PIPADOR REVISION

MRCOG Part 1 Revision Notes

Autosomal Recessive Disorders

GENETICS • LECTURE 83

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 83: Autosomal Recessive Disorders

Genetics • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

AFFECTED / CF	CARRIER	HAEMOGLOBIN	SCREENING	METABOLIC / OTHER

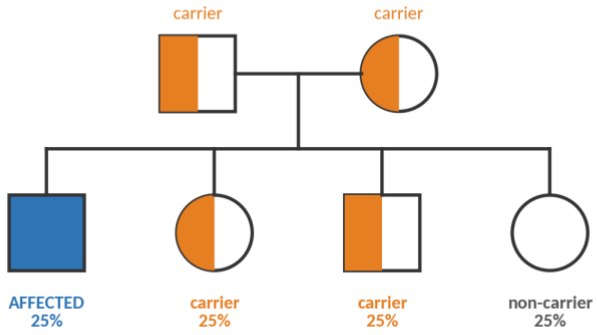
LEARNING OBJECTIVES — tick off as you go

- ☐ Recognise AR inheritance and calculate carrier and recurrence risks.
- ☐ Explain heterozygote advantage, founder effects and consanguinity.
- ☐ Describe CF, sickle cell, the thalassaemias and CAH.
- ☐ Know UK antenatal and newborn screening for AR conditions.
- ☐ Manage pregnancy in women with sickle cell, CF, PKU and thalassaemia.

1 Inheritance and Risk

IN ONE LINE: *Both copies faulty: affected siblings with healthy (carrier) parents, both sexes, 25% each pregnancy. Most carriers never know until they have an affected child — hence screening.*

Autosomal recessive — two carriers (orange half = carrier, blue = affected)



Every pregnancy	1 in 4 affected — chance has no memory
Healthy sibling	⅔ chance of being a carrier
Carrier × non-carrier	no affected children; ½ carriers
Affected × carrier	½ affected ('pseudo-dominant' in consanguineous / high-frequency groups)
Affected × non-carrier	all children carriers

Figure 1. Two carriers.

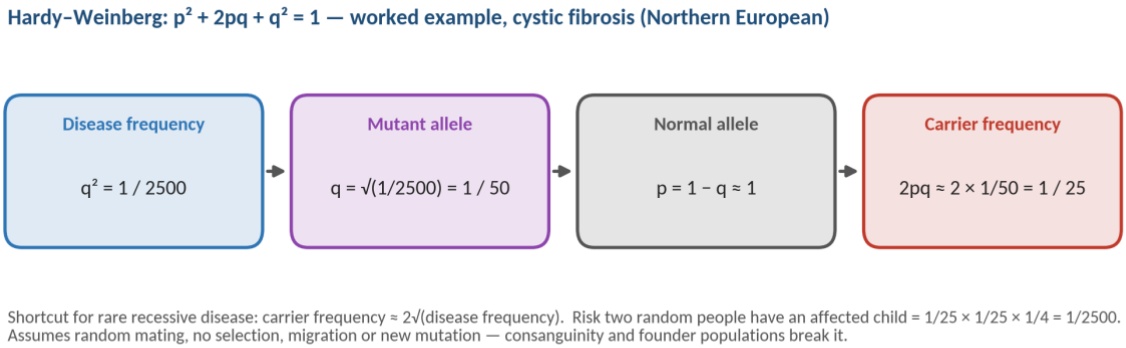


Figure 2. Hardy–Weinberg (from Lecture 78).

- **Heterozygote advantage**: sickle and thalassaemia carriers resist severe malaria → high carrier rates where malaria was common. **Founder effects**: a small founding population → high frequency (Tay–Sachs in Ashkenazi Jews).

2 Key Conditions

Condition	Gene	Notes
Cystic fibrosis	CFTR (7q31)	Carriers ~1 in 25 (N Europe); F508del ~70% of alleles; lungs, pancreas, meconium ileus, CBAVD; sweat chloride; modulators (elexacaftor/tezacaftor/ivacaftor) transforming survival
Sickle cell	HBB Glu6Val	HbSS (also HbSC, HbS/β-thal); crises, asplenia, stroke
β-thalassaemia	HBB	Carrier: microcytosis, HbA2 > 3.5%; major: transfusion-dependent from ~6 months
α-thalassaemia	HBA1/HBA2	4 genes — see figure 3
CAH (21-OH)	CYP21A2	Carriers ~1 in 60; classical ~1 in 15,000 (¾ salt-wasting); non-classical mimics PCOS (Lecture 65)
Tay–Sachs / Gaucher	HEXA / GBA	Ashkenazi founders; Gaucher has enzyme replacement
PKU / galactosaemia	PAH / GALT	PKU on heel prick; diet
SMA	SMN1	Carriers ~1 in 40–50; nusinersen, gene therapy, risdiplam
Haemochromatosis / Wilson / Friedreich	HFE / ATP7B / FXN	Iron overload (C282Y) / copper / GAA repeat ataxia

