LETTER TO THE EDITOR

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

Recently, we have proposed that a testis determining gene(s) subject 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.¹ 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.¹⁻⁹ 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 permit 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.^{1,3,8,9}

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.¹⁰ We speculate that TDF-X may func-

tion 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^{1,2} which is comparable to that found in SRY mutations.¹²

The schematic representation of the hypothesis 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 testis formation. In normal females, because of 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 the same as in normal males; SRY can sufficiently repress the function of TDF-X, leading to testis formation. However, in patients with active partial Xp disomies encompassing the critical region, SRY may be insufficient to repress the function of two active copies of TDF-X, so that testis formation genes remain to be suppressed by TDF-X, resulting in gonadal dysgenesis under one X chromosome. Furthermore, it may be possible that gain of function mutation of TDF-X leads to male 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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Figure 1 Correlation between disomic segment and sexual development in genetic male patients with a functional partial Xp disomy. All the patients have normal SRY region. The bars indicate the disomic segments. The critical region for sex reversal is shown by an arrow. References: case 1, Ogata et al,¹ cases 2 and 3, Bernstein et al,² cases 4 and 5, Scherer et al,³ case 6, May et al,⁴ case 7, Stern et al,⁵ case 8, Nielsen and Langkjær,⁶ case 9, Narahara et al,⁷ case 10, Coles et al,⁸ cases 11 to 13, Bardoni et al.⁹

Figure 2 Schematic representation of a possible role of TDF-X in testis determination.

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