Transcriptional regulation of testis differentiation

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16/01/2022
**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 78

This document contains 1 pathway and 18 reactions (see Table of Contents)
In humans, primordial germ cells (PGCs) are specified about 2 weeks after fertilization, a time before gastrulation (reviewed in Svingen and Koopman 2013, Mäkelä et al. 2019). PGCs are initially located extraembryonically and then migrate to colonize the gonadal ridges (genital ridges) of the embryo during the fifth week after fertilization. At this time, either ovaries and testes can originate from the gonadal ridges. That is, the cells of the gonadal ridges are initially bipotential and remain bipotential until about 42 days after conception, when transient expression of the SRY gene located on the Y chromosome in male embryos is initiated in some somatic cells of the gonadal primordium (reviewed in Sekido and Lovell-Badge 2013, Barrionuevo et al. 2013, Svingen et al. 2013, Mäkelä et al. 2019).

The transcription factors WT1, GATA4, ZFPM2 (FOG2), and the nuclear receptor NR5A1 (SF1) activate transcription of SRY (Shimamura et al. 1997, Hossain and Saunders 2001, De Santa Barbara et al. 2001, Miyamoto et al. 2008, and inferred from mouse homologs). SRY and NR5A1 then activate transcription of SOX9, one of the master regulators of testis development and maintenance (Knower et al. 2011, Croft et al. 2018, inferred from mouse homologs, reviewed in Gonen and Lovell-Badge 2019). Regulation of genes by SRY and then, when expression of SRY decreases, by SOX9 causes the specification of Sertoli cells that further organize formation of the testis by encasing the primordial germ cells in protocords, which then form fully developed testis cords.

SOX9 directly activates its own promoter to maintain SOX9 expression through development and into adulthood (Croft et al. 2018, and inferred from mouse homologs). SOX9 and GATA4 directly activate DMRT1 (inferred from mouse homologs), which maintains testis specification by maintaining expression of SOX9 and other testis-related genes. DMRT1 also acts to suppress ovarian specification by binding and repressing FOXL2 and WNT4 genes (inferred from mouse homologs). SOX9 directly activates FGF9 (inferred from mouse homologs), which acts via FGFR2 to maintain SOX9 expression, and PTGDS (inferred from mouse homologs), which converts Prostaglandin H2 to Prostaglandin D2, a critical hormone-like
lipid that recruits supporting cells to Sertoli cells and acts indirectly to maintain SOX9 expression. SOX9, NR5A1, and GATA4 directly activate AMH (De Santa Barbara et al. 1998, and inferred from mouse homologs), an extracellular signaling molecule which causes regression of the Muellerian duct of the female reproductive system. SOX9 also directly activates many other genes, including DHH (Rahmoun et al. 2017, and inferred from mouse homologs), an intercellular signaling molecule required for testis formation.

Literature references


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WT1, NR5A1 (SF1), GATA4, ZFPM2 bind the SRY gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692250

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Wt1, Nr5a1 (Sf1), Gata4, Zfpm2 (Fog2) bind the Sry gene (Mus musculus)

The transcription factors WT1 (Shimamura et al. 1997, Hossain and Saunders 2001, Miyamoto et al. 2008, also inferred from mouse homologs), NR5A1 (also called SF1) (De Santa Barbara et al. 2001), GATA4:ZFPM2 (also called GATA4:FOG2) (Miyamoto et al. 2008, also inferred from mouse homologs) bind the promoter of the SRY gene and activate transcription of SRY. SRY is a mammal-specific gene located on the Y chromosome that is responsible for male sex determination.

**Followed by:** Expression of SRY in testis differentiation

**Literature references**


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https://reactome.org
Expression of SRY in testis differentiation

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692241

**Type:** uncertain

**Compartments:** nucleoplasm

**Inferred from:** Expression of Sry in testis differentiation (Mus musculus)

In the gonadal ridge (genital ridge), the SRY gene is transcribed to yield mRNA and the mRNA is translated to yield SRY protein (De Santa Barbara et al. 2001, Hossain and Saunders 2001, Miyamoto et al. 2008, also inferred from mouse homologs). Transcription of SRY is activated by WT1 (Hossain and Saunders 2001, Miyamoto et al. 2008), GATA4:ZFPM2 (also called GATA4:FOG2) (Miyamoto et al. 2008), and NR5A1 (also called SF1) (De Santa Barbara et al. 2001).

**Preceded by:** WT1, NR5A1 (SF1), GATA4, ZFPM2 bind the SRY gene

**Followed by:** SRY and NR5A1 (SF1) bind SOX9 gene

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SRY and NR5A1 (SF1) bind SOX9 gene

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9690414

Type: binding

Compartments: nucleoplasm

Inferred from: Sry and Nr5a1 (Sf1) bind Sox9 gene (Mus musculus)

SRY and NR5A1 (SF1) bind several sites in the TES enhancer upstream of the SOX9 coding region (Knower et al. 2011) and the eALDI enhancer upstream of TES (Croft et al. 2018, and inferred from mouse homologs). SRY weakly enhances SOX9 expression only when NR5A1 is also bound to the TES enhancer (inferred from mouse homologs). SRY bound to eALDI more strongly activates SOX9 (Croft et al. 2018).

