

# The significance of genomic imprinting in assisted reproduction

Øjvind Lidegaard

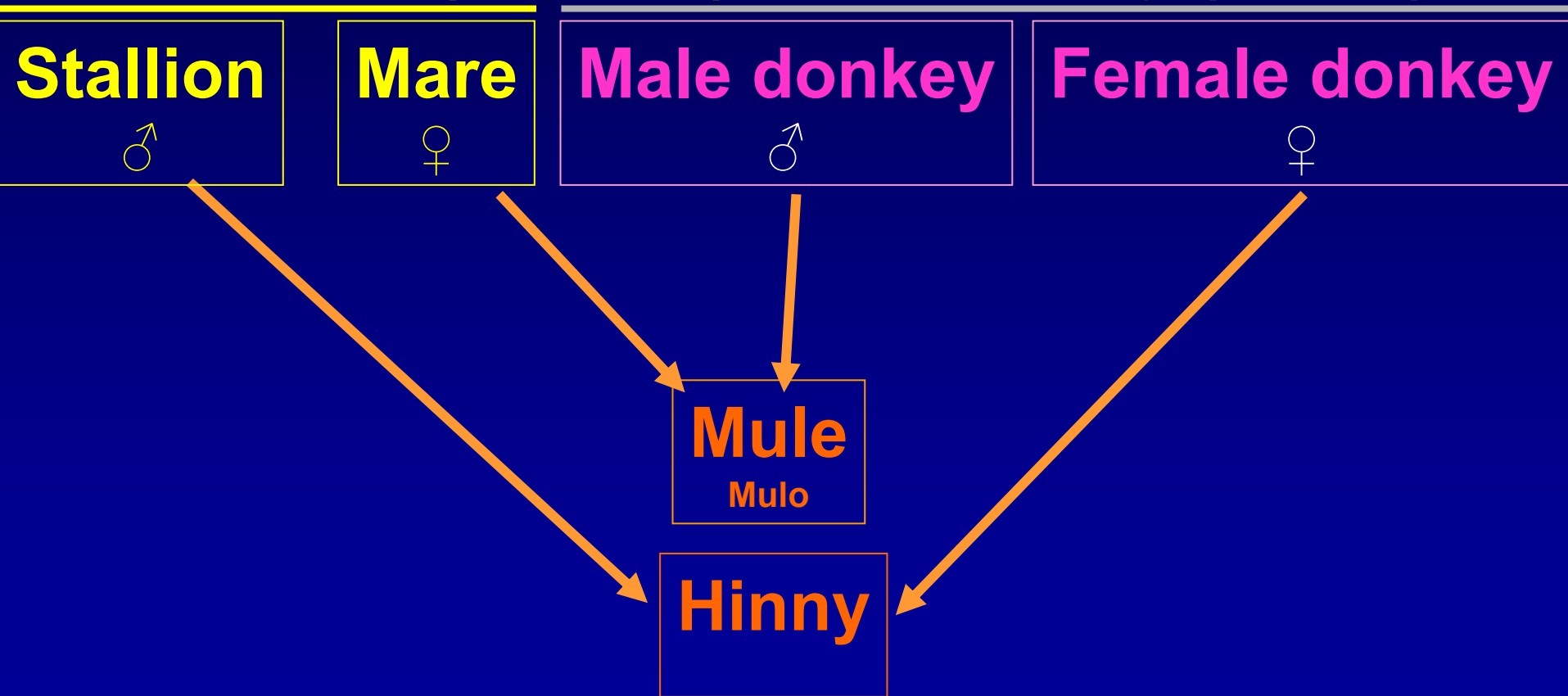
Gynaecological Clinic  
Rigshospitalet  
Copenhagen University

An aerial photograph of the Rigshospitalet (Copenhagen University Hospital) campus in Copenhagen, Denmark. The image shows several large, modern buildings with dark facades and perforated walls, interspersed with green spaces and trees. A white arrow points from the text box in the bottom left towards a specific building in the lower right quadrant of the image.

