WEAVE SPRINT · PAPER I

Psychiatric Genetics

From family resemblance to the genome and back: how psychiatric risk is inherited, how it is mapped, and how it is read at the bedside. One complete set of notes, built around methods you can tell apart.

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Psychiatric Genetics

Six sections · 16 topics · one complete notes document

Psychiatric disorders are among the most heritable conditions in medicine, yet almost none of them obey Mendel. This chapter is built as a toolkit: each method answers one question about where the risk lives. **Learn the tool, not just the result.** The order runs the way the field itself moved: first establish that a disorder is familial and heritable (family, twin, adoption studies), then locate the risk (linkage, then genome-wide association, then rare variants and sequencing), then read it back as mechanism (epigenetics, endophenotypes, neurodevelopment), as clinical fact (heritability figures, the schizophrenia story, pharmacogenetics), and finally as something you can apply in a counselling room. Almost every answer here rewards the candidate who names the right study design and the key finding together, rather than reciting a list of genes.

HOW TO USE THESE NOTES

Every figure declares one axis and codes it in colour and shape, with a small legend. The colours are consistent throughout: **petrol** marks the method, the structure and the neutral relay; **coral** marks risk, pathology or a rare large-effect variant; and **marigold** highlights the key finding or the common-variant signal. Watch for the boxes marked **Good to remember**: they gather every named gene, locus, allele and hard number in one place so the reference facts sit apart from the reasoning.

Foundations

1 · Orientation and the genetics toolkit

Before the detail, the frame. Psychiatric disorders sit on a paradox you have to hold throughout: they are among the *most heritable* conditions in medicine, yet almost none of them are inherited in a clean Mendelian way. There is no single gene for schizophrenia the way there is one for Huntington disease. Instead, risk is **polygenic and complex**: thousands of common variants each add a sliver of liability, a minority of rare large-effect variants (copy-number variants and de novo mutations) shove a few individuals hard toward illness, and the whole thing plays out on a developing brain over time. The single move that runs through this material, repeated in the margin: **heritable but not Mendelian, common-variant-mostly but rare-variant-punchy, and read out through neurodevelopment**. Hold that and every method below has a job to do.

The reason genetics is a Paper-1 staple is that examiners test the *logic of the toolkit*, not just facts: each study design answers exactly one question, and the designs form a ladder from the crudest (does it run in families?) to the most granular (which base changed?). The classic epidemiological trio (Kaplan & Sadock 2024) establishes *that* genes matter and roughly how much; the molecular methods then ask *which* genes, and the modern aggregate methods ask *how much of one person's risk* we can now read from their genome. This topic lays out the whole map so that when a later topic drills into schizophrenia or pharmacogenomics, you already know which rung of the ladder it is standing on.

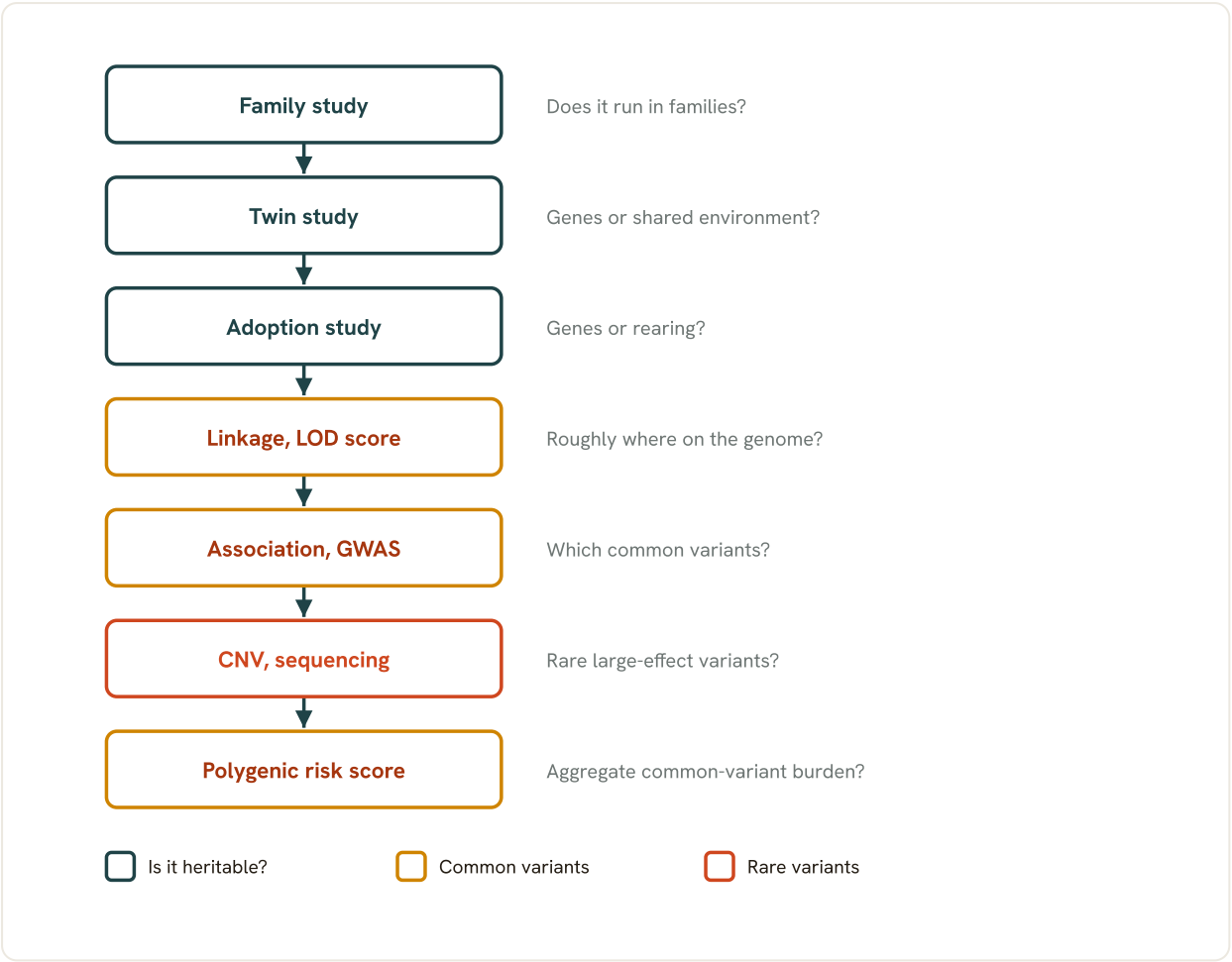


Fig 3.1 The psychiatric genetics toolkit as an evidence hierarchy. Each method answers one question, and the field moved down the ladder in this order: family, twin and adoption studies first establish that risk is heritable and separate genes from environment; linkage then genome-wide association locate the risk with rising resolution; copy-number and sequencing methods catch the rare large-effect variants; and the polygenic risk score aggregates the common-variant burden. Colour marks the job: petrol establishes heritability, marigold locates common variants, coral flags rare variants.

1.1 The central paradox: highly heritable, non-Mendelian, mostly polygenic

The frame for the whole set of notes. High **heritability** (the proportion of population variation in a trait attributable to genetic variation) tells you genes matter a great deal, but it says nothing about *how many* genes or *what kind*. Common psychiatric disorders show high heritability yet failed the classical single-gene approaches that cracked Mendelian diseases (Kaplan & Sadock 2024). The resolution is a two-tier architecture (Sullivan; Kaplan & Sadock 2024): the bulk of liability comes from a very large number of **common variants of individually tiny effect** (the polygenic component, odds ratios typically around 1.1 each), plus a smaller contribution from **rare, large-effect variants** (CNVs, de novo mutations) that individually raise risk many-fold but explain illness in only a minority. This is the liability-threshold model: many small risks summed against a threshold.

COMMON TRAP

Do not equate "high heritability" with "genetically determined" or with "inherited in families in a simple pattern." Heritability is a population statistic about variance, not a statement about an individual, and a highly heritable disorder can still be overwhelmingly polygenic with no single causative gene. Equally, a high heritability does not mean environment is irrelevant: it is a partitioning of variance in a particular population, not a fixed biological constant.

RULE **High heritability, non-Mendelian, mostly polygenic.** Common psychiatric disorders are among the most heritable in medicine yet obey no clean single-gene pattern; hold that paradox and every method below has a job.

1.2 The missing heritability, and why development is the read-out

Two loose ends these notes keep returning to. First, **missing heritability**: the variance explained by the variants we can actually measure falls well short of the heritability that twin studies imply (Manolio et al. 2009; Kaplan & Sadock 2024). For schizophrenia, SNP-based heritability captures roughly 17 to 45 percent of variance and a polygenic risk score built from GWAS explains on the order of 7 percent, against twin-study heritability estimates near 80 percent (New Oxford Textbook of Psychiatry). The gap is filled, in part, by rare variants, gene-gene and gene-environment interactions, and structural variation the arrays miss. Second, **neurodevelopment as the mechanism**: genetic risk is largely expressed by shaping how the brain is built, wired, and pruned, so the same risk allele can surface as a childhood neurodevelopmental phenotype or an adult psychosis depending on timing. Genetic risk for a childhood-onset disorder like ADHD does not differ between paediatric and adult samples, underscoring that it indexes a developmental trajectory rather than a discrete adult lesion (Kaplan & Sadock 2024).

~80%	17-45%	~7%
TWIN HERITABILITY, SCHIZOPHRENIA	SNP-BASED HERITABILITY	VARIANCE A PRS EXPLAINS

TRAP Do not read "high heritability" as "genetically determined": a highly heritable disorder can still be overwhelmingly polygenic, and heritability is a population variance ratio, silent about any individual.

1.3 The toolkit as a map: each method answers one question

This is the spine of these notes. The genetics toolkit is a ladder of study designs, and the discriminating exam answer is to bind each method to the *single question it can answer* and no more. Read the definition list as a ladder from crudest to most granular: the first three are the classical epidemiological designs (they establish *that* genes matter), the middle three are molecular localisation and discovery methods (they find *which* variants), and the last is the aggregate clinical read-out (how much of one person's risk we can now quantify).

Family studies

Ask: *does it run in families?* Compare the risk (or relative risk) of the disorder in relatives of an affected proband against the general-population rate, graded by degree of relatedness. Establishes familial

aggregation but cannot separate shared genes from shared upbringing.

Twin studies

Ask: *is the familial resemblance genetic or shared-environmental?* Compare concordance in monozygotic twins (who share effectively 100 percent of their genome) with dizygotic twins (who share on average 50 percent). A higher MZ than DZ concordance points to genetic influence, and the design yields a heritability estimate plus estimates of shared and unique environment (New Oxford Textbook of Psychiatry).

Adoption studies

Ask: *can we physically separate genes from rearing?* Adopted-away children share genes with their biological relatives but environment with their adoptive family, so higher rates in biological than adoptive relatives isolate a genetic contribution. The most rigorous separation of the two, but increasingly infeasible as adoptions decline (New Oxford Textbook of Psychiatry).

Linkage analysis

Ask: *roughly where on the genome does a risk gene sit?* Track co-inheritance of a disease with genetic markers through pedigrees; a marker that segregates with illness flags a nearby chromosomal region. Quantified by the LOD score. Powerful for rare large-effect Mendelian genes, largely unproductive for polygenic psychiatric disorders (Kaplan & Sadock 2024).

Association and GWAS

Ask: *which common variants are over-represented in cases?* Compare allele frequencies at SNP markers between cases and controls. The genome-wide association study (GWAS) does this at millions of SNPs simultaneously using microarrays, detecting common variants of small effect once samples reach tens to hundreds of thousands (Kaplan & Sadock 2024).

CNV and sequencing methods

Ask: *which rare, large-effect variants are present?* Copy-number variant mapping (via array comparative genomic hybridisation or GWAS-chip intensity) finds sub-microscopic deletions and duplications; whole-exome and whole-genome sequencing find rare point mutations and de novo variants. These uncover the punchy, individually rare risk variants (Kaplan & Sadock 2024).

Polygenic risk scores

Ask: *how much common-variant burden does this one person carry?* Sum the risk alleles across the genome, each weighted by its GWAS effect size, into a single score of genetic liability. The aggregate read-out that turns GWAS summary statistics into an individual-level index (Kaplan & Sadock 2024).

The high-yield structure: the top three designs answer *whether and how much* without touching DNA directly; linkage and association/GWAS answer *where and which*; CNV/sequencing answers *which rare variant*; and the polygenic risk score is the only tool that reports back on a single individual. Modern genome-wide approaches (GWAS, CNV mapping, polygenic analysis, sequencing) have supplanted the older linkage and candidate-gene strategies for complex psychiatric disorders (Kaplan & Sadock 2024).

1.4 The two-architecture picture: common-small versus rare-large

The reason the toolkit splits into GWAS on one side and CNV/sequencing on the other is that the two variant classes have opposite profiles, and examiners test the contrast directly. GWAS is built to catch variants that are *common but weak*; CNV and sequencing are built to catch variants that are *rare but strong*. The full genetic risk for a disorder is the sum of both.

FEATURE	COMMON VARIANTS (GWAS)	RARE LARGE-EFFECT VARIANTS (CNV / SEQUENCING)
Population frequency	Common (minor allele frequency >1%)	**Rare, often de novo (new, non-inherited)**
Effect size per variant	Tiny: odds ratio roughly 1 to 2 for schizophrenia	**Large: odds ratio roughly 20 to 100 for schizophrenia**
Detecting tool	Genome-wide association study (SNP microarray)	**Array CGH / CNV mapping; whole-exome or whole-genome sequencing**
Sample size needed	Very large (tens to hundreds of thousands) to reach significance	**Large too, but signal is per-variant strong; low signal-to-noise for proving causality**
Aggregated as	**Polygenic risk score**	Total CNV burden; individual pathogenic variant

The classic figure (Singh, Neale & Daly, adapted in Kaplan & Sadock 2024): common variants like complement C4 raise schizophrenia odds one- to two-fold, whereas the 22q11.2 deletion and rare protein-truncating variants raise odds by 20- to 100-fold. Both tails matter, and only summing them captures full genetic risk.

1.5 The toolkit in one ladder, and the master mnemonic seeded

Before the material fans out, bind the whole ladder into one image to redraw from memory. This pearl is the spine of these notes; each later topic pays it back in detail.

THE TOOLKIT IN ONE LADDER

Climb from crude to granular, each rung a sharper question. **Family**: does it run in families? **Twin**: genes or shared environment? (MZ vs DZ concordance gives heritability.) **Adoption**: separate genes from rearing physically. **Linkage**: roughly *where* on the genome? (LOD score; good for rare Mendelian, poor for polygenic.) **Association / GWAS**: *which* common variants? (millions of SNPs, tiny effects, huge samples). **CNV / sequencing**: which rare large-effect variants? (deletions, duplications, de novo mutations, 20- to 100-fold effects). **Polygenic risk score**: how much aggregate common-variant burden does this one person carry? The first three say *whether*, the middle say *where and which*, the last says *how much, for whom*.

MNEMONIC

Families Try Adopting Little Genetic Clues Personally

Walks the ladder in order: **F**amily, **T**win, **A**doption (the classical epidemiological trio) → **L**inkage, **G**WAS/association (localisation and common-variant discovery) → **C**NV and sequencing (rare large-effect) → **P**olygenic risk score (individual aggregate). Seed it now; the consolidation block at the end pays it back as a whole-subject synthesis map.

HOLD THIS

Each method answers exactly one question. The toolkit is a ladder from crudest to most granular: family (does it run in families?), twin (genes or shared environment?), adoption (genes or rearing?), linkage (roughly where?), GWAS (which common variants?), CNV/sequencing (which rare large-effect variants?), polygenic risk score (how much aggregate burden, for whom?).

1.6 Cross-references: what is owned elsewhere

This material is the substantive genetics of psychiatric illness, not the generic machinery of study design or drug metabolism, both of which live in other notes and are only pointed to here.

Study design and biostatistics taxonomy

The general anatomy of study designs (cohort, case-control, cross-sectional), measures of association (odds ratio, relative risk), and the statistics of significance and multiple testing are owned by the Schizophrenia: aetiology, phenomenology, classification & course notes. These notes borrow those tools as applied to genetics (for example why the GWAS significance threshold is set stringently at 5×10^{-8} to correct for a million simultaneous tests) but do not re-teach the biostatistics from scratch. When a genetics topic invokes an odds ratio or a correction for multiple comparisons, point back to the Schizophrenia: aetiology, phenomenology, classification & course notes.

CYP450 and pharmacokinetic metabolism

The cytochrome P450 enzyme system, its isoenzymes and inhibitor/inducer interactions, was established on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes. The pharmacogenetics and pharmacogenomics topic here builds the *genetic variation* in those enzymes (poor, intermediate, extensive and ultra-rapid metaboliser phenotypes, and the CPIC/DPWG prescribing guidance) on top of that pharmacokinetic foundation rather than re-deriving CYP450 itself.

GOOD TO REMEMBER

- **Schizophrenia twin-study heritability:** approximately 80 percent (New Oxford Textbook of Psychiatry), among the highest in psychiatry.
- **Schizophrenia SNP-based heritability:** roughly 17 to 45 percent of variance captured by common SNPs, illustrating the missing-heritability gap (New Oxford Textbook of Psychiatry).
- **Schizophrenia polygenic risk score:** explains on the order of 7 percent of variance in current data (New Oxford Textbook of Psychiatry).
- **ADHD heritability:** approximately 70 to 80 percent from twin meta-analyses, on a par with autism, bipolar disorder and schizophrenia (New Oxford Textbook of Psychiatry).
- **GWAS genome-wide significance threshold:** $p < 5 \times 10^{-8}$, correcting for roughly a million independent tests (Kaplan & Sadock 2024).
- **Common-variant effect size (schizophrenia):** odds ratio approximately 1 to 2 per risk allele (Kaplan & Sadock 2024).
- **Rare / CNV effect size (schizophrenia):** odds ratio approximately 20 to 100 per variant (Kaplan & Sadock 2024).
- **22q11.2 deletion (velocardiofacial / DiGeorge) syndrome:** raises schizophrenia odds by about 50-fold versus the general population (Kaplan & Sadock 2024).
- **Copy-number variant definition:** structural deletion or duplication typically larger than 1 kilobase; CNVs span about 12 percent of the genome in aggregate (Kaplan & Sadock 2024).
- **Common variant (SNP) definition:** polymorphism with minor allele frequency greater than 1 percent (Kaplan & Sadock 2024).
- **Manolio et al. 2009:** the landmark "Finding the missing heritability of complex diseases" (Nature), the reference for the missing-heritability problem.
- **LOD score:** the logarithm-of-odds statistic quantifying linkage; the metric of the pre-GWAS linkage era.

2 · Modes of inheritance and transmission models

Psychiatric disorders are the paradigm case of **complex inheritance**: they cluster in families but almost never segregate in the tidy ratios that Mendel described for the garden pea. The examinable skill is therefore to hold two frameworks in mind at once, the classical **Mendelian** single-gene patterns that underlie a handful of psychiatrically important syndromes, and the **non-Mendelian** and quantitative models that account for the common disorders. **Why it matters.** Examiners test whether you can say, with confidence, that schizophrenia, bipolar disorder, autism, ADHD and depression are **multifactorial** and **polygenic** rather than Mendelian, and whether you can then deploy the **threshold model** to explain the observations that flow from that: rising recurrence risk with severity, with number of affected relatives, and the sex-specific pattern of the Carter effect.

This topic sets out the full menu of **modes of inheritance**, contrasts single-gene with oligogenic, polygenic and multifactorial architectures, and then develops the **multifactorial-threshold (liability) model** in detail because it is the single most exam-relevant transmission model in psychiatry (Kaplan & Sadock 2024; New Oxford 2020). Pedigree reading is introduced here only briefly, as an orientation; the systematic pedigree-interpretation drill is the discrimination topic.

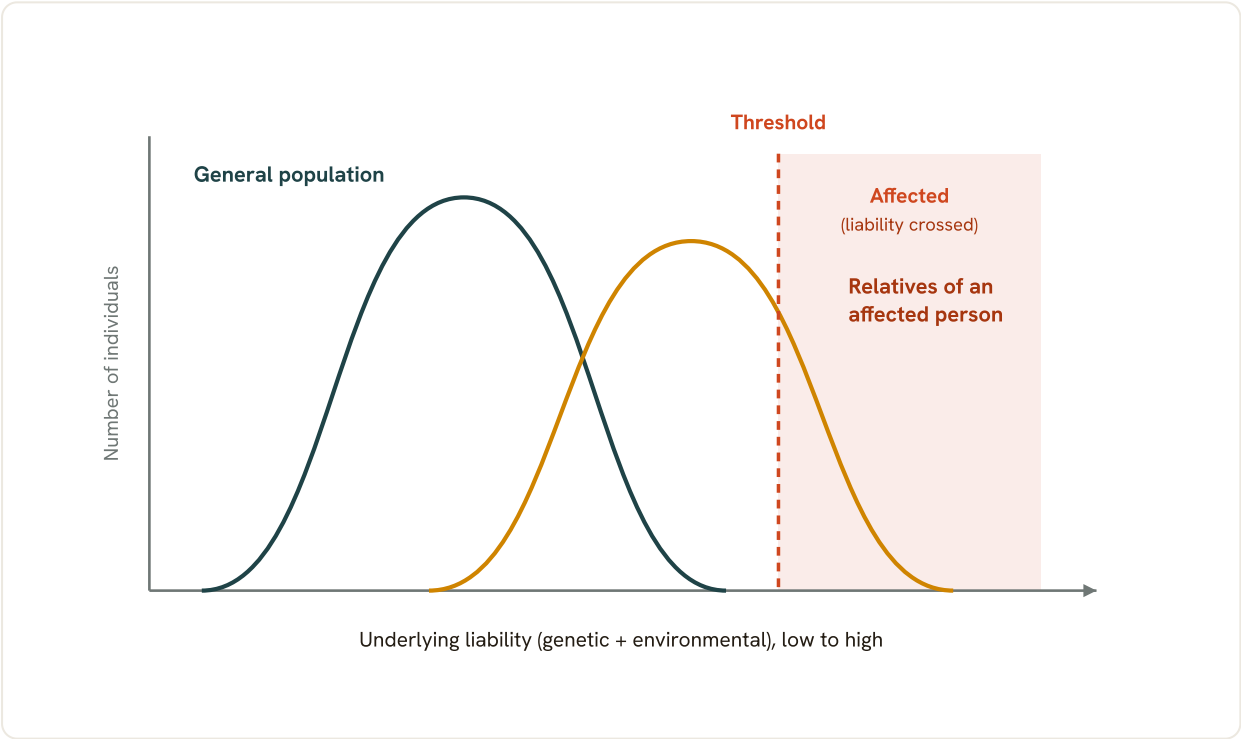


Fig 3.2 The multifactorial-threshold (liability) model. Liability, the summed effect of many genes and the environment, is normally distributed; a person is affected only once their liability crosses a threshold. Relatives of an affected person carry more of the risk alleles, so their whole distribution is shifted right (marigold) and a larger share falls beyond the threshold, which is why recurrence risk is higher in close relatives and rises with the number of affected family members. When one sex is affected less often, its threshold is higher, so its relatives carry higher risk (the basis of the Carter effect).

2.1 Mendel's three laws as the baseline

The rules a complex disorder breaks. Mendel's laws are the reference against which non-Mendelian behaviour is defined. The **Law of Dominance and Uniformity** holds that a dominant

allele masks a recessive one in the heterozygote; the **Law of Segregation** holds that the two alleles at a locus separate during gametogenesis so each parent transmits only one; and the **Law of Independent Assortment** holds that alleles at different loci are transmitted independently (an idealisation that breaks down for linked loci on the same chromosome). A disorder that obeys these laws is **monogenic** or single-gene, shows characteristic pedigree signatures, and gives fixed, high recurrence risks. The point for psychiatry is that the common disorders do exactly the opposite: their familial distributions are, in the words of the standard text, "inconsistent with simple Mendelian modes of inheritance" (Kaplan & Sadock 2024).

2.2 The three Mendelian patterns and their pedigree signatures

Autosomal dominant. One dominant allele on an autosome is sufficient to express the phenotype, so the condition affects both sexes equally, is transmitted vertically through every generation (rarely skips a generation), and confers a 50% risk to each child of an affected heterozygote. Complications examiners exploit are **reduced penetrance** (a carrier who does not express, so the pedigree appears to skip), **variable expressivity**, late age of onset (as in Huntington disease, where the family history may look negative in still-young relatives), and *de novo* mutation, which explains sporadic cases with unaffected parents. **Autosomal recessive.** Two copies are needed, so the phenotype typically appears horizontally in a single sibship of otherwise unaffected, often consanguineous, parents; the recurrence risk to a further child of two carriers is 25%. **X-linked recessive.** The mutant allele lies on the X chromosome, so affected individuals are predominantly male, there is no male-to-male transmission, and transmission runs through unaffected carrier mothers to sons (with knight's-move inheritance across the pedigree).

Penetrance

The proportion of individuals carrying a disease genotype who actually express the phenotype; reduced penetrance makes a dominant pedigree appear to skip generations.

Expressivity

The degree or severity of phenotype among those who do express it; variable expressivity means the same genotype produces different clinical pictures.

de novo mutation

A mutation arising for the first time in the affected individual (or parental germline), producing an isolated case; germline mosaicism can raise sibling recurrence risk above the near-zero expectation.

2.3 Reading a pedigree: an orientation

What the shapes encode. A pedigree is the fastest bedside route to a mode of inheritance. Squares are males, circles females, a filled symbol is affected, a horizontal line joins a mating pair, a vertical line drops to offspring, and a diagonal strike denotes a deceased individual; a double horizontal line marks consanguinity. Reading it, you ask three questions in sequence: are both sexes affected equally (autosomal) or is there a male excess (consider X-linked); is transmission vertical across generations (dominant) or clustered in one sibship (recessive); and is there male-to-male transmission (which excludes X-linkage). The systematic drill, including the

discriminators that separate mitochondrial from X-linked and dominant-with-reduced-penetrance from recessive, is developed in the pedigree-interpretation topic.

2.4 Non-Mendelian mechanism: mitochondrial (maternal) inheritance

Matrilineal, never paternal. Mitochondrial DNA is inherited almost exclusively through the ovum, so a pathogenic mtDNA variant passes from an affected mother to all of her children but is transmitted by none of her affected sons. The pedigree signature is therefore transmission through the maternal line only, with both sexes affected but only females passing the trait on. **Heteroplasmy** (a mixture of mutant and wild-type mitochondria whose ratio must exceed a tissue-specific threshold to cause disease) explains the variable severity within a matriline. Mitochondrial disorders are relevant to psychiatry as a cause of syndromic presentations with neuropsychiatric features and as one of the classic non-Mendelian patterns examiners contrast against X-linkage (New Oxford 2020).

2.5 Non-Mendelian mechanism: genomic imprinting and parent-of-origin effects

Which parent the allele came from matters. Imprinting is the parent-of-origin-specific silencing of an allele by DNA methylation established in the germline, so that the phenotype depends on whether the transmitting parent was the mother or the father (Companion to Psychiatric Studies 2010). The teaching pair is the 15q11-q13 region: loss of the paternally expressed genes produces **Prader-Willi syndrome** (hyperphagia, obesity, intellectual disability, and features overlapping OCD and psychosis), whereas loss of the maternally expressed *UBE3A* gives **Angelman syndrome** (severe intellectual disability, ataxia, and a characteristic happy affect). The same deletion thus yields two entirely different disorders according to parent of origin, which is the defining violation of Mendelian expectation that imprinting demonstrates.

RULE **Same 15q11-q13 deletion, opposite parent: two different syndromes.** Paternal loss gives Prader-Willi; maternal loss (of *UBE3A*) gives Angelman. Parent-of-origin dependence means imprinting.

2.6 Non-Mendelian mechanism: anticipation and dynamic mutation

Earlier and worse each generation. Anticipation describes a disorder that appears at a progressively earlier age and with increasing severity in successive generations. Its molecular basis is **dynamic mutation**, the unstable expansion of a trinucleotide (triplet) repeat during gametogenesis (Companion to Psychiatric Studies 2010). The two archetypes are **Huntington disease** (an expanding CAG repeat in *HTT*, where larger repeats give earlier onset, most markedly with paternal transmission) and **fragile-X syndrome** (a CGG repeat in the 5-prime untranslated region of *FMR1* on the X chromosome; once the repeat expands past the full-mutation range it silences the gene by methylation, the commonest inherited cause of intellectual disability and a recognised association with autism). It is worth noting for the exam that although repeat expansions cause these syndromic and learning-disability phenotypes, no convincing evidence links repeat expansions to the common psychiatric illnesses such as schizophrenia or bipolar disorder (Companion to Psychiatric Studies 2010).

RULE **Earlier and worse each generation means an expanding trinucleotide repeat.** Anticipation flags dynamic mutation: CAG in *HTT* (Huntington), CGG in *FMR1* (fragile-X).

2.7 From single-gene to polygenic: the spectrum of genetic architecture

A continuum, not a dichotomy. Genetic architecture is best pictured as a spectrum of the number of contributing loci and their individual effect sizes. A **single-gene (monogenic)** disorder is driven by one locus of large effect. An **oligogenic** disorder involves a small number of loci of moderate effect. A **polygenic** trait is influenced by very many loci, each of individually tiny effect, whose effects sum; this is **polygenicity**, and it is the genetic architecture now firmly established for schizophrenia, bipolar disorder, ADHD and major depression (Kaplan & Sadock 2024). A **multifactorial** trait is one in which many genes of small effect combine with environmental factors to produce risk; in psychiatry "polygenic" and "multifactorial" are used almost interchangeably because both genetic and environmental contributions are continuously distributed. The empirical signature of polygenicity is the marked inverse relationship between allele effect size and frequency: common variants each carry odds ratios below about 1.3 but, as a group, account for roughly a third of the genetic liability, while rare variants (including copy number variants) can carry large individual effects (Kaplan & Sadock 2024).

ARCHITECTURE	LOCI AND EFFECT	PSYCHIATRIC EXAMPLE	DISTINGUISHING FEATURE
Single-gene (Mendelian)	One locus, large effect	Huntington disease, fragile-X	**Mendelian pedigree; fixed high recurrence risk**
Oligogenic	Few loci, moderate effect	Some syndromic forms	**Non-Mendelian ratios but tractable locus count**
Polygenic	Very many loci, each tiny effect, additive	Schizophrenia, bipolar, ADHD, MDD	**Effect size falls as allele frequency rises**
Multifactorial	Many genes of small effect plus environment	Common psychiatric disorders	**Continuous liability crossing a threshold**

The genetic-architecture spectrum, from the single large-effect locus of Mendelian disease to the many-small-effect-genes-plus-environment model of the common psychiatric disorders.

2.8 The multifactorial-threshold (liability) model in full

A continuous liability with a categorical outcome. The **threshold model**, also called the **liability threshold** or multifactorial-threshold model, reconciles a discontinuous (present or absent) diagnosis with a continuous underlying cause. Its postulate is that every individual carries an underlying **liability**, the summed burden of all genetic and environmental risk and protective factors, which is approximately normally (Gaussian) distributed across the population. The disorder manifests only in those whose liability exceeds a critical **threshold**; below the threshold the person is unaffected, above it they are affected (New Oxford 2020). Because liability is the additive sum of many small contributions, the central-limit theorem makes its population distribution normal, which is precisely what justifies the bell-curve depiction. This model is the workhorse for conceptualising complex disorders such as ADHD, which is described as

"manifestations of an underlying continuously distributed liability, with the diagnosis lying above a certain threshold on this liability curve" (New Oxford 2020).

Why relatives sit further to the right. The crucial move is what the model predicts for relatives of an affected proband. Because relatives share genes (and often environment) with the proband, their liability distribution is shifted rightward, closer to the threshold, than that of the general population. A larger fraction of that shifted distribution therefore lies beyond the threshold, so the recurrence risk in relatives exceeds the population prevalence, and it does so more for closer relatives who share more of the proband's liability. This is exactly the pattern seen for congenital malformations and complex traits, where the first-degree-relative recurrence risk is of the order of 1 to 5% against a population incidence often of 0.1% or less (Kaplan & Sadock 2024).

2.9 Predictions the threshold model makes (and the exam loves)

Recurrence risk rises with severity. A more severe case implies a proband whose liability lies further beyond the threshold, which implies a family carrying a greater liability burden overall, which shifts the relatives' distribution further right and raises their recurrence risk. Hence more severe index cases predict higher risk to relatives. **Recurrence risk rises with the number of affected relatives.** Each additional affected relative is further evidence of a high-liability family, again shifting the relevant distribution rightward and increasing risk for the remaining members; risk is therefore not fixed as in Mendelian disease but conditional on the loading already visible in the pedigree. **Concordance and the heritability gap.** Twin studies quantify the genetic share of liability: schizophrenia has an estimated twin heritability of about 80% (Kaplan & Sadock 2024), yet current schizophrenia polygenic risk scores explain only about 7 to 7.7% of the variance on the liability scale (around 24% on the observed 0-to-1 scale), leaving a substantial "heritability gap" attributed to environmental effects, rare variants, gene-environment interplay and assortative mating (Kaplan & Sadock 2024).

