

Exercise walk-through

6.2

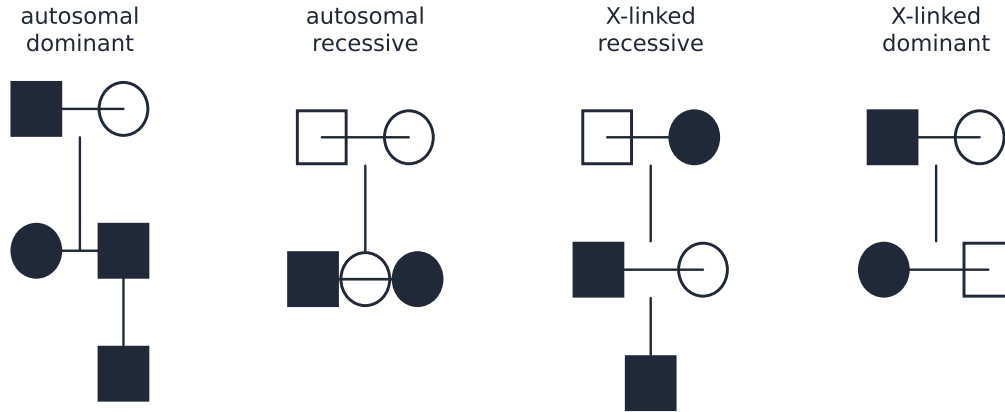
Mendelian inheritance and pedigrees

University Medicine

Mendelian inheritance: four signatures, four grids

- 1 Signatures** AD: every generation, father-to-son. AR: horizontal, consanguinity. **X-linked recessive**: NO male-to-male. X-linked dominant: all daughters of affected fathers.
- 2 Grids** $Aa \times Aa \rightarrow 3:1$; carriers $\rightarrow 1/4$ affected; **carrier** mother (XLR) $\rightarrow 1/2$ sons affected, $1/2$ daughters carriers.
- 3 Modifiers** Age-of-onset trims risk by Bayes; $\sim 80\%$ of achondroplasia is de-novo (paternal age).

Mendelian inheritance - the figure



The four **pedigree** patterns side by side.

Exercises 2.1-2.3

2.1 Which pattern never shows male-to-male transmission? [3]

2.2 Two carriers' affected-child risk? [3]

2.3 An affected father (X-linked dominant) has daughters – risk? [3]

Exercises 2.1-2.3

2.1 Which pattern never shows male-to-male transmission? [3]

2.1

- X-linked (both recessive and dominant).

2.2 Two carriers' affected-child risk? [3]

2.2

- $1/4$ ✓.

2.3 An affected father (X-linked dominant) has daughters – risk? [3]

2.3

- All daughters affected (100 %), no sons affected ✓.

Exercise 3.1

3.1 A woman (28, unaffected) has an affected parent with an adult-onset AD condition (fictional).

Compute her prior risk ($1/2$). Explain how being unaffected at 28 modifies it (onset distribution – Bayes). State what a predictive test would change. [7]

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- Prior risk $1/2$ (affected parent is Aa).
- If say 40 % of carriers have onset by 28: $P(\text{unaffected at 28} \mid \text{carrier}) = 0.6 \rightarrow \text{posterior} = (1/2 \times 0.6) / (1/2 \times 0.6 + 1/2 \times 1) = 0.375$ – evidence, not proof.
- Predictive testing resolves it to ~ 0 or ~ 1 (with counselling on insurability and psychological burden).

Exercise 3.2

3.2 Achondroplasia in a child of two average-height parents (fictional).

Explain the de-novo mutation logic (~80 %, paternal age). Give the sib recurrence (near population) and the child's own offspring risk (1/2). State the germline-mosaicism caveat.

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3.2

- ~80 % de-novo (FGFR3, paternal age effect).
- Sib recurrence near population risk; the child's own children at 1/2.
- Germline mosaicism in a parent gives a small recurrence above population (~1 %).