性分化　update

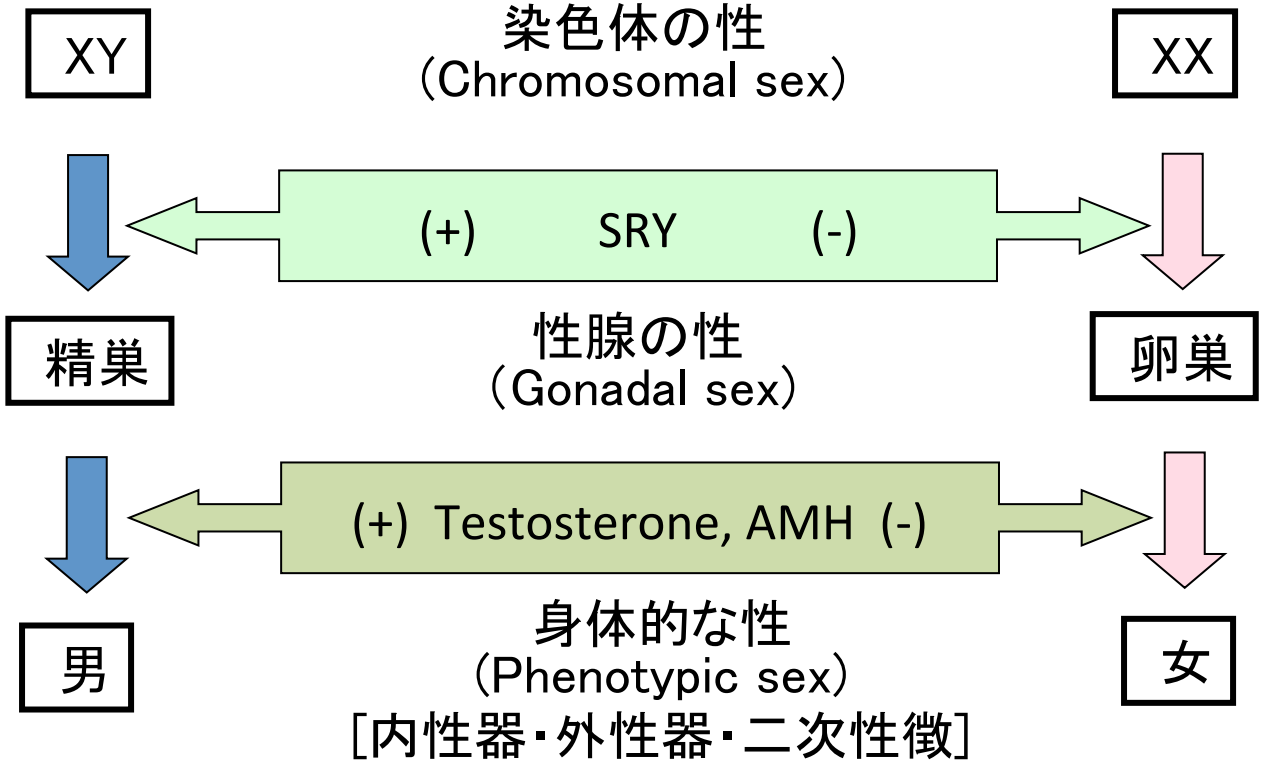
2014年小児内分泌学会
東京医科歯科大学 (TMDU)
鹿島田　健一

日本小児内分泌学会
COI開示

筆頭発表者名：　鹿島田健一

演題発表に関連し、開示すべきCOI関係にある企業等はありません。

ヒトの性分化



法律上の性
心理的な性
社会的な性
(Psychosocial sex, Gender)

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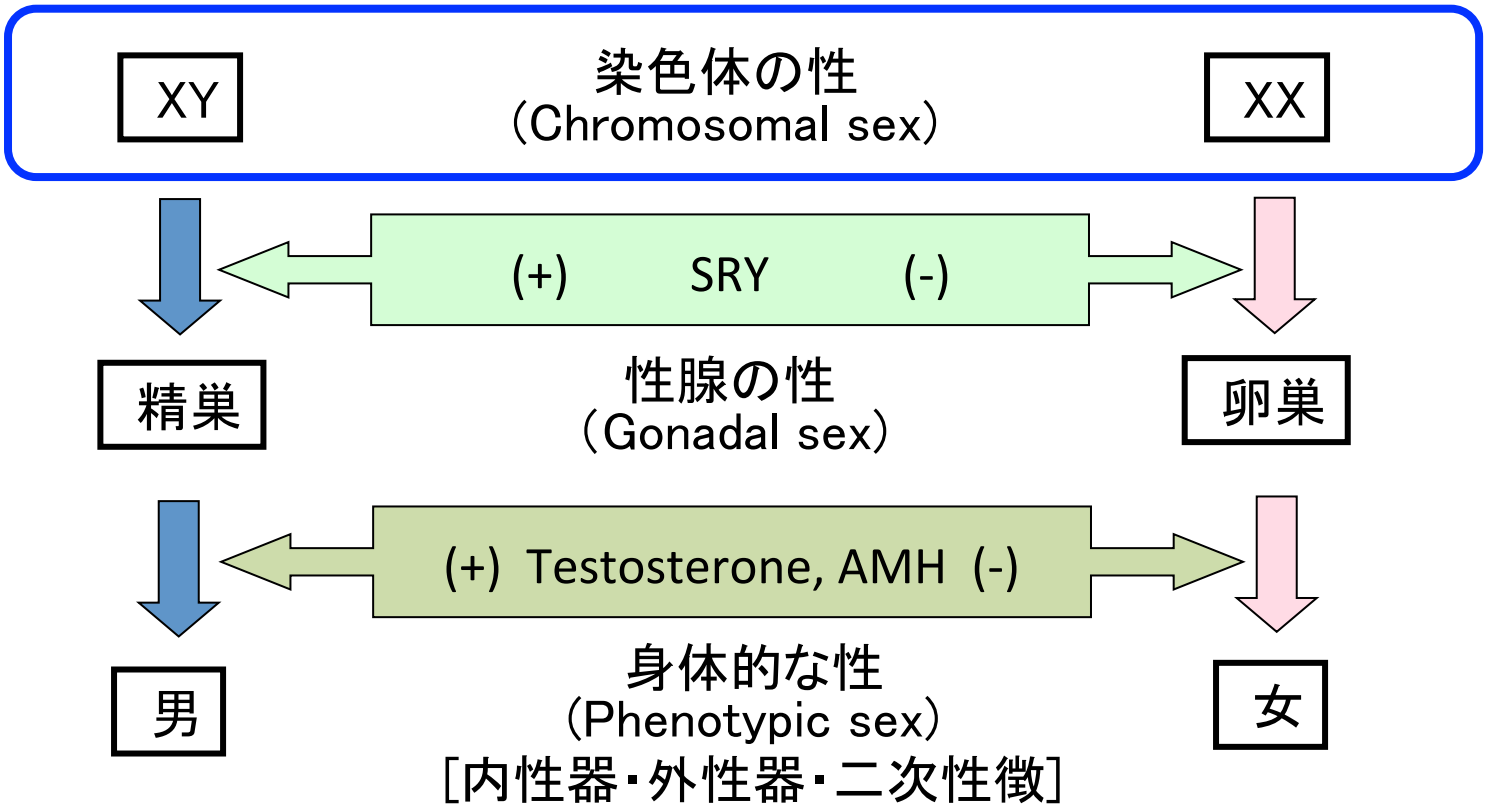
今日の内容

- Y染色体
  - *Sry*と*Eif2s3y*
- 性腺分化
  - 精巣分化
    - SRY制御、TESCOとSOX分子
  - 精巣、卵巣分化cascadeの拮抗的な作用
- 性腺分化以降
  - IMAGe 症候群

ヒトの性分化



法律上の性
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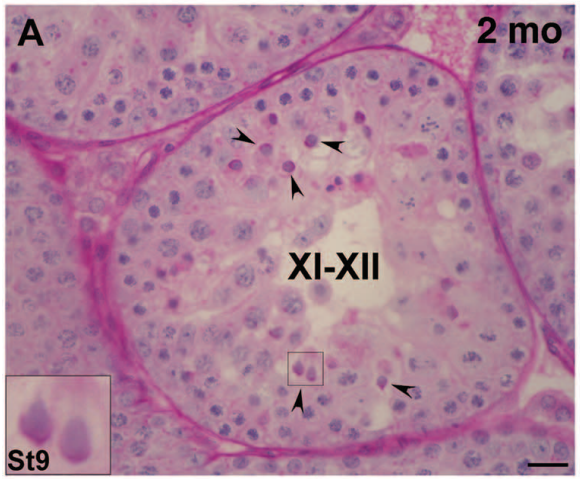
The Minimalist Y

