Chromosome X

Technical genetic content provided by Dr. Iosif Lurie, M.D. Ph.D
Medical Geneticist and CDO Medical Consultant/Advisor.
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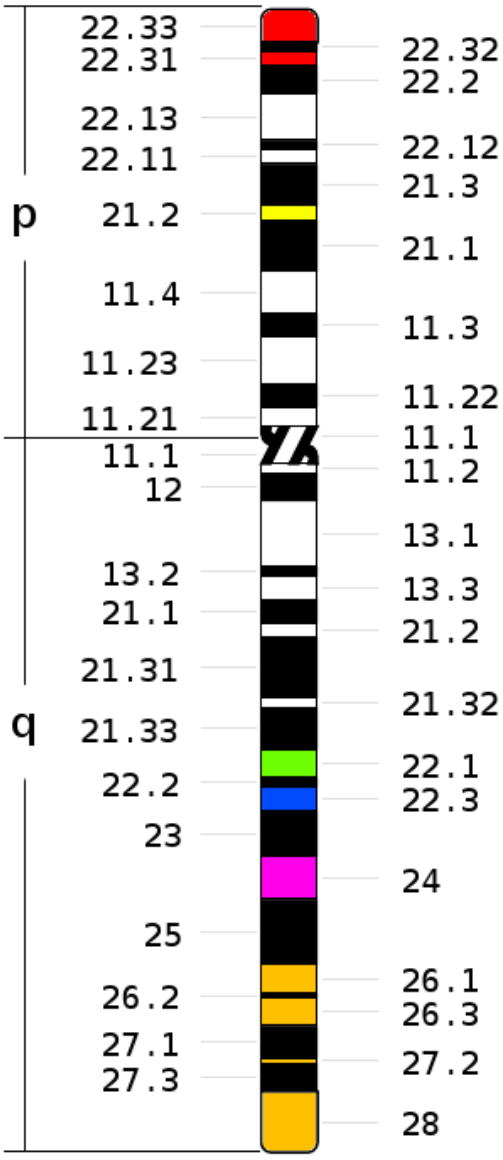

Introduction

The genetic size of chromosome X is 155 Mb. It is ~5% of the total genetic material of the human genome. The length of the short arm of this chromosome is ~60 Mb; the length of its long arm is 95 Mb. Chromosome X is a gene–rich area. It contains ~1,000–1,300 genes. Many of these genes are crucial for maintaining numerous functions.

In normal conditions, each female has two X–chromosomes, whereas males usually have only one X–chromosome and a gene deprived Y–chromosome. There is a specific mechanism leading to the inactivation of one of the X–chromosomes in each diploid cell of the female organism. Inactivation occurs basically randomly, and a resulting number of cells with an inactive X–chromosome inherited from the mother is approximately the same as the number of cells with an inactive paternal X–chromosome. [There are some examples of a selective (“skewed”) inactivation of the X–chromosome bearing some pathological genes, but these details are out of the scope of this review]. Inactivation is irreversible. All cells occurring from the cell with an inactive paternal X–chromosome will also have an inactive paternal X–chromosome, and vice–versa. This mechanism, also known as lyonization of the X–chromosome (by the name of Mary Lyon, who reported this phenomenon) explains why women usually do not have well–known X–linked recessive conditions such as hemophilia or Duchenne muscular dystrophy: the effect of the genes from a normal X–chromosome will be enough to sustain normal functions in females who have one X–chromosome carrying the mutant gene. Inactivation itself depends on the activity of “inactivation centers” located in the long arm of the X–chromosome. Strictly speaking, there are some small areas of the X–chromosome that escape inactivation. These areas may contain genes complimentary to some genes on the Y–chromosome. These areas are called “pseudoautosomal” regions.