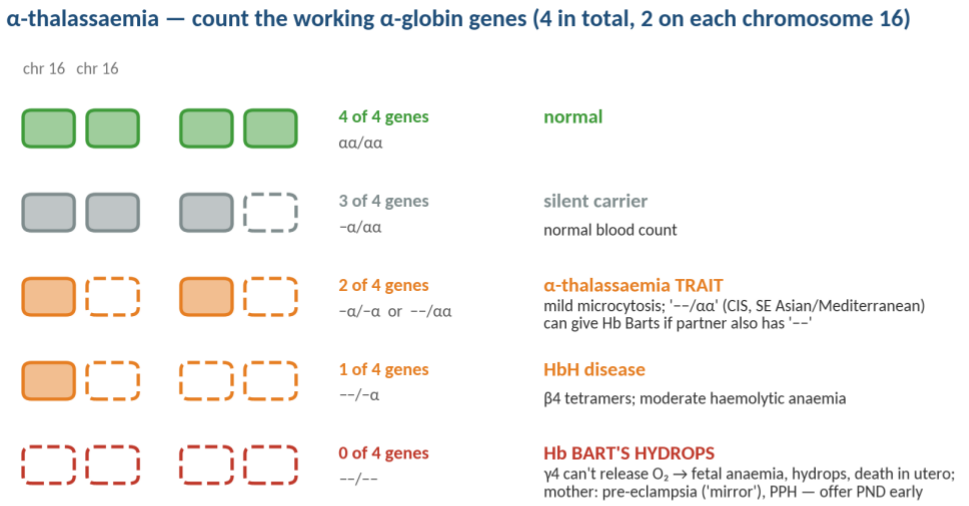


Figure 3. α- and β-thalassaemia and sickle.

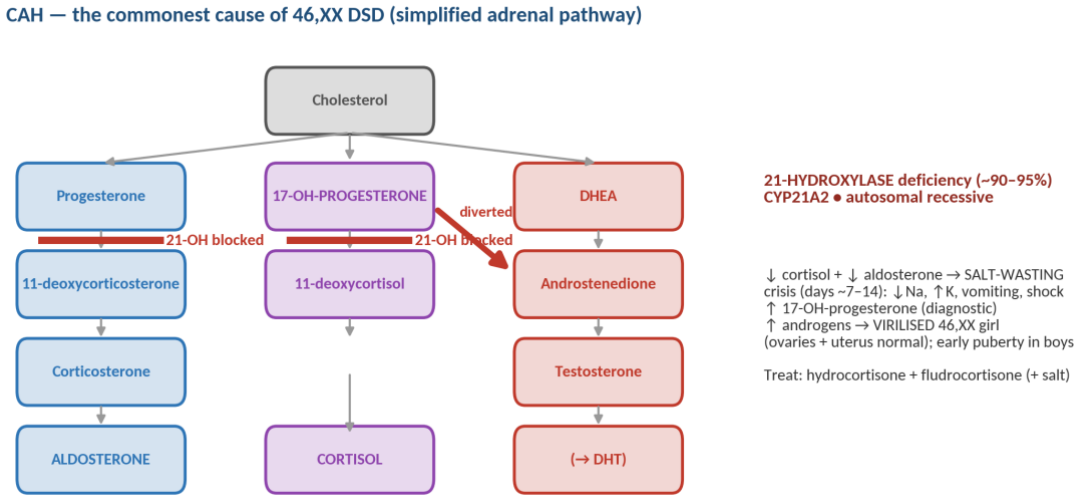


Figure 4. CAH (from Lecture 65).

- **CAH antenatal dexamethasone** to reduce virilisation of 46,XX fetuses is **experimental/controversial** (exposure of unaffected fetuses; long-term safety) — research settings only.

