PIPADOR REVISION

MRCOG Part 1 Revision Notes

X-Linked Disorders

GENETICS • LECTURE 84

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 84: X-Linked Disorders

Genetics • Visual revision edition — builds on Lecture 81

COLOUR CODE USED THROUGHOUT THESE NOTES

DMD / SEVERE	NORMAL / FETAL	X-LINKED DOMINANT / FRAGILE X	HAEMOPHILIA / BECKER	MANAGEMENT

LEARNING OBJECTIVES — tick off as you go

- ☐ Explain DMD vs Becker (reading-frame rule) and carrier risks.
- ☐ Know haemophilia severity, genetics and pregnancy management of carriers.
- ☐ Understand fragile X full mutation vs premutation, POI and prenatal testing.
- ☐ Recognise G6PD deficiency, X-linked ichthyosis, ALD, Hunter and SCID.
- ☐ Recognise X-linked dominant disorders and counsel on reproductive options.

1 Duchenne and Becker Muscular Dystrophy

IN ONE LINE: *Same gene, different frame: frameshift → no dystrophin (Duchenne); in-frame → shorter working dystrophin (Becker).*

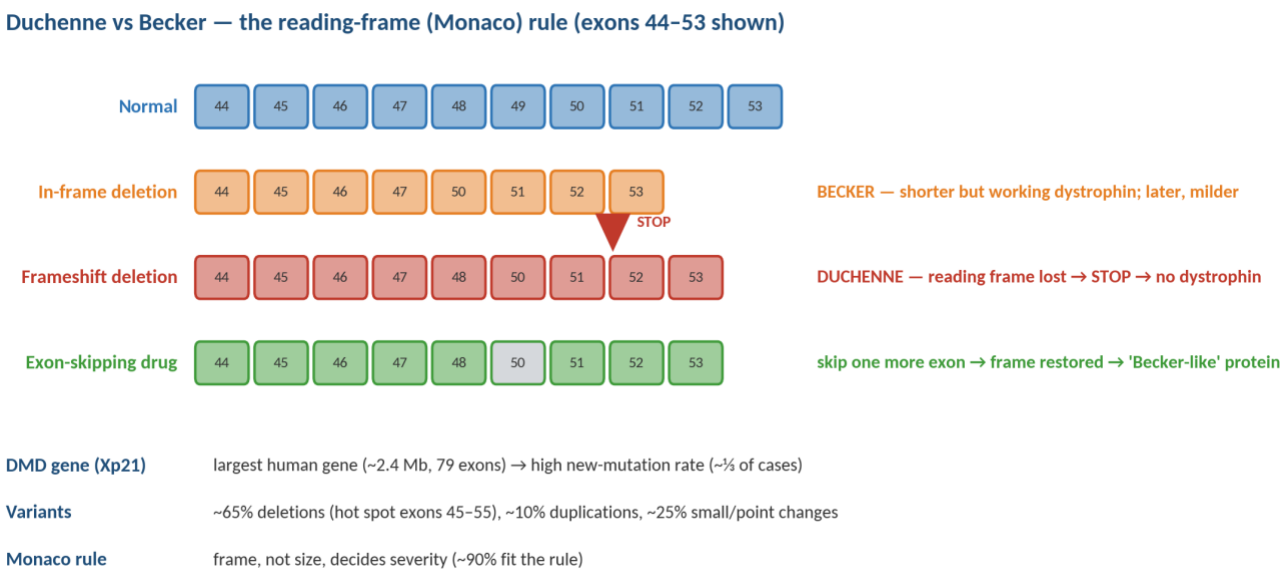


Figure 1. The reading-frame rule.

Topic	Key points
Duchenne	~1 in 3500–5000 boys; weakness from 3–5 y, calf pseudohypertrophy, Gowers' sign, CK very high; wheelchair ~12 y; cardiomyopathy + respiratory failure
Becker	Later onset, slower; cardiomyopathy may dominate
Treatment	Steroids, cardiac + respiratory care; exon-skipping drugs (licensed in the USA for specific exons); gene therapy emerging

Topic	Key points
Carriers	CK raised in many (not all); some weakness (manifesting); dilated cardiomyopathy → regular cardiac review (e.g. echo every 3–5 years) + anaesthetic planning
Mother of an isolated case	Carrier in ~⅔ (Haldane); germline mosaicism means a negative blood test still leaves some recurrence risk