2.10 Sex-specific thresholds and the Carter effect

The less-often-affected sex needs more liability. When a disorder has an unequal sex ratio, the multifactorial model accommodates it by positing **sex-specific thresholds**: the less commonly affected sex has a higher threshold, meaning a member of that sex must carry a greater liability burden to cross into the affected state. The consequence, known as the **Carter effect**, is that affected individuals of the less-often-affected (higher-threshold) sex carry, on average, a heavier liability load, and therefore transmit a higher recurrence risk to their relatives than affected individuals of the more commonly affected sex. The classic non-psychiatric illustration is pyloric stenosis (commoner in males), where the relatives of affected females carry the higher risk. In psychiatry the same logic is invoked for sex-biased conditions such as ADHD and autism, where an affected female, being of the higher-threshold sex, implies greater familial loading. Recognising that the higher-risk-transmitting relatives are those of the rarely affected sex is a frequently tested application of the model (New Oxford 2020).

HOLD THIS

Liability is normally distributed; disease appears above a threshold. Relatives sit shifted rightward, so recurrence risk exceeds prevalence, rises with closeness of relationship, severity of the index case and number affected, and (Carter effect) is higher in relatives of the rarely affected, higher-threshold sex.

COMMON TRAP

Do not call schizophrenia or bipolar disorder "Mendelian" or attribute them to a single gene. Their familial distributions are explicitly incompatible with single-major-locus inheritance and fit a polygenic, multifactorial-threshold model. Equally, do not confuse the shifted-relatives logic: the raised recurrence risk in relatives comes from their liability distribution sitting closer to the threshold, not from any single high-penetrance allele.

PEARL

Anticipation (earlier onset, greater severity each generation) should immediately make you think of an expanding trinucleotide repeat, and parent-of-origin dependence (same deletion, two different syndromes) should immediately make you think of imprinting. These two non-Mendelian mechanisms are the pair most reliably tested against the "why does this not follow Mendel" stem.

MNEMONIC

MITochondria: Mother's line, Inherited by all, Transmitted by none of the affected males.

Use this to lock the maternal-inheritance signature that separates mitochondrial from X-linked recessive: in mitochondrial disease an affected father transmits to no one, whereas in X-linked recessive an affected father transmits carrier status to all daughters.

INDIA

High rates of consanguineous marriage in parts of India raise the population load of autosomal recessive conditions, so a horizontal sibship pattern with related parents should prompt an explicit pedigree enquiry into consanguinity. For the common multifactorial psychiatric disorders, family risk counselling in Indian practice is best framed in threshold-model terms (risk raised above population baseline but not Mendelian) rather than as a fixed inherited certainty, which also keeps the message non-stigmatising.

GOOD TO REMEMBER

- **Schizophrenia twin heritability:** approximately 80% (Kaplan & Sadock 2024).
- **Schizophrenia PRS variance explained:** about 7 to 7.7% on the liability scale, around 24% on the observed 0-to-1 scale (Kaplan & Sadock 2024).
- **Common small-effect alleles in schizophrenia:** account for at least about 25% of total liability and roughly a third of genetic liability; individual odds ratios below about 1.3 (Kaplan & Sadock 2024).
- **ADHD twin heritability:** approximately 70 to 80% (New Oxford 2020).
- **Multifactorial first-degree-relative recurrence risk:** of the order of 1 to 5%, against a population incidence often 0.1% or less (Kaplan & Sadock 2024).
- **HTT (Huntington disease):** expanding CAG trinucleotide repeat; anticipation, earlier onset with larger repeats and paternal transmission.
- **FMR1 (fragile-X syndrome):** CGG repeat in the 5-prime untranslated region on the X chromosome; full-mutation methylation silencing; commonest inherited intellectual disability, autism association.
- **15q11-q13 imprinting pair:** paternal loss gives Prader-Willi syndrome, maternal loss (of *UBE3A*) gives Angelman syndrome.
- **Carter effect:** relatives of an affected individual of the less-often-affected (higher-threshold) sex carry the higher recurrence risk.

3 · Quantitative genetics: family, twin and adoption studies

Before a single risk gene had been identified, the classical epidemiological triad of family, twin and adoption studies had already established that virtually every major psychiatric disorder is substantially heritable. These designs are the historical and conceptual foundation of psychiatric genetics: they partition the observed clustering of a disorder in relatives into genetic and environmental sources, and they generate the heritability estimates that every downstream molecular study (linkage, GWAS, polygenic scores) sets out to explain. **Why it matters.** The examiner expects a candidate to move fluently from the raw observation that a disorder runs in families, through the twin comparison that says *whether* the familial aggregation is genetic, to the adoption design that *separates* genes from the rearing environment, and finally to the biometric machinery (the **ACE model**, path analysis, variance-components modelling) that turns concordance figures into numbers. Knowing the landmark studies, the core assumptions, and the standard critiques is high-yield across MCQs and vivas.

The logic is sequential and each design answers a question the previous one leaves open. A **family study** establishes that a disorder aggregates in relatives but cannot separate shared genes from shared environment. A **twin study** exploits the difference in genetic sharing between monozygotic and dizygotic pairs to ask whether that aggregation is genetic. An **adoption study** physically separates the genetic parent from the rearing environment and so provides the strongest single test of a genetic contribution in humans (Tasman 2015). Read together, they yielded an unequivocal answer for schizophrenia, mood disorders and most of psychiatry: genes matter, and they matter a great deal.

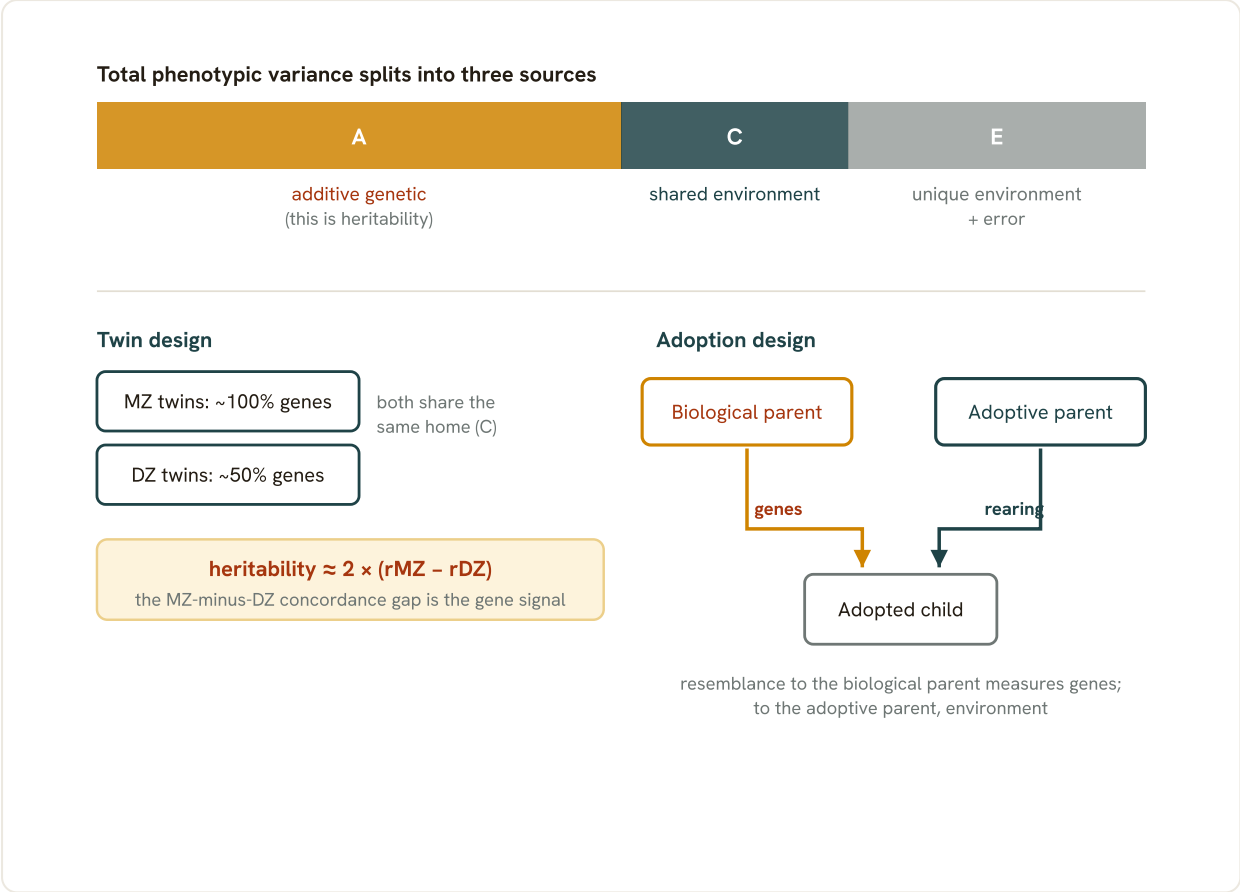


Fig 3.3 The two designs that separate genes from environment. The classical twin study exploits the fact that monozygotic twins share nearly all their genes and dizygotic twins about half, while both share the same home: the extra concordance in MZ over DZ pairs estimates heritability (Falconer's approximation, twice the MZ minus DZ correlation). The adoption study pulls genes and rearing apart in a different way: an adopted child's resemblance to the biological parent indexes genes, and resemblance to the adoptive parent indexes environment. Both feed the ACE model that partitions total variance into additive genetic (A), shared environment (C) and unique environment plus error (E).

3.1 Family studies: recurrence risk and the relative risk ratio

The starting design. A **family study** ascertains probands with the disorder and systematically assesses their relatives, comparing the frequency of the disorder among first-degree relatives (parents, siblings, offspring, who share on average 50% of their genes) with the population base rate. The output is a **recurrence risk** (the morbid risk in relatives) and, more usefully for comparison across disorders, the **relative risk ratio**, conventionally written lambda (the risk in relatives of a proband divided by the population risk). For first-degree relatives this is lambda-one; for siblings, lambda-s. Schizophrenia carries a first-degree-relative recurrence risk of roughly 6 to 10%, about a tenfold increase over the general-population risk of near 1%, so lambda-s for schizophrenia is of the order of 8 to 10 (Kaplan & Sadock 2024). **The interpretive limit.** Aggregation in a family is necessary but not sufficient evidence of genetic causation, because families share their environment as well as their genes. A family study can never, on its own, distinguish nature from nurture; it defines the phenotype's familiality and sets up the twin and adoption designs that follow.

3.2 The classical twin design: MZ versus DZ concordance

The natural experiment. The **twin study** rests on a simple genetic contrast: monozygotic (MZ) twins share essentially 100% of their DNA, whereas dizygotic (DZ) twins share on average 50%, the same as ordinary siblings, yet both twin types are assumed to share their rearing environment to a comparable degree. If a disorder is genetic, MZ pairs should show markedly higher **concordance** (the probability that the co-twin is affected given one twin is affected) than DZ pairs. If MZ and DZ concordance are equal, the familial aggregation is environmental. The greater the excess of MZ over DZ concordance, the greater the inferred heritability (New Oxford 2020).

Probandwise versus pairwise concordance. Two estimators are used and they are not interchangeable. The **pairwise** method divides concordant pairs by all pairs with at least one affected twin. The **probandwise** method counts each independently ascertained affected twin as a proband, so a doubly-ascertained concordant pair is counted twice; it yields a higher figure and is the estimator comparable to a population morbid risk. Probandwise concordance is the modern standard (Torrey 1994). Being aware of which figure a study quotes explains much of the apparent variation in published concordance rates.

3.3 Falconer's formula and heritability

From concordance to a number. **Heritability** (h-squared) is the proportion of the total phenotypic variance in a population attributable to genetic variance; it is a population parameter, not a statement about any individual, and it is specific to the population and environment studied. The classic first approximation from twin correlations is **Falconer's formula**, h-squared is approximately twice the difference between the MZ and DZ correlations, that is 2(rMZ minus rDZ) (Falconer, cited in New Oxford 2020). The doubling reflects the halving of shared genes from MZ to DZ pairs. **A worked intuition.** If rMZ is 0.5 and rDZ is 0.2, the naive estimate is 2(0.5 minus 0.2) equals 0.6, so about 60% of the variance is genetic. The formula is only a rough guide because it assumes purely additive genes and can exceed unity or misbehave when non-additive (dominance) effects or shared environment are present; formal variance-components modelling supersedes it (see 3.6).

RULE **Heritability is roughly twice the MZ-minus-DZ correlation gap.** Falconer: h-squared is about 2(rMZ - rDZ); the doubling reflects the halving of shared genes from MZ to DZ pairs.

COMMON TRAP

Heritability is not a fixed biological constant and does not describe how "genetic" a given person's illness is. A high heritability means that, in the population and environment studied, most of the variation between people is genetic; it says nothing about the modifiability of the trait, nor about the cause in any single patient. A highly heritable disorder can still be entirely prevented or treated environmentally (phenylketonuria is the standard cautionary example). Do not read h-squared of 0.8 as "80% genetic in this patient."

3.4 The ACE model and variance decomposition

Partitioning the phenotypic variance. The workhorse of modern twin analysis is the **ACE model**, which decomposes total phenotypic variance into three latent components: **A**, additive genetic variance; **C**, common (shared) environment, the environmental influences that make co-twins alike regardless of zygosity; and **E**, unique (non-shared) environment, the influences that make co-twins differ, which also absorbs measurement error. Under the model, MZ pairs correlate as A plus C and DZ pairs as one-half A plus C; the divergence between them identifies A, the residual within-MZ difference identifies E, and any residual similarity common to both twin types identifies C (New Oxford 2020). Where non-additive genetic effects are suspected the model is extended to ADE (A, dominance D, and E). Notably the **variance component** E always includes the discordance of MZ pairs, which is why any pair of identical twins discordant for a disorder is direct evidence for non-shared environmental (including stochastic and epigenetic) causation.

3.5 The equal-environments assumption and its critique

The load-bearing assumption. The entire inference from the twin design depends on the **equal-environments assumption** (EEA): that MZ and DZ twins are exposed to trait-relevant environments to an equal degree, so that any excess MZ similarity is genetic rather than environmental. **The critique.** Critics (notably Joseph) argue MZ twins are in fact treated more alike, dress alike, are confused for one another, spend more time together and evoke more similar responses, so that greater MZ concordance could partly reflect a more shared environment, inflating heritability estimates. **The defence.** The mainstream position is that the EEA holds for trait-relevant exposures: studies of twins mistaken about their own zygosity show resemblance tracks true (biological) zygosity rather than perceived zygosity, and greater MZ environmental similarity appears to be largely a consequence of their genetic identity (evoked or selected), not an independent cause of phenotypic similarity (New Oxford 2020). The EEA is the single most examinable methodological criticism of twin studies.

CLASSIC TRAP If asked for the load-bearing weakness of the twin design, name the **equal-environments assumption**: if MZ twins share more trait-relevant environment than DZ twins, heritability is inflated.

3.6 MZ twins reared apart, path analysis and segregation analysis

The strongest twin variant. The **MZ-twins-reared-apart** design studies genetically identical individuals separated early and raised in different families; their phenotypic correlation is a near-direct estimate of heritability because their shared environment (C) is minimised, so rMZ-apart approximates A. The best-known example is the Minnesota Study of Twins Reared Apart, whose reared-apart MZ correlations for many traits were only modestly below reared-together values, supporting substantial heritability (Kaplan & Sadock 2024). The design's weaknesses are selective (non-random) placement, late separation, and small, hard-to-ascertain samples.

The quantitative-methods toolkit. Three named analytic methods recur in the syllabus. **Path analysis** is a structural-equation technique that represents the causal paths from latent A, C and

E factors to the observed phenotype as a diagram, letting the A, C and E variance components be estimated (and their fit compared) simultaneously across MZ and DZ correlations (Tasman 2015). **Variance-components** (biometric) modelling is the general maximum-likelihood framework that fits the ACE or ADE models to raw twin (and family) data and formally tests whether dropping C or D worsens fit, superseding Falconer's arithmetic. **Segregation analysis** works on family (pedigree) data and asks whether the observed pattern of transmission fits a single major gene of Mendelian effect, a polygenic (many-small-genes) model, or a mixed model; for the major psychiatric disorders segregation analyses consistently rejected a single major gene and favoured polygenic or oligogenic inheritance, anticipating the highly polygenic architecture later confirmed by GWAS (New Oxford 2020).

3.7 Adoption designs: separating genes from rearing

Three configurations. The **adoption study** is the most powerful human design for disentangling genetic transmission from the family environment, because the adoptee's genetic parents and rearing parents are different people. Three canonical variants exist. In the *adoptee (adoptees') study* design, the adopted-away offspring of affected biological parents are compared with adopted-away offspring of unaffected biological parents; excess disorder in the former indexes genetic transmission (this is the Heston design). In the *adoptee's-family (parent-as-proband)* design, one starts from affected adoptees and examines rates of the disorder in their biological versus adoptive relatives; a genetic effect predicts higher rates among biological relatives. In the *cross-fostering* design, one compares adoptees with affected biological but healthy adoptive parents against adoptees with healthy biological but affected adoptive parents, directly pitting the genetic against the rearing contribution (Kaplan & Sadock 2024).

3.8 The landmark adoption studies

Heston (1966), the first. Leonard Heston's Oregon study followed 47 offspring born to hospitalised mothers with schizophrenia and adopted away in infancy, against 50 matched control adoptees; roughly 11% (5 of 47) of the index adoptees developed schizophrenia versus none of the controls, with excess sociopathy and neurosis besides. This was the first adoption evidence that the familial risk for schizophrenia is genetically transmitted, since the affected offspring never lived with their ill mothers (Companion 2010; Tasman 2015). **The Danish adoption studies.** Heston's finding was confirmed and greatly extended by the collaborative Danish-American programme of Rosenthal, Wender, Kety and Schulsinger, exploiting Denmark's national adoption and psychiatric registers. Using both the adoptee and the adoptee's-family strategies, they showed a marked excess of schizophrenia and schizophrenia-spectrum disorders among the biological relatives of schizophrenic adoptees, but not among their adoptive relatives, and the cross-fostering arm found that being reared by an ill adoptive parent did not raise risk in genetically low-risk adoptees (Tasman 2015). These studies established the schizophrenia spectrum concept and remain the paradigmatic adoption evidence in psychiatry. **The Finnish Adoptive Family Study.** Tienari's ongoing Finnish study of adopted-away offspring of mothers with schizophrenia added the crucial modern twist: risk in high-genetic-risk adoptees was concentrated in those raised in dysfunctional adoptive families, whereas a healthy adoptive

family environment appeared protective, demonstrating gene-environment interaction rather than genetic determinism (New Oxford 2020). Adoption designs were also decisive for mood disorder (Mendlewicz & Rainer 1977, showing genetic transmission of manic-depressive illness) and for antisocial personality and substance use (Crowe 1974; the Swedish Stockholm adoption studies of Cloninger, Bohman and Sigvardsson).

HOLD THIS

Three nested designs, each removing a confound the last could not. Family study proves aggregation; twin study separates genes from shared environment; adoption study severs genes from rearing. Heston (1966) was the first schizophrenia adoption study; the Danish studies (Kety, Rosenthal, Wender) established the schizophrenia spectrum.

DESIGN	GENETIC SHARING EXPLOITED	WHAT IT CONTROLS FOR	PRINCIPAL LIMITATION
Family study	Graded by relatedness (50% in first-degree)	**Nothing separates genes from shared environment**	Cannot distinguish nature from nurture
Twin study (MZ vs DZ)	MZ 100% vs DZ 50%, environment assumed equal	**Holds shared environment roughly constant across zygosity**	Rests on the equal-environments assumption
MZ reared apart	MZ 100%, shared rearing environment removed	**Removes the common environment (C) directly**	Selective placement, late separation, tiny samples
Adoption study	Biological vs adoptive relatedness dissociated	**Physically separates genes from the rearing family**	Selective placement, prenatal and perinatal confounds, register limits

The three classical designs answer successively harder questions: family studies establish familiality, twin studies test whether it is genetic, and adoption studies (especially the reared-apart and cross-fostering variants) sever genes from rearing altogether. The discriminator for each is what it holds constant or removes.

3.9 Gene-environment interaction and gene-environment correlation

Two distinct phenomena, often confused. **Gene-environment interaction** (GxE) means the effect of an environmental exposure on the phenotype differs according to genotype (or equivalently, genetic risk is expressed only, or more strongly, under a given exposure); the Finnish adoption finding above is a textbook example, and the classic molecular illustration is the moderation of the effect of childhood maltreatment on antisocial outcome by MAOA activity (Caspi 2002, contested in later meta-analyses). **Gene-environment correlation** (rGE) is different: it means exposure to an environment is itself partly under genetic control, so genes and environment are non-randomly associated (Plomin, DeFries & Loehlin 1977).

Three forms of gene-environment correlation. Following Plomin and later Scarr and McCartney (1983), rGE takes three forms. **Passive rGE**: the child passively inherits both risk genes and a correlated rearing environment from the same biological parents (an anxious parent transmits both anxiety-related genes and an anxious home). **Evocative (reactive) rGE**: the child's genetically influenced behaviour evokes correlated responses from others (an irritable,

genetically-influenced temperament elicits harsh parenting). **Active (niche-picking) rGE**: the individual actively seeks out environments correlated with their genotype (a sensation-seeking adolescent selects a deviant peer group). The developmental prediction is that passive rGE dominates in early childhood and gives way to active rGE with increasing autonomy (New Oxford 2020). Recognising rGE is essential because it means an apparently "environmental" risk factor identified in a family study may be a marker of genetic risk, one reason adoption and twin designs remain indispensable.

PEARL

A clean one-line discriminator: gene-environment *interaction* is about the environment having a different *effect* depending on the genes (multiplicative moderation); gene-environment *correlation* is about the genes influencing which *environment* a person encounters (non-random exposure). Interaction changes the slope; correlation changes the exposure.

MNEMONIC

ACE decomposes; PEA are the three correlations

The twin variance components are **A**dditive genetic, **C**ommon environment, **E**nvironment (unique). The three gene-environment correlations, in developmental order, are **P**assive (inherited genes plus inherited environment), **E**vocative (behaviour evokes responses), **A**ctive (niche-picking). ACE for the model, PEA for the correlations.

INDIA

Formal twin and adoption registries comparable to the Danish, Swedish and Finnish national registers do not exist at scale in India, so most Indian genetic-epidemiology data derive from family (morbid-risk) studies rather than twin or adoption designs. When counselling Indian families about recurrence risk, the practical figures used are the first-degree-relative risks from these family studies (of the order of 6 to 10% for schizophrenia in a first-degree relative), while remembering that consanguinity, common in parts of India, can inflate familial aggregation for recessive contributions and complicate the interpretation of a family history.

GOOD TO REMEMBER

- **Falconer's formula:** h-squared is approximately 2(rMZ minus rDZ); the doubling reflects the halving of shared genes from MZ to DZ.
- **ACE model:** variance equals A (additive genetic) plus C (common/shared environment) plus E (unique environment plus error); MZ correlate as A+C, DZ as one-half A + C.
- **Schizophrenia twin concordance (probandwise):** Farmer 1987 reported MZ 47.6% vs DZ 9.5%; Onstad 1991 reported MZ 48% vs DZ 4%.
- **Schizophrenia heritability (modern):** Hilker 2018 (Danish twin/psychiatric registers, over 30,000 pairs) found MZ 33% vs DZ 7% probandwise concordance and heritability of 79% (73% for the spectrum).
- **Autism twin data:** Folstein & Rutter reported MZ 36% vs DZ 0% pairwise (higher with broader phenotype); Sandin 2017 (over 37,000 twin pairs) estimated ASD heritability at about 83%.
- **First-degree-relative recurrence risk, schizophrenia:** roughly 6 to 10%, about a tenfold increase over the general-population risk of near 1% (lambda-s of the order of 8 to 10).
- **Heston (1966):** first schizophrenia adoption study (Oregon); about 11%, 5 of 47, of adopted-away offspring of schizophrenic mothers developed schizophrenia vs 0 of 50 controls.
- **Danish adoption studies:** Rosenthal, Wender, Kety & Schulsinger; excess schizophrenia-spectrum disorder in biological (not adoptive) relatives of schizophrenic adoptees; established the schizophrenia spectrum concept.
- **Finnish Adoptive Family Study (Tienari):** genetic risk expressed mainly in dysfunctional adoptive families, demonstrating gene-environment interaction.
- **Mood disorder adoption evidence:** Mendlewicz & Rainer 1977, genetic transmission of manic-depressive illness.
- **Equal-environments assumption:** the critical, load-bearing assumption of the twin design; challenged by Joseph, defended by misassigned-zygosity data.
- **Gene-environment correlation (Plomin 1977; Scarr & McCartney 1983):** passive, evocative, active, shifting from passive to active across development.

Methods: locating the risk

4 · Linkage analysis, LOD score and gene mapping

Before the genome-wide association era, the dominant strategy for finding disease genes was to follow a marker and a putative disease locus *through families* and ask whether they travel together more often than chance allows. This is **linkage analysis**, and its scoring statistic, the **LOD score**, is a recurring viva favourite: examiners want the value of 3, its meaning as 1000:1 odds, and why a method that cracked Huntington disease and cystic fibrosis **largely failed** in schizophrenia and bipolar disorder. That failure is the whole reason the field pivoted to genome-wide association, so this topic is the conceptual hinge of these notes.

The examinable core is a chain of ideas: recombination gives a measurable **genetic distance**; genetic **markers** (RFLP to microsatellite to SNP) let you track chromosomal segments; the recombination fraction feeds a likelihood ratio that becomes the LOD score; parametric linkage needs a specified model, non-parametric (affected sib-pair) does not; and the endpoint is **gene mapping** by positional cloning. Grasp that chain and you can answer any permutation the paper

throws at you (Companion to Psychiatric Studies 2010; New Oxford Textbook of Psychiatry 2020).

4.1 Linkage versus association: the fundamental split

Two different questions, two different units. **Linkage** asks whether a marker and a disease locus *co-segregate within families*, tracked across meioses in pedigrees; the unit of analysis is the family. **Association** asks whether a marker allele *co-occurs with disease at the population level*, i.e. is more common in cases than controls; the unit is the unrelated individual. Linkage tolerates any allele at the linked marker (it cares only about recombinant versus non-recombinant transmission), whereas association implicates a specific allele. Linkage detects loci at coarse resolution over tens of centimorgans; association, exploiting the short range of linkage disequilibrium, localises to well under 1 cM (Companion to Psychiatric Studies 2010).

4.2 Recombination fraction theta and genetic distance

Recombination is the ruler. During meiosis, crossing-over between homologous chromosomes reshuffles alleles. The **recombination fraction** (theta) is the probability that a crossover falls between two loci, so it ranges from 0 (the marker is physically inside the gene and never separates) to 0.5 (independent assortment, i.e. unlinked). The nearer two loci sit, the smaller theta and the more often they are inherited together. The Companion likens it to cutting a pack of cards: adjacent cards are least likely to be separated by repeated cuts, distant cards as likely as not. The unit of genetic distance is the **centimorgan (cM)**, defined so that 1 cM corresponds to a 1% recombination frequency; across the human genome 1 cM averages roughly 1 megabase, but the two maps are not interchangeable (see 4.8).

4.3 Genetic markers through history: RFLP to STR to SNP

You cannot track a segment you cannot see. Linkage needs polymorphic markers of known Mendelian inheritance densely spaced along the genome. The marker technology evolved in three generations, and knowing the sequence is a clean exam point (New Oxford Textbook of Psychiatry 2020; genetic-mapping primer, Ott lab).

RFLP (restriction fragment length polymorphism)

First-generation DNA marker (1980s). Sequence variants create or abolish restriction-enzyme cut sites, giving differently sized fragments. Sparse, mostly biallelic, low information content. RFLPs revived family linkage as a genome-wide method.

Microsatellite / STR (short tandem repeat)

Second generation (1990s). Di-, tri- or tetra-nucleotide repeats varying in copy number; highly polymorphic and multi-allelic, so far more informative per locus. Panels of a few hundred microsatellites powered the classic genome-wide linkage scans.

SNP (single-nucleotide polymorphism)

Current standard. Single base-pair variants, usually biallelic but present in millions across the genome and amenable to chip-based genotyping. Individually less informative than an STR but hugely denser; SNPs made genome-wide association feasible.

4.4 Parametric linkage and the LOD score

The scoring statistic examiners want by name. **Parametric** (model-based) linkage specifies the mode of inheritance in advance: penetrance, disease-allele frequency and the recombination fraction. The recombination fraction is estimated by maximum likelihood, and the evidence for linkage is expressed as the **LOD score** (logarithm of the odds; log10 of a likelihood ratio). The numerator is the likelihood of the observed pedigree data assuming linkage at a given theta; the denominator is the likelihood assuming no linkage (theta = 0.5). By convention a **LOD score of +3** is accepted as proof of linkage, corresponding to odds of **1000:1** in favour (10 to the power 3), and a **LOD score of -2** excludes linkage, corresponding to odds of **100:1 against** (Companion to Psychiatric Studies 2010). If good model parameters are known, parametric linkage is very powerful; when the model is uncertain, mis-specification erodes that power.

> **PEARL**
> A LOD score is a base-10 logarithm, so it converts multiplicatively: LOD 3 means 10^3 = 1000:1 odds for linkage, LOD -2 means 10^2 = 100:1 odds against. The asymmetric thresholds (+3 to accept, -2 to exclude) reflect the low prior probability that any two random loci are linked, which is why more evidence is demanded to declare linkage than to reject it.

4.5 Non-parametric linkage: the affected sib-pair method

Model-free linkage for complex traits. When the mode of inheritance is unknown (true of every psychiatric disorder), parametric linkage is unsafe because a wrong model destroys power. **Non-parametric** (model-free) linkage sidesteps this by asking only about *allele sharing*. The prototype is the **affected sib-pair** method: two affected siblings share, by chance, 0, 1 or 2 alleles identical-by-descent at any locus, with expected proportions 25%, 50%, 25%. If a locus contributes to the disease, affected sibs share marker alleles at that locus *more often than chance*. The method makes no assumption about penetrance or dominance, relying only on the known Mendelian transmission of the markers. A particular form of affected-sib-pair analysis has a 1:1 correspondence with LOD-score analysis for a fully penetrant recessive disease, and many allele-sharing results are still reported as LOD scores (Ott lab genetic-mapping primer; Companion to Psychiatric Studies 2010).

TRAP Parametric (model-based) linkage needs the mode of inheritance specified in advance, so it is unsafe for psychiatric disorders where the model is unknown; use the model-free affected-sib-pair method instead.

4.6 From linkage to gene: positional cloning

Linkage gives a region, not a gene. **Positional cloning** is the strategy of moving from a mapped chromosomal interval to the actual causal gene using position alone, without prior knowledge of the gene's function (contrast the functional-candidate approach, which starts from a gene of known biology). The pipeline: a genome-wide linkage scan localises the disease to a broad interval; the interval is progressively narrowed by additional markers and by linkage disequilibrium; candidate genes within the region are then sequenced for causal variants. Positional cloning delivered the great single-gene successes (Huntington disease, cystic fibrosis)

and, in psychiatry, identified *DISC1* by cloning the breakpoint of a balanced t(1;11) translocation that co-segregated with major psychiatric illness in a large Scottish family (Millar et al 2000; Blackwood et al 2001).

4.7 Fine-mapping with linkage disequilibrium

Sharpening a coarse hit. Once linkage flags an approximate location, **fine-mapping** narrows it using **linkage disequilibrium** (LD), the non-random co-occurrence of alleles at nearby loci in a population. Because a founder mutation stays coupled with neighbouring marker alleles for many generations, disease-associated alleles cluster in a small window around the true gene. In large outbred populations LD decays over very short distances (of the order of 0.3 cM, i.e. a few hundred kilobases), giving far higher mapping resolution than family linkage. Isolated founder populations (the classic example being the Afrikaans-speaking population of South Africa) retain LD over several centimorgans, which can help or hinder depending on the design (Ott lab genetic-mapping primer 2001). Family-based LD designs use the case-parent *trio* and compare transmitted versus non-transmitted parental alleles, which controls for population stratification.

4.8 Genetic maps versus physical maps

Two rulers for one genome. A **genetic (linkage) map** orders loci by recombination frequency, with distance in centimorgans; it reflects how often crossovers separate loci. A **physical map** orders loci by actual DNA base pairs, with distance in kilobases or megabases, and the ultimate physical map is the reference genome sequence itself. The two do not scale uniformly: recombination is not evenly distributed, so recombination hotspots stretch the genetic map relative to the physical map, while cold regions (for example near centromeres) compress it. Roughly 1 cM averages 1 Mb genome-wide, but this ratio varies severalfold by location, which is why a linkage peak defines a region that must then be resolved on the physical map.

