

Postgraduate course in human genetics

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Abnormalities of the sex chromosomes **and sex differentiation**

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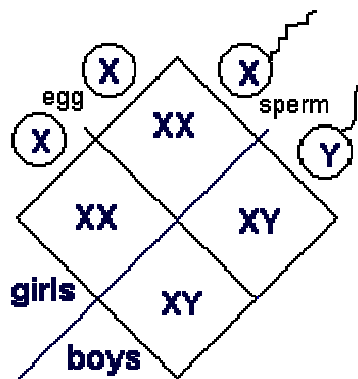
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1. Normal Sexual differentiation

A. History

-1940 role of the gonads: in the 40's Alfred Jost showed that ablation of the gonads in a fetus at the undifferentiated stage resulted in female development. Jost also observed that while testosterone was required for Wolffian duct development, the regression of the Müllerian duct was due to another substance. This was later determined to be Müllerian inhibiting substance (MIS).

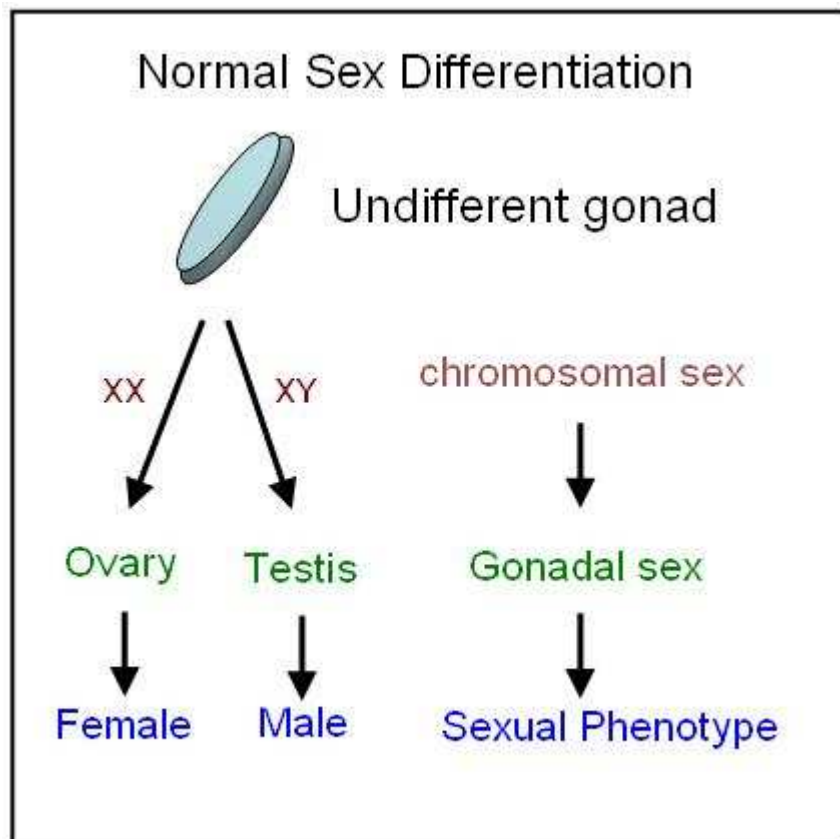
-1960 discovery of the role of the Y chromosome, by Welshons and Russel. Studies of patients with Turner Syndrome (45X) and Klinefelter (XXY) led to the conclusion that the presence of Y chromosome was necessary for the development of testis. There was a factor (named TDF Testis Determining Factor) coded on Y, responsible for the differentiation of the gonad into testis.



-1989 discovery of SRY It's only 20 years ago that the factor was identified by the team of Lovell-badge. The search for the testis-determining gene was based on the identification and molecular analysis of certain sex-reversed 46,XY females who were deleted for Y-specific sequences and 46,XX males who carried variable portions of the Y chromosome in their genome.

