Molecular biology of Turner’s syndrome

Turner’s syndrome was first described in 1938 and results in a clinical picture most frequently comprising short stature and gonadal dysgenesis. Other features may include coarctation of the aorta, renal anomalies, neck webbing, and lymphoedema. The clinical phenotype can be extremely variable even in patients with the same karyotype. The chromosomal basis of the condition was established in 1959 when a patient was described who exhibited loss of one sex chromosome. Approximately 50% of cases have a 45,X karyotype with the remainder having mosaic karyotypes with one 45,X cell line and another cell line often containing a structurally abnormal X chromosome such as a ring X.

Turner’s syndrome is one of the commonest chromosomal anomalies in man with an incidence of at least one in 1850 live female births. Recently more interest has been focused on this condition because of the advent of recombinant growth hormone treatment, and patients with Turner’s syndrome now comprise a large proportion of the cases attending paediatric growth clinics. In spite of the fact that it has been recognised as an entity for a considerable length of time, the molecular biology of the condition has not been fully elucidated. Recent research using molecular genetic techniques has improved our understanding of the condition but more work is still required in this field.

Parental origin of the retained X chromosome
The loss of one of the sex chromosomes that is the basis for Turner’s syndrome probably occurs after the zygote has formed or just after the fusion of the gametes. This being the case one would expect an equal chance of either parental X being retained. In practice, however, in 70–80% of cases the retained X is maternal in origin. This observation has led to the speculation that there may be genes present on the X chromosome which are expressed differently depending upon whether they are maternally or paternally derived. This process is called ‘genomic imprinting’ and has been described in a number of conditions including Prader-Willi and Angelman’s syndromes. It has been postulated that imprinting may play a part in the high intrauterine mortality and variable phenotype seen in Turner’s syndrome. Evidence for this has been contradictory. One study showed that the morphological appearances of fetuses retaining the paternal X differed from those retaining the maternal X in a small sample, perhaps indicating that fetuses retaining the paternal X did ‘less well’ than those retaining the maternal X. This led to conjecture that loss of the maternal sex chromosome may be less compatible with intrauterine survival than loss of the paternal sex chromosome. However, the pathological descriptions of 45,X abortuses do not indicate any unusual degree of developmental abnormality and the percentage of aborted fetuses retaining the maternal X chromosome is the same as in liveborns. Therefore imprinting does not seem to play an important part in the high fetal loss in Turner’s syndrome concepuses.

Imprinting may affect the phenotype and recent work has indicated that patients retaining the paternal X have a greater incidence of cardiovascular anomalies and neck webbing than those retaining the paternal X and also that the pretreatment height of those retaining the maternal X correlates very strongly with maternal height but not with paternal height. The interpretation of such findings are complicated by the possibility of undetected mosaicism for a second sex chromosome.

Sex chromosome mosaicism in Turner’s syndrome
Approximately one in 50 of all conceptuses are associated with a 45,X genotype but there is high intrauterine lethality such that only 1% of such conceptuses survive to term. There is a higher percentage of mosaic karyotypes than monosomy X in liveborns compared with fetuses which has led to the speculation that all liveborn infants with Turner’s syndrome are mosaic in a cell line critical for fetal survival. This hypothesis has not been supported by studies on blood using Southern blotting with hypervariable probes from the X chromosome or on cytogenetic studies examining multiple tissues where the authors found that 20% of patients still appear to have monosomy X. It is possible that with more sensitive techniques low level mosaicism may be detected. As mentioned previously, approximately 70–80% of cases of Turner’s syndrome retain the maternal X. As the missing sex chromosome may be either an X or a Y theoretically 35–40% of cases may have occult Y mosaicism. This has clinical relevance because if Y material is present there is a risk of up to 30% of gonadoblastoma developing in the dysgenetic gonads. At present if a Y chromosome is identified on cytogenetic analysis, gonadectomy is recommended but counselling is more difficult if there is an abnormal Y or a fragment of the Y. It would be helpful to define an ‘at risk’ locus, the presence of which would indicate a need for gonadectomy and there is a postulated ‘gonadoblastoma locus’ on the Y chromosome which is believed to be situated on the long arm of the Y just below the centromere. Although there is debate about the need to screen patients with Turner’s syndrome for occult Y mosaicism, if such screening were to be implemented it would be logical to include analysis for this particular area of the Y chromosome in the screening strategy, and recent publication of polymerase chain reaction (PCR) primers covering the whole of the Y chromosome makes this a fairly straightforward procedure.