# What is the difference between a mule and a hinny?

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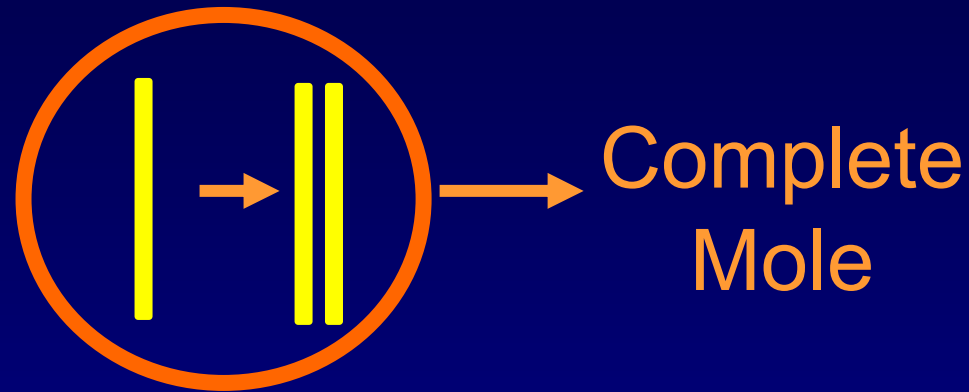
Horse (Caballo) ↔ Donkey (Burro)



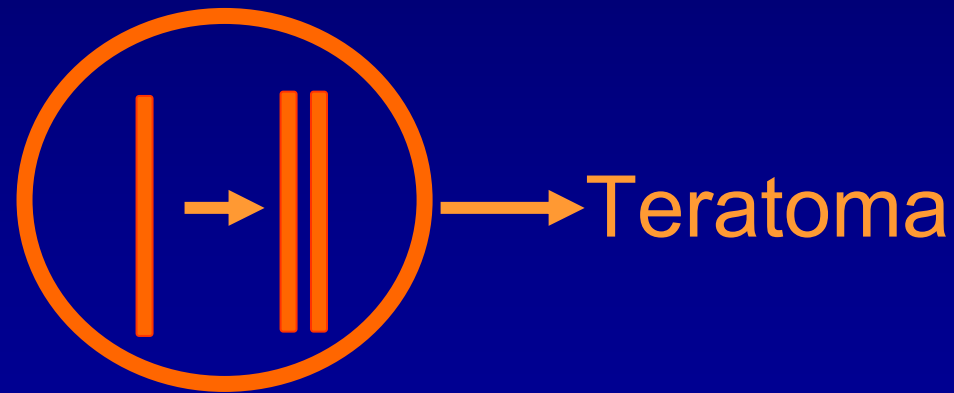
# Uniparental-disomia

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Egg without nucleus,  
fertilised by one  
sperm. Duplication of  
sperm genome



Duplication of egg  
genome without  
fertilisation



**Conclusion:** Total uniparental disomy has  
always fatal consequences for the pregnancy

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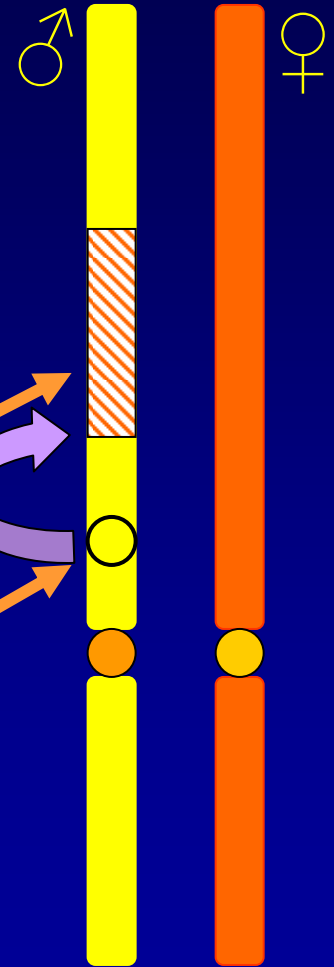
# Genomic imprinting

