# Inheritance of the Sex-Determining Factor in the Absence of a Complete Y Chromosome in 46,XX Human Males

JOHN R. D. STALVEY AND ROBERT P. ERICKSON

*Departments of Human Genetics and Pediatrics*
*Univesity of Michigan*
*Ann Arbor, Michigan 48109-0618*

Sex determination in mammals depends on the presence or absence of a testis-determining factor (TDF) located on the Y chromosome. In humans, it has been proposed that TDF is localized on the short arm of the Y chromosome.[1] Approximately 1 in 20,000 phenotypic males have a 46,XX genotype;[2] these men are infertile and have small testes. Many XX males have visible translocations of Y chromosomal material to one of the X chromosomes. High resolution cytogenetic analyses of these X:Y translocations indicate that the Y fragment is probably a derivative of the tip of the short arm of the Y chromosome.[3] Some 46,XX males have no visible translocation, however. Do these individuals also have Y-derived sequences in their genome?

We have studied seven 46,XX males, three with, and four without, visible translocations of Y material, by Southern analysis. The results are summarized in TABLE 1. All six individuals were negative for the Y centromeric probe Y97,[4] consistent with the absence of a complete Y chromosome. The genomic probe p75/79 was previously subcloned from cosmid Y75 from a human Y library[5] and recognizes a 2.0 kb *Eco RI* fragment localized on the short arm of the Y chromosome by somatic cell genetics and on the tip of the Y short arm by *in situ* hybridization. The 3 XX males with visible translocations were positive for the Y-specific 2.0 kb *Eco RI* fragment recognized by p75/79. Even in the absence of a visible translocation, DNA from the other 3 XX males also contained the 2.0 kb *Eco RI* fragment. In addition, DNA from two XX males with visible translocations was hybridized with p52d,[6] which recognizes Y short arm sequences centromeric to p75/79. One is positive, and one is negative for p52d, indicating that variable amounts of Y material were translocated. It appears that XX males inherit a small, though variable portion of DNA from the proximal end of the short arm of the Y chromosome, which appears to contain the sex-determining region. The simple explanation for the mode of inheritance in cases with visible translocation is that Y material has been added onto the paternal X chromosome. Could XX males, however, with no visible translocations arise by way of crossing-over between the X and Y chromosome just outside the pseudoautosomal region (a region of shared X, Y homology with one obligate crossover per meiosis), which is located at the proximal end of the X and Y short arms? We are currently using a probe localized on the lower boundary of the pseudoautosomal region to investigate this possible mode of inheritance of the sex-determining factor in 46,XX human males.

In brief summary, 46,XX males have Y short arm-derived material containing a presumptive sex-determining factor termed the testis-determining factor,

TABLE 1. Detection of Y Specific Sequences in 46,XX Males by Southern Analysis with Several Genomic Probes Derived from the Y Chromosome

| Patient | Karyotype | Y97[b] | p75/79 | p52d |
|---|---|---|---|---|
| KWI | 46,XX[a] | — | + | + |
| SWE | 46,XX[a] | — | + | — |
| GORE | 46,XX[a] | — | + | nd[c] |
| HIN | 46,XX | — | + | nd |
| WER | 46,XX | — | + | nd |
| GIM | 46,XX | — | + | nd |
| DAB | 46,XX | — | + | nd |

[a] Visible translocation of Y material.

[b] Y97 detects Y centromeric sequences, whereas p75/79 and p52d detect sequences localized to the proximal short arm of the Y chromosome.

[c] nd = not determined.

whether or not there is a visible translocation of Y material. The amount of Y material inherited is variable. The molecular approach provides a very sensitive method for tracking the movement of Y chromosomal material in 46,XX males.

## REFERENCES

1. GOODFELLOW, P., S. DARLING & J. WOLFE. 1985. The human Y chromosome. J. Med. Genet. **22:** 329–344.
2. DE LA CHAPELLE, A. 1972. Analytical Review: Nature and origin of males with XX sex chromosomes. Am. J. Hum. Genet. **24:** 71–105.
3. DE LA CHAPELLE, A. 1981. The etiology of maleness in XX men. Hum. Genet. **58:** 105–116.
4. WOLFE, J., S. M. DARLING, R. P. ERICKSON, I. W. CRAIG, V. J. BUCKLE, P. W. J. RIGBY, H. F. WILLARD & P. N. GOODFELLOW. 1985. Isolation and characterization of an alphoid centromeric repeat family from the human T chromosome. J. Mol. Biol. **182:** 477–485.
5. WOLFE, J., R. P. ERICKSON, P. W. J. RIGBY & P. N. GOODFELLOW. 1984. Cosmid clones derived from both euchromatic and heterochromatic regions of the human Y chromosome. EMBO J. **3:** 1997–2003.
6. BISHOP, C., G. GUELLAEN, D. GELWERTH, M. FELLOUS & J. WEISSENBACH. 1984. Extensive sequence homologies between Y and other human chromosomes. J. Mol. Biol. **173:** 403–417.