

# Model organisms and developmental biology

仲寒冰

[zhonghb@sustc.edu.cn](mailto:zhonghb@sustc.edu.cn)

# Determination of the sexual phenotype

# Biological sex VS Gender

- Biological sex identifies a person as either female, male, or intersex. It is determined by a person's sexual anatomy, chromosomes, and hormones. Biological sex is often simply referred to as "sex."
- Gender is a person's self representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation (FDA).

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### BASIC INFORMATION

Birth Date December 6

Birth Year 1976

Gender

Custom ▾

Gender

 Friends ▾

A

Agender

Androgynous

Androgynous

Male

Male to Female

Pangender

Trans

Trans Female

Trans Male

Trans Male

 Friends

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# California law allows transgender students to pick bathrooms, sports teams they identify with



Gov. Jerry Brown gives his State of the State address at the Capitol in Sacramento, Calif., Thursday, Jan. 23, 2013.  
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**SACRAMENTO, CALIFORNIA** | California on Monday became the first state to enshrine certain rights for transgender kindergarten-through-12th grade students in state law, requiring public schools to allow those students access to whichever restroom and locker room they want.

## VIEWPOINT

# The Olympic Games and Athletic Sex Assignment

**Myron Genel, MD**

Yale Child Health Research Center, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

**Joe Leigh Simpson, MD**

Herbert Wertheim College of Medicine, Florida International University, Miami; and March of Dimes Foundation, White Plains, New York, New York.

**Albert de la Chapelle, MD, PhD**

Human Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, Columbus.

**At least 2 women athletes** subjected to intense media scrutiny in the past several years—Caster Semenya and Dutee Chand—are likely to attract additional attention in the forthcoming 2016 Summer Olympic Games in Brazil. Both women had pivotal, although inadvertent, involvement in the evolution of the currently suspended **hyperandrogenism (testosterone)** policies of the International Olympic Committee (IOC) and of the International Association of Athletic Federations (IAAF). Competitors had raised concerns regarding their “masculine” appearance and eligibility, and these concerns were further amplified by an intrusive media and social media.

Semenya emerged suddenly at the IAAF’s 2009 World Games in Berlin, where she easily won the 800-meter event—even though her time was far from the world record. Her appearance prompted complaints from her competitors and provoked her suspension pending thorough medical evaluation. Upon return to competition several months later, Semenya’s appearance was unchanged and she remained highly competitive but no longer excelled. Ultimately her case contributed to development of the so-called **hyperandrogenism policy**, which established a **testosterone eligibility threshold of 10 nmol/L (288 ng/dL)** for female athletes, unless the athlete is demonstrated to be **insensitive to**

serum testosterone levels “enjoy such a substantial performance advantage”<sup>1</sup> that their participation is unfair. Although the IOC was not a formal party to the dispute, this ruling effects the IOC as well as other sport-specific athletic federations that had adopted the hyperandrogenism policies.

Subsequently, Chand qualified for the Indian Olympic team on June 25, 2016, with times just below the 100-meter Olympic qualifying threshold of 11.32 seconds, becoming the first Indian woman in 36 years to qualify in that event. She is unlikely to win a medal—her best time of 11.24 seconds would have placed 15th in the London semifinals. On the other hand, Semenya has had an excellent pre-Olympic year, setting world best times for the year in both the 400-meter and 800-meter events, the most recent was an 800-meter time of 1 minute, 55.43 seconds, just under her breakthrough victory time 7 years earlier. Semenya’s reestablished preeminence was ascribed by her coach to more rigorous and consistent training. In Rio, should she come close to replicating her recent performances, the intense scrutiny from the media and complaints from other athletes likely will resume. Some will surely call for restoration of the testosterone threshold.

This is just the latest chapter of a saga that has extended over 80 years,<sup>2</sup> in part reflecting societal changes fostering greater participation of women in competitive



**U.S. Department of Justice**  
*Civil Rights Division*

**U.S. Department of Education**  
*Office for Civil Rights*



May 13, 2016

Dear Colleague:

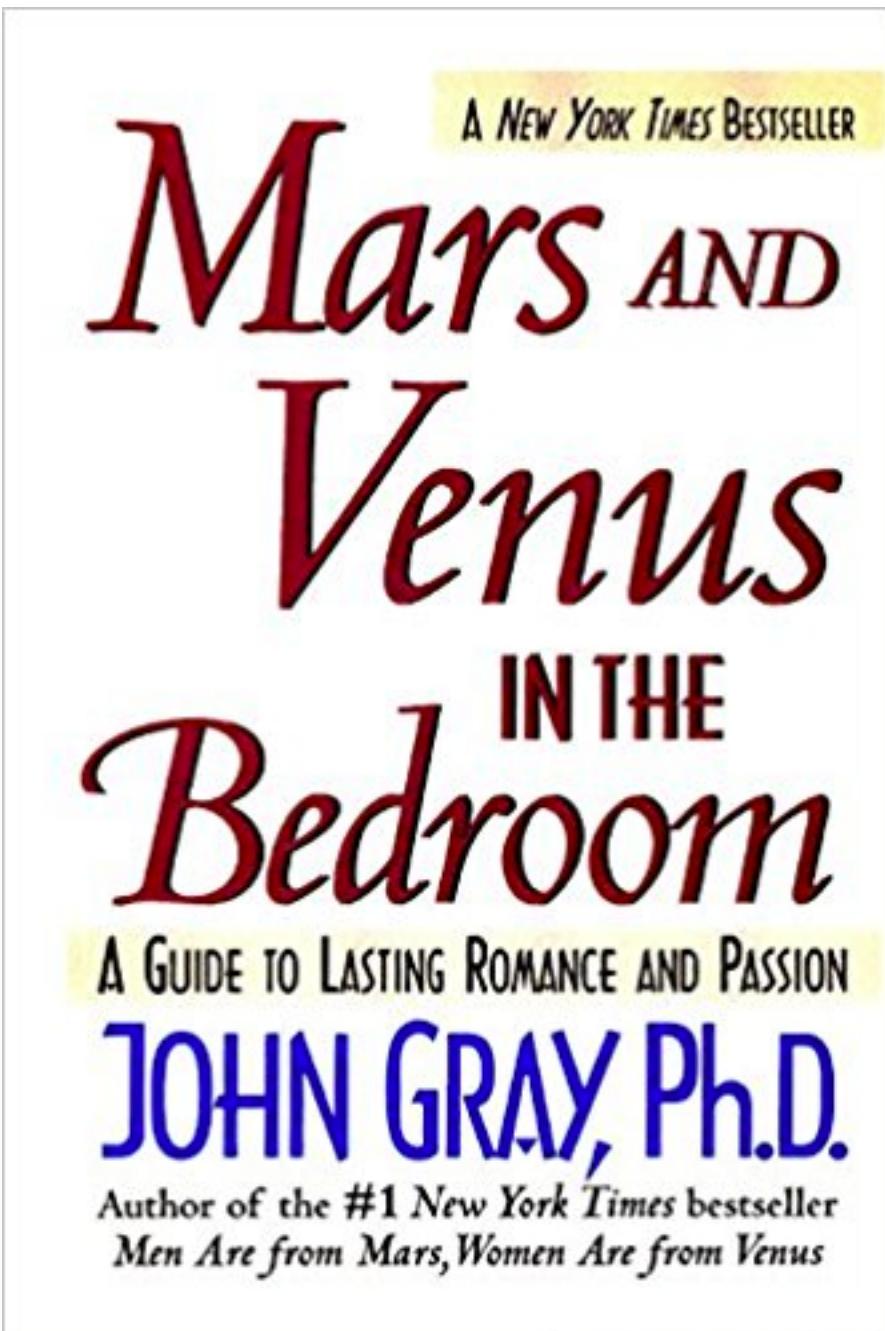
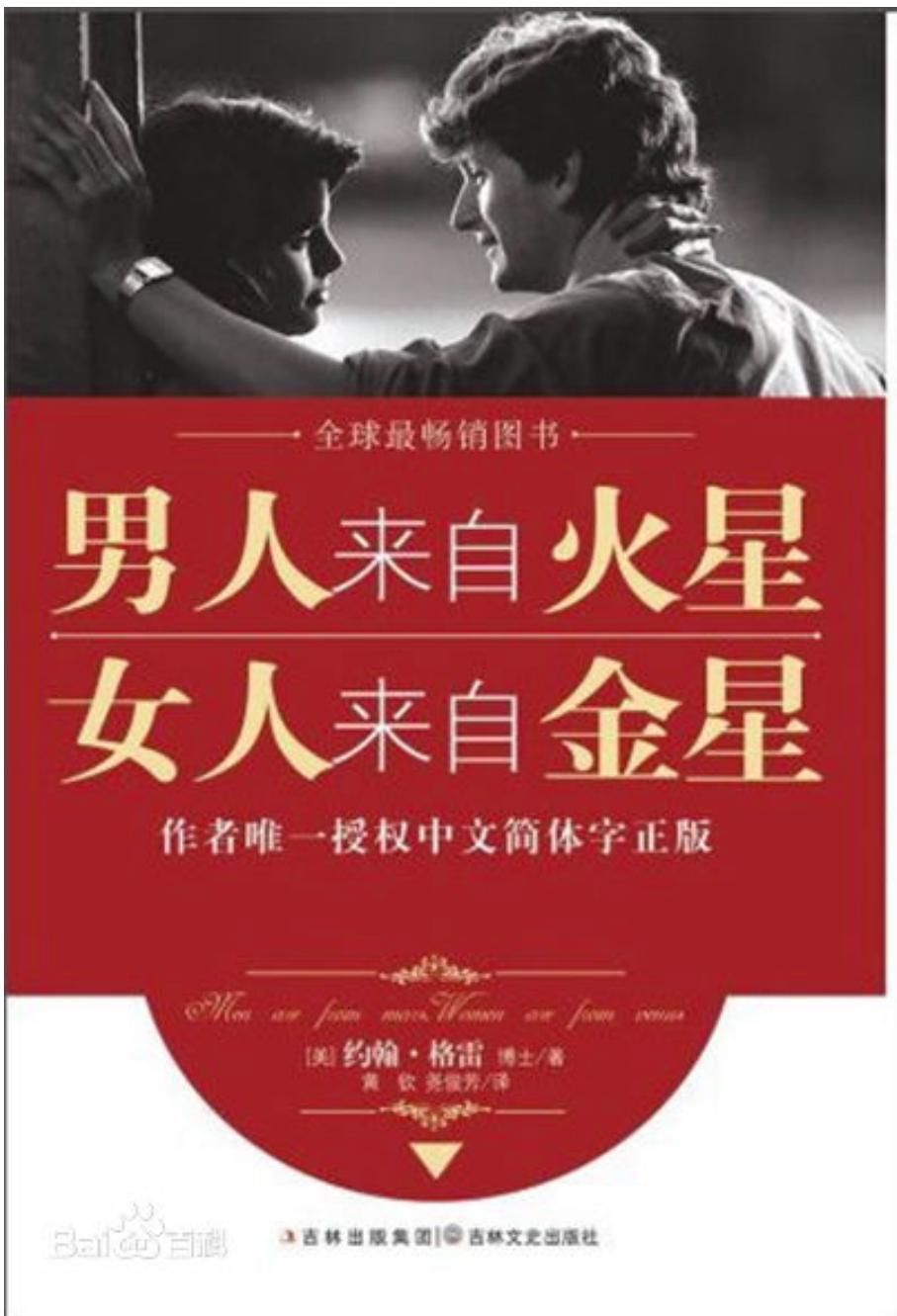
Schools across the country strive to create and sustain inclusive, supportive, safe, and nondiscriminatory communities for all students. In recent years, we have received an increasing number of questions from parents, teachers, principals, and school superintendents about civil rights protections for transgender students. Title IX of the Education Amendments of 1972 (Title IX) and its implementing regulations prohibit sex discrimination in educational programs and activities operated by recipients of Federal financial assistance.<sup>1</sup> This prohibition encompasses discrimination based on a student's gender identity, including discrimination based on a student's transgender status. This letter summarizes a school's Title IX obligations regarding transgender students and explains how the U.S. Department of Education (ED) and the U.S. Department of Justice (DOJ) evaluate a school's compliance with these obligations.

ED and DOJ (the Departments) have determined that this letter is *significant guidance*.<sup>2</sup> This guidance does not add requirements to applicable law, but provides information and examples to inform recipients about how the Departments evaluate whether covered entities are complying with their legal obligations. If you have questions or are interested in commenting on this guidance, please contact ED at [ocr@ed.gov](mailto:ocr@ed.gov) or 800-421-3481 (TDD 800-877-8339); or DOJ at [education@usdoj.gov](mailto:education@usdoj.gov) or 877-292-3804 (TTY: 800-514-0383).

Accompanying this letter is a separate document from ED's Office of Elementary and Secondary Education, *Examples of Policies and Emerging Practices for Supporting Transgender Students*. The examples in that document are taken from policies that school districts, state education agencies, and high school athletics associations around the country have adopted to help ensure that transgender students enjoy a supportive and nondiscriminatory school environment. Schools are encouraged to consult that document for practical ways to meet Title IX's requirements.<sup>3</sup>

### **Terminology**

- Gender identity* refers to an individual's internal sense of gender. A person's gender identity may be different from or the same as the person's sex assigned at birth.



