

Special Report: International Turner Syndrome Symposium— November 9-11, 1987, San Francisco, California

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Several aspects of Turner syndrome—including its natural history, therapy of short stature, and intellectual and psychosocial development—were discussed at this five-session symposium.

During one session on the genetics, organogenesis, and incidence of Turner syndrome, much attention was directed to the genes found on the X and Y chromosomes. Portions of that session are highlighted in this report.

Dr. L. Shapiro (University of California, Los Angeles) discussed an area of complete homology on the tips of the p (or short) arm of the X and Y chromosomes. This region, called the "pseudoautosomal region," escapes inactivation in the inactivated X chromosome. Currently, two functional genes are known to exist in this region: a steroid sulfatase gene in mice and a MIC 2 (surface antigen) in human beings. The pseudoautosomal region has 5-7 megabases. There is room for several hundred as yet undefined genes in this region.

Dr. C. Epstein (University of California, San Francisco) emphasized that aneuploidy is a disorder of gene dose and that gene dosage effects may perturb structure, function, or both. The Y chromosome carries a gene or genes for sex determination and prevents Turner syndrome. The "inactive" X chromosome does not have inac-

tivation of the pseudoautosomal region. Regions of the X chromosome appear to have an oocyte-maintaining function, as there are families whose members have premature menopause associated with minor deletions of the X chromosome. Dr. Epstein suggested that the Y chromosome be inspected for genes that affect somatic development because the Y chromosome is much easier to study than the X in many respects. He described two phenotypic females (karyotype 46, XY) with lymphedema who had minor deletions of the Yp.

The intrauterine mortality of 45, X fetuses is 95% to 99%, but death does not necessarily result from fetal defects; however, death could occur because of an abnormal placental karyotype. Interestingly, the paternal X is lost more frequently than the maternal X in Turner syndrome, and the paternally derived X is more likely to be the inactivated X in 46, XX individuals.

Dr. D. Page (Massachusetts Institute of Technology) hypothesized that a single gene on the Y chromosome, known as the gene for testicular differentiating factor (TDF), is sex determining. Its locus is on the p arm just proximal to the pseudoautosomal region. The question was raised as to whether a similar region is also present on the X chromosome. If the TDF gene is present on both the X and Y chromosomes, testicular differentiation alternatively could be an effect of gene dosage and not necessarily due to one gene on the

Y chromosome. Of 26 XX males studied, 24 had Y material on the X chromosome. These 24 may have had XY interchange at paternal meiosis of the sperm.

Among the 155 46,XY individuals with Y deletions who were studied, there were nine subgroups based on mapping of the missing loci on the Yp. Of the 24 XX males with Y material, all had Y region 1A2 present. This region, which appears to be critical for male differentiation, was "lost" in 46, XY females. The TDF gene is not the gene for the HY antigen since the two map to different areas of the Y chromosome; HY antigen maps to the 4B region of Yp. The TDF does not code for a hormone but rather for a DNA-binding protein. Dr. Page postulated that the two XX males without identifiable Y material, of the 26 XX males studied, may have a mutation of another gene, possibly an autosome.

An extension of this type of study was reported by Dr. C. Distèche (University of Washington), who used cytogenetic assays and DNA probes to study XY females who were not short. A deletion of the TDF loci area was identified. The area on Yp, which is believed to account for the short stature seen in Turner syndrome, is therefore not the TDF loci.

Dr. Distèche also discussed the seven regions on the Y chromosome. Region 7, a long segment at the distal end of the long arm, is brightly fluorescent. Its deletion does not produce significant problems, although two patients

with a small Y had small teeth and petite bones. Stature was unaffected. The development of gonadoblastoma in those patients with Turner syndrome who have a partial Y chromosome(s) could result from a normal Y gene that continues to function in the absence of normal testicular tissue. It could also be caused by a defective gene on the Y chromosome, or it might be secondary to tissue disorganization.

Dr. S. Ohno (Loma Linda, California) led a discussion about homologies between the testis and the ovary. Spermatogonia are homologous with oogonia, Sertoli cells with granulosa cells, and Leydig cells with thecal cells. He then described a species of fish whose gonads can change from ovary to testis during adulthood. There is always one male in the school of fish. If the male dies or disappears, the dominant female becomes the male for the school by differentiation of the ovary into a testis.

The HY antigen (HY Ag) was discussed by several symposium participants. Three assays for HY Ag exist: (1) transplant rejection, (2) cell mediated cytotoxicity, and (3) serological. The latter assay employs a male-specific polypeptide antigen, 18-20 D in size, that is present in body fluids and expressed in Sertoli and Leydig cells. Dr. Page tried to clarify the issues: HY Ag was initially defined as a transplantation-rejection antigen. T-cell assays recognize transplant Ag. There is no evidence that the serological Ag is

the same HY Ag that is identified by the other two assays. The conclusion was that the nomenclature regarding HY antigens is totally inadequate. The result is that we are often talking about different things when we discuss Hy Ag.

Dr. C. Lau (University of California, San Francisco) extended the discussion, stating that the serological HY Ag in humans is a glycoprotein of 185 amino acids; it is found in both males and females. The gene is not localized on the Y chromosome but on chromosome 6. The Hy Ag gene identified by the other two assays is located on the Y chromosome.

Dr. J.L. Simpson (Memphis, Tennessee) postulated that (1) the X and Y chromosomes are not solely responsible for gonadal differentiation; (2) X and Y determining factors are solely regulatory; (3) the structural loci for gonads are on autosomes; and (4) X and Y gonadal determining genes are identical and the different effects result because of a dosage effect produced by X inactivation in the female. The latter postulate would be theoretically possible and consistent, in part, with the concepts presented by Dr. Page. For example, the female would have half the gene dosage for TDF as the male since one X is inactivated.

Dr. Simpson reported that more than 12 45,XO patients have become pregnant. He emphasized that oocytes can develop in testicular tissue, and gonadal stroma may therefore play a role in gonadal differentiation, at least in cer-

tain instances. The existence of 46,XY individuals with female phenotype or ambiguity as part of the gonado-palato-cardiac syndrome supports this concept. The gonads in persons with this syndrome have been variously reported to be streaks, ovaries, and testes.

Primary amenorrhea resulting from deletions of the short arm and from small deletions of Xq 11.2-11.4 was also reported. Deletions at Xq 13 may be associated with secondary amenorrhea. A gene or genes in that region would appear to be associated with ovarian maintenance and thus prevent premature menopause. Individuals with deletions between or including Xq 21-25 have minimal abnormalities (although they are not necessarily normal) and frequently have secondary amenorrhea.

Dr. Judith Hall (University of British Columbia) said that many of the phenotypic defects observed in Turner syndrome may be secondary to intrauterine lymphedema and pressure phenomena resulting from this edema. Even coarctation of the aorta could be secondary to this phenomenon. She states that the dysmorphology in Noonan's syndrome might be related to intrauterine lymphedema. This concept, if true, would make it unproductive to look for specific genes responsible for each phenotypic feature.

The data presented during this session add greatly to our understanding of Turner syndrome.