4.9 Why linkage largely failed in psychiatry, and the shift to association

The exam's punchline. Linkage is powerful for rare, highly penetrant, single-gene (Mendelian) disorders where one locus of large effect segregates cleanly in pedigrees. Psychiatric disorders are the opposite: *polygenic*, built from many common variants each of tiny effect, with incomplete penetrance, phenocopies, genetic heterogeneity (different loci in different families) and no clear mode of inheritance. Under these conditions family linkage is badly underpowered, its handful of variants of large effect simply are not there to be found, and the early psychiatric linkage literature became notorious for non-replication (New Oxford Textbook of Psychiatry 2020). Because association (case-control) designs detect common variants of small effect far more efficiently, and dense SNP chips made this genome-wide, the field abandoned linkage for the **genome-wide association study** (GWAS), which is hypothesis-neutral, needs no candidate pre-selection, and permits rigorous ancestry matching. This shift is why modern psychiatric genetics reports polygenic loci and polygenic risk scores rather than single linked genes.

HOLD THIS

Linkage cracks rare Mendelian genes but largely failed in psychiatry. Polygenic architecture, incomplete penetrance, phenocopies and locus heterogeneity leave family linkage underpowered, which is exactly why the field pivoted to genome-wide association.

COMMON TRAP

Do not equate a linkage peak with a gene. Linkage localises a disease to a chromosomal *region* spanning many megabases and dozens of genes; identifying the causal gene requires the further steps of fine-mapping and positional cloning. Similarly, do not confuse the two failure modes of linkage in psychiatry: the problem is not measurement but biology, namely many small-effect variants that no family-based linkage design is powered to catch.

CLINICAL ANCHOR

The clearest psychiatric payoff of positional cloning is *DISC1* (Disrupted-in-Schizophrenia-1), named after the t(1;11) breakpoint it disrupts. The translocation co-segregated with schizophrenia and affective psychosis in a Scottish pedigree at a LOD score of 7.1, far above the threshold of 3, illustrating that when a single large-effect variant genuinely exists in a family, linkage remains decisive. Such variants are the exception, not the rule, in common psychiatric illness.

FEATURE	LINKAGE ANALYSIS	ASSOCIATION STUDY
Unit of analysis	Families / pedigrees (co-segregation across meioses)	**Unrelated individuals (case-control population co-occurrence)**
Effect size detectable	**Rare variants of large effect (Mendelian loci)**	Common variants of small effect (polygenic)
Allele specificity	Allele-agnostic (recombinant vs non-recombinant)	**Implicates a specific allele**
Statistic / threshold	LOD score; +3 proof, -2 exclusion	P value; genome-wide significance $p < 5 \times 10^{-8}$
Mapping resolution	Coarse (tens of cM, many megabases)	**Fine (sub-cM, exploits short-range LD)**
Success in psychiatry	**Largely failed for common disorders; non-replication**	Now dominant; hundreds of polygenic loci, PRS

Linkage versus association across the four axes examiners test: unit of analysis, detectable effect size, resolution, and track record in psychiatric disorders.

MNEMONIC

"LOD 3, odds 1000; minus 2, out the door"

LOD +3 accepts linkage at 1000:1 odds in favour; LOD -2 excludes it at 100:1 against. Pair this with the direction check: positive LOD supports linkage, negative LOD argues against it.

GOOD TO REMEMBER

- **LOD score +3:** conventional threshold for proof of linkage, equals odds of 1000:1 (10^3) in favour (parametric linkage).
- **LOD score -2:** conventional threshold to exclude linkage, equals odds of 100:1 (10^2) against.
- **Recombination fraction (theta):** ranges 0 (never separated, i.e. inside the gene) to 0.5 (unlinked, independent assortment).
- **Centimorgan (cM):** unit of genetic distance, 1 cM = 1% recombination, averaging roughly 1 megabase genome-wide (varies by location).
- **Affected sib-pair sharing:** expected identity-by-descent proportions 25% / 50% / 25% for 0 / 1 / 2 shared alleles under no linkage; excess sharing indicates a disease locus.
- **RFLP, microsatellite/STR, SNP:** three successive marker generations underpinning gene mapping.
- **DISC1 (t(1;11)):** schizophrenia/affective-psychosis candidate cloned from a balanced translocation breakpoint in a Scottish family; linkage LOD 7.1 (Millar et al 2000; Blackwood et al 2001).
- **GWAS genome-wide significance:** conventional threshold $p < 5 \times 10$ to the -8, correcting for roughly one million independent common variants.

5 · Association, GWAS, candidate genes, CNVs and polygenic risk scores

Why this matters. Psychiatric genetics moved in one generation from a graveyard of irreproducible **candidate gene** claims to a robust, sample-size-driven **genome-wide association study** (GWAS) enterprise. The examiner wants you to narrate that arc: why underpowered candidate studies failed, how the **common-disease-common-variant** hypothesis and consortium-scale GWAS finally delivered replicable hits, where rare **copy number variants** sit on the risk spectrum, and why a **polygenic risk score** that captures real biology still cannot predict any individual's diagnosis. The unifying idea is the genetic architecture of complex disorders: many common alleles of tiny effect plus a few rare variants of large effect, with a persistent **missing heritability** gap between them.

Ground your answer in named findings rather than generalities: the 22q11.2 deletion as the single largest known genetic risk for schizophrenia, the MHC/complement-C4 signal, and the shared loci (e.g. CACNA1C) that blur the schizophrenia to bipolar boundary. These are the load-bearing facts, drawn from Kaplan and Sadock (2024), the New Oxford Textbook, and the Companion to Psychiatric Studies.

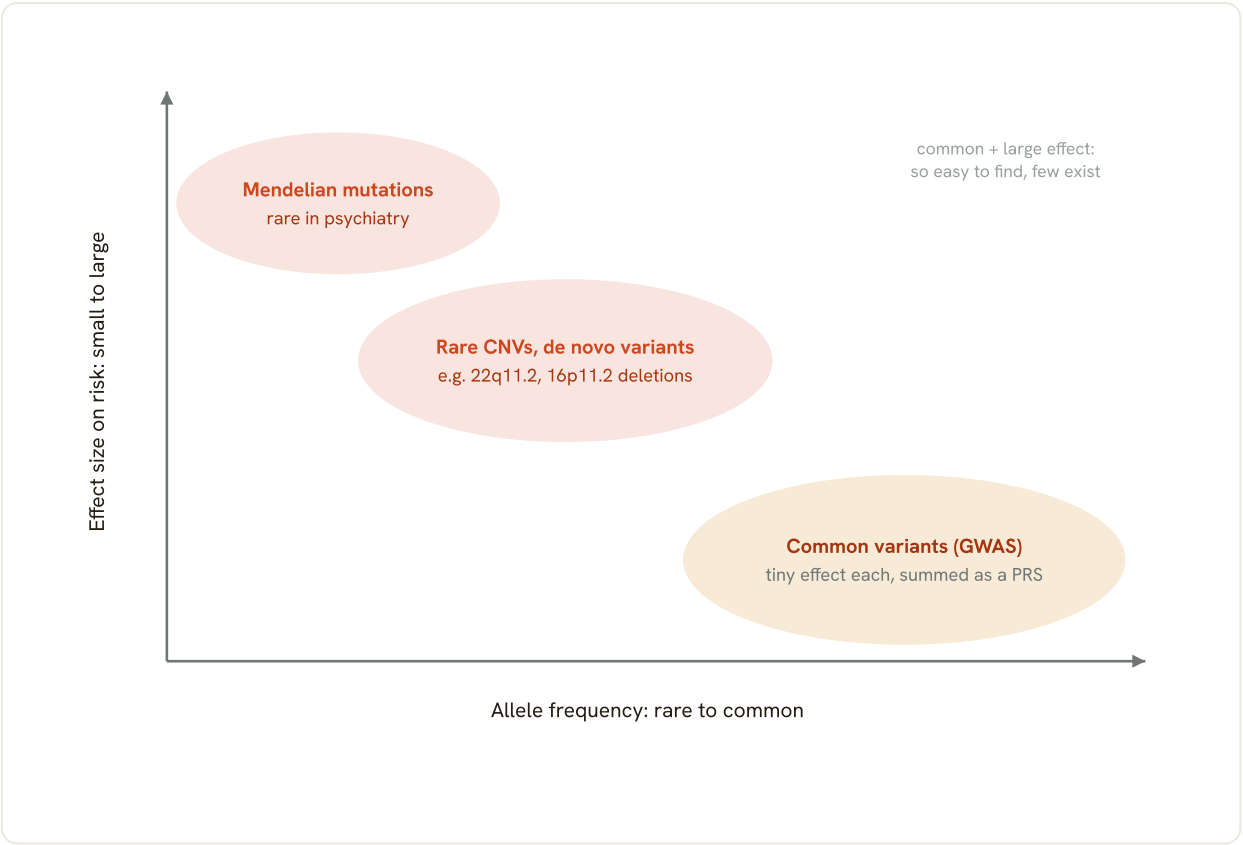
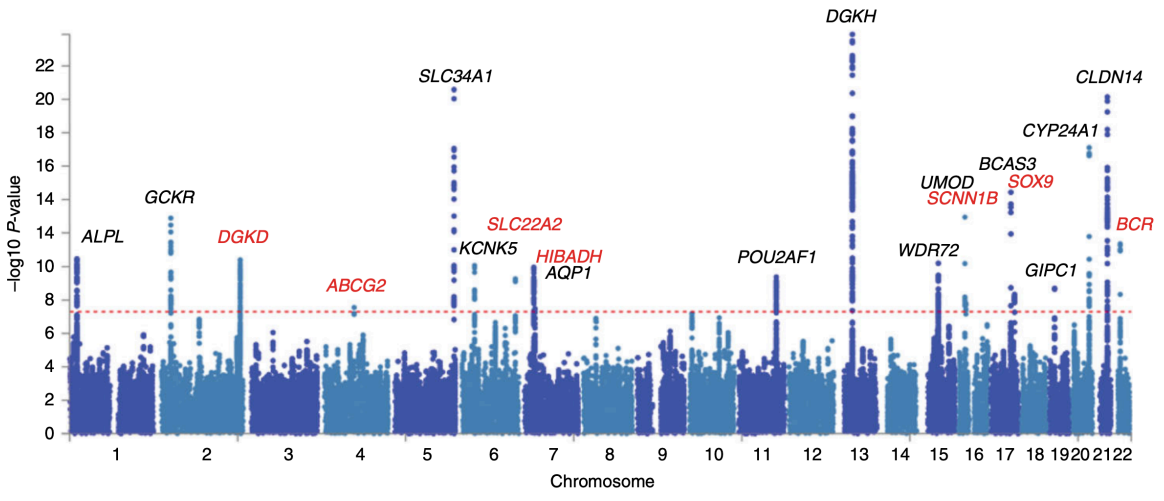


Fig 3.4 The genetic architecture of psychiatric disorders on the allele-frequency by effect-size plane. Risk variants trade off frequency against effect: a very few rare mutations carry large effects (top left, uncommon in psychiatry), rare copy-number and de novo variants sit in the upper band with moderate-to-large effects (the 22q11.2 deletion is the clearest example in schizophrenia), and the bulk of common inherited risk lies bottom right as thousands of common variants each of tiny effect, which genome-wide association detects and a polygenic risk score sums. The empty top-right corner (common and large effect) explains why such variants would already have been found, and the gap between what these methods capture and twin heritability is the missing heritability problem.



Representative GWAS Manhattan plot: S. A. Howles, A. Wiberg, M. Goldsworthy et al., CC BY 4.0, via Wikimedia Commons

Fig 3.5 What a genome-wide association study produces: a Manhattan plot. Each dot is one single-nucleotide polymorphism, placed left to right by its position along the chromosomes, and its height is the strength of association (the negative log base ten of the p-value). The dashed horizontal line marks genome-wide significance (5 x 10 to the minus 8); the peaks rising above it are the associated loci. A psychiatric GWAS looks exactly like this: each significant peak adds only a sliver of risk, which a polygenic risk score later sums across the genome. The plot shown is a representative GWAS used to illustrate the method.

5.1 Association studies: the basic logic and its currencies

The design. An **association study** compares allele frequencies at a genetic marker between unrelated cases and controls: if an allele is over-represented in cases, it (or a variant near it) may raise risk. This is more powerful than linkage for common variants of small effect, which is exactly the architecture complex psychiatric disorders turned out to have (Companion to Psychiatric Studies).

Direct vs indirect association. Because alleles are inherited in blocks, a typed marker need not be causal: **linkage disequilibrium** (LD, the non-random co-inheritance of nearby alleles) means a neutral tag SNP can flag a nearby functional risk allele. GWAS exploits this, so most GWAS hits are markers pointing to a region rather than the causal variant itself (Kaplan and Sadock 2024).

SNP (single-nucleotide polymorphism)

A single base-pair change (e.g. adenine to guanine); occurs roughly once per 1,200 bases; the workhorse marker of GWAS.

Common variant

Minor allele frequency above 1% in the population.

Linkage disequilibrium (LD)

Non-random association of alleles at nearby loci, decaying with recombination distance; lets a tag SNP stand in for an untyped causal allele.

Pleiotropy

One gene affecting multiple traits or disorders; many of the same loci raise risk for schizophrenia, bipolar disorder and ASD.

5.2 The candidate-gene era and its replication failure

The approach. Before genome-wide genotyping, researchers were forced to pre-select a handful of **candidate genes**, chosen either positionally (under a linkage peak) or functionally (a biologically plausible neurotransmitter gene). For schizophrenia alone, more than 1,500 studies examined nearly 800 candidate genes (Tasman 2015).

The cautionary tale. Almost none survived. Farrell and colleagues (2015), reviewing the most-discussed schizophrenia candidates (COMT, DTNBP1/dysbindin, DISC1, DAOA, RGS4, HTR2A, DRD3) against genome-wide data, found the classic candidate literature did not yield clear insight into the genetic basis of schizophrenia: these historical candidates were not supported at genome-wide significance, and the original serotonin-transporter and DISC1 psychiatric associations largely did not replicate (Companion to Psychiatric Studies).

Why they failed. Underpowered samples chasing tiny true effects, publication bias toward positive results, weak priors on which genes to test, and flexible analytic choices produced a literature dominated by false positives (Ioannidis and colleagues). Even where a real effect existed, replication studies were themselves too small to confirm it. The lesson embedded in every modern GWAS is the need for enormous samples and built-in replication.

COMMON TRAP

Do not quote COMT val158met or 5-HTTLPR (the serotonin-transporter length polymorphism, SLC6A4) as established risk genes for a psychiatric disorder. In the exam these are the canonical examples of candidate-gene claims that did not replicate at genome-wide significance. The safe framing: "historically studied candidate, not supported by well-powered GWAS." DISC1 (Disrupted-in-Schizophrenia-1) belongs in the same cautionary basket.

5.3 The common-disease-common-variant hypothesis

The pivot from linkage. Linkage studies, so successful for Mendelian disease, failed to deliver reproducible schizophrenia loci; no Mendelian form of schizophrenia was ever found. This failure was read as evidence against a few genes of major effect, and reframed as the **common-disease-common-variant** (CD/CV) hypothesis: risk is conferred by many common variants, each of small effect, that are old enough to be widespread in the population (Tasman 2015).

Why it justified GWAS. If risk alleles are common, they can be tagged by common SNPs on an array and detected in case-control samples, provided the sample is large enough to see effects with odds ratios near 1.1 to 1.4. CD/CV is the theoretical warrant for genome-wide genotyping; it does not exclude a complementary role for rare, high-penetrance variants (the two-tier architecture in 5.7).

5.4 GWAS methodology: arrays, the Manhattan plot and the 5e-8 threshold

The platform. A GWAS uses a DNA microarray ("gene chip") to assay hundreds of thousands to millions of SNPs across the whole **genome-wide** span simultaneously in tens to hundreds of thousands of people, then tests each SNP for a frequency difference between cases and controls (Kaplan and Sadock 2024).

The Manhattan plot. Results are displayed with chromosomal position on the x-axis and the negative log10 of each SNP's p-value on the y-axis, so the strongest associations rise as skyscraper-like peaks (hence "Manhattan"). A horizontal line marks the significance threshold; peaks crossing it are the reported loci.

Genome-wide significance = 5e-8. Because roughly a million independent tests are performed, the conventional threshold is set at p less than 5 x 10 to the power minus 8 (5e-8), a Bonferroni-style correction for the predicted false positives when a million tests are run (Kaplan and Sadock 2024). Meeting this bar is what separates a credible locus from noise, and is why so many early, small psychiatric GWAS reported nothing.

The QQ plot. A quantile-quantile plot graphs observed against expected p-values under the null. Points hugging the diagonal until an upward tail at the extreme suggest true polygenic signal; an early, uniform lift of the whole line signals confounding (typically population stratification or cryptic relatedness), quantified by the genomic inflation factor lambda. The QQ plot is the standard quality-control read-out for a GWAS.

RULE **Genome-wide significance is $p < 5 \times 10^{-8}$.** It is a Bonferroni-style correction for roughly a million independent common-variant tests, and is the bar that separates a credible locus from noise.

5.5 The Psychiatric Genomics Consortium and sample-size scaling

Size was the missing ingredient. The decisive move was collaborative pooling. The **Psychiatric Genomics Consortium** (PGC) aggregated samples across more than 30 countries, and the schizophrenia signal scaled almost linearly with case number: an early GWAS reporting a handful of loci grew, once tens of thousands of cases were assembled, into the landmark 2014 analysis of about 36,989 cases and 113,075 controls that identified 128 independent associations across 108 distinct genomic loci (Companion to Psychiatric Studies; Kaplan and Sadock 2024).

What the hits mean biologically. At least three-quarters of these loci contained protein-coding genes, enriched for dopamine (DRD2), glutamate (GRIN2A, GRM3) and voltage-gated calcium-channel (CACNA1C) signalling. Most associated variants do not change protein sequence; they most likely alter gene expression, which makes functional interpretation hard (Companion to Psychiatric Studies).

CLINICAL ANCHOR

Named schizophrenia findings worth carrying into a viva. The **MHC/complement-C4 signal** on chromosome 6 is the single most robustly associated locus, though its effect is modest (odds ratio about 1.2); Sekar and colleagues (2016) showed the association is driven by structural variation raising expression of complement component C4A, plausibly linked to excessive synaptic pruning. **DRD2** (the target of every antipsychotic) emerging as a GWAS hit closed a satisfying loop between genetics and pharmacology. **CACNA1C** is a canonical cross-disorder locus shared with bipolar disorder, underlining that genetic boundaries between the two are permeable.

5.6 Copy number variants and named recurrent syndromes

Definition. A **copy number variant** (CNV) is a structural change, a deletion or duplication of a DNA segment larger than 1 kilobase, altering gene dosage. CNVs are common in aggregate (about 12% of the genome is copy-number variable) and mostly benign, but a subset of large, recurrent, gene-rich CNVs carry substantial psychiatric risk (Kaplan and Sadock 2024).

22q11.2 deletion: the flagship. The recurrent hemizygous microdeletion at 22q11.2 was the first de novo CNV described in schizophrenia (Karayiorgou 1995) and, before the GWAS era, the only DNA variant indisputably pathogenic for the disorder (Companion to Psychiatric Studies). It causes velocardiofacial syndrome (DiGeorge syndrome), with cardiac outflow defects, palatal anomalies, hypocalcaemia and learning difficulty, and raises the odds of schizophrenia roughly 50-fold, the single largest known genetic risk (Kaplan and Sadock 2024). Because carriers are recognisable clinically, the psychosis link was demonstrable early.

Other recurrent risk CNVs. A recurring set of loci shows a similar many-to-one, pleiotropic pattern (one CNV, several neurodevelopmental outcomes): 16p11.2 (deletion and duplication, strongly tied to autism and developmental delay), 1q21.1, the 15q11-13 region, 3q29, and

deletions disrupting NRXN1 (neurexin-1, a presynaptic cell-adhesion gene). Total CNV burden is elevated in schizophrenia and autism relative to controls, and disease-associated CNVs are larger and more gene-rich than benign ones. Chromosomal microarray is now standard first-line testing in autism and intellectual disability, yielding a molecular diagnosis in over 20% of children tested (Kaplan and Sadock 2024).

~50-fold	~12%	>20%
22Q11.2 RAISES SCHIZOPHRENIA ODDS	OF GENOME IS COPY-NUMBER VARIABLE	CMA MOLECULAR-DIAGNOSIS YIELD IN ASD/ID

LOCUS	CHANGE	SYNDROME / EPONYM	PRINCIPAL PSYCHIATRIC ASSOCIATION
22q11.2	Deletion	**Velocardiofacial / DiGeorge**	**Schizophrenia (about 50-fold; largest known single risk); ADHD, anxiety**
16p11.2	Deletion / duplication	16p11.2 microdeletion/duplication	Autism, developmental delay, intellectual disability
1q21.1	Deletion / duplication	1q21.1 recurrent CNV	Schizophrenia, autism, developmental delay
15q11-13	Duplication	15q duplication (maternal)	Autism; (paternal deletion gives Prader-Willi)
15q11.2	Deletion	15q11.2 (BP1-BP2)	Schizophrenia, epilepsy, developmental delay
NRXN1 (2p16.3)	Deletion	NRXN1 deletion	Schizophrenia, autism, intellectual disability

Recurrent, high-risk copy number variants and their named cytogenetic syndromes; 22q11.2 deletion is the flagship, carrying the single largest known genetic risk for schizophrenia (Kaplan and Sadock 2024; Companion to Psychiatric Studies).

5.7 The genetic architecture plane: allele frequency vs effect size

The core inverse relationship. Plot allele frequency against effect size and a clear gradient appears. Common GWAS SNPs are frequent but tiny in effect (odds ratios about 1.1 to 1.4). Rare CNVs and protein-truncating variants are the opposite: uncommon in the population but with large effect (odds ratios of roughly 20 to 100 for the strongest, e.g. 22q11.2). Mendelian, single-gene disorders sit in the far corner: very rare, near-deterministic effect (Kaplan and Sadock 2024).

Why the corners are empty. There are essentially no common variants of large effect for schizophrenia (a variant that common and that harmful would be culled by natural selection, because affected individuals have markedly reduced fecundity). This is why the disorder is polygenic on the common-variant side and driven by rare, often de novo, variants on the large-effect side. Both tiers must be summed to understand an individual's total genetic liability.

5.8 Polygenic risk scores: construction and limits

Construction. A **polygenic risk score** (PRS, also risk-profile scoring) is built from GWAS summary statistics. In a discovery sample, each SNP is assigned a weight (its estimated effect size); in an independent target individual, you count the risk alleles carried and sum them, weighted, to a single number, an estimate of that person's common-variant genetic liability (Kaplan and Sadock 2024). The method traces to the International Schizophrenia Consortium (ISC), which set a deliberately loose p-value threshold, reasoning that although most such alleles are false, a highly polygenic disorder would still carry a detectable aggregate burden. The ISC confirmed this and estimated the common-variant component is spread across at least 1,000 alleles, contributing roughly one-third of the genetic risk (Companion to Psychiatric Studies).

Variance explained. Even from the largest studies, a schizophrenia **PRS** accounts for only about 7% of the variance in liability; the PGC common-variant signal explains only about 3 to 4% (New Oxford Textbook; Companion to Psychiatric Studies). Across disorders the figures are modest, and for ADHD current PRS explains on the order of 0.1 to 2% of phenotypic variance (New Oxford Textbook).

Why PRS is not yet clinically predictive. Three reasons dominate. First, low variance explained: high PRS shifts population-average risk but the distributions of cases and controls overlap heavily, so an individual score has poor discrimination. Second, portability: GWAS samples are overwhelmingly of European ancestry, and PRS performs worse when applied across ancestries (an equity problem for use in Indian and other non-European populations). Third, PRS captures only the common-variant tier, ignoring the large-effect CNVs and rare variants that matter most for the highest-risk individuals. PRS is a powerful research instrument for genetic architecture, but not a diagnostic test.

HOLD THIS

A PRS sums common-variant burden but cannot diagnose an individual. It explains only about 7% of schizophrenia liability, case and control distributions overlap heavily, and European-derived scores transport poorly to other ancestries.

TRAP Do not quote COMT val158met, 5-HTTLPR (SLC6A4) or DISC1 as established risk genes: they are the canonical candidate-gene claims that did not replicate at genome-wide significance.

INDIA

The Eurocentric ancestry bias of GWAS discovery samples is not an abstraction for Indian practice. A PRS derived in European cohorts loses accuracy in South Asian genomes because LD structure and allele frequencies differ, so any near-term "genetic risk report" marketed for Indian patients should be read with strong caution. Broadening reference panels to non-European ancestries is the stated route to more equitable PRS.

5.9 Missing heritability: where the rest may hide

The gap. Twin studies put schizophrenia heritability high (broadly in the 60 to 80% range for the most heritable psychiatric disorders), yet SNP-heritability (the variance captured by common

GWAS variants) and PRS explain only a single-digit-to-modest fraction. The difference is **missing heritability** (Manolio and colleagues 2009).

Candidate hiding places. Several, and probably several at once: (1) rare variants of larger effect, including CNVs and protein-truncating single-nucleotide variants, poorly tagged by common-SNP arrays; (2) many more common variants of effect too small to reach 5e-8 at current sample sizes (still-larger GWAS keep finding them); (3) gene-gene and gene-environment interactions and structural variation not well captured; (4) overestimation of twin heritability itself (shared-environment and equal-environment assumptions). The field's working answer is that no single mechanism accounts for the gap; ever-larger biobank-scale GWAS plus whole-genome and exome sequencing for rare variants are chipping at it from both ends (Companion to Psychiatric Studies; New Oxford Textbook).

MNEMONIC

Common is Small, Rare is Tall

The genetic architecture plane in one line: common variants (GWAS SNPs) are frequent but Small in effect; rare variants (CNVs, protein-truncating variants) are uncommon but Tall in effect. The empty corner (common and tall) is emptied by natural selection.

PEARL

The whole story is a parable about statistical power. Candidate-gene studies failed not because the biology was wrong but because they were underpowered and multiplicity-uncorrected; GWAS succeeded not because it was cleverer but because consortia made it big enough. The genome-wide significance threshold of 5e-8 is the institutional memory of that lesson.

GOOD TO REMEMBER

- **Genome-wide significance threshold:** p less than 5 x 10 to the power minus 8 (5e-8), correcting for about a million tests.
- **22q11.2 deletion:** velocardiofacial / DiGeorge syndrome; single largest known genetic risk for schizophrenia, about 50-fold increased odds; first de novo CNV described in schizophrenia (Karayiorgou 1995).
- **16p11.2 (deletion/duplication):** recurrent CNV, autism and developmental delay.
- **1q21.1:** recurrent deletion/duplication; schizophrenia, autism, developmental delay.
- **15q11-13 (maternal duplication):** autism (paternal deletion of the region gives Prader-Willi).
- **NRXN1 (neurexin-1, 2p16.3) deletion:** schizophrenia, autism, intellectual disability.
- **MHC / complement C4A:** most robustly associated schizophrenia locus (chromosome 6), effect modest (odds ratio about 1.2); C4A implicated in synaptic pruning (Sekar 2016).
- **DRD2:** GWAS-significant schizophrenia locus; antipsychotic target, closing the genetics-pharmacology loop.
- **CACNA1C:** voltage-gated calcium channel; cross-disorder locus shared by schizophrenia and bipolar disorder.
- **COMT (val158met), 5-HTTLPR (SLC6A4), DISC1:** classic candidate genes that largely failed to replicate at genome-wide significance (Farrell 2015); the cautionary examples.
- **PGC schizophrenia GWAS (2014):** about 36,989 cases, 113,075 controls; 128 independent associations at 108 distinct loci.
- **ISC (2009):** common-variant risk spread across at least 1,000 alleles, contributing roughly one-third of genetic risk; origin of polygenic risk scoring.
- **Schizophrenia PRS variance explained:** about 7% of liability (PGC common-variant signal about 3 to 4%); not clinically predictive at the individual level.
- **ADHD PRS variance explained:** about 0.1 to 2% of phenotypic variance.
- **Twin heritability (most heritable psychiatric disorders):** broadly 60 to 80%; the gap to SNP-heritability is the missing heritability (Manolio 2009).

6 · Novel genetic approaches and gene therapy

Array-based **GWAS** gave psychiatric genetics its first robust, replicable common-variant hits, but it is deliberately blind to two things: the rare, large-effect variation that a genotyping chip does not carry, and the biological **mechanism** that turns a statistical association at a locus into a disease. This topic is the Paper-1 delta on everything that has moved beyond the chip: high-throughput **sequencing** to find rare and *de novo* variation, **functional genomics** and stem-cell models to translate a locus into a mechanism, **causal-inference** methods such as Mendelian randomization, **biobank**-scale cohorts, polygenic scores as a research and emerging stratification tool, and finally **gene therapy**, where the honest examination answer is that monogenic neurology has moved but polygenic psychiatry has not (Kaplan & Sadock 2024; New Oxford 2020).

Why it matters. Examiners increasingly ask you to place a method against a question: which technology finds rare variants, which infers causality from observational genetic data, why a polygenic disorder is a poor candidate for gene editing. **Framing.** Hold one organising idea throughout: *the architecture dictates the tool*. Rare large-effect variants (autism, intellectual disability, some schizophrenia) are found by sequencing and are conceptually near a targeted

therapy; common small-effect variants (the bulk of adult psychiatric liability) are found by GWAS, summarised by polygenic scores, and are nowhere near a molecular cure.

6.1 Sequencing: whole-exome and whole-genome sequencing

What each reads, and why the choice matters. **Whole-exome sequencing** (WES) captures and sequences only the protein-coding portion of the genome, about 1.5 to 3% of the total, which lowers cost and greatly improves interpretability because a coding variant has a readable consequence on protein (Kaplan & Sadock 2024; Wang et al. 2019). It is described in the standard reference as "good for finding gene-disrupting rare variants" (Kaplan & Sadock 2024). **Whole-genome sequencing** (WGS) resequences the entire genome and can in principle detect every class of variation at once, single-nucleotide variants, small insertions and deletions, and structural and copy-number variants, including the regulatory, non-coding variation that WES misses; it is the more comprehensive but more expensive choice. Both have supplanted the older linkage and candidate-gene strategies for gene discovery (Kaplan & Sadock 2024).

RULE **The architecture dictates the tool.** Rare large-effect variants are found by sequencing and sit near a targeted therapy; common small-effect variants are found by GWAS, summed as a PRS, and are nowhere near a molecular cure.

6.2 Rare-variant burden testing

Counting damaging variants against chance. Because any single rare variant is, by definition, seen in too few people to reach significance on its own, the analytic trick is the **rare-variant burden test**: aggregate all rare (minor allele frequency below 1%), predicted-damaging variants within a gene or gene-set and ask whether cases collectively carry a heavier burden than controls. This requires very large samples but has been productive, most famously the finding of an increased burden of ultra-rare protein-altering variants among people with schizophrenia (Genovese et al. 2016, in Wang et al. 2019). A key statistical companion is the **mutation-intolerance** metric: genes can be scored for how strongly they resist loss-of-function variation (the pLI score, probability of loss-of-function intolerance), so that a damaging variant landing in a highly intolerant gene is prioritised as likely pathogenic (Kaplan & Sadock 2024; Wang et al. 2019).

6.3 De novo mutations, autism, and the paternal-age effect

New mutations in the child, absent in the parents. A **de novo mutation** is one present in the affected proband but in neither biological parent, so it is discovered by sequencing parent-child **trios** (two parents plus affected child) or quads (adding an unaffected sibling) and filtering the child's variants against both parents (Wang et al. 2019). De novo variants are individually rare but tend to be more disruptive than inherited variants, which makes them a powerful route into sporadic disease. Their contribution is greatest in the early-onset neurodevelopmental disorders: penetrant de novo mutations are estimated to contribute to autism risk in roughly 11% of trio families, and of de novo loss-of-function variants in autism about 43% are estimated to be pathogenic (against about 13% of de novo missense variants) (Iossifov et al. 2014; Sanders et al. 2015, in Wang et al. 2019). Autism (ICD-11 6A02, DSM-5-TR autism spectrum disorder) and

intellectual developmental disorders together dominate the de novo literature. **The paternal-age effect.** Because the male germline keeps dividing across the lifespan, the number of de novo point mutations transmitted rises steadily with paternal age; this is the molecular basis for the epidemiological association of advancing paternal age with schizophrenia and autism in offspring (Malaspina et al. 2001, in Wang et al. 2019). It is the mechanistic pearl that links a demographic risk factor to a class of variant.

