PIPADOR REVISION

MRCOG Part 1 Revision Notes

Regulation of the Embryonic Genome

EMBRYOLOGY • LECTURE 54

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 54: Regulation of the Embryonic Genome

Embryology • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

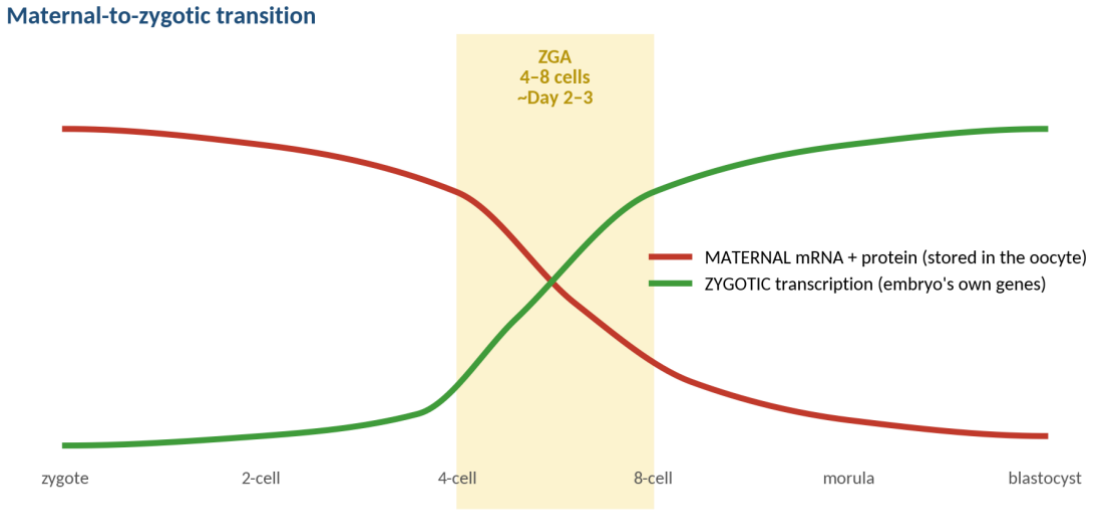
MATERNAL	PATERNAL	EPIGENETICS	SIGNALLING	CLINICAL

LEARNING OBJECTIVES — tick off as you go

- ☐ Describe the maternal-to-zygotic transition.
- ☐ Explain the two waves of epigenetic reprogramming.
- ☐ Describe X-inactivation and its clinical consequences.
- ☐ Explain genomic imprinting and the main imprinting disorders, UPD and moles.
- ☐ Name lineage transcription factors, HOX genes and the main signalling pathways.
- ☐ Apply to ART, mosaicism, PGT and developmental programming.

1 Maternal-to-Zygotic Transition

IN ONE LINE: *The egg's stored RNA and protein run the first divisions; the embryo's own genome takes over at the 4–8-cell stage (~Day 2–3).*



Failure of ZGA → cleavage arrest (seen in some IVF embryos). Key human ZGA factors include DUX4.

Figure 1. Handover from maternal to zygotic control.

