appears to account for certain aspects of the phenotype, such as small penis size.

Turner Syndrome

Turner syndrome results from complete or partial monosomy of the X chromosome and is characterized primarily by hypogonadism in phenotypic females. It is the most common sex chromosome abnormality in females, affecting about 1 in 2500 live-born females.

With routine cytogenetic methods, three types of karyotypic abnormalities are seen in individuals with Turner syndrome.

- *Approximately 57% are missing an entire X chromosome, resulting in a 45,X karyotype.* Of the remaining 43%, approximately one third (approximately 14%) have structural abnormalities of the X chromosomes, and two thirds (approximately 29%) are mosaics.
- *The common feature of the structural abnormalities is to produce partial monosomy of the X chromosome.* In order of frequency, the structural abnormalities of the X chromosome include (1) an isochromosome of the long arm, 46,X,i(X)(q10) resulting in the loss of the short arm; (2) deletion of portions of both long and short arms, resulting in the formation of a ring chromosome, 46,X,r(X); and (3) deletion of portions of the short or long arm, 46X,del(Xq) or 46X,del(Xp).
- *The mosaic patients have a 45,X cell population along with one or more karyotypically normal or abnormal cell types.* Examples of karyotypes that mosaic Turner females may have are the following: (1) 45,X/46,XX; (2) 45,X/46,XY; (3) 45,X/47,XXX; or (4) 45,X/46,X,i(X)(q10). Studies suggest that the prevalence of mosaicism in Turner syndrome may be much higher than the 30% detected by conventional cytogenetic studies. With the use of more sensitive techniques, the prevalence of mosaic Turner syndrome increases to 75%. Because 99% of conceptuses with an apparent 45,X karyotype are nonviable, many authorities believe that there are no truly nonmosaic Turner syndrome patients. While this issue remains controversial, it is important to appreciate the karyotypic heterogeneity associated with Turner syndrome, because it is responsible for significant variations in phenotype. In patients in whom the proportion of 45,X cells is high, the phenotypic changes are more severe than in those who have readily detectable mosaicism. The latter may have an almost normal appearance and may present only with primary amenorrhea.

Five percent to 10% of patients with Turner syndrome have Y chromosome sequences either as a complete Y chromosome (e.g., 45,X/46,XY karyotype) or as fragments of Y chromosomes translocated on other chromosomes. These patients are at a higher risk for development of a gonadal tumor (gonadoblastoma).

The most severely affected patients generally present during infancy with edema of the dorsum of the hand and foot due to lymph stasis, and sometimes *swelling of the nape of the neck.* The latter is related to markedly distended lymphatic channels, producing a so-called cystic hygroma (Chapter 10). As these infants develop, the swellings subside but often leave bilateral *neck webbing* and persistent looseness of skin on the back of the neck. *Congenital heart disease* is also common, affecting 25% to 50% of patients. Left-sided cardiovascular abnormalities, particularly preductal coarctation of the aorta and bicuspid aortic valve, are seen most frequently. *Cardiovascular abnormalities are the most important cause of increased mortality in children* with Turner syndrome.

The principal clinical features in the adolescent and adult are illustrated in Figure 5-22. At puberty there is *failure to develop normal secondary sex characteristics.* The genitalia remain infantile, breast development is inadequate, and there is little pubic hair. The mental status of these patients is usually normal, but subtle defects in nonverbal, visual-spatial information processing have been noted. Of particular importance in establishing the diagnosis in the adult is the shortness of stature (rarely exceeding 150 cm in height) and amenorrhea. *Turner syndrome is the single most important cause of primary amenorrhea*, accounting for approximately one third of the cases. For reasons not clear, approximately 50% of patients develop autoantibodies that react with the thyroid gland, and up to half of these develop clinically manifest hypothyroidism. Equally mysterious is the presence of glucose intolerance, obesity, and insulin resistance in a minority of patients. The last mentioned is significant, because therapy with growth hormone, commonly used in these patients, worsens insulin resistance.

The molecular pathogenesis of Turner syndrome is not completely understood, but studies have begun to shed some light. In approximately 75% of cases the X- chromosome is maternal in origin, thus suggesting that there is an abnormality in paternal gametogenesis. As mentioned earlier, both X chromosomes are active during oogenesis and are essential for normal development of the ovaries. During normal fetal development, ovaries contain as many as 7 million oocytes. The oocytes gradually disappear so that by menarche their numbers have dwindled to a mere 400,000, and when menopause occurs fewer than 10,000 remain. In Turner syndrome, fetal ovaries develop normally early in embryogenesis, but the absence of the second X chromosome leads to an accelerated loss of oocytes, which is complete by age 2 years. In a sense, therefore, "menopause occurs before menarche," and the ovaries are reduced to atrophic fibrous strands, devoid of ova and follicles *(streak ovaries).* Because patients with Turner syndrome also have other (nongonadal) abnormalities, it follows that some genes for normal growth and development of somatic tissues must also reside on the X chromosome. Among the genes involved in the Turner phenotype is the short stature homeobox (*SHOX*) gene at Xp22.33. This is one of several genes that remain active in both X chromosomes and has an active homologue on the short arm of the Y chromosome. Thus, both normal males and females have two copies of this gene. Haploinsufficiency of *SHOX* gives rise to short stature. Indeed, deletions of the *SHOX* gene are noted in 2% to 5% of otherwise normal children with short stature. In keeping with its role as a critical regulator of growth, the *SHOX* gene is expressed during fetal life in the growth plates of several long bones including the radius, ulna, tibia, and fibula. It is also expressed in the first and second pharyngeal arches. Just as the loss of *SHOX* is always associated with short stature, excess copies of this gene are associated with tall stature. Whereas haploinsufficiency of *SHOX* can explain growth deficit in Turner syndrome, it cannot explain other clinical