6.4 Functional genomics: from a locus to a mechanism

Bridging the association gap. Most GWAS hits sit in non-coding regulatory DNA, so knowing the associated variant does not tell you which gene it acts on or how. Functional genomics is the toolkit that closes that gap. **eQTL** mapping (expression quantitative trait loci) identifies variants that predict the expression level of a gene, so a risk variant that is also an eQTL points to the gene whose dosage it alters (Kaplan & Sadock 2024). **TWAS** (transcriptome-wide association study) formalises this: it imputes genetically-predicted gene expression from eQTL reference data and tests that predicted expression against disease, moving the unit of association from an anonymous SNP to a named gene. **Chromatin conformation** methods, notably **Hi-C** (a chromosome-conformation-capture assay), reveal which physically distant regulatory regions loop into contact with a promoter, so a non-coding variant can be assigned to the gene it actually regulates in three dimensions (Kaplan & Sadock 2024). **Single-cell** RNA sequencing resolves which specific cell type expresses a risk gene, and **MPRA** (massively parallel reporter assay) tests thousands of candidate regulatory variants at once for their effect on expression. Together these define the mechanistic chain: variant, regulatory element, target gene, cell type, pathway.

6.5 Cellular models: iPSC-derived neurons and brain organoids

Patient biology in a dish. The Nobel-winning discovery that adult somatic cells (skin fibroblasts, hair-follicle cells) can be reprogrammed into **induced pluripotent stem cells** (iPSCs) lets us build neurons that carry an individual patient's exact genetic background, then differentiate them into the neuronal and glial types relevant to the disorder (Yamanaka; New Oxford 2020). iPSC-derived neurons from lithium-responsive bipolar patients show hyperexcitability and dysregulated calcium signalling that lithium itself corrects, tying a clinical phenotype to a cellular one (New Oxford 2020). **Brain organoids** are self-organising three-dimensional cultures that histologically resemble developing human brain and model architecture and connectivity that flat cultures cannot (Kaplan & Sadock 2024; New Oxford 2020). These models are where a genetic finding is functionally validated, and, combined with **CRISPR**/Cas9 editing to introduce or reverse a candidate variant, they let one ask whether a specific mutation is causal for a cellular phenotype (New Oxford 2020).

6.6 Causal inference: Mendelian randomization

Genes as nature's randomised trial. Observational associations cannot distinguish cause from confounding or reverse causation. **Mendelian randomization** (MR) exploits the fact that alleles are randomly allocated at conception, so a genetic variant that raises an exposure (a putative risk factor) acts as an **instrumental variable** that is largely free of the confounding and reverse causation that plague conventional epidemiology (Kaplan & Sadock 2024). If the variant that

raises the exposure also raises disease risk, that supports a causal path. The examinable psychiatric applications are instructive precisely because they cut both ways: two-sample MR has supported a causal influence of cannabis use liability on schizophrenia risk, whereas MR has failed to find that genetically-predicted thyroid function causally influences major depression, and has not found that smoking heaviness causally influences anxiety or depression (Kaplan & Sadock 2024; New Oxford 2020). MR is now a standard way to interrogate whether an epidemiological correlate of psychiatric illness is cause or bystander.

6.7 Biobank-scale genetics

Scale as the enabling technology. The recurring lesson of psychiatric genetics is that discovery is sample-size limited, and the modern answer is the population **biobank**: cohorts of hundreds of thousands with linked genotype, deep phenotype, imaging, and health-record data. The **UK Biobank** (about 500,000 participants) has enabled analyses ranging from the medical consequences of pathogenic CNVs in adults to multimodal population brain imaging, and the US **All of Us** programme is explicitly building a more ancestrally diverse resource (Kaplan & Sadock 2024). Biobanks power the large GWAS, provide the replication samples for polygenic scores, and supply the instruments and outcomes for Mendelian randomization; they are the substrate on which the other methods run.

6.8 Polygenic scores as research tool and emerging stratifier

Summing thousands of tiny effects into one number. A **polygenic risk score** (PRS) sums an individual's risk alleles across the genome, each weighted by its GWAS effect size, into a single estimate of genetic liability (Kaplan & Sadock 2024). As a research tool it is well established: PRS quantifies SNP-based heritability, tests genetic overlap between disorders (a schizophrenia PRS also predicts bipolar liability), and positions categorical diagnosis at the tail of a continuous population liability. As a **clinical stratification** tool it remains emerging rather than deployed: current scores explain only a modest fraction of liability, so they shift population-level probabilities rather than diagnose individuals, and, critically, they are derived overwhelmingly from European-ancestry samples and therefore transport poorly to other ancestries, an equity limitation the standard text flags explicitly (Kaplan & Sadock 2024). The honest exam line: a research workhorse and a plausible future stratifier, not yet a clinical test.

6.9 Gene therapy: the monogenic-neurology precedent

Where molecular correction already works. Gene therapy has become real in single-gene neurological disease, which is the precedent examiners want you to cite. In **spinal muscular atrophy** (SMA), an autosomal-recessive motor-neuron disease caused by loss of *SMN1*, two mechanistically distinct approaches are licensed: **nusinersen**, an **antisense oligonucleotide** directed at the *SMN2* gene that modifies its splicing to raise functional SMN protein, given as a repeated intrathecal infusion; and a one-time gene-replacement therapy that uses an **AAV** (adeno-associated virus) vector to deliver a working copy of *SMN1* to motor neurons, raising SMN protein and improving survival (Kaplan & Sadock 2024). In **Huntington disease**, an autosomal-dominant expanded-CAG-repeat disorder, huntingtin-lowering antisense oligonucleotides reached human trials, the proof-of-concept that a defined, single-gene

neuropsychiatric disorder is a tractable target even though efficacy results have been mixed. The general toolkit, then, is three-fold: **antisense oligonucleotides** that alter splicing or knock down a transcript, **AAV**-vector gene replacement, and **CRISPR**/Cas9 editing that introduces or reverses a mutation at the DNA level (New Oxford 2020; Kaplan & Sadock 2024).

6.10 Why polygenic psychiatry is not near gene therapy

Architecture forbids a single target. Every gene-therapy success above shares a feature the common psychiatric disorders lack: a single, known, large-effect causal gene. Schizophrenia, bipolar disorder, and major depression are polygenic, driven by thousands of common variants each of tiny effect (individual odds ratios typically below 1.3) plus a scatter of rare variants and heavy environmental contribution, so there is no one locus to edit or replace, and correcting any single variant would move risk negligibly (Kaplan & Sadock 2024). The realistic near-term yield of psychiatric genetics is therefore not a cure but mechanism, drug-target nomination (a GWAS gene as a pharmacological lead), risk stratification, and pharmacogenomics, not germline or somatic editing of a polygenic phenotype.

HOLD THIS

Gene therapy works for single-gene neurology, not polygenic psychiatry. Every precedent (spinal muscular atrophy, Huntington disease) has one large-effect causal gene; schizophrenia, bipolar disorder and depression have no single locus to edit or replace.

6.11 Sequencing versus array-GWAS: choosing the tool

A one-glance comparison. The following table is the examinable summary of which technology answers which question, the point being that no single platform does everything.

METHOD	VARIATION CAPTURED	BEST USE CASE	KEY LIMITATION
Array-GWAS	Common SNPs (chip content)	Common small-effect risk loci, PRS, heritability	**Blind to rare and novel variants; misses de novo**
Whole-exome sequencing	Coding variants (about 1.5 to 3% of genome)	Rare gene-disrupting and de novo coding variants	**Misses non-coding regulatory and most structural variation**
Whole-genome sequencing	All classes (SNV, indel, CNV, structural)	Comprehensive rare and regulatory variant discovery	**Highest cost; heavy interpretation burden for non-coding hits**
Trio de novo design	De novo variants absent in parents	Sporadic autism, intellectual disability, severe cases	**Needs parent samples; small yield outside neurodevelopmental disorders**

Discovery technologies mapped to the variant class each is built to find; the take-home is that architecture, common versus rare versus de novo, dictates the tool.

COMMON TRAP

Do not describe gene therapy as an emerging treatment for schizophrenia, bipolar disorder, or depression. The gene-therapy precedents (SMA, Huntington disease) are all single-gene disorders with a defined causal target; the common psychiatric disorders are polygenic with no such target, which is exactly why they are not near gene therapy. Equally, do not conflate WES and WGS: WES reads only the coding exome and misses non-coding and most structural variation, whereas WGS reads the whole genome.

COMMON TRAP

An eQTL, TWAS, or Mendelian-randomization result is not proof of a mechanism by itself; it is a prioritisation or a causal-inference signal that still needs functional validation (typically iPSC or organoid models plus CRISPR editing). Mendelian randomization in particular is only as good as its instrument: a variant with pleiotropic effects violates the core assumption and can produce a false causal claim.

PEARL

The paternal-age effect is the cleanest link between epidemiology and molecular genetics: the male germline keeps dividing, so older fathers transmit more de novo point mutations, which is the mechanistic explanation for advancing paternal age as a risk factor for schizophrenia and autism. If a stem asks why paternal (not maternal) age matters and why de novo variants are the currency, this is the answer.

MNEMONIC

SEQ-FM-CB-P: SEQuence it, work out the Function and Model it, infer Causality in a Biobank, then score the Polygene.

Walks the modern pipeline in order: sequencing (WES/WGS, de novo, burden) to find variants; functional genomics and cellular models (eQTL, TWAS, Hi-C, iPSC, organoids) to reach mechanism; causal inference (Mendelian randomization) and biobank scale to test and power it; polygenic scores as the summary output. Gene therapy sits outside this loop, reserved for the monogenic disorders.

INDIA

Two practical points for Indian practice. First, the ancestry bias of GWAS and polygenic scores is not abstract: scores trained on European-ancestry biobanks transport poorly to South Asian populations, so a PRS quoted in the literature should not be applied clinically to Indian patients without ancestry-matched validation. Second, the gene-therapies discussed are extremely high-cost, single-gene neurology interventions; when counselling families about the common polygenic psychiatric disorders, the message is that management is pharmacological and psychosocial, framed in liability terms, with no genetic cure on the horizon, which also keeps counselling non-stigmatising.

GOOD TO REMEMBER

- **WES (whole-exome sequencing):** captures protein-coding genome, about 1.5 to 3%; good for rare gene-disrupting variants (Kaplan & Sadock 2024).
- **WGS (whole-genome sequencing):** reads all variant classes (SNV, indel, CNV, structural); more comprehensive, more expensive.
- **De novo mutation yield in autism:** penetrant de novo mutations contribute to about 11% of trio families; about 43% of de novo loss-of-function variants estimated pathogenic (about 13% of missense) (Iossifov et al. 2014; Sanders et al. 2015).
- **Detected DNM rate (predominantly whole-exome):** roughly 1.3 de novo mutations per individual across neuropsychiatric sequencing cohorts in denovo-db, a sequenced-exome yield and not the genome-wide new-mutation rate (Wang et al. 2019).
- **SETD1A:** loss-of-function variants implicated as a schizophrenia susceptibility gene (Takata et al. 2014).
- **Schizophrenia ultra-rare variant burden:** increased burden of ultra-rare protein-altering variants in schizophrenia (Genovese et al. 2016).
- **GWAS genome-wide significance threshold:** P = 5 x 10 to the minus 8 (Kaplan & Sadock 2024).
- **Common psychiatric risk alleles:** individual odds ratios typically below 1.3 (Kaplan & Sadock 2024).
- **UK Biobank:** about 500,000 participants with linked genotype, phenotype, imaging, and records; All of Us builds a more diverse US resource.
- **Nusinersen:** SMN2-directed antisense oligonucleotide (splice modifier) for spinal muscular atrophy, intrathecal (Kaplan & Sadock 2024).
- **SMA AAV gene replacement:** one-time AAV-vector delivery of a working SMN1 copy (Kaplan & Sadock 2024).
- **Huntingtin-lowering ASO:** antisense oligonucleotide against HTT reached human Huntington disease trials; efficacy mixed.
- **CRISPR/Cas9:** genome-editing tool to introduce or reverse disease-associated mutations, used experimentally with iPSC and organoid models (New Oxford 2020).
- **Cannabis and schizophrenia:** two-sample Mendelian randomization supports a causal influence of cannabis use liability on schizophrenia risk (Kaplan & Sadock 2024).

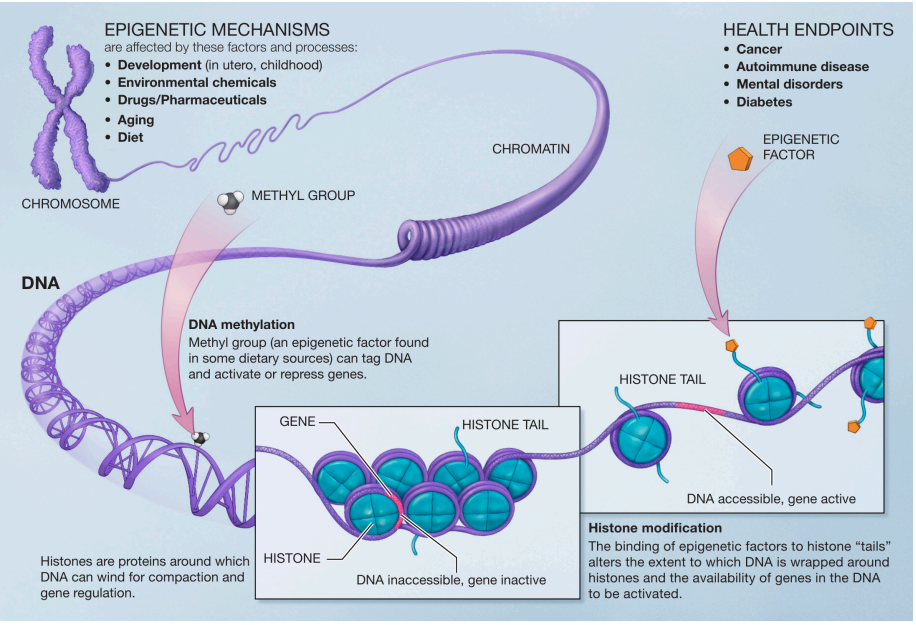
Mechanisms

7 · Epigenetics in psychiatry

The missing half of nature and nurture. Twin studies fix the heritability of schizophrenia near 81 percent and of bipolar disorder near 85 percent (Kaplan & Sadock 2024), yet common variants explain only a fraction of that liability, and monozygotic concordance for schizophrenia sits slightly below 50 percent. **Epigenetics** occupies exactly this gap: it is the molecular layer through which environment writes onto a fixed genome, and it is the single most examinable route by which stress, adversity, and development translate into altered gene expression without touching the DNA sequence.

For the exam, hold three anchors: a clean **definition**, the four **mechanisms** (DNA methylation, histone modification, non-coding RNA, chromatin remodelling), and the flagship human stories (genomic imprinting in Prader-Willi versus Angelman; maternal-care and glucocorticoid-receptor

methylation; the FKBP5 gene-by-environment interaction in PTSD). Epigenetics is the substrate that makes gene-environment interaction mechanistic rather than statistical.



Epigenetic mechanisms: National Institutes of Health, public domain, via Wikimedia Commons

Fig 3.6 The two main epigenetic mechanisms, shown from chromosome to DNA. DNA methylation adds a methyl group that tags the sequence and tends to silence transcription without changing the letters of the code. Histone modification alters how tightly DNA is wound around the nucleosome: loosely wound DNA is accessible and its genes active, tightly wound DNA is inaccessible and silent. These marks are laid down by development, early-life environment, drugs, ageing and diet, which is how experience becomes a stable, sometimes heritable, change in gene expression.

7.1 Definition and why it matters

Waddington's term, sharpened. Conrad Waddington fused "genetics" and "epigenesis" in 1942; the working definition today is a stable, potentially heritable change in gene expression that arises from a modification of the chromosome without any alteration of the underlying DNA sequence (Kaplan & Sadock 2024). The genetic code is one-dimensional, identical in every cell, and unmoved by environment. The epigenetic code is a dynamic three-dimensional layer of proteins and non-coding RNAs, unique to each cell type, and it changes rapidly in response to environmental cues. This is how one genome builds a neuron and a hepatocyte, and how a postmitotic neuron rewrites synaptic-plasticity genes after experience.

~81%	~85%	<50%
SCHIZOPHRENIA HERITABILITY	BIPOLAR DISORDER HERITABILITY	MZ CONCORDANCE, SCHIZOPHRENIA

7.2 DNA methylation and CpG islands

The most examined mechanism. DNA methyltransferases (DNMTs) transfer a methyl group to the 5 position of the cytosine ring at a CpG dinucleotide, generating 5-methylcytosine (Kaplan & Sadock 2024). CpG dinucleotides cluster at high density in **CpG islands** that mark the promoters of active housekeeping genes and are normally unmethylated; aberrant methylation of an island produces a highly repressive, often heritable, chromatin state (X-inactivation and

imprinted genes are the classic examples). Methylation silences transcription two ways: it blocks a transcription factor from binding, or it recruits a methyl-binding protein (for example MeCP2) that pulls in HDAC-containing repressive complexes such as NuRD. Three DNMTs matter: DNMT3a and DNMT3b establish methylation de novo, while DNMT1 is the maintenance enzyme that copies the pattern onto the daughter strand at the replication fork, which is why methylation is heritable across mitosis.

7.3 Histone modification: the histone code

Acetylation opens, methylation reads either way. DNA is wound around a histone octamer (H2A, H2B, H3, H4) to form the nucleosome; the protruding N-terminal tails carry reversible marks that set chromatin accessibility (Kaplan & Sadock 2024). **Acetylation** neutralises positively charged lysines, loosens the histone-DNA grip, and activates transcription; histone acetyltransferases (HATs, for example CBP/p300) write it and histone deacetylases (HDACs) erase it. **Histone methylation** is context-dependent: H3K4, H3K36, and H3K79 methylation activate, whereas H3K9, H3K27, and H4K20 methylation repress. This combinatorial logic is the histone code, and it is the direct target of the therapeutic HDAC inhibitors discussed below.

RULE **Methylation silences, acetylation opens.** DNA methylation tends to repress transcription; histone acetylation loosens the histone-DNA grip and activates it, all without changing the base sequence.

7.4 Non-coding RNA and chromatin remodelling

The other two mechanisms. Small and long non-coding RNAs, including microRNAs (miRNAs), silence transcripts and guide chromatin-modifying complexes to specific loci; altered miRNA expression is reported across depression and psychosis, and, critically, miRNA in sperm has been implicated in transmitting the effects of early trauma to offspring (see 7.8). **ATP-dependent chromatin remodellers** (SWI/SNF and related families) hydrolyse ATP to slide, evict, or reposition nucleosomes, maintaining nucleosome-free regions at active promoters. These four mechanisms do not act in isolation: methylation recruits histone modifiers, which recruit remodellers, forming the self-reinforcing cascades that make epigenetic states stable.

7.5 Genomic imprinting: Prader-Willi versus Angelman

The single best imprinting question in psychiatry. Genomic imprinting is parent-of-origin-specific gene expression established by methylation marks laid down in the germline. Prader-Willi and Angelman syndromes both arise from the same 15q11-q13 locus, and which syndrome results depends entirely on which parental copy is lost (Kaplan & Sadock 2024). Prader-Willi (ICD-11 LD90.3) follows loss of the paternally expressed genes (paternal deletion, or maternal uniparental disomy) and presents with neonatal hypotonia and failure to thrive giving way to hyperphagia, childhood obesity, hypogonadism, and mild intellectual disability. Angelman syndrome follows loss of maternal UBE3A function (maternal deletion, paternal disomy, or a maternal UBE3A mutation) and presents with severe intellectual disability, ataxia, seizures, and a characteristic happy, excitable demeanour.

FEATURE	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
Locus	15q11-q13	**15q11-q13 (same region)**
Parent-of-origin lesion	**Loss of paternal contribution**	**Loss of maternal UBE3A**
Usual mechanism	Paternal deletion or maternal uniparental disomy	Maternal deletion, paternal disomy, or maternal UBE3A mutation
Key genes	SNRPN, NDN, SNORD116 (paternally expressed)	**UBE3A (maternally expressed)**
Core phenotype	Hypotonia then hyperphagia, obesity, hypogonadism, mild ID	Severe ID, ataxia, seizures, inappropriate laughter
Feeding history	**Failure to thrive, then insatiable appetite**	Not the defining feature

Same 15q11-q13 locus, opposite parental origin: the archetypal demonstration that methylation, not sequence, decides the phenotype.

7.6 Early-life programming: maternal care and the glucocorticoid receptor

The Meaney model. In rodents, high maternal licking-and-grooming during the first postnatal week produces adult offspring with reduced methylation at the hippocampal glucocorticoid-receptor promoter, higher GR expression, and a better-regulated, less reactive stress axis; low-care offspring show the opposite pattern (Meaney and Szyf, summarised in Kaplan & Sadock 2024). The mark is developmentally programmed yet pharmacologically reversible: HDAC inhibitors demethylate and raise GR, while intracerebral methionine (a methyl donor) re-methylates the promoter and increases stress reactivity in adults. This is the paradigm case of behaviour writing a stable epigenetic mark on a stress-axis gene.

7.7 Childhood adversity, FKBP5, and the human translation

From rat brain to human suicide brain. Postmortem hippocampus from suicide decedents with documented childhood abuse shows increased methylation at the GR promoter and reduced GR expression, mirroring the low-care rat (McGowan and colleagues, in Kaplan & Sadock 2024). The mechanistically richest human example is **FKBP5**, a co-chaperone that restrains the glucocorticoid receptor. The rs1360780 risk allele permits stronger stress-induced FKBP5 induction; in carriers, childhood trauma drives demethylation of a functional glucocorticoid-response element, locking in a GR-resistant, hyper-reactive HPA phenotype and raising PTSD and depression risk in a dose-dependent way (Klengel et al. 2013). This is gene-by-environment interaction made molecular: the genotype sets susceptibility, early trauma supplies the epigenetic hit, and only the combination produces disorder.

HOLD THIS

Methylation is the molecular bridge from environment to gene expression. FKBP5 is the flagship: the rs1360780 risk allele plus childhood trauma demethylates a glucocorticoid-response element, locking in a GR-resistant, hyper-reactive HPA phenotype and raising PTSD and depression risk (Klengel 2013).

7.8 Transgenerational epigenetic inheritance (state the caveat)

Real signals, contested mechanism. Human observational data are suggestive: prenatal exposure during the Dutch Hunger Winter of 1944 to 1945 was associated, six decades later, with reduced methylation of the imprinted IGF2 gene, specific to periconceptional timing (Heijmans et al. 2008); offspring of Holocaust survivors show altered FKBP5 methylation and cortisol (Yehuda et al. 2016). Animal work is stronger: odour fear-conditioning before conception transmits behavioural and sperm-methylation changes across two generations, and injecting sperm RNA from stressed males into naive oocytes reproduces the offspring phenotype (Gapp et al. 2014). The caveat to state explicitly in any answer: true germline transgenerational inheritance in humans remains unproven, because most marks are erased at two global demethylation waves (gametogenesis and post-fertilisation), and confounding by shared environment, in-utero exposure, and maternal effects is very hard to exclude.

TRAP Do not overclaim epigenetic heredity: true germline transgenerational inheritance in humans remains unproven, because marks are largely reset at two demethylation waves.

7.9 Epigenetic clocks and accelerated biological ageing

A quantifiable biomarker. **Epigenetic clocks** estimate chronological age from DNA-methylation levels at a defined panel of CpG sites with high accuracy (Horvath 2013). When methylation age runs ahead of calendar age the excess is termed epigenetic age acceleration, and it is reported in severe mental illness, in trauma exposure, and with adverse environmental exposures such as tobacco smoke. The appeal for psychiatry is practical: methylation is a stable analyte measurable from a very small number of cells, which is exactly the property a field with no validated diagnostic biomarker needs; SKA2 methylation as a candidate predictor of suicidal behaviour is discussed in this same K&S chapter as an example of the biomarker promise.

7.10 Therapeutic angle: HDAC inhibitors and epigenetic editing

Drugs that move the marks. Several established agents act epigenetically. **Valproate** is a class I HDAC inhibitor in addition to its ion-channel and GABAergic actions, which is one proposed contributor to its mood-stabilising and neuroprotective profile (Stahl 2021); this HDAC-inhibitory activity also underlies its recognised teratogenicity. In schizophrenia models, DNMT inhibitors raise the reduced reelin expression, and chronic clozapine downregulates the mGlu2 receptor via increased HDAC2 binding at its promoter, showing that antipsychotics themselves reshape the histone landscape (Kurita et al., in Kaplan & Sadock 2024). On the horizon, dCas9-based epigenetic editing can add or remove methylation at a chosen locus without cutting DNA, and the Prader-Willi work in which G9A histone-methyltransferase inhibitors (UNC0638, UNC0642) partially reactivated the silenced maternal locus in mice is a proof of concept for locus-specific epigenetic therapy (Kaplan & Sadock 2024).

COMMON TRAP

Do not conflate epigenetic reprogramming with mutation: DNA methylation and histone marks leave the base sequence untouched and Watson-Crick pairing intact. And do not overclaim heredity: acetylation and methylation are reversible and mostly reset in the germline, so "epigenetic inheritance" in humans is far weaker than the popular framing suggests.

PEARL

The one-line integration to give an examiner: methylation is the "molecular bridge" between the genetic code and the environment, converting a statistical gene-by-environment interaction (for example the FKBP5 risk allele plus childhood trauma) into a concrete, measurable, and in principle reversible change in gene expression.

MNEMONIC

MHNC = "My Histones Need Care"

The four epigenetic mechanisms: **M**ethylation of DNA, **H**istone modification, **N**on-coding RNA, **C**hromatin remodelling.

GOOD TO REMEMBER

- **Schizophrenia heritability:** near 81 percent (K&S 2024); MZ concordance slightly below 50 percent.
- **Bipolar disorder heritability:** near 85 percent (K&S 2024).
- **15q11-q13:** shared locus for Prader-Willi (paternal loss) and Angelman (maternal UBE3A loss).
- **Prader-Willi prevalence:** roughly 1 in 15,000 to 30,000; ICD-11 LD90.3.
- **UBE3A:** maternally expressed gene; its loss of function causes Angelman syndrome.
- **SNRPN / SNORD116 / NDN:** paternally expressed 15q11-q13 genes lost in Prader-Willi.
- **MeCP2:** methyl-CpG-binding protein; X-linked mutation causes Rett syndrome.
- **DNMT1:** maintenance methyltransferase (heritability across mitosis); DNMT3a and DNMT3b establish methylation de novo.
- **FKBP5 rs1360780:** risk allele plus childhood trauma leads to GRE demethylation, GR resistance, higher PTSD and depression risk (Klengel et al. 2013).
- **IGF2:** imprinted gene hypomethylated after periconceptional Dutch Hunger Winter exposure (Heijmans et al. 2008).
- **Glucocorticoid-receptor (NR3C1) promoter:** methylation increased by low maternal care in rats (Meaney) and by childhood abuse in human suicide brains (McGowan).
- **Horvath clock (2013):** DNA-methylation estimator of biological age; acceleration reported in severe mental illness.
- **Valproate:** class I HDAC inhibitor (Stahl 2021); links to mood stabilisation and to teratogenicity.
- **Gapp et al. 2014:** sperm-RNA-mediated transgenerational transmission of early-life trauma effects in mice.

8 · Endophenotypes and genetic markers

Why this matters. The heritability of a disorder like schizophrenia is high (60 to 80% from twin studies), yet the road from the genome to the diagnostic checklist is long and noisy. A DSM or

ICD label is a **categorical**, subjectively rated, heterogeneous endpoint: two patients carrying the same diagnosis may share almost no symptoms, and unaffected relatives who carry risk alleles score as unaffected. The **endophenotype** strategy was designed to shorten that road, by mapping genes to heritable, quantitative, biologically simpler intermediate traits that sit inside the genotype-to-phenotype pathway rather than at its clinical terminus (Kaplan and Sadock 2024). The examiner wants two things: the Gottesman and Gould (2003) criteria that define a valid endophenotype, and a working list of the named neurophysiological and neurocognitive endophenotypes of schizophrenia with the criteria they satisfy.

The concept also carries a cautionary coda you must deliver: after two decades, endophenotypes have **underdelivered**. A key meta-analysis (Flint and Munafo 2007) concluded that currently identified psychiatric endophenotypes are not superior to conventional phenotypic disease definitions for gene finding, because the endophenotype often turned out to be no simpler genetically, and no more heritable, than the disorder it was meant to decompose (New Oxford Textbook of Psychiatry). Anchor the answer in the named markers (P50, prepulse inhibition, mismatch negativity, antisaccade, working memory) and in the Research Domain Criteria (RDoC) framework that inherited the endophenotype logic.

8.1 The rationale: closing the genotype-to-phenotype gap

The problem. Psychiatric gene mapping relied for decades on categorical diagnoses, and this is argued to be one of the chief obstacles to progress: diagnosis rests on subjective clinical evaluation, and the menu-based classification means two people with the same disorder can display largely non-overlapping symptom sets, likely reflecting distinct underlying causes (Kaplan and Sadock 2024).

The proposed fix. Map **quantitative traits** hypothesised to lie between the genes and the disorder, and that may be simpler to map genetically. Gottesman and Shields imported the term "endophenotype" into schizophrenia research, and Gottesman and Gould (2003) formalised it; the application of these traits to gene finding is now called **deep phenotyping**. Because an endophenotype is "closer to genes" than a diagnostic category, it is expected to carry more power in gene-mapping studies. For a disorder with about 1% prevalence and 60 to 80% heritability, analysing a quantitative endophenotype has been estimated to be roughly 100-fold more efficient than analysing the categorical diagnosis, translating to about a 10-fold increase in statistical power (Greenwood et al. 2019).

8.2 Terminology: endophenotype, intermediate phenotype, biomarker

Endophenotype

A heritable, quantitative trait on the pathway between genotype and clinical phenotype; internal (not visible to the naked eye), measured by biochemical, neurophysiological, neuropsychological or neuroimaging methods (Gottesman and Gould 2003).

Intermediate phenotype

Used interchangeably with endophenotype in Kaplan and Sadock and the New Oxford Textbook; strictly, some authors reserve "intermediate phenotype" for any trait between gene and disease without requiring familial co-segregation.

Biomarker

Any measurable indicator of a biological state; broader than endophenotype, which additionally requires heritability and a specified relation to illness in families. A state marker tracks the active illness; a trait marker (the endophenotype ideal) persists in remission.

Trait vs state

The state-independence criterion is exactly what separates an endophenotype (trait marker, present whether or not the person is currently ill) from a state marker (present only during the episode).

8.2b The Gottesman and Gould (2003) criteria

The five criteria. A candidate must satisfy the following to qualify as a useful endophenotype (Gottesman and Gould 2003; Kaplan and Sadock 2024). These are the load-bearing list for a viva.

MNEMONIC

A HERD Co-segregates

Associated with illness in the population; **HER**itable; state-independent (the "unchanging" trait, here folded under HERD as the stable trait); **D**etectable in unaffected relatives at higher rates than the general population; and it **Co-segregates** with the illness within families. Unpacked as five: (1) associated with the illness in the population, (2) heritable, (3) state-independent (present whether or not the illness is active, with good test-retest stability), (4) co-segregates with the illness within families, (5) found in non-affected family members at a higher rate than in the general population. A practical sixth requirement for gene finding is that it be reliably and objectively measurable.

Why relatives are the crux. Criteria 4 and 5 are what make an endophenotype worth the extra effort: an unaffected relative who carries the risk alleles but has not crossed the clinical threshold still shows the trait, so the trait indexes latent genetic liability rather than the illness or its treatment. This is why endophenotype studies are typically family-based and enriched for genetic loading (Greenwood et al. 2019).

RULE **The family criteria are what make an endophenotype worth the effort.** Beyond heritable and state-independent, it must co-segregate with illness in families and appear in unaffected relatives above the population rate, so it indexes latent liability rather than the illness or its treatment.

8.3 Sensory gating: P50 suppression

The paradigm. **P50** is an early positive component of the auditory event-related potential recorded at the vertex about 50 ms after a click. In the paired-click paradigm, two identical clicks are presented about 500 ms apart; in healthy subjects the P50 to the second click is markedly attenuated relative to the first. This suppression is a measure of **sensory gating**, the brain's ability to suppress its response to repeated, irrelevant stimuli. People with schizophrenia show less P50 suppression, interpreted as a failure of inhibitory gating (Tasman 2015).

TRAP Do not call an endophenotype "just a biomarker" or "an early symptom": a state marker present only in the acute episode is disqualified by the state-independence criterion.

Genetic anchor. A linkage of the sensory-gating deficit to the alpha-7 nicotinic acetylcholine receptor gene (CHRNA7) on chromosome 15q13-14 has been reported, and nicotine transiently normalises the deficit (most antipsychotics, except possibly clozapine, do not). This makes P50 the prototypical schizophrenia endophenotype with a plausible molecular substrate (Tasman 2015). The deficit persists in medicated patients (state-independence) and occurs in unaffected relatives, but it is not specific to schizophrenia, appearing in other psychiatric and neurological conditions.

8.4 Sensorimotor gating: prepulse inhibition (PPI)

The paradigm. Prepulse inhibition is the normal reduction of the acoustic startle reflex (measured as eye-blink electromyography) when a weak prepulse precedes the startling pulse by roughly 30 to 120 ms. It indexes **sensorimotor gating** (it engages both a sensory stimulus and a motor reflex). PPI is reduced in schizophrenia relative to controls, and the deficit is relatively stable across time (Tasman 2015).

