PIPADOR REVISION

MRCOG Part 1 Revision Notes

Mutations and DNA Repair

MOLECULAR BIOLOGY • LECTURE 90

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 90: Mutations and DNA Repair

Molecular biology • Visual revision edition — builds on Lecture 87

COLOUR CODE USED THROUGHOUT THESE NOTES

PURINE / INFO	MUTATION / DAMAGE	REPAIR / BENIGN	SYNDROMES / METHYLATION	CLINICAL / DRUGS

LEARNING OBJECTIVES — tick off as you go

- ☐ Classify mutations, including transitions, transversions and structural changes.
- ☐ Explain spontaneous and induced causes of mutation, including the CpG hotspot.
- ☐ Describe the repair pathways and the syndromes caused by their failure.
- ☐ Know mutation rates, the paternal age effect, HGVS naming and variant classification.
- ☐ Apply to tumour testing, pharmacogenomics and genomic medicine in the UK.

1 Types of Mutation

IN ONE LINE: *A mutation is a heritable change in DNA sequence — from one base to whole chromosome segments. Where it falls (coding, splice site, regulatory) and whether it keeps the reading frame decide its effect.*

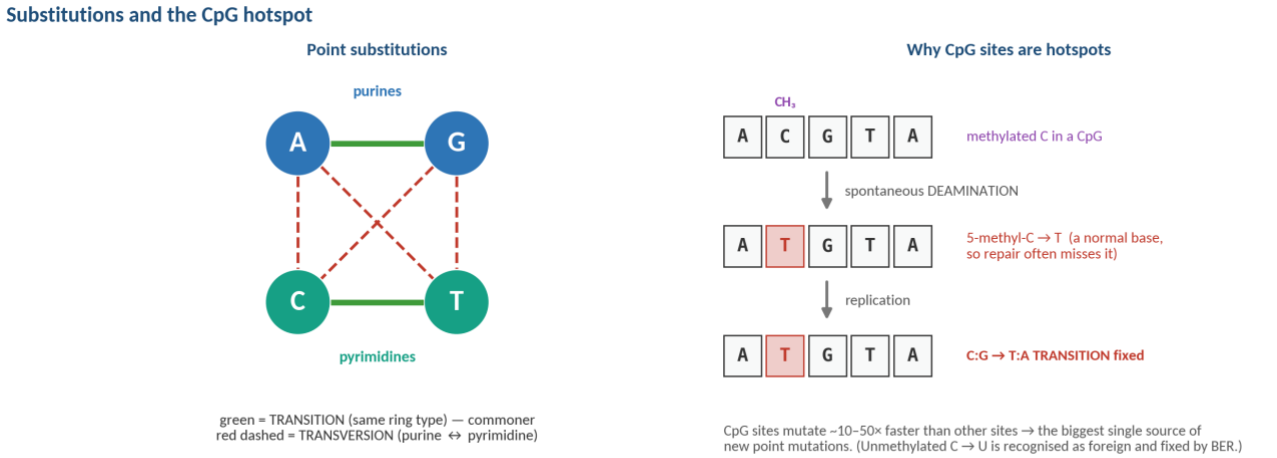


Figure 1. Transitions, transversions and CpG deamination.