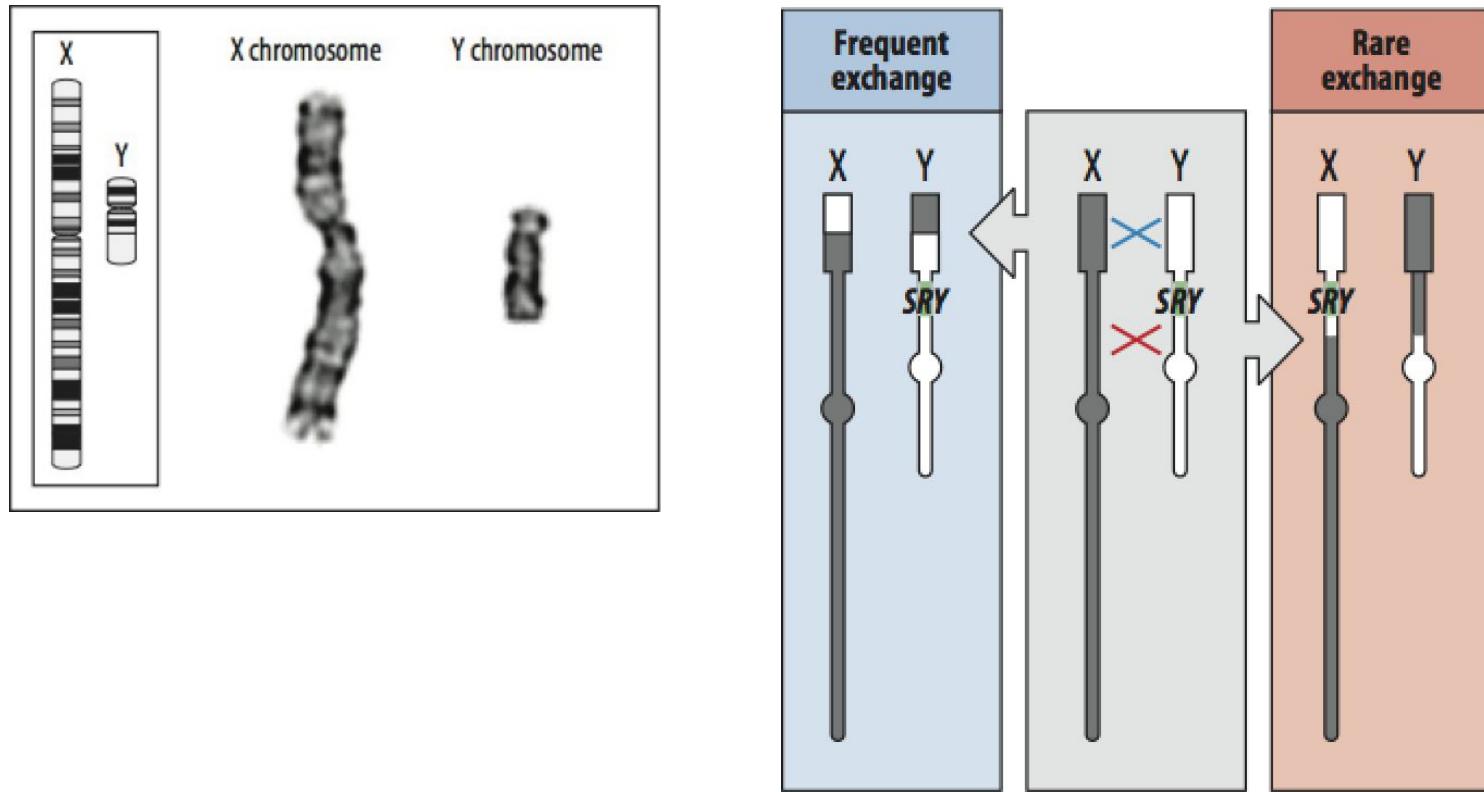
# Sex determination

- **Primary sex determination** is the determination of gonads – ovaries or testes.

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- **Secondary sex determination** is the determination of the male or female phenotype by the hormones produced by the gonads.

# The primary sex-determining gene in mammals is on the Y chromosome



# A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif

Andrew H. Sinclair, Philippe Berta<sup>†</sup>, Mark S. Palmer, J. Ross Hawkins,  
Beatrice L. Griffiths, Matthijs J. Smith, Jamie W. Foster<sup>†</sup>, Anna-Maria Frischauf,  
Robin Lovell-Badge<sup>†</sup> & Peter N. Goodfellow

Human Molecular Genetics Laboratory, Imperial Cancer Research Fund, PO Box 123, Lincoln's Inn Fields, London, WC2A 3PX, UK

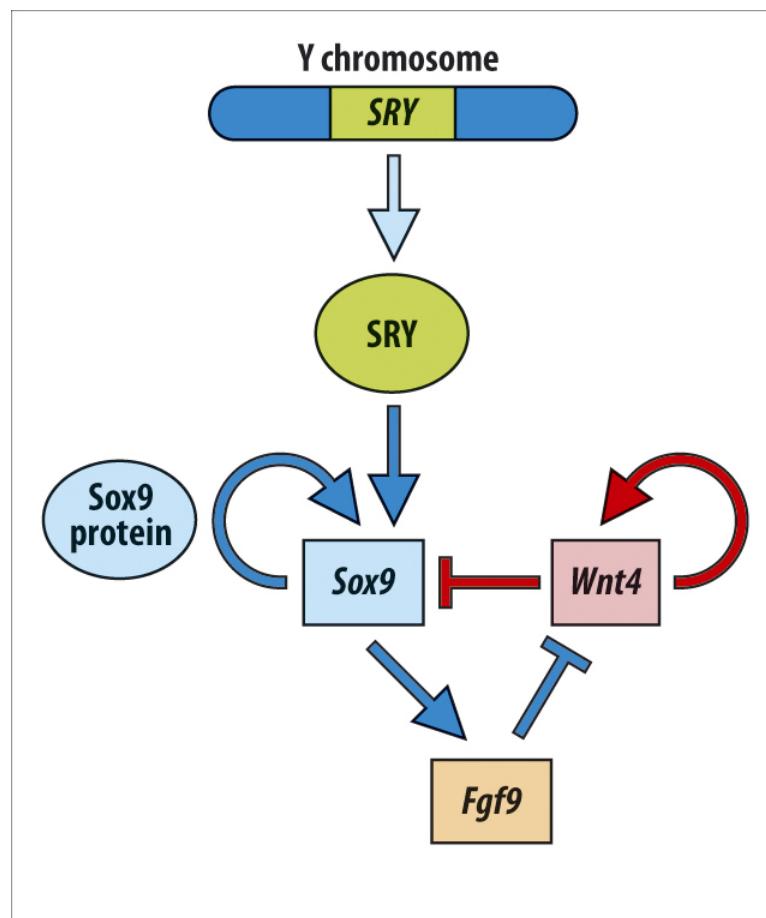
<sup>†</sup> Laboratory of Eukaryotic Molecular Genetics, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

A search of a 35-kilobase region of the human Y chromosome necessary for male sex determination has resulted in the identification of a new gene. This gene is conserved and Y-specific among a wide range of mammals, and encodes a testis-specific transcript. It shares homology with the mating-type protein, Mc, from the fission yeast *Schizosaccharomyces pombe* and a conserved DNA-binding motif present in the nuclear high-mobility-group proteins HMG1 and HMG2. This gene has been termed *SRY* (for sex-determining region Y) and proposed to be a candidate for the elusive testis-determining gene, *TDF*.

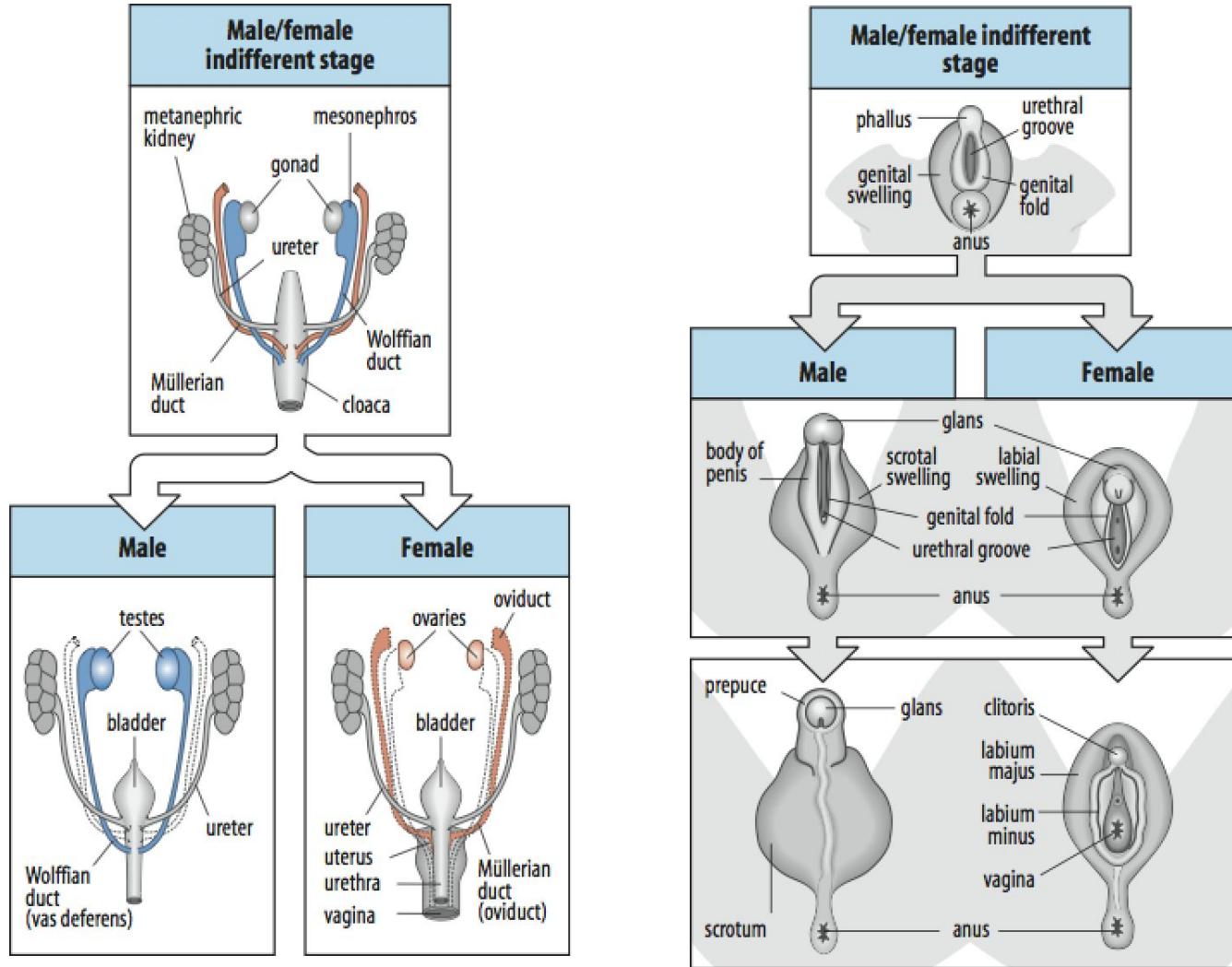
a chromosome walk initiated 130-kilobase (kb) proximal to the CpG-rich region, and subsequently named *ZFY* (ref. 10). The sequences present in a particular XX male (LGL203) and absent in an XY female (WHT1013) were used to define the position of *TDF* to within an interval of 140 kb and *ZFY* was isolated from this region. Other evidence consistent with identity between *ZFY* and *TDF* included the finding of *ZFY*-related sequences on the Y chromosome of all eutherian mammals tested; the presence of a *ZFY*-related gene, *Zfy-1*, in *Sxr'* (the smallest part of the mouse Y chromosome known to be sex-determining) and the structure of the *ZFY*-encoded protein, which has many features in common with transcription factors<sup>10,11</sup>. But there were several unexpected findings: first, *ZFX*—a homologue of *ZFY*—was found on the eutherian X chromosome and shown in humans to escape inactivation<sup>11,12</sup>; and second, in metatherian mammals (marsupials), *ZFY*-related sequences were found not on the Y or X chromosome, but on the autosomes<sup>13</sup>.