Two Y Genes Can Replace the Entire Y Chromosome for Assisted Reproduction in the Mouse

Yasuhiro Yamauchi, Jonathan M. Riel, Zoia Stoytcheva, Monika A. Ward*

SCIENCE VOL 343 3 JANUARY 2014



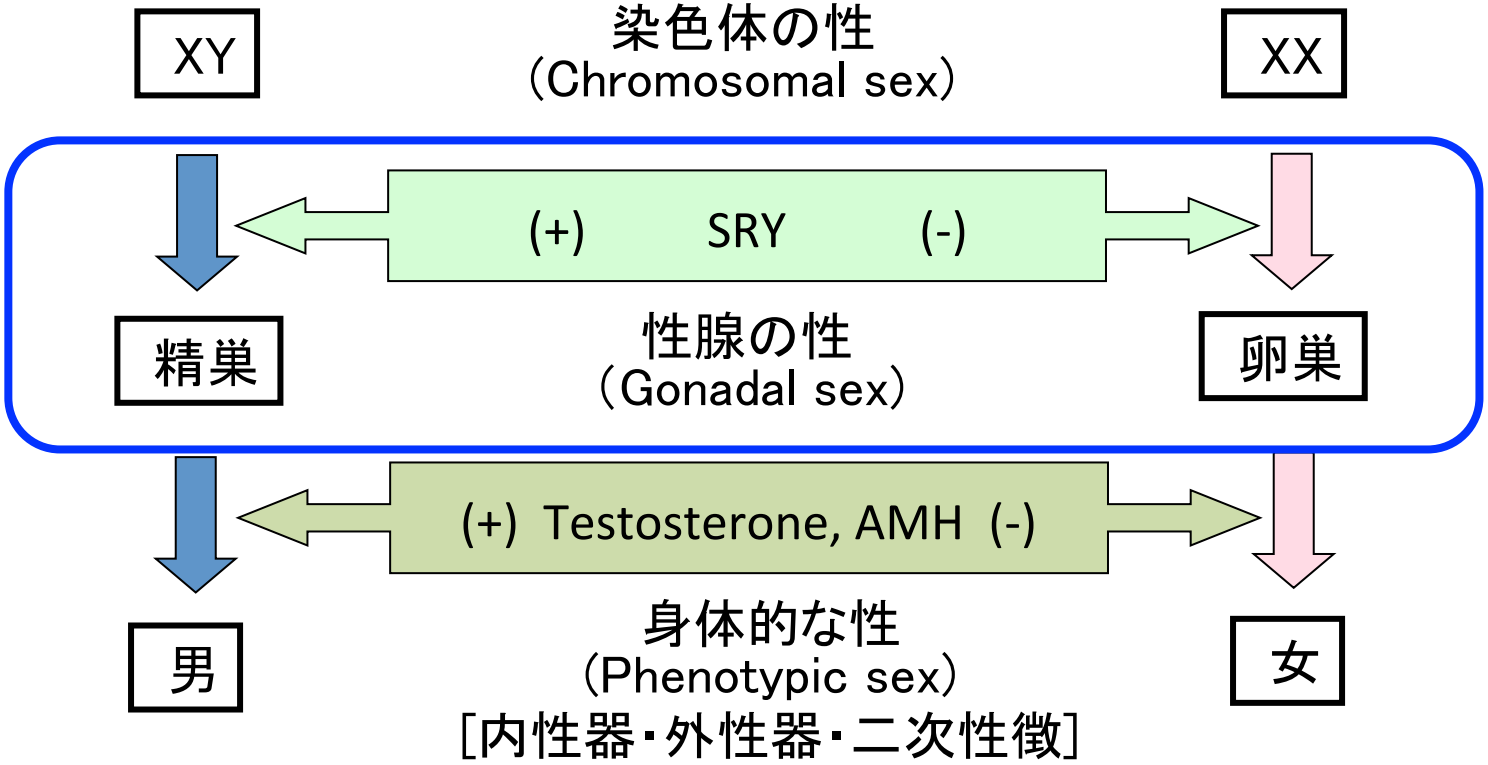
- Sry Tg XXマウスでは性腺の体細胞は精巣に分化するものの、精子形成は認めなかった

P020 斎藤先生

(Koopman et al, 1991, Nature)

- ２つの遺伝子、*Sry*と*Eif2s3y*のみをもつY染色体をもつマウスから取り出したgerm cellを用いることで、生きた仔マウスを作成することに成功

ヒトの性分化



法律上の性
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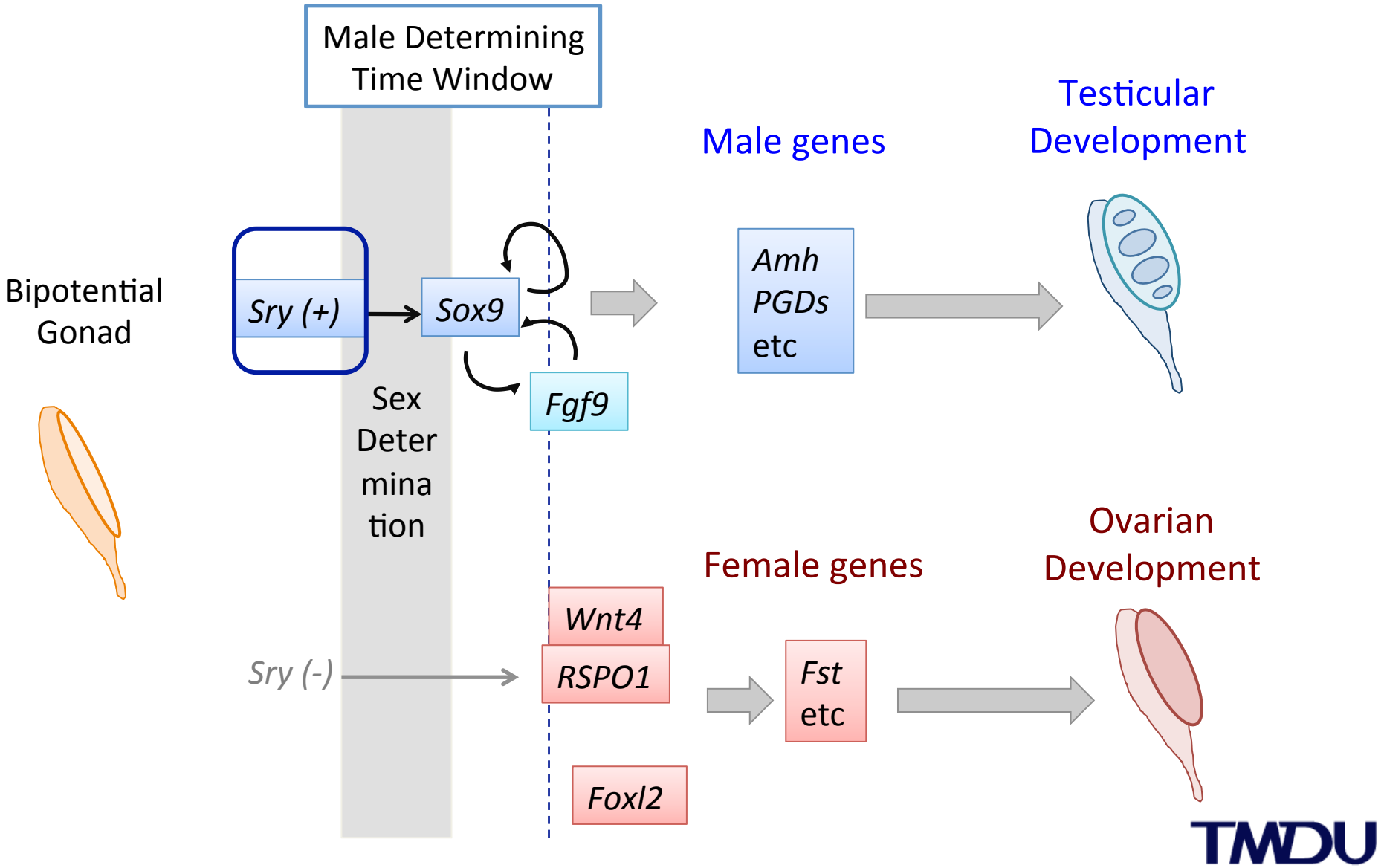
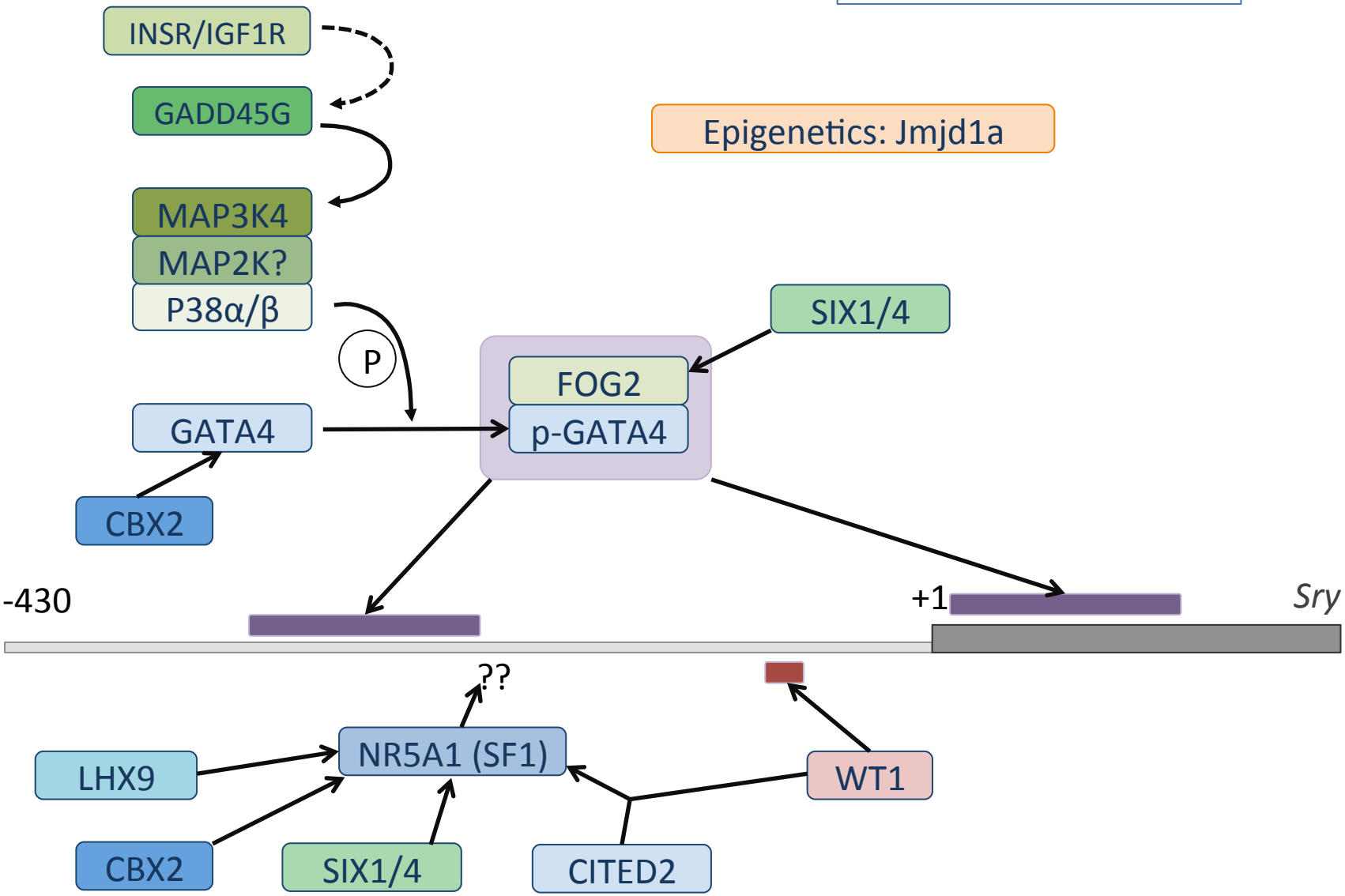
性腺における性決定