2 Epigenetic Reprogramming

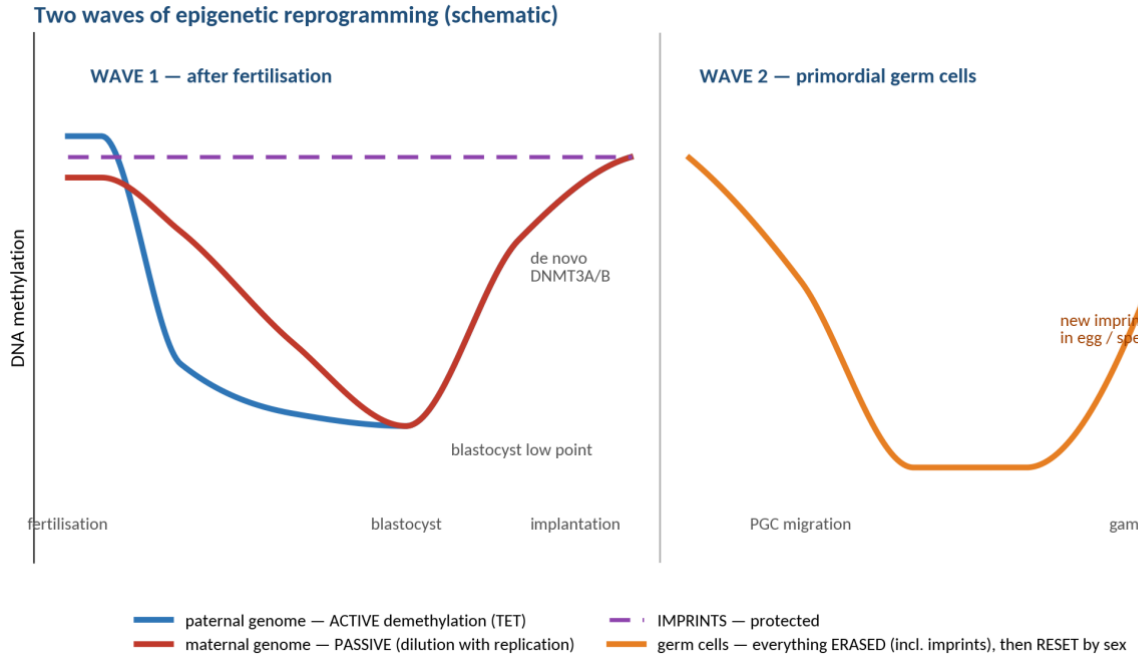


Figure 2. Two waves of DNA methylation reprogramming.

Wave	What happens
1 — after fertilisation	Genome-wide demethylation → totipotency. Paternal: active (TET: 5mC → 5hmC → 5fC → 5caC → base-excision repair). Maternal: mainly passive (dilution with replication). Imprints protected
Re-methylation	From implantation, lineage-specific de novo methylation (DNMT3A/B); DNMT1 maintains patterns at each division
2 — germ cells	PGCs erase everything, including imprints, then set new sex-specific imprints during gametogenesis

3 X-Chromosome Inactivation

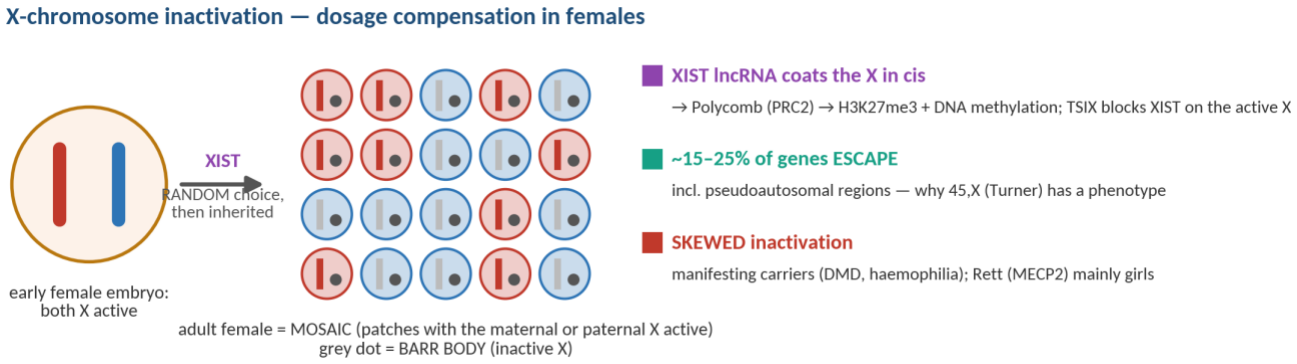


Figure 3. X-inactivation makes every female a mosaic.

- **Timing** in humans is around implantation (human early embryos show XIST on both X chromosomes first). **Imprinted** inactivation of the paternal X in extra-embryonic tissue is clear in **mice**; in the human placenta it appears largely **random**.
- **Klinefelter (47,XXY)**: one X inactivated; extra escape-gene and PAR dosage contribute. **Turner (45,X)**: missing escape-gene dosage.

4 Genomic Imprinting

- **Parent-of-origin, one-allele expression**, set in the gametes by methylation of **imprinting control regions (ICRs)**, kept for life, reset in the germline. Many imprinted genes control **growth** — the 'conflict' idea: paternal genes push growth, maternal genes restrain it.