Preceded by: Expression of SRY in testis differentiation

Followed by: Expression of SOX9 in testis differentiation

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Expression of SOX9 in testis differentiation

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9690404

Type: uncertain

Compartments: nucleoplasm

Inferred from: Expression of Sox9 in testis differentiation (Mus musculus)

Subsequent to SRY expression in the gonadal ridge, the SOX9 gene is transcribed to yield mRNA and the mRNA is translated to yield SOX9 protein (Knower et al. 2011, Croft et al. 2018). SRY and NR5A1 (SF1) bound at the TES enhancer (Knower et al. 2011) and the eALDI enhancer (upstream of the TES enhancer, Croft et al. 2018) of the SOX9 gene initially activate transcription of SOX9 (Knower et al. 2011, Croft et al. 2018, and inferred from mouse homologs). Later, SOX9 and NR5A1 activate the TES enhancer, providing a mechanism for autoregulation (Knower et al. 2011). DMRT1, itself directly activated by SOX9, also directly activates SOX9 (inferred from mouse homologs). FGF9 acting through FGFR2 (inferred from mouse homologs) and Prostaglandin D2 (Malki et al. 2005), the product of PTGDS, activate SOX9 through less well characterized mechanisms.

Preceded by: SRY and NR5A1 (SF1) bind SOX9 gene

Followed by: SOX9 binds the FGF9 gene, SOX9 binds the PTGDS gene, SOX9 binds the SOX9 gene, SOX9 binds the DHH gene, SOX9 and GATA4 bind the DMRT1 gene, SOX9, NR5A1 (SF1), and GATA4 bind the AMH gene, Expression of DHH in testis differentiation

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SOX9 binds the SOX9 gene

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9690395

Type: omitted

Compartments: nucleoplasm

Inferred from: Sox9 binds the Sox9 gene (Mus musculus)

SOX9 together with NR5A1 (SF1) binds the TES enhancer and other enhancers upstream of the SOX coding region (Croft et al. 2018 and inferred from mouse homologs) and thereby activates its own expression. As SRY expression decreases during testis differentiation, SOX9 and, later, DMRT1 become responsible for maintaining expression of SOX9.

Preceded by: Expression of SOX9 in testis differentiation

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SOX9 and GATA4 bind the DMRT1 gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9690896

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Sox9 and Gata4 bind the Dmrt1 gene (Mus musculus)

SOX9 and GATA4 bind a "Sertoli Cell Signature" sequence upstream of the DMRT1 coding region (inferred from mouse homologs).

**Preceded by:** Expression of SOX9 in testis differentiation

**Followed by:** Expression of DMRT1 in testis differentiation

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Expression of DMRT1 in testis differentiation

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9690877

Type: uncertain

Compartments: nucleoplasm

Inferred from: Expression of Dmrt1 in testis differentiation (Mus musculus)

In the gonadal ridge, the DMRT1 gene is transcribed to yield mRNA and the mRNA is translated to yield DMRT1 protein (Jørgensen et al. 2012, Rahmoun et al. 2017 and inferred from mouse homologs). SOX9 and GATA4 bind the promoter of the DMRT1 gene and activate transcription of DMRT1 (Rahmoun et al. 2017 and inferred from mouse homologs). DMRT1 is initially expressed in Sertoli cells at 8-20 weeks of gestation (Jørgensen et al. 2012). Expression then shifts to spermatogonial cells.

Preceded by: SOX9 and GATA4 bind the DMRT1 gene

Followed by: DMRT1 binds the FOXL2 gene, DMRT1 binds the WNT4 gene, DMRT1 binds the SOX9 gene

Literature references


SOX9 binds the FGF9 gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692131

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Sox9 binds the Fgf9 gene (Mus musculus)

SOX9 binds the promoter of the FGF9 gene (inferred from mouse homologs)

**Preceded by:** Expression of SOX9 in testis differentiation

**Followed by:** Expression of FGF9 in testis differentiation

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Expression of FGF9 in testis differentiation

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692134

**Type:** uncertain

**Compartments:** nucleoplasm, extracellular region

**Inferred from:** Expression of Fgf9 in testis differentiation (Mus musculus)

The FGF9 gene is transcribed to yield mRNA and the mRNA is translated to yield FGF9 protein (inferred from mouse homologs). In the developing testis, FGF9 transcription is activated by SOX9 (inferred from mouse homologs).

**Preceded by:** SOX9 binds the FGF9 gene

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SOX9 binds the PTGDS gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692154

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Sox9 binds the Ptgs gene (Mus musculus)

SOX9 binds the promoter of the PTGDS gene (inferred from mouse homologs).