Two recent reports have further questioned the role of *ZFY*

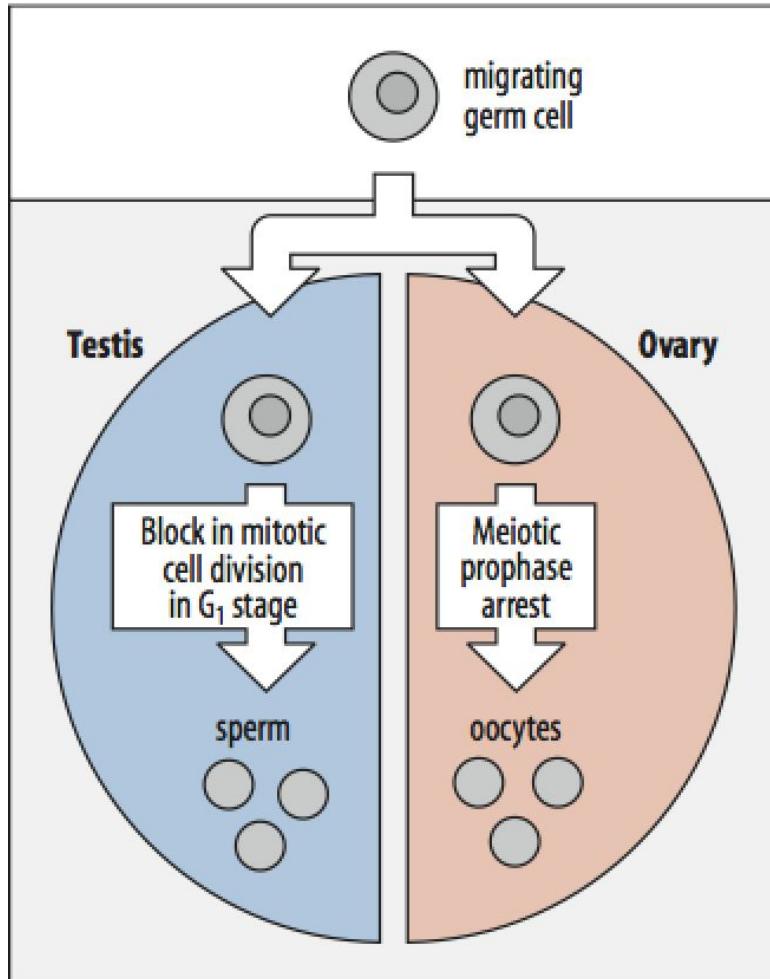
# Genetic interactions that determine the sex of the gonads in mammals



# Development of the gonads and related structures in mammals



# Determination of germ-cell sex depends on both genetic constitution and intercellular signals

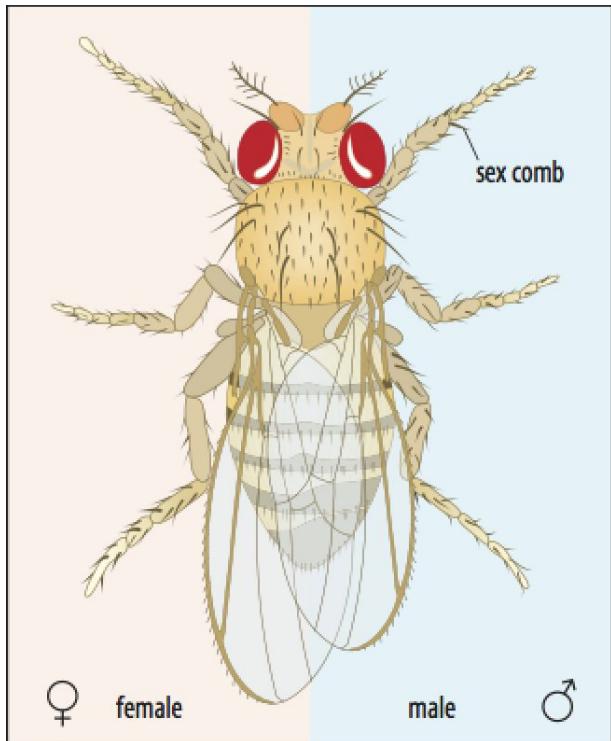


Strongly influenced by the signals they received when they become part of a gonad.

Germ cells from male mouse embryos can develop into oocyte rather than sperm if grafted into female embryonic gonads and vice versa.

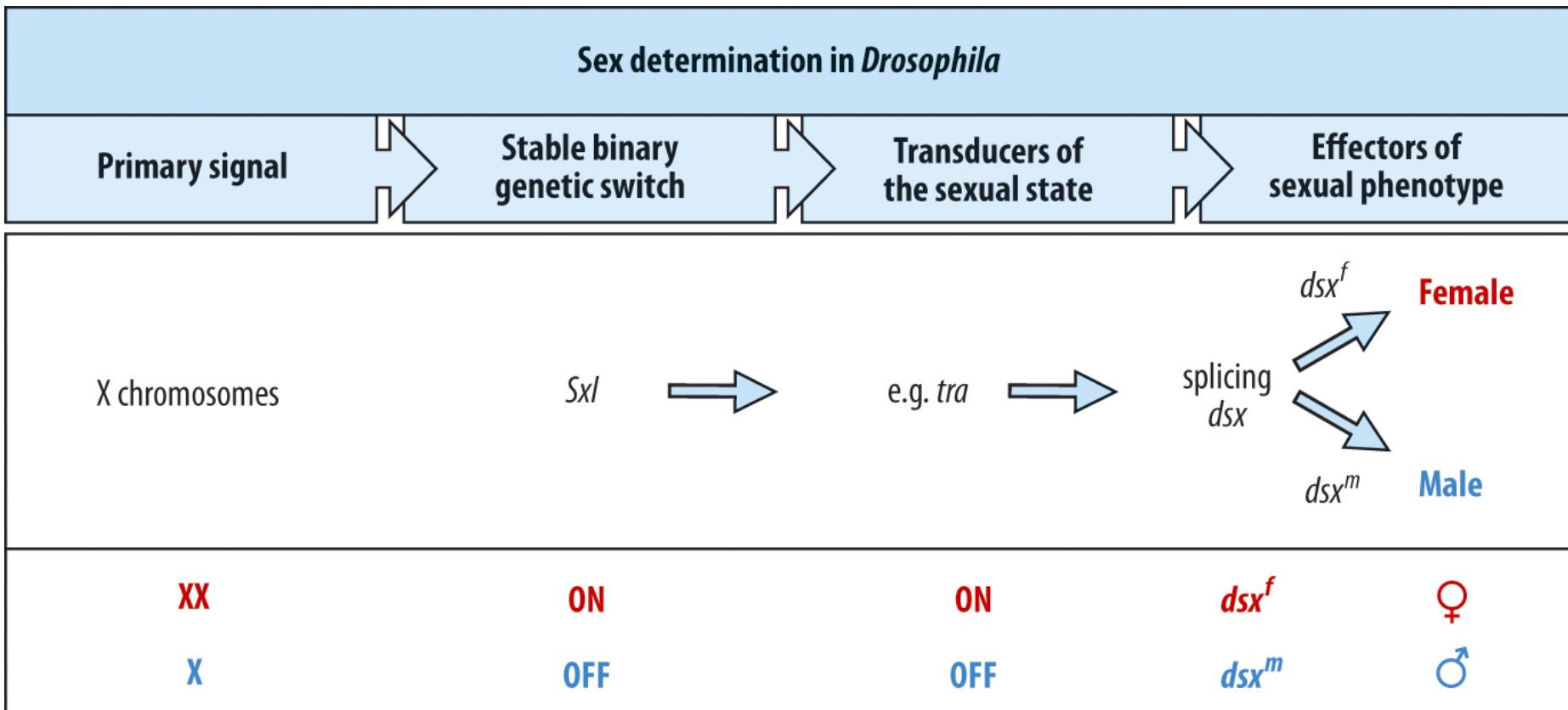
So there could be a “Y” oocyte.

In *Drosophila*, the primary sex is determined by the number of X chromosomes

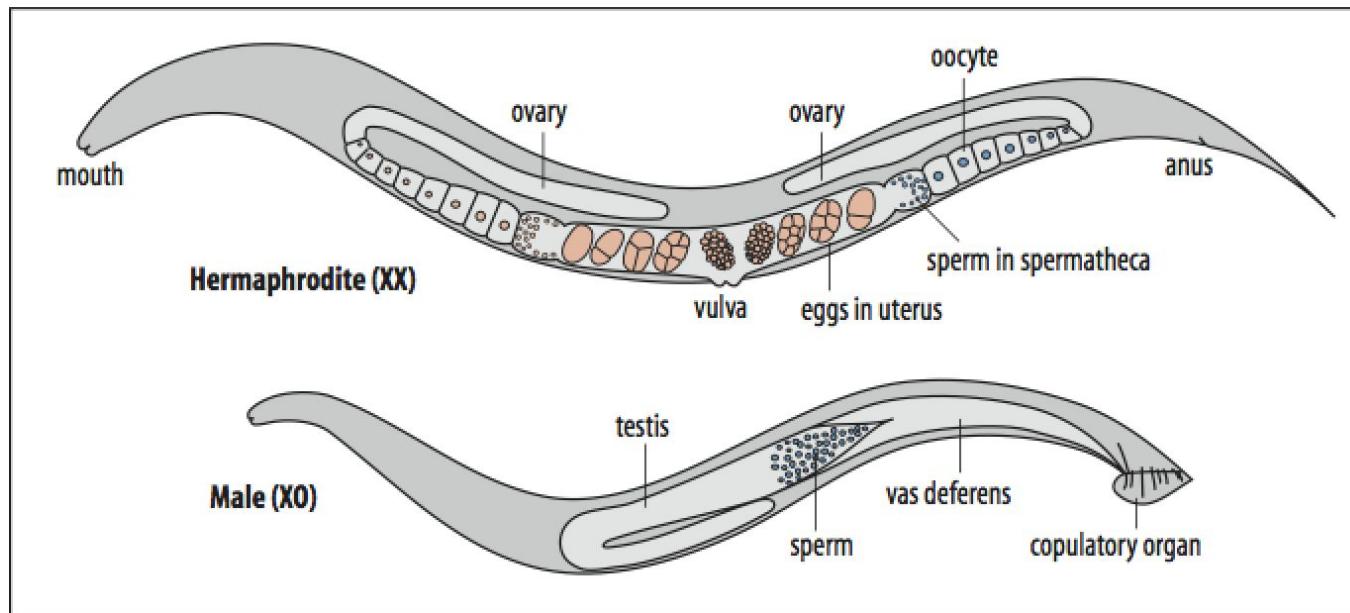


XY, male  
XX, female  
XXY, female

In *Drosophila*, the primary sex is determined by the number of X chromosomes



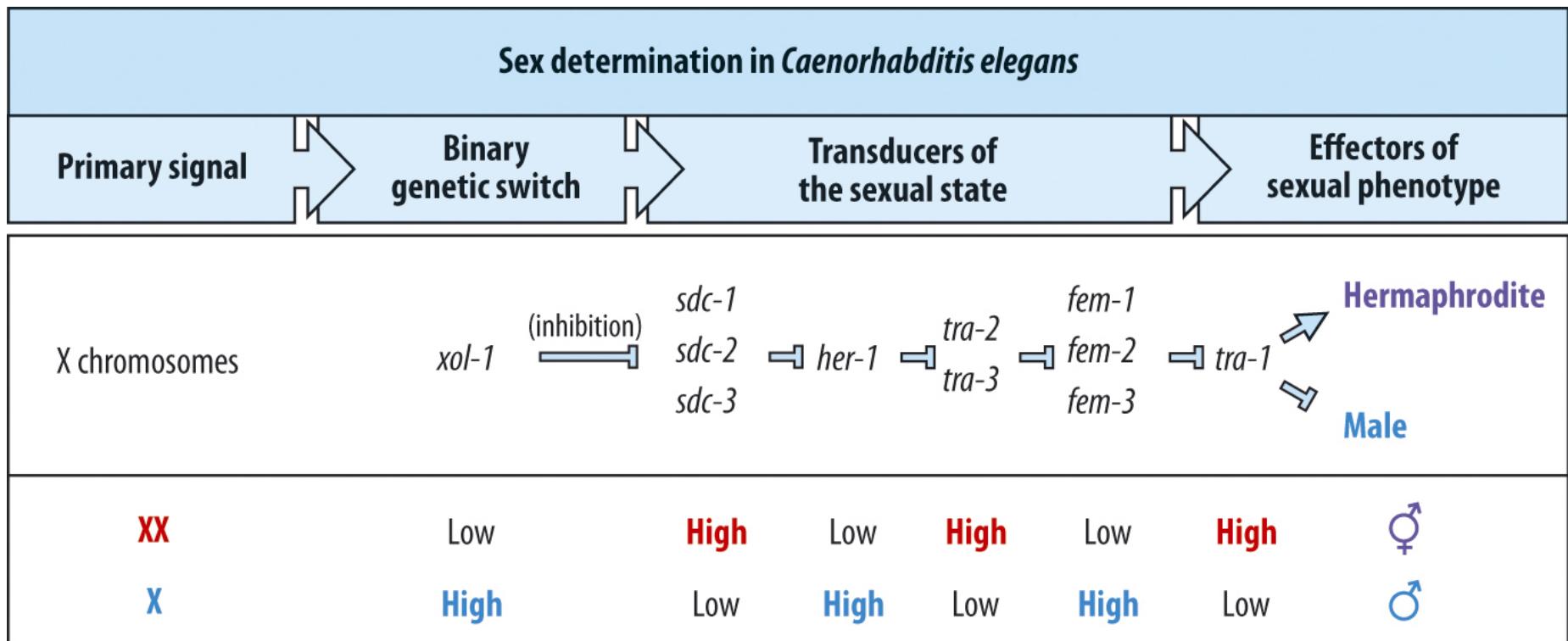
In *C.elegans*, the primary sex is determined by the number of X chromosomes



