Medical Genetics

Curated preclinical study track (not a medical degree, no licensure claim). Original explanations and practice only, following the reviewed course handout.

Inheritance made quantitative

- Transmission rules first (chromosomes, Mendel, the exceptions), then variation and populations, then the clinic.
- Every risk is a probability you compute - segregation ratios, Hardy-Weinberg, Bayesian updates.

Chromosomes: the machine and its misfires

1. **Count** 46 = 23 pairs; **meiosis** (1 duplication, 2 divisions) → 4 haploid gametes.
2. **Ratios Nondisjunction** I → 2:2 (n+1 : n−1); II → 1:1:2 (n+1 : n−1 : n, n).
3. **Survivors** Trisomy 21 ~1/700 (mostly maternal meiosis I); 45,X the only viable monosomy; sex-chromosome aneuploidies buffered.

Chromosomes - the figure

nondisjunction I



n+1 n+1 n−1 n−1

gamete ratio 2 : 2 (n+1 : n−1)

nondisjunction II



n+1 n−1 n n

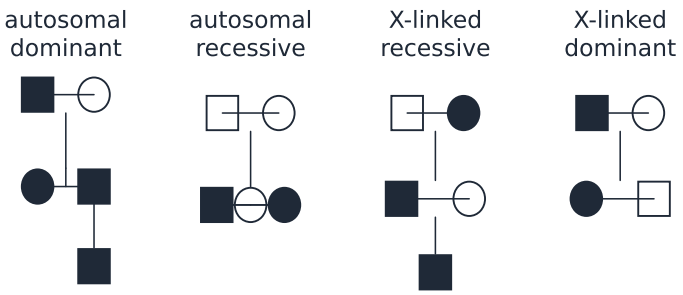
gamete ratio 1 : 1 : 2

Mis-segregation windows I vs II: gamete ratios 2:2 and 1:1:2.

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; ~80% of achondroplasia is de-novo (paternal age).

Mendelian inheritance - the figure

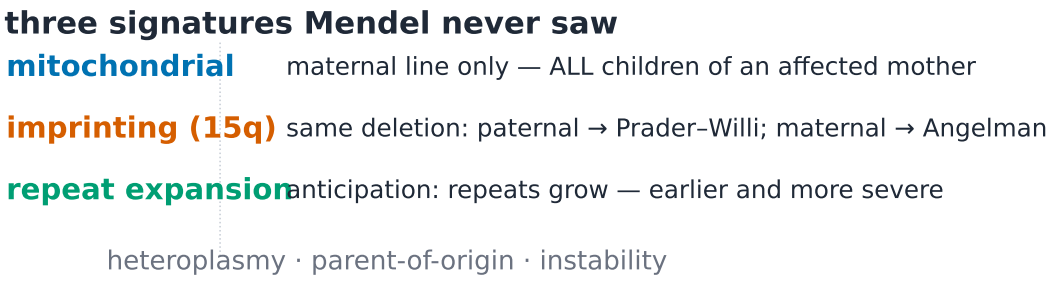


The four **pedigree** patterns side by side.

Non-Mendelian: three extra layers

1. **mtDNA** Maternal line only; all children of an affected mother at risk; heteroplasmy = severity lottery.
2. **Imprinting** Same 15q deletion: paternal → Prader-Willi, maternal → Angelman - parent of origin IS the disease.
3. **Repeats Anticipation**: CAG/CGG repeats expand each **meiosis** - earlier, more severe (fragile-X premutation 55-200 → full >200).

Non-Mendelian - the figure

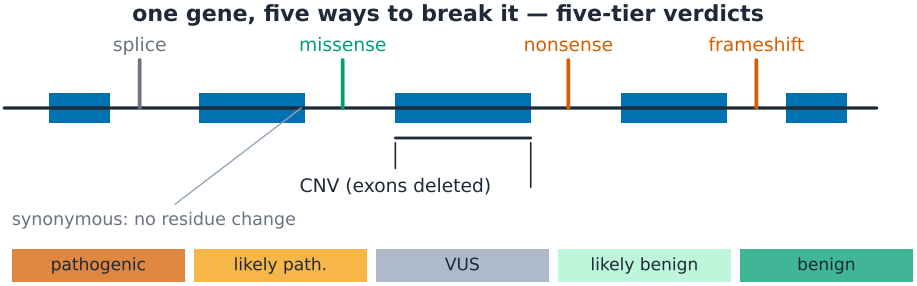


Mitochondrial, imprinting, repeat-expansion signatures compared.