Male Determining
Time Window
Testicular
Development
Male genes
Bipotential
Gonad
Sry (+)
Sox9
Amh
PGDs
etc
Fgf9
Sex
Deter
mina
tion
Ovarian
Development
Female genes
Wnt4
Sry (-)
RSPO1
Fst
etc
Foxl2

*Sry*の制御機構



Modified (*Larney et al, 2014, Development)*

SRYの制御に関わる分子

Protein/ Gene	Type of the protein	Human (LOF)	Mice (LOF)
WT1 (+KTS)	Transcription factor?	Frasier syndrome (Nat Genet. 1997 17:467)	XY sex reversal (Cell, 2001, Vol. 106, 319)
CBX2/M33	Transcriptional cofactor	XY sex reversal (AmJHumGenet. 2009 84:658)	XY sex reversal (Nature. 1998 18;393)
GATA4/FOG2	Transcription factor/ co repressor?	XY DSD (GATA4) (PNAS 2011 108:1597)	XY sex reversal (Development 2002 129:4627)
Insulin recetpros (Ir, Irr, Igf1r)	Receptors		XY sex reversal (TKO) (Nature. 2003 426:291)
MAP3K4/Gadd45G	Kinase (enzyme)	XY DSD (MAP3K1) (AmJHumGenet. 2010, 87:898) (HMG. 2013, 23: 1073)	XY sex reversal (PLoS Biol.2009 7(9):e1000) (Dev Cell. 2012 23(5):1020) (PLoS One. 2013;8(3):e58751)
SIX1 and SIX4	Transcription Factor (Target: Sf1 and Fog2)		XY reversal (DKO) (Dev Cell. 2013 26(4):416)
Jmjd1a	H3K9 demethylase		XY sex reversal (Science. 2013;341:1106)

赤字: 2010年以降の論文

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GATA4

- 心臓の発生に重要で、Null mouseは早期胎生致死

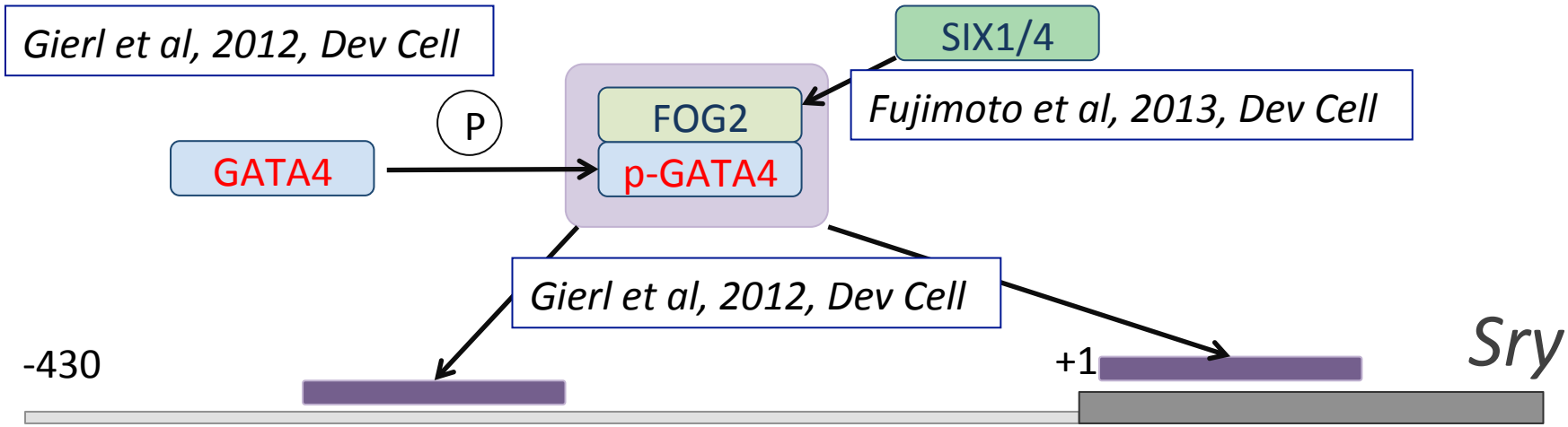
  *(Molekentin et al, 1997, **Gen&Dev**, Kuo et al, 1997, **Gen&Dev**, Garg et al, 2003 **Nature**)*

- *Sry*の発現に必須

  *(Tevosian et al, 2002, **Development**)*

- 原始性腺(生殖隆起:genital ridge)の発生に必須

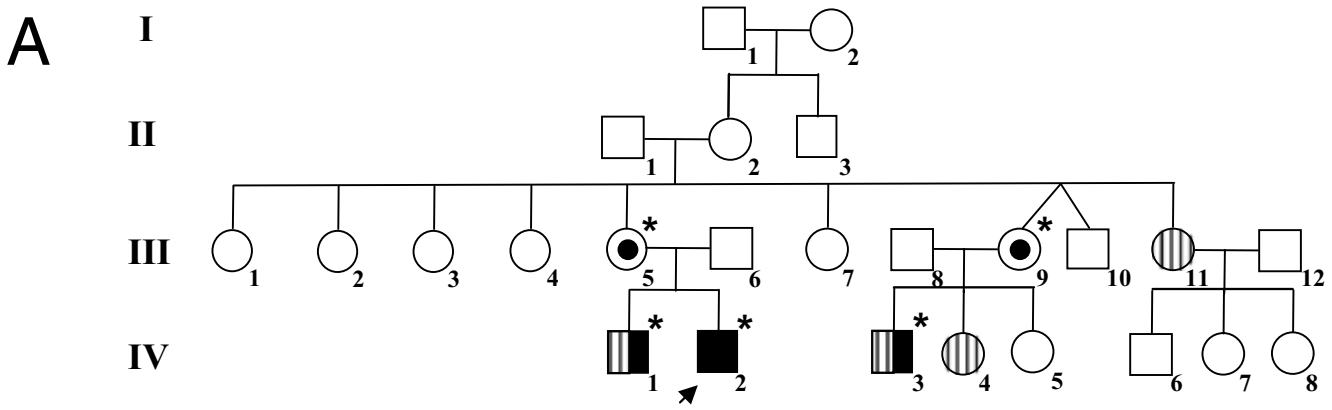
  *(Hu et al, 2013, **PLos Gen**)*



Loss-of-function mutation in *GATA4* causes anomalies of human testicular development