XX, hermaphrodite

XO, male

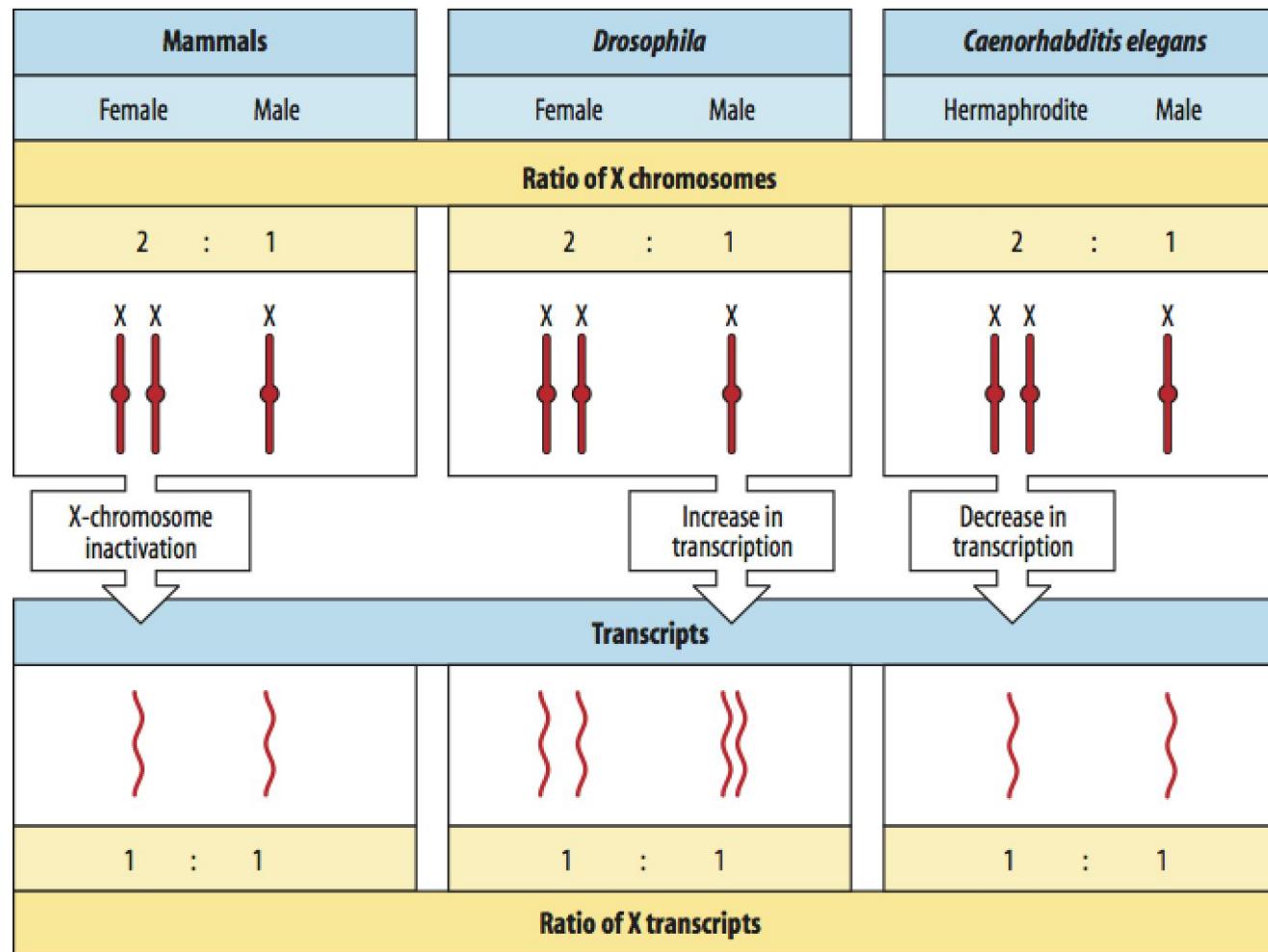
In *C.elegans*, the primary sex is determined by the number of X chromosomes



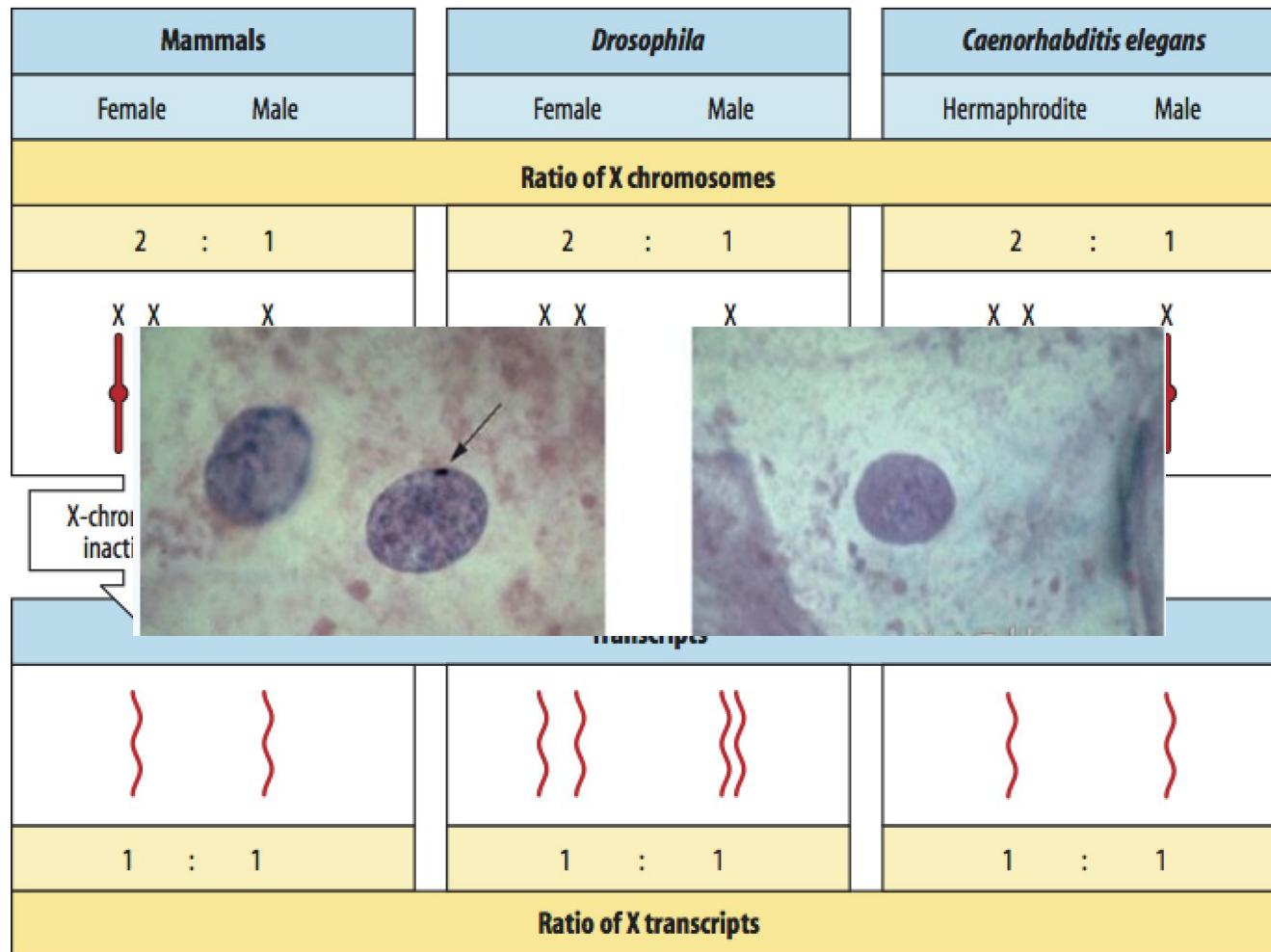
XX, hermaphrodite

XO, male

# Various strategies are used for dosage compensation of X-linked genes



# Various strategies are used for dosage compensation of X-linked genes



# Tortoiseshell and tortoiseshell cat

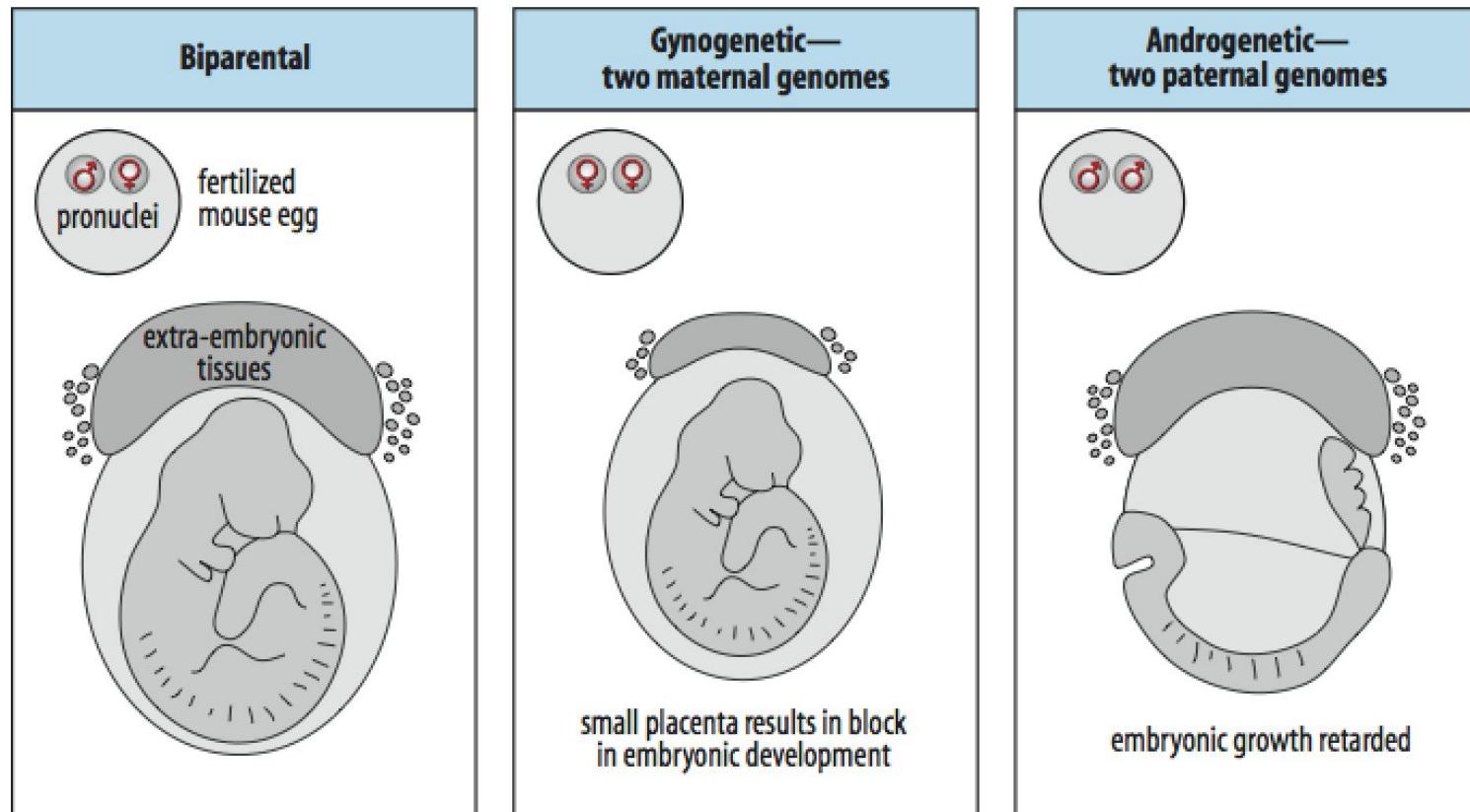


# Genomic imprinting

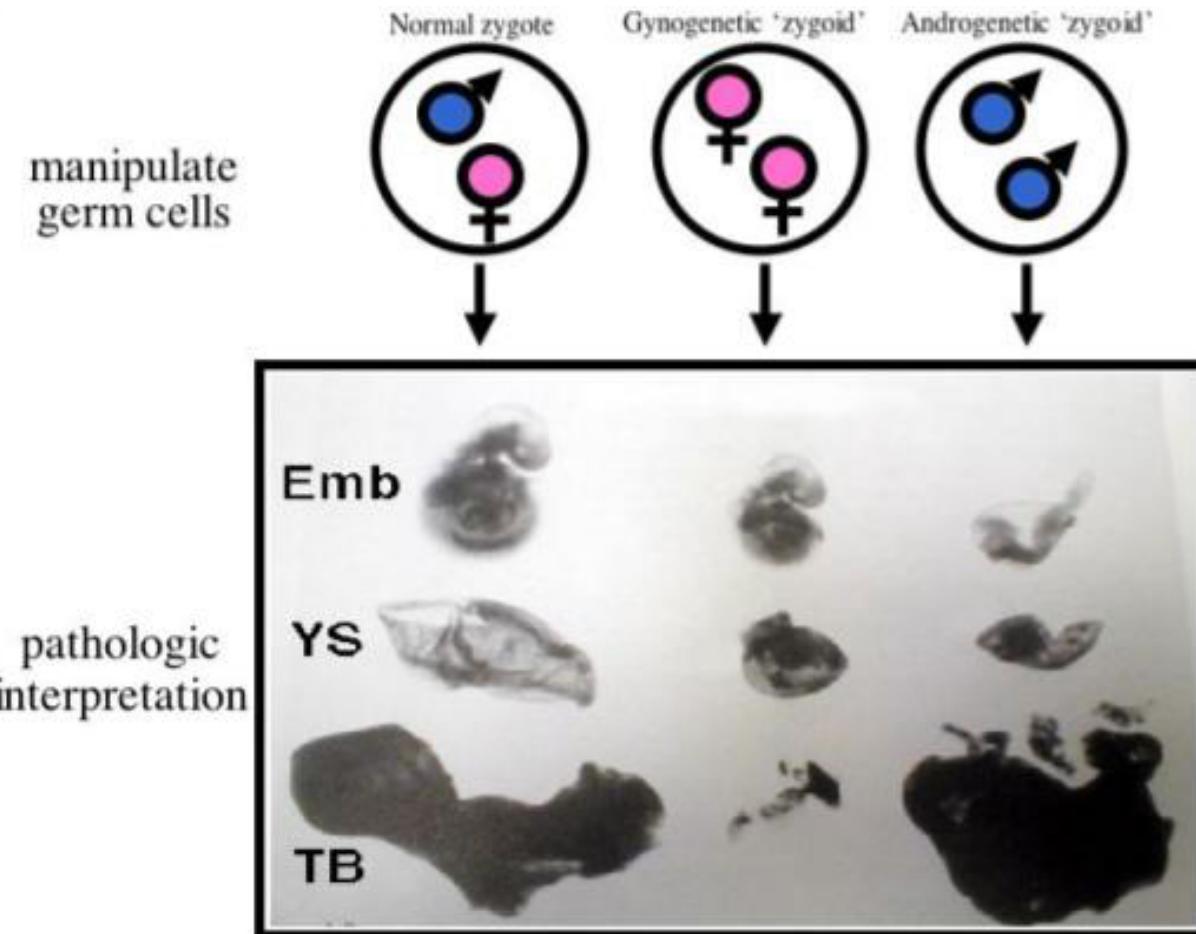
# Genomic imprinting

- Certain genes are switched off in either the egg or the sperm during their development and remain silenced in the genome of the early embryo / individual animal.
- Androgenetic embryos, two paternal genomes. Extra-embryonic tissues are normal. Embryo itself is not.
- Gynogenetic embryos, two maternal genomes. Extra-embryonic tissues, placenta and yolk sac are abnormal. Embryo is relative normal.
- So mammals can not be naturally produced parthenogenetically.