Locus	Maternally expressed	Paternally expressed	Disorders
15q11–q13	UBE3A	SNRPN, NDN, MAGEL2	Loss of paternal → Prader–Willi; loss of maternal → Angelman
11p15.5	H19, CDKN1C	IGF2, KCNQ1OT1	Beckwith–Wiedemann (overgrowth) / Silver–Russell (undergrowth)
6q24	—	PLAGL1, HYMAI	Paternal over-expression → transient neonatal diabetes
14q32	MEG3	DLK1	Temple (mat UPD14) / Kagami–Ogata (pat UPD14)

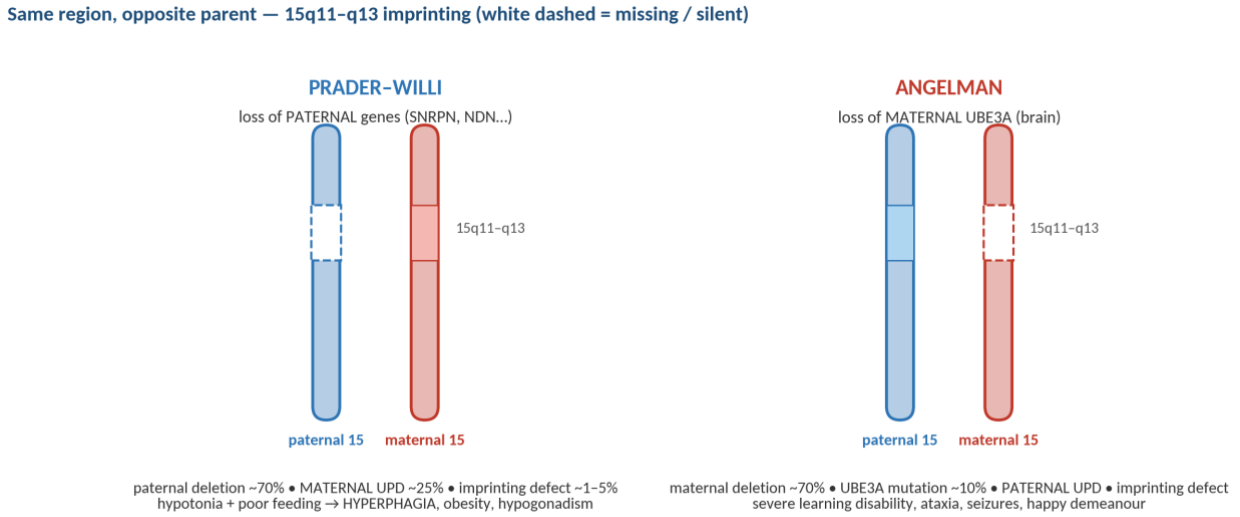


Figure 4. Prader–Willi vs Angelman.

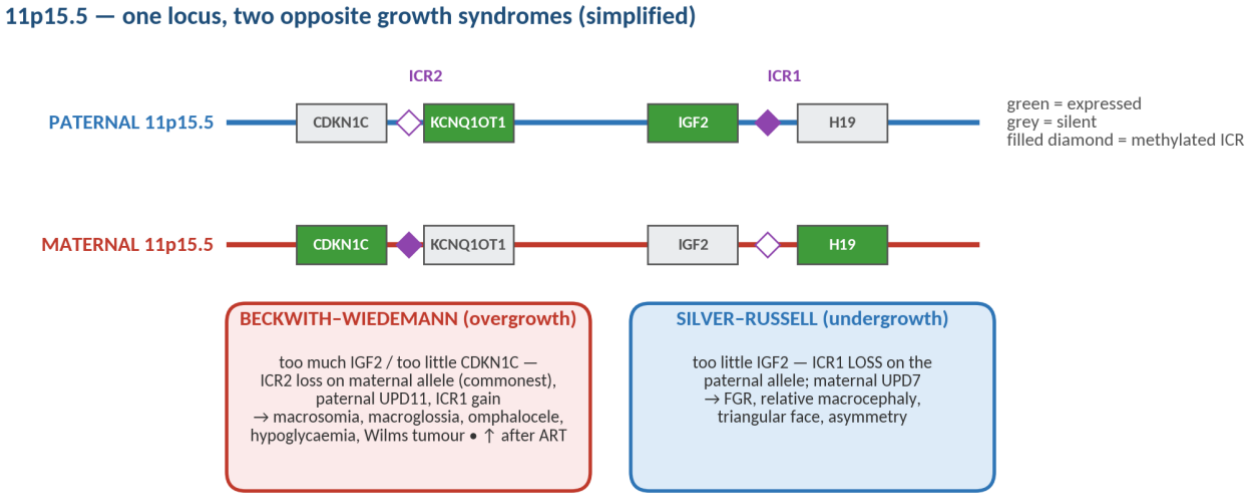


Figure 5. 11p15.5 — BWS and SRS.

