

# GENETIC MECHANISMS UNDERLYING SEX DETERMINATION AND GONAD DIFFERENTIATION IN MAMMALS

## Summary

Sex determination and gonadal differentiation are crucial for reproductive success of an individual because they are directly responsible for correct development of gonads that orchestrate sex features and produce gametes. If germ cells are placed in a sex reversed gonad, their genetic sex will be opposite to gonadal sex, which will cause disturbance during spermatogenesis or oogenesis. This indicates that gonadal sex has to be compatible with genetic sex. A lack of compatibility is the direct cause of infertility in disorders such as sex reversal or hermaphroditism. It may be assumed that there is a system of protection against switching on genetic pathways involved in differentiation of the opposite sex gonad. In fact, genetic mechanisms underlying sex determination make up a network of positive and negative molecular interactions, both of which lead to structural changes and prevent sex reversal.

All sex determination pathways depend on the existence of *Sry*, expression of which has to take place within a critical time window so that a testis can develop. Moreover a threshold of both *Sry* expression level and number of *Sry*-positive cells needs to be overcome. The key event of male sex determination is DNA bending by SRY, which causes direct or indirect upregulation of *Sox9*. Most likely SOX9 switches on the expression of multiple genes, driving a bipotential gonad towards differentiation into a testis. Surprisingly, proteins such as DAX1 and WNT4, originally recognized as anti-testis factors, have turned out to be necessary for testis development. Another important discovery was establishing that r-spondin 1 is an essential factor in the female pathway, the loss of which results in a complete sex reversal, which indicates that *Sry* is not an irreplaceable testis determining factor under some conditions.