial deletions of the X chromosome may also impair ovarian function. In general, deletions affecting Xp11 result in ovarian failure in about half of patients, while the other half have menstrual function.[42] With more distal deletions, such as at Xp21, the phenotype is usually less severe. Most women with Xp deletions are short, regardless of ovarian function, further supporting that other statural determinant genes could reside within these regions. Several families with Xp deletions have also been reported.[42] Available evidence suggests that a complete deletion of the short arm of the X (Xp-) is sufficient result in the TS phenotype since a pure cell line of 46,X,i(Xq), which consists of two Xq and no Xp arms, is found in some TS patients.

Deletions of Xq may also result in ovarian failure. Similar to Xp deletions, proximal Xq (such as Xq13) deletions are usually more severe, and these patients have absent breast development, primary amenorrhea, and gonadal failure. In fact, the Xq26-q28 region has been designated POF1 while Xq13.3-q21.1 has been identified as POF2, as both of these regions were proposed to contain ovarian determinant genes. Identified genes on the X chromosome that affect ovarian function include *FMR1*[43] and *BMP15*[44] since mutations in either results in hypergonadotropic hypogonadism. Chromosomal rearrangements involving the X chromosome have also been reported to disrupt ovarian gene function.[42]

Conclusions

Turner syndrome is a complex reproductive developmental disorder. Postnatal presentation is more likely to demonstrate a more severe phenotype than if it is ascertained prenatally. However, it should be remembered that long-term follow-up of patients diagnosed prenatally is necessary; and this follow-up is lacking in the literature. Most first trimester TS karyotypes are pure 45,X, while most postnatal, living TS are mosaics. Ascertainment of TS patients is clearly biased—practitioners taking care of children are more likely to find patients with short stature and somatic anomalies, while health care workers seeing adolescents and adults will more commonly identify TS patients with short stature and menstrual abnormalities. These biases contribute to the great variation of phenotypic and karyotypic differences. Pubertal development and reproductive function are clearly impaired, and should the TS patient conceive spontaneously, there is an increased risk of reproductive loss, congenital anomalies, sex chromosome abnormalities, and Down syndrome.

The precise genetic basis of TS is not clear, but it appears that deletion of Xp (or loss of the Y) is sufficient to cause the full syndrome, thereby implicating haploinsufficiency of a variety of genes including *SHOX*. Turner syndrome is not related to advanced maternal age; and in fact, is more likely due to instability of the Y chromosome leading to its loss during male meiosis since 75–80% of X chromosomes in TS patients are maternal in origin.

Acknowledgments

L.C.L. was supported from NIH grant HD33004 for portions of this work.

References

1. Turner HH. A syndrome of infantilism, congenital webbed neck and cubitus valgus. Endcrinol. 1938; 23:566–8.

2. Ford CE, Jones KW, Polani PE, De Almeida JC, Briggs JH. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet. 1959; 1:711–3. [PubMed: 13642858]

3. Greenblatt RB, Byrd JR, McDonough PG, Mahesh VB. The spectrum of gonadal dysgenesis. A clinical, cytogenetic, and pathologic study. Am J Obstet Gynecol. 1967; 98:151–72. [PubMed: 6023669]

4. McDonough PG, Byrd JR. Gonadal dysgenesis. Clin Obstet Gynecol. 1977; 20:565–79. [PubMed: 891055]

5. McDonough PG, Byrd JR, Tho PT, Mahesh VB. Phenotypic and cytogenetic findings in eighty-two patients with ovarian failure--changing trends. Fertil Steril. 1977; 28:638–41. [PubMed: 862976]

6. Reindollar RH, Byrd JR, McDonough PG. Delayed sexual development:study of 252 patients. Am J Obstet Gynecol. 1981; 140:371–80. [PubMed: 7246652]

7. Sybert VP. Phenotypic effects of mosaicism for a 47,XXX cell line in Turner syndrome. J Med Genet. 2002; 39:217–20. [PubMed: 11897829]

8. Lippe, B.; Westra, SJ.; Boechat, MI. Ovarian function in Turner syndrome: recognizing the spectrum. In: Hibi, I.; Takano, K., editors. Basic and Clinical Approach to Turner syndrome. Elsevier Science Publishers; 1993. p. 117-22.