Diana Lourenço[a], Raja Brauner[b], Magda Rybczyńska[a], Claire Nihoul-Fékété[c], Ken McElreavey[a,1], and Anu Bashamboo[a,1]

2011, PNAS



■ :affected

▥ :cardiac disease

- 46XY, DSD
- Dysgenetic testis
- Mullerian structures present
- Ambiguous genitalia

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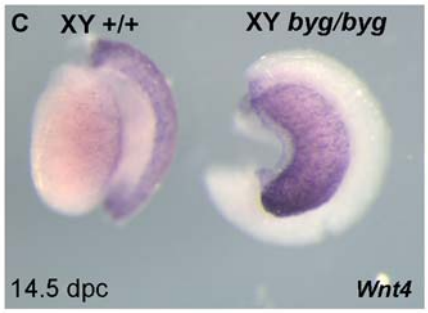
MAP3K

MAP3K4 (MEKK4)

- *Sry*の発現を制御し、null miceはXY sex reversalを起こす

(Bogani et al, 2009, PLos Biology)



Mutations in *MAP3K1* Cause 46,XY Disorders of Sex Development and Implicate a Common Signal Transduction Pathway in Human Testis Determination

Alexander Pearlman,[1] Johnny Loke,[1] Cedric Le Caignec,[2,3] Stefan White,[4] Lisa Chin,[1] Andrew Friedman,[1] Nicholas Warr,[5] John Willan,[5] David Brauer,[1] Charles Farmer,[1] Eric Brooks,[1] Carole Oddoux,[1] Bridget Riley,[1] Shahin Shajahan,[1] Giovanna Camerino,[6] Tessa Homfray,[7] Andrew H. Crosby,[7] Jenny Couper,[8] Albert David,[2] Andy Greenfield,[5] Andrew Sinclair,[4] and Harry Ostrer[1,*]

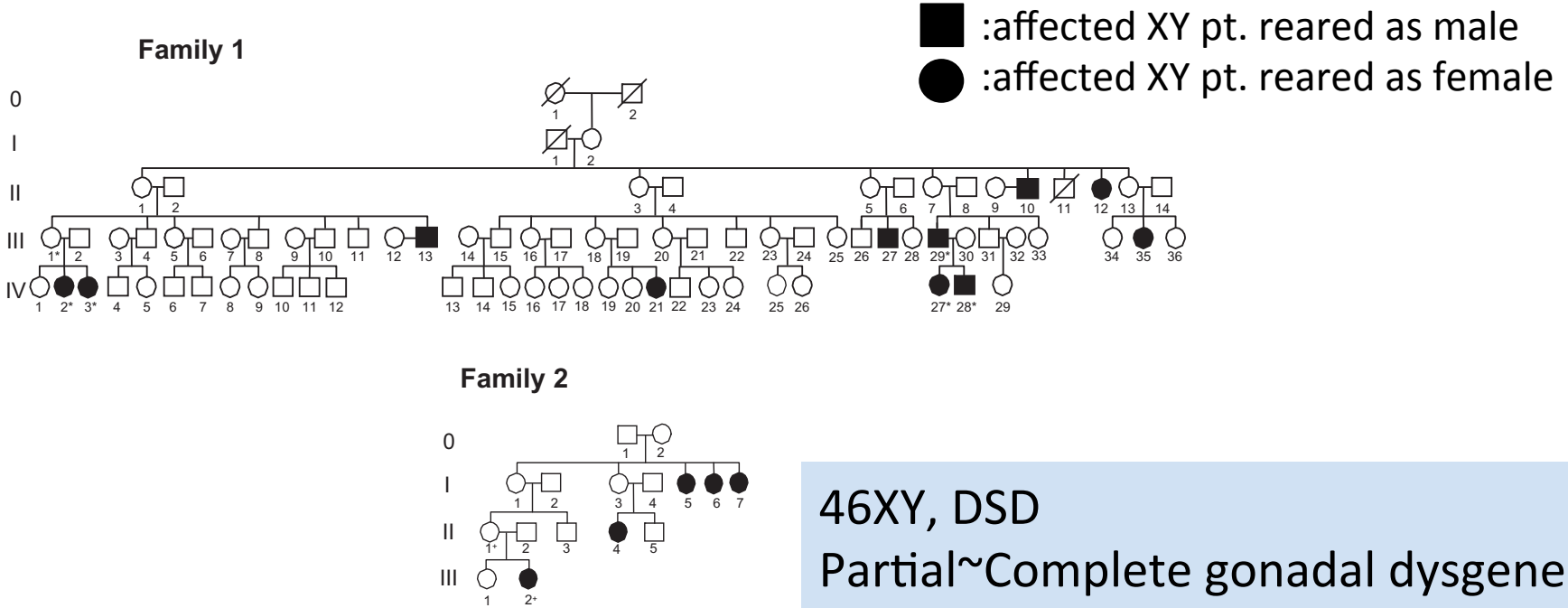


Figure 1. Pedigrees from Two Families of Interest Exhibiting Sex-Limited Autosomal-Dominant Mendelian Inheritance of 46,XY DSD
Shading indicates that the individual has 46,XY DSD or 46,XY complete gonadal dysgenesis. Circles indicate female sex of rearing, and squares indicate male sex of rearing. Asterisks (*) indicate individuals who were tested and found to have the c.IVS2-8T>A mutation. Plus signs (+) indicate individuals who were tested and found to have the p.Gly616Arg mutation. A strikethrough indicates a deceased individual.

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MAP3K1 と *Map3k4*

MAP3K1

- 46XY,DSD 患者の変異MAP3K1蛋白は、in vitroで下流分子(p38, MAPK1, MAPK3)のリン酸化を促進する
- *Map3k1* k/o mouse：性腺の表現型(-)

(Pearlman et al, 2011, AJHG)

- *MAP3K1*の機能獲得変異が精巣発生に影響を与える可能性がある

(Loke et al, 2014, HMG)

Map3k4

- *Map3k4* null mouseではGATA4のリン酸化が進まず、*Sry*の発現を低下させ、XY sex reversalを起こす

(Gierl et al, 2012, Dev Cell)

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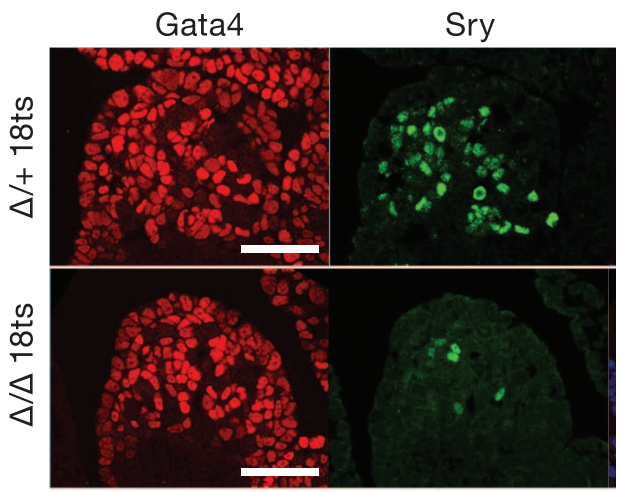
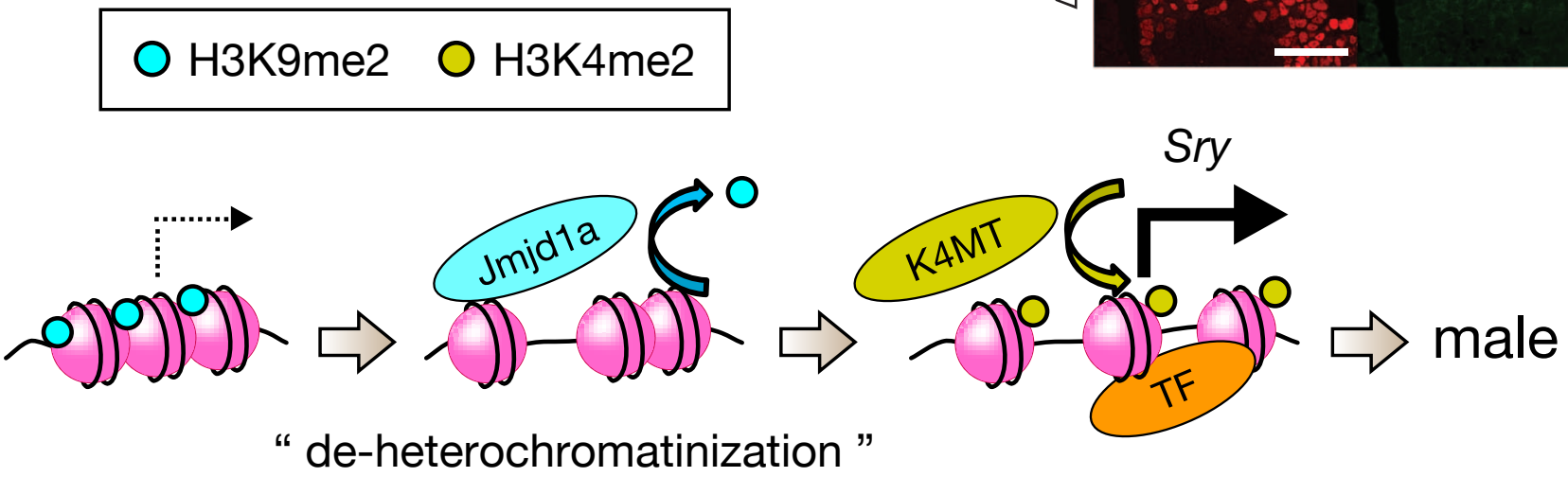
Epigenetic control of *Sry*