B. General picture

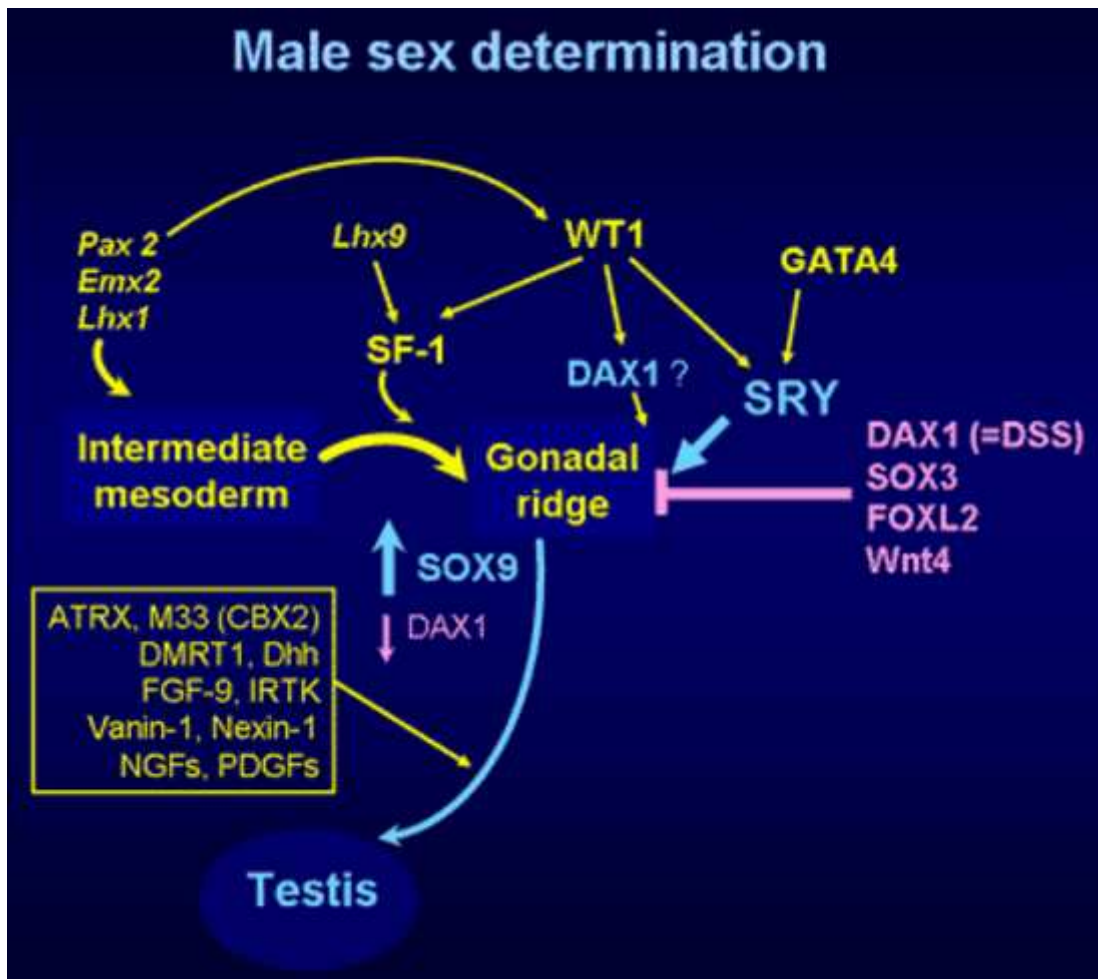
At the beginning, gonads, in a "bipotential state," may develop into either testes or ovaries depending on the consequent events. Up until the seventh week, male and female fetuses appear identical.



In the XY fetus, the initially amorphous cluster of gonadal cells segregate into two compartments. The interaction between differentiating peritubular myoid cells and Sertoli cells results in the formation of testicular cords surrounded by a basal membrane that enclose germ cells, while mesenchymal cells and matrix and blood vessels fill the interstitial space, in which Leydig cells will soon appear. Cell migration from the mesonephros largely contributes to testicular organogenesis and is antagonized by the initiation of meiosis in germ cells.