9. Wolff DJ, Van Dyke DL, Powell CM. Laboratory guideline for Turner syndrome. Genet Med. 2010; 12:52–5. [PubMed: 20081420]

10. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004; 351:1227–38. [PubMed: 15371580]

11. Lin AE, Lippe BM, Geffner ME, et al. Aortic dilation, dissection, and rupture in patients with Turner syndrome. J Pediatr. 1986; 109:820–6. [PubMed: 3772661]

12. Miller MJ, Geffner ME, Lippe BM, et al. Echocardiography reveals a high incidence of bicuspid aortic valve in Turner syndrome. J Pediatr. 1983; 102:47–50. [PubMed: 6848727]

13. Lippe B, Geffner ME, Dietrich RB, Boechat MI, Kangarloo H. Renal malformations in patients with Turner syndrome: imaging in 141 patients. Pediatrics. 1988; 82:852–6. [PubMed: 3054787]

14. Jacobs P, Dalton P, James R, et al. Turner syndrome: a cytogenetic and molecular study. Ann Hum Genet. 1997; 61:471–83. [PubMed: 9543547]

15. Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev. 2006; 27:468–84. [PubMed: 16735607]

16. Lopez M, Canto P, Aguinaga M, et al. Frequency of Y chromosomal material in Mexican patients with Ullrich-Turner syndrome. Am J Med Genet. 1998; 76:120–4. [PubMed: 9511973]

17. Kaneko N, Kawagoe S, Hiroi M. Turner's syndrome--review of the literature with reference to a successful pregnancy outcome. Gynecol Obstet Invest. 1990; 29:81–7. [PubMed: 2185981]

18. Layman, L. Familial ovarian failure. In: RL, editor. Perimenopause. New York: Springer-Verlag; 1997. p. 46-77.

19. Tarani L, Lampariello S, Raguso G, et al. Pregnancy in patients with Turner's syndrome: six new cases and review of literature. Gynecol Endocrinol. 1998; 12:83–7. [PubMed: 9610420]

20. Gantt PA, Byrd JR, Greenblatt RB, McDonough PG. A clinical and cytogenetic study of fifteen patients with 45,X/46XY gonadal dysgenesis. Fertil Steril. 1980; 34:216–21. [PubMed: 7409242]

21. Layman LC, Tho SP, Clark AD, Kulharya A, McDonough PG. Phenotypic spectrum of 45,X/46,XY males with a ring Y chromosome and bilaterally descended testes. Fertil Steril. 2009; 91:791–7. [PubMed: 18555994]

22. Salo P, Kaariainen H, Petrovic V, Peltomaki P, Page DC, de la Chapelle A. Molecular mapping of the putative gonadoblastoma locus on the Y chromosome. Genes Chromosomes Cancer. 1995; 14:210–4. [PubMed: 8589038]

23. Tsuchiya K, Reijo R, Page DC, Disteche CM. Gonadoblastoma: molecular definition of the susceptibility region on the Y chromosome. Am J Hum Genet. 1995; 57:1400–7. [PubMed: 8533770]

24. Hook EB, Warburton D. 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. Hum Genet. 1983; 64:24–7. [PubMed: 6683706]

