SRY and its Role in Gonadal Dysfunction

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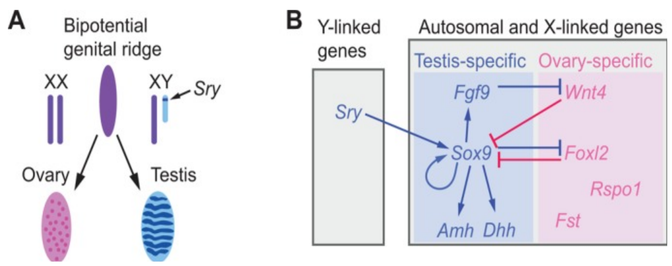
ABSTRACT

The sex-determining region Y (SRY) protein, also known as the testis-determining factor (TDF), is a DNA binding protein. It is the gene-regulatory transcription factor that is encoded by the SRY gene and is responsible for the initiation of male sex determination in placental mammals as well as marsupials. While it is understood that the expression of SRY is known to be dependent on the presence of GATA4, NR5A1 and WT1 transcription factors, they trigger a cascade that influences sex-specific development throughout an organism. Thus, we still lack an understanding of whether these transcription factors each bind to a single critical site, or whether the binding site for these factors are clustered or dispersed. In order to further understand how these factors act coordinately, this review sought to determine how several epigenetic modifiers, transcription factors and kinases are implicated in regulating the SRY transcription, and how mutation of genes in the SRY sex-determining region of the Y-chromosome leads to a range of sex development disorders such as gonadal dysgenesis (GD).

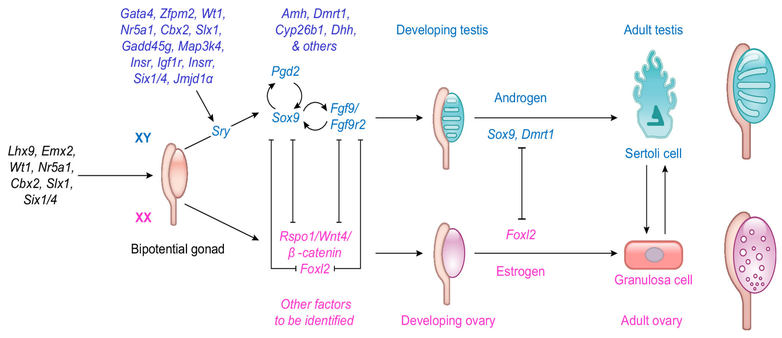
METHODS

A comprehensive literature review was performed analyzing the SRY gene and its role in Gonadal Dysfunction. A total of 25 studies, reviews as well as reports are included. These papers goes over what the SRY gene is and what it does and how mutation in a gene can lead to Gonadal dysfunction.

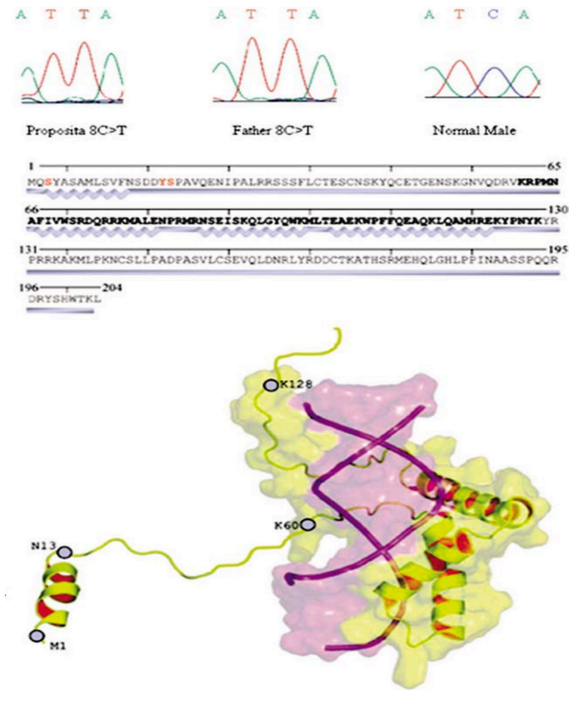
RESULTS



Christian Larney, Timothy L. Bailey, Peter Koopman; Switching on sex: transcriptional regulation of the testis-determining gene *Sry*. *Development* 1 June 2014; 141 (11): 2195–2205. doi: https://doi.org/10.1242/dev.107052



Nagahama Y, Chakraborty T, Paul-Prasanth B, Ohta K, Nakamura M. Sex determination, gonadal sex differentiation, and plasticity in vertebrate species. *Physiol Rev.* 2021;101(3):1237-1308. doi:10.1152/physrev.00044.2019



Gimelli, G., Gimelli, S., Dimasi, N. *et al.* Identification and molecular modelling of a novel familial mutation in the *SRY* gene implicated in the pure gonadal dysgenesis. *Eur J Hum Genet* **15**, 76–80 (2007). https://doi.org/10.1038/sj.ejhg.5201719

> sex is determined by SRY gene.

> Expression of the SRY in the genital ridges results in their development into testes, and in the absence results in ovaries

> Figure 1A. Figure 1B shows SRY that triggers a downstream cascade promoting male development while simultaneously impeding the gene network that drives ovarian development.

> Overview of key genes and pathways that leads to bipotential gonads to form testis or ovary development.

> Under number of positive regulator, SRY initiate Sox9 with a positive feedback loop between Pdg2/Sox9 AND fGF9/sOX9.

> In adult gonads, SOX9 and DMRT1 along with androgen and FOXL2 along with estrogen requires the maintenance of testicular and ovarian function respectfully each acting antagonistically of each other .

> The protein encoded by SRY contains a homeobox(HMG) domain which is a DNA binding domain.

> Pure GD, mutation is localized within the HMG box causing alteration in DNA binding/ bending.

> A study done on a XY female with pure GD patient and her phenotypically normal father where chromosome analysis was performed on peripheral blood from patient and father.

> Results showed a novel point mutation in the SRY gene at nucleotide position 8 where the Cytosine in the codon 3rd position is replaced with thymine (8C>T), this mutation changed a serine with a leucine in amino acid position 3 of the entire SRY protein (S3L). This mutation could form a alpha helix from amino acid position 2-13. The secondary structure prediction of serine to leucine could potentially disrupt the N-terminal alpha helix in the SRY protein.

> These mutation plays a role in impeding the normal function of the SRY protein.

CONCLUSIONS

> GD is caused by a mutation in the SRY gene.

> in vitro and mouse models have allowed for a better understanding of the causal pathologic pathway between a mutation in SRY and patient presentation.

> specific binding sites that are occupied by GATA4, WT1 and NR5A1 and the functionality of those sites have yet to be confirmed with in vivo evidence

FUTURE DIRECTIONS

Future research should focus on site-directed mutational analysis to investigate associated phenotypic changes at the molecular and cellular level to gain a better perspective cause of GD, as well as better insight into human sexual development.

BIBLIOGRAPHY

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