PIPADOR REVISION

MRCOG Part 1 Revision Notes

Sex-Linked Disorders

GENETICS • LECTURE 81

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 81: Sex-Linked Disorders

Genetics • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

X-LINKED RECESSIVE	NORMAL X	Y CHROMOSOME	X-LINKED DOMINANT	CLINICAL

LEARNING OBJECTIVES — tick off as you go

- ☐ Know the X and Y chromosomes, pseudoautosomal regions and X-inactivation.
- ☐ Distinguish X-linked recessive, X-linked dominant and Y-linked patterns.
- ☐ Explain fragile X repeat sizes, expansion and premutation effects.
- ☐ Explain manifesting carriers and new-mutation rates.
- ☐ Manage carrier pregnancies — especially haemophilia, DMD and fragile X.

1 The Sex Chromosomes

IN ONE LINE: *Almost all sex-linked disease is X-LINKED: the X carries ~800 genes, the Y fewer than 100 (sex determination + spermatogenesis).*

X: ~800 protein-coding genes • Y: < 100 (mostly sex + fertility) • yellow = pseudoautosomal (inherited like autosomes)

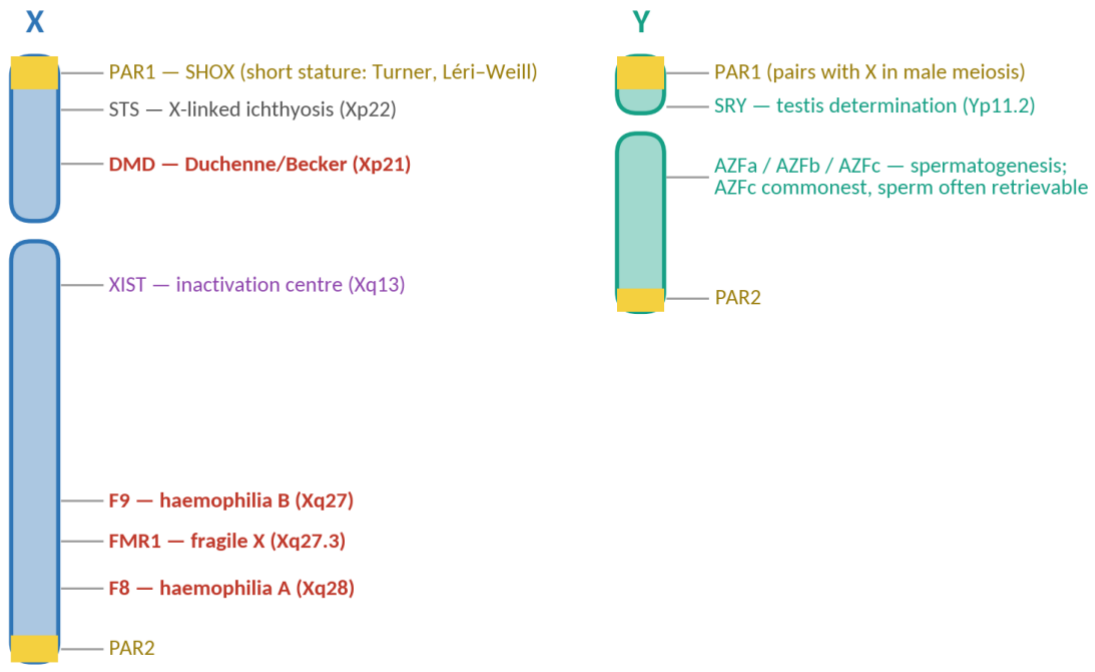


Figure 1. X and Y gene map.

- **Pseudoautosomal regions** (PAR1, PAR2) pair and recombine in male meiosis → inherited like autosomes. **SHOX** (PAR1): one copy → short stature (Turner, Léri–Weill).