## Definition:

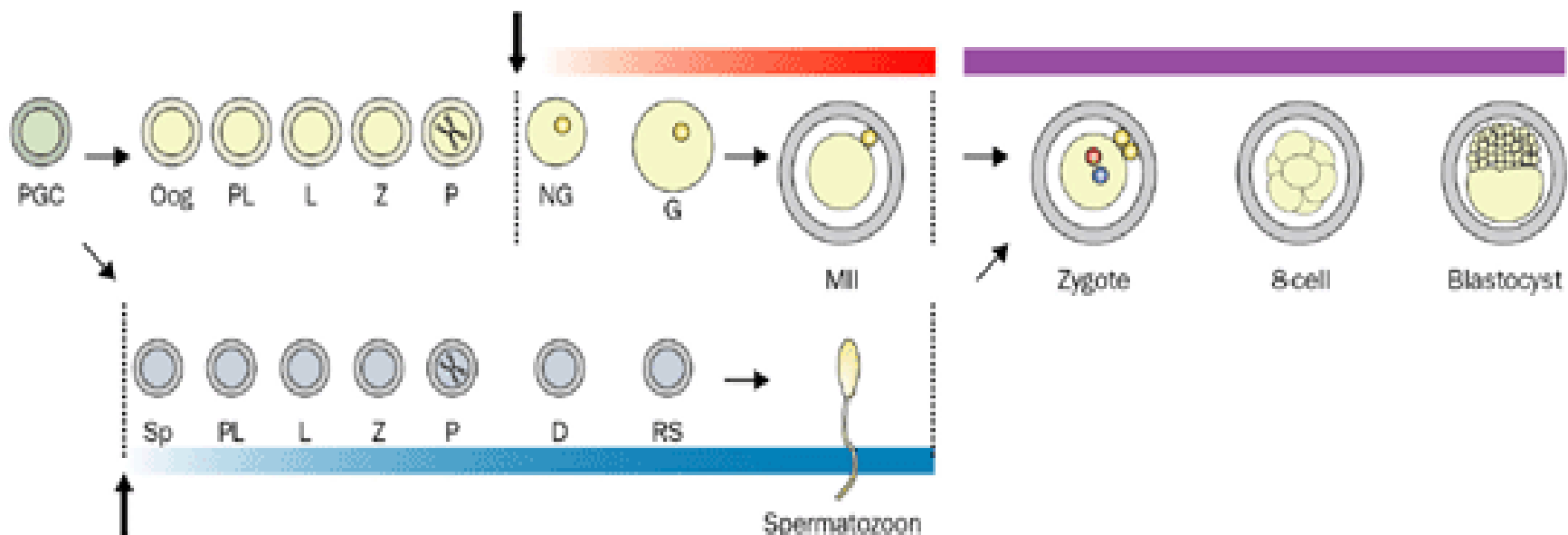
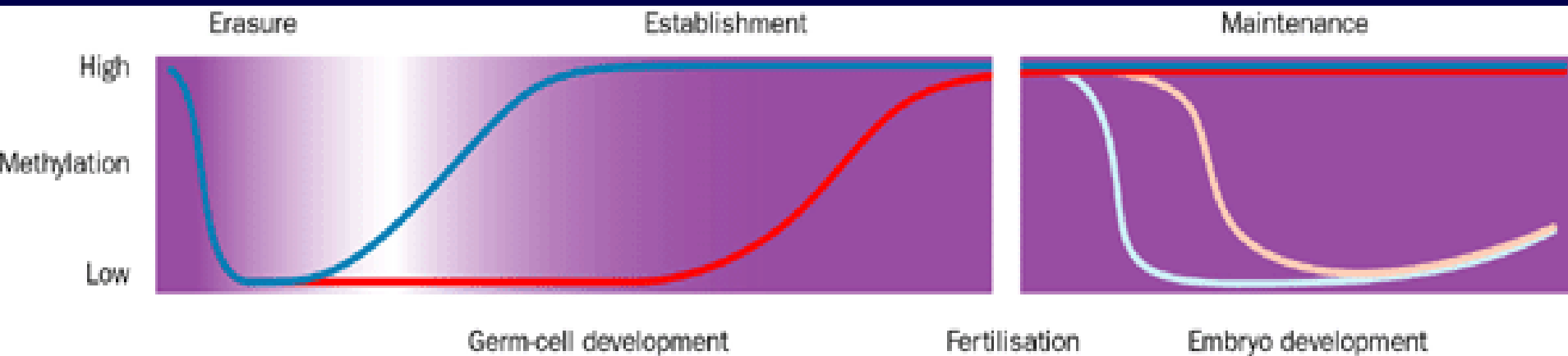
An epigenetic modification of the genome, in which some genes in the allele from one of the parents are "closed" down (methylated)