Epigenetic Regulation of Mouse Sex Determination by the Histone Demethylase Jmjd1a

Shunsuke Kuroki,[1] Shogo Matoba,[2] Mika Akiyoshi,[1] Yasuko Matsumura,[1] Hitoshi Miyachi,[1] Nathan Mise,[2]* Kuniya Abe,[2] Atsuo Ogura,[2] Dagmar Wilhelm,[3]† Peter Koopman,[3] Masami Nozaki,[4] Yoshiakira Kanai,[5] Yoichi Shinkai,[6]‡ Makoto Tachibana[1,7]‡

Kuroki et al, 2013, Science





“ de-heterochromatinization ”

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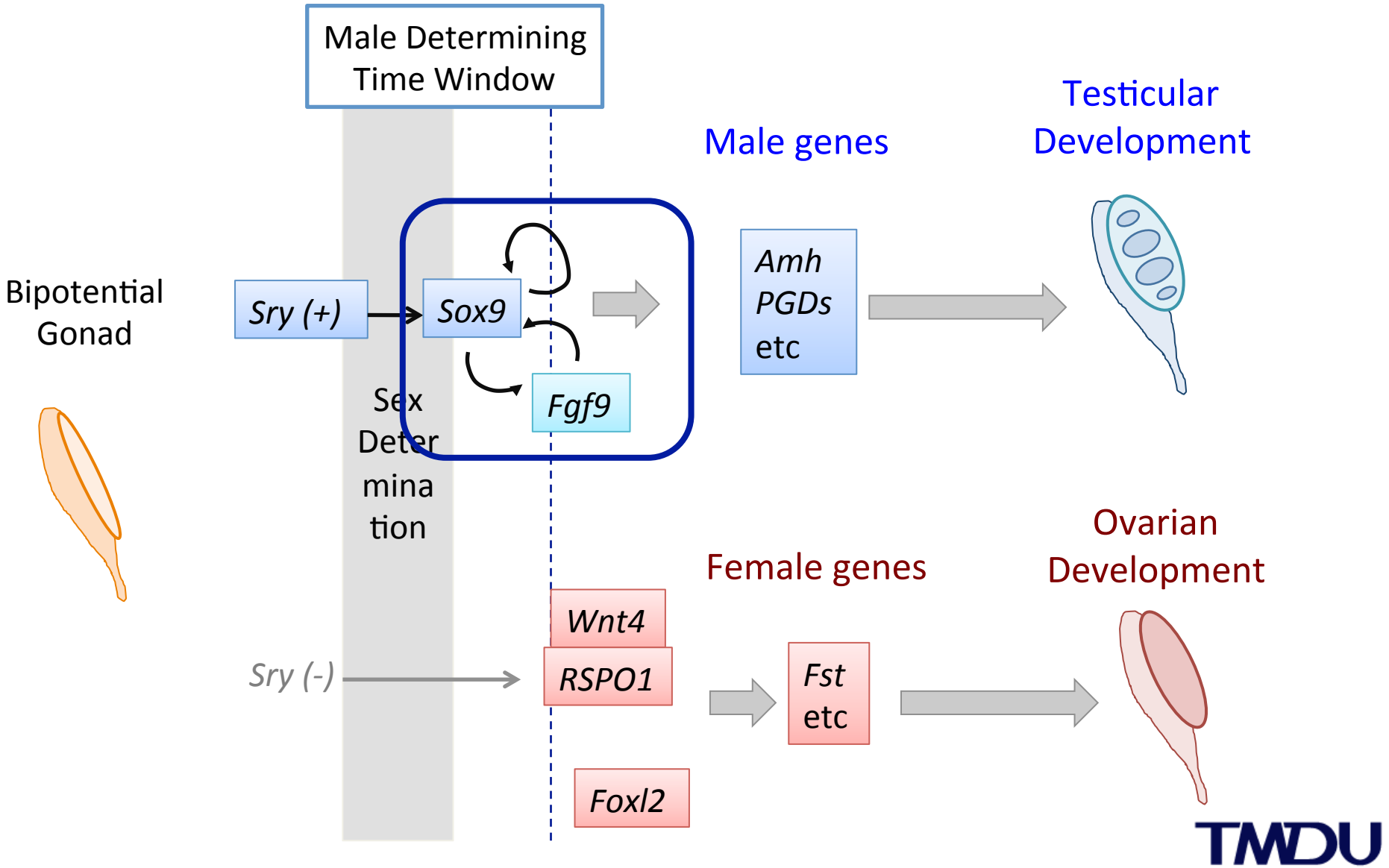
Sry制御のまとめ

- GATA4などを中心とした転写因子による制御
  - ただし性腺特異的エンハンサーは未同定
- Epigeneticな制御

性腺における性決定

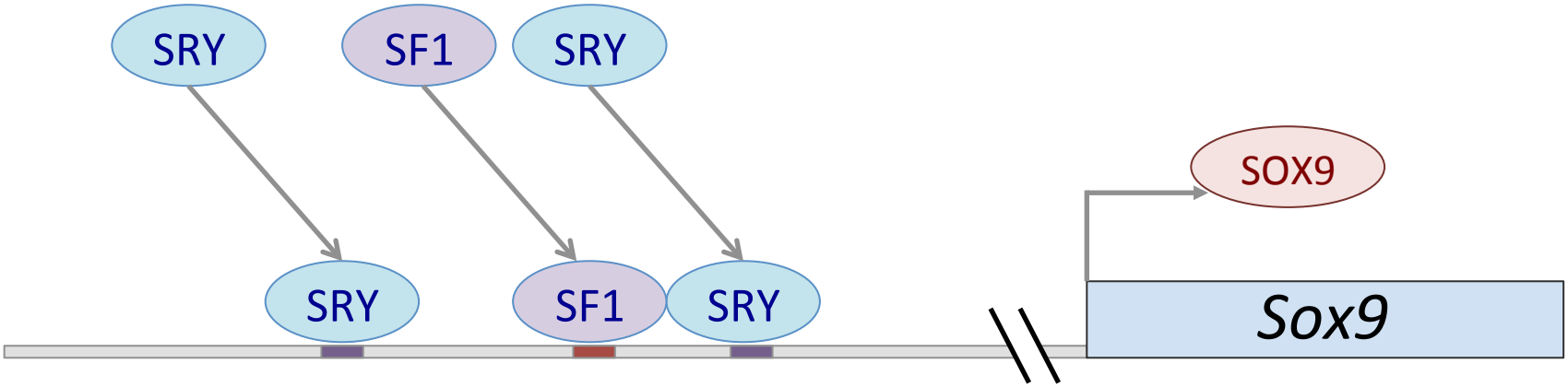

Male Determining Time Window
Male genes
Testicular Development
Bipotential Gonad
Sry (+)
Sox9
Fgf9
Amh
PGDs
etc
Sex Determination
Female genes
Ovarian Development
Wnt4
RSPO1
Sry (-)
Fst
etc
Foxl2

TESCO(Sox9 性腺特異的エンハンサー)の同定

(Sekido and Badge, 2008, ***Nature***)