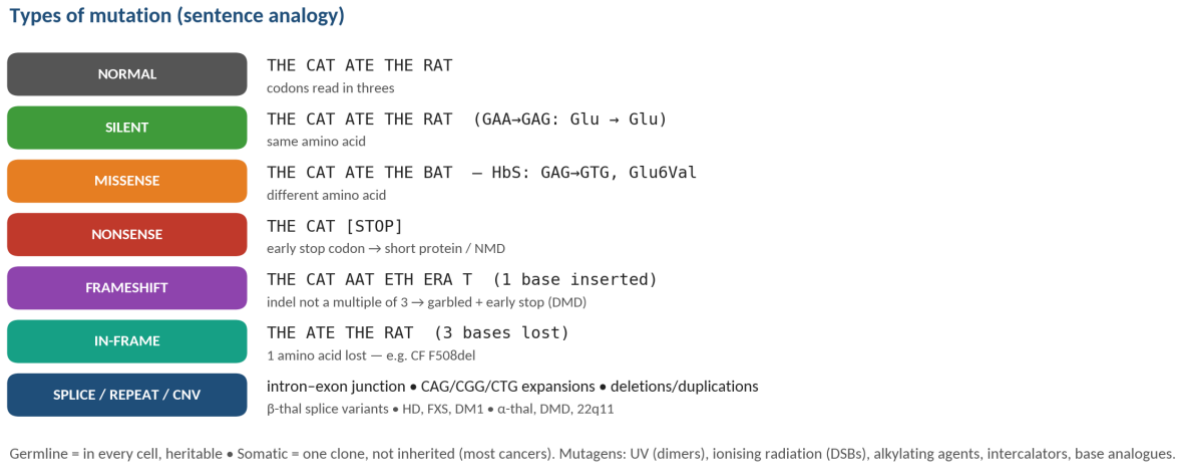


Figure 2. Mutation types (from Lecture 87).

Larger / regulatory changes	Examples
Large deletions / duplications, CNVs	DMD deletions; 22q11.2 deletion (DiGeorge); PMP22 duplication (Charcot–Marie–Tooth 1A); α-thalassaemia deletions
Translocations / inversions	Balanced carriers → miscarriage, unbalanced offspring (Lecture 86, PGT-SR); F8 intron-22 inversion
Repeat expansions	HD (CAG), DM1 (CTG), fragile X (CGG), Friedreich (GAA) — replication slippage → anticipation
Regulatory / UTR	Promoter (some β-thal), enhancer (tissue-specific), UTR (stability/translation)

2 Causes of Mutation

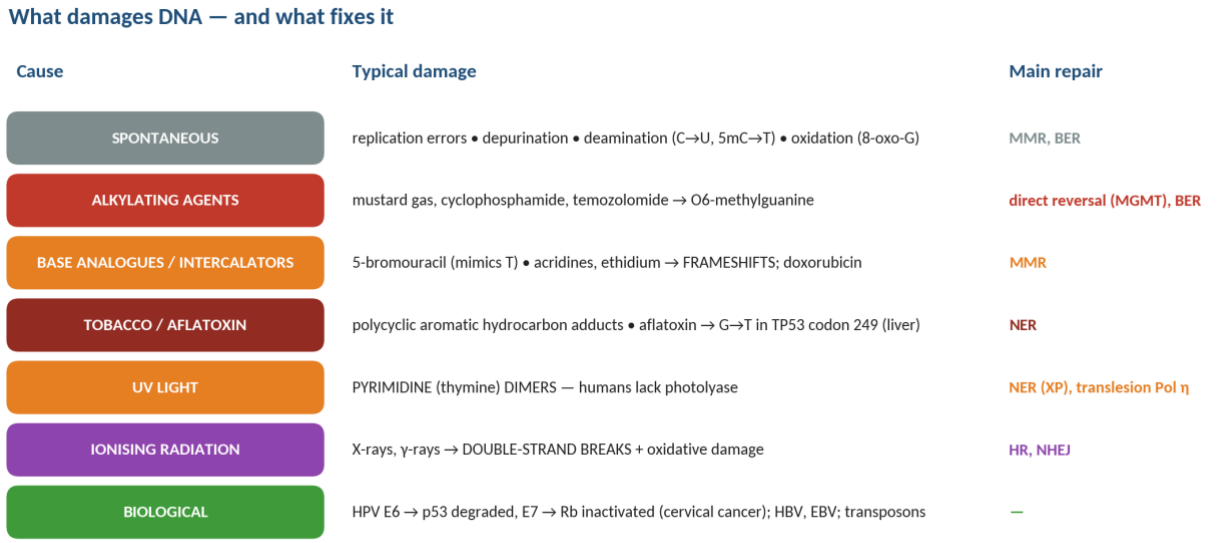


Figure 3. Mutagens and their repair.