# Paternal and maternal genomes are both required for normal mouse development



# Paternal and maternal genomes are both required for normal mouse development

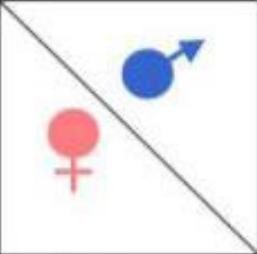
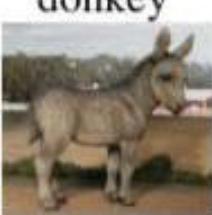
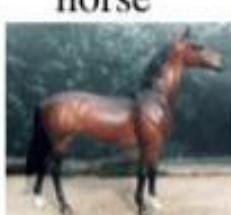
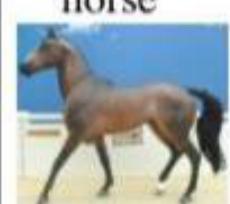
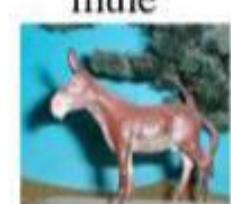
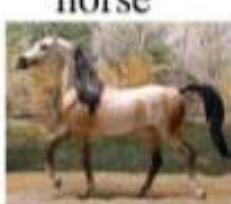


Surani, McGrath and Solter, 1984-1987

TB, trophoblast

# An ancient example

駝子

	 donkey	 horse
 donkey	 donkey	 hinny
 horse	 驥子 mule	 horse

Images credit: <http://www.imeha.org/>

Mule breeders 3 millennia ago observed that a horse mare crossed with a jack donkey yields a mule, whereas a horse stallion crossed with a jennet donkey produces a hinny, which has shorter ears, a thicker mane and tail, and stronger legs than the mule; thus indicating parental sex-dependent influence on phenotype

# Genomic imprinting and epigenetics

- Epigenetics is the study of heritable changes in gene activity which are not caused by changes in the DNA sequence. Usually refer to DNA methylation and histone modulation.
- Genomic imprinting, by which certain genes are switched off in either the egg or the sperm during their development and remain silenced in the genome of the early embryo, including but not limited to DNA methylation, histone modulation (methylation and acetylation), ....

# REVIEWS

## Gene expression regulation mediated through reversible m<sup>6</sup>A RNA methylation

*Ye Fu<sup>1</sup>, Dan Dominissini<sup>1,2,3</sup>, Gideon Rechavi<sup>2,3</sup> and Chuan He<sup>1</sup>*

**Abstract** | Cellular RNAs carry diverse chemical modifications that used to be regarded as static and having minor roles in ‘fine-tuning’ structural and functional properties of RNAs. In this Review, we focus on reversible methylation through the most prevalent mammalian mRNA internal modification, N<sup>6</sup>-methyladenosine (m<sup>6</sup>A). Recent studies have discovered protein ‘writers’, ‘erasers’ and ‘readers’ of this RNA chemical mark, as well as its dynamic deposition on mRNA and other types of nuclear RNA. These findings strongly indicate dynamic regulatory roles that are analogous to the well-known reversible epigenetic modifications of DNA and histone proteins. This reversible RNA methylation adds a new dimension to the developing picture of post-transcriptional regulation of gene expression.

# Sperm, but Not Oocyte, DNA Methylome Is Inherited by Zebrafish Early Embryos

Lan Jiang,<sup>1,3,7</sup> Jing Zhang,<sup>1,7</sup> Jing-Jing Wang,<sup>1,3,7</sup> Lu Wang,<sup>1,3</sup> Li Zhang,<sup>1</sup> Guoqiang Li,<sup>1,3</sup> Xiaodan Yang,<sup>2</sup> Xin Ma,<sup>1,3</sup> Xin Sun,<sup>1</sup> Jun Cai,<sup>1</sup> Jun Zhang,<sup>4</sup> Xingxu Huang,<sup>4</sup> Miao Yu,<sup>5</sup> Xuegeng Wang,<sup>6</sup> Feng Liu,<sup>2</sup> Chung-I Wu,<sup>1</sup> Chuan He,<sup>5</sup> Bo Zhang,<sup>6</sup> Weimin Ci,<sup>1,\*</sup> and Jiang Liu<sup>1,\*</sup>

<sup>1</sup>CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics

<sup>2</sup>State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology Chinese Academy of Sciences, Beijing 100101, China

<sup>3</sup>University of Chinese Academy of Sciences, Beijing 100049, China

<sup>4</sup>Model Animal Research Center, Nanjing University, Nanjing 210061, China

<sup>5</sup>Department of Chemistry and Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL 60637, USA

<sup>6</sup>Key Laboratory of Cell Proliferation and Differentiation of Ministry of Education, College of Life Sciences, Peking University, Beijing 100871, China

<sup>7</sup>These authors contributed equally to this work

\*Correspondence: ciwm@big.ac.cn (W.C.), liuj@big.ac.cn (J.L.)

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## SUMMARY

5-methylcytosine is a major epigenetic modification that is sometimes called “the fifth nucleotide.” However, our knowledge of how offspring inherit the DNA methylome from parents is limited. We generated nine single-base resolution DNA methylomes, including zebrafish gametes and early embryos. The oocyte methylome is significantly hypomethylated compared to sperm. Strikingly, the paternal DNA methylation pattern is maintained throughout early embryogenesis. The maternal DNA methylation pattern is maintained until the 16-cell stage. Then, the oocyte methylome is gradually discarded through cell division and is progressively reprogrammed to a pattern similar to that of the sperm methylome. The passive demethylation rate and the de novo methylation rate are similar in the maternal DNA. By the midblastula stage, the embryo’s methylome is virtually identical to the sperm methylome. Moreover, inheritance of the sperm methylome facilitates the epigenetic regulation of embryogenesis. Therefore, besides DNA sequences, sperm DNA methylome is also inherited in zebrafish early embryos.

offspring is limited. Recent studies show that epigenetic modifications from gametes in general are cleared and reestablished after fertilization (Blewitt et al., 2006; Daxlinger and Whitelaw, 2010, 2012; Feng et al., 2010b; Henderson and Jacobsen, 2007; Wu and Zhang, 2010) except that a number of loci in some model organisms are resistant to the clearing (Arteaga-Vazquez and Chandler, 2010; Cavalli and Paro, 1998; Morgan et al., 1999). However, this theory lacks evidence in the form of high-resolution epigenetic maps in oocytes, sperm, and early embryos.

DNA methylation is one major epigenetic modification that is crucial for the development and differentiation of various cell types in an organism (Li et al., 1992; Okano et al., 1999). In mammals, DNA demethylation occurs in the whole-genome level after fertilization, but not in some loci, such as intracisternal A particle (IAP) (Daxlinger and Whitelaw, 2010; Wu and Zhang, 2010). To further understand how offspring obtain DNA methylation information from parents, reduced representation bisulfite sequencing (RRBS) was used to achieve the most comprehensive genome-scale methylomes in mouse gametes and prespecified embryos (Smallwood and Kelsey, 2012; Smith et al., 2012), which explored the unique regulatory phase of DNA methylation in early mammalian embryos. Unfortunately, the RRBS method covers only 5% of the genome for the comparative analysis (Ball et al., 2009; Harris et al., 2010; Smith et al., 2012). The limited genome coverage in oocyte and early embryos prevents a full understanding of how much DNA methylation information is

# Programming and Inheritance of Parental DNA Methylomes in Mammals

Lu Wang,<sup>1,3,9</sup> Jun Zhang,<sup>4,9</sup> Jialei Duan,<sup>1,9</sup> Xinxing Gao,<sup>4,9</sup> Wei Zhu,<sup>1,3</sup> Xingyu Lu,<sup>5</sup> Lu Yang,<sup>6</sup> Jing Zhang,<sup>1</sup> Guoqiang Li,<sup>1,3</sup> Weimin Ci,<sup>2</sup> Wei Li,<sup>7</sup> Qi Zhou,<sup>7</sup> Neel Aluru,<sup>8</sup> Fuchou Tang,<sup>6</sup> Chuan He,<sup>5</sup> Xingxu Huang,<sup>4,\*</sup> and Jiang Liu<sup>1,\*</sup>

<sup>1</sup>CAS Key Laboratory of Genome Sciences and Information

<sup>2</sup>Laboratory of Disease Genomics and Individualized Medicine

Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China

<sup>3</sup>University of Chinese Academy of Sciences, Beijing 100049, China

<sup>4</sup>MOE Key Laboratory of Model Animal for Disease Study, Nanjing University, Nanjing 210061, China

<sup>5</sup>Department of Chemistry and Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL 60637, USA

<sup>6</sup>Biodynamic Optical Imaging Center, College of Life Sciences, Peking University, Beijing 100871, China

<sup>7</sup>State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China

<sup>8</sup>Biology Department, Woods Hole Oceanographic Institution, MA 02543, USA

<sup>9</sup>Co-first authors

\*Correspondence: [xingxuhuang@mail.nju.edu.cn](mailto:xingxuhuang@mail.nju.edu.cn) (X.H.), [liuj@big.ac.cn](mailto:liuj@big.ac.cn) (J.L.)

