Epigenetics and sex

Sex genes and chromosomes

Sex without sex chromosomes

Epigenetics in environmental sex
Human sex chromosomes and genes

X  X
X  Y

TDF = ZFY

TDF

(testis)
hormones

male
Human sex determination

- Female: XX
- Male: XY

- SRY gene
- Testis
- Hormones
- Male
Sex determination pathway in mammals

- **SRY**
- **WT1**
- **DAX1**
- **SOX9**
- **FGF9/FGFR2**
- **AMH**
- **ATRX**
- **DHH**
- **DMRT1**
- **MAP3K1**
- **GADD45γ**
- **MAP3K4**
- **p38**
- **GATA4**
- **RSPO1**
- **WNT4**
- **β-catenin**

Testis

- **FOXL2**
- **DMRT1**

Ovary

Bipotential gonad
Sex chromosomes are weird

- X: Smart, Sexy X
  - 1669 genes
  - Many different functions
  - Many sex, intelligence genes
  - Brains and balls genes

- Y: Wimpy Y
  - Only 27 genes specific to Y
  - Many copies, most inactive
  - Male-specific functions
  - Sex and spermatogenesis

- SRY

Shared by X and Y
- Contains 24 genes
XY evolution

Once the X and Y were an ordinary pair

The Y is a degraded X
Y genes evolved from X genes

SOX3
Mental retardation spermatogenesis

RBMX
Mental retardation?

TSPX
Cell cycle?

20/27 Y genes have copies on X

SRY
Sex determination

RBMY
Spermatogenesis

TSPY
Spermatogenesis?

X
Brains-and-balls genes

Y
sex and sperm genes
When will our Y disappear?

166 MYA – the Y had 1669 genes
Today – the Y has 45
Genes lost per MY = \( \approx \frac{1624}{166} = \approx 9.8 \)
At this rate Y will disappear in 4.6 MY
Will males disappear?

Parthenogenetic females?

New sex determining genes?
e.g. CBX2 in spiny rat
Sex chromosomes defined by sex gene

**Male heterogamety**

**Female**
- Sex chromosomes: XX
- Heterogamety

**Male**
- Sex chromosomes: XY
- Male dominant gene on Y
  - Example: human

**Female dominant gene on W**
- Example: Xenopus laevis

**Dosage-sensitive male-determining gene on Z**
- Example: birds
ZW in birds and snakes

Birds
- Emu

Snakes
- Pythons
- Vipers
Vertebrate sex chromosome evolution

Same genome, but different regions determine sex

- Snakes: ZW
- Birds: ZW
- Platypus: XY
- Kangaroo: XY
- Human: XY

Ancestral vertebrate:
- DMRT1
- AMH

Vertebrate sex chromosome evolution:

- DMRT1: 1
- AMH: 5
- SOX3: micro...

SRY, mammal XY are only ~150 MY old
Vertebrate sex genes

**MAMMALS**
- **Mammals**
  - Therians
    - *SRY (SOX3 mutant)*
  - Monotremes
    - *AMH*

**BIRDS**
- *DMRT1*

**AMPHIBIANS**
- *Xenopus*
  - Inactive *DMRT1* copy (*DMW*)
- *Wrinkled frog*
  - *SOX3*

**FISH**
- *Oryzias*
  - *DMRT1* copy (*DMY*), *GSDF, SOX3*
- *Pejerry*
  - *AMH* copy
- *Fugu*
  - *AMHR2* (single SNP)
- *Tongue sole*
  - *DMRT1*, methylated in female
- *Salmonids*
  - *SDY = interferon-r factor 9*
Vertebrate sex genes

Same genes independently evolved sex function

**MAMMALS**
- **Therians**
  - *SRY* (*SOX3* mutant), *CBX2*
- **Monotremes**
  - *AMH*

**BIRDS**
- *DMRT1*

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- **WT1**
- **FOXL2**
- **Testis**
- **Ovary**

**Gene Expression**: JMJD1A, DHH, ATRX, DMRT1, MAP3K1
Temperature sex determination

e.g. Crocodiles and marine turtles have no sex chromosomes

- >34°C - all males
- >32°C - all females

Epigenetic
Epigenetics

"Over the gene" - Waddington 1942 – expression changes in development

Epigenetic silencing 1960s
X chromosome inactivation
Lyon 1961

Molecular mechanism 1980s
Transcriptional repression
Graves & Gartler 1986

DNA methylation
Graves 1982

Histone modification
• active marks
• inactive marks
Some reptiles do both

Dragon lizard *Pogona vitticeps*

**Genetic Sex Determination**

Epigenetic temperature override

![Genealogy chart and chromosome image]

<table>
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<th>Temperature</th>
<th>% males</th>
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<td>50</td>
<td>ZZ males</td>
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<tr>
<td>ZW females</td>
<td></td>
</tr>
</tbody>
</table>

Ezaz Chrom Res 2005

Quinn et al 2007 Science
Epigenetic sex determination

Half smooth tongue sole
Chen et al Nature, Shao et al Genome Res

dmrt1

DNA methylation

male

female
Epigenetic sex determination in teleost fish

e.g. sea bass has GSD, influenced by temperature,
Upregulates hormones, ts factors, epigenetic regulatory genes
(hdac11, dicer1, ehmt2, jarid2a, pcgf2, suz12, mettl22)

Some fish change sex during development (e.g. angelfish M → F)

Some fish **change sex** on social cues (e.g. bluehead wrasse)

The usual suspects

- stress genes
- epigenetic marks
- hormones (esp aromatase)
- transcription factors
**SRY activation by epigenetic factors**

Jumonji gene *JMJD1A* erases Histone 3K9 methylation (removes repression)

*CBX* (subunit of polycomb-repressive complex 1) interacts with *JMJD1A*

DNA methylation at *SRY* promoter removed

Multiple transcription factors bind to *SRY*.
Sex determination pathway in mammals

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- **JMD1A**
- **ATRX**
- **FOXL2**

Pathways:
- Bipotential gonad
- Testis: DMRT1
- Ovary: FOXL2

Related proteins:
- **WT1**
- **SF1**
- **CBX2**
Many different ways to determine sex!

Toilet sign spotted in Tokyo Medical and Dental School
No sex chromosomes

Marine turtles

Turtle Chr 6 = bird ZW
Turtle Chr 4 = mammal XY

An evolutionary ground state?
Discovering the testis determining gene

Jamie Foster, Andrew Sinclair
ZFy is the wrong gene
SRY is the right gene
Goodfellow Lab, London, Cambridge
SOX3 ancestor of SRY