Meets the criteria. PPI deficits are present in unaffected relatives and are significantly heritable within schizophrenia families (about 45 to 50%); broad-sense heritability rises to about 47% in families with high genetic vulnerability versus about 29% when family history is not considered, so PPI behaves as a marker of risk rather than a consequence of illness (Greenwood et al. 2019). It is cross-species (measurable in rodents, where dopamine agonists like apomorphine disrupt it), which is why it is a favoured translational endophenotype for RDoC. Distinguish from P50: P50 is EEG-based habituation of an evoked potential; PPI is EMG-based reflex modulation and is not a form of habituation; the two are only weakly correlated.

8.5 Oculomotor markers: smooth pursuit and antisaccade

Smooth-pursuit eye movements. Impaired smooth-pursuit tracking of a moving target (with intrusive saccades) is one of the oldest and most replicated schizophrenia markers, present in patients and in a substantial fraction of their unaffected first-degree relatives, and a classic candidate endophenotype (New Oxford Textbook).

Antisaccade (AS). The subject must fixate a central target and, when a peripheral cue appears, look in the opposite direction; performance is the ratio of correct antisaccades to interpretable saccades. It is an electrophysiological measure of inhibitory failure. Schizophrenia patients show a large deficit (effect size about 1.0), the measure is stable, it is documented in first-degree relatives, and heritability is about 42 to 57% (Greenwood et al. 2019). A B-SNIP consortium GWAS of pursuit initiation and antisaccade error rate implicated genes in nuclear trafficking (IPO8), axon guidance (PCDH12), nerve-signal transduction (NRSN1) and synaptic glutamate release (SH3GL2).

8.6 Auditory deviance: mismatch negativity (MMN)

The paradigm. Mismatch negativity is the ERP component elicited when an infrequent "deviant" auditory stimulus interrupts a train of "standard" stimuli; it is the difference waveform (deviant minus standard) peaking about 150 to 250 ms after the deviant, and, like PPI, it is preattentive (elicited whether or not the subject attends). Reduced MMN amplitude is one of the

most robust findings in schizophrenia, with a large effect size of about 1.0 that is largely unaffected by medication and stable across symptom fluctuations (Greenwood et al. 2019).

Meets the criteria and predicts onset. MMN is about 68% heritable and is present in individuals at genetic risk; reduced MMN has shown promise for predicting transition to psychosis in clinical high-risk cohorts, giving it a prognostic edge over most other markers. It reflects NMDA-receptor-dependent auditory prediction-error, tying it to the glutamate hypothesis (Greenwood et al. 2019).

8.7 Neurocognitive endophenotypes: working memory and attention

Working memory (letter-number sequencing, LNS). A Wechsler Memory Scale subtest requiring the subject to reorder an intermixed string of letters and numbers; it taps verbal working memory with manipulation. Schizophrenia patients and their relatives show persistent deficits; the LNS is highly heritable (about 39% individually) and ranks well for stability and effect size, making working memory a core neurocognitive endophenotype (Greenwood et al. 2019). Working-memory deficits also serve as an endophenotype in ADHD.

Sustained attention (continuous performance test, CPT). Attention deficits date to Bleuler's original descriptions. CPTs (degraded-stimulus DS-CPT, identical-pairs CPT-IP) measure vigilance; patients show large deficits (mean effect size about 1.18), typically unaffected by psychotropics and stable over time. Deficits are reliably present in unaffected relatives, with heritability about 39 to 49% in healthy families and about 38 to 79% in schizophrenia families (Greenwood et al. 2019). General cognitive ability itself is genetically anticorrelated with schizophrenia (COGENT reported a genetic correlation of about minus 0.17).

8.8 Endophenotypes beyond schizophrenia and the imaging tier

Mood and other disorders. In major depression, endophenotypes include heightened processing of negative stimuli, executive and memory deficits, and abnormal prefrontal-amygdala activation on fMRI; the New Oxford Textbook notes their use to reduce the heterogeneity of depression. In bipolar disorder, candidate endophenotypes include cognitive deficits (executive function, attention), altered P300, and structural amygdala and prefrontal changes. In ADHD, response inhibition, working memory and reduced P300 are studied; in ASD, social-cognition and sensory-processing deficits; in OCD, impaired cognitive flexibility and response inhibition with orbitofrontal-striatal hyperactivity (New Oxford Textbook). An impulsivity endophenotype has been proposed as a marker of vulnerability to stimulant addiction (New Oxford Textbook).

Imaging and RDoC. Structural and functional MRI measures (hippocampal volume reduction, prefrontal activation, connectivity) are treated as imaging endophenotypes or "imaging intermediate phenotypes." The endophenotype logic was explicitly adopted by the NIMH **Research Domain Criteria** (RDoC), which takes objectively measurable, dimensional constructs across units of analysis (from genes to circuits to behaviour) as its starting point, on the assumption that specific neural systems underlie specific behavioural dimensions cutting across DSM categories (Tasman 2015).

ENDOPHENOTYPE	DOMAIN / MEASURE	SZ EFFECT (APPROX)	HERITABILITY	IN RELATIVES	STATE-INDEPENDENT
P50 suppression	Sensory gating (auditory ERP, paired click)	Reduced suppression	**Heritable; linked to CHRNA7 (15q13-14)**	**Yes**	Yes (persists on medication)
Prepulse inhibition (PPI)	Sensorimotor gating (startle EMG)	Reduced PPI	**about 45 to 50%**	**Yes**	Yes (stable over time)
Mismatch negativity (MMN)	Preattentive auditory deviance (ERP)	Reduced amplitude, d about 1.0	**about 68%**	**Yes (at-risk carriers)**	Yes (medication-independent)
Antisaccade (AS)	Oculomotor inhibition	Reduced correct ratio, d about 1.0	**about 42 to 57%**	**Yes (first-degree)**	Yes (stable)
Smooth-pursuit	Oculomotor tracking	Impaired pursuit, intrusive saccades	Heritable (classic marker)	**Yes (first-degree)**	Yes
Letter-number sequencing (LNS)	Verbal working memory	Reduced score	**about 39%**	**Yes**	Yes (persistent)
Continuous performance test (CPT)	Sustained attention	Reduced, d about 1.18	**about 39 to 79% (SZ families)**	**Yes**	Yes (psychotropic-independent)

Named schizophrenia endophenotypes mapped against the Gottesman and Gould (2003) criteria: heritable, present in unaffected relatives above population rate, and state-independent. Effect sizes and heritabilities from the PMC review of SZ endophenotypes (Greenwood et al. 2019) and Tasman 2015.

8.9 The genes behind the endophenotypes: a glutamate and neuregulin network

Convergence on a pathway. The Consortium on the Genetics of Schizophrenia (COGS) genotyped candidate genes against these endophenotypes and found 71 SNP-endophenotype associations across 28 genes, with 8 genes showing pleiotropic association across multiple endophenotypes: CTNNA2, ERBB4, GRID2, GRIK3, GRIK4, NOS1AP, NRG1 and RELN (Greenwood et al. 2019). Independent GWAS of schizophrenia diagnosis and of neurocognitive endophenotypes implicated an overlapping set (ATXN7, CSMD1, DRD2, GRIN2A, GRIN3A, GRM3), and rare-variant burden fell on GRIN1, GRIN3A and SLC1A2 (Singh et al. 2022). The network converges on **glutamatergic neurotransmission and synaptic plasticity**, consistent with the glutamate (NMDA-hypofunction) hypothesis and with NRG1-ErbB4 signalling.

Largest single endophenotype GWAS. The largest GWAS of PPI to date (LOGOS) identified and replicated common variants in NGF and CALN1 at genome-wide significance, and higher schizophrenia polygenic risk was associated with worse PPI, tying the endophenotype back to the polygenic architecture of the disorder (Greenwood et al. 2019).

8.10 Why endophenotypes underdelivered

The core disappointment. The founding promise was that an endophenotype would be genetically simpler than the disorder, controlled by fewer genes of larger effect and therefore easier to map. This largely did not hold: most psychiatric endophenotypes turned out to be about as polygenic and often no more heritable than the disorders themselves, so the expected gain in gene-finding power failed to materialise. A meta-analysis by Flint and Munafo (2007) concluded that identified endophenotypes are not superior to conventional phenotypic disease definitions for this purpose (New Oxford Textbook). The LOGOS PPI result (many small-effect loci) exemplifies the polygenicity even at the endophenotype level (Greenwood et al. 2019).

Other limits. Endophenotypes are effortful and expensive to assess, reducing achievable sample sizes just when large samples turned out to be the decisive ingredient in psychiatric gene finding. Many candidate markers (P50, PPI, MMN) are also non-specific, appearing across schizophrenia, bipolar disorder and other conditions, so a positive marker does not cleanly index one disorder. The field's response has been to fold the endophenotype logic into dimensional frameworks (RDoC) and into biobank-scale studies rather than to expect single traits to crack the genetic architecture alone (New Oxford Textbook; Tasman 2015).

HOLD THIS

The endophenotype bet mostly lost: the intermediate trait was usually just as polygenic as the diagnosis. Flint and Munafo (2007) found identified endophenotypes are not superior to conventional disease definitions for gene finding; the enduring legacies are the five Gottesman-Gould criteria and the dimensional RDoC framework.

CLINICAL ANCHOR

None of these markers is a clinical test. There is no validated blood, ERP or eye-tracking assay that diagnoses schizophrenia or predicts it in an individual patient; they operate at the group level and index latent liability, not diagnosis. Their real clinical relevance is conceptual: they explain why an unaffected sibling of a patient with schizophrenia can carry measurable neurophysiological "soft signs" of the illness without being ill, and they underpin high-risk research (reduced MMN as a candidate psychosis-transition predictor).

COMMON TRAP

Do not describe an endophenotype as merely "a biomarker" or "an early symptom." The distinguishing features an examiner is listening for are heritability and the family criteria: present in unaffected relatives above the population rate, and co-segregating with illness in families. A marker that appears only during the acute episode (a state marker) is explicitly disqualified by the state-independence criterion. Also do not overclaim: the honest examination answer states that endophenotypes have underdelivered as gene-finding shortcuts (Flint and Munafo 2007).

INDIA

Endophenotype paradigms (P50, PPI, MMN, antisaccade, CPT) are relatively low-cost, equipment-based and culture-fair compared with lengthy neuropsychological batteries, which suits high-risk and first-episode research in Indian academic settings where large biobank-scale GWAS infrastructure is limited. The specificity and underdelivery caveats apply identically: these remain research tools, not diagnostic assays for clinical use.

PEARL

The endophenotype was a bet that the trait between gene and diagnosis would be genetically simpler than the diagnosis. The bet mostly lost: the intermediate trait was usually just as polygenic. The enduring legacies are conceptual, not methodological, the five Gottesman and Gould criteria as a rigorous definition of a heritable trait marker, and RDoC as the dimensional framework that absorbed the idea.

GOOD TO REMEMBER

- **Gottesman and Gould (2003):** five endophenotype criteria: associated with illness in the population; heritable; state-independent; co-segregates within families; found in unaffected relatives above the general-population rate (plus reliably measurable).
- **Efficiency claim:** for a disorder with about 1% prevalence and 60 to 80% heritability, a quantitative endophenotype is about 100-fold more efficient than the categorical diagnosis (about 10-fold power gain).
- **P50 suppression:** auditory ERP paired-click sensory gating; deficit linked to CHRNA7 (alpha-7 nicotinic receptor, chromosome 15q13-14); normalised transiently by nicotine, not by most antipsychotics.
- **Prepulse inhibition (PPI):** startle sensorimotor gating; heritability about 45 to 50% (about 47% in high-vulnerability families vs about 29% otherwise); cross-species; largest GWAS (LOGOS) implicated NGF and CALN1.
- **Mismatch negativity (MMN):** preattentive auditory-deviance ERP; effect size about 1.0; heritability about 68%; NMDA-dependent; candidate predictor of psychosis transition.
- **Antisaccade:** oculomotor inhibition; effect size about 1.0; heritability about 42 to 57%; B-SNIP GWAS implicated IPO8, PCDH12, NRSN1, SH3GL2.
- **Smooth-pursuit eye movements:** classic, highly replicated schizophrenia marker; deficits in first-degree relatives.
- **Letter-number sequencing (working memory):** heritability about 39%; deficits in patients and relatives.
- **Continuous performance test (sustained attention):** effect size about 1.18; heritability about 39 to 79% in schizophrenia families.
- **COGS pleiotropic gene set (8 genes across endophenotypes):** CTNNA2, ERBB4, GRID2, GRIK3, GRIK4, NOS1AP, NRG1, RELN; network converges on glutamate and NRG1-ErbB4 signalling.
- **Diagnosis-overlap GWAS genes:** DRD2, GRIN2A, GRIN3A, GRM3, ATXN7, CSMD1; rare-variant burden in GRIN1, GRIN3A, SLC1A2.
- **Underdelivery (Flint and Munafo 2007):** identified psychiatric endophenotypes are not superior to conventional phenotypic disease definitions for gene finding; most are as polygenic as the disorder.
- **RDoC:** NIMH Research Domain Criteria adopted the endophenotype logic as dimensional, cross-diagnostic constructs measurable from genes to circuits to behaviour.

9 · Neurodevelopmental genetics and cross-disorder pleiotropy

This is the topic that reframes everything else in these notes. Heritability and GWAS tell you *how much* of the risk is genetic; this topic tells you *how* that risk is enacted, and the answer is through **neurodevelopment**. Psychiatric risk genes are not scattered at random across the genome or across the lifespan: they cluster in genes that build and prune synapses, remodel chromatin, and regulate transcription, and their protein products are most active in the prenatal and early postnatal brain. Hold that single idea, that genetic liability is a developmental programme gone slightly awry, and both the **neurodevelopmental hypothesis** of schizophrenia and the modern picture of autism as a disorder of fetal cortical wiring fall out of the same logic (Owen et al., New Oxford Textbook 2020).

Exam framing. The second half of this topic is where the field has moved fastest and where examiners now probe: **cross-disorder pleiotropy**. Common-variant risk does not respect diagnostic borders. The same alleles push liability across schizophrenia, bipolar disorder, depression, ADHD and autism, producing high **genetic overlap** and a possible **p-factor**, a general dimension of psychopathology. This is the genetic engine behind the categorical-versus-dimensional debate, so learn the two halves, the neurodevelopmental mechanism and the cross-disorder architecture, as one argument: shared developmental genes give shared disorders. Cross-reference the novel-approaches topic for de novo mutation detection and the polygenic risk score material.

9.1 The neurodevelopmental model: genetic risk is a developmental lesion, not an adult one

The **neurodevelopmental hypothesis** holds that the genetic and early-environmental liability to major psychiatric disorders acts on the developing brain long before symptoms appear, leaving a static or slowly evolving vulnerability that is later unmasked by maturation and stress (Kaplan & Sadock 2024). Schizophrenia is the paradigm: the same children who later develop psychosis show, on average, an excess of minor neurodevelopmental abnormalities, delayed milestones, and neurological soft signs years before onset, and the risk-conferring biology is expressed in fetal and perinatal life. The corollary that examiners love is that adult-onset disorders are increasingly reconceptualised as having identifiable prodromal and subclinical childhood manifestations, so the "adult" and "developmental" categories are a continuum in time, not a dichotomy (Kaplan & Sadock 2024).

Two-hit framing. The **two-hit model** gives the mechanism a shape: a first hit (a genetic variant, or an early insult such as a copy number variant, obstetric complication or prenatal infection) primes the developing circuit, and a second hit (adolescent synaptic pruning, cannabis, psychosocial stress) is required to convert latent vulnerability into overt illness. Adolescence matters because it is the period of steep synaptic elimination in association cortex, precisely the process implicated by the risk genes below.

RULE **Genetic risk is enacted through neurodevelopment, not an adult lesion.** Risk genes cluster in synapse, chromatin and transcription and are most active in the prenatal and early postnatal brain; a first hit primes the circuit and a second (pruning, cannabis, stress) unmasks it.

9.2 What the risk genes actually do: synapse, chromatin and FMRP-target enrichment

The single most important empirical fact of modern psychiatric genetics is that risk genes are not random: gene-set enrichment analyses converge on a small number of neurodevelopmental biological processes (Owen et al., New Oxford Textbook 2020). Autism risk genes discovered by whole-exome sequencing illustrate this convergence best, because rare disruptive variants point to individual genes.

Synaptic function

Risk genes encode postsynaptic scaffolding proteins, cell-adhesion molecules and ion channels at excitatory synapses. Convergence on *synapse formation and function* is the dominant theme across autism, schizophrenia and intellectual disability.

Chromatin remodelling and transcriptional regulation

A large fraction of high-confidence autism genes are chromatin remodellers and transcription factors (the prototype is *CHD8*). These are master regulators: disrupting one perturbs the expression of hundreds of downstream neurodevelopmental genes.

FMRP targets

Autism and schizophrenia risk genes are significantly enriched for messenger RNAs bound by the **fragile X mental retardation protein (FMRP)**, the translational repressor lost in fragile X syndrome. This links idiopathic (non-syndromic) disorder back to a monogenic model of synaptic protein dysregulation.

Wnt and MAPK signalling

Additional convergent developmental pathways governing neuronal proliferation, migration and differentiation.

Spatiotemporal signature. Beyond *what* the genes do, *when and where* they act is diagnostic. Autism risk genes are preferentially expressed in **cortical pyramidal (glutamatergic projection) neurons during mid-fetal development** (Owen et al., New Oxford Textbook 2020). This prenatal, cortical, excitatory-neuron signature is the molecular fingerprint of a neurodevelopmental disorder and is exactly why the illness is framed as a wiring problem laid down before birth.

TRAP A low common-variant genetic correlation (schizophrenia-autism 0.16) can coexist with strong overlap at the rare-variant level (shared CNVs and de novo genes): the level of analysis changes the answer.

CLINICAL ANCHOR

The complement gene *C4* is the cleanest schizophrenia example of this developmental logic. C4 tags synapses for elimination by microglia; a common structural allele that raises C4 expression is associated with schizophrenia and is biologically plausible because *excessive synaptic pruning* in adolescence would thin association-cortex connectivity precisely when the disorder declares itself (Kaplan & Sadock 2024). One risk allele, one developmental process, one age of onset.

9.3 De novo mutations and the paternal-age effect

Where a disorder has high heritability yet a very large monozygotic-to-dizygotic concordance gap, **de novo mutations** (new variants present in the child but neither parent) are implicated as a constant source of rare, high-penetrance risk (Tasman 2015). They are the genetic reason a "highly heritable" disorder can appear sporadically in a family with no affected relatives.

The autism de novo story. Three groups simultaneously published exome scans of de novo variation in autism in 2012 (Kaplan & Sadock 2024). Likely-gene-disrupting de novo variants (nonsense, splice-site, frameshift) in brain-expressed genes carry large effects, and recurrent hits on the same gene across unrelated probands is what identifies high-confidence risk genes. Two exam-critical features:

- **Paternal origin, roughly 4:1.** De novo point mutations are overwhelmingly paternal in origin, in about a **4-to-1** ratio, because spermatogonia keep dividing throughout a man's life and accumulate replication errors (Kaplan & Sadock 2024).
- **Paternal-age effect.** De novo mutation load, and consequently offspring risk of autism and schizophrenia, rises with **advanced paternal age** (Tasman 2015). This is the mechanistic bridge between an epidemiological risk factor and molecular genetics, and a favourite single-best-answer link.

De novo CNVs. The recurrent 22q11.2 microdeletion was the first de novo copy number variant described in schizophrenia; genome-wide scans then showed de novo CNVs occur at higher rates in schizophrenia and autism than in controls, and that the genes they hit are enriched for neural and synaptic function (Tasman 2015). Because strong negative selection removes these variants from the population within a few generations, recurrent pathogenic CNVs must keep arising through independent de novo events.

9.4 The neurodevelopmental continuum: a severity gradient from ID to schizophrenia

The same genetic and biological machinery, dosed differently, appears to produce a graded family of conditions rather than discrete diseases. Intellectual disability, autism, ADHD and schizophrenia share risk factors and are increasingly viewed as points along a **neurodevelopmental continuum** or gradient of severity (Owen et al., New Oxford Textbook 2020).

Two lines of evidence anchor the gradient. First, *burden tracks severity*: large, damaging copy number variants and the most disruptive de novo variants are commonest in intellectual disability and syndromic autism, less common in higher-functioning autism, and rarer still in schizophrenia and ADHD, where common-variant polygenic risk carries relatively more of the load. Second, the ADHD GWAS showed that common-variant risk for the clinical diagnosis is genetically continuous with population-wide cognitive and behavioural traits, supporting the view that a categorical diagnosis sits at the extreme tail of a continuously distributed liability in the general population (Kaplan & Sadock 2024).

PEARL

Read the gradient as a dial on two variables at once: **variant rarity/severity** and **developmental timing**. The earlier and more severe the developmental disruption, the more you see rare high-penetrance variants and the more the phenotype shifts toward intellectual disability and syndromic autism; the later and subtler the disruption, the more it is polygenic common-variant risk and the phenotype shifts toward ADHD, schizophrenia and affective illness. Same genes, different dose and timing.

9.5 Cross-disorder pleiotropy: shared common-variant risk and genetic correlations

Pleiotropy is the property of one gene, or one variant, influencing more than one trait or disorder. It is now regarded as a pervasive, not exceptional, feature of psychiatric genetics: a substantial fraction of the genetic influence on psychopathology transcends diagnostic boundaries (Smoller et al. 2019; Gandal & Geschwind 2021). Pleiotropy is measured at every level, from single loci up to genome-wide **genetic correlation** (the correlation between two disorders of the effect sizes of shared SNPs, estimated by methods such as LD score regression).

The PGC cross-disorder analyses. The 2013 Cross-Disorder Group of the Psychiatric Genomics Consortium examined five disorders (autism, ADHD, bipolar disorder, major depression, schizophrenia) and found substantial **genetic overlap** (Cross-Disorder Group of the PGC 2013). The correlations were disorder-specific in magnitude, which is why the exact numbers are worth carrying, and they slot neatly onto the continuum from 9.4.

DISORDER PAIR	SNP-BASED GENETIC CORRELATION (RG)	READING
Schizophrenia and bipolar disorder	**0.68**	Highest pair; the two are largely a shared genetic liability
Major depression and bipolar disorder	0.47	Strong mood-axis overlap
Major depression and schizophrenia	0.43	Substantial affective-psychotic overlap
Major depression and ADHD	0.32	Moderate
Schizophrenia and autism	0.16	Modest at the common-variant level

SNP-based genetic correlations from the 2013 PGC cross-disorder analysis. The discriminator is the schizophrenia-bipolar value of 0.68, the exam anchor for the collapse of the Kraepelinian dichotomy at the genetic level.

0.68 SCZ-BD GENETIC CORRELATION (HIGHEST)	**~75%** CAUSAL COMMON VARIANTS SHARED, SCZ-BD	**0.16** SCZ-ASD (MODEST, COMMON-VARIANT)

How much is truly shared. Causal-mixture modelling of the schizophrenia-bipolar overlap estimated that about **75%** of the causal common variants influencing the two disorders are shared (Smoller et al. 2019). Independent evidence converges: post-mortem cortical transcriptomic profiles across these disorders correlate strongly with their pairwise genetic

correlations (r about 0.79), and the Brainstorm Consortium, mapping 25 brain disorders, found genetic correlations clustered tightly among the psychiatric disorders (ADHD, depression, bipolar, anxiety, schizophrenia) but little overlap with neurological disorders, showing psychiatric pleiotropy is specific, not an artefact (Smoller et al. 2019). Individual loci show it too: *CACNA1C* is associated with bipolar disorder, schizophrenia and autism (Smoller et al. 2019).

COMMON TRAP

Do not equate a high genetic correlation with genes acting in the same direction, and do not read it as clinical interchangeability. Genetic correlation is a population-level average across thousands of SNPs; two disorders with rg = 0.68 still have distinct clinical courses, treatment responses and disorder-specific variants. Equally, a low rg (schizophrenia-autism at 0.16) at the *common-variant* level coexists with *strong* overlap at the *rare-variant* level (shared CNVs, shared de novo genes). The level of analysis, common versus rare variant, changes the answer, which is exactly the point examiners test.

9.6 The genetic p-factor and the structure of psychopathology

If common-variant risk is so widely shared, does a general dimension of psychopathology exist at the genetic level? Applying **genomic structural equation modelling** to eight disorders, the PGC decomposed the genetic correlation matrix into **three correlated genomic factors** that together accounted for more than half of the genetic variation across these disorders (Smoller et al. 2019):

Factor 1: compulsive/perfectionistic

Anorexia nervosa, obsessive-compulsive disorder, Tourette syndrome.

Factor 2: mood and psychotic

Schizophrenia, bipolar disorder, major depression.

Factor 3: early-onset neurodevelopmental

Autism, ADHD, Tourette syndrome, with major depression also loading here.

The p-factor. That these three factors are themselves correlated is the genetic case for a **p-factor**, a single general dimension of liability to psychopathology sitting above the specific factors, the genomic analogue of the general "p" originally derived from phenotypic covariation. The neurodevelopmental factor is the most genetically integrated, consistent with the theme of this whole topic: shared developmental genes are what generate shared liability.

Where the field is in 2025. The scale has grown. A 2019 PGC analysis of eight disorders found 136 genome-wide loci, of which 109 were pleiotropic (shared across more than one disorder); a 2024 functional follow-up (Won and Sullivan, in *Cell*) showed that pleiotropic variants are active for *longer* across brain development and hit genes more sensitive to disruption than disorder-specific variants, reinforcing the developmental basis of shared risk. A 2025 cross-disorder analysis of 14 disorders in *Nature* identified several hundred loci, a large share of them pleiotropic. The clinical promise, still on the horizon, is that pleiotropic variants may be optimal

drug targets because one intervention could act across multiple disorders (Won and Sullivan 2024).

HOLD THIS

Shared developmental genes produce shared disorders. Pervasive pleiotropy and a genetic p-factor mean common-variant risk crosses diagnostic borders; the schizophrenia-bipolar rg of 0.68 is the single strongest genetic argument against the Kraepelinian dichotomy.

9.7 Implications for the categorical-versus-dimensional debate

This is where the genetics feeds directly back into nosology and gives you a ready-made discussion answer. The DSM and ICD categories are, by design, atheoretical and drawn around clinical syndromes; the genetic data are telling us those borders do not map cleanly onto biology (Smoller et al. 2019).

- **Against pure categories.** Pervasive pleiotropy, high genetic correlations, shared CNVs and a genetic p-factor all argue that liability is continuous and trans-diagnostic, not carved at discrete joints. The schizophrenia-bipolar rg of 0.68 is the single strongest genetic argument against the Kraepelinian dichotomy.
- **Not purely dimensional either.** Disorders retain *specific* genetic signal and specific loci alongside the shared component, and clinical course and treatment response still discriminate them. The honest position is *hierarchical*: a general p-factor and a few broad factors on top, with disorder-specific liability underneath.
- **Toward a bottom-up nosology.** Genomic factor structures offer an empirical, biology-first reorganisation of psychopathology, the same impulse behind dimensional frameworks such as RDoC and HiTOP. The likely future is a system that keeps clinically useful categories while formally acknowledging shared, continuously distributed neurodevelopmental liability underneath them (Smoller et al. 2019).

MNEMONIC

"SHARED DEVELOPMENT"

Synaptic, chromatin and FMRP-target enrichment; **H**igh genetic correlations (SCZ-BD 0.68); **A**utism = mid-fetal cortical pyramidal neurons; **R**are de novo variants, paternal 4:1; **E**ight-disorder three-factor structure; **D**imensional p-factor. The common thread is that shared *developmental* genes produce shared *disorders*.

GOOD TO REMEMBER

- **SCZ-BD genetic correlation rg = 0.68:** highest cross-disorder pair (2013 PGC); the genetic collapse of the Kraepelinian dichotomy.
- **MDD-BD rg = 0.47; MDD-SCZ rg = 0.43; MDD-ADHD rg = 0.32; SCZ-ASD rg = 0.16:** the other 2013 PGC five-disorder correlations.
- **~75% shared causal common variants (SCZ-BD):** causal-mixture estimate of the proportion of common causal variants shared between schizophrenia and bipolar disorder.
- **PGC eight-disorder genomic SEM: three factors:** compulsive (AN, OCD, TS); mood-psychotic (SCZ, BD, MDD); early-onset neurodevelopmental (ASD, ADHD, TS, MDD); >50% of genetic variation; genetic basis of the p-factor.
- **2019 PGC: 136 loci, 109 pleiotropic:** eight-disorder cross-disorder GWAS.
- **Won and Sullivan 2024 (Cell): 683 variants:** pleiotropic variants active longer in neurodevelopment and hit more disruption-sensitive genes than disorder-specific ones.
- **2025 Nature, 14 psychiatric disorders:** several hundred loci mapped, a large share pleiotropic; latest cross-disorder landscape.
- **CACNA1C:** classic pleiotropic locus associated with bipolar disorder, schizophrenia and autism.
- **22q11.2 deletion:** first de novo CNV described in schizophrenia; raises schizophrenia odds roughly 50-fold; the paradigm pleiotropic CNV.
- **Complement C4 allele:** higher-expression C4 allele associated with schizophrenia via excessive adolescent synaptic pruning.
- **CHD8:** prototypical high-confidence autism gene; a chromatin remodeller.
- **FMR1 / FMRP targets:** autism and schizophrenia risk genes enriched for FMRP-bound transcripts (link to fragile X syndrome).
- **65 ASD risk genes:** from combined de novo exome and CNV data across >5000 families (Autism Genome Project and Simons Simplex Collection).
- **De novo point mutations ~4:1 paternal bias:** and positively correlated with advanced paternal age, the mechanism behind the paternal-age effect in autism and schizophrenia.
- **Brainstorm Consortium:** genetic correlations cluster among psychiatric disorders with little overlap with neurological disorders (pleiotropy is specific).

Findings in the clinic

10 · Heritability across major disorders

A single comparative table of heritability and twin concordance across the major psychiatric disorders is one of the highest-yield objects in all of psychiatric genetics: it is asked directly in MCQs ("which disorder is most heritable?"), it frames vivas on any single condition, and it anchors the conceptual questions about what heritability actually means. The candidate is expected to reproduce an ordered hierarchy from the highly heritable neurodevelopmental and psychotic disorders at the top, through the moderately heritable substance-use and eating disorders, down to the internalising (depressive and anxiety) disorders at the base, and then to state precisely what a heritability figure does and does not claim. **Why it matters.** The numbers are examinable to the decade, but the deeper marks are won by knowing that heritability is a population variance ratio in a specified environment, not a property of an individual patient and not a statement about immutability (Kaplan & Sadock 2024).

The hierarchy is remarkably stable across textbooks and across the two great methodologies (classical twin studies and modern population-register sibling studies). Broadly, the neurodevelopmental disorders (autism, ADHD) and the two classic functional psychoses on the psychotic and mood axes (schizophrenia, bipolar disorder) cluster at heritabilities of roughly 0.75 to 0.85; anorexia nervosa, alcohol use disorder and obsessive-compulsive disorder sit in the 0.4 to 0.6 band; and major depression, the generalised anxiety and stress-related disorders occupy the low 0.3s (New Oxford 2020). The same ordering recurs whether one reads concordance rates or variance-decomposition heritabilities, which is itself the strongest internal validation of the twin design.

10.1 Reading the two currencies: concordance and heritability

Concordance is a probability; heritability is a variance ratio. **Concordance** is the probability that the co-twin is affected given that one twin is affected (probandwise is the modern standard, and is the figure comparable to a morbid risk). **Heritability** (narrow-sense h-squared) is the proportion of the total phenotypic variance in a population that is attributable to additive genetic variance. The bridge between them is the excess of monozygotic (MZ) over dizygotic (DZ) concordance: a large MZ-over-DZ gap implies high heritability (Falconer's first approximation, h-squared is about 2 times the difference in twin correlations). The two currencies carry the same ordering of disorders but are not interchangeable numbers, and mixing them is a common source of error when quoting figures.

10.2 The comparative table across disorders

The core object. The table below collates the standard exam figures. The heritability column gives the twin-study or family-study estimate quoted in the reference texts; the concordance column gives representative probandwise MZ and DZ rates where a canonical figure exists. Ranges reflect genuine between-study variation, not uncertainty about which is "correct"; where a single landmark estimate is conventionally quoted, it is named in the source column.