Variant interpretation: five ways, five tiers

1. **Types Synonymous**, **missense**, **nonsense** (stop/truncation), frameshift, splice - plus CNVs (exon/gene deletions).
2. **Tiers** Pathogenic / likely pathogenic / VUS / likely benign / benign.
3. **Filter** Population frequency first: a 1-in-100 variant for a 1-in-10 000 dominant disease could affect at most 1 carrier in 100, so it cannot be a fully penetrant cause.

Variant interpretation - the figure

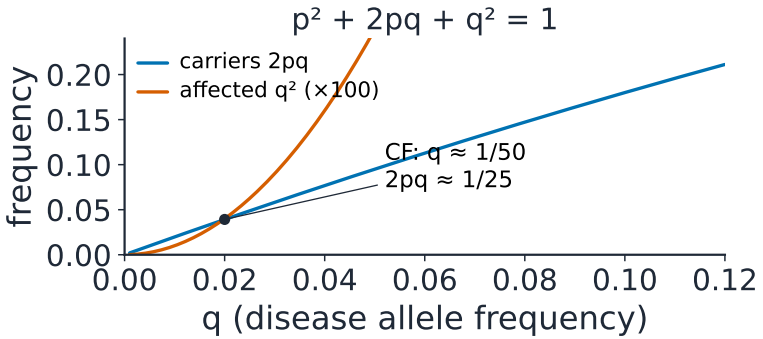


A gene model annotated with variant types and verdict tiers.

Population genetics: one equation does the work

1. **Equation** $p^2 + 2pq + q^2 = 1$; carriers are 2pq, NOT q^2.
2. **CF** $q^2 = 1/2500 \rightarrow q = 1/50 \rightarrow 2pq \approx 1/25$ - the 4% **carrier** rate from a disease rate.
3. **Screening** Couple risk $1/25 \times 1/300$ (residual after negative screen) $\times\ 1/4 \approx 1/30\ 000$ - quoted residuals, never zero.

Population genetics - the figure



Carrier 2pq and affected q^2 curves against q.

Genetic testing: the question chooses the window

1. **Windows Karyotype** ($\geq$5–10 Mb, balanced seen); CMA (CNVs 50–100 kb, balanced MISSED); **FISH** (targeted fast); **sequencing** (base-level, chosen scope).
2. **Mapping** Aneuploidy $\rightarrow$ karyotype/FISH; developmental delay $\rightarrow$ CMA first; known familial variant $\rightarrow$ targeted Sanger.
3. **Cascade** One positive familial result $\rightarrow$ 1/2 for each first-degree relative; negatives return to population risk.

Genetic testing - the figure

the question chooses the window

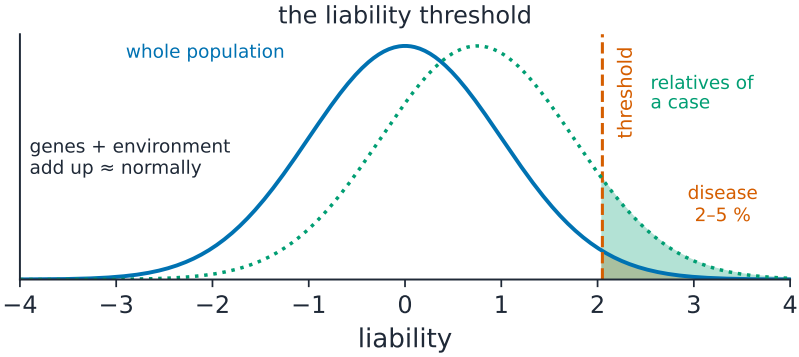
karyotype	whole genome, ≥5–10 Mb	balanced rearrangements seen
microarray (CMA)	genome-wide CNVs ~50–100 kb	balanced changes MISSED
FISH	targeted, fast	one probe, one question
sequencing	base-level, chosen scope	Sanger → panel → exome/genome

> Four methods, four resolutions, one comparison.

Multifactorial disease: the bell and its threshold

1. **Model** Liability (genes + environment) $\approx$ normal; disease past a threshold.
2. **Risks** Empiric 2–5% after one affected; rising with more affected relatives, severity, and an affected person of the less often affected sex (toward 10% with two).
3. **PGx** CYP2C19/clopidogrel (poor metabolisers, ~15% of East Asians); TPMT/thiopurines; HLA-B*57:01/abacavir - screen before prescribing.

Multifactorial disease - the figure



The liability bell with its threshold and the shifted family curve.

Check yourself

- **Nondisjunction** II gamete ratio? (1:1:2.)
- CF carriers from 1/2500? ($\approx$1/25.)
- Affected-child risk, **carrier** + screened partner? ($\approx$1/1200.)
- Multifactorial recurrence after one child? (2–5 %.)