TESCOの発見でわかったこと

- SRYは「転写因子」として直接*Sox9*の転写を活性化
- *Sox9*はSRYの（生理的意義が証明された）唯一の標的



TESCO(Sox9 性腺特異的エンハンサー)の同定

(Sekido and Badge, 2008, ***Nature***)

TESCOの発見でわかったこと

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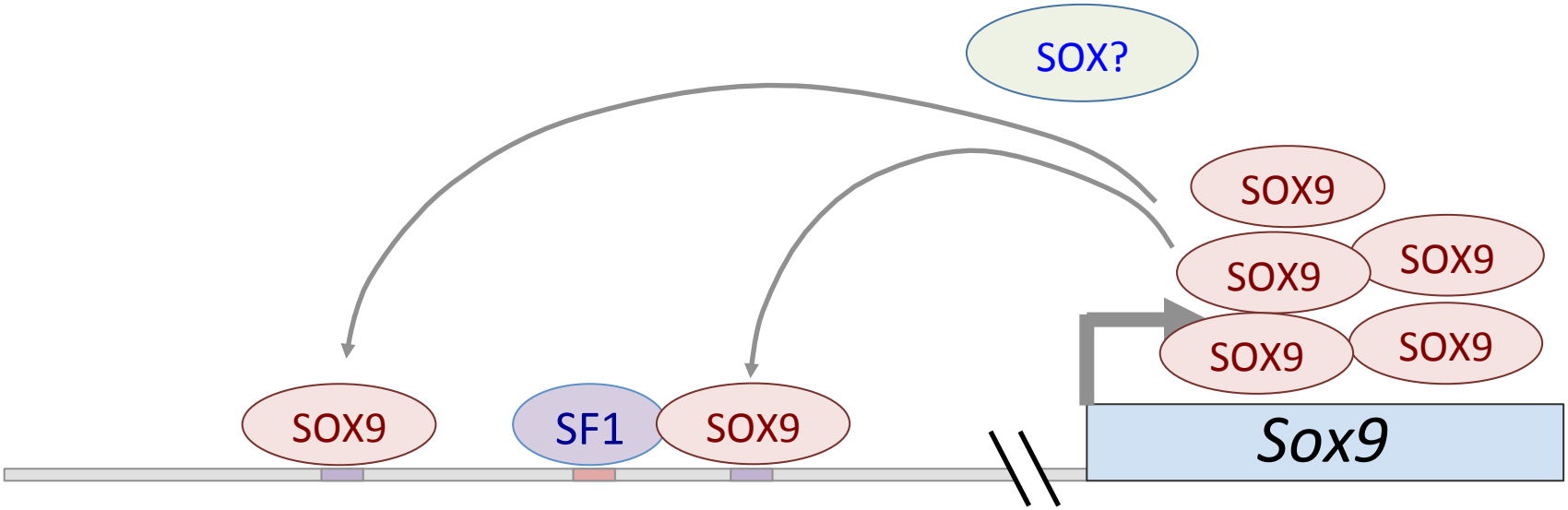
- *Sox9*はSRYの（生理的意義が証明された）唯一の標的
- SOX9が*Sox9*を正に制御する (positive feedback loop)

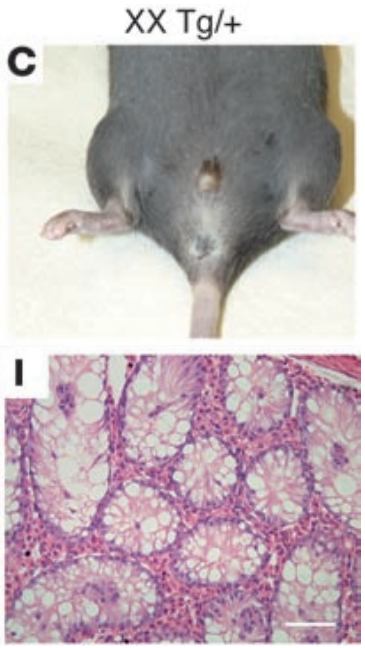


(*Journal of Clinical Investigation*, 2011)

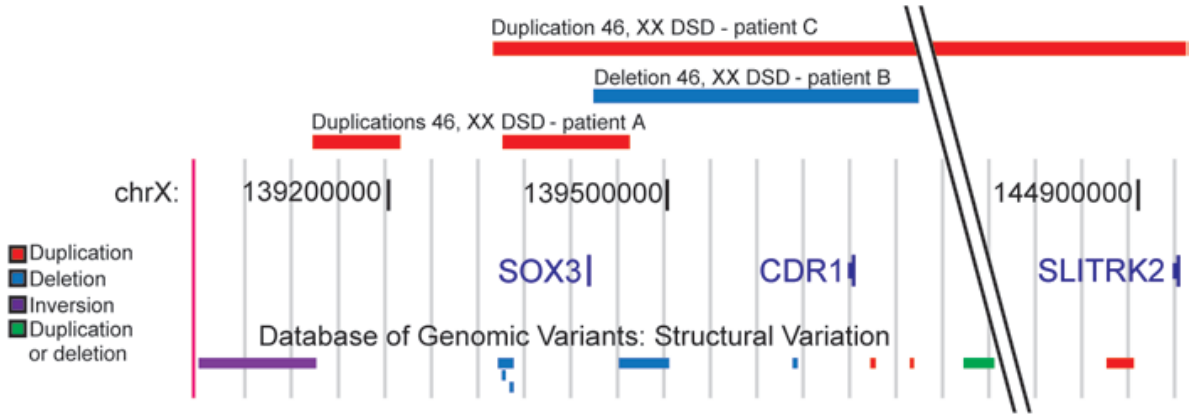
Research article

Identification of *SOX3* as an XX male sex reversal gene in mice and humans

Edwina Sutton,[1] James Hughes,[1] Stefan White,[2] Ryohei Sekido,[3] Jacqueline Tan,[2]
Valerie Arboleda,[4] Nicholas Rogers,[1] Kevin Knower,[5] Lynn Rowley,[2] Helen Eyre,[6] Karine Rizzoti,[3]
Dale McAninch,[1] Joao Goncalves,[7] Jennie Slee,[8] Erin Turbitt,[2] Damien Bruno,[2] Henrik Bengtsson,[9]
Vincent Harley,[5] Eric Vilain,[4] Andrew Sinclair,[2] Robin Lovell-Badge,[3] and Paul Thomas[1]



Sox3/SOX3 : X染色体に位置する、
*SRY*は*SOX3*に由来する
*SOX3*領域が重複する3例の46, XX DSDを報告



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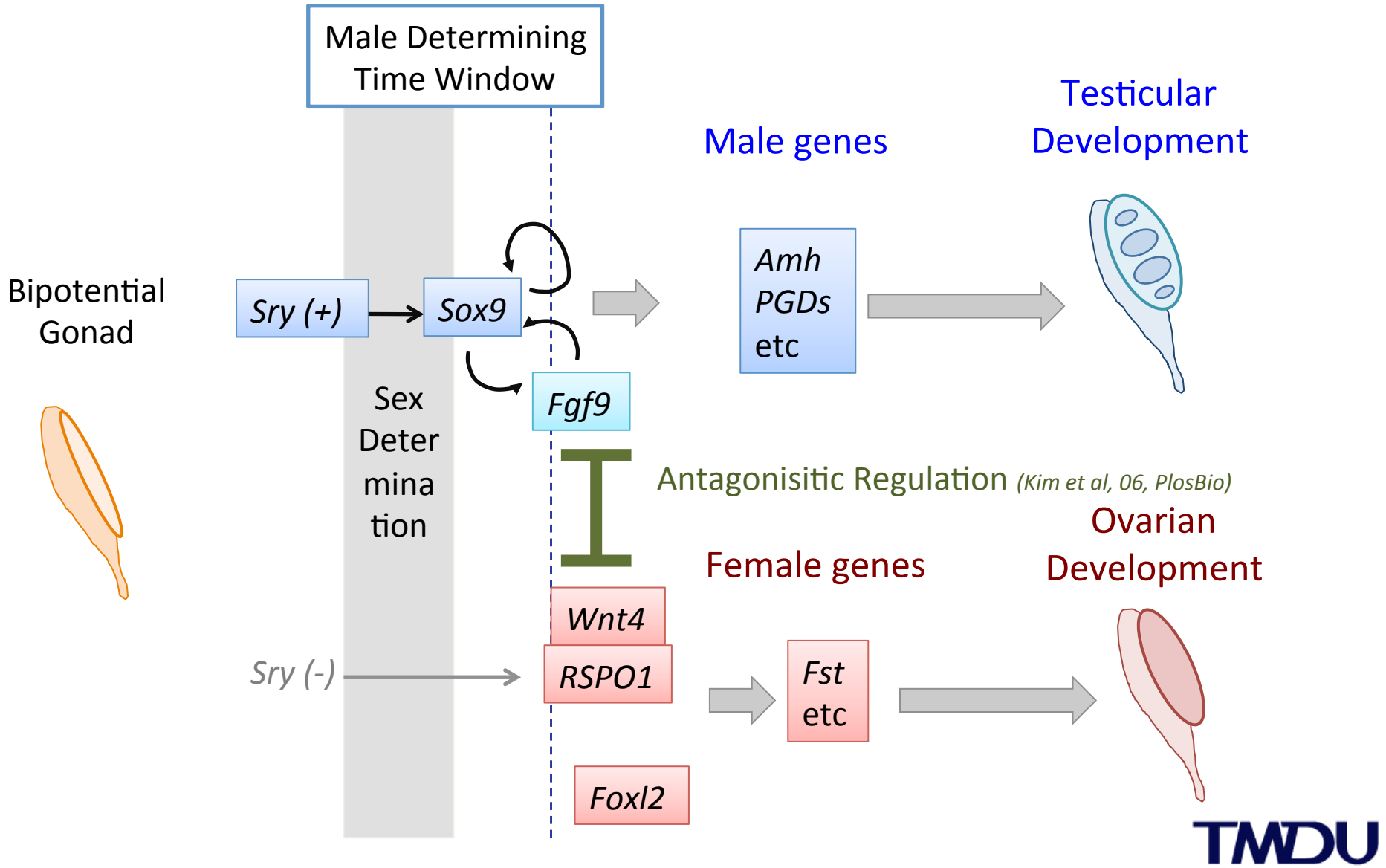
性腺における性決定