DISORDER (ICD-11 / DSM-5-TR)	MZ VS DZ CONCORDANCE	HERITABILITY (H-SQUARED)	SOURCE / LANDMARK
Schizophrenia (6A20)	**MZ ~46 to 50% vs DZ ~9 to 14%**	~0.79 to 0.81	Sullivan meta-analysis 2003 (81%); Hilker 2018 Danish registers (79%)
Bipolar disorder (6A60)	**MZ ~40 to 70% (often quoted ~60%) vs DZ ~5 to 20%**	~0.85 (up to ~0.9)	McGuffin 2003; Kieseppa 2004 (0.93 for narrow BP-I); K&S 2024
Autism spectrum disorder (6A02)	MZ high vs DZ low (early studies MZ ~60 to 90%, DZ ~0 to 10%)	~0.80 (range ~0.5 to 0.9)	Sandin 2017 twin meta-analysis (~0.83); New Oxford 2020
ADHD (6A05)	MZ markedly > DZ	~0.74 to 0.76 (twin ~0.70 to 0.80)	Faraone; twin-study consensus (K&S 2024)

DISORDER (ICD-11 / DSM-5-TR)	MZ VS DZ CONCORDANCE	HERITABILITY (H-SQUARED)	SOURCE / LANDMARK
Anorexia nervosa (6B80)	MZ > DZ	~0.5 to 0.6 (twin), family ~0.4	Bulik; New Oxford range 0.28 to 0.74
Alcohol use disorder / dependence (6C40)	MZ > DZ	~0.5	K&S 2024; Prescott & Kendler
Obsessive-compulsive disorder (6B20)	MZ > DZ; higher in child-onset	Child-onset ~0.45 to 0.65; adult-onset ~0.27 to 0.47	van Grootheest twin meta-analysis 2005
Major depressive disorder (6A70)	MZ ~40% vs DZ ~20%	~0.37	Sullivan meta-analysis 2000 (0.37); family est. ~0.30 to 0.41
Generalised anxiety disorder (6B00)	MZ > DZ (modest)	~0.30	Hettema meta-analysis 2001 (~0.32); K&S 2024
Post-traumatic stress disorder (6B40)	MZ > DZ	~0.30	True 1993 (Vietnam twin registry); New Oxford 2020
Tourette syndrome / tic disorder (8A05.0)	**MZ 53% (TS) and 77% (any tic) vs DZ 8% and 23%**	High (~0.6 to 0.8)	Price 1985; twin-study consensus
Alzheimer disease (late-onset) (8A20)	MZ > DZ	High (~0.6 to 0.8); APOE-e4 major locus	Gatz 2006 Swedish twins (~0.58 to 0.79); APOE on chr 19

The heritability hierarchy: neurodevelopmental and psychotic/bipolar disorders at the top (~0.75 to 0.9), eating, substance-use and OCD in the middle (~0.4 to 0.6), depressive and anxiety and stress-related disorders at the base (~0.3). Concordance and heritability carry the same ordering. Several concordance and heritability entries carry genuine between-study spread and are flagged for verification in the metadata.

~0.85	~0.80	~0.37	~0.30
BIPOLAR (MOST HERITABLE)	SCHIZOPHRENIA AND AUTISM	MAJOR DEPRESSION	GAD AND PTSD (BASE)

10.3 The top of the hierarchy: schizophrenia, bipolar, autism, ADHD

The most heritable common psychiatric disorders. The landmark modern figure for schizophrenia is the Sullivan, Kendler and Neale twin meta-analysis of 2003, which gave a heritability of 81% (95% confidence interval roughly 73 to 90%), later corroborated by Hilker's 2018 analysis of the Danish twin and psychiatric registers (over 30,000 pairs) at 79% for narrow schizophrenia and 73% for the spectrum (New Oxford 2020). Bipolar disorder is quoted as the single most heritable major psychiatric disorder, around 0.85 and rising toward 0.9 for narrowly defined bipolar-I, with the MZ co-twin concordance conventionally given as about 60% against a DZ rate an order lower (Kaplan & Sadock 2024; McGuffin 2003). Autism and ADHD are the highly heritable neurodevelopmental disorders, autism around 0.8 (Sandin's 2017 twin meta-analysis gave about 0.83) and ADHD around 0.74 to 0.76, with twin studies clustering at 0.70 to 0.80. **The examinable point.** These four disorders form the "high-heritability" cluster and are the

ones for which environmental variance, though real, contributes the smaller share of population variance.

10.4 The base of the hierarchy: depression, anxiety, PTSD

The internalising disorders are the least heritable of the common conditions. Major depressive disorder has a heritability of about 0.37 (Sullivan's 2000 meta-analysis), with MZ concordance around 40% against DZ around 20%; the large Swedish population sibling study gave a family-based estimate of 0.30, the lowest of the eight disorders it examined. Generalised anxiety disorder sits at about 0.30 (Hettema's 2001 meta-analysis of the anxiety disorders gave roughly 0.32), and post-traumatic stress disorder at about 0.30, first established in True's 1993 study of the Vietnam-era twin registry. **The interpretive corollary.** The lower heritabilities do not make these disorders "less biological"; they mean that in the studied populations a larger fraction of the variance between people is environmental (including, for PTSD, the necessary environmental trigger of trauma exposure, which caps the achievable heritability). Depression, anxiety and OCD were precisely the disorders the authors of the Swedish register study singled out as the ones where environmental aetiological research is most likely to be fruitful (heritability under 0.50).

10.5 The special cases: OCD child-onset, anorexia, alcohol, Tourette, Alzheimer

OCD: an age-of-onset split. The single most examinable nuance in the middle of the table is that obsessive-compulsive disorder is more heritable when it begins in childhood. van Grootheest's twin meta-analysis (2005) reported obsessive-compulsive symptom heritability of roughly 0.45 to 0.65 in children against about 0.27 to 0.47 in adults, consistent with a more strongly genetic early-onset form (New Oxford 2020). **Anorexia nervosa** is moderately-to-highly heritable, twin estimates around 0.5 to 0.6 (the New Oxford range is wide, 0.28 to 0.74), with a family-register estimate of about 0.4. **Alcohol use disorder** is conventionally quoted at a heritability of about 0.5. **Tourette syndrome** is highly heritable with a very high MZ concordance (53% for the full syndrome and 77% for any tic, against 8% and 23% respectively in DZ pairs (Price 1985)), reflecting a strong, largely polygenic genetic contribution. **Alzheimer disease** (late-onset) has a high heritability, around 0.58 to 0.79 in Gatz's 2006 Swedish twin study, with the APOE-e4 allele on chromosome 19 the single largest common-variant risk locus (a heterozygote carries about a two- to three-fold risk, a homozygote considerably more).

HOLD THIS

Psychosis and neurodevelopment high, internalising low. Bipolar, autism, schizophrenia and ADHD cluster at ~0.75 to 0.9; anorexia, alcohol use and OCD in the middle; depression, GAD and PTSD near 0.3. The single richest nuance: OCD is more heritable when it starts in childhood.

CLINICAL ANCHOR

When a family asks "will my child get this too?", the heritability figure is not the answer they need; the recurrence risk is. A heritability of 0.8 for schizophrenia does not mean an 80% chance of transmission, it means that in the studied population most of the variation in liability between people is genetic. The first-degree-relative recurrence risk for schizophrenia is of the order of 6 to 10%, an order of magnitude smaller than the heritability figure, because the disorder is highly polygenic and each relative shares only half the risk alleles. Keeping heritability and recurrence risk separate in your counselling prevents both false reassurance and needless alarm.

10.6 What heritability is, and what it is not

A population parameter, not an individual one. **Heritability** is the ratio of genetic variance to total phenotypic variance in a defined population and environment. It is not the proportion of a given patient's illness that is "genetic", it is not a fixed biological constant, and it says nothing about whether a trait can be changed. The standard cautionary example is phenylketonuria: an essentially fully genetic (single-gene) disorder that is nonetheless completely preventable by an environmental intervention (dietary phenylalanine restriction). A high heritability and full environmental modifiability coexist without contradiction (Kaplan & Sadock 2024).

RULE **Heritability is a population variance ratio, not an individual statement and not immutability.** Phenylketonuria is essentially fully genetic yet fully preventable by diet; a high h-squared says nothing about modifiability or the cause in one patient.

Heritability changes with the environment. Because it is a ratio, heritability rises when environmental variance falls and falls when environmental variance rises. In a population where everyone is exposed to identical environments, the only remaining variance is genetic and heritability approaches unity; in a population with wildly variable environments the same trait can show lower heritability. Heritability is therefore always local to the population and era studied, and figures from Scandinavian registers need not transfer unchanged to other populations. It also tells you nothing about the mean level of a trait, only about the sources of variation around that mean.

10.7 The twin-heritability versus SNP-heritability gap

The missing heritability problem. Twin and family studies estimate **broad or narrow-sense heritability** from the resemblance of relatives; genome-wide association data estimate **SNP-heritability** (h-squared-SNP), the variance captured by common measured single-nucleotide polymorphisms. SNP-heritability is consistently and substantially lower than twin-heritability: in the large Swedish comparison, family-based estimates ran from 0.30 (major depression) to 0.80 (ADHD), whereas the SNP-based estimates from the same diagnoses ran from about 0.10 (alcohol dependence) to 0.28 (OCD). For schizophrenia the case-control SNP-heritability is on the order of 0.23 against a twin-heritability of about 0.81 (New Oxford 2020). **Why the gap.** The shortfall (the "missing heritability") reflects that common SNPs do not tag rare and structural variants (copy-number variants, rare coding variants), incomplete linkage-disequilibrium tagging, non-additive (dominance and epistatic) effects, gene-environment interaction absorbed into the twin

estimate, and possible upward bias in twin estimates from violations of the equal-environments assumption. The largest twin-to-SNP gaps in that study were for the neurodevelopmental disorders (ADHD, autism) and schizophrenia, precisely the disorders for which rare and structural variants are known to contribute.

TRAP Do not quote the SNP-heritability of schizophrenia (~0.23) as "the heritability of schizophrenia": the twin-heritability is ~0.81, and the SNP figure is only a lower bound on what common variants capture.

COMMON TRAP

Do not read a heritability of 0.8 as "80% of this patient's illness is genetic" or as "80% chance of passing it on". Heritability is a population-level variance ratio, silent about any individual and silent about transmission risk. Equally, do not treat SNP-heritability and twin-heritability as the same quantity: the SNP figure is a lower bound on what common variants capture, not a correction to the twin figure. Quoting the SNP-heritability of schizophrenia (about 0.23) as "the heritability of schizophrenia" is wrong; the twin-heritability is about 0.81.

PEARL

A clean one-line ordering to carry into the viva: bipolar and autism and schizophrenia and ADHD are the "high" disorders (heritability roughly 0.75 to 0.9); anorexia, alcohol use disorder and OCD are "middle" (0.4 to 0.6); depression, generalised anxiety and PTSD are "low" (about 0.3). The mnemonic hierarchy runs "psychosis and neurodevelopment high, internalising low", and the single richest nuance is that OCD is more heritable when it starts in childhood.

MNEMONIC

Big Brains Are Adaptable, Ordinary Anxious Depressives

Descending the heritability ladder: **B**ipolar (~0.85), **B**rain-development autism (~0.8), **A**utism-and schizophrenia cluster and **A**DHD (~0.75), **O**CD and anorexia and alcohol (~0.4 to 0.6), then the **A**nxiety and **D**epression base (~0.3). The device just fixes the top-to-bottom order; the exact figures still have to be learned.

INDIA

Almost every heritability figure in this table derives from Scandinavian (Swedish, Danish, Finnish) or Anglo-American twin and register cohorts; India has no national twin or adoption register at comparable scale, so Indian genetic-epidemiology data come mainly from family morbid-risk studies. Because heritability is environment-specific, the imported figures should be quoted as the best available estimates rather than as validated Indian values, and consanguinity (common in parts of India) can inflate familial aggregation for any recessive contribution, complicating a family history.

GOOD TO REMEMBER

- **Schizophrenia heritability:** ~0.81 (Sullivan meta-analysis 2003, 95% CI ~73 to 90%); Hilker 2018 Danish registers 0.79 (narrow), 0.73 (spectrum).
- **Bipolar disorder heritability:** ~0.85, the most heritable major psychiatric disorder; MZ concordance often quoted ~60%; Kieseppa 2004 ~0.93 for narrow bipolar-I.
- **Autism heritability:** ~0.80 (Sandin 2017 twin meta-analysis ~0.83); early twin studies MZ concordance far exceeding DZ.
- **ADHD heritability:** ~0.74 to 0.76 (twin studies ~0.70 to 0.80); Faraone consensus.
- **Anorexia nervosa heritability:** ~0.5 to 0.6 twin (New Oxford range 0.28 to 0.74); family estimate ~0.4.
- **Alcohol use disorder heritability:** ~0.5.
- **OCD heritability:** child-onset ~0.45 to 0.65, adult-onset ~0.27 to 0.47 (van Grootheest twin meta-analysis 2005); higher in child-onset is the key nuance.
- **Major depressive disorder heritability:** ~0.37 (Sullivan meta-analysis 2000); family-register estimate ~0.30, the lowest of eight disorders.
- **Generalised anxiety disorder heritability:** ~0.30 (Hettema meta-analysis 2001, ~0.32).
- **PTSD heritability:** ~0.30 (True 1993, Vietnam-era twin registry).
- **Tourette syndrome:** high heritability; MZ concordance 53% for TS and 77% for any tic vs DZ 8% and 23% (Price 1985).
- **Alzheimer disease (late-onset):** heritability ~0.58 to 0.79 (Gatz 2006 Swedish twins); APOE-e4 (chromosome 19) the major common-variant risk allele, heterozygote ~2 to 3 fold risk.
- **SNP-heritability vs twin-heritability gap:** Swedish comparison, family-based 0.30 (MDD) to 0.80 (ADHD) vs SNP-based ~0.10 (alcohol dependence) to 0.28 (OCD); schizophrenia SNP-h-squared ~0.23 vs twin ~0.81.
- **Falconer's formula:** h-squared is approximately 2 times the difference between MZ and DZ twin correlations.

11 · Schizophrenia genetics: the integrative flagship

Why this matters. This is the essay the first paper is built to elicit: take one disorder and let it carry every method taught in these notes. **Schizophrenia** is the ideal vehicle because it is the most intensively genotyped psychiatric phenotype, and its story runs cleanly from classical genetic epidemiology (a heritability near 80% that no candidate gene could explain) through the modern two-tier architecture (a highly polygenic common-variant burden plus rare large-effect structural variants), to a mechanistic hook the examiner loves (the complement C4A signal and synaptic pruning), and finally to the clinical frontier of the polygenic risk score. A strong answer is not a list of genes; it is an argument that schizophrenia is a **neurodevelopmental** disorder of polygenic liability, in which many common alleles of tiny effect and a few rare variants of large effect converge on synaptic and neurodevelopmental biology, with environment tipping vulnerable brains over a threshold.

Anchor the whole essay on a handful of load-bearing, examinable facts: heritability of the order of 80% with monozygotic concordance far above dizygotic; the 22q11.2 deletion as the single largest known genetic risk; the MHC/C4A complement signal as the most robust common-variant locus; the collapse of the candidate-gene era (COMT, DISC1, NRG1, dysbindin); and a substantial genetic overlap with bipolar disorder that makes the two-disorder boundary

permeable. These are grounded in Kaplan and Sadock (2024), the New Oxford Textbook (2020) and Tasman (2015).

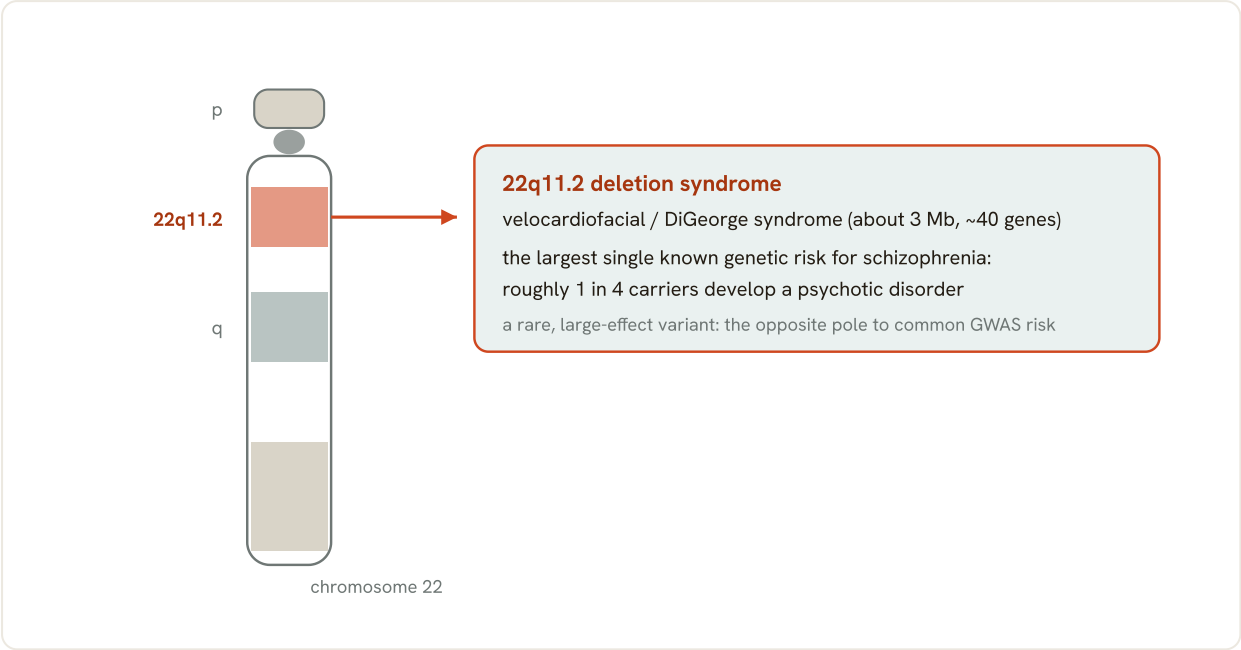


Fig 3.7 The 22q11.2 microdeletion on the long arm of chromosome 22. This roughly 3 megabase deletion of about forty genes causes velocardiofacial (DiGeorge) syndrome and is the single largest known genetic risk factor for schizophrenia: around a quarter of carriers develop a psychotic disorder. It illustrates the rare, large-effect end of the architecture spectrum from Fig 3.4, in contrast to the thousands of common small-effect variants that make up most inherited risk.

11.1 The framing move: state the architecture before the evidence

Open with the thesis. The examiner rewards a candidate who names the target before marshalling data. State it as: schizophrenia has a **complex, polygenic, multifactorial-threshold** architecture, not a Mendelian one. No single-gene form of schizophrenia has ever been found; familial distributions are, in the words of the standard text, inconsistent with simple Mendelian inheritance (Kaplan and Sadock 2024). Everything that follows, twin heritability, GWAS, CNVs, gene-environment interaction, is evidence for and refinement of that one architectural claim.

The two-tier model. Risk is carried at two ends of the frequency-effect spectrum: many **common variants** of individually tiny effect (odds ratios near 1.1, tagged by GWAS), plus rare **copy number variants** and de novo mutations of large effect (odds ratios of several-fold to fifty-fold). Between them sits the **missing heritability** gap: twin heritability near 80% but common-SNP heritability capturing only part of it. Say this once, early, and the rest of the essay slots into it.

RULE **State the architecture before the evidence.** Open the essay by naming schizophrenia as a complex, polygenic, multifactorial-threshold disorder, not a Mendelian one; every finding that follows is refinement of that claim.

11.2 Heritability and the classical evidence: twin and adoption studies

The number to know. Schizophrenia heritability is of the order of 80%, among the highest in psychiatry, with the largest twin meta-analyses placing it near 79 to 81% (Sullivan and

colleagues; Hilker and colleagues 2018, the Danish twin registry). Population-register estimates run a little lower (about 64% in Lichtenstein and colleagues 2009), a discrepancy examiners like to probe: twin designs may inflate heritability by capturing gene-environment correlation and non-additive effects (New Oxford 2020).

Twin concordance. Concordance is far higher in monozygotic than dizygotic twins: Kaplan and Sadock (2024) give roughly 47 to 56% for monozygotic and 12 to 16% for dizygotic pairs, rising above 80% in monozygotic pairs with severe, typical illness. The MZ-versus-DZ gap is the core quantitative argument for a genetic contribution; the fact that MZ concordance is well below 100% is the equally important argument that genes are not the whole story (environment and stochastic development matter).

Adoption studies remove shared rearing. The Danish and Finnish adoption studies (Kety, Rosenthal, Tienari) showed that the biological relatives of adopted-away probands, not the adoptive relatives, carry the raised risk, and that offspring of affected biological parents remain at elevated risk even when reared in unaffected adoptive homes. The Finnish Adoptive Family Study (Tienari) added the gene-environment message: the biological high-risk children fared worst specifically when reared in disturbed adoptive families, an early demonstration of interaction rather than pure genetic determinism.

COMMON TRAP

Do not read heritability of 0.8 as "80% genetic in this patient." Heritability is a population variance statistic: it describes how much of the variation between people in a given population and environment is attributable to genetic differences. It says nothing about the cause in any individual, and nothing about modifiability, a highly heritable disorder can still be entirely environmentally treatable (phenylketonuria is the standard cautionary example). Misstating this is a classic viva stumble.

11.3 The candidate-gene era and the lesson it taught

What was done. Before genome-wide genotyping, researchers pre-selected a handful of biologically plausible or positionally implicated **candidate genes**. For schizophrenia, more than 1,500 studies examined nearly 800 candidates (Tasman 2015). The most-cited were COMT (catechol-O-methyltransferase, the val158met functional polymorphism, dopamine catabolism), DISC1 (Disrupted-in-Schizophrenia-1, from a Scottish family with a balanced translocation), NRG1 (neuregulin-1, synaptic and glutamatergic signalling) and DTNBP1 (dysbindin, presynaptic).

What happened. Almost none survived well-powered genome-wide scrutiny. When Farrell and colleagues (2015) tested the classic candidates against GWAS data, the historical candidate literature did not yield clear, genome-wide-significant support. Underpowered samples chasing tiny true effects, publication bias, weak priors and flexible analysis had produced a literature dominated by false positives.

The lesson, and the nuance. The examinable lesson is methodological: complex-trait genetics needs enormous samples and built-in replication, which is exactly what GWAS institutionalised. The nuance worth adding for a top answer: DISC1 illustrates why the target was wrong as much as the method. The original translocation family carried both psychosis and mood disorder, and independent studies later linked DISC1 to schizophrenia, schizoaffective disorder and bipolar disorder (Kaplan and Sadock 2024), so the gene never respected the schizophrenia construct it was named for. The candidates were not testing schizophrenia; they were testing a diagnostic category that does not map cleanly onto biology.

11.4 GWAS and the Psychiatric Genomics Consortium: the common-variant tier

Sample size was the missing ingredient. A **genome-wide association study** (GWAS) assays hundreds of thousands to millions of single-nucleotide polymorphisms across the whole genome and tests each for a case-control frequency difference, at the stringent genome-wide significance threshold of p less than 5 x 10 to the power minus 8 (correcting for about a million tests). Early psychiatric GWAS reported nothing because they were too small. The decisive move was consortium pooling: the **Psychiatric Genomics Consortium** (PGC) aggregated samples across dozens of countries, and the schizophrenia signal scaled almost linearly with case number.

The landmark result. The PGC schizophrenia GWAS (2014) analysed about 36,989 cases and 113,075 controls and identified 108 independent genome-wide-significant loci (Kaplan and Sadock 2024). At least three-quarters contained protein-coding genes, enriched for dopamine (DRD2, the target of every antipsychotic), glutamate and synaptic plasticity (GRM3, GRIN2A, GRIA1, SRR) and voltage-gated calcium-channel signalling (CACNA1C, CACNB2). Associations were also enriched in immune-related tissue, foreshadowing the complement story. Most associated variants are non-coding, so they most likely act by altering gene expression, which makes functional interpretation the hard part.

The satisfying loop. DRD2 emerging as a GWAS hit closed the circle between unbiased genetics and 60 years of dopamine pharmacology: the receptor blocked by antipsychotics is also a genome-wide-significant risk locus. That single fact is worth a sentence in any answer.

~80%	108	~50-fold
TWIN HERITABILITY	GWAS LOCI (PGC 2014)	22Q11.2 DELETION RISK (LARGEST SINGLE)

11.5 The MHC/C4A complement signal and the synaptic-pruning hypothesis

The most robust locus. The strongest and most replicable common-variant association in schizophrenia lies in the major histocompatibility complex (MHC) on chromosome 6, a gene-dense region of extensive linkage disequilibrium. Fine-mapping this signal is the standout mechanistic success of psychiatric GWAS (Sekar and colleagues 2016).

What Sekar and colleagues showed. Human complement component 4 is encoded by two genes, C4A and C4B, which vary in structure (a HERV insertion giving long or short forms) and copy number. Sekar and colleagues genotyped these structural alleles and found that alleles raising C4A expression in brain raised schizophrenia risk in proportion to their effect on

expression, with relative risks for the common structural alleles ranging from about 1.0 to 1.27. Post-mortem brain confirmed higher C4A RNA in patients than controls.

The pruning hypothesis. Complement tags synapses for elimination by microglia (C4 promotes C3 activation; C3 marks synapses for removal). In a C4-knockout mouse, C3 deposition and synaptic refinement in the visual pathway were disrupted. The inference: excess C4A drives excessive **synaptic pruning** during adolescence, plausibly the molecular basis of the long-observed grey-matter loss and reduced synaptic density in schizophrenia. This is the mechanism that links a GWAS peak to the neurodevelopmental model and to the adolescent onset of illness, the single most quotable convergence in the field.

HOLD THIS

MHC/C4A is the most robust locus, and the only one with a worked-out mechanism. Structural alleles raising C4A expression raise risk (relative risk up to about 1.27) by driving excess synaptic pruning in adolescence, tying a GWAS peak to the neurodevelopmental model and the age of onset (Sekar 2016).

CLINICAL ANCHOR

Three named common-variant findings to carry into a viva. The **MHC/C4A** signal is the most robust schizophrenia locus, effect modest (relative risk up to about 1.27), and the only one with a worked-out mechanism (excess pruning). **DRD2** as a GWAS hit unites genetics with antipsychotic pharmacology. **CACNA1C** is a canonical cross-disorder calcium-channel locus shared with bipolar disorder, the clearest single illustration that the schizophrenia-bipolar genetic boundary is porous.

11.6 The rare-variant tier: 22q11.2 deletion, recurrent CNVs and de novo mutation

22q11.2: the largest single risk. The recurrent hemizygous microdeletion at **22q11.2** was the first de novo CNV described in schizophrenia (Karayiorgou 1995) and, before the GWAS era, the only DNA variant indisputably pathogenic for the disorder. It causes velocardiofacial (DiGeorge) syndrome, cardiac outflow defects, palatal anomalies, hypocalcaemia and learning difficulty, and raises the odds of schizophrenia roughly 25 to 30-fold (often quoted as up to fiftyfold), the single largest known genetic risk (Kaplan and Sadock 2024). About one in four carriers develops a psychotic illness, so 22q11.2 deletion syndrome is a naturally occurring genetic model of schizophrenia.

A shared, pleiotropic set. A recurring group of large CNVs shows a many-to-one pattern (one CNV, several neurodevelopmental outcomes): 16p11.2 (deletion and duplication, autism and developmental delay), 1q21.1, 15q11.2, 15q13.3 (which spans CHRNA7, the alpha-7 nicotinic receptor gene tied to the P50 gating deficit) and NRXN1 (neurexin-1) deletions. Total CNV burden is elevated in schizophrenia relative to controls, and risk CNVs are larger and more gene-rich than benign ones.

De novo mutation and the paternal-age link. An excess of de novo point mutations and CNVs, disrupting synaptic and chromatin genes, is found particularly in sporadic cases. This dovetails with the epidemiological association of advanced paternal age with schizophrenia risk, since de

novo mutations accumulate in the paternal germline with age, a neat gene-to-epidemiology bridge.

LOCUS / CLASS	FREQUENCY	EFFECT SIZE	DETECTION METHOD	EXAMPLE
Common SNP	Minor allele >1%	**Tiny (OR about 1.05 to 1.2)**	GWAS	MHC/C4A, DRD2, CACNA1C
Recurrent CNV	Rare	**Large (OR several-fold to about 30 to 50-fold)**	Chromosomal microarray	**22q11.2 deletion (largest single risk)**
De novo mutation	Very rare, sporadic	Large; often severe phenotype	Exome/genome sequencing	Synaptic and chromatin genes; paternal-age effect

The two-tier architecture of schizophrenia: an inverse frequency-effect relationship, common variants abundant but weak, rare structural variants scarce but powerful, with de novo mutation a sporadic third source.

11.7 Endophenotypes: neurophysiological markers of latent liability

The rationale. An **endophenotype** is a heritable, state-independent, familial trait that co-segregates with illness and is present in unaffected relatives above the population rate (the Gottesman and Gould 2003 criteria). The bet was that a trait between gene and diagnosis would be genetically simpler than the diagnosis itself, and so easier to map. Three markers recur in schizophrenia.

P50 sensory gating

Auditory evoked potential about 50 ms after a click; in the paired-click paradigm the response to the second click is normally suppressed. Reduced suppression in schizophrenia indexes failed inhibitory gating, linked to CHRNA7 (alpha-7 nicotinic receptor, 15q13-14) and transiently normalised by nicotine (Tasman 2015).

Prepulse inhibition (PPI)

Normal reduction of the acoustic startle blink when a weak prepulse precedes the pulse; indexes sensorimotor gating. Reduced in schizophrenia, heritable (about 45 to 50% within families), cross-species and dopamine-sensitive, hence a favoured translational marker.

Eye-tracking

Smooth-pursuit eye-movement dysfunction and antisaccade errors are among the oldest and best-replicated schizophrenia trait markers, present in unaffected first-degree relatives, indexing frontal-executive oculomotor control.

The verdict. Endophenotypes underdelivered as gene-finding shortcuts, the intermediate trait usually proved just as polygenic as the diagnosis (Flint and Munafo 2007). Their enduring value is conceptual: they explain how an unaffected sibling can carry measurable neurophysiological soft signs of the illness without being ill, and they seeded the dimensional RDoC framework.

11.8 Gene-environment interaction: environment tips vulnerable brains over threshold

The principle. High heritability leaves real room for environment (MZ concordance is well below 100%), and the modern model is interactional: environmental exposures raise risk chiefly in

genetically vulnerable individuals, tipping latent liability over the disease threshold. The examinable exposures cluster around early neurodevelopment and adolescence.

Cannabis

Adolescent, heavy, high-potency cannabis use is associated with roughly doubled odds of later psychosis, dose-dependently; Mendelian randomisation supports a causal effect of cannabis-use liability on schizophrenia risk (Kaplan and Sadock 2024). Interaction with COMT and other risk variants has been proposed.

Urbanicity

Being born and raised in an urban environment raises schizophrenia risk in a dose-dependent way; the effect is not explained by drift and interacts with familial liability.

Migration

First- and second-generation migrant status raises risk, most markedly where the migrant group is a visible minority, implicating social defeat and chronic adversity rather than genetics of the migrating population.

Obstetric complications

Prenatal infection and maternal immune activation, hypoxia and obstetric complications, and winter-spring birth are replicated early risk factors, consistent with a prenatal neurodevelopmental insult.

Advanced paternal age

Raises risk, mechanistically tied to the accumulation of de novo mutations in the ageing paternal germline (link to 11.6).

11.9 The neurodevelopmental synthesis

The unifying model. Pull the threads together with the **neurodevelopmental** hypothesis (Weinberger, Murray): schizophrenia is the late clinical expression of an early, largely genetic disturbance of brain development, unmasked by the normal maturational events of adolescence and young adulthood. Its strongest empirical support is convergent: gene-set enrichment analyses show that schizophrenia risk genes are not random but cluster in neurodevelopmental and synaptic processes (Owen and colleagues, New Oxford 2020).

Why adolescence. The C4A pruning story gives the model a molecular clock: adolescence is the period of steep synaptic elimination in association cortex, precisely the process the complement signal implicates. Excess pruning of an already atypically wired brain plausibly explains why a disorder of neurodevelopmental origin declares itself in the late teens and twenties. Common variants set the baseline liability, rare variants and de novo mutations add large hits in a minority, and environmental exposures (cannabis, obstetric insult, urban adversity) tip the vulnerable brain over threshold, the "multiple-hit" reading of the multifactorial-threshold model.

11.10 Polygenic risk scores and the clinical horizon

Construction. A **polygenic risk score** (PRS) sums an individual's risk alleles across the genome, each weighted by its GWAS effect size, into a single number capturing common-variant liability. The schizophrenia PRS is derived directly from the PGC common-variant signal.

The honest limits. The schizophrenia PRS explains roughly 7% of liability on the liability scale (the common-variant signal itself about 3 to 4% of variance), enough to shift population risk between deciles but nowhere near enough to predict any individual's diagnosis. PRS is a research and stratification tool, not a diagnostic test; it cannot yet counsel a specific patient. Say this plainly, examiners test whether candidates over-claim.

The frontier (currency). The useful clinical horizon is cross-disorder and pharmacogenomic rather than diagnostic: PRS as one axis of transdiagnostic risk stratification, integration with rare-variant and CNV screening in early-onset or syndromic presentations, and the wider pharmacogenomic move (CPIC and DPWG CYP2D6/CYP2C19 guidance) that is already actionable for drug dosing while diagnostic PRS is not.