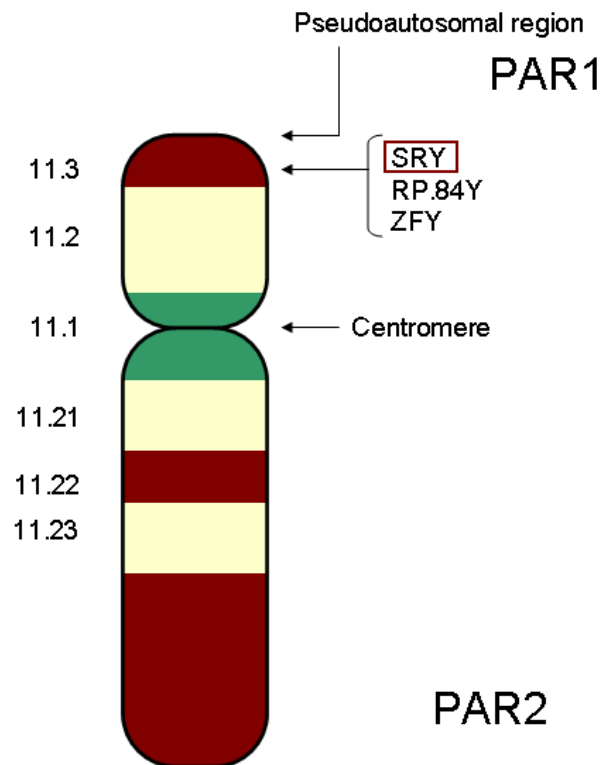
C. Genes implicated

The mammalian Y chromosome acts as a dominant male determinant as a result of the action of a single gene, *Sry*, whose role in sex determination is to initiate testis rather than ovary development from early bipotential gonads.



Gène	Location	action
SRY	Y 5 (Yp11.3)	Testis differentiation (M)
SF1	9 (9q33)	regulation of steroidogenesis (M et F)
WT1	11 (11p13)	genital crest morphogenesis and regulation of SRY (M et F)
DAX1	X (Xp21.3-21.2)	inhibition of SF1 (F)
SOX 9	17 (17q24.3-q25.1)	activate expression of AMH gene (M)
WNT 4a1		regulation of female development, antagonism of testosterone (F)
AMH	19 (19p 13..3)	regression of the Mullerian ducts (M)

SRY is a member of a family of DNA-binding proteins bearing a high mobility group (HMG) box and maps to the short arm of the Y chromosome Yp11.3, very close to the pseudoautosomal region 1 (PAR1).



The molecular mechanisms by which it triggers testicular differentiation from the gonadal ridge are as yet poorly understood.

Others genes implicated :

DAX1 encodes an unusual member of the nuclear hormone-receptor superfamily, may be responsible for sex-reversal syndrome in humans. Dax1 antagonizes Sry action in mammalian sex determination.

SOX 9 essential for Sertoli cell differentiation, upregulated by SRY and SF1

WNT4 has been shown to inhibit the development of androgen-producing Leydig cells in early mouse embryos. A duplication of 1p31-35, where human WNT4 maps, causes ambiguous genitalia of XY patients

RSPO1 recently, a team at the University of Pavia in Italy has discovered that mutation in a specific gene also turns girls into boys.