2 Haemophilia A and B

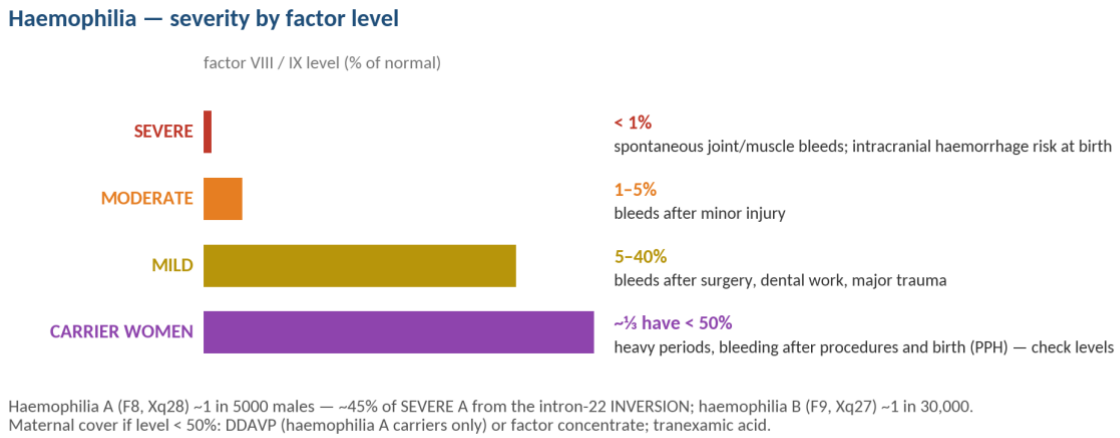


Figure 2. Severity and carriers.

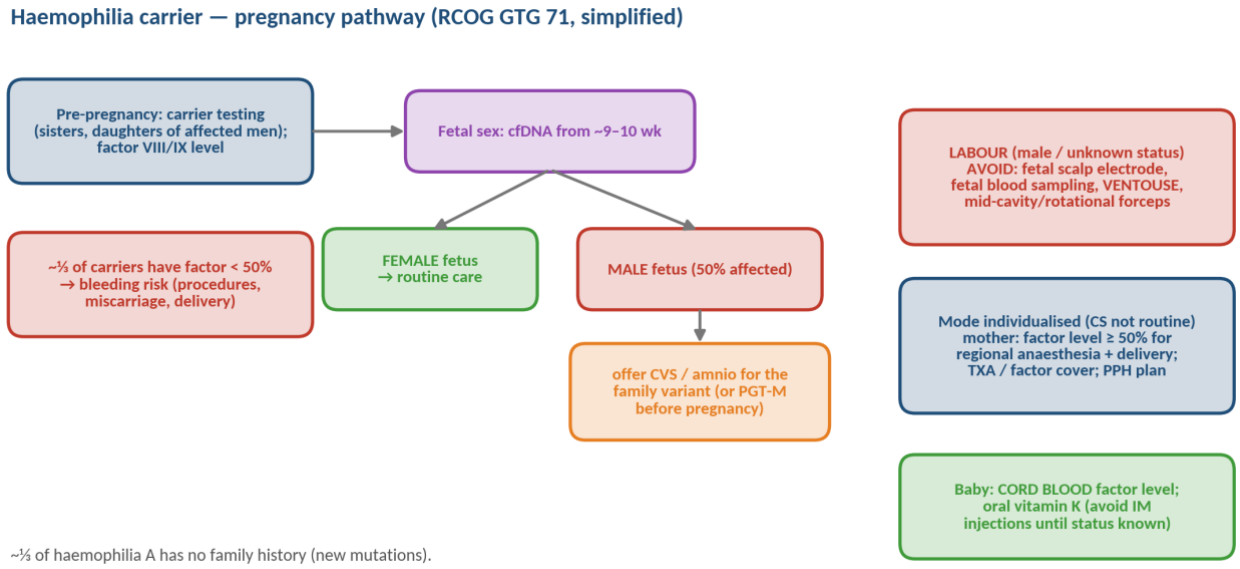


Figure 3. Carrier pregnancy pathway (from Lecture 81).