**Preceded by:** Expression of SOX9 in testis differentiation

**Followed by:** Expression of PTGDS in testis differentiation

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Expression of PTGDS in testis differentiation

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9692129

Type: uncertain

Compartments: endoplasmic reticulum membrane, nucleoplasm

Inferred from: Expression of Ptgds in testis differentiation (Mus musculus)

In the developing testis, the PTGDS gene is transcribed to yield mRNA and the mRNA is translated to yield PTGDS protein (inferred from mouse homologs). Transcription of PTGDS is directly activated by SOX9 (inferred from mouse homologs).

Preceded by: SOX9 binds the PTGDS gene

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SOX9, NR5A1 (SF1), and GATA4 bind the AMH gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692135

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Sox9 and Nr5a1 (Sf1) bind the Amh gene (Mus musculus)

SOX9, NR5A1 (SF1), and GATA4 bind the promoter of the AMH gene (De Santa Barbara et al. 1998 and inferred from mouse homologs). SOX9 and NR5A1 interact directly (De Santa Barbara et al. 1998).

**Preceded by:** Expression of SOX9 in testis differentiation

**Followed by:** Expression of AMH in testis differentiation

**Literature references**


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Expression of AMH in testis differentiation

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9693009

Type: uncertain

Compartments: nucleoplasm, extracellular region

Inferred from: Expression of Amh in testis differentiation (Mus musculus)

In differentiating Sertoli cells of the testis, the AMH gene is transcribed to yield mRNA and the mRNA is translated to yield AMH protein (De Santa Barbara et al. 1998, Rahmoun et al. 2017, and inferred from mouse homologs). SOX9, NR5A1 (SF1), and GATA4 bind the promoter of the AMH gene and activate transcription (De Santa Barbara et al. 1998, Rahmoun et al. 2017, and inferred from mouse homologs). AMH is secreted and acts via the AMHR receptor to suppress formation of the Mullerian duct.

Preceded by: SOX9, NR5A1 (SF1), and GATA4 bind the AMH gene

Literature references


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SOX9 binds the DHH gene

Location: Transcriptional regulation of testis differentiation
Stable identifier: R-HSA-9692150
Type: binding
Compartments: nucleoplasm
Inferred from: Sox9 binds the Dhh gene (Mus musculus)

SOX9 binds the promoter of the DHH gene (inferred from mouse homologs).

Preceded by: Expression of SOX9 in testis differentiation

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Expression of DHH in testis differentiation

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9692146

Type: uncertain

Compartments: nucleoplasm, extracellular region

Inferred from: Expression of Dhh in testis differentiation (Mus musculus)

The DHH gene is transcribed to yield mRNA and the mRNA is translated to yield DHH protein (Rahmoun et al. 2017 and inferred from mouse homologs). Transcription of DHH is directly activated by SOX9 (inferred from mouse homologs). DHH is secreted from pre-Sertoli cells (Rahmoun et al. 2017 and inferred from mouse homologs) and acts via the PTCH1 receptor to regulate testis development.

Preceded by: Expression of SOX9 in testis differentiation

Literature references


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DMRT1 binds the SOX9 gene

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9692228

Type: binding

Compartments: nucleoplasm

Inferred from: Dmrt1 binds the Sox9 gene (Mus musculus)

DMRT1, a direct target of SOX9, binds the promoter of the SOX9 gene (inferred from mouse homologs). DMRT1 and SOX9 are responsible for maintaining expression of SOX9 after SOX9 is initially activated by SRY.

Preceded by: Expression of DMRT1 in testis differentiation

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DMRT1 binds the FOXL2 gene

Location: Transcriptional regulation of testis differentiation

Stable identifier: R-HSA-9692236

Type: binding

Compartments: nucleoplasm

Inferred from: Dmrt1 binds the Foxl2 gene (Mus musculus)

DMRT1 binds the FOXL2 gene and represses transcription of FOXL2, a promoter of ovary differentiation (inferred from mouse homologs).

Preceded by: Expression of DMRT1 in testis differentiation

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DMRT1 binds the WNT4 gene

**Location:** Transcriptional regulation of testis differentiation

**Stable identifier:** R-HSA-9692297

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Dmrt1 binds the Wnt4 gene (Mus musculus)

DMRT1 binds the WNT4 gene and represses transcription of WNT4, a promoter of ovary differentiation (inferred from mouse homologs).

**Preceded by:** Expression of DMRT1 in testis differentiation

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- **Expression of SOX9 in testis differentiation**
- **SOX9 binds the SOX9 gene**
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- **SOX9 binds the FGF9 gene**
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- **SOX9, NR5A1 (SF1), and GATA4 bind the AMH gene**
- **Expression of AMH in testis differentiation**
- **SOX9 binds the DHH gene**
- **Expression of DHH in testis differentiation**
- **DMRT1 binds the SOX9 gene**
- **DMRT1 binds the FOXL2 gene**
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