TRAP Do not over-claim the schizophrenia PRS: it explains only about 7% of liability, enough to shift population risk but nowhere near enough to predict any individual's diagnosis.

11.11 Genetic overlap with bipolar disorder: the permeable boundary

The evidence. Schizophrenia and bipolar disorder share substantial genetic liability. Family and twin data show cross-transmission (a schizophrenia diagnosis in one twin raises the co-twin's risk of both schizophrenia and affective psychosis), and the PGC cross-disorder analysis gives a schizophrenia-bipolar genetic correlation of about 0.6 to 0.68, the highest between any two major psychiatric disorders (Kaplan and Sadock 2024). Shared specific loci (CACNA1C, and historically DISC1, NRG1, dysbindin, G72/DAOA) sit at the interface, and 22q11.2 and other CNVs raise risk across the psychosis spectrum.

The correct reading. A genetic correlation of 0.6 does not mean the disorders are the same: two disorders with high rg still have distinct courses, treatment responses and disorder-specific variants (New Oxford 2020). The examinable conclusion is that genetic liability to psychosis is continuous and partly transdiagnostic, evidence that the Kraepelinian dichotomy is a clinical convention that genetics only partly respects, not a natural biological joint.

MNEMONIC

"HANDS on Cannabis, Urban, Migrant Paths"

Architecture in one breath: **H**eritability ~80%, **A**rchitecture two-tier (common + rare), **N**eurodevelopmental model, **D**eletion 22q11.2 (largest single risk), **S**ynaptic pruning via C4A. Then the environmental quintet: **C**annabis, **U**rbanicity, **M**igration, **P**aternal age, obstetric insult (prenatal).

PEARL

The single most integrative sentence you can write: schizophrenia is a highly heritable, polygenic neurodevelopmental disorder in which common variants of tiny effect (converging via C4A on excess synaptic pruning) set baseline liability, rare large-effect CNVs such as 22q11.2 add powerful hits in a minority, and environmental exposures tip the vulnerable adolescent brain over a multifactorial threshold, with a genetic architecture that overlaps substantially with bipolar disorder rather than respecting the diagnostic boundary between them.

INDIA

Formal twin and adoption registers on the Danish, Swedish or Finnish scale do not exist in India, so most Indian genetic-epidemiology data come from family (morbid-risk) studies rather than twin or adoption designs. When counselling an Indian family about recurrence, the practical figures are the first-degree-relative risks (of the order of 6 to 10% for schizophrenia in a first-degree relative), framed against a population risk near 1%. Two culturally specific cautions: consanguinity, common in parts of India, can inflate familial aggregation for recessive contributions and complicate a family history; and strong family expectation around marriage and childbearing means recurrence-risk counselling must be handled with care, giving population-level probabilities without implying determinism, and without naming a diagnosis to the family in a way that stigmatises the proband or unaffected relatives.

GOOD TO REMEMBER

- **Heritability:** of the order of 80% (twin meta-analyses about 79 to 81%; population registers lower, about 64% in Lichtenstein 2009).
- **Twin concordance:** monozygotic about 47 to 56% versus dizygotic about 12 to 16% (Kaplan and Sadock 2024); above 80% in severe typical illness.
- **First-degree-relative recurrence risk:** of the order of 6 to 10% against a population risk near 1%.
- **Genome-wide significance threshold:** p less than 5 x 10 to the power minus 8 (about a million tests).
- **PGC schizophrenia GWAS (2014):** about 36,989 cases and 113,075 controls; 108 genome-wide-significant loci (Kaplan and Sadock 2024).
- **MHC / complement C4A:** most robust common-variant locus (chromosome 6); structural alleles raise C4A expression and risk (relative risk up to about 1.27); excess synaptic pruning mechanism (Sekar 2016).
- **DRD2:** genome-wide-significant locus and antipsychotic target; unites genetics and pharmacology.
- **CACNA1C:** voltage-gated calcium channel; cross-disorder locus shared with bipolar disorder.
- **22q11.2 deletion:** velocardiofacial / DiGeorge syndrome; single largest known genetic risk for schizophrenia (about 25 to 30-fold, quoted up to 50-fold); roughly one in four carriers develops psychosis; first de novo CNV described (Karayiorgou 1995).
- **Other recurrent CNVs:** 16p11.2, 1q21.1, 15q11.2, 15q13.3 (spans CHRNA7), NRXN1 deletion; pleiotropic across the neurodevelopmental spectrum.
- **Candidate genes (failed to replicate at genome-wide significance):** COMT (val158met), DISC1, NRG1 (neuregulin-1), DTNBP1 (dysbindin); the cautionary examples (Farrell 2015).
- **Endophenotypes:** P50 sensory gating (CHRNA7, 15q13-14), prepulse inhibition (heritability about 45 to 50%), smooth-pursuit / antisaccade eye-tracking; Gottesman and Gould (2003) criteria.
- **Schizophrenia PRS:** explains about 7% of liability (common-variant signal about 3 to 4% of variance); not individually predictive.
- **Schizophrenia-bipolar genetic correlation:** rg about 0.6 to 0.68 (PGC cross-disorder), the highest between two major psychiatric disorders.
- **Environmental risk factors:** cannabis (about doubled odds, MR-supported causal), urbanicity, migration, obstetric complications / prenatal infection, advanced paternal age.

12 · Pharmacogenetics and pharmacogenomics

Interindividual variation in drug response is one of the oldest observations in clinical psychiatry: two patients on the same molecule at the same dose may show remission, no effect, or a serious adverse reaction. **Pharmacogenetics** is the study of how variation in *single genes* (classically drug-metabolising enzymes) shapes drug response, while **pharmacogenomics** is the broader, genome-wide study of drug response, including polygenic architecture and treatment-response polygenic risk scores (Kaplan & Sadock 2024, Licinio & Wong). Both terms are used interchangeably in much of the literature, but the distinction matters for the exam: single-gene, actionable, guideline-backed (pharmacogenetic) versus multi-gene, exploratory, precision-medicine frontier (pharmacogenomic).

Why it matters. Only a handful of drug-gene pairs are genuinely actionable, and one of them, **HLA-B*15:02** before carbamazepine, is a life-saving screen that is mandated in patients of Asian ancestry, which makes it a high-yield item for an Indian exam. The rest of the topic is a

controlled deflation of hype: combinatorial commercial panels (GeneSight and similar) have weak and mixed randomised-trial support, and treatment-response polygenic scores are not yet clinical. Examiners reward candidates who can separate the evidence-based actionable core from the marketing. Cross-reference the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes for the underlying CYP450 induction and inhibition mechanics.

12.1 Two overlapping definitions

Pharmacogenetics. The study of how variation in a *single gene*, most often a drug-metabolising enzyme or an immune-response gene, alters the efficacy or toxicity of a drug (Kaplan & Sadock 2024). It is the older, narrower term, and its wins are concrete single drug-gene pairs with dosing guidance.

Pharmacogenomics

The genome-wide study of how the whole genetic profile, interacting with diet, microbiome, age and lifestyle, determines drug response. It is a multi-omic, exploratory approach that includes treatment-response polygenic risk scores and pathway analysis (psychscenehub 2023; New Oxford Textbook of Psychiatry).

Pharmacokinetic (PK) genes

Genes affecting drug absorption, distribution, metabolism and elimination, i.e. what the body does to the drug. In psychiatry, the cytochrome P450 enzymes, above all **CYP2D6** and **CYP2C19**.

Pharmacodynamic (PD) genes

Genes affecting the drug target or the tissue response, i.e. what the drug does to the body. Includes receptor and transporter variants (HTR2A, HTR2C, SLC6A4) and immune/HLA alleles that drive idiosyncratic hypersensitivity.

12.2 Metaboliser phenotypes and the activity score

Star-allele nomenclature. CYP alleles are named with the star (asterisk) system, e.g. CYP2D6*1 (reference, fully functional), *4 (null), *10 (decreased function). The combination of two inherited alleles is translated into a **metaboliser** phenotype (Kaplan & Sadock 2024).

The four phenotypes. *Poor metaboliser* (PM): two nonfunctional alleles, little or no enzyme activity, drug accumulates. *Intermediate metaboliser* (IM): reduced-function alleles, activity between poor and normal. *Normal (extensive) metaboliser* (NM/EM): standard activity, the reference phenotype. *Ultrarapid metaboliser* (UM): gene duplication or multiplication, greater than normal activity, drug cleared too fast.

The clinical trap. A UM on a standard dose looks like a non-responder (subtherapeutic levels) and a PM on a standard dose looks intolerant (accumulation and adverse effects); both are often mislabelled as treatment-refractory when the real problem is a dose mismatched to their metabolic capacity (Kaplan & Sadock 2024). For prodrugs the logic inverts: a codeine UM overproduces morphine and risks respiratory depression, while a codeine PM gets no analgesia.

Activity score (AS). Because two alleles combine and function varies continuously, CPIC assigns each allele a value (0 for null, 0.25 or 0.5 for decreased, 1 for normal) and sums them: an activity score of 0 predicts PM, 0.5 predicts IM, 1 to 2 predicts NM, and above 2 predicts UM (Gaedigk,

cited in Kaplan & Sadock 2024). The score is more granular than the four discrete labels and can be substrate-dependent.

RULE **Activity score sets the phenotype: 0 is poor, 0.5 intermediate, 1 to 2 normal, above 2 ultrarapid.** A poor metaboliser on a standard dose looks intolerant; an ultrarapid one looks like a non-responder.

12.3 CYP2D6: the antipsychotic and TCA enzyme

Scope. CYP2D6 (chromosome 22) metabolises roughly **25 percent** of clinically used drugs and is arguably the single most important PK gene in psychiatry: it handles all tricyclic antidepressants, several SSRIs (fluoxetine, paroxetine, fluvoxamine), venlafaxine and duloxetine, and the antipsychotics haloperidol, risperidone, aripiprazole and perphenazine (Kaplan & Sadock 2024; Tasman). Key actionable pairs are risperidone and aripiprazole (PM: higher levels, adverse effects; UM: possible loss of effect), tricyclics (PM: reduce starting dose by roughly 50 percent and use therapeutic drug monitoring), and atomoxetine.

Atomoxetine worked example. Atomoxetine levels peak about **10-fold** higher in CYP2D6 poor metabolisers, which is why a normally rare sedation signal is over-represented in PMs and why the FDA label carries CYP2D6 dosing guidance ().

Phenocopying. A CYP2D6 inhibitor (e.g. paroxetine, bupropion, fluoxetine) can convert a genotypic normal metaboliser into a functional PM, a phenomenon called phenocopying; a drug that inhibits its own metabolism at steady state produces autophenocopying (Kaplan & Sadock 2024). Genotype therefore predicts, but co-medication modifies, the observed phenotype. See the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes for the CYP inhibition and induction mechanics behind this.

12.4 CYP2C19: the SSRI and clozapine enzyme

Scope. CYP2C19 (chromosome 10q24) metabolises citalopram, escitalopram and sertraline, the tertiary-amine TCAs (imipramine, amitriptyline, clomipramine), and contributes to clozapine metabolism (Kaplan & Sadock 2024; Maudsley Prescribing Guidelines). Loss-of-function alleles *2 and *3 reduce activity (PM), while the gain-of-function *17 allele increases it (UM); all three belong on a minimal PK testing panel.

Escitalopram and citalopram. CYP2C19 poor metabolisers accumulate (es)citalopram and, because these drugs are dose-dependently QT-prolonging, a maximum dose of **20 mg** citalopram is advised in PMs; CYP2C19 ultrarapid metabolisers may under-respond, and CPIC suggests choosing an alternative not primarily metabolised by CYP2C19 (CPIC). Note the *17 allele adds only about 20 percent enzyme capacity, tempering the clinical size of the UM effect.

Sertraline and clozapine. CYP2C19 PMs have higher dose-adjusted sertraline concentrations; for clozapine, genotype-informed metabolic classification (PM, IM, NM) helps interpret plasma levels, though CYP1A2 is the dominant clozapine enzyme and CYP2D6 plays almost no role (Maudsley).

12.5 HLA alleles: idiosyncratic immune reactions

HLA-B*15:02 and carbamazepine. This is the flagship pharmacodynamic (immune) pharmacogenetic association. Carriers of HLA-B*15:02 are markedly more likely to develop carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN); the allele is common in Han-Chinese and several South-East and South-Asian groups and rare in Europeans (Kaplan & Sadock 2024). CPIC and the FDA recommend genotyping before starting carbamazepine in patients of Asian ancestry; the allele also flags cross-risk with oxcarbazepine and phenytoin. Genotyping never replaces clinical vigilance.

HLA-A*31:01. A separate allele associated with carbamazepine hypersensitivity, including SJS/TEN, DRESS and maculopapular exanthema, across a broader range of ancestries than HLA-B*15:02 (Kaplan & Sadock 2024).

TPMT and azathioprine. Outside psychiatry but a classic exemplar: thiopurine S-methyltransferase (TPMT) poor-metaboliser variants cause severe, potentially fatal myelosuppression with standard-dose azathioprine, so TPMT (and NUDT15) status guides thiopurine dosing (Kaplan & Sadock 2024, PharmGKB). It is the textbook example of a PK-driven toxicity screen.

RULE **Screen HLA-B*15:02 before carbamazepine in patients of Asian ancestry.** If positive, avoid carbamazepine (and the cross-risk agents oxcarbazepine and phenytoin); it is the one mandated, life-saving pre-prescription test in psychiatry.

12.6 Pharmacodynamic response signals: HTR2A and ANK3

HTR2A. The serotonin 2A receptor gene, a candidate pharmacodynamic marker included on several commercial panels (GeneSight, Genecept), studied for antidepressant response and tolerability; its independent clinical validity remains modest (Kaplan & Sadock 2024).

ANK3. Ankyrin-3, a robust GWAS-implicated bipolar susceptibility gene, has also been examined as a pharmacogenetic signal for lithium and mood-stabiliser response; the pharmacogenomic response evidence is preliminary rather than actionable. These loci illustrate the shift from single-gene PK certainties to multi-gene PD probabilities.

12.7 Guidelines, databases and resources

CPIC

Clinical Pharmacogenetics Implementation Consortium: NIH-funded, publishes gene-drug dosing guidelines (which drug to avoid or how to adjust for a given phenotype). The dominant clinical resource.

DPWG

Dutch Pharmacogenetics Working Group: the European equivalent, issues therapeutic recommendations for actionable variants; CPIC and DPWG broadly agree but differ on some thresholds.

PharmGKB

Pharmacogenomics Knowledgebase: curated repository of variant-drug annotations, allele-frequency data and clinical-annotation levels of evidence.

PharmVar

Pharmacogene Variation Consortium: the reference catalogue of CYP star alleles (for example, more than 170 CYP2D6 alleles).

12.8 Combinatorial commercial testing and the weak evidence base

What they are. Combinatorial pharmacogenomic panels (Myriad's GeneSight, Genomind's Genecept, Invitae's panel) genotype a bundle of PK and PD genes and return a proprietary weighted, colour-coded prescribing report. GeneSight, for instance, covers eight genes (PK: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4; PD: HTR2A and SLC6A4) (Kaplan & Sadock 2024).

The evidence. Meta-analyses of randomised controlled trials comparing genetically guided to unguided prescribing (e.g. Bousman et al. 2018) suggest a modest improvement in depression remission, but the trials are heterogeneous, several are industry-sponsored and often unblinded, and large independent studies have been more equivocal, so professional bodies frame these panels as decision-support tools, not mandates (psychscenehub 2023; International Society of Psychiatric Genetics 2019). The single-drug CYP and HLA pairs, not the combinatorial algorithms, carry the real actionable weight.

12.9 The pharmacogenomic frontier: PRS for treatment response

Beyond single genes. The genuinely pharmacogenomic (as opposed to pharmacogenetic) horizon is the treatment-response polygenic risk score: aggregating thousands of common variants to predict antidepressant, antipsychotic or lithium response. Current PRS explain little variance and are not clinically recommended (International Society of Psychiatric Genetics 2019; New Oxford Textbook of Psychiatry). Biobank-scale samples and cross-ancestry GWAS, including work on lithium response, are the active research direction; a recurring caveat for Indian practice is that South-Asian populations remain under-represented in the discovery cohorts, limiting portability of European-derived scores.

HOLD THIS

The actionable core is single drug-gene pairs, not the combinatorial panels. HLA-B*15:02 before carbamazepine and CYP-based dosing of tricyclics and citalopram carry guideline weight; GeneSight-type panels and treatment-response PRS have weak, mixed evidence and are not clinically ready.

INDIA

HLA-B*15:02 is the highest-yield actionable pharmacogenetic screen for Indian practice. The allele is common across South and South-East Asian populations, and Indian cohorts show a strong association between HLA-B*15:02 and carbamazepine-induced SJS/TEN, mirroring the Han-Chinese and Thai data (Kaplan & Sadock 2024; Lim, Kwan & Tan 2008). CPIC and FDA guidance to genotype before starting carbamazepine in patients of Asian ancestry therefore applies directly to Indian patients; where testing is unavailable, heightened clinical vigilance for early rash in the first weeks and a low threshold to stop the drug are essential. India is genetically stratified (North, South and East Indian populations are distinct), so pooling all Indians as one Asian group in dosing algorithms is a recognised limitation.

CLINICAL ANCHOR

Before starting carbamazepine in a patient of Asian ancestry, screen for HLA-B*15:02 if available; if positive, avoid carbamazepine (and oxcarbazepine and phenytoin, which share cross-risk) and select an alternative mood stabiliser. For the common antidepressants and antipsychotics, order CYP2D6 or CYP2C19 genotyping reactively, when a patient reports unusually severe adverse effects or unexplained non-response on an actionable drug (a TCA, citalopram, risperidone, aripiprazole, atomoxetine), rather than as a routine pre-prescription panel.

COMMON TRAP

Do not conflate the evidence tiers. HLA-B*15:02 to carbamazepine and CYP-based dosing of tricyclics and citalopram are actionable single-gene pairs with guideline backing. Combinatorial commercial panels and treatment-response polygenic scores are not: their randomised-trial evidence is weak, mixed and often industry-linked, and PRS for response is explicitly not recommended for clinical use. Calling GeneSight "proven" or PRS "clinically ready" is a marked-down answer.

GENE	VARIANT / PHENOTYPE	DRUG	CLINICAL ACTION
CYP2D6	Poor metaboliser (e.g. *4/*4)	Tricyclics, risperidone, aripiprazole, perphenazine	**Reduce starting dose (roughly 50 percent for TCAs), use TDM, or choose a non-CYP2D6 drug**
CYP2D6	Poor metaboliser	Atomoxetine	**Levels peak about 10-fold higher; adjust dose per FDA label, watch for sedation**
CYP2D6	Ultrarapid metaboliser	Codeine, tramadol (prodrugs)	**Avoid: overproduction of active metabolite risks respiratory depression**

GENE	VARIANT / PHENOTYPE	DRUG	CLINICAL ACTION
CYP2C19	Poor metaboliser	Citalopram, escitalopram	**Accumulation and QT risk; cap citalopram at 20 mg or use an alternative**
CYP2C19	Ultrarapid metaboliser (*17)	Escitalopram, tertiary-amine TCAs	**Possible under-response; consider a non-CYP2C19 alternative**
CYP2C19	Poor metaboliser	Sertraline, clozapine	**Higher dose-adjusted levels; interpret plasma concentrations accordingly**
HLA-B	*15:02 positive	Carbamazepine (also oxcarbazepine, phenytoin)	**Avoid: high SJS/TEN risk; screen before starting in Asian-ancestry patients**
HLA-A	*31:01 positive	Carbamazepine	**Increased hypersensitivity (SJS/TEN, DRESS) across ancestries; caution**
TPMT	Poor metaboliser	Azathioprine (thiopurines)	**Reduce dose sharply or avoid: risk of severe myelosuppression**

Actionable psychiatric drug-gene pairs: pharmacokinetic CYP and TPMT pairs (dose adjustment) versus pharmacodynamic HLA pairs (avoidance for idiosyncratic toxicity).

MNEMONIC

"2D6 = Doses; 2C19 = Citalopram; HLA = Halt"

CYP2D6 problems are dose problems (tricyclics, risperidone, aripiprazole, atomoxetine, all metabolic, all fixed by dose adjustment or drug switch). CYP2C19 keys to Citalopram and escitalopram (the QT and 20 mg cap). HLA-B*15:02 means Halt the carbamazepine, the one immune, life-threatening, screen-before-you-start pair.

PEARL

The single most examinable distinction: pharmacogenetic PK pairs (CYP2D6, CYP2C19) tell you *how much* drug to give, whereas the pharmacodynamic HLA pairs tell you *whether* to give the drug at all. Only HLA-B*15:02 before carbamazepine in Asian-ancestry patients is a genuinely mandated, life-saving pre-prescription test in psychiatry; everything else is dose-tuning or research.

GOOD TO REMEMBER

- **CYP2D6 (chr 22):** metabolises about 25 percent of drugs; all TCAs, some SSRIs, risperidone, aripiprazole, atomoxetine; PM accumulates, UM under-responds.
- **CYP2D6*4:** commonest null allele driving the poor-metaboliser phenotype (about 75 percent of PMs are *4 homozygotes).
- **CYP2D6*10:** decreased-function allele, high frequency in East and South Asian populations.
- **CYP2C19 (chr 10q24):** citalopram, escitalopram, sertraline, tertiary-amine TCAs; *2 and *3 = loss of function (PM), *17 = gain of function (UM).
- **CYP2C19 PM + citalopram:** accumulation and QT prolongation; cap citalopram at 20 mg.
- **Activity score:** 0 = PM, 0.5 = IM, 1 to 2 = NM, above 2 = UM (CPIC/Gaedigk).
- **HLA-B*15:02:** carbamazepine-induced SJS/TEN; common in Han-Chinese and South/South-East Asians; screen before starting; cross-risk with oxcarbazepine and phenytoin.
- **HLA-A*31:01:** carbamazepine hypersensitivity (SJS/TEN, DRESS) across broader ancestries.
- **TPMT (and NUDT15):** poor-metaboliser variants cause severe azathioprine myelosuppression; screen before thiopurines.
- **HTR2A, ANK3:** candidate pharmacodynamic response signals; ANK3 is a robust bipolar GWAS locus; response evidence preliminary, not actionable.
- **Atomoxetine in CYP2D6 PM:** levels peak about 10-fold higher (FDA-labelled).
- **Resources:** CPIC and DPWG (dosing guidelines), PharmGKB (variant-drug annotations), PharmVar (CYP star-allele catalogue).
- **GeneSight:** 8-gene combinatorial panel (PK: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP2D6; PD: HTR2A, SLC6A4); weak, mixed RCT evidence, decision-support only.
- **PRS for treatment response:** the pharmacogenomic frontier; explains little variance, not clinically recommended; South-Asian under-representation limits portability.

Discriminate

13 · Discriminate: match the finding to the right design and read a pedigree

These notes have walked through every genetic method one at a time. The examinable skill, and the reason this topic exists, is the opposite move: given a clinical or research *question*, name the **study design** that answers it, and given a family drawn on paper, read the **pedigree** correctly. Vivas and single-best-answer stems rarely ask "define a twin study"; they ask "which design would tell you whether the aggregation is genetic or environmental?" and expect you to say twin study without hesitation. This is a discrimination drill, not a definitions list.

The whole set of notes collapses into one decision tree that Kaplan and Sadock frame as a logical progression of five questions (Kaplan & Sadock 2024): does it run in families, how much is genes versus environment, how is it transmitted, roughly where is the gene, and which specific variants. Bolt on to that the modern clinical add-ons (rare-variant testing, aggregate risk prediction, drug-response prediction) and the classic reading errors that trap the unwary, and you can answer any permutation the paper throws at the material. Then the second half: the standard **pedigree** and **genogram** symbols, recognising an inheritance pattern from them, and turning a family drawing into a recurrence-risk estimate.

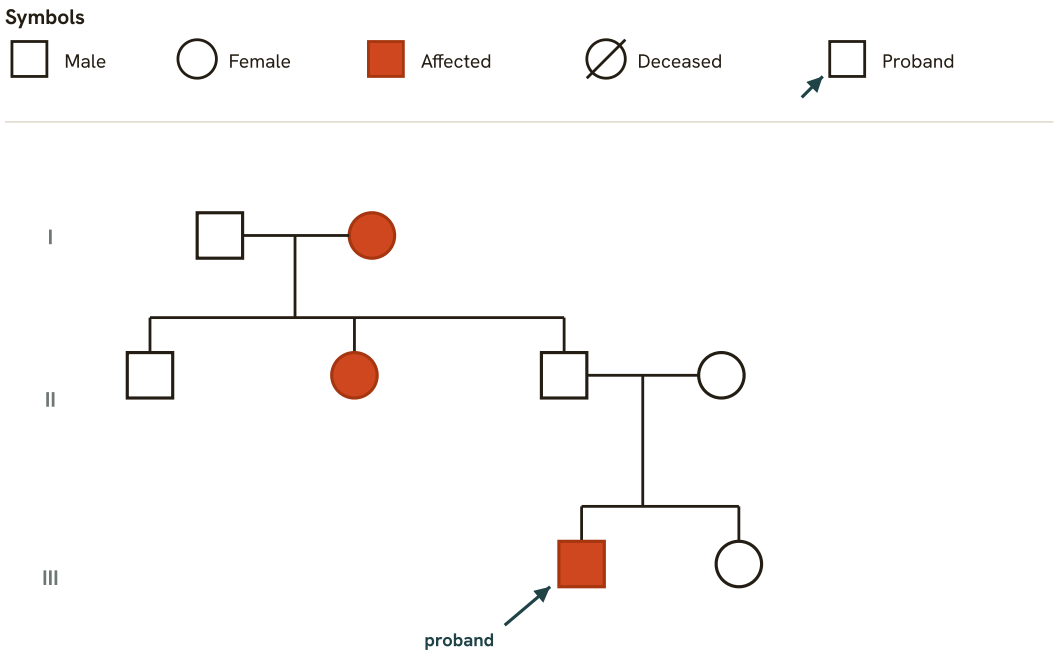


Fig 3.8 Reading a pedigree. The legend gives the standard symbols: squares are male, circles female, a filled symbol is affected, a slash marks deceased, and the arrow marks the proband, the person through whom the family came to attention. In the worked three-generation pedigree, affected members appear in each generation and in both sexes with no clean skipping, which reads as familial aggregation on a multifactorial background rather than a single-gene Mendelian pattern. Recognising the pattern is the first step in choosing the right study design and estimating recurrence risk in counselling.

13.1 The question drives the design: the five-question spine

Answer the question with the cheapest sufficient tool. Genetic epidemiology proceeds as an ordered sequence, and each rung has exactly one design that answers it (Kaplan & Sadock 2024). "Does the phenotype run in families?" is answered by a **family study** (compare disorder rates in relatives of affected probands versus relatives of controls; if genetic, risk rises with closeness of relationship). Familial aggregation alone cannot separate genes from a shared household, so the next question, "how much is genes versus shared environment?", needs a **twin study** (monozygotic versus dizygotic concordance yields heritability). To strip out the confound that families share both genes and rearing, the **adoption study** separates genetic parents from rearing parents. "How is it transmitted?" is a **segregation analysis** (fit Mendelian and non-Mendelian models to pedigree data). "Roughly where is the gene?" is **linkage analysis**, reported as a LOD score. "Which specific variants?" is an **association study**, at genome-wide scale a GWAS. The trick in choosing which design is to read what the stem asks you to *rule out*.

RULE **Answer the question with the cheapest sufficient tool, and read what the stem asks you to rule out.** "Genes or environment?" is a twin study; add "controlling for rearing" and it becomes an adoption study.

13.2 The discrimination table: research question to correct design

This is the memory anchor for the whole set of notes. Read the question in the left column, commit the design in the middle, and note the single word in the right column that discriminates it from its neighbours. The three classic epidemiological designs (family, twin, adoption) form a nested logic: each is introduced to remove a confound the previous one cannot (New Oxford Textbook of Psychiatry 2020; Kaplan & Sadock 2024).

RESEARCH QUESTION (AS THE STEM PHRASES IT)	CORRECT DESIGN	WHAT ONLY THIS DESIGN SETTLES
Does the disorder run in families?	Family study	**Familial aggregation; risk scales with degree of relationship**
Is the aggregation genes or shared environment?	Twin study (MZ vs DZ concordance)	**Separates genes from environment; yields heritability**
Is it genes or the rearing environment specifically?	Adoption study	**Splits genetic parents from rearing parents**
How is the trait transmitted through generations?	Segregation analysis	Tests goodness-of-fit of Mendelian vs complex models
Roughly where on the chromosomes is the locus?	Linkage analysis (LOD score)	**Coarse chromosomal region via co-segregation in families**
Which common variants raise risk across the population?	Association study / GWAS	**Specific common alleles; unit is the unrelated individual**
Is there a specific rare cause in this one patient?	Chromosomal microarray (CMA) for CNVs; sequencing (WES/WGS)	**Individual molecular diagnosis, not population inference**
What is this patient's aggregate inherited liability?	Polygenic risk score (PRS)	Sums weighted effects of many common SNPs into one score
Will this drug work or harm this patient?	Pharmacogenetic test (e.g. CYP metaboliser status, HLA risk allele)	**Predicts drug response or toxicity, not disease risk**

The decision tree in one grid: match the phrasing of the stem to the design, then check the discriminator that separates it from its nearest rival.

13.3 The two commonest confusions: which design, and which level

Family versus twin, and population versus individual. Two axes trip candidates. First, **which design** along the family-to-molecular axis: a family study proves aggregation but can never separate genes from a shared household, so any stem that says "distinguish genetic from environmental transmission" demands a twin study, and one that adds "controlling for the rearing environment" demands an adoption study. Second, the *level* of inference: family, twin, adoption, linkage and association all make *population-level* statements about a disorder, whereas CMA, sequencing, PRS and pharmacogenetic testing make statements about *this individual patient in front of you*. When a stem is framed clinically ("a 6-year-old boy with autism and dysmorphism", "an antidepressant non-responder"), the answer is almost always an individual-level test

(microarray, sequencing, or a pharmacogenetic panel), not a research design (Kaplan & Sadock 2024).

HOLD THIS

Population design or individual test? A clinical stem means an individual-level test. Family, twin, adoption, linkage and association make population statements; CMA, sequencing, PRS and pharmacogenetic testing speak to the one patient in front of you.

COMMON TRAP

Do not answer "twin study" when the stem asks to separate genetic transmission from the *rearing* environment specifically: that is the adoption study's job, because twins reared together share both genes and household. And do not answer "GWAS" for a single patient's diagnostic workup: GWAS is a population design that discovers common risk alleles, whereas a chromosomal microarray or sequencing panel is what yields a molecular diagnosis in one child.

13.4 Reading a pedigree: the standard symbols

You cannot interpret a family you cannot decode. A pedigree (the clinical drawing is a **genogram** when it also carries relationship and social detail) uses a fixed symbol set that examiners expect you to read on sight. Learn the core glyphs cold; a mislabelled proband or a missed consanguinity line changes the whole interpretation.

Square
Male.

Circle
Female.

Diamond
Sex unknown or unspecified.

Filled (shaded) symbol
Affected individual. A half-filled or dotted symbol conventionally marks a carrier or a milder/subthreshold phenotype.

Open (unfilled) symbol
Unaffected.

Diagonal line (slash) through a symbol
Deceased.

Arrow (with "P")
The proband, i.e. the index case through whom the family was ascertained.

Horizontal line joining two symbols
A mating (partnership).

Double horizontal line
Consanguineous mating (partners are blood relatives): a major clue to autosomal recessive inheritance.

Vertical line down to a horizontal sibship line
Offspring of the mating; siblings hang off the sibship line left to right by birth order.

Roman numerals (I, II, III) down the left margin

Generations, oldest at the top. Individuals within a generation are numbered left to right in Arabic numerals, so "II-3" is a specific person.

13.5 Recognising the inheritance pattern from the drawing

The pattern is in the geometry. Once decoded, the shape of shading across generations suggests the mode of transmission, and this is a favourite viva move. Autosomal dominant: affected individuals in every generation (vertical transmission), roughly half of offspring affected, and male-to-male transmission is possible. Autosomal recessive: affected individuals cluster in a single sibship with unaffected parents (horizontal pattern), and consanguinity (the double line) raises the odds; both sexes affected equally. X-linked recessive: mostly affected males, transmitted through unaffected carrier females, with *no* male-to-male transmission (a father cannot pass his X to a son). X-linked dominant: affected in every generation, but affected fathers transmit to all daughters and no sons. Mitochondrial: transmitted only through the maternal line, all children of an affected mother at risk, no transmission through affected fathers. Psychiatric disorders fit *none* of these cleanly, which is itself the exam point: they are polygenic and multifactorial, so a pedigree shows aggregation without a recognisable Mendelian signature (New Oxford Textbook of Psychiatry 2020).