3 Repair Pathways

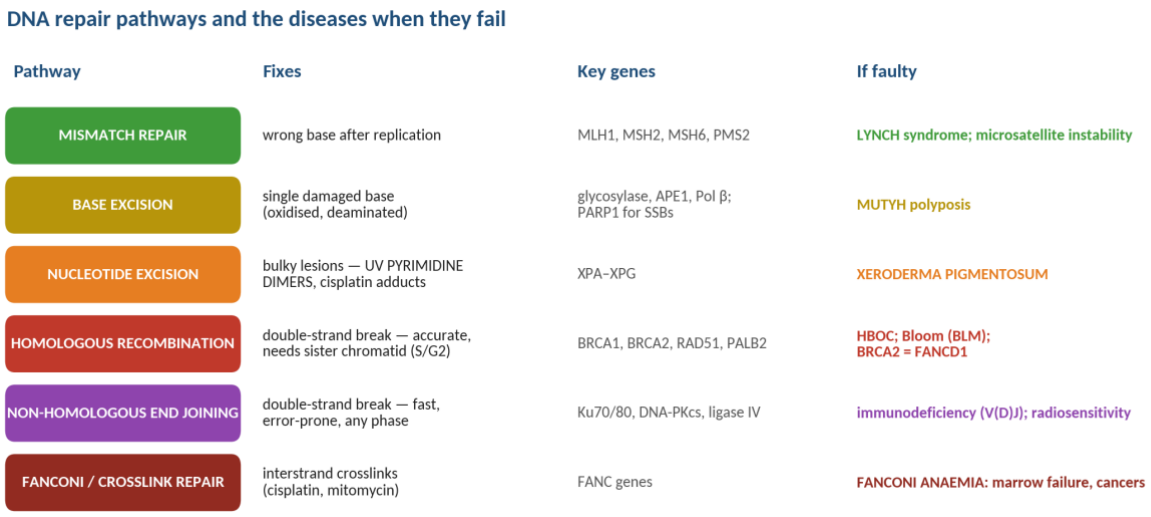


Figure 4. Repair pathways (from Lecture 87).

Extra pathway	Key points
Direct reversal	MGMT removes alkyl groups from O6-methylguanine (silenced MGMT in glioma predicts temozolomide response); photolyase reverses UV dimers in many organisms but NOT in placental mammals
Translesion synthesis	Low-fidelity polymerases (η, ζ, ι, κ) copy past damage; Pol η loss → XP variant
HR vs NHEJ	HR: accurate, S/G2, BRCA1/2, RAD51, ATM/ATR, MRN. NHEJ: fast, error-prone, any phase, Ku70/80, DNA-PKcs, XRCC4, ligase IV — also used in V(D)J recombination

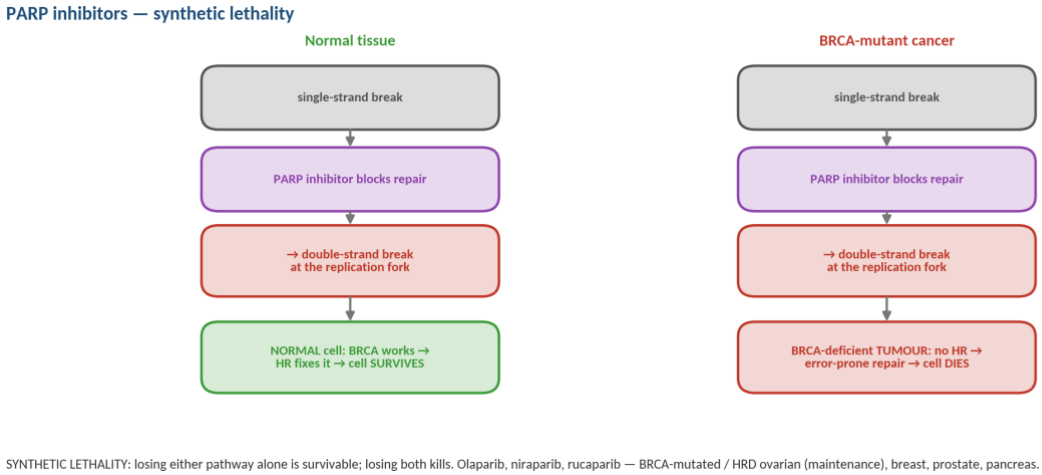


Figure 5. PARP inhibitors (from Lecture 87).