3 Screening

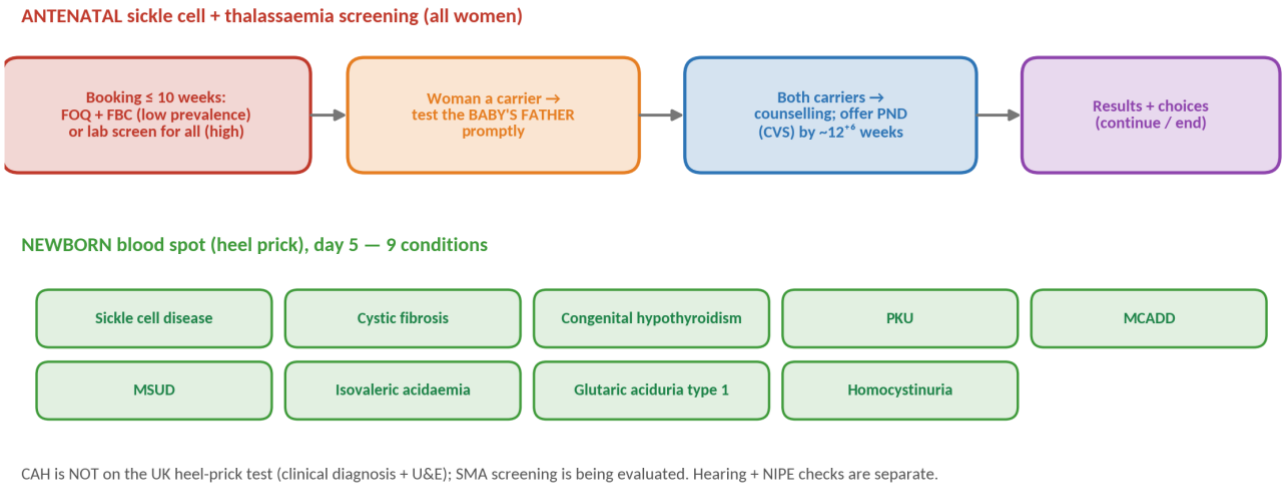


Figure 5. UK antenatal and newborn screening.

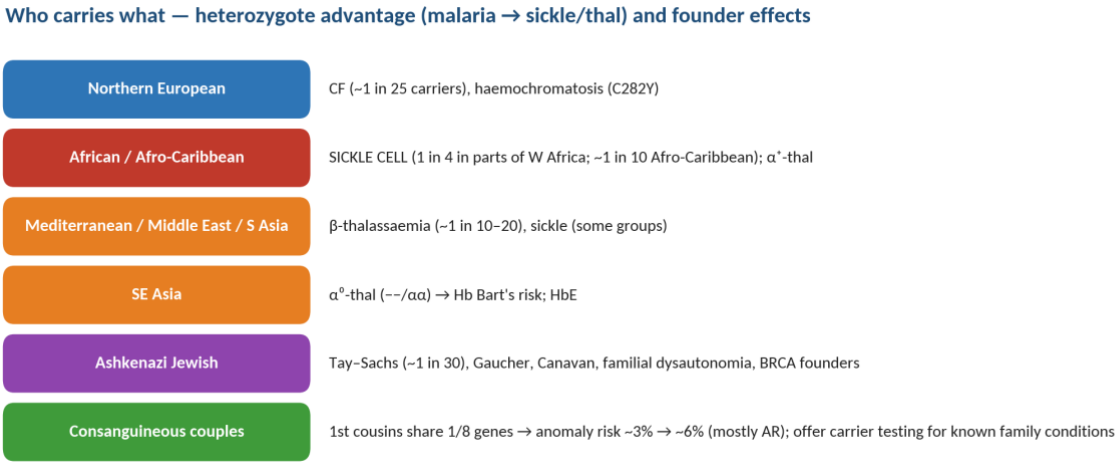


Figure 6. Ancestry, founders and consanguinity.

- **Expanded (pan-ethnic) carrier screening** tests hundreds of genes regardless of ancestry; finds ~1–4% of couples both carrying a severe condition. Available privately; **not NHS routine**.

MNEMONIC / MEMORY HOOK

'Both carriers? Four options' — natural conception + prenatal diagnosis, PGT-M, donor gametes, or accept/adopt. Test the father EARLY so CVS can be offered.