- **Mode of birth** is decided on obstetric grounds — caesarean is **not** routinely needed for a possibly affected boy; avoid prolonged labour, ventouse, mid-cavity/rotational forceps, FSE and FBS. Check maternal levels in the third trimester; cover with DDAVP (haemophilia A) or factor concentrate if < 50%.

MNEMONIC / MEMORY HOOK

'Haemophilia A = Eight (Xq28), B = nine (Christmas, Xq27)' — A is ~6× commoner; ~45% of severe A is the intron-22 inversion.

3 Fragile X and the Premutation

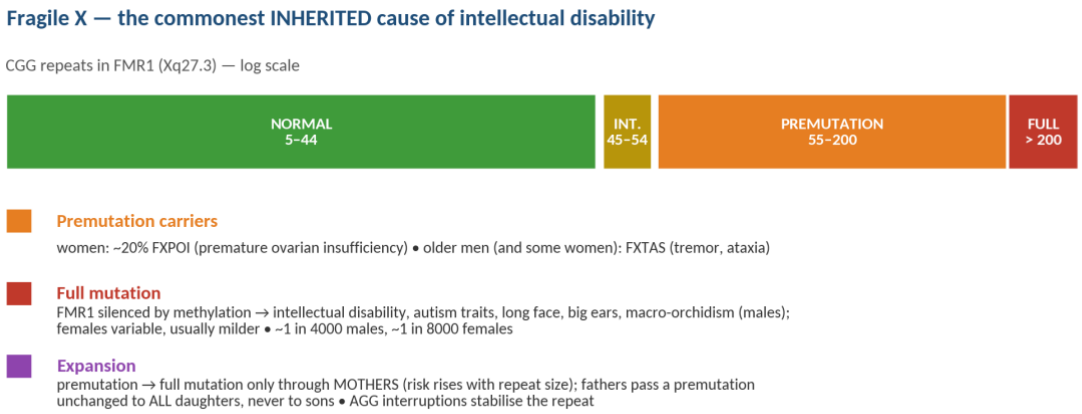


Figure 4. Repeat sizes (from Lecture 81).

Topic	Key points
Full mutation (> 200)	FMR1 methylated → no FMRP (synaptic protein) → intellectual disability, autism, long face, large ears, macro-orchidism, hypermobility, MVP; girls milder
Premutation (55–200)	FXPOI ~20% of women; FXTAS (tremor, ataxia) mainly older men; not 'just a carrier'
Who to test	Unexplained POI (premutation in ~2–5% isolated, ~10–15% familial), family history of learning disability/autism, ataxia
Prenatal testing	CVS or amnio — repeat size by PCR + Southern blot; methylation may be incomplete in chorionic villi → amniocentesis sometimes needed to confirm

4 Other X-Linked Recessive Conditions

Condition	Key points
G6PD deficiency	Commonest enzyme deficiency; African, Mediterranean, Asian; haemolysis with fava beans, primaquine, dapsone, sulfonamides, nitrofurantoin, rasburicase, methylene blue, infection; neonatal jaundice
X-linked ichthyosis	STS deletion → low maternal oestriol, prolonged labour (figure 5)
Adrenoleukodystrophy	ABCD1; very-long-chain fatty acids; childhood cerebral form or adult AMN; adrenal insufficiency
X-SCID / Wiskott–Aldrich	Severe immunodeficiency; SCID newborn screening under evaluation in England; no live vaccines (BCG) until excluded
Hunter (MPS II)	IDS — the only X-linked MPS; enzyme replacement

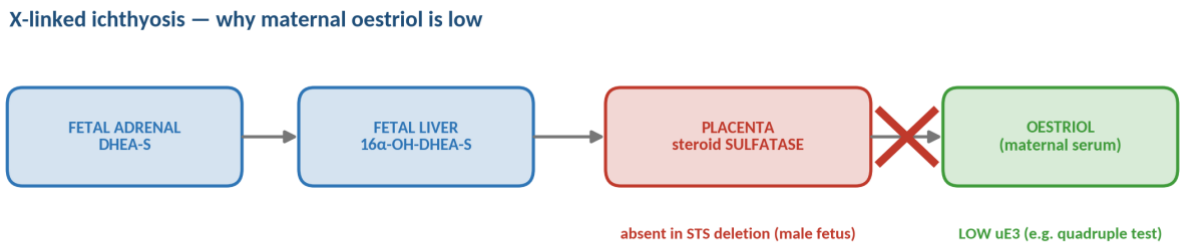


Figure 5. Why oestriol is low.

