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A review of current concepts on sex determination in animals

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Despite being a complex development process, sex determination is important in reproduction of farm animals. Chromosome sex, which is based on the presence of sex chromosomes, is the most common to scientists. Most common to the layman, is what can be termed phenotypic sex, which is based on what can be seen in an individual. It encompasses the urogenital, external features, such as the external genitalia and secondary sex characteristics. From a molecular genetics point of view, there is also what is termed genetic sex, which is based on the presence of a sex-determining gene. In other words, an XY individual without the sex-determining gene is not a genetic male. The sex-determining gene is located on the Y-chromosome. Since 1959, when the Y-chromosome was shown to be the male-determining factor, there has been controversy as to what really determines sex in animals. However, the identification of what has been termed the sex-determining gene on the Y-chromosome (SRY) in 1990 has narrowed the controversy to the actual mechanism of sex determination. This review focuses on the genetic sex-determination mechanism by which genes determine sex, the fate of the supporting cells and evidence on issues, which are still inconclusive.

Keywords: Sex determination; genetic sex; sex-determining gene on Y-chromosome.

Introduction

An understanding of the mechanism of sex determination is important in reproduction of farm animals for efficient gender selection for purposes like (1) production of more female progeny from superior females for herd and flock replacements and increased milk and meat production; (2) production of more males for meat production from culled females and cross-breeding schemes; and (3) ensuring male progeny as herd sires from top dam-sire crosses (Hafez, 1993). The genetic sex is determined *in utero* at the time of conception and this governs the development of the gonadal sex of the individual. It is, therefore, important to differentiate chromosomal sex from genetic sex. Chromosomal sex is a determination

method based on the presence of sex chromosomes, while genetic sex is based on the presence of a sex-determining gene (Hing-Sung Yu, 1994). An XY individual without the sex-determining gene is still not a genetic male. In brief, the genetic sex is established at conception and governs the development of the gonadal sex of the individual. The sequential events in the determination of genetic sex, gonadal sex and phenotypic sex are shown in Figure 1. Since sex determination is based on genes this discussion is going to be mainly on genetic sex, although some aspects of chromosomal sex will be explained initially.

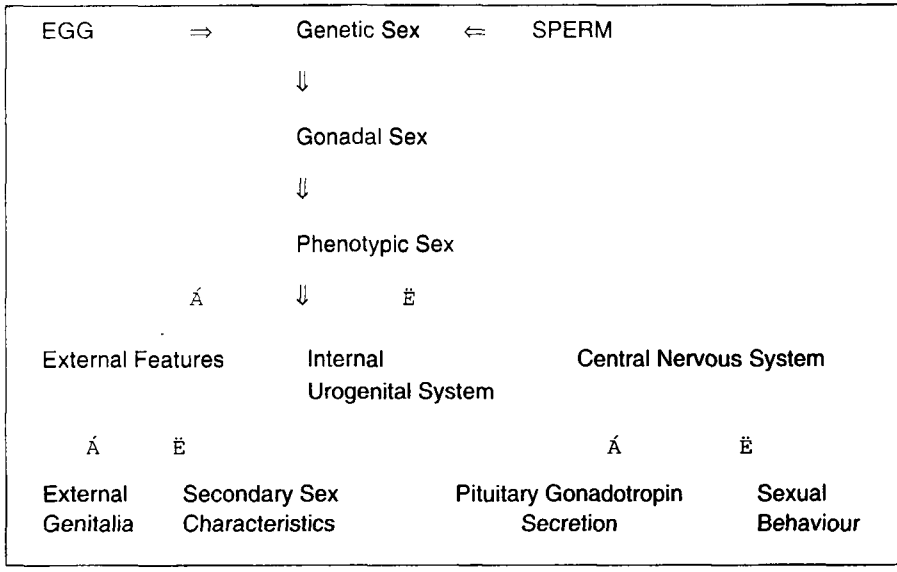

Figure 1: Sequential events in the determination of genetic, gonadal, and phenotypic sex.

Source: Hadley (1994).