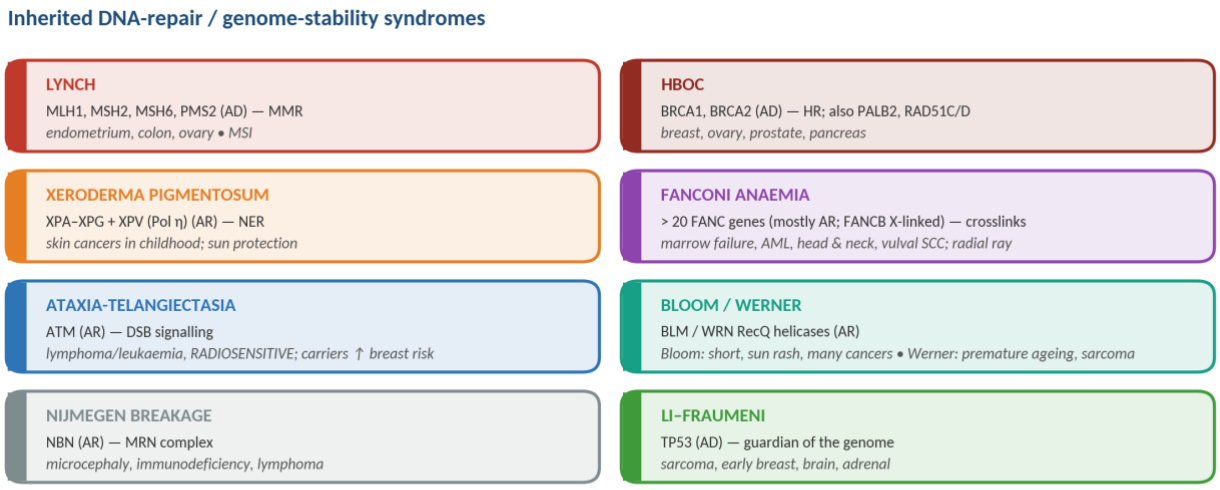


Figure 6. Repair-defect syndromes.

MNEMONIC / MEMORY HOOK

'Lynch Mismatches, XP Excises, BRCA Recombines, Fanconi Fixes crosslinks, ATM Alarms' — one pathway per syndrome.

4 Rates, Naming and Classification

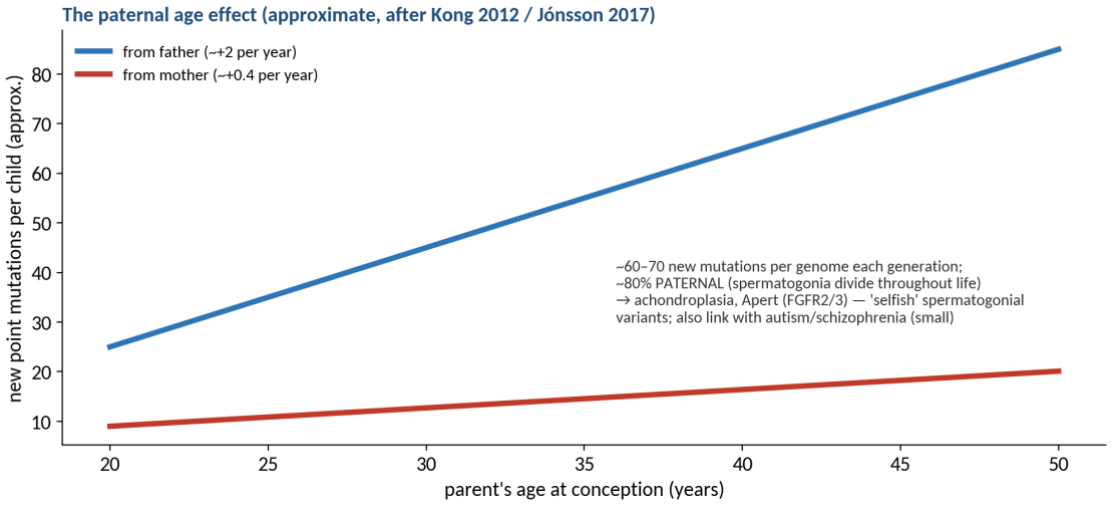


Figure 7. The paternal age effect.

