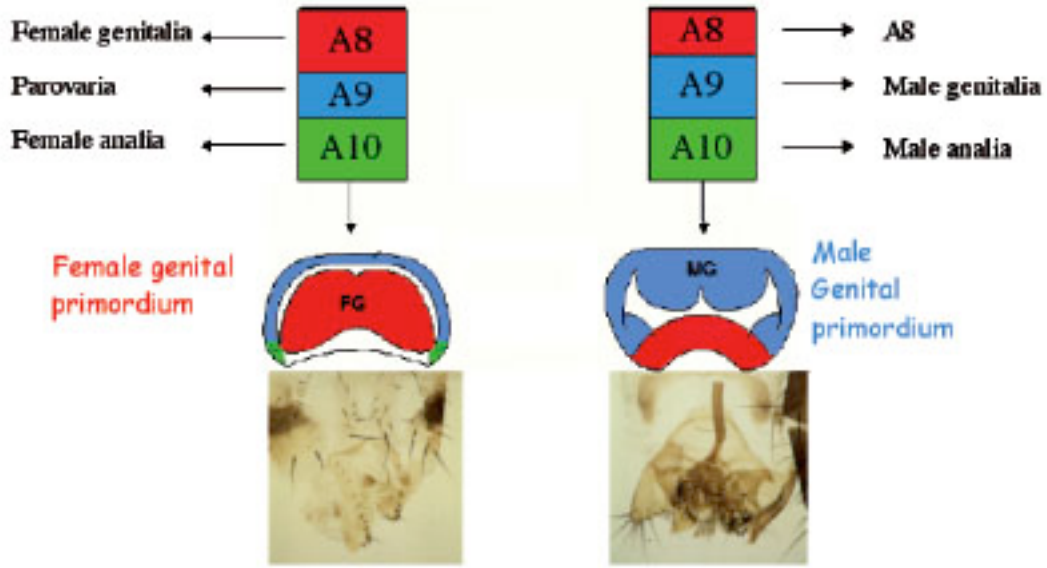
## Sex in model systems (HS)

In mammals primary sex determination, whether the gonads develop as ovaries or testes, depends on the presence of absence of a Y chromosome. Secondary sex determination, the male/female phenotype of the rest of the body depends on the presence or absence of hormones secreted by the testes. In fruit flies and nematodes primary sex determination depends on the ratio of X chromosomes to autosomes. X0 individuals develop as males even though no Y chromosome is present. Neither animal possesses the equivalent of systematically acting sex hormones. In *Drosophila* sex determination is entirely cell autonomous (in somatic cells) and in *C. elegans* only short range cell-cell signalling is involved.

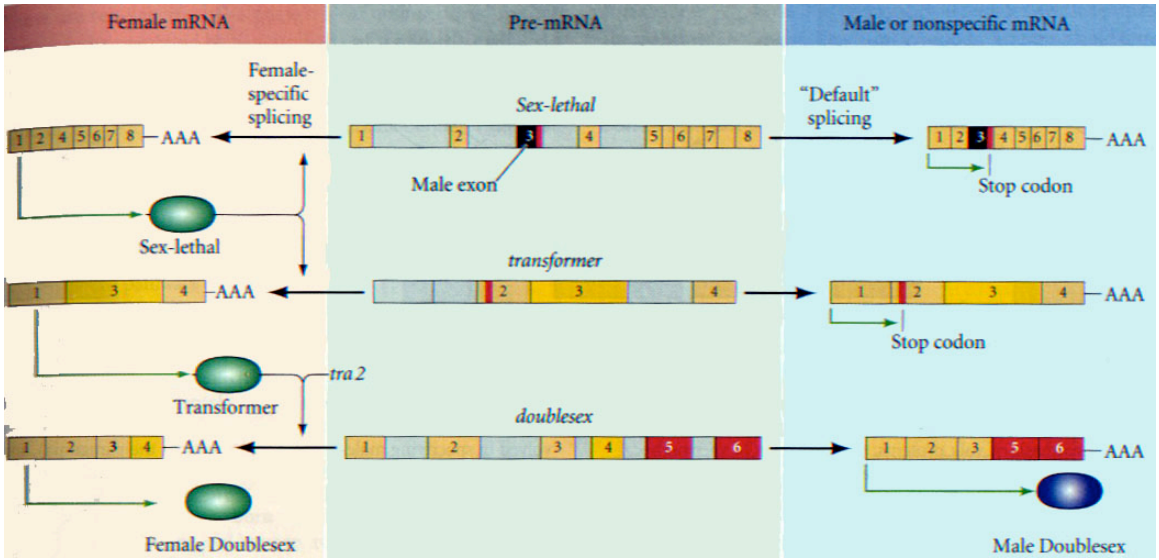
*Drosophila* male and female genitalia and analia develop from the genital imaginal disc. Three abdominal segments give rise to this disc, A8, A9 and A10. The A10 derived portion of the disc gives to the analia of both sexes, A8 to female genitalia and A9 to male genitalia. In females the growth of A8 is promoted at the expense of A9 and the reverse is true in
males.