Chromosomal sex determination

Chromosomal sex is determined on the basis of chromosomal constitution of the individual. There are basically two sex chromosomes (X and Y) in humans and many other mammals. These chromosomes differ in size (a phenomenon known as heterochromatism) (Hing-Sing Yu, 1994). The male is heterogametic (XY) and the female is homogametic (XX). Chromosomal sex is strictly at the level of chromosomal structures without considering the genes inside. It is, therefore, important to note that an XY individual may not necessarily be male due to the absence of a sex-determining region on Y (SRY).

In birds and some other vertebrates the male is homogametic (ZZ) and the female is heterogametic (ZW) (Hadley, 1994; Hing-Sing Yu, 1994). Both sex-

determining schemes (XX/XY of male heterogamety or ZW/ZZ of female heterogamety) are found in reptiles, amphibians, and teleosts (Hing-Sing Yu, 1994). For example, *Rana pipiens* (frog) and *Drosophila melanogaster* (fruit-fly) have the XX/XY scheme, while *Xenopus laevis* (toad) and *Gallus domesticus* (chicken) have the ZW/ZZ scheme. Some species of fishes are even synchronous or asynchronous hermaphrodites, which means that, they are able to shed both eggs and sperm at the same time or, alternately, one or the other of the gametes during a particular development state (Hadley, 1984). In reptiles all-female parthenogenic or gynogenic species have been discovered. Although the genetic sex of the species determines the direction in which the gonads initially differentiate, the exogenous administration of sex steroids at a critical time can induce permanent gonadal sex-reversal (Ganong, 1993). It is, therefore, important to note that whether the male or female is the heterogametic individual sex has an important bearing on the role of hormones in gonadal and phenotypic development.

Chromosomal abnormalities and sex determinants

There are also chromosomal abnormalities such as infertile XO females with Turner's Syndrome in humans (similar XO female mice are fertile), super females (XXX), seminiferous tubule dysgenesis (XXY and variants) (Klinefelter's Syndrome). The infertility of XO humans is explained by the way that dosage compensation of specific genes is achieved (Ashworth, Rastan, Loverll-Badge, and Kay 1991). In grasshoppers and cockroaches normal males are XO (UCDE, 1997). Since a chromosomal male (XY) may not be able to express the gonadal sex it is critical to examine genetic sex as regards its importance in sex determination.

The SRY and genetic sex determination

According to Ganong (1993), the Y chromosome is necessary and sufficient for the production of testes, and the testis-determining gene product is in all probability encoded by a gene called SRY (sex-determining region of the Y Chromosome). To show that the SRY gene is important in sex-determination, female mice carrying the normal pair of X chromosomes were injected with a small fragment of Y chromosome DNA containing the SRY gene (Ganong, 1993). The results were that they grew up as males with testes and male behaviour.

The discovery of the best candidate yet for the long-sought-after testis-determining gene in mammals (Figures 2 and 3) was in 1990 (McLaren, 1991). In both the human being and the mouse the SRY is located within the region that constitute the smallest amount of Y chromosome DNA known to induce masculinization, and in humans it appears to be the only gene within the relevant 35 - kilobase region (Figures 2 and 3). It is therefore named SRY (human), Sry (mouse), for sex-determining region of the Y chromosome. Sry is expressed in the developing mouse gonad at the expected time for testis determination and unlike the previous best bet, Zinc Finger on Y (ZFY), it is not expressed in the developing ovary of mouse embryos in which the testis-determining gene on the Y chromosome (Tdy) was known to be defective (McLaren, 1991).