Imprinted gene

Imprinting is controlled by imprinting centers (IC) located nearby the imprinted areas on the same chromosome



# Imprinting in gameto and embryogenesis



Gosden et al. Lancet 2003; 361: 1975-77

# Principal imprinting and modification

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Gametogenesis: **Principal imprinting process**

Day 1: Fertilisation

Day 1-5: **Modification of imprinting**

Day 5-7: Implantation

Day 5+: Differentiation

**Principal:** determined by the parental origin.

**Modification:** controlled by the physical environment during early stages of cleavage. Could be a mechanism by which the embryo adapts to the prevailing physical environment

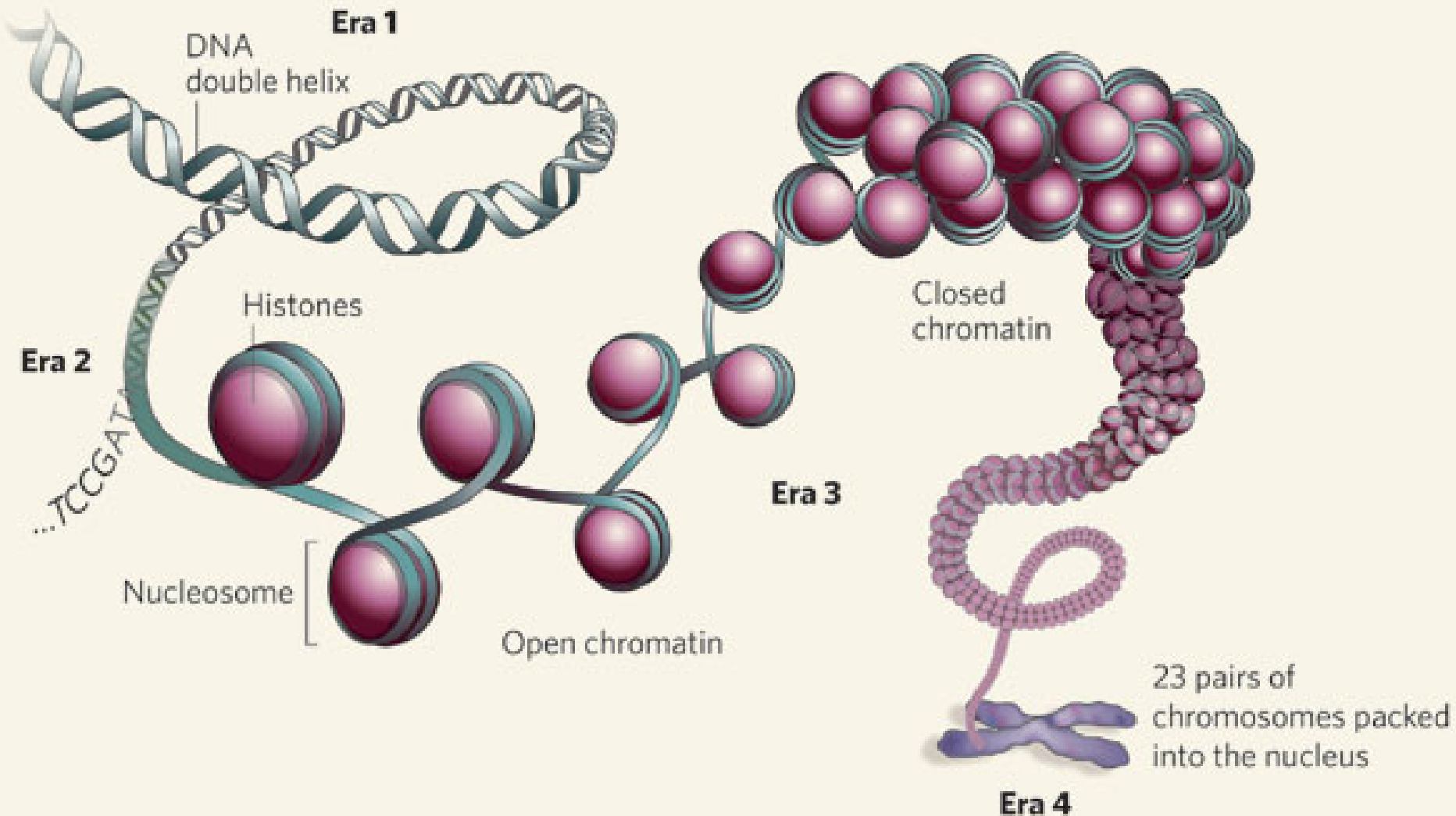
# Imprinting and epigenesis

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**Epigenetic control** is the general closure or activation of genes taking place both during gametogenesis, embryogenesis (differentiation) and in adult life (cell renewal).

**Imprinting** is a particular type of epigenetic control in which parental specific alleles are activated or silenced.

# The epigenomic era opens





# Genomic hard- and software

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**DNA sequence** could be considered as the indelible ink that is faithfully transcribed from cell to cell and from generation to generation (**Pen – hardware**)

**Epigenetics** is represented by methyl groups added to cytosine and covalent changes in histone proteins, responsible for differentiation of each single cell. (**Pencil remarks–software**)

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**Gosden & Feinberg. N Engl J Med 2007; 356: 731-3**

**Baylin & Schuebel. Nature 2007; 448: 548-9**

# Genomic imprinting

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- Number of imprinted human genes: >500 ?

*These genes are of significance for at least*

- growth regulation
- placental growth
- embryonic and postnatal development
- brain function
- behaviour, psychological traits
- neoplastic transformation

# Imprinting diseases 1

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Dysregulation of imprinted genes are now described in several human diseases, which are characterised by:

- growth abnormalities
- placental abnormalities
- mental retardation, abn. psychological traits