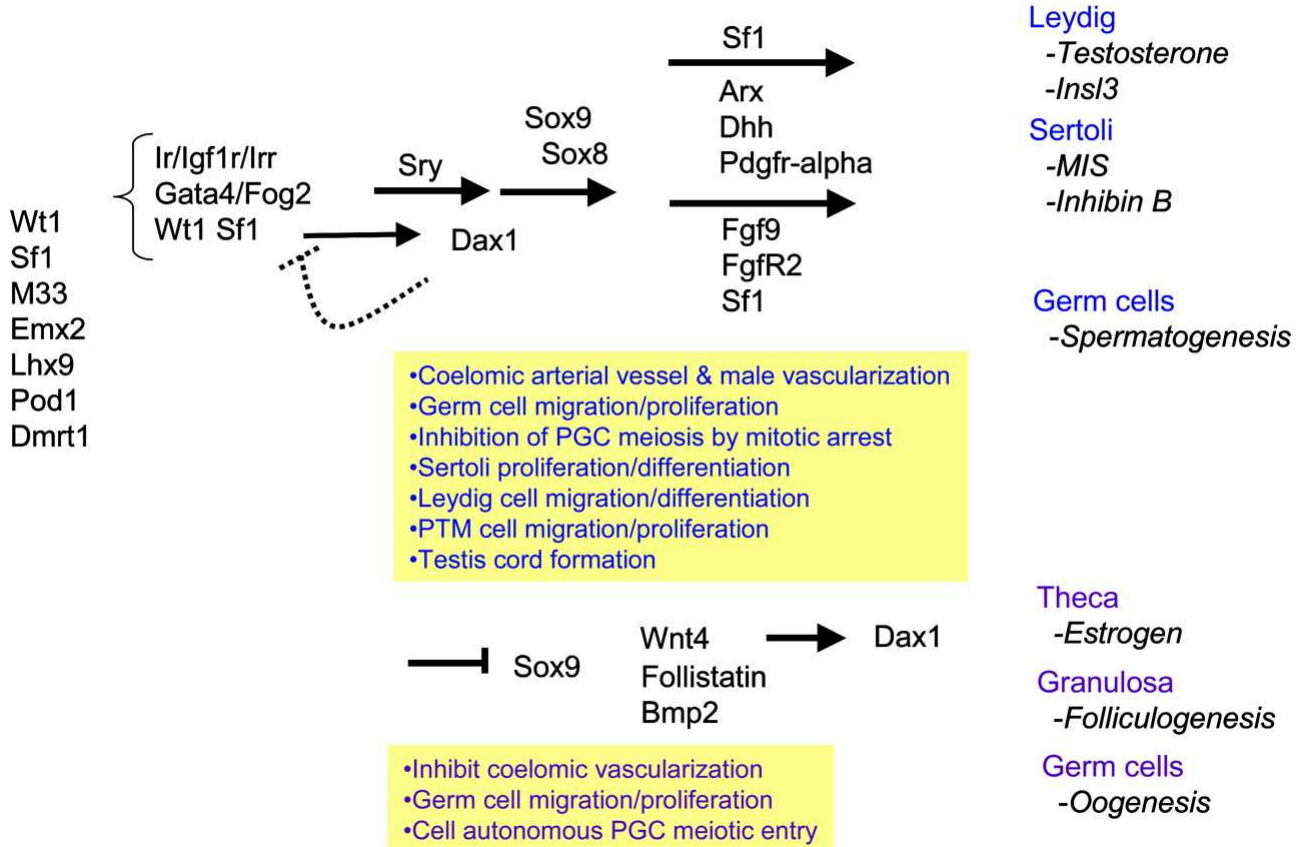
In a family, four brothers were each XX, but none carried the SRY gene. Instead, all bore a mutation in a gene called RSPO1.

Scientists suppose that, in females, SOX9 might be inhibited by RSPO1. Its inhibition leads to the development of ovaries. Mutation of RSPO1 failed to inhibit SOX9 leading to its activation and male development.

Bipotential Gonad

Testis/Ovary Development

Function



2. Anomalies of the sexual differentiation

Between 0.1% and 0.2% of live births are ambiguous enough to become the subject of specialist medical attention. But for a lot of the following syndromes, problems may only appear at puberty or later (infertility).

A. Abnormal number of sex Chromosomes:

Aneuploidy involving the sex chromosomes is more common than autosomal aneuploidy. Aneuploidies come about due to errors in meiosis during the gamete formation in one of the parents so the zygote starts out with the wrong chromosomal count.