Although theoretically 35–40% of patients with Turner’s syndrome may have Y mosaicism, in practice this has not been demonstrated. Studies to date have used either Southern blotting with Y specific probes or PCR with one or two Y specific primers and have shown between 4–8% of cases of Turner’s syndrome have Y material present. Recently a new technique using Southern blotting of DNA previously amplified by PCR has purported to demonstrate a very high incidence of unsuspected Y mosaicism in patients with Turner’s syndrome. This particular technique is extremely sensitive but is also very prone to contamination from external sources so that such results should be interpreted with care. An added difficulty in interpreting these findings is the uncertainty of the effects of very low level mosaicism found in blood.

X inactivation of structurally abnormal X chromosomes
Another factor which may affect the phenotype in Turner’s syndrome is X inactivation of structurally abnormal X chromosomes. Inactivation of most of one of the two X chromosomes occurs in normal females at an early stage of embryogenesis so that there is equal gene dosage between
males and females. Thus only one X chromosome should be active in each cell. Inactivation of the X chromosome is controlled from the X inactivation centre situated on the X long arm. Although X inactivation is initially thought to be random, in cases with a structurally abnormal X chromosome the cell line in which the normal X is active gradually takes over.20

Anomalous X inactivation has been postulated to be implicated in the phenotype found in a subgroup of patients with Turner’s syndrome and small ring X chromosomes who have dysmorphic faces, syndactyly of the hands and feet, and severe mental retardation.21 A proportion of these small rings remain active in the same cells as the normal X and these cells therefore have functional duplication of areas of the X. The mechanism for these rings remaining active was initially thought to be simple loss of the X inactivation centre situated on the X long arm (Xq13) due to the small size of the rings. However, recent work looking at expression of a gene that is only expressed from the inactive X-XIST (X inactive specific transcripts) has shown that the inactivation centre is often present in these small rings22 but its expression may not be normal, possibly due to mutations in the gene.23

The search for Turner ‘genes’

The particular phenotype seen in Turner’s syndrome can occur with a number of different karyotypic pictures and certain features have been tentatively mapped to areas of the X chromosome, for instance short stature to the X short arm, ovarian function to both the long and short arms.24 The phenotype in Turner’s syndrome is thus not thought to be due to loss of the entire X chromosome but rather to haploid dosage of a gene or genes. If there is a Turner’s syndrome gene it must have the following characteristics: it must escape inactivation and it must have a homologue on the Y chromosome or all XY individuals would have the Turner phenotype. One gene fulfilling these criteria, RPS4X/RPS4Y, was put forward as a likely candidate but has the disadvantage of being located on the X long arm and gene expression studies in patients with X isochromosomes have shown that it is expressed from the abnormal X.25 Several other genes also fulfil these criteria: XE7 whose function is unknown, MIC2 which encodes a glycoprotein involved in T cell adhesion, and ZFX/ZFY which encodes a zinc finger protein. It is probable that more genes with these characteristics have yet to be discovered.

In conclusion, Turner’s syndrome is a relatively common condition and its variable phenotype causes difficulties in diagnosis and counselling. The various factors affecting the phenotype have not yet been fully elucidated but include occult mosaicism, imprinting, and anomalous X inactivation. Thus far investigations have mainly concentrated on blood but analysis of other tissues may also help explain the variability and make counselling patients easier.

CE CHU
J M CONNOR
Duncan Guthrie Institute of Medical Genetics,
Yorkhill,
Glasgow G3 8SJ

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C E Chu and J M Connor

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