

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

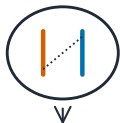
- Transmission rules first (chromosomes, Mendel, the exceptions), then variation and populations, then the clinic.
- Every risk is a probability you compute - segregation ratios, Hardy-Weinberg, Bayesian updates.

Chromosomes: the machine and its misfires

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

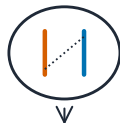
Chromosomes - the figure

nondisjunction I



gamete ratio 2 : 2 ($n+1$: $n-1$)

nondisjunction II



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; $\sim 80\%$ of achondroplasia is de-novo (paternal age).

Mendelian inheritance - the figure

autosomal
dominant



autosomal
recessive



X-linked
recessive



X-linked
dominant



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

three signatures Mendel never saw

mitochondrial maternal line only — ALL children of an affected mother

imprinting (15q) same deletion: paternal → Prader-Willi; maternal → Angelman

repeat expansion anticipation: repeats grow — earlier and more severe

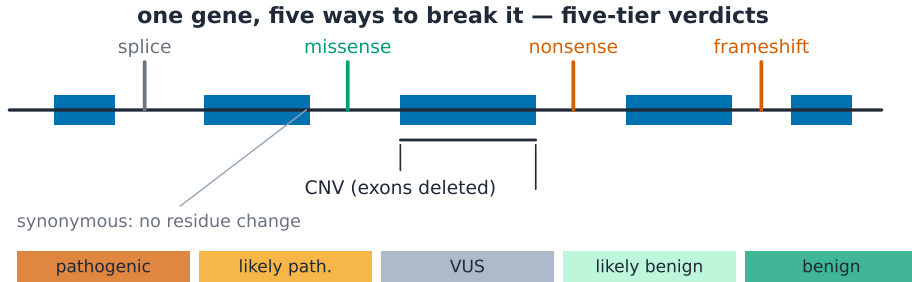
heteroplasmy · parent-of-origin · instability

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

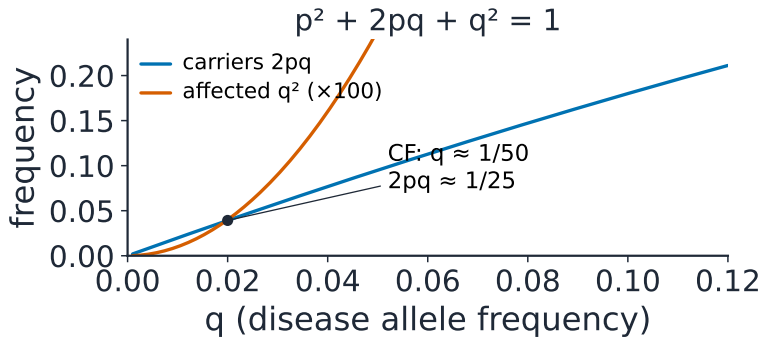


A gene model annotated with variant types and verdict tiers.

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** ($\geq 5\text{--}10$ 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

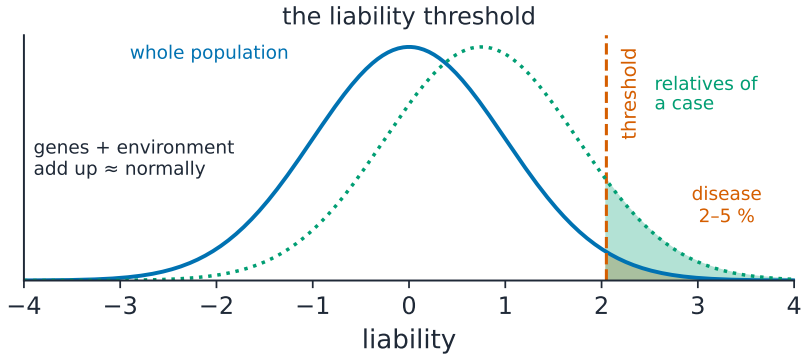
karyotype	whole genome, $\geq 5\text{--}10\text{ Mb}$	balanced rearrangements seen
microarray (CMA)	genome-wide CNVs $\sim 50\text{--}100\text{ kb}$	balanced changes MISSED
FISH	targeted, fast	one probe, one question
sequencing	base-level, chosen scope	Sanger $\rightarrow$ panel $\rightarrow$ exome/genome

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 %.)