MNEMONIC / MEMORY HOOK

'Paternal Prader, Maternal Angelman' — the syndrome is named by the parent whose genes are MISSING. PWS = no paternal 15q11–13 (deletion or maternal UPD); Angelman = no maternal UBE3A.

- **Moles**: complete mole = **androgenetic** diploid (paternal only) → trophoblast overgrowth, no fetus; partial = diandric **triploid** — showing paternal genomes drive trophoblast.

5 Transcription Factors and Signalling

Decision	Key factors
Trophectoderm vs ICM	CDX2 vs OCT4 / NANOG
Epiblast vs hypoblast	OCT4, NANOG, SOX2 vs GATA6, GATA4, SOX17
Germ layers	Endoderm SOX17, FOXA2 • mesoderm BRACHYURY (T), MIXL1 • ectoderm SOX1, PAX6

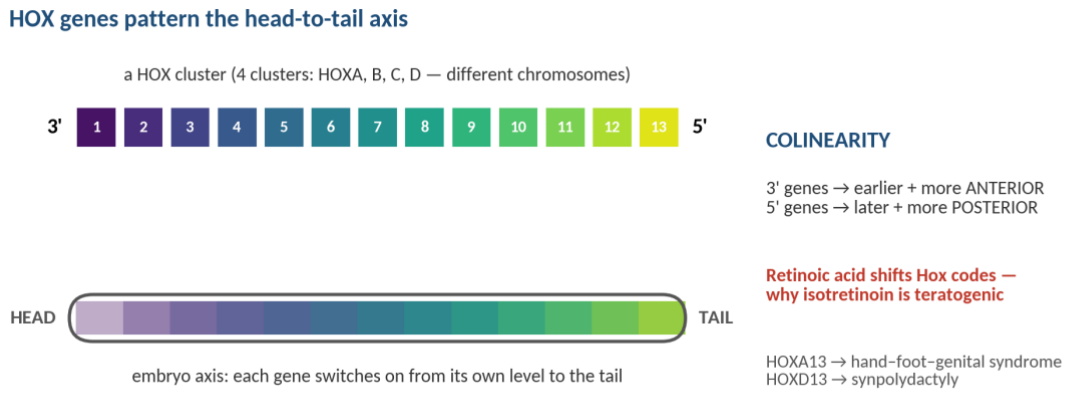


Figure 6. HOX colinearity.

Pathway	Where	Roles / defects
SHH	Notochord, floor plate, limb ZPA	Ventral neural tube, digit pattern; loss → holoprosencephaly
WNT	Dorsal neural tube, many sites	Axis, limb growth, organogenesis
BMP	Roof plate, ventral mesoderm	Dorsal fates, bone; skeletal/cardiac anomalies
FGF	Limb AER	Limb outgrowth; FGFR3 → achondroplasia
NODAL	Node, left side	Left–right asymmetry
NOTCH	Presomitic mesoderm	Somite 'clock', neurogenesis (spondylocostal dysostosis)
Retinoic acid	Mesonephros, paraxial mesoderm	Hox codes, female meiosis onset; excess (isotretinoin) teratogenic

- **Apoptosis** sculpts (e.g. digit separation — failure → **syndactyly**); **Polycomb/Trithorax** keep chromatin states; telomerase is highly active in early embryos and germ cells.

