LETTER TO THE EDITOR

Testis determining gene(s) on the X chromosome short arm: chromosomal localisation and possible roles in testis determination

Recently, we have proposed that a testis determining gene(s) located to X inactivation is present on Xp (TDF-X), and that two active copies of TDF-X hinder testis formation in the presence of SRY. In this follow up letter, we refine the chromosomal location of TDF-X, and speculate on the role of TDF-X in testis determination. For chromosomal localisation, we surveyed published reports for genetic male patients with an active partial Xp disomy and an apparently normal SRY region, and found a total of 13 informative patients. Karyotype-phenotype correlations in the 13 patients indicate that, in the presence of SRY, disomies encompassing the Xp21.2-p21.3 region result in sex reversal (gonadal dysgenesis), whereas other disomies permissively male sex development (testis formation) (fig 1). This implies that Xp21.2-p21.3 is the critical region for sex reversal, and that TDF-X is located in this region. In addition, molecular studies in four patients suggest that TDF-X may be present between DXS28 and OTC.1-4

Regarding the role of TDF-X in testis determination, a simple question would be why two active copies of TDF-X result in gonadal dysgenesis in the presence of SRY, while the combination of SRY and a single active copy of TDF-X leads to normal testis formation. In this regard, it is worth pointing out that testis determining genes consist of: (1) testis formation genes that directly induce testis development, and (2) switch genes that regulate the operation of testis formation genes.5 We speculate that TDF-X may function as a suppressor of testis formation genes, and that SRY may permit the operation of the testis formation genes by repressing the function of TDF-X. The hypothesis is primarily based on the recent report that SRY can function as a transcriptional repressor,11 and assumes that the interaction between SRY and TDF-X may constitute the switch system for testis determination. In support of the possibility that TDF-X functions in the early stage of testis determination, the combination of SRY and two active copies of TDF-X causes complete gonadal dysgenesis,1 which is comparable to that found in SRY mutations.12

The schematic representation is shown in fig 2. In normal males, SRY works as a repressor, turning off the function of TDF-X. As a consequence, testis formation genes become free from suppression by TDF-X, leading to normal testis formation. In normal females, the absence of SRY, TDF-X remains turned on, keeping testis formation genes suppressed. As a result, ovary is formed under two normal X chromosomes. In Klinefelter patients who have two X chromosomes but have a single active copy of TDF-X, the situation is reversed, yielding a function of TDF-X to lead to female sex reversal and loss of function mutation of TDF-X results in female to male sex reversal. The hypothesis will be tested when TDF-X has been cloned.
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