2 X-Inactivation

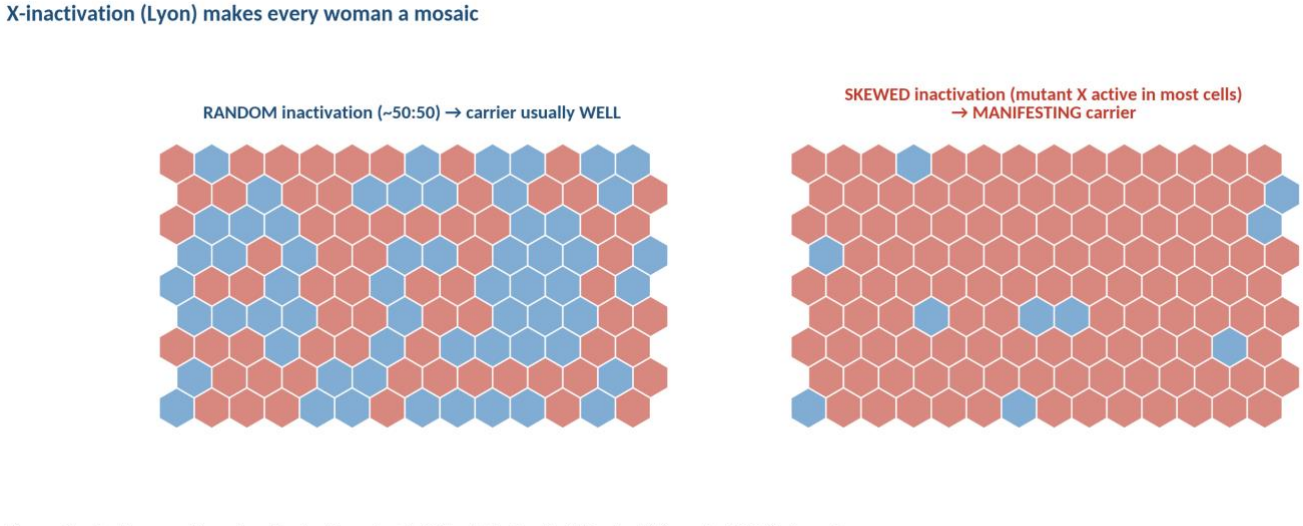


Figure 2. Random vs skewed inactivation.

- In the embryo proper XCI is **random**; it is imprinted (paternal X off) in mouse placenta, but in the **human placenta it is largely random**. Affected females can also arise from homozygosity, X-autosome translocation (normal X switched off), Turner (45,X) or UPD.

3 Inheritance Patterns

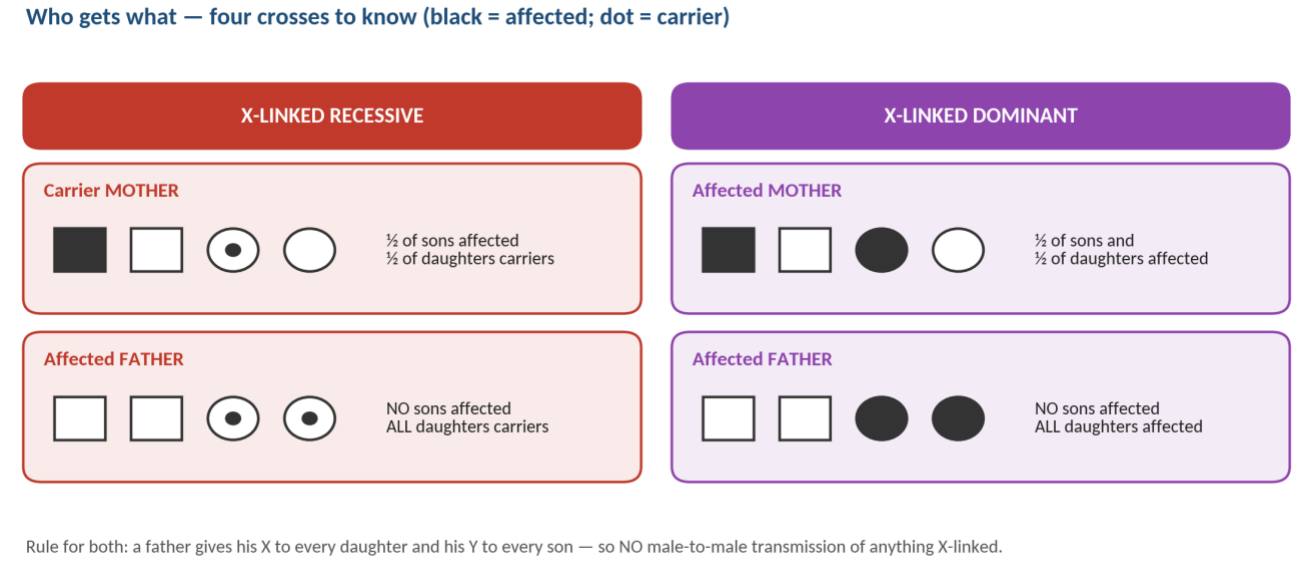


Figure 3. The four crosses.