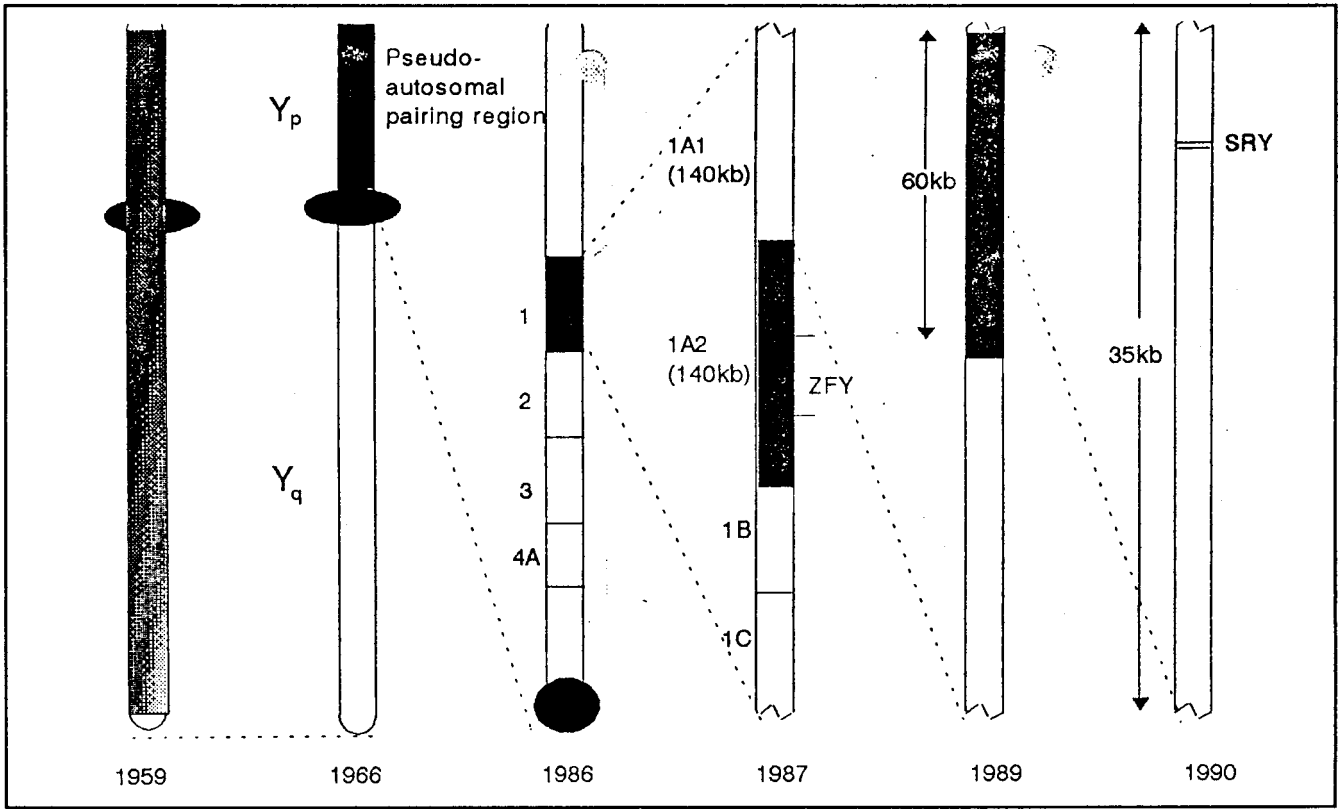

Figure 2: The hunt for the testis determining factor from 1959, when the Y chromosome was shown to be male determining in both mouse and man, to 1990 and the identification of the sex determining region (SRY in humans, Sry in mice Molaren, 1991).

According to Hadley (1984), the testes differentiate under the influence of the Y chromosome during the seventh week of gestation in humans, whereas ovarian development usually does not proceed before 13 to 16 weeks. The Sry also turns to be expressed in the gonadal somatic cells previously shown to be responsible for testis determination (McLaren, 1991). The gene was absent from the Tdy-defective mouse mutant, and two sex-reversal XY women were found to have mutations in Sry that were not present in their father's gene (McLaren, 1991).

Mechanism by which genes determine sex

Having located the most probable region, that is critical for sex determination (SRY) it is important to explain the mechanism by which the gene determines the sex of an individual. According to Hodgkin (1990) and Nonet and Meyer (1991), sex determination mechanisms and dosage compensation pathways are known to involve transcriptional regulation and alternate RNA splicing in *Drosophila Melanogaster*, DNA rearrangements in *Saccharomyces cerevisiae* and transcriptional regulation in mammals.