5 X-Linked Dominant and Manifesting Carriers

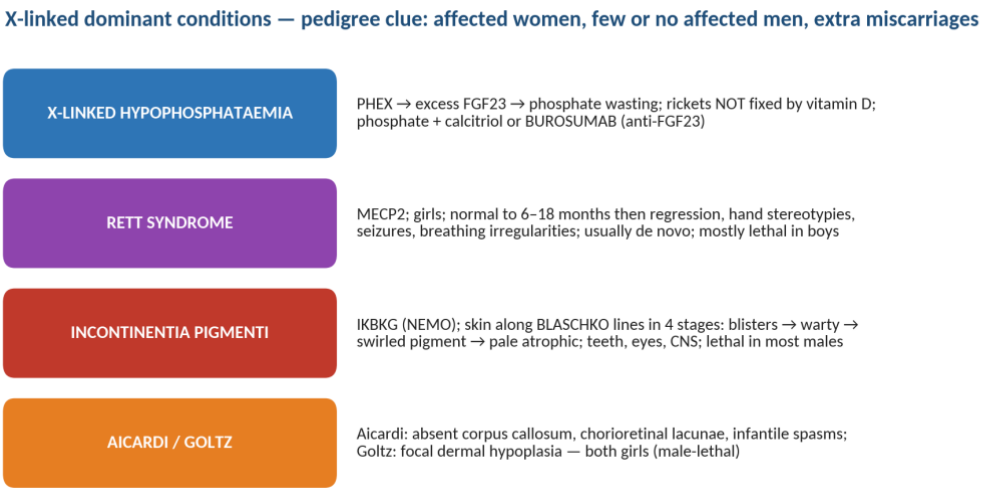


Figure 6. X-linked dominant conditions.

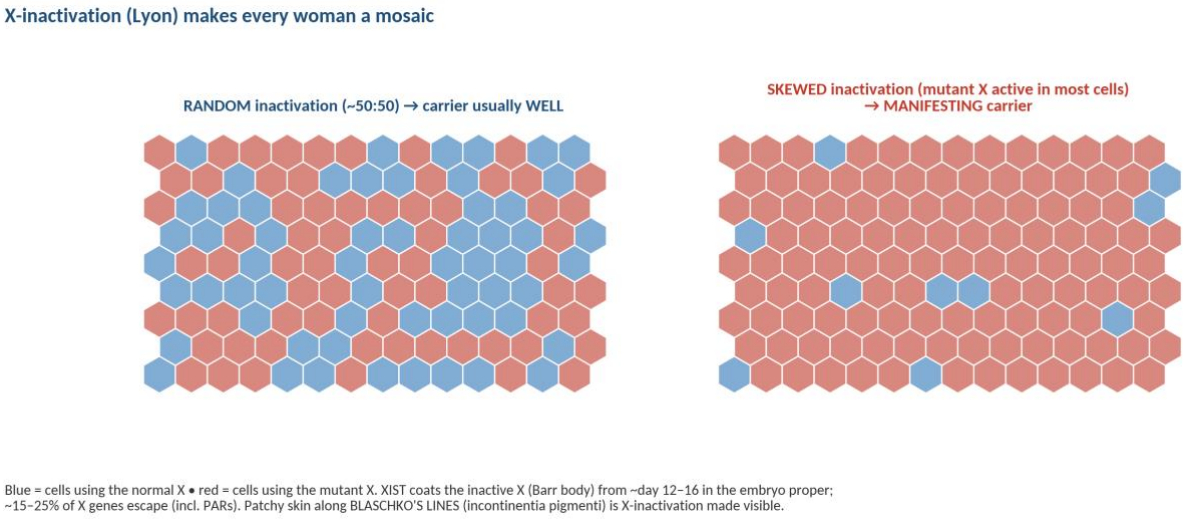


Figure 7. Random vs skewed X-inactivation (from Lecture 81).