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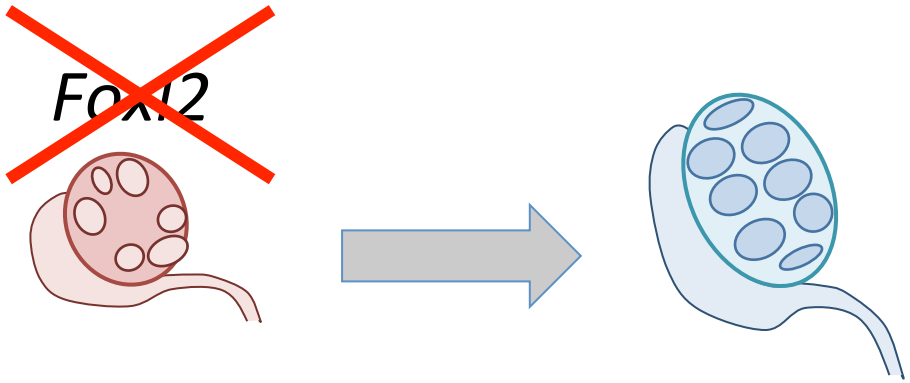
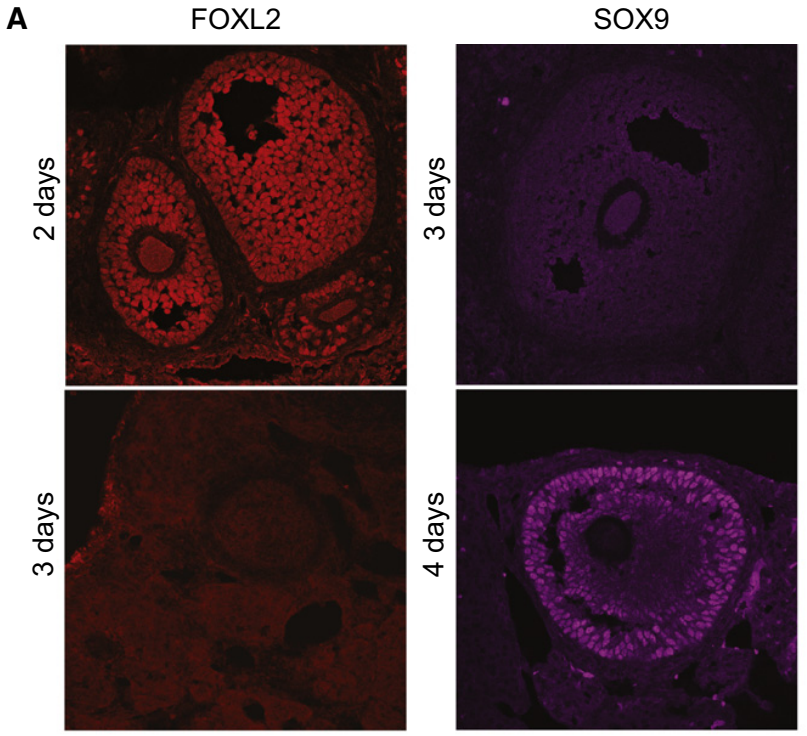
Somatic Sex Reprogramming of Adult Ovaries to Testes by FOXL2 Ablation

N. Henriette Uhlenhaut,[1,7] Susanne Jakob,[2] Katrin Anlag,[1] Tobias Eisenberger,[1] Ryohei Sekido,[2] Jana Kress,[1] Anna-Corina Treier,[1] Claudia Klugmann,[1] Christian Klasen,[1] Nadine I. Holter,[1] Dieter Riethmacher,[3] Günther Schütz,[4] Austin J. Cooney,[5] Robin Lovell-Badge,[2] and Mathias Treier[1,6,*]

Cell *139*, 1130–1142, December 11, 2009

成獣マウスの*Foxl2*をノックアウトすると、卵巣が精巣に分化転換する





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LETTER

doi:10.1038/nature10239

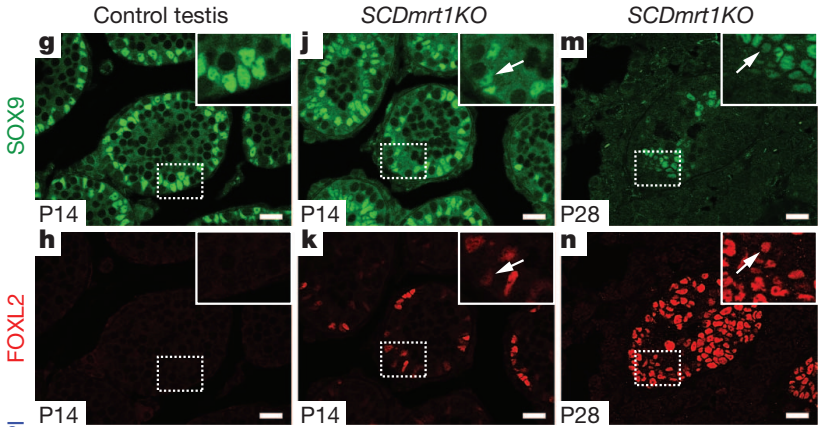
DMRT1 prevents female reprogramming in the postnatal mammalian testis

Clinton K. Matson[1,2], Mark W. Murphy[1], Aaron L. Sarver[3], Michael D. Griswold[4], Vivian J. Bardwell[1,2,3] & David Zarkower[1,2,3]

2011, Nature

Dmrt1

- 転写因子 (セルトリ細胞、germ cellに発現)
- メダカ、鶏では男性決定因子 (Matsuda et al, 2002, Nature, Smith et al, 2010, Nature)
- KOマウス: 精巣異形成、精子形成(-) (Raymond et al, 2000, GenDev)