The Y chromosome-linked sex-determining locus (Sry) responsible for testis determination in mammals contains a DNA-binding motif (high mobility group (HMG box)) that is conserved across species of marsupial and placental mammals (intraclasses metatheria and eutheria, respectively) (Tucker and Lundrigan, 1993; Whitefield, Lovell-Badge and Goodfellow, 1993). According to Tucker and Lundrigan (1993), the human/mouse SRY/Sry transcript probably consists of a single exon with an open reading frame consisting of a central HMG DNA-binding domain flanked by N-terminal and C-terminal regions. The DNA-binding activity of HMG box and mutations in this region are associated with sex reversal in XY females. According to Tucker and Lundrigan (1993), the N-terminus/HMG box is the most conserved region of the gene and the C-terminus is the least conserved. Although SRY is an important developmental regulator, its sequence was observed to be poorly conserved between species apart from the HMG-box domain.

The fate of supporting cells

This review will be incomplete if the fate of the supporting cells is not considered. According to Hing-Sing Yu (1994), mammalian sex determination is mediated via the lineage of somatic cells in the foetal gonad. During initial gonadal development, the fate of the supporting cell population is determined by the testis determining factor (TDF) gene expression. If this gene fails to express at an appropriate temporal sequence in a sufficient number of supporting cells, both XX and XY supporting cells differentiate as pre-follicle cells and develop along the female direction. If there are sufficient supporting cells with the TDF gene expressed in a timely manner, they will differentiate into pre-sertoli cells, followed by the formation of testis cords and the development of the gonad in a male direction (Hing-Sing Yu, 1994).

If XX supporting cells are also present, a few may be recruited into the pre-sertoli population and participate in testis cord formation. The subsequent fate of

pre-follicle cells depends critically on interaction with the germ cell population in the developing gonad. If germ cells are absent, the gonad may be partially masculinized and/or degenerated (Hing-Sing Yu, 1994). The presence of an appropriate population of germ cells is thus crucial in completing the process of gonadal sex determination.

Knowledge gaps

From this review, it can be argued that SRY is the best candidate for sex determination to date, although the evidence available is still not conclusive. Some of the puzzles, which are still to be filled concerning the SRY gene in sex determination are: — whether, an intact copy of SRY is necessary for testis's determination, or whether SRY, in absence of the rest of the Y chromosome, is sufficient for sex determination. For example Koopman, Gubbay, Vivian, Goodfellow and Lovell-Badge (1991) described 11 XX mice transgenics for SRY on a 14 kilobase DNA fragment. Three were sex-reversed males while eight were females. It is not clear why only three were sex-reversed males while eight were females. It is not clear why only three were sex-reversed males (after the experiment). Or was it that the three males carried more copies of SRY than the other eight? It is also not clear whether SRY was expressed in all 11 transgenics, or whether the eight females failed to express it because it was inserted in an inappropriate region of the genome. According to Whitefield *et al.* (1993), reduced or inappropriate SRY activity can cause sex-reversal and the rapid evolution of SRY producing populations with different SRY sequences could be a significant cause of reproductive isolation.

According to McLaren (1991), of the XX human individuals who showed masculinization with only 35kb of SRY-containing Y chromosome DNA, all developed testicles but none fully showed normal development of male genitalia. From the above results it can be observed that certain unsatisfactory features remain with regards to the SRY gene as the best bet for sex determination. Some organisms like *Drosophila* and *Caenorhabditis (nematodes)* have a complex cascade of sex-determining genes (Hodgkin, 1991; Nonet and Meyer, 1991). Probably this may also be the situation in humans/mice. However, if such cascades are to be in human/mice, the SRY/Sry must be the major part of that cascade.

Conclusion

Current evidence indicates that the best candidate to date for sex determination is the SRY gene. This gene determines genetic sex, which governs all types of phenotypic sex. However, the expression of phenotypic sex depends on how and when those sex-specific processes at all levels respond to environmental conditions.

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