6 Clinical Correlates

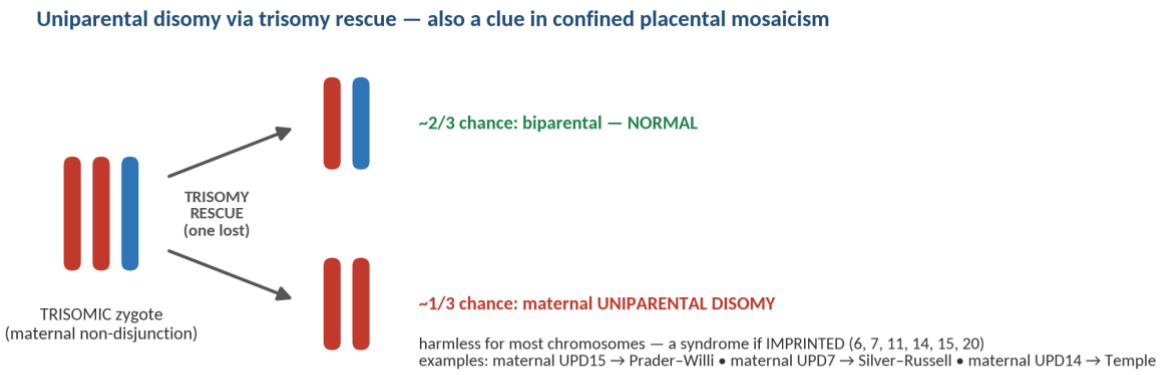


Figure 7. Uniparental disomy through trisomy rescue.

ART AND IMPRINTING

- Small relative increase in **BWS**, Angelman, SRS after ART
- **Absolute risk stays low** — counsel accordingly
- Possible causes: culture, stimulation, underlying subfertility

MOSAICISM + PGT

- Early cleavage errors → mosaicism; **confined placental mosaicism** can cause discordant **NIPT**
- PGT-A / PGT-M / PGT-SR on **trophectoderm biopsy**
- Some embryos are mosaic; **mosaic embryos can still give healthy babies**

DEVELOPMENTAL PROGRAMMING

- Diet, smoking, stress alter fetal methylation
- **Dutch Hunger Winter**: altered **IGF2** methylation decades later
- **Barker / DOHaD**: fetal environment → adult disease

X-LINKED EXAM POINTS

- **Manifesting carriers** from skewed inactivation (DMD, haemophilia, fragile X)
- **Rett** (MECP2) — nearly all girls
- Turner / Klinefelter phenotypes reflect escape genes

★ PEARL

Imprints survive wave 1 but are wiped in wave 2 — that is how each generation re-sets them by sex.

UPD only matters for imprinted chromosomes (6, 7, 11, 14, 15, 20) — or if it makes a recessive mutation homozygous.

7 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

4–8 cells Zygotic genome activation	**~Day 2–3** ZGA timing	**2** Reprogramming waves	**15–25%** X genes escaping
~70% PWS/AS from deletion	**~25%** PWS from maternal UPD	**4** HOX clusters	**6, 7, 11, 14, 15, 20** Imprinted chromosomes

HIGH-YIELD CHECKLIST

- ☐ Maternal RNA drives early cleavage; ZGA at 4–8 cells.
- ☐ Wave 1: paternal active (TET), maternal passive; imprints protected.
- ☐ Wave 2 in PGCs: imprints erased and reset by sex.
- ☐ XIST coats the inactive X → Barr body; random choice → mosaic females.
- ☐ ~15–25% of X genes escape; skewing → manifesting carriers.
- ☐ PWS = no paternal 15q11–13; Angelman = no maternal UBE3A.
- ☐ 11p15.5: BWS (overgrowth, ↑ after ART) vs SRS (undergrowth).
- ☐ 6q24 paternal over-expression → transient neonatal diabetes.
- ☐ CDX2 vs OCT4/NANOG; Brachyury mesoderm; SOX17/FOXA2 endoderm.
- ☐ HOX colinearity; SHH, WNT, BMP, FGF, NODAL, NOTCH, retinoic acid.
- ☐ UPD via trisomy rescue; CPM and discordant NIPT.

Self-assessment — cover the right-hand column

Question	Answer
When is the embryonic genome activated in humans?	4–8-cell stage (~Day 2–3)
Which genome is actively demethylated after fertilisation?	Paternal (TET enzymes)
When are imprints erased?	In primordial germ cells (wave 2)
Which RNA silences the inactive X?	XIST
Why are female carriers sometimes affected?	Skewed X-inactivation
Prader–Willi mechanisms?	Paternal deletion, maternal UPD15, imprinting defect
Angelman gene?	Maternal UBE3A
Imprinting disorder linked to omphalocele and ART?	Beckwith–Wiedemann
Genetic make-up of a complete mole?	Diploid, all paternal (androgenetic)
How does UPD arise most often?	Trisomy rescue

8 References

- Sadler TW. Langman's Medical Embryology. 14th ed. 2019.
- Strachan T, Read A. Human Molecular Genetics. 5th ed. 2018.
- HFEA. Pre-implantation genetic testing and treatment add-ons (online guidance).