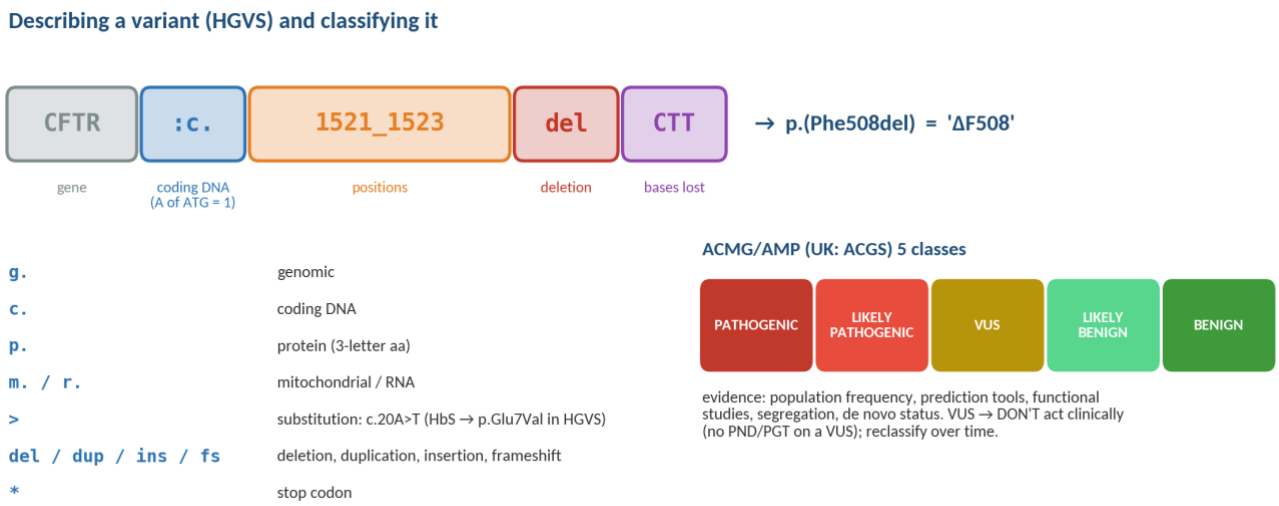


Figure 8. HGVS and variant classes.

5 Clinical Correlates

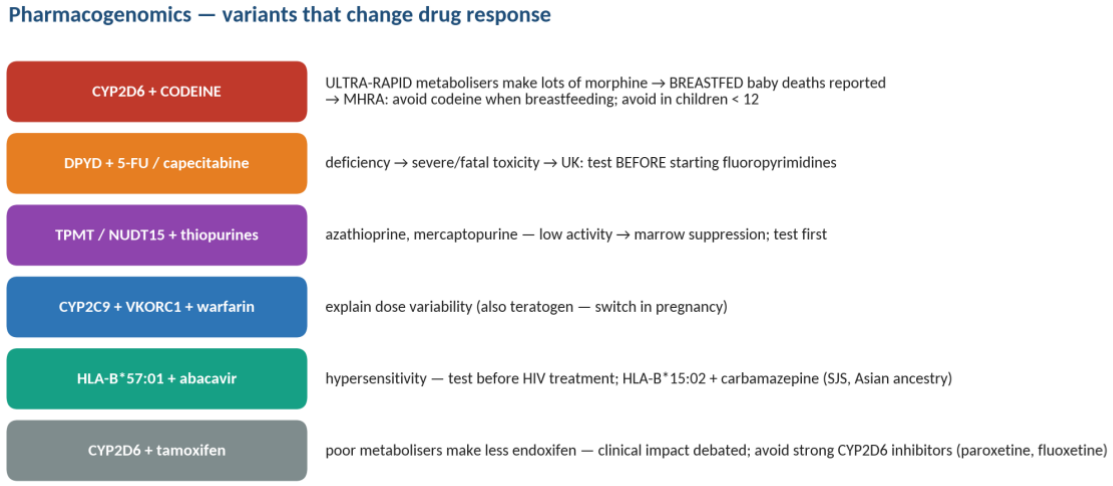


Figure 9. Pharmacogenomics.

