Chromosome Y

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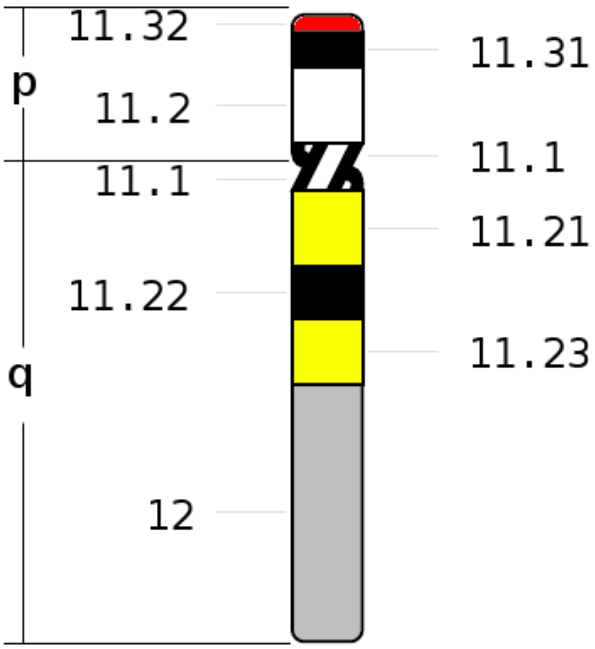

Introduction

The Y–chromosome is one of sex chromosomes in humans. It exists only in men and (normally) in one copy. This chromosome is unique. All other human chromosomes exist in pairs, and during meiosis there is a recombination (exchange) of genetic material between homologous regions of the paired chromosomes. As a result, these chromosomes have significant changes in each generation. The Y–chromosome does not have a homologue, and, therefore, there is no recombination. The Y–chromosome remains virtually unchanged through many generations. It allows usage of some characteristics of this chromosome to study the genetic origin of different populations.

The Y–chromosome is ~2% of the total length of the genetic material in humans. Its genetic length is ~57 Mb. Its short arm has ~13 Mb, and its long arm has ~44 Mb. Chromosome Y is an extremely gene–poor area. Some estimates show that this chromosome contains only 75–80 genes or 10 times less than chromosome 20, which has a similar size. It is less than 1.5 genes per 1 Mb of genetic material. Almost all of these genes are involved in either determining the gender or performing sex–related functions.

Deletions of the Y–chromosome are very common, but clinical consequences of these deletions are very different from deletions of autosomes. Almost all of these deletions affect either sex determination or maintaining sexual functions in males.

The main sex determinant is the SRY–gene, which is located on the tip of the short arm of the Y–chromosome (~2 Mb from the telomere). It should be noted that early human embryos have undifferentiated gonads. These gonads may become testes only in response to the expression of the SRY–gene. If a gonad develops as testis, it will produce the testosterone necessary for the differentiation of the Wolffian ducts into seminal vesicles. Of course, the SRY–gene is not the only player in this chain, but it is definitely the most important. If the SRY–gene does not exist (via deletion) or does not functions properly (via mutation), the development of male genitalia becomes impossible. As a result, the patient with a deleted Y–

chromosome (or mutated SRY–gene) will develop into a phenotypic female. In most persons, deletions of the short arm of the Y–chromosome are relatively small. Most of these deletions may not be found upon “standard” cytogenetic examination. Actually, there are specific FISH–probes for SRY, which allows us to determine whether the person has a deletion of SRY or not. Large deletions of the short arm of the Y–chromosome are relatively rare; in most patients, these deletions are associated with other structural defects of the Y–chromosome or with mosaicism with a 45,X clone. Some persons with “large” Yp deletions may reveal Turner–like features (short stature, webbed neck, heart defects), but the vast majority of patients with Yp deletions are phenotypically normal females.

As a rule, there are no concerns regarding sexual development of the child until puberty. Only when a “girl” does not reveal any age–appropriate changes (development of breasts or the beginning of the menstrual cycle), the parents visit the pediatrician (gynecologist, endocrinologist) who starts necessary testing, which shows that the child actually has not two normal X– chromosomes, but one X–chromosome and one deleted Y–chromosome. This condition is called 46,XY complete gonadal dysgenesis. The gonads of these persons do not progress beyond the indifferent stage. If for some reasons diagnosis becomes clear in the first months or years of age, it becomes necessary to make a decision regarding the gender of the child. Some parents prefer to grow the child as a boy; some have the opposite decision. There is no general agreement regarding the choice of gender in such a patient.

If diagnosis of 46,XY complete gonadal dysgenesis becomes clear in a 12–14 year–old person, most patients continue to be regarded as girls, although they do not have age–appropriate sex characteristics and cannot have their own children.

Deletions of the SRY–gene are not the only reasons of complete gonadal dysgenesis. Other factors, both chromosomal (deletion of the short arm of chromosome 9, deletion of the long arm of chromosome 17) and monogenic may participate in the development of this condition. There are some estimates that ~15% of all persons with complete gonadal dysgenesis have deletions of the SRY–gene.

46,XY complete gonadal dysgenesis is the only type of pathology caused by deletions of the short arm of chromosome Y. Loss of genetic material between the SRY–gene (if this gene is preserved) and the centromere does not seem to be clinically significant.

The proximal part of Yq (from centromere to Yq11.23) contains several “azoospermic” regions (deletions of these regions lead to azoospermia [absence of sperm in the semen]). The patients with these deletions are phenotypically normal males without a delay in development, dysmorphias or birth defects. Only when these patients became adults and their wives are unable to conceive, they visit the specialists who diagnose azoospermia (or oligospermia). Further investigations show that the reason for azoospermia in a given patient is a tiny deletion in one of the “azoospermic” regions of Yq. There are thousands of patients with azoospermia caused by (micro)deletions, affecting one of the “azoospermic” regions within Yq11.

The large distal part of Yq (Yq12, which takes almost a half of the total length of chromosome Y) does not contain any important genes and may be lost without any clinical consequences (formerly, it was known as a “short” or “minute” Y–chromosome).
In the whole literature, there are less than 10 reports on patients with deletions of the long

arm of the Y–chromosome in association with intellectual disability, facial dysmorphism, or physical abnormalities. However, clinical manifestations in these patients do not constitute any recognizable syndrome. Moreover, the same deleted Y–chromosome was found in fathers of several of these patients. Therefore, there are good reasons to believe that deletions of the Y–chromosome in these boys were not causal factors of the reported defects, but just coincidental abnormalities.