- abdominal wall defects
- increased risk of early cancers

# Imprinting diseases 2

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## Specific imprinting diseases in humans

- Beckwith-Wiedemann syndrome (BWS)  
*Imprinting disorder on chromosome 11p*
- Prader-Willis syndrome (PWS)  
*Imprinting disorder on chromosome 15q*
- Angelman syndrome (AS)  
*Imprinting disorder on chromosome 15q*
- Childhood cancers

# Imprinting diseases 3

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## Childhood cancers

- Wilms tumour
- Neuroblastoma (m1p and p2)
- Acute myeloblastic leukaemia (p7)
- Rhabdomyosarcoma (m11p)
- Osteosarcoma (m13)

All these diseases are rare; 1-10/10,000 born

# Growth media and imprinted genes in mouse

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- Small changes in physical composition of growth media after in vitro fertilisation have consequences for the embryo
- These consequences are at least partly mediated through an altered imprinting
- These changes during first days after fertilisation are irreversible

# Imprinting diseases and IVF

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- Several case-reference studies have suggested a higher proportion of IVF in children with imprinting disorders as compared with a reference population
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# Imprinting diseases and IVF

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If ART are more frequent in children with imprinting diseases it could be a result of

- The in vitro culture of the embryos
- Imprinting disturbances in infertile couples

To address this issue scientifically demands

- Long-term follow up
  - Assessment of the molecular mechanism
  - Routine registration of the specific imprinting disorders
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# Imprinting diseases and IVF

Case study	N	n	Syndr	IVF/ICSI	Ref
DeBaum 03	65	3	BW	3	0.8% AB
Gicquel 03	149	6	BW	4/2	1.3% AB
Maher 03	149	6	BW	3/3	1.2% AB
Halliday 04	37	4	BW	3/1	1/148 MC
Chang 05	341	19	BW	5/5	None
Sutcliffe 06	213	6	BW	1/5	0.8% AB
Cox 02	2	2	AS	0/2	None
Ørstavik 03	1	1	AS	1	None
Ludwig 05	79	3	AS	0/3	None
Sutcliffe 06	384	0	AS	0/0	0.8% AB
Sutcliffe 06	522	2	PWS	0/2	0.8% AB
Moll 03	NA	5	RB	4/1	1.5% AB

Lidegaard et al. *Curr Opin Obstet Gynecol* 2006; 18: 293-6.