<http://dx.doi.org/10.1016/j.cell.2014.04.017>

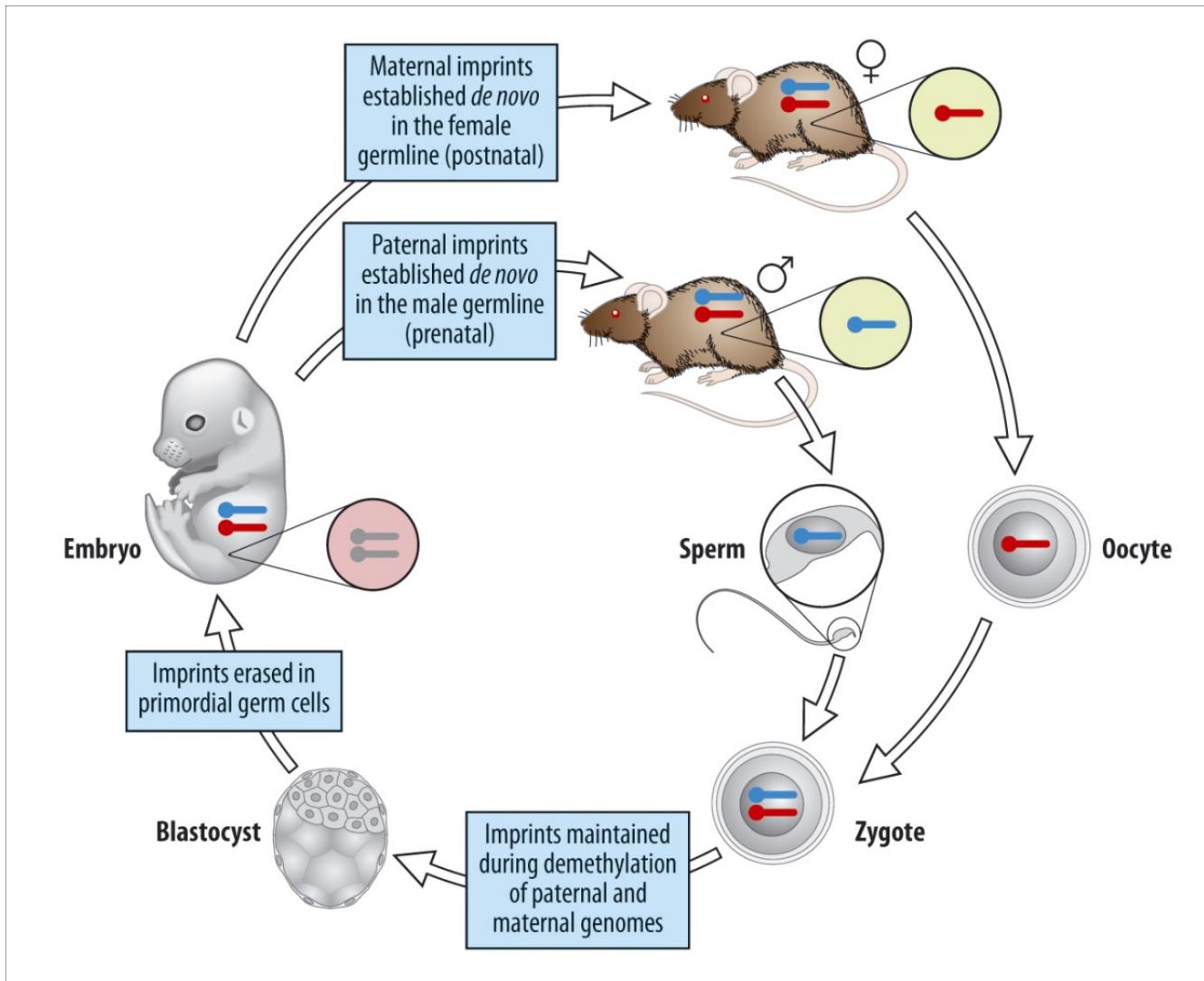
## SUMMARY

The reprogramming of parental methylomes is essential for embryonic development. In mammals, paternal 5-methylcytosines (5mCs) have been proposed to be actively converted to oxidized bases. These paternal oxidized bases and maternal 5mCs are believed to be passively diluted by cell divisions. By generating single-base resolution, allele-specific DNA methylomes from mouse gametes, early embryos, and primordial germ cell (PGC), as well as single-base-resolution maps of oxidized cytosine bases for early embryos, we report the existence of 5hmC and 5fC in both maternal and paternal genomes and find that 5mC or its oxidized derivatives, at the majority of demethylated CpGs, are converted to unmodified cytosines independent of passive dilution from gametes to four-cell embryos. Therefore, we conclude that paternal methylome and at least a significant proportion of maternal methylome go through active demethylation during embryonic development. Additionally, all the known imprinting control regions (ICRs) were classified into germ-line or somatic ICRs.

the sperm pattern (Jiang et al., 2013; Potok et al., 2013). In mammals, two waves of genome-wide DNA demethylation take place during primordial germ cell (PGC) development and early embryogenesis (Seisenberger et al., 2013; Wu and Zhang, 2014). However, our knowledge on genome-wide demethylation is still limited due to the lack of single-base resolution DNA methylomes for mouse oocyte and early embryos.

Currently, it is generally believed that paternal DNA is actively demethylated by oxidizing 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) by Tet3 (Gu et al., 2011; He et al., 2011; Inoue et al., 2011; Inoue and Zhang, 2011; Ito et al., 2011). Studies using cell immunostaining suggested that the oxidized derivatives of 5mC is further diluted passively by DNA replication over early cell divisions (Inoue et al., 2011; Inoue and Zhang, 2011; Wu and Zhang, 2014). Alternatively, the oxidized 5mC bases could be replaced to unmodified cytosines through the base excision repair pathway similar to what has been found in mouse embryonic stem cells (He et al., 2011; Zhang et al., 2012). Moreover, it is claimed that the oxidized 5mC bases only exist in paternal genome but not in maternal genome during early embryogenesis (Gu et al., 2011; Inoue et al., 2011; Inoue and Zhang, 2011; Iqbal et al., 2011; Xie et al., 2012). Previous study also proposed that 5mC in maternal DNA is protected from the oxidization by Stella in early embryos (Nakamura et al., 2012). Therefore, it has been generally believed that 5mC on maternal DNA is passively diluted through early cell

# Establishment, maintenance and erasure of genomic imprints during mouse life cycle



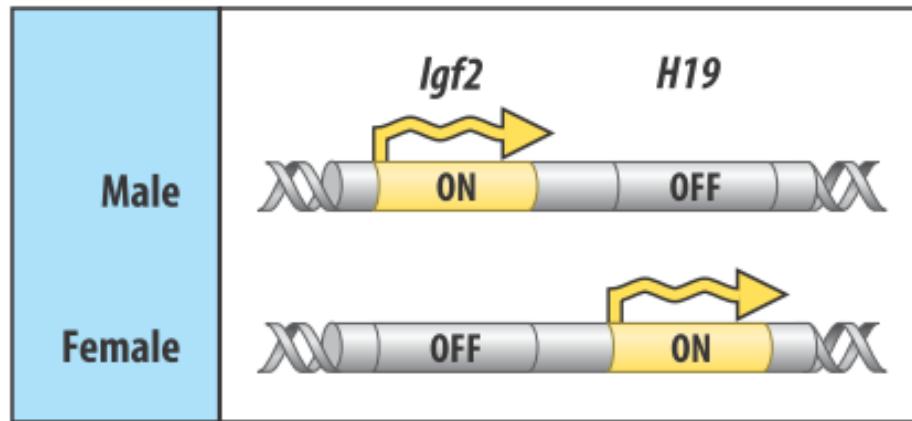


Fig. 9.12 Imprinting of genes controlling embryonic growth. In mouse embryos, the paternal gene for insulin-like growth factor 2 (*Igf2*) is on, but the gene on the maternal chromosome is off. In contrast, the closely linked gene *H19* is switched on in the maternal genome but silenced in the paternal genome.

# A Single *IGF1* Allele Is a Major Determinant of Small Size in Dogs

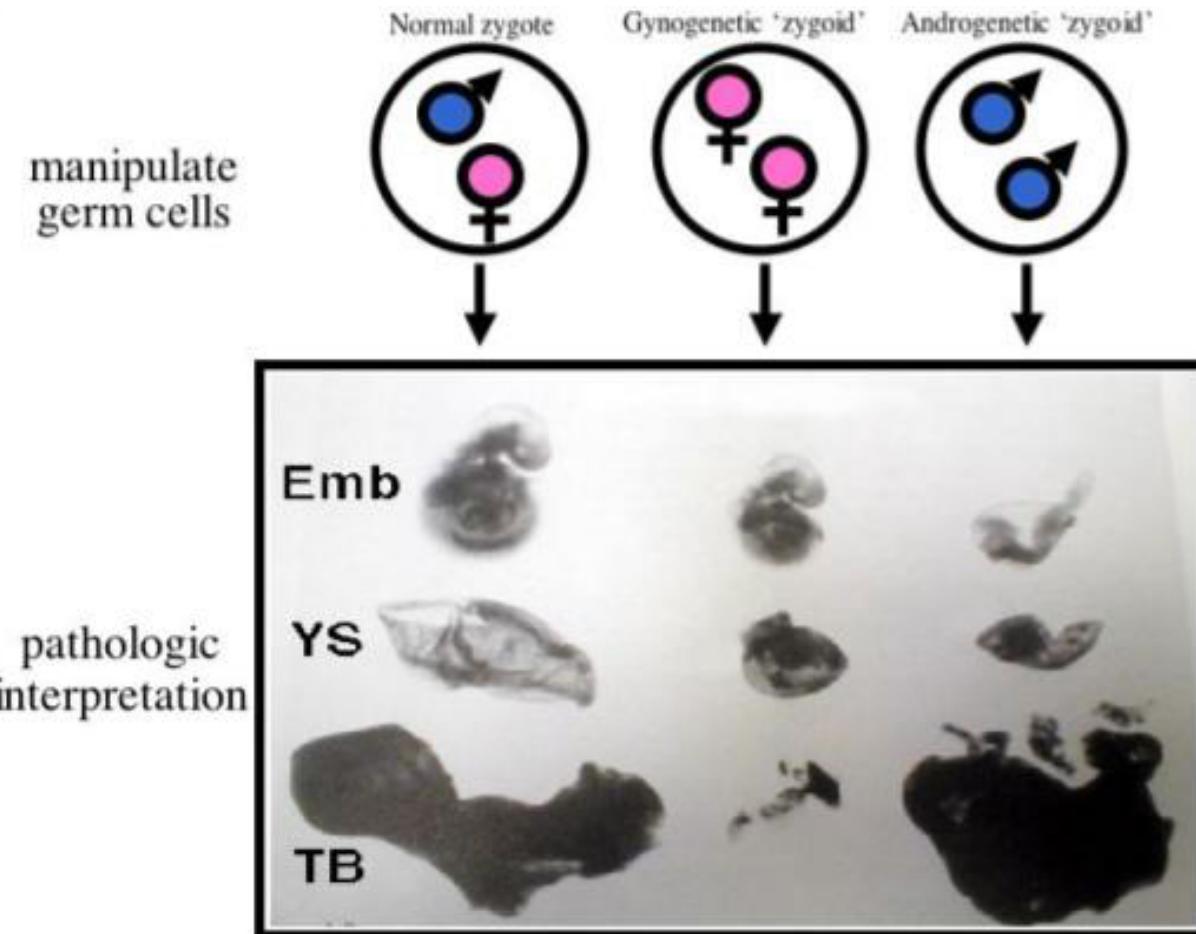
Nathan B. Sutter,<sup>1</sup> Carlos D. Bustamante,<sup>2</sup> Kevin Chase,<sup>3</sup> Melissa M. Gray,<sup>4</sup> Keyan Zhao,<sup>5</sup> Lan Zhu,<sup>2</sup> Badri Padhukasahasram,<sup>2</sup> Eric Karlins,<sup>1</sup> Sean Davis,<sup>1</sup> Paul G. Jones,<sup>6</sup> Pascale Quignon,<sup>1</sup> Gary S. Johnson,<sup>7</sup> Heidi G. Parker,<sup>1</sup> Neale Fretwell,<sup>6</sup> Dana S. Mosher,<sup>1</sup> Dennis F. Lawler,<sup>8</sup> Ebenezer Satyaraj,<sup>8</sup> Magnus Nordborg,<sup>5</sup> K. Gordon Lark,<sup>3</sup> Robert K. Wayne,<sup>4</sup> Elaine A. Ostrander<sup>1\*</sup>

The domestic dog exhibits greater diversity in body size than any other terrestrial vertebrate. We used a strategy that exploits the breed structure of dogs to investigate the genetic basis of size. First, through a genome-wide scan, we identified a major quantitative trait locus (QTL) on chromosome 15 influencing size variation within a single breed. Second, we examined genetic variation in the 15-megabase interval surrounding the QTL in small and giant breeds and found marked evidence for a selective sweep spanning a single gene (*IGF1*), encoding insulin-like growth factor 1. A single *IGF1* single-nucleotide polymorphism haplotype is common to all small breeds and nearly absent from giant breeds, suggesting that the same causal sequence variant is a major contributor to body size in all small dogs.

# Parental-conflict theory

- The theory that the reproductive strategies of the father and mother are different.
- Paternal imprinting promotes embryonic growth, whereas maternal imprinting reduces it, for example. The father wants to have maximal growth for his own offspring, so that his genes have a good chance of surviving and being carried on. This can be achieved by having a large placenta, as a result of producing growth hormone, whose production is stimulated by IGF-2. The mother, who may mate with different males, benefits more by spreading her resources over all her offspring, and so wishes to prevent too much growth in any one embryo. Thus, a gene that promotes embryonic growth is turned off in the mother.

# Paternal and maternal genomes are both required for normal mouse development



Surani, McGrath and Solter, 1984-1987

TB, trophoblast

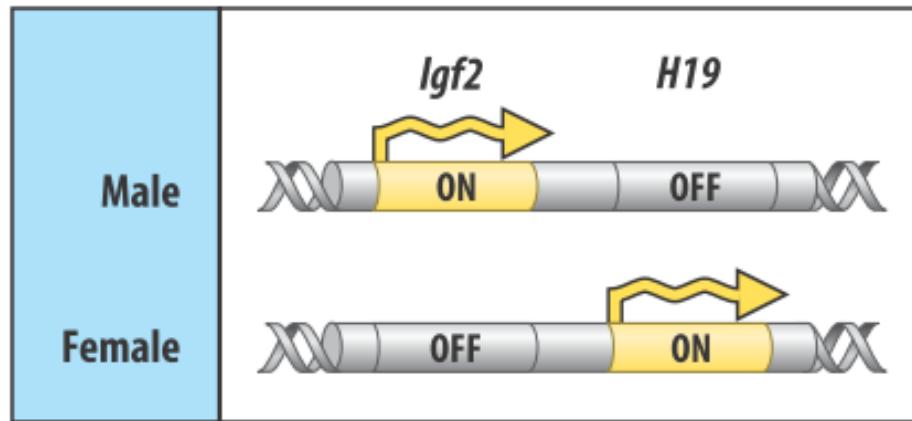
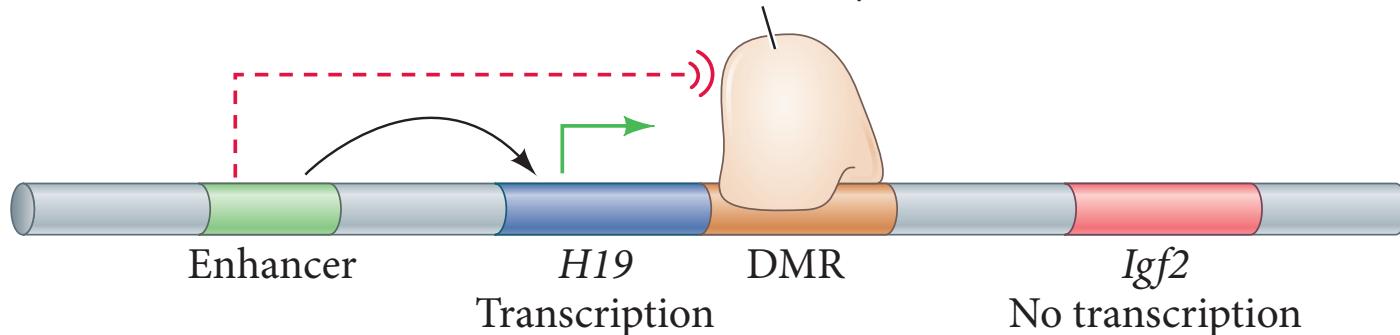


