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Ferguson-Smith M A. Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. *J. Med. Genet.* 2:142-56, 1965.
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In 307 patients with gonadal dysgenesis, monosomy for the short arm of the X chromosome was found to be the decisive factor in the causation of short stature and congenital malformations in Turner's syndrome. Similar features were found in some patients with Y chromosome deletions, suggesting the existence of active X and Y homologous genes and, thus, that part of the X chromosome carries Y-homologous loci that escape X-inactivation. [The *SCI*® indicates that this paper has been cited in more than 350 publications, making it the most-cited paper from this journal.]

Active X and Y Homologous Genes

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Although this review was published in 1965 from the Department of Genetics at Glasgow University, it was initiated during a fellowship appointment in medicine with V.A. McKusick at Johns Hopkins Hospital, Baltimore, Maryland, from 1959 to 1961. J. Lejeune[1] had just reported the chromosome abnormality in Down's syndrome, and I was encouraged to start one of the first chromosome diagnostic laboratories in the US. I was fortunate to have the opportunity to study the chromosomes of a unique series of patients with gonadal dysgenesis and intersexuality who were referred to the late L. Wilkins, pioneer in pediatric endocrinology, and H.W. Jones, Jr., the distinguished Baltimore gynecologist.

The results in a series of 30 patients with gonadal dysgenesis were published in 1964,[2] followed by the subject of this commentary. In it, the phenotypic abnormalities associated with Turner's syndrome were explained for the first time on the basis of variable deletion of the X and Y chromosomes, with or without sex chromosome mosaicism. The analysis led to the original and inescapable conclusion that the short stature and stigmata of Turner's syndrome were due to monosomy of X and Y homologous regions that, in the X chromosome, must escape X-inactivation. In other words, the products of the genetic loci involved in these abnormal features were present in single dose in the patients and in double dose in normal males and females.

This was heresy at the time, for it was thought that, apart from sex determination, the Y chromosome was genetically inert and, according to M. Lyon's hypothesis,[3] one of the two X chromosomes in female somatic cells was completely inactive.

Despite the fact that chromosome banding did not become available for many years, most of the structural chromosome abnormalities seem to have been correctly identified. Unfortunately, it was not possible to map the testis determining factor (TDF) to the terminal part of the short arm of the Y, because only two cases of long arm isochromosomes of the Y were known at the time; one was female and the other was a male intersex. On hindsight, both must have had isodicentric Y chromosomes with breakpoints proximal and distal to TDF.[4] However, the main correlations have been confirmed repeatedly and this, plus the controversial nature of the paper, possibly accounts for the unusual number of citations.

The hypothesis of X-Y homology, however, remained dormant for about 20 years until molecular studies began to demonstrate DNA sequence homology not only in the X-Y pairing segment, but in other regions as well.[5] It took almost as long to show that a number of genes on the short arm of the X escape inactivation and that the Y chromosome contains active genes not only for testis determination but also for stature, H-Y antigen, spermatogenesis, and other functions.[6] Papers published in the current year discuss "anti-Turner" loci on the X and Y, and efforts are being made to clone the sequences responsible. It is pleasing to reflect that my colleagues and graduate students continue to contribute to this exercise[7] and seem to derive the same fun and excitement that I enjoyed in this pursuit more than 30 years ago.

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