6 In Clinic

X-linked conditions in clinic — recognise, test, cascade

Presentation	Think	Test	Then
Boy, 3–5 y: late walking, calf hypertrophy, Gowers' sign	DMD	CK (very high) → DMD deletion/duplication test	test MOTHER, sisters, maternal aunts; carrier cardiac checks
Boy with bleeding after circumcision / big bruises	HAEMOPHILIA	APTT ↑, factor VIII / IX assay	carrier testing; plan future pregnancies (fetal sex, CVS)
Woman < 40 with POI	FRAGILE X PREMUTATION	FMR1 repeat size (+ karyotype, antibodies)	~2–5% of isolated POI, ~10–15% if familial
Boy with intellectual disability ± autism, long face, big ears	FRAGILE X	FMR1 PCR + methylation	mother is a carrier; test her relatives
Haemolysis after primaquine, sulfonamide, nitrofurantoin, fava beans	G6PD DEFICIENCY	G6PD assay (after recovery — young cells mask it)	avoid triggers (also dapsone, rasburicase, methylene blue)
Girl: regression at 6–18 mo, hand-wringing, seizures	RETT (XLD)	MECP2 testing	usually NEW — low recurrence

Figure 8. Presentations, tests and cascade.

REPRODUCTIVE OPTIONS

- **cfDNA fetal sex** ~9–10 wk (> 99% accurate) → invasive testing for boys only
- CVS 11^{+0}–13^{+6} / amnio ≥ 15 wk (~0.5% loss risk or less)
- **PGT-M** (HFEA list); sex selection only where no specific test
- Non-medical sex selection (incl. sperm sorting) is **illegal in the UK**

CASCADE TESTING

- After a diagnosis, offer testing to the mother, sisters, maternal aunts and their daughters
- Female carriers can then plan pregnancies
- Remember carriers' own health: DMD heart, haemophilia bleeding, FXPOI

★ PEARL

Monaco rule: frame, not size — frameshift = Duchenne, in-frame = Becker.

Low uE3 on serum screening with a male fetus → think X-linked ichthyosis (and Smith–Lemli–Opitz, T18).

7 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

Xp21 DMD gene	**~65%** DMD deletions	**< 1 / 1–5 / 5–40%** Severe / mod / mild	**~45%** Severe A = inversion
~⅓ Carriers factor < 50%	**~20%** FXPOI	**2–5%** Isolated POI = premut.	**~⅓** New mutations (lethal XLR)

HIGH-YIELD CHECKLIST

- ☐ DMD Xp21, largest gene; frameshift = DMD, in-frame = Becker; exon skipping.
- ☐ DMD carriers: CK, weakness, cardiomyopathy surveillance.
- ☐ Haemophilia A (F8, Xq28) > B (F9); severity by factor level; intron-22 inversion.
- ☐ Carrier pregnancy: levels, cfDNA sex, no FSE/FBS/ventouse/rotational forceps, cord blood, oral vit K.
- ☐ Fragile X: full > 200 (methylated); premutation → FXPOI, FXTAS.
- ☐ Test FMR1 in unexplained POI.
- ☐ G6PD triggers; X-linked ichthyosis → low oestriol.
- ☐ XLD: XLH (burosumab), Rett, incontinentia pigmenti (Blaschko lines).
- ☐ Manifesting carriers = skewed XCI (or X-autosome translocation).
- ☐ Options: cfDNA sex, CVS/amnio, PGT-M; no non-medical sex selection in UK.

Self-assessment — cover the right-hand column

Question	Answer
State the Monaco rule.	Frameshift deletion → Duchenne; in-frame → Becker
Cardiac risk in DMD carriers?	Dilated cardiomyopathy
Gene and locus of haemophilia A?	F8, Xq28
Commonest variant in severe haemophilia A?	Intron-22 inversion (~45%)
Is caesarean routine for a possibly affected boy?	No — decide on obstetric grounds
Which premutation complication affects women?	FXPOI (~20%)
Why may CVS be inconclusive for fragile X?	Methylation may be incomplete in chorionic villi
Three drugs to avoid in G6PD deficiency?	Primaquine, dapsone, nitrofurantoin (also sulfonamides, rasburicase)
Why is oestriol low in X-linked ichthyosis?	No placental steroid sulfatase to process fetal DHEA-S
Skin pattern in incontinentia pigmenti?	Lines of Blaschko (4 stages)

8 References

- RCOG Green-top Guideline No. 71. Management of Inherited Bleeding Disorders in Pregnancy. 2017.
- Birnkrant DJ et al. Diagnosis and management of Duchenne muscular dystrophy. Lancet Neurol 2018.
- Hagerman RJ et al. Fragile X syndrome. Nat Rev Dis Primers 2017.