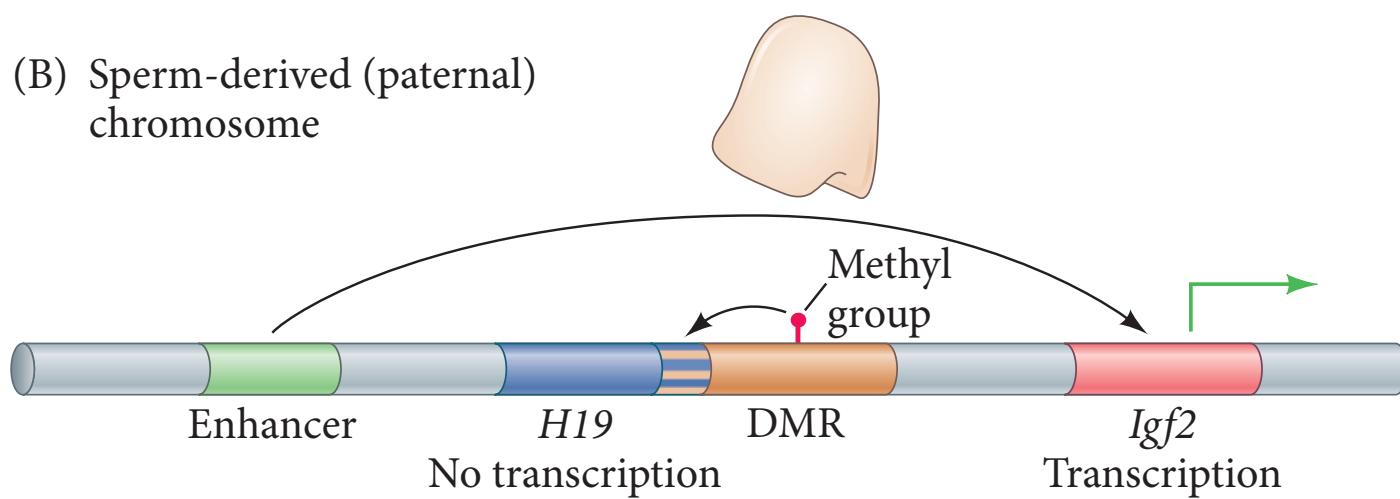
Fig. 9.12 Imprinting of genes controlling embryonic growth. In mouse embryos, the paternal gene for insulin-like growth factor 2 (*Igf2*) is on, but the gene on the maternal chromosome is off. In contrast, the closely linked gene *H19* is switched on in the maternal genome but silenced in the paternal genome.

(A) Egg-derived (maternal) chromosome

CTCF insulator protein binds to unmethylated DMR



(B) Sperm-derived (paternal) chromosome



# Parthenogenetic haploid embryonic stem cells efficiently support mouse generation by oocyte injection

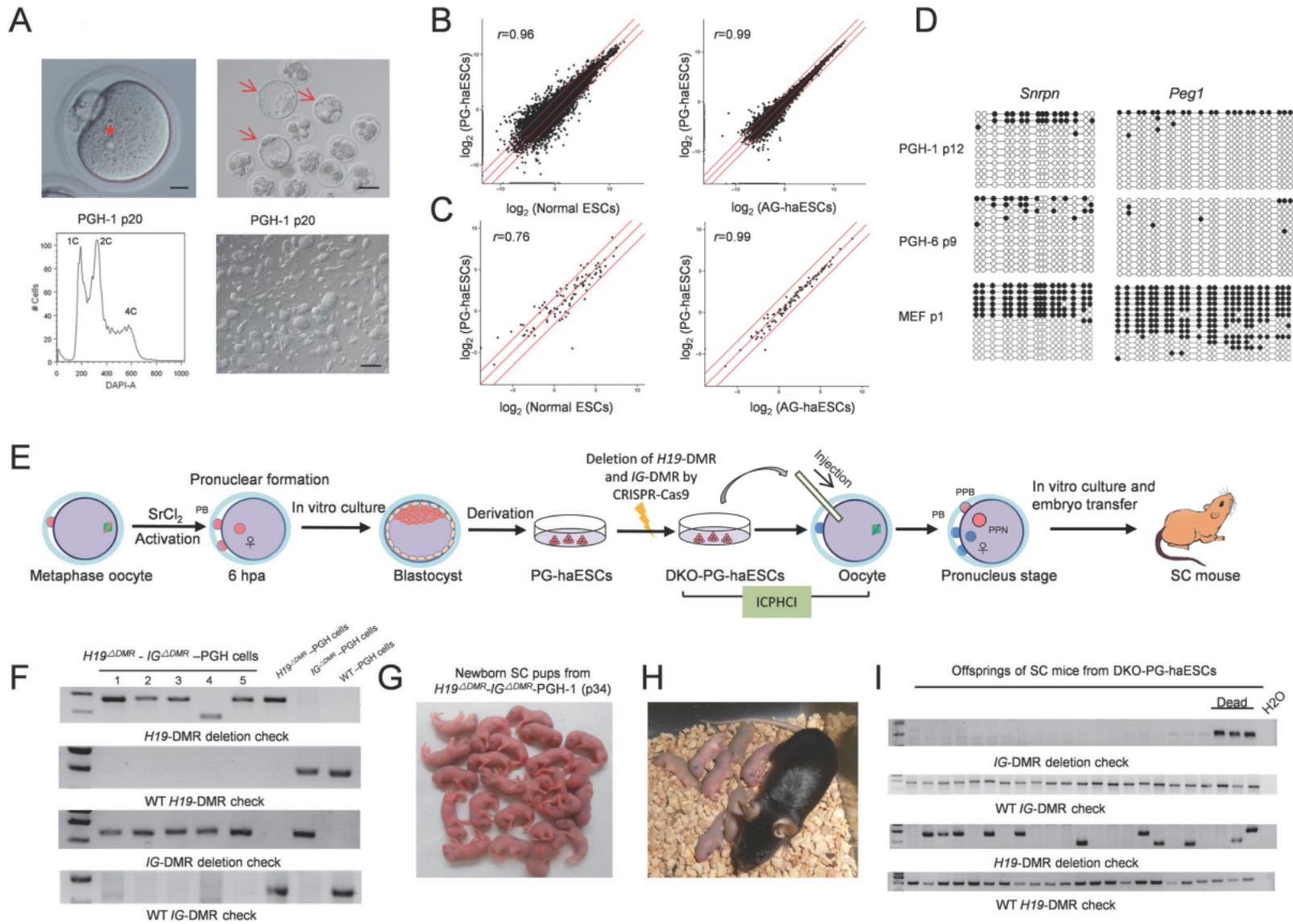
*Cell Research* (2016) **26**:131-134. doi:10.1038/cr.2015.132; published online 17 November 2015

Dear Editor,

Mammalian haploid embryonic stem cells (haESCs) have been recently generated from parthenogenetic and androgenetic embryos [1, 2]. Both parthenogenetic haESCs (PG-haESCs) and androgenetic haESCs (AG-haESCs) can be used for cell-based reverse and forward genetic screens on a whole-genome scale [3, 4]. AG-haESCs, after intracytoplasmic injection into oocytes (referred to as ICAHCI), can be used as a sperm replacement to produce healthy semi-cloned (SC) mice at a rate of ~2% of transferred embryos [5, 6]. Interestingly, after inhibiting the expression of two paternally imprinted genes (*H19* and *Gtl2*) in AG-haESCs by removal of their differentially methylated DNA regions (DMRs), these cells can efficiently and stably support the generation of healthy SC pups at a rate of ~20% [7]. Nevertheless, the feasibility of using PG-haESCs for generation of SC mice via oocyte injection has not yet been demonstrated. We reason that, if PG-haESCs can support the efficient

and S1B). We then tested whether PG-haESCs could support full-term development of mouse embryos upon injection into mature oocytes. To this end, we performed intracytoplasmic PG-haESCs injection (ICPHCI). Briefly, FACS-enriched cells containing one set of chromosome were expanded in ESC culture medium for several days and arrested at the M phase by treatment with 0.05 mg/ml demecolcine for 8 h before injection. Each nucleus from M-phase haploid cells was injected into a MII-arrested oocyte to make an SC embryo as previously reported [6]. We found that PG-haESCs failed to support embryonic development after injection into oocytes (Supplementary information, Table S1). This result is not surprising as ICPHCI-derived SC embryos, containing two copies of female genomes, were actually parthenogenetic diploid embryos that cannot develop to term *in vivo* [9].

Next, we attempted to reveal the differences between PG-haESCs and AG-haESCs by comparing the gene expression profiles of PG-haESCs with those of AG-



## Reconstitution *in vitro* of the entire cycle of the mouse female germ line

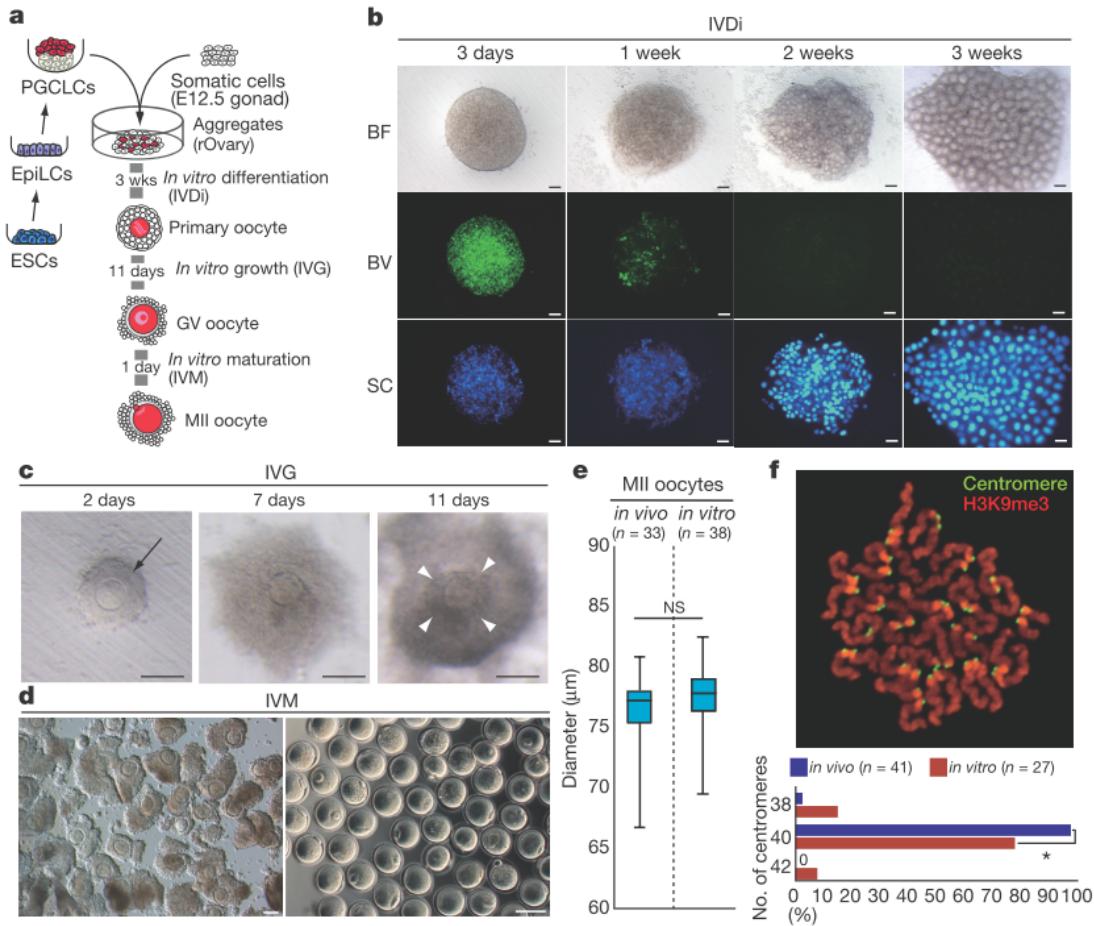
Orie Hikabe<sup>1\*</sup>, Nobuhiko Hamazaki<sup>1</sup>, Go Nagamatsu<sup>1</sup>, Yayoi Obata<sup>2</sup>, Yuji Hirao<sup>3</sup>, Norio Hamada<sup>1,4</sup>, So Shimamoto<sup>1</sup>, Takuya Imamura<sup>1</sup>, Kinichi Nakashima<sup>1</sup>, Mitinori Saitou<sup>5,6,7,8</sup> & Katsuhiko Hayashi<sup>1,9\*</sup>

The female germ line undergoes a unique sequence of differentiation processes that confers totipotency to the egg<sup>1,2</sup>. The reconstitution of these events *in vitro* using pluripotent stem cells is a key achievement in reproductive biology and regenerative medicine. Here we report successful reconstitution *in vitro* of the entire process of oogenesis from mouse pluripotent stem cells. Fully potent mature oocytes were generated in culture from embryonic stem cells and from induced pluripotent stem cells derived from both embryonic fibroblasts and adult tail tip fibroblasts. Moreover, pluripotent stem cell lines were re-derived from the eggs that were generated *in vitro*, thereby reconstituting the full female germline cycle in a dish. This culture system will provide a platform for elucidating the molecular mechanisms underlying totipotency and the production of oocytes of other mammalian species in culture.