XY gonad

Dmrt1 KO マウス:
成獣後に精巣が卵巣に分化転換する

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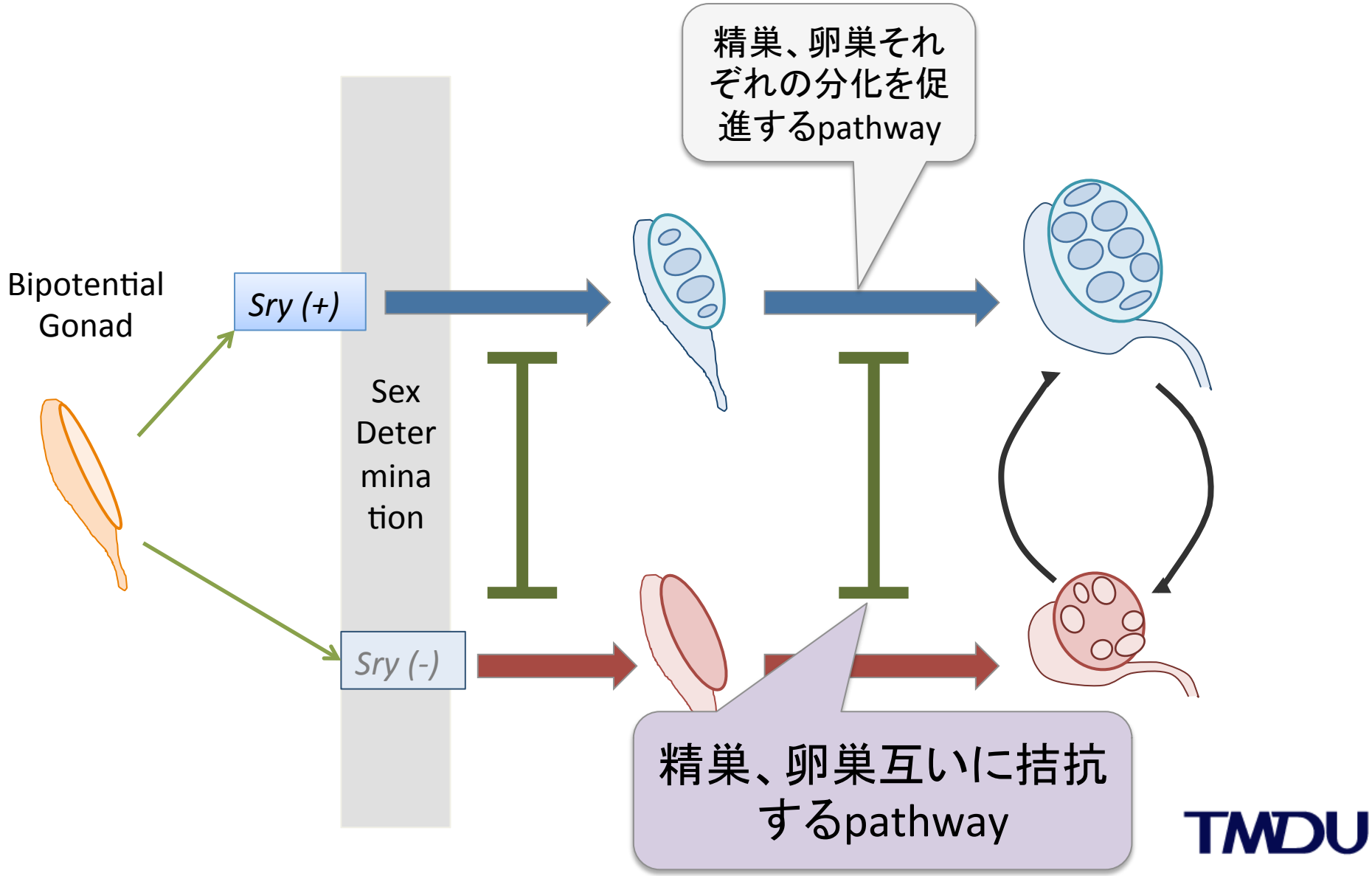
性腺における性の決定と維持



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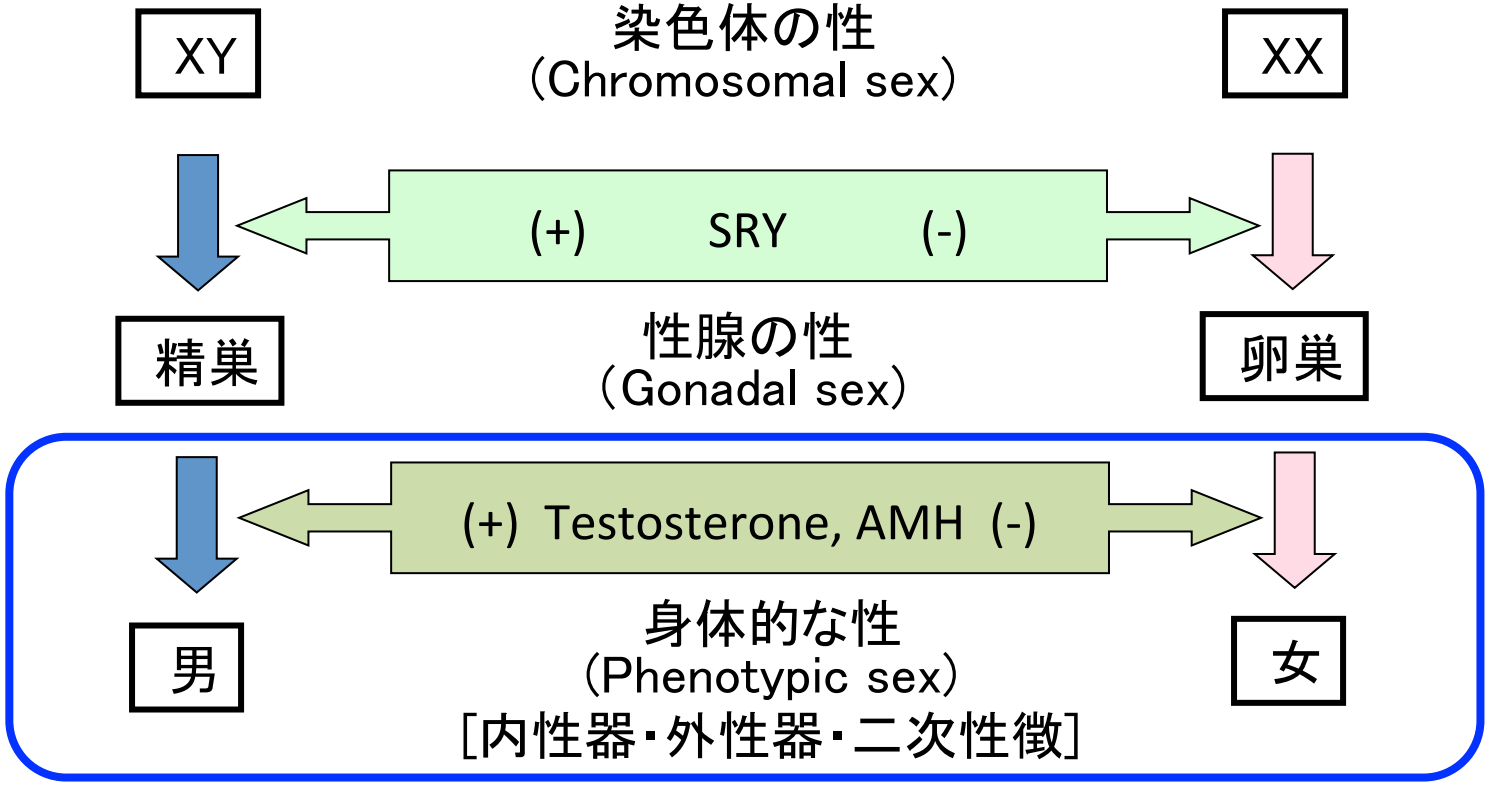
拮抗的作用の役割

- それぞれの性腺への分化を効果的に行う
- 「ゆらぎ」による可塑性の保持

ヒトの性分化



法律上の性
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IMAGe syndrome

(Intrauterine growth restriction, Metaphyseal dysplasia,
congenital Adrenal hypoplasia, Genital anomalies)

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CDKN1C

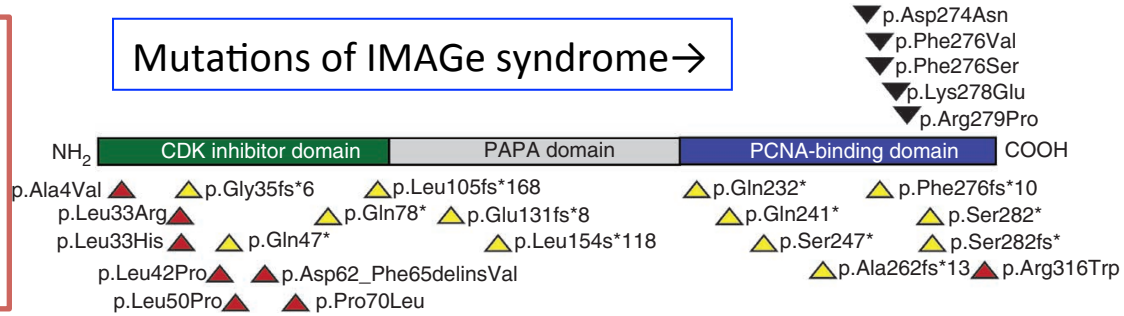

FIG. 1. a: Frontal view showing frontal bossing, depressed nasal bridge, and short nose. b: Profile showing simple, low-set cupped ears. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

CO 06 中島先生

- CDKN1C: 細胞周期に重要な役割を果たす
- IMAGeの変異: ユビキチン化が障害される
  >蛋白の安定性増加=機能獲得変異
  ←→Beckwith-Wiedemann Synd. の変異

TMDU

今日の内容

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  - *SryとEif2s3y*
- 性腺分化
  - 精巣分化
    - SRY制御、TESCOとSOX分子
  - 精巣、卵巣分化cascadeの拮抗的な作用
- 性腺分化以降
  - IMAGe 症候群

“Minimalist Y”

新たなDSD原因遺伝子の発見へ

「ゆらぐ」性

ご清聴ありがとうございました