To determine whether to follow the female or male pathway depends on the activity of a series of sex determining genes in each cell. These include the RNA splicing regulators Sxl, tra and tra2, the dsx and the  ix loci. Sxl has two promoters. In early development one is inactive and the state of the other depends on the relative activity of various X-linked numerator and autosome-linked denominator genes. Numerator proteins can bind to and activate the Sxl promoter except when bound to denominator proteins. In XX individual which have equal numbers of copies of X and autosomal genes sufficient numerator protein is available to activate the promoter. The short transcript produced from this promoter is spliced to remove an exon containing a pre-mature stop codon and full length Sxl protein is made.

Later, when numerator and denominator proteins cease to be made, a second more 5' promoter of the Sxl gene becomes active. This produces a longer transcript, for which the splicing machinery requires Sxl protein to splice out the stop codon. In males, because early synthesis of Sxl is not activated this splicing does not occur and no active Sxl protein can be made.

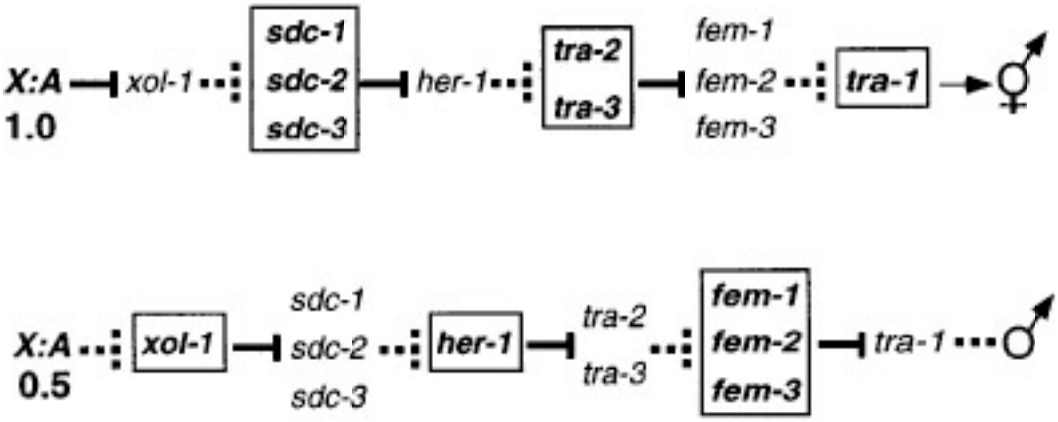
Sxl also regulates the splicing out of a stop codon containing exon in the tra gene. Its presence in females and absence in males mean that tra protein is only synthesised in females. Tra and tra2 regulate the splicing of dsx in females so that exons 5 and six are excised – in males in the absence of tra/tra2 splicing between exons 3 and 5 removes exon four. Both splice forms produce active proteins but the female-specific form forms a complex with the ix gene product that promotes female-specific gene expression while the male form activates male-specific patterns of expression.




While this genetic pathway is used to determine the sex of somatic cells a somewhat different combination of genes regulates the sex of germ cells - whether they differentiate as sperm or eggs. The embryonic gonad is a separate organ from the genital discs, which originates as an outgrowth of the mid-gut into which germ cells migrate and coalesce with the somatic cells around 12 hours post-fertilisation. As in mice, the germ cell development depends on signals from the surrounding somatic cells. In both cases chromosomally male germ cell with begin to develop as eggs when transplanted into ovaries and female germ cells will begin to develop as spermatozoa when transplanted into testes. In both mice and flies, however the subsequent development and proliferation of transplanted germ cells becomes abnormal, in mice very few sperm generated from transplanted XX germ cells survive in the adult mouse and in flies XY germ cells form ovarian tumours. Clearly some germ cell-autonomous gene expression is required for normal development. In flies, for example, there is a requirement for sxl and other genes not involved in somatic cell sex determination such as ovarian tumor (out) in female germ cell development.

Also as in mice the genes at the top of the sex determination pathway are evolutionarily labile. Just as Sry is found only in marsupials and eutherian mammals, sex-specific expression of Sxl is confined to the *Drosophila* genus. House flies and medflies both use a male determining factor on the Y chromsome to repress tra function.

In *C. elegans* the two sexes are males and hermaphrodites with the XX hermaphrodites being essentially females that produce and store a few sperm at the beginning of adult life. The sex determination pathway in *C.elegans* is genetically complex. A gene called xol-1 responds to a numerator:denominator signal and, through a series on negative regulators, this determines the expression of a transcription factor called tra-1, which is off in males and on in females.




One of the downstream targets of tra-1 one is the male ray determinant mab-3 which shows homology with the male-specific form of Drosophila dsx and the vertebrate gene DMRT1. Recent evidence indicates that DMRT1 also acts as a downstream male determinant. It is upregulated in the male genital ridge of mice, chicks and alligators and deletions of DMRT1 in humans are associated with XY sex reversal.

***References***

Gilbert 9th ed Chapter 17 pp 543-552

Sex determination gene and pathway evolution in nematodes (2003) Stothard P and Pilgrim D Bioessays vol 25 pp221-231