One of the key goals in developmental and reproductive biology is to reconstitute the entire process of gametogenesis in culture. Specifically, owing to its biological significance, reconstitution of oogenesis using pluripotent stem cells that yields functional eggs has long been sought<sup>3–5</sup>. Eggs originate from primordial germ cells (PGCs), which are specified at around embryonic day 6.5 (E6.5) in mice<sup>6</sup>. PGCs then migrate into the gonads, enter meiosis in female embryos<sup>7</sup>, and therefore become primary oocytes. Following puberty, primary oocytes

the combination of media yielded a high number of primary oocytes with a follicle structure in preliminary culture experiments (Extended Data Fig. 1a). To prevent multiple oocyte follicle formation such as that seen frequently in culture (Extended Data Fig. 1b), we added the oestrogen inhibitor ICI182780 to the culture<sup>9</sup>. The rOvaries were filled throughout with follicle structures, each of which possesses a single oocyte, in an ICI182780-dependent manner (Extended Data Fig. 1b, c). During IVDi culture, BV, a marker of early PGCs<sup>10</sup>, was detectable at 3 days of culture, but became weak after one week of culture (Fig. 1b). At two weeks of culture, BV disappeared and SC—a marker of both oocytes and PGCs—became prominent in rOvaries, and at three weeks of culture, a number of SC-positive primary oocytes were observed in rOvaries (Fig. 1b). The close observation of IVDi revealed that clusters of PGCLCs were formed by 5 days of culture and gradually fragmented from 5 to 9 days, after which, follicles were formed around 11 days of culture (Extended Data Fig. 2a). Foxl2, a functional marker of granulosa cells, was detectable in cells surrounding the oocytes at 21 days of culture (Extended Data Fig. 2a). Immunofluorescence analysis of the meiotic chromosome revealed the robust progression of meiotic prophase I from 5 to 9 days of culture (Extended Data Fig. 2b, c). PGCLCs before aggregation are equivalent to E9.5 (refs 8, 11). Therefore, the meiotic prophase I in PGCLCs progresses during the period corresponding to

RESEARCH LETTER



# Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA

Lin Zhang<sup>1,\*</sup>, Dongxia Hou<sup>1,\*</sup>, Xi Chen<sup>1,\*</sup>, Donghai Li<sup>1,\*</sup>, Lingyun Zhu<sup>1,2</sup>, Yujing Zhang<sup>1</sup>, Jing Li<sup>1</sup>, Zhen Bian<sup>1</sup>, Xiangying Liang<sup>1</sup>, Xing Cai<sup>1</sup>, Yuan Yin<sup>1</sup>, Cheng Wang<sup>1</sup>, Tianfu Zhang<sup>1</sup>, Dihan Zhu<sup>1</sup>, Dianmu Zhang<sup>1</sup>, Jie Xu<sup>1</sup>, Qun Chen<sup>1</sup>, Yi Ba<sup>3</sup>, Jing Liu<sup>1</sup>, Qiang Wang<sup>1</sup>, Jianqun Chen<sup>1</sup>, Jin Wang<sup>1</sup>, Meng Wang<sup>1</sup>, Qipeng Zhang<sup>1</sup>, Junfeng Zhang<sup>1</sup>, Ke Zen<sup>1</sup>, Chen-Yu Zhang<sup>1</sup>

<sup>1</sup>Jiangsu Engineering Research Center for microRNA Biology and Biotechnology, State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, 22 Hankou Road, Nanjing, Jiangsu 210093, China; <sup>2</sup>Department of Chemistry and Biology, School of Science, National University of Defense Technology, Changsha, Hunan 410073, China; <sup>3</sup>Tianjin Medical University Cancer Institute and Hospital, Huanhuxi Road, Tiyuanbei, Tianjin 300060, China

Our previous studies have demonstrated that stable microRNAs (miRNAs) in mammalian serum and plasma are actively secreted from tissues and cells and can serve as a novel class of biomarkers for diseases, and act as signaling molecules in intercellular communication. Here, we report the surprising finding that exogenous plant miRNAs are present in the sera and tissues of various animals and that these exogenous plant miRNAs are primarily acquired orally, through food intake. MIR168a is abundant in rice and is one of the most highly enriched exogenous plant miRNAs in the sera of Chinese subjects. Functional studies *in vitro* and *in vivo* demonstrated that MIR168a could bind to the human/mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA, inhibit LDLRAP1 expression in liver, and consequently decrease LDL removal from mouse plasma. These findings demonstrate that exogenous plant miRNAs in food can regulate the expression of target genes in mammals.

**Keywords:** microRNA; MIR168a; LDLRAP1; low-density lipoprotein; microvesicle; cross-kingdom  
*Cell Research* (2012) 22:107-126. doi:10.1038/cr.2011.158; published online 20 September 2011

**Thanks!**

# Genomic imprinting

- Imprinting is reversible. Because in the next generation, any of the chromosomes could end up in male or female germ cells.
- Inherited imprinting is probably erased during early germ-cell development. Why?
- Inner cell mass cells from gynogenetic embryos -> normal embryos, growth is retarded by as much as 50%.
- Inner cell mass cells from androgenetic embryos -> normal embryos, growth is increased by as much as 50%.

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## Breast milk stem cells may be incorporated into baby

- › 14:53 03 November 2014 by Clare Wilson
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BREAST milk is known for being full of goodies – but could that include stem cells from mum that go on to transform into parts of the baby's body?

Preliminary evidence has shown this happens in mice, suggesting it also does in people.

Stem cells have the unusual ability to regenerate themselves and develop into a variety of tissues. Several sources of stem cells are being developed for therapeutic use, including embryos, umbilical-cord blood and adult tissues.

It was discovered seven years ago that [human breast milk](#) also contains a kind of [stem cell](#). The question was whether these cells do anything useful for the baby or if they simply leak unavoidably into breast milk.

The latest findings, presented at the [National Breastfeeding and Lactation Symposium](#) in London last week, suggest that in mice at least, breast milk stem cells cross into the offspring's blood from their stomach and play a

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If what's true for mice is also true for humans, it's a

## Presence of fetal DNA in maternal plasma and serum

*Y M Dennis Lo, Noemi Corbetta, Paul F Chamberlain, Vik Rai, Ian L Sargent, Christopher W G Redman, James S Wainscoat*

### Summary

**Background** The potential use of plasma and serum for molecular diagnosis has generated interest. Tumour DNA has been found in the plasma and serum of cancer patients, and molecular analysis has been done on this material. We investigated the equivalent condition in pregnancy—that is, whether fetal DNA is present in maternal plasma and serum.

**Methods** We used a rapid-boiling method to extract DNA from plasma and serum. DNA from plasma, serum, and nucleated blood cells from 43 pregnant women underwent a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses.

**Findings** Fetus-derived Y sequences were detected in 24 (80%) of the 30 maternal plasma samples, and in 21 (70%) of the 30 maternal serum samples, from women bearing male fetuses. These results were obtained with only 10 µL of the samples. When DNA from nucleated blood cells extracted from a similar volume of blood was used, only five (17%) of the 30 samples gave a positive Y signal. None of the 13 women bearing female fetuses, and none of the ten non-pregnant control women, had positive results for plasma, serum or nucleated blood cells.

**Interpretation** Our finding of circulating fetal DNA in maternal plasma may have implications for non-invasive prenatal diagnosis, and for improving our understanding of the fetomaternal relationship.

### Introduction

The passage of nucleated cells between mother and fetus is well recognised.<sup>1,2</sup> One important clinical application is the use of fetal cells in maternal blood for non-invasive prenatal diagnosis.<sup>3</sup> This approach avoids the risks associated with conventional invasive techniques, such as amniocentesis and chorionic-villus sampling. Substantial advances have been made in the enrichment and isolation of fetal cells for analysis.<sup>3,4</sup> However, most techniques are time-consuming or require expensive equipment.

There has been much interest in the use of DNA derived from plasma or serum for molecular diagnosis.<sup>5</sup> In particular, there have been reports that tumour DNA can be detected by molecular techniques in the plasma or serum of cancer patients.<sup>6-8</sup> Such reports prompted us to investigate whether fetal DNA can be detected in maternal plasma and serum.

### Methods

#### Patients

Pregnant women attending the John Radcliffe Hospital (Oxford, UK) were recruited before amniocentesis or delivery. We obtained approval of the project from the Central Oxfordshire Research Ethics Committee. Informed consent was obtained in each case. 5–10 mL maternal peripheral blood was collected into one tube containing edetic acid and one plain tube. For women undergoing amniocentesis, maternal blood was always taken before the procedure, and 10 mL amniotic fluid was also collected for fetal sex determination. For women recruited just before delivery, fetal

# Prenatal diagnosis

## THE LANCET

The Lancet, Volume 293, Issue 7606, Pages 1119 - 1122, 7 June 1969  
doi:10.1016/S0140-6736(69)91642-0

### PRACTICAL AND THEORETICAL IMPLICATIONS OF FETAL/MATERNAL LYMPHOCYTE TRANSFER

Janina Walknowska , Felix A. Conte , Melvin M. Grumbach

#### Abstract

---

Lymphocyte cultures were prepared from peripheral-blood samples taken from thirty pregnant women. In twenty-one cultures one or more euploid metaphase figures with 5 small acrocentric chromosomes interpreted as 46/"XY" were found. Nineteen of the twenty-one women gave birth to male infants, and two gave birth to females ( $P=0.0001$ ). The two "false-positive" results were in women in whom only 1 cell with 5 small acrocentric chromosomes had been found, whereas all ten patients in whom 2 or more cells were found gave birth to males. Artefact or chimærism for fetal 46/XY cells persisting from an earlier pregnancy may account for the two false-positive results. In nine other women, no "XY" cells were found. Six gave birth to female infants while three gave birth to males. Cells with 46/XY karyotype in the maternal circulation were detected as early as the 14th week of gestation (the earliest age studied). The data suggest that the fetomaternal transfer of lymphocytes is common, happens at least as early as the 14th week of gestation, and may be a consequence of transplacental migration of circulating fetal lymphoid cells, as well as leakage of blood. The antenatal diagnosis of a male fetus can be made by karyotypic analysis of lymphocytes in maternal blood. Similarly, it should be possible to identify fetal chromosome abnormalities by this procedure. Transfer of fetal lymphocytes to the mother may play a part in the acceptance of the fetus as a homograft.

## Plenary paper

### Transmaternal cell flow leads to antigen-experienced cord blood

Miranda P. Dierselhuis,<sup>1</sup> Els C. Blokland,<sup>1</sup> Jos Pool,<sup>1</sup> Ellen Schrama,<sup>1</sup> Sicco A. Scherjon,<sup>1,2</sup> and Els Goulym<sup>1</sup>

<sup>1</sup>Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands; and <sup>2</sup>Department of Obstetrics and Gynaecology, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands

Umbilical cord blood (UCB) is used for HSCT. It is known that UCB can comprise Ag-specific T cells. Here we question whether solely transmaternal cell flow may immunize UCB. Twenty-three female UCB samples were collected from healthy mothers and analyzed for minor histocompatibility Ag HY-specific responses. Forty-

two of 104 tetramer<sup>pos</sup> T-cell clones, isolated from 16 of 17 UCB samples, showed male-specific lysis in vitro. Male microchimerism was present in 6 of 12 UCB samples analyzed. In conclusion, female UCB comprises HY-specific cytotoxic T cells. The immunization is presumably caused by transmaternal cell flow of male

microchimerism present in the mother. The presence of immune cells in UCB that are not directed against maternal foreign Ags is remarkable and may explain the reported clinical observation of improved HSCT outcome with younger sibling donors. (*Blood*. 2012;120(3):505-510)

# Understanding Gender

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For many people, the terms "gender" and "sex" are used interchangeably, and thus incorrectly. This idea has become so common, particularly in western societies, that it is rarely questioned. We are born, assigned a sex, and sent out into the world. For many people, this is cause for little, if any dissonance. Yet biological sex and gender are different; gender is not inherently nor solely connected to one's physical anatomy.

*Biological Gender (sex)* includes physical attributes such as external genitalia, sex chromosomes, gonads, sex hormones, and internal reproductive structures. At birth, it is used to assign sex, that is, to identify individuals as male or female. *Gender* on the other hand is far more complicated. It is the complex interrelationship between an individual's sex (gender biology), one's internal sense of self as male, female, both or neither (gender identity) as well as one's outward presentations and behaviors (gender expression) related to that perception, including their gender role. Together, the intersection of these three dimensions produces one's authentic sense of gender, both in how people experience their own gender as well as how others perceive it.

## The Gender Spectrum

Western culture has come to view gender as a binary concept, with two rigidly fixed options: male or female, both grounded in a person's physical anatomy. When a child is born, a quick glance between the legs determines the gender label that the child will carry for life. But even if gender is to be restricted to basic biology, a binary concept still fails to capture the rich variation that exists. Rather

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