Disorder	Gene	Notes
Duchenne / Becker	DMD (Xp21)	Proximal weakness, high CK; ~⅓ new mutations; carrier cardiomyopathy
Haemophilia A / B	F8 / F9	A ~1 in 5000 males, B ~1 in 30,000; ~⅓ have no family history
G6PD deficiency	G6PD	Haemolysis with fava beans, some drugs, infection

Disorder	Gene	Notes
Red–green colour blindness	OPN1LW/MW	~8% of men
X-linked ichthyosis	STS	Placental sulphatase deficiency → low maternal oestriol, prolonged labour
X-linked SCID / Hunter / Lesch–Nyhan	IL2RG / IDS / HPRT1	Immunodeficiency / MPS II / gout + self-injury
X-linked dominant	PHEX, MECP2, IKBKG	Hypophosphataemic rickets; Rett and incontinentia pigmenti (usually lethal in males); Aicardi
Y-linked	AZFa/b/c	Azoospermia; AZFc → ICSI possible, sons inherit the deletion

MNEMONIC / MEMORY HOOK

'Dad's X goes to every daughter, Dad's Y to every son' — explains every X-linked father rule (no male-to-male; XLR → all daughters carriers; XLD → all daughters affected).

- **Haldane's one-third**: for a lethal (non-reproducing) X-linked recessive disease at equilibrium, ~⅓ of affected males carry a **new** mutation — so ~⅔ of mothers of an isolated case are carriers (usually less in practice). (Not to be confused with 'Haldane's rule' in evolutionary biology.)

4 Fragile X

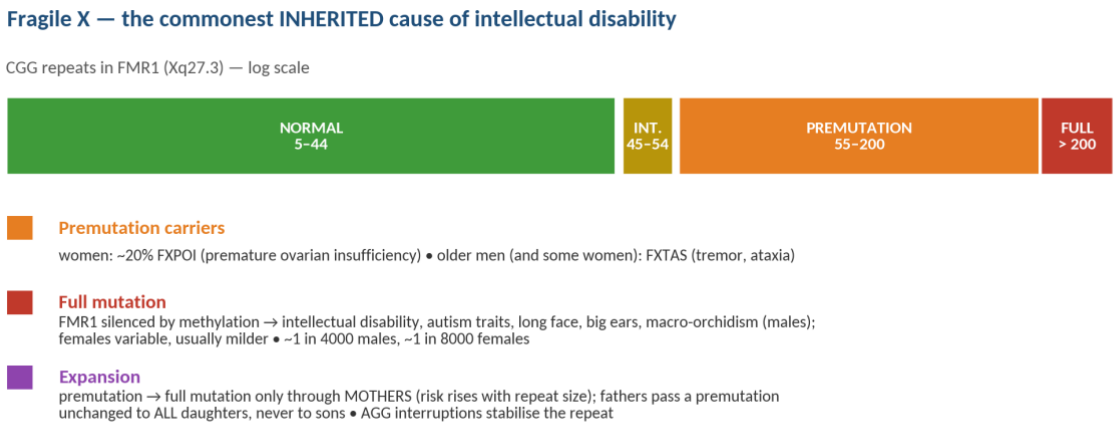


Figure 4. Repeat sizes and consequences.