Turner Syndrome (45 X, monosomy X)

- Common cause of female hypogonadism
- No Barr body present
- Failure to develop secondary sex characteristics
- Short stature
- Atrophic streaked ovaries
- Primary amenorrhea
- Infertility
- Cystic hygroma and Hydrops fetalis.
- Congenital Heart disease, including coarction of the aorta

YY and **YO** are fatal. (We all must have at least one X chromosome to survive.)

Trisomy X (XXX)

Klinefelter syndrome (XXY) and Klinefelter variants (XXXY, XXXXY, etc)

- Caused by meiotic nondisjunction
- Common cause of male hypogonadism
- Testicular atrophy
- Infertility due to azoospermia
- Female distribution of hair
- Gynecomastia.

XYY

mosaic karyotype, XO/XY

Cause of gonadal dysgenesis

B. Abnormal sex differentiation with normal Karyotype

Congenital Adrenal Hyperplasia (CAH) caused by a deficiency of the steroid 21-Hydroxylase (90 % of the cases). This enzyme is necessary for the conversion of CHOLESTEROL into Aldosterone and Cortisol. This leads to an excess of androgen and virilization of female fetuses. CAH is the most frequent cause of ambiguous genitalia in the newborn, constituting approximately 60% of all intersex cases. CAH is an autosomal recessive condition resulting in a female pseudohermaphrodite, which is a gonadal female with a virilized phenotype.

In 10% of the cases CAH is due to a 11-Hydroxylase deficiency: In rare cases, CAH could be caused by 3-beta-hydroxysteroid. Generally the degree of virilization is less important.

5 alpha-reductase deficiency: 46,XY fetus with normal testes but lacking the enzyme 5-alpha reductase cannot produce DHT. This leads to minimally virilized external genitalia (pseudovagina, hypospadias). Extreme virilization at puberty, presumably caused by direct action of testosterone on the phallus. Gender assignment is very controversial and has to be discussed case by case.

XY female, (Swyer syndrome): Defects in SRY lead to 46,XY complete gonadal dysgenesis. This leads to rapid gonadal degeneration leaving only "streak gonads" of fibrous tissue and ovarian stroma. At puberty there is no development of secondary sexual characteristics. These patients have female external genitalia, in contrast 46,XY partial gonadal dysgenesis patients have ambiguous genitalia.

Persistent Müllerian Duct Syndrome (PMDS): due to mutations of the AMH and/or AMH receptor gene. Patients are externally normally virilized, and persistence of Müllerian duct derivatives are discovered at surgery for either inguinal hernia or cryptorchidism.

SOX9 mutation Heterozygous mutations result in haploinsufficiency resulting in campomelic dysplasia, a polymalformative syndrome that includes sex-reversal due to gonadal dysgenesis in XY individuals.

Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) congenital condition of the female reproductive system that affects approximately 1 out of every 5000 females. Girls diagnosed with MRKH have **vaginal agenesis** or incomplete vagina. The uterus is also very small or absent. Patients have normal ovaries and will experience puberty without having periods. Often found associated with unilateral renal agenesis or adysplasia as well as skeletal malformations (MURCS association).

Kallmann syndrome association of congenital hypogonadotropic hypogonadism with anosmia or hyposmia. Affecting 1 in 10.000 to 60.000 individuals. Males predominate in a ratio of 5:1. The syndrome can occur as an inherited or sporadic disorder. X-linked, autosomal dominant, and autosomal recessive modes of inheritance have been described
The basic defect leading to hypogonadism in this syndrome is an abnormality of hypothalamic GnRH secretion secondary to failure of gonadotropin-releasing hormone(GnRH)-producing neurons to migrate from the olfactory placode to the brain, and to agenesis of the olfactory bulbs.

Androgen insensitivity syndrome (AIS) characterized by feminization of the external genitalia at birth, abnormal secondary sexual development at puberty, and infertility in individuals with a 46,XY karyotype. AIS can be subdivided into three subtypes:

- complete androgen insensitivity syndrome (CAIS), with typical female genitalia;
- partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous genitalia;
- mild androgen insensitivity syndrome (MAIS) with typical male genitalia.