# Imprinting diseases and IVF

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- Several case-reference studies have suggested a higher proportion of IVF in children with imprinting disorders as compared with a reference population
  - The studies are small, insufficiently matched
  - No consensus whether ICSI implies a differential risk as compared with conventional IVF
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# Imprinting diseases and IVF

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Follow-up Study	ART	Contr	Imprinting dis.	
			ART	Contr
Lidegaard 05	6052	442,349	0	54
Källén 05	16,280	2,039,943	2	NA

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## Conclusion:

Minor differences cannot be excluded, but there is not a high increase in risk of imprinting disorders after IVF.

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**Lidegaard et al. Hum Reprod 2005; 20: 950-4**  
**Källén et al. Birth Defects Res 2005; 73: 162-9**

# Imprinting diseases and IVF

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## Dutch case-reference study

**Cases:** 63 AS, 86 PWS, 71 BWS, total 220.  
born from 1983 to 2003

**Reference:** All 4,038,279 born 1983-2003

	<b>Cases</b>	<b>Siblings</b>	<b>Reference</b>
TTP>12m	15	8	141,340 (3.5%)
ART preg	14	8	68,651 (1.7%)
Ratio	0.9	1,0	0.5

**Concl:** No difference in ART prevalence when accounting for infertility.

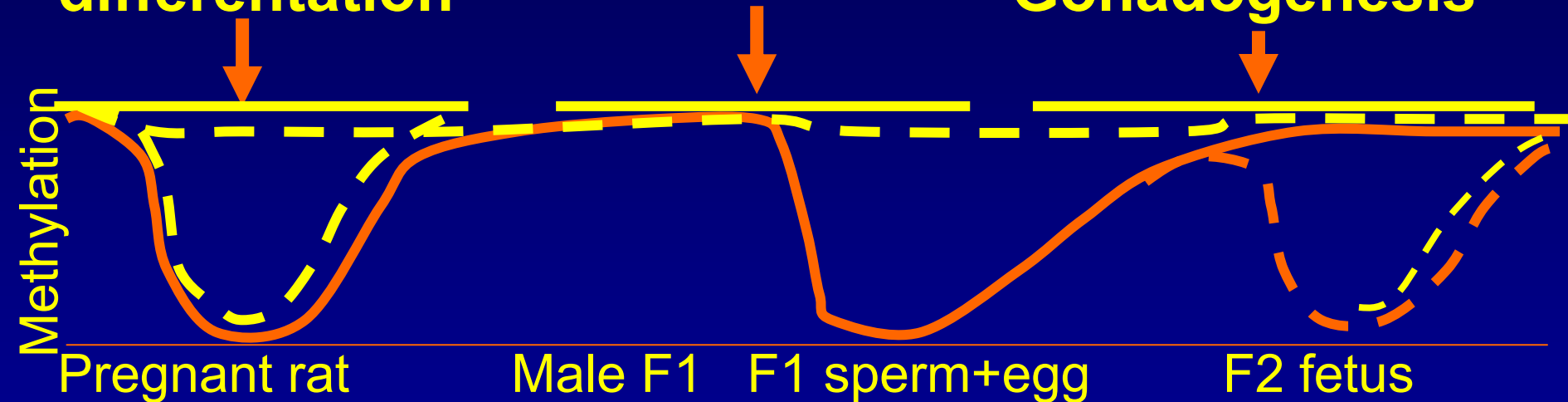
# Transgenerational transmission

Before conception    At conception    After conception

Germ cell  
differentiation

Fertilisation

During  
Gonadogenesis

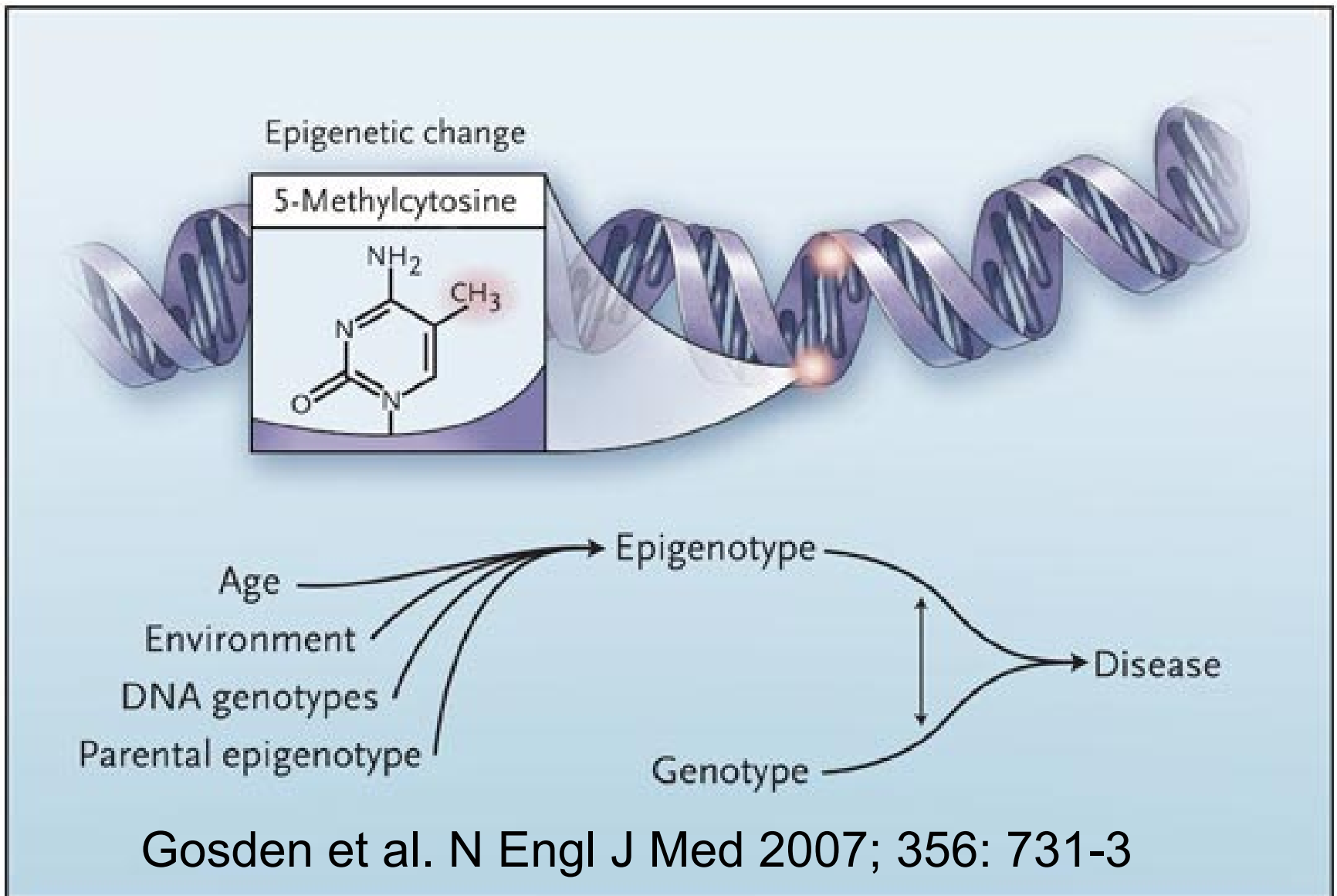


— Somatic cell line (stem cells) in F1

- - - Gonadal cell line (stem cells) in F1

- - - Imprinted genes in F1

# Genetic and epigenetic interaction



# Possible imprinting diseases

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- Autism
- Schizophrenia
- Alzheimer
- Infertility (male)
- Diabetes (IGF-2 disturbances)
- Colon cancer
- Atopic diseases
- Sexual orientation

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**Santos-Reboucas et al. Eur J Hum Genetics 2007; 15: 10-17**  
**Roman et al. Human Fertility 2006; 9: 171-4**

# Thank you

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The presentation will be available on  
[www.Lidegaard.dk/slides](http://www.Lidegaard.dk/slides)  
from Friday

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