4 Pregnancy in Women with AR Conditions

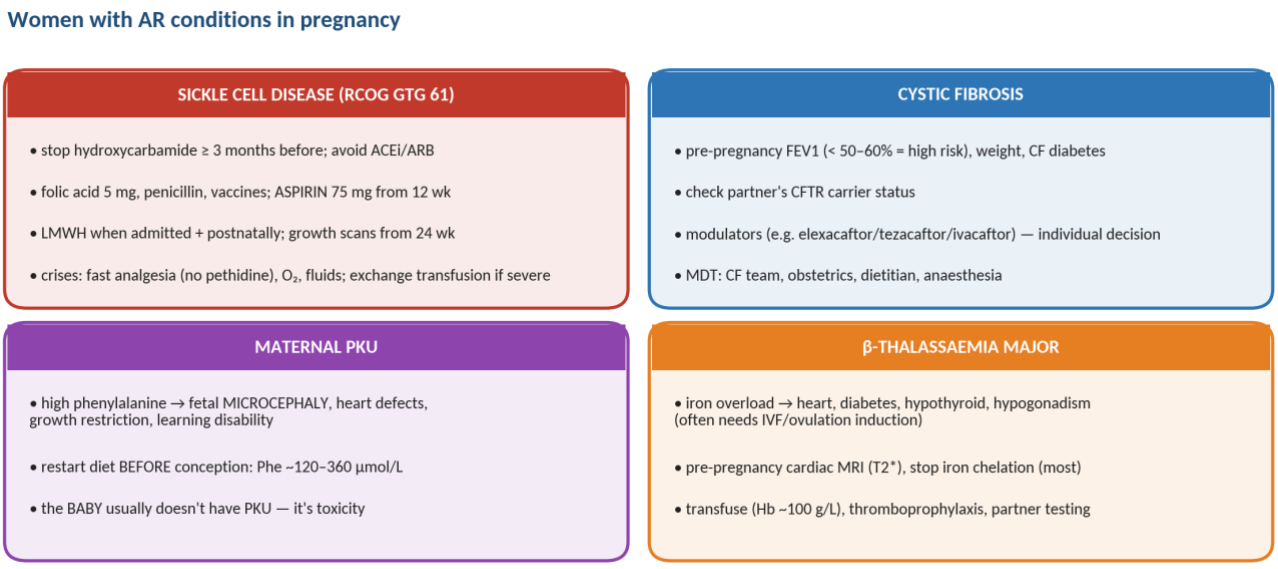


Figure 7. Pregnancy management.

★ **PEARL**

Woman is a sickle/thal carrier → test the baby's father now. Both carriers → PND by ~12^{+6} weeks if wanted.

α^0 (−−/αα) carriers (SE Asian/Mediterranean) risk Hb Bart's hydrops; α^+ (−α/−α) carriers (often African) do not.

5 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

25% / 50% / 25% Affected / carrier / clear	**⅔** Healthy sib a carrier	**1 in 25** CF carriers	**~70%** F508del alleles
> 3.5% HbA2 in β-thal trait	**≤ 10 wk** SCT screen by	**9** Heel-prick conditions	**120–360** Maternal PKU Phe (µmol/L)

HIGH-YIELD CHECKLIST

- ☐ AR: horizontal, carrier parents, 25%; healthy sib ⅔ carrier.
- ☐ Hardy–Weinberg: carriers ≈ 2√(incidence).
- ☐ Heterozygote advantage (malaria); founder effects; consanguinity ~3% → ~6%.
- ☐ CF: CFTR, F508del, CBAVD, sweat test, modulators.
- ☐ Sickle: Glu6Val; β-thal trait HbA2 > 3.5%.
- ☐ α-thal: 4 genes; cis −−/αα → Hb Bart's risk.
- ☐ CAH: 21-OH; salt-wasting; NOT on UK heel prick.
- ☐ UK heel prick: 9 conditions; antenatal SCT ≤ 10 wk, partner test, PND by ~12^{+6}.
- ☐ Sickle pregnancy: aspirin, 5 mg folate, LMWH on admission + postnatal, stop hydroxycarbamide.
- ☐ Maternal PKU: diet before conception (Phe 120–360).

Self-assessment — cover the right-hand column

Question	Answer
Risk of an affected child for two carriers?	25% each pregnancy
Carrier frequency if incidence is 1 in 10,000?	q = 1/100 → ~1 in 50
Commonest CF variant?	F508del (ΔF508)
Male infertility in CF?	Congenital bilateral absence of the vas deferens
β-thal trait lab clue?	Microcytosis with HbA2 > 3.5%
Genotype causing Hb Bart's hydrops?	−−/−− (all four α genes deleted)
Is CAH on the UK heel-prick test?	No
Booking test for haemoglobinopathy — by when?	≤ 10 weeks
Low-dose aspirin in sickle cell pregnancy?	Yes, from 12 weeks
Fetal effect of uncontrolled maternal PKU?	Microcephaly, heart defects, FGR, learning disability

6 References

- RCOG Green-top Guideline No. 61. Management of Sickle Cell Disease in Pregnancy. 2011.
- RCOG Green-top Guideline No. 66. Management of Beta Thalassaemia in Pregnancy. 2014.
- NHS Sickle Cell and Thalassaemia Screening Programme; NHS Newborn Blood Spot Screening Programme — standards.