C. True Hermaphroditism

Definition: Presence of both ovarian and testicular tissue within an individual, exceptionally rare. True hermaphroditism is an uncommon cause of genital ambiguity accounting for fewer than 10% of all intersex cases.

Genetic Sex: The most common karyotype is 46,XX, although mosaicism is common.

Gonadal Sex: Ovary on one side and testes on the other or Ovotestes (gonad with both testicular and ovarian tissue). Ovotestes is most common and is found in approximately two thirds of patients.

Phenotypic sex : Ambiguous genitalia

D. Induced pseudohermaphroditism

Drug induced

Although rare, female pseudohermaphroditism may occur if progestational agents or androgens are used during the first trimester of pregnancy. After the first trimester, these drugs cause only phallic enlargement without labioscrotal fusion.

Induced by maternal endocrine disorder

Endocrine abnormality in the mother as a source of virilizing hormones is even more rare because these abnormalities, if initially present, usually prevent development of a pregnancy. However, a variety of ovarian tumors (eg, arrhenoblastomas, Krukenberg tumors, luteomas, lipoid tumors of the ovary, stromal cell tumors) have reportedly produced virilization of a female fetus.

3. References

1. The sex chromosomes and their abnormalities in Thompson & Thompson, Genetics in Medicine. P98-113.
2. Mishina Y et al. Genetic analysis of the Müllerian-inhibiting substance signal transduction pathway in mammalian sexual differentiation. Genes and Development 1996, 10 : 2577-2587.
3. Marshall Graves J. Human Y Chromosome, Sex Determination, and Spermatogenesis—A Feminist View. Biology of reproduction 2000, 63 : 667B-676.
4. Langman, Jan; Thomas Sadler (2006). *Langman's medical embryology*. Hagerstown, MD: Lippincott Williams & Wilkins, 252.
5. De Marchi M, Carbonara AO, Carozzi F, et al. True hermaphroditism with XX/XY sex chromosome mosaicism: report of a case. Clin. Genet. 1976, 10 : (5): 265–72.
6. Sekido R, Lovell-Badge R. Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer.
7. Lee P A et al. Consensus statement on management of intersex disorder. Paediatrics 2006 ; 118 :488-500.
8. Burgoyne P. Y chromosome function in mammalian development. Adv Dev Biol 1992; 1:1–29.1.
9. Mc El Reavey K. A regulatory cascade hypothesis for mammalian sex determination: SRY represses a negative regulator of male development. Proc Natl Acad Sci USA 1993; 90: 3368-3372.
10. Lee et al. Consensus statement on management of Intersex disorders. Pediatrics 2006; 118: 487-500.
11. Le Merrer M et al. Lethal acrodysgenital dwarfism a severe lethal condition resembling Smith Lemli Opitz syndrome. Journal of medical genetics 1988; 25: 88-95.
12. Joffe M. Infertility and environmental pollutants. Brit Med Bull 2003; 68:47-70.
13. Welshons WJ, Russel LB. The Y chromosome as the bearer of male determining factors in the mouse. Proc Natl Acad Sci USA 1959; 45:560–566.
14. Hauschild M , Theintz G. Le développement de la fonction testiculaire. Paediatrica 2008 ; 19-3 : 51-55
15. Sinclair A. Eleven years of sex discovery. Genome Biology 2001; 2.7: 4017.1-4017.3.
16. Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Küster-Hauser syndrome (congenital absence of uterus and vagina) – phenotypic manifestations and genetic approaches. J Negat Results Biomed. 2006; 5: 1.

Interesting reading

Middlesex. Jeffrey Eugenides. 2002. Seuil. ISBN 2.02.066961.7.

Web:

1. intersex society of north America <http://www.isna.org/faq/conditions/mrkh>
2. orphanet <http://www.orpha.net> (in French)