Deletions of the X–chromosome in Females

In normal conditions, inactivation of the X–chromosome is basically random. However, if one of the X–chromosomes is structurally damaged, it will be inactivated in all cells. As a result, in the patients with large (microscopically visible) deletions of Xp, some large deletions of Xq, as well as other structural abnormalities (isochromosomes Xq, ring X chromosome, some X–autosomal translocations), a structurally abnormal X–chromosome will be inactivated in all cells. Therefore, such patients may have the same phenotypic consequences as patients with 45,X karyotype.

Karyotype 45,X is responsible for the well–known Turner syndrome. The main manifestations of this syndrome are significant growth retardation, short webbed neck, sometimes ptosis. Approximately 25–30% of patients with classical Turner syndrome have heart defects, usually non–life–threatening coarctation of aorta or bicuspid aortic valve). Systemic urologic examination showed an increase of kidney defects in Turner syndrome patients. Intellectual development of such persons is usually normal.

The most significant abnormality associated with Turner syndrome is gonadal dysgenesis. The development and normal functioning of the ovaries requires the presence of two X–chromosomes. In patients with Turner syndrome, the gonads remain underdeveloped. These ovaries are not able to synthesize hormones and are unable to produce egg–cells. Practically, most patients with Turner syndrome became diagnosed when these girls did not show pubertal changes typical for normal girls of the same age.

The patients with “large” deletions of the short arm of the X–chromosome, some “large” deletions of the long arm, as well as persons with ring X chromosome or iso–chromosome Xq will have similar manifestations. Turner syndrome may be diagnosed clinically, but cytogenetic examination of each patient is absolutely necessary to determine the exact sub–type of the disease.

Some patients with X–chromosome deletions are mosaics with the existence of the normal 46,XX clone. It is remarkable that the proportion of patients with mosaicism for persons with X–chromosome deletions is much higher than for the persons with any autosomal deletion. Clinical manifestations in such persons are usually less severe. Such girls will be not so short and may have regular periods, although the individual prognosis in each person will depend on the ratio between the normal and abnormal clones.

The patients with distal deletions of the long arm may present “pure gonadal dysgenesis”. It means that they will have sexual infantilism, amenorrhea and sterility, but will not have short stature, webbed neck, heart defects and other non–gonad–related manifestations of Turner syndrome. It should be noted that dysgenetic gonads have an increased risk of developing tumors, including dysgerminomas.

Small interstitial deletions of Xq, recognizable only using methods of molecular cytogenetics, are associated with developmental delay and abnormal behavior in deletions Xq22.1, nephropathies in deletions Xq22.3q23, hemihyperplasia in deletions Xq25. However, not a single well–delineated syndrome associated with interstitial deletions of Xq has been reported so far.

Very distal deletions of Xq (Xq26 or more terminal) may lead to premature ovarian failure, when previously functioning ovaries stop their function in woman before 40. Deletions of the genes, which normally escape inactivation, lead to haploinsufficiency for these genes. However, deletions of the distal part of Xq are a very rare cause of premature ovarian failure.

Deletions of the X–chromosome in Males

In normal conditions, males have only one X–chromosome. Because this chromosome is relatively gene–rich, deletions of the X–chromosome in males will cause nullisomy for the genes in the deleted area. If the deletion is large (at least recognizable by “standard” cytogenetic examination) it will cause nullisomy for tens or hundreds of genes, and this effect will be lethal. Male embryos having large deletions of the X–chromosome will die in utero. Introduction of molecular cytogenetics allowed the detection of relatively small deletions, which lead to nullisomy for several genes. As a result there is an increasing number of reports on males with small deletions of the X–chromosome. Phenotypic consequences of these deletions depend on the localization of the deletion and basically produce disorders known to be caused by mutations of the X–linked genes. Deletions of Xp21, for example, may produce Duchenne muscular dystrophy, deletions of Xp22.3 may lead to chondrodysplasia punctata (a skeletal pathology with stippled calcifications at the epiphyseal areas), deletions of Xq24 may cause an association of seizures, absent speech, hirsutism and mild genital anomalies). However, all of these deletions are very rare: the vast majority of patients with these conditions have mutations within a gene or deletions of a part of the gene.