5 Carriers in Pregnancy

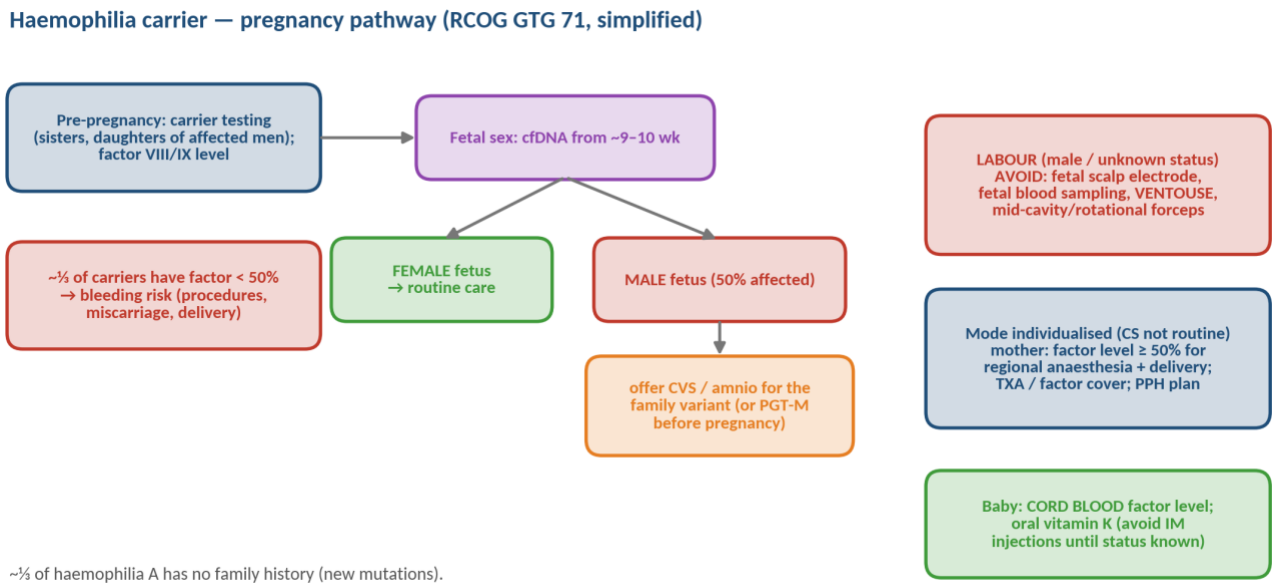


Figure 5. Haemophilia carrier pathway.

DMD CARRIERS

- Some have weakness (manifesting carriers)
- **Dilated cardiomyopathy** — cardiac surveillance (echo/ECG), anaesthetic review
- Fetal sex → CVS for males, or PGT-M

FRAGILE X PREMUTATION

- ~20% FXPOI → don't delay pregnancy; consider egg freezing
- Expansion risk to full mutation rises with repeat size
- Offer cascade testing; PGT-M or prenatal diagnosis

REPRODUCTIVE OPTIONS

- **cfDNA fetal sex** from ~9–10 weeks → invasive test only for males
- CVS 11^{+0}–13^{+6}; amnio ≥ 15 weeks
- PGT-M (or sex selection only where no mutation test exists, HFEA)
- Donor gametes

MALE-LETHAL XLD

- Affected male pregnancies often miscarry
- Pedigree: affected women, few/no affected men, excess miscarriages
- Rett is usually a NEW mutation — low recurrence

★ PEARL

Haemophilia carrier in labour: avoid FSE, FBS, ventouse and mid-cavity/rotational forceps if the baby may be affected; check cord blood.

Fragile X expands only through mothers; fathers pass the premutation unchanged to all daughters.

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

~800 / < 100 Genes on X / Y	**15–25%** X genes escape XCI	**55–200** FMR1 premutation	**> 200** Full mutation
~20% FXPOI in premutation	**~⅓** Haemophilia/DMD new	**~⅓** Carriers factor < 50%	**~9–10 wk** cfDNA fetal sex

HIGH-YIELD CHECKLIST

- ☐ No male-to-male X-linked transmission.
- ☐ XLR: affected father → all daughters carriers; carrier mother → ½ sons affected.
- ☐ XLD: affected father → all daughters affected; some male-lethal (Rett, IP).
- ☐ Y-linked: father → son; AZF deletions, ICSI.
- ☐ PAR genes inherit like autosomes (SHOX).
- ☐ XCI random → mosaic; skewing → manifesting carriers; Blaschko lines.
- ☐ Fragile X ranges; maternal expansion; FXPOI ~20%, FXTAS.
- ☐ Haldane: ~⅓ of isolated lethal XLR cases are new mutations.
- ☐ Haemophilia carrier: factor level, cfDNA sex, avoid FSE/FBS/ventouse, cord blood.
- ☐ X-linked ichthyosis → low oestriol.

Self-assessment — cover the right-hand column

Question	Answer
Can a man pass an X-linked disease to his son?	No — sons get his Y
Daughters of a man with haemophilia?	All obligate carriers
Daughters of a man with XL hypophosphataemia?	All affected
Mechanism of a manifesting carrier?	Skewed X-inactivation
FMR1 premutation range?	55–200 CGG repeats
Ovarian problem in premutation carriers?	Premature ovarian insufficiency (~20%)
Which X-linked dominant disease is usually lethal in males?	Incontinentia pigmenti (also Rett)
Gene in PAR1 linked to short stature?	SHOX
Haemophilia carrier — instruments to avoid?	Ventouse, mid-cavity/rotational forceps (also FSE, FBS)
Pregnancy clue to X-linked ichthyosis?	Low maternal oestriol

7 References

- RCOG Green-top Guideline No. 71. Management of Inherited Bleeding Disorders in Pregnancy. 2017.
- Turnpenny P, Ellard S. Emery's Elements of Medical Genetics. 16th ed. 2021.
- Hagerman RJ et al. Fragile X syndrome. Nat Rev Dis Primers 2017.