TUMOUR TESTING

- NICE: test **all endometrial** (DG42) and **colorectal** (DG27) cancers for MMR deficiency → germline testing → cascade
- BRCA/HRD testing in **ovarian cancer** guides PARP inhibitors and family testing
- Somatic vs germline: tumour findings may need blood confirmation

GENOMIC MEDICINE (UK)

- NHS Genomic Medicine Service + national test directory
- Whole genome sequencing for rare disease and some cancers; rapid trio exome in sick neonates and fetuses
- Genomics England **Generation Study** (2024–): genome sequencing of up to 100,000 newborns for treatable conditions — research

★ PEARL

Methylated C at CpG deaminates to T — the commonest cause of new point mutations (C:G → T:A transitions).

Most new mutations come from FATHERS (~+2 per year of paternal age). VUS = don't act on it. Avoid codeine when breastfeeding (CYP2D6 ultra-rapid metabolisers).

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

~10^{-8} Per base per generation	**~60–70** New mutations per child	**~80%** Paternal origin	**~+2/yr** Paternal age increment
5 ACMG classes	**> 20** FANC genes	**~25–30 nt** NER excision patch	**c.1521_1523del** CF F508del

HIGH-YIELD CHECKLIST

- ☐ Transitions (same ring) vs transversions (purine ↔ pyrimidine).
- ☐ Silent, missense (HbS), nonsense, frameshift, in-frame (F508del), splice, repeat, CNV.
- ☐ CpG hotspot: 5-methyl-C → T.
- ☐ Mutagens: alkylating, intercalating (frameshift), UV (dimers), ionising (DSB), HPV E6/E7.
- ☐ Direct reversal (MGMT), BER, NER, MMR, HR, NHEJ, translesion.
- ☐ Lynch, HBOC, XP, Fanconi, A-T, Bloom, Werner, Nijmegen, Li–Fraumeni.
- ☐ ~60–70 new mutations per child; mostly paternal.
- ☐ HGVS: g./c./p.; ACMG/ACGS 5 classes; never act on a VUS.
- ☐ PGx: CYP2D6 codeine (breastfeeding), DPYD 5-FU, TPMT thiopurines, HLA-B*57:01.
- ☐ Universal MMR testing of endometrial/colorectal cancers.

Self-assessment — cover the right-hand column

Question	Answer
Define a transition.	Purine ↔ purine or pyrimidine ↔ pyrimidine substitution
Why are CpG sites hotspots?	Methylated C deaminates to T, which repair often misses
Mutagen type causing frameshifts?	Intercalating agents (e.g. acridines)
Lesion caused by UV light?	Pyrimidine (thymine) dimers
Pathway repairing UV dimers in humans?	Nucleotide excision repair
Gene in ataxia-telangiectasia?	ATM
Why do most new mutations come from fathers?	Continuous spermatogonial divisions
What does 'c.' mean in HGVS?	Coding DNA reference sequence
Should a VUS guide PGT or prenatal diagnosis?	No
Why avoid codeine in breastfeeding?	CYP2D6 ultra-rapid metabolisers → infant morphine toxicity

7 References

- Richards S et al. ACMG/AMP standards for interpretation of sequence variants. Genet Med 2015; ACGS Best Practice Guidelines (UK).
- NICE DG42 (endometrial) and DG27 (colorectal) — Lynch syndrome testing.

- MHRA Drug Safety Update: codeine and breastfeeding (2013); DPYD testing before fluoropyrimidines (2020).