25. Wheeler M, Peakman D, Robinson A, Henry G. 45,X/46,XY mosaicism: contrast of prenatal and postnatal diagnosis. Am J Med Genet. 1988; 29:565–71. [PubMed: 3376999]
26. Chang HJ, Clark RD, Bachman H. The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. Am J Hum Genet. 1990; 46:156–67. [PubMed: 2294747]
27. Hsu LY. Prenatal diagnosis of 45,X/46,XY mosaicism--a review and update. Prenat Diagn. 1989; 9:31–48. [PubMed: 2664755]
28. Koeberl DD, McGillivray B, Sybert VP. Prenatal diagnosis of 45,X/46,XX mosaicism and 45,X: implications for postnatal outcome. Am J Hum Genet. 1995; 57:661–6. [PubMed: 7668295]
29. Hsu LY, Benn PA. Revised guidelines for the diagnosis of mosaicism in amniocytes. Prenat Diagn. 1999; 19:1081–82. [PubMed: 10589067]
30. Hook EB. Exclusion of chromosomal mosaicism: tables of 90%, 95% and 99% confidence limits and comments on use. Am J Hum Genet. 1977; 29:94–7. [PubMed: 835578]
31. Russell LM, Strike P, Browne CE, Jacobs PA. X chromosome loss and ageing. Cytogenet Genome Res. 2007; 116:181–5. [PubMed: 17317957]
32. Wiktor AE, Van Dyke DL. Detection of low level sex chromosome mosaicism in Ullrich-Turner syndrome patients. Am J Med Genet A. 2005; 138A:259–61. [PubMed: 16158437]
33. Nishi MY, Domenice S, Medeiros MA, Mendonca BB, Billerbeck AE. Detection of Y-specific sequences in 122 patients with Turner syndrome: nested PCR is not a reliable method. Am J Med Genet. 2002; 107:299–305. [PubMed: 11840486]
34. McDonough, PG.; Tho, SPT. In: Gravholt, CH.; Bondy, CA., editors. Clinical implications of overt and cryptic Y mosaicism in indivduals with dysgenetic gonads; Wellness for Girls and Women with Turner Syndrome Proceedings of the Consensus Conference; April 6–9, 2006; Elsivier; 2006. p. 13-20.
35. Held KR, Kerber S, Kaminsky E, et al. Mosaicism in 45,X Turner syndrome: does survival in early pregnancy depend on the presence of two sex chromosomes? Hum Genet. 1992; 88:288–94. [PubMed: 1733830]
36. Fernandez-Garcia R, Garcia-Doval S, Costoya S, Pasaro E. Analysis of sex chromosome aneuploidy in 41 patients with Turner syndrome: a study of ‘hidden’ mosaicism. Clin Genet. 2000; 58:201–8. [PubMed: 11076042]
37. Uematsu A, Yorifuji T, Muroi J, et al. Parental origin of normal X chromosomes in Turner syndrome patients with various karyotypes: implications for the mechanism leading to generation of a 45,X karyotype. Am J Med Genet. 2002; 111:134–9. [PubMed: 12210339]
38. Hassold T, Benham F, Leppert M. Cytogenetic and molecular analysis of sex-chromosome monosomy. Am J Hum Genet. 1988; 42:534–41. [PubMed: 2894760]
39. Callen DF, Mulley JC, Baker EG, Sutherland GR. Determining the origin of human X isochromosomes by use of DNA sequence polymorphisms and detection of an apparent i(Xq) with Xp sequences. Hum Genet. 1987; 77:236–40. [PubMed: 3479386]
40. Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. Horm Res Paediatr. 2011; 75:81–9. [PubMed: 21325865]
41. Cormier-Daire V, Belin V, Cusin V, et al. SHOX gene mutations and deletions in dyschondrosteosis or Leri-Weill syndrome. Acta Paediatr Suppl. 1999; 88:55–9. [PubMed: 10626546]
42. Layman LC. Human gene mutations causing infertility. J Med Genet. 2002; 39:153–61. [PubMed: 11897813]
43. Allingham-Hawkins DJ, Babul-Hirji R, Chitayat D, et al. Fragile X premutation is a significant risk factor for premature ovarian failure: the International Collaborative POF in Fragile X study--preliminary data. Am J Med Genet. 1999; 83:322–5. [PubMed: 10208170]
44. Di Pasquale E, Beck-Peccoz P, Persani L. Hypergonadotropic ovarian failure associated with an inherited mutation of human bone morphogenetic protein-15 (BMP15) gene. Am J Hum Genet. 2004; 75:106–11. [PubMed: 15136966]

Table 1

Sexual development and differentiation in Turner Syndrome

Genotype	Phenotype
45,X	Sexual infantilism (90%)
	Normal puberty and menses (10%)
45,X mosaic (without Y) (46,XiXq, 46,XX, 47,XXX, 46,X,del(Xp))	Sexual infantilism (30–58%)
	Normal puberty and spontaneous menarche (70%) * (Sybert7)
	Normal puberty and spontaneous menarche (42%); only half (21%) had consistent menses in adulthood (Lippe et al8)
45,X/46,XY mosaic with:	
Bilateral intraabdominal streak gonads	Sexual infantilism
Intraabdominal streak + intraabdominal testis	Clitoromegaly
Intraabdominal streak + scrotal testis	Sexual ambiguity
Bilatral scrotal testes	Normal male with infertility

* Ovarian and menstrual function may be short-lived indicating a high degree of gonadal dysfunction.