TRAP Do not force a psychiatric pedigree into a Mendelian pattern: familial aggregation without a clean dominant, recessive or X-linked signature is the expected picture for a polygenic, multifactorial disorder.

13.6 Estimating recurrence risk from the genogram

From drawing to a number for counselling. For a clear single-gene pattern, recurrence risk follows Mendelian arithmetic: autosomal dominant gives about 50% to each child of an affected parent, autosomal recessive about 25% to the next child of two carrier parents (one in four), X-linked recessive gives 50% of sons of a carrier mother affected and 50% of daughters carriers. For the multifactorial psychiatric disorders you actually counsel on, there is no Mendelian fraction; you fall back on **empirical recurrence risks** derived from family studies. For schizophrenia these are the numbers to carry: roughly 5 to 15% for a first-degree relative against a population baseline near 1%, rising steeply with the number of affected relatives and with closeness of relationship (Kaplan & Sadock 2024). Recurrence risk in multifactorial disease also rises with severity of the index case and with the number already affected in the family, and it falls off faster than the Mendelian halving as you move to more distant relatives.

CLINICAL ANCHOR

A CMA (chromosomal microarray) finding of a 22q11.2 deletion in a child reframes the whole pedigree: this single CNV carries an associated risk of roughly 25 to 30% of developing a psychotic disorder (Kaplan & Sadock 2024), a far larger per-carrier effect than any common SNP. It is the standard worked example of why, for an individual patient with intellectual disability or syndromic features, you order a microarray (an individual-level rare-variant test) rather than reasoning from population heritability.

13.7 The classic false conclusions when reading families

Aggregation is not proof of a shared gene. The reason twin and adoption designs exist is that a pedigree can mislead in half a dozen stereotyped ways, and naming these is a reliable viva question. Each is a way a family can look genetic when it is not, or look non-genetic when it is (Kaplan & Sadock 2024; New Oxford Textbook of Psychiatry 2020).

Assortative mating

Affected individuals partner non-randomly with similarly affected partners, concentrating risk alleles in a lineage and inflating apparent aggregation beyond simple transmission.

Phenocopy

An environmentally produced case clinically identical to the genetic form; an affected person in the pedigree who carries none of the family's risk variants, blurring co-segregation.

Incomplete (reduced) penetrance

A gene carrier who never manifests the disorder appears as an unaffected symbol, so the gene seems to "skip" and dominant inheritance is missed.

Variable expressivity

The same variant produces different or milder phenotypes across relatives (a hallmark of many CNVs, e.g. 16p11.2), so the "same" gene looks like different conditions in one family.

Genetic (locus) heterogeneity

Different genes cause the same phenotype in different families; pooling pedigrees dilutes any single linkage signal, a core reason linkage failed in psychiatry.

Shared environment mistaken for shared genes

A common household exposure (diet, toxin, trauma, infection) aggregates in relatives and mimics genetic transmission; only twin and adoption designs can distinguish it.

PEARL

Every one of these six is a reason a pedigree alone cannot prove a genetic cause, which is exactly why the field built twin and adoption designs on top of the family study. Turn the list around at exam time: if asked "why is familial aggregation not sufficient evidence of a genetic cause?", these six confounders (led by shared environment) are your answer.

MNEMONIC

FAMILY - TWIN - ADOPT - SEGREGATE - LINK - ASSOCIATE

Runs it? FAMILY study. Genes or environment? TWIN. Genes or rearing? ADOPT. How transmitted? SEGREGATE. Where is it? LINK (LOD). Which variant? ASSOCIATE (GWAS). The order is also the historical and logical order in which each question can only be asked once the previous is answered.

GOOD TO REMEMBER

- **Family study:** answers "does it run in families?"; proband and relatives vs control relatives; risk scales with degree of relationship (first-degree share ~50% of genes).
- **Twin study:** answers "genes vs environment?"; MZ vs DZ concordance yields heritability.
- **Adoption study:** answers "genes vs rearing environment?"; separates genetic from rearing parents.
- **Linkage analysis:** answers "roughly where?"; LOD +3 = proof (1000:1 odds for), LOD -2 = exclusion.
- **Association / GWAS:** answers "which common variant?"; genome-wide significance threshold p < 5 x 10 to the -8.
- **Schizophrenia empirical recurrence risk:** first-degree relative ~5 to 15% vs population ~1% (Kaplan & Sadock 2024).
- **Schizophrenia twin concordance:** MZ ~40 to 60%, DZ ~10 to 16%; heritability ~80% (Kaplan & Sadock 2024).
- **22q11.2 deletion syndrome:** CNV detectable on CMA; associated psychosis risk ~25 to 30% per carrier (Kaplan & Sadock 2024).
- **16p11.2 CNV:** variable expressivity, linked across ASD, schizophrenia and bipolar disorder (Tasman 2015).
- **PRS for schizophrenia:** best current score explains ~11% of liability; theoretical ceiling ~25% (Kaplan & Sadock 2024).
- **Pedigree symbols:** square male, circle female, filled affected, diagonal deceased, arrow proband, double line consanguinity, generations in Roman numerals.

Apply and consolidate

14 · Genetic counselling in psychiatry

Genetic counselling in psychiatry is the clinical process of helping a patient and family understand the genetic and environmental contributions to a psychiatric disorder, appreciate the chance of recurrence in relatives, and reach their own decisions about reproduction, testing and life planning (Kaplan & Sadock 2024; Austin 2020). It is deliberately distinct from the Mendelian counselling of single-gene disease: psychiatric disorders are complex and polygenic, so recurrence chances are quoted as **empirical risks** derived from family, twin and adoption studies, not from Mendelian ratios. The modern model, well developed in the psychiatric genetic-counselling outcomes literature, treats the encounter as more existential than arithmetical, centred on the question "Why me?" and on relieving guilt, blame and fear rather than on delivering a number (Inglis et al. 2015; Austin 2020).

Why it matters. This is a high-yield exam topic that sits at the junction of genetics, ethics and Indian practice. Examiners reward candidates who can state the standard empirical figures for schizophrenia and bipolar disorder, articulate the **non-directive** stance, know when to refer to clinical genetics, and place the whole discussion inside a consent and capacity framework. The India layer, consanguinity, arranged-marriage disclosure pressure and family-level decision-making, is what turns a textbook answer into a distinction answer. For the underlying consent, capacity and ethics scaffolding, cross-reference paper iii.

14.1 What genetic counselling is, and is not

A communication process, not a verdict. The classic definition frames genetic counselling as a communication process dealing with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family: helping the individual comprehend the medical facts, appreciate how heredity contributes, understand the options for dealing with recurrence, choose the course of action congruent with their goals and values, and make the best adjustment to the disorder (Resta et al. 2006, adapting Fraser). Every clause is about supported autonomous decision-making, not about reducing the incidence of illness.

Not eugenics. A goal of reducing the birth rate of a condition is explicitly eugenic and is not an acceptable aim of counselling; the counsellor must not present any reproductive decision as correct or advantageous for the patient or for society (National Academies consensus). This principle is load-bearing for the ethics viva.

Delivered increasingly by specialists. Reproductive genetic counselling is now largely the province of medical geneticists and certified genetic counsellors rather than psychiatrists, given the pace of testing technology; but the psychiatrist must recognise the situations in which counselling is indicated and make the referral (Harrison et al., Shorter Oxford Textbook of Psychiatry 2018). Dedicated psychiatric genetic-counselling clinics (for example the Adapt clinic, British Columbia) accept both physician referrals and self-referrals (Inglis et al. 2015).

14.2 Non-directiveness: the governing stance

Definition. **Non-directive counselling** means the counsellor provides balanced, accurate information and emotional support but does not steer the patient toward any particular reproductive or testing decision; the choice, and the values that drive it, belong to the patient (Kaplan & Sadock 2024). It is the declared standard of care for reproductive planning and for counselling around untreatable disorders.

Why psychiatry stresses it. People weigh reproductive risk by their felt ability to cope with an affected child far more than by precise numerical probabilities, and risk perception is shaped by control, treatability, visibility and whether they know an affected person (Lippman-Hand & Fraser). A directive stance overrides exactly the personal calculus that counselling exists to protect.

The realistic caveat. Pure non-directiveness is an ideal; skilled counsellors still shape the frame through which information is presented, so the safeguard is transparency and reflection rather than a pretence of value-neutrality.

RULE **Non-directive, and never eugenic.** Supply balanced information and support, leave the reproductive decision to the patient, and never frame reducing the birth rate of a condition as a goal of counselling.

14.3 Step one: establish the diagnosis and build the pedigree

Diagnosis first. No risk figure is meaningful until the proband's diagnosis is secure, because empirical risks are disorder-specific and the schizophrenia figures differ from the mood-disorder

figures. A misassigned diagnosis propagates a wrong risk estimate to the whole family.

The three-generation pedigree. Best-practice psychiatric genetic counselling bases chances on a detailed, systematically taken three-generation family history, then applies empirical data to that specific pedigree rather than quoting a generic textbook number (Austin et al. 2008; Austin 2020). Family loading (number and closeness of affected relatives, early onset) shifts the individualised estimate above or below the population figure.

Contracting. Fewer than half of patients presenting for psychiatric genetic counselling actually want a recurrence number at referral; the counsellor contracts explicitly, discusses aetiology and recovery first, then checks again whether the patient wants specific figures. After that discussion only around 40 percent opt to hear specific chances, and interest often falls once the emotional driver behind the question is addressed (Borle et al. 2018).

14.4 Step two: communicate empirical recurrence risks

Empirical, not Mendelian. Because liability is polygenic and multifactorial, recurrence chances come from observed rates in relatives of probands (corrected for the age of risk, so-called expectancy rates or **morbid risks**), not from Mendelian segregation ratios (Shorter Oxford Textbook of Psychiatry 2018). Figures are best given as absolute risks and frequencies with broad ranges, always anchored against the roughly 1 percent population baseline for schizophrenia (Austin et al. 2008; Borle et al. 2018).

Schizophrenia. Using the pooled lifetime-risk figures (Gottesman, reproduced in Shorter Oxford Textbook of Psychiatry 2018): a sibling of a proband carries about 9 percent, a child of one affected parent about 13 to 17 percent, a child of two affected parents about 46 percent, and the monozygotic co-twin about 48 percent (with twin studies converging on 40 to 50 percent). Bipolar disorder: the first-degree-relative risk is of the order of 10 to 15 percent in the narrower estimates commonly quoted in counselling, with older broad-liability family studies giving figures as high as 25 to 27 percent for offspring of one affected parent; the monozygotic co-twin concordance is around 60 percent (Shorter Oxford Textbook of Psychiatry 2018). The spread itself is the teaching point: quote a range, name the source, and never imply false precision.

How to frame the number. Present risk in the context of the population rate, avoid framing that inflates dread ("a 13 percent chance of illness" also means an 87 percent chance of no illness), and pair every figure with the reminder that genes set liability while environment and chance decide expression.

RELATIONSHIP TO PROBAND	SCHIZOPHRENIA LIFETIME RISK	BIPOLAR DISORDER RISK
General population (baseline)	~1%	**~1%**
Sibling	~9%	**~5 to 10%**
Child, one affected parent	~13 to 17%	**~10 to 15% (up to ~25 to 27% in broad-liability studies)**
Child, both parents affected	~46%	**markedly higher (broad studies quote up to ~74%)**
Dizygotic co-twin	~17%	**~20%**
Monozygotic co-twin	~48% (range 40 to 50%)	**~60%**

Empirical recurrence risks by relationship: schizophrenia figures from the Gottesman pooled data (Shorter Oxford 2018); bipolar figures span narrow counselling estimates and older broad-liability family studies, hence the ranges.

~1%	~9%	~13%	~46%
GENERAL POPULATION, SCHIZOPHRENIA	SIBLING OF A PROBAND	CHILD OF ONE AFFECTED PARENT	CHILD OF TWO AFFECTED PARENTS

14.5 When to refer to clinical genetics

The referral triggers. The psychiatrist should refer to a medical geneticist or genetic-counselling service when features suggest a discrete, testable cause rather than ordinary polygenic liability: *dysmorphology* (an unusual facial gestalt or congenital anomalies), *intellectual disability* or global developmental delay accompanying the psychiatric presentation, a *suspected syndromic or copy-number cause* (for example 22q11.2 deletion presenting with psychosis, or fragile X in ID with autism features), and *consanguinity*, which raises the yield of autosomal-recessive and homozygous-variant conditions.

Why it matters clinically. These situations may carry a much larger, sometimes near-Mendelian, individual risk than the polygenic average: an individual with a 3q29 deletion has been estimated to have roughly a one-in-three chance of developing schizophrenia, and chromosomal microarray is now a routine test in selected patients (Shorter Oxford Textbook of Psychiatry 2018; Baker et al. 2014). A syndromic diagnosis also reframes counselling, prognosis and, occasionally, targeted management.

Practical rule. Ordinary schizophrenia or bipolar disorder without dysmorphology, ID or a suggestive family pattern is counselled with empirical risks; add-red-flag features earn a genetics referral and possible cytogenetic or microarray testing.

HOLD THIS

Counsel with empirical, not Mendelian, risks; refer the red flags. Polygenic liability means recurrence comes from family-study rates against the ~1% baseline; dysmorphology, intellectual disability, a suspected CNV or consanguinity earn a clinical-genetics referral.

14.6 Predictive and prenatal testing, and their ethical weight

No clinical predictive test exists for common psychiatric disorders. For schizophrenia and bipolar disorder there is no validated genetic test that predicts who will fall ill; the honest answer

to "will it happen again?" is that we cannot predict with certainty (Austin & Peay). Predictive testing in the true sense applies to the rare high-penetrance neuropsychiatric conditions, above all Huntington's disease, where presymptomatic DNA testing is possible and mandates pre-test counselling by a clinical geneticist (Companion to Psychiatric Studies; MacLeod et al. 2013).

The weight of a presymptomatic result. Learning one's status for an untreatable condition carries risks to mood, self-image, reproductive and career decisions and insurability; a positive result has implications for other family members who may not wish to know theirs (New Oxford Textbook of Psychiatry; Kaplan & Sadock 2024). Protocols therefore insist on informed consent, a cooling-off structure, and support before and after disclosure.

Prenatal testing. Prenatal or preimplantation testing is meaningful only for the rare identifiable single-gene or chromosomal causes, not for polygenic psychiatric liability; where offered, non-directiveness and full pre- and post-test counselling are the standard, and the decision to test or to continue a pregnancy is left to the couple (National Academies consensus).

14.7 Incidental findings and the meaning of a "negative"

Incidental (secondary) findings. Broad testing such as chromosomal microarray or exome sequencing can reveal variants unrelated to the presenting complaint, including variants of uncertain significance and medically actionable secondary findings; consent must cover in advance what will be returned and what the patient wishes to know (Kaplan & Sadock 2024).

The two-sided interpretation trap. Because these are susceptibility not diagnostic tests, many people with a clear psychiatric diagnosis carry no identified variant, and many carriers never fall ill. A "negative" result may wrongly make a patient doubt the validity of their diagnosis or reduce treatment adherence, and may paradoxically increase parental guilt by removing a biological explanation; a positive susceptibility result labels risk without certainty (Kaplan & Sadock 2024). Pre-test counselling must rehearse the meaning of both outcomes.

14.8 Polygenic risk scores: not yet clinical

What a PRS is. A **polygenic risk score** sums the effects of many common risk alleles weighted by GWAS data to estimate an individual's genetic liability to a disorder (Kaplan & Sadock 2024). It captures the en-masse effect of variants that are not individually genome-wide significant.

Why it is not used in counselling. Current PRS modify a family-history-based estimate only marginally, are not definitively predictive, and are far less informative outside populations of European ancestry because the discovery datasets are predominantly European, an equity problem acute for Indian patients (Kaplan & Sadock 2024; Murray et al. 2021; Wray et al. 2021). The consensus through 2026 is that PRS remain a research tool, not a clinical counselling instrument, and should not be quoted as an individual risk to a patient. Communicating a non-definitive score risks being read as higher than warranted or being discounted, in ways that vary with the patient's coping style (Kaplan & Sadock 2024).

INDIA

Consanguinity. Consanguineous marriage is common in parts of India and raises the yield of autosomal-recessive and syndromic causes of intellectual disability, autism and epilepsy that can present with psychiatric features; a consanguineous pedigree is itself a trigger to consider a clinical-genetics referral rather than to quote polygenic empirical risks alone. **Disclosure pressure.** In the arranged-marriage context a family history of mental illness carries heavy stigma, and families may face pressure either to conceal a psychiatric diagnosis during matchmaking or to demand disclosure from the other party. The counsellor's duty is to the patient's confidentiality and autonomy: information about a proband is shared only with the patient and, where relevant, guardians of a dependent child, never volunteered to grandparents or prospective in-laws (Borle et al. 2018). Framing risk to reduce stigma, and resisting any eugenic or "don't marry / don't have children" steer, matters more here than anywhere. **Family-level decisions.** Reproductive and marital choices are frequently made at the level of the extended family rather than the individual, so non-directive counselling in India often means engaging the family unit while still protecting the individual patient's consent and confidentiality. See paper iii for the consent, capacity and confidentiality framework these tensions sit within.

COMMON TRAP

Quoting Mendelian ratios (25 percent, 50 percent) for schizophrenia or bipolar disorder. These are polygenic conditions; recurrence is given as *empirical* risk from family and twin studies, corrected for age of risk. A "25 percent" answer for a first-degree relative may coincidentally resemble a broad-liability figure for bipolar disorder, but the reasoning (autosomal-dominant segregation) is wrong and loses marks.

PEARL

The best-evidenced *outcome* of psychiatric genetic counselling is increased patient empowerment and reduced guilt, not changed reproductive decisions, and the largest gains occur in people who initially wanted a recurrence number but changed their mind after discussing aetiology and recovery (Borle et al. 2018; Inglis et al. 2015). The number is often the ticket in, not the therapeutic ingredient.

CLINICAL ANCHOR

A 28-year-old woman with schizophrenia (ICD-11 6A20; DSM-5-TR schizophrenia) asks what chance her future child has of the illness. You secure the diagnosis, take a three-generation pedigree (no other affected relatives), and, after contracting, offer an empirical figure of roughly 13 percent for a child of one affected parent against a population baseline near 1 percent, framed non-directively and alongside the 87 percent chance of no illness. No PRS is quoted. Because there is no dysmorphology, intellectual disability or consanguinity, no clinical-genetics referral is needed.

MNEMONIC

DR PACE

Diagnosis confirmed, **R**ecords and three-generation pedigree, **P**opulation-anchored empirical risk (not Mendelian), **A**utonomy and non-directiveness, **C**onsent for predictive or prenatal testing (and paper iii capacity/ethics), **E**motional support and follow-up. The steady pace of psychiatric genetic counselling: diagnosis before numbers, support around the numbers.

GOOD TO REMEMBER

- **Schizophrenia, sibling of proband:** ~9% lifetime risk (Gottesman, Shorter Oxford 2018).
- **Schizophrenia, child of one affected parent:** ~13 to 17% (classic Gottesman figure ~13%; Shorter Oxford table lists 17%).
- **Schizophrenia, child of two affected parents:** ~46%.
- **Schizophrenia, monozygotic co-twin:** ~48% (twin-study range 40 to 50%); dizygotic co-twin ~17%.
- **Schizophrenia population baseline:** ~1%.
- **Bipolar disorder, first-degree relative / child of one parent:** ~10 to 15% in narrow counselling estimates; older broad-liability family studies give up to ~25 to 27%.
- **Bipolar disorder, monozygotic co-twin concordance:** ~60%; dizygotic ~20%.
- **3q29 deletion:** ~1-in-3 (~33%) chance of developing schizophrenia, an example of a high-risk CNV warranting clinical-genetics referral.
- **22q11.2 deletion:** syndromic cause of psychosis; a referral trigger when psychosis co-occurs with dysmorphology or developmental features.
- **Huntington's disease:** the exemplar of true presymptomatic (predictive) DNA testing, mandating pre-test genetic counselling.
- **Polygenic risk score (PRS):** sums many common GWAS alleles; NOT clinically actionable in counselling as of 2026, and less valid in non-European (including Indian) populations.

15 · Apply: four genetics vignettes

The whole set of notes converges here. Psychiatric genetics earns its exam marks only when a family history, an ancestry, a dysmorphic phenotype or a metaboliser report is made to *predict* a clinical consequence and then force a first move. These four vignettes are deliberately drawn from four corners of the discipline, so the discriminator in each is a different genetic tool: an **empirical recurrence risk** read off polygenic familial data, a **pharmacogenomic HLA test** that averts a fatal skin reaction, a **copy-number variant** hunted with a cytogenetic assay, and a **pedigree read alongside a CYP genotype**. Each runs to the three-beat rhythm the examiners reward: the **presentation**, then the **genetic reasoning** that alone explains it, then the **counselling, testing or dosing action** the genetics forces.

Read each as a reasoning drill, not a fact to memorise. If you can name the tool the moment the stem lands, whether the answer is a probability given non-directively, an allele screened before a drug, an assay ordered before a referral, or a study design chosen to match a transmission pattern, the response is already written. Numbers that carry weight are given only where a canonical source verifies them, and any figure to confirm against a current guideline or formulary before quoting is flagged (Kaplan & Sadock 2024; New Oxford 2020; Maudsley 2021). A hard rule

threaded through all four: give population-level probabilities without implying determinism, and never name a diagnosis to a family in a way that stigmatises the proband or an unaffected relative.

15.1 Vignette 1: a couple ask about their child's risk when one partner has bipolar disorder, the empirical-risk counselling drill

CLINICAL ANCHOR

Case: a couple attend for pre-conception advice. The husband has an established diagnosis of bipolar type I disorder (ICD-11 6A60; DSM-5-TR bipolar I disorder), well controlled on lithium. The wife has no psychiatric history and no affected relatives. They ask, directly, what the chance is that a future child will develop the same illness, and whether they should have children at all.

Reasoning. Bipolar disorder is the single most heritable major psychiatric disorder (heritability around 0.85, rising toward 0.9 for narrowly defined bipolar-I; MZ co-twin concordance conventionally around 60 percent against a DZ rate an order lower), yet its inheritance is *polygenic and non-Mendelian*: it does not segregate in simple ratios, so there is no single-gene calculation to offer (Kaplan & Sadock 2024; McGuffin 2003). What counselling uses instead is the **empirical recurrence risk**, the observed rate of illness in relatives of probands read straight off family-study data. For a child with one affected parent the empirical risk of bipolar disorder is of the order of 10 to 15 percent, several-fold above the roughly 1 to 2 percent population baseline; the risk of any mood disorder (including unipolar depression) in that child is higher still, and the figure climbs further, toward 40 to 50 percent, if both parents are affected (verify the exact figures against a current text before quoting). Recurrence risk in this model rises with the severity of the index case and with the number of affected relatives, the same liability-threshold logic that governs all the common disorders.

Counselling action (non-directive). The mechanism dictates the manner. Genetic counselling here is **non-directive**: you supply the empirical probability as a probability, frame it against the population baseline so it is neither minimised nor catastrophised, and explicitly leave the reproductive decision to the couple rather than advising for or against childbearing. Add the constructive counterweight that most children of an affected parent do *not* develop bipolar disorder, that no prenatal or predictive genetic test exists for a polygenic condition of this kind, and that early recognition and treatment of any future illness improves outcome. Where relevant, fold in the separate, drug-specific reproductive-safety discussion (lithium and first-trimester exposure) as its own strand, and route the detailed peri-conception medication protocol to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not quote a Mendelian fraction (a "one in four" or "one in two") for a polygenic psychiatric disorder: that arithmetic belongs to single-gene conditions and misrepresents the biology. And do not drift into directive advice ("you shouldn't have children") or false reassurance ("it won't be passed on"). The examinable failure modes are the Mendelian-ratio error and the loss of non-directiveness; the correct answer is an empirical percentage, delivered neutrally, with the decision left to the couple.

15.2 Vignette 2: carbamazepine in a patient of Han-Chinese or South-Asian ancestry, the HLA-B*15:02 screen before starting

CLINICAL ANCHOR

Case: a 30-year-old man of Han-Chinese ancestry (the same caution applies across South-East and South Asian populations, including Thai and many Indian groups) is to be started on carbamazepine, whether for a mood-stabilising indication in bipolar disorder or for trigeminal neuralgia or epilepsy. He is treatment-naive to the drug. Before writing the prescription, the question is what to check.

Reasoning. Carbamazepine can precipitate the life-threatening severe cutaneous adverse reactions **Stevens-Johnson syndrome** and **toxic epidermal necrolysis (SJS/TEN)**. The susceptibility is pharmacogenomic and strongly ancestry-linked: the class I HLA allele **HLA-B*15:02** is the established risk marker for carbamazepine-induced SJS/TEN, and its carrier frequency is substantial in Han-Chinese, Thai and many South and South-East Asian populations while being rare in Europeans (Kaplan & Sadock 2024). The mechanism is immunogenetic, not metabolic: the risk allele shapes the HLA-restricted T-cell response to the drug, so this is a pharmacodynamic pharmacogenetic marker of a hypersensitivity reaction rather than a dose-handling problem. Because the reaction is idiosyncratic and severe, the genetic test is deployed *pre-emptively*, before the first dose, in the at-risk ancestry groups.

Testing action. Screen for **HLA-B*15:02** before initiating carbamazepine in patients of the relevant ancestry, and if the patient is positive, *avoid carbamazepine* and choose an alternative agent unless the benefit clearly outweighs the risk. Two examinable refinements: HLA-B*15:02 positivity also flags cross-risk with other aromatic antiepileptics that cause SJS/TEN, notably phenytoin and oxcarbazepine, so phenytoin is *not* a safe substitute in a positive patient; and a distinct allele, HLA-A*31:01, is linked to a broader spectrum of carbamazepine hypersensitivity (including DRESS and maculopapular eruption) across other ancestries including Europeans. Genotyping does not replace clinical vigilance: counsel every starter about the early rash and mucosal warning signs and the instruction to stop and present immediately (verify current screening thresholds and the exact at-risk populations against a live guideline; Kaplan & Sadock 2024; Maudsley 2021).

INDIA

This vignette is squarely an Indian-practice issue: HLA-B*15:02 carriage is appreciable across several South Asian groups, so ancestry-based pre-carbamazepine screening is directly relevant to prescribing here, not a Western-only footnote. Where testing is not readily available or affordable, the pragmatic and defensible move is to favour an alternative mood stabiliser or antiepileptic in a patient from a high-frequency background, and to document an explicit informed discussion of the SJS/TEN risk and the early warning signs.

15.3 Vignette 3: developmental delay, dysmorphism and later psychosis, recognising 22q11.2 and ordering the right assay

CLINICAL ANCHOR

Case: a young person carries a history of developmental delay and learning difficulty from childhood, with subtle dysmorphic features, a history of a congenital cardiac anomaly and recurrent infections, and a characteristically nasal quality to the speech. In late adolescence he now presents with a first episode of psychosis (ICD-11 6A20 schizophrenia; DSM-5-TR schizophrenia). The task is to recognise the pattern and act on it.

Reasoning. The constellation of developmental delay, dysmorphism, a conotruncal cardiac lesion, immune and palatal features, and a markedly elevated risk of psychosis is the signature of the **22q11.2 deletion syndrome** (velocardiofacial syndrome / DiGeorge syndrome), a microdeletion on the long arm of chromosome 22. It is the single best-characterised and highest-yield copy-number variant in psychiatric genetics: it is a large recurrent deletion that confers one of the strongest known monogenic-scale risks of schizophrenia, with a substantial minority of 22q11.2-deletion carriers developing a schizophrenia-spectrum psychosis, which is why the deletion has focused attention on genes in that region as predisposing to psychosis in general (New Oxford 2020; Shorter Oxford 2018). Unlike a single-nucleotide polymorphism, a CNV of this size behaves like a miniature chromosomal abnormality of high penetrance, so recognising the somatic phenotype behind the psychosis is what converts a routine first-episode presentation into a specific genetic diagnosis.

Testing and referral action. Order a genetic test that can detect a submicroscopic deletion: **chromosomal microarray (CMA)** is the first-line genome-wide assay for copy-number variants and is the appropriate broad test when the differential is open, while a *targeted* assay, fluorescence in-situ hybridisation (FISH) for the 22q11.2 locus (or MLPA), confirms the deletion quickly when 22q11.2 is specifically suspected on the phenotype. A standard karyotype will typically *miss* a microdeletion of this size and is the wrong test. Refer to **clinical genetics** for confirmation, cascade family testing and formal genetic counselling, because the deletion is often de novo but can be inherited, and coordinate the multisystem workup (cardiac, immune, endocrine including calcium). The psychiatric management of the psychosis itself follows standard first-episode lines and belongs to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not order a conventional karyotype expecting it to find 22q11.2: it resolves whole-chromosome and large structural changes, not a microdeletion of this scale, so a normal karyotype is falsely reassuring. The correct first-line for CNV detection across an undifferentiated developmental-delay-plus-dysmorphism-plus-psychosis picture is chromosomal microarray; FISH (or MLPA) is the fast targeted confirmatory step when the phenotype points specifically at 22q11.2.

15.4 Vignette 4: a three-generation pedigree plus a CYP2D6 poor-metaboliser report, reading the pattern and adjusting the drug

CLINICAL ANCHOR

Case: you are handed a three-generation pedigree of a family with recurrent depressive illness and a laboratory report on the index patient stating she is a **CYP2D6 poor metaboliser** (for example homozygous for a null allele such as CYP2D6*4). She has developed marked adverse effects on a standard dose of a CYP2D6-dependent antidepressant. Two separate questions are embedded: what does the pedigree tell you about study design, and what does the genotype tell you about her drug.

Reasoning, part one: reading the pedigree for a study design. A pedigree with illness appearing across successive generations but *not* segregating in clean Mendelian ratios, affecting both sexes, with variable expression and incomplete penetrance, is the familiar picture of a common, polygenic psychiatric disorder rather than a single-gene trait. The genetic-epidemiology tool matched to that pattern is *not* classical parametric linkage, which assumes a specified single-locus model and a known mode of inheritance and is powerful only for rare monogenic traits; it is the family-based and population approaches suited to complex inheritance: non-parametric linkage or affected-sib-pair methods, and above all association designs (genome-wide association studies) that detect the many small-effect common variants. The reading skill is to let the transmission pattern pick the design: male-to-male transmission excludes X-linkage, a clean vertical dominant or clustered recessive pattern would invite a Mendelian linkage approach, whereas this "familial but not Mendelian" pedigree signals a polygenic architecture and an association or non-parametric strategy (Kaplan & Sadock 2024; New Oxford 2020).

Reasoning, part two, and the dosing action. The **CYP2D6** report is a pharmacokinetic pharmacogenetic result about a hepatic drug-metabolising enzyme. A **poor metaboliser** (two non-functional alleles, activity score 0) clears CYP2D6-dependent drugs slowly, so at a standard dose plasma concentrations run high and dose-related adverse effects and toxicity follow, exactly her picture. The action the genotype forces is to *reduce the dose* of the CYP2D6-substrate antidepressant, or switch to an agent not dependent on CYP2D6, guided by the genotype and by therapeutic drug monitoring where available; the mirror-image caution is the *ultrarapid* metaboliser (gene duplication) who under-responds at standard doses because the drug is cleared too fast. This is the corner of pharmacogenetics closest to immediate clinical translation, with the important honesty that the evidence base for single-gene dose adjustment is stronger than that for combinatorial multi-gene "which drug" panels (Kaplan & Sadock 2024; Maudsley 2021).

PEARL

Keep the two halves of this vignette in separate drawers, because the exam fuses them to test whether you can. The *pedigree* answers a genetic-epidemiology question (which study design fits which inheritance pattern: linkage for Mendelian, association/GWAS for polygenic). The *CYP2D6 report* answers a pharmacology question (poor metaboliser means lower dose; ultrarapid means higher dose or switch). One family, two tools: one reads transmission to choose a design, the other reads an enzyme genotype to choose a dose.

15.5 The four vignettes at a glance: tool, discriminator, first move

The consolidating grid. Read the discriminator column first: in each stem it is the single feature that names the genetic tool and therefore writes the answer.

VIGNETTE	GENETIC TOOL	DISCRIMINATOR IN THE STEM	FIRST MOVE
1. Couple with one bipolar partner ask about a child's risk	Empirical recurrence risk (polygenic, non-Mendelian)	**Bipolar I in one parent, no Mendelian pattern; a probability is requested**	Counsel the empirical offspring risk (~10 to 15% for BD) non-directively; decision left to the couple
2. Carbamazepine in a Han-Chinese or South-Asian patient	Pharmacogenomic HLA screening (immunogenetic)	**At-risk ancestry plus a planned carbamazepine start; SJS/TEN risk**	Screen HLA-B*15:02 before the first dose; if positive, avoid carbamazepine (and phenytoin)
3. Developmental delay, dysmorphism, cardiac anomaly, later psychosis	Copy-number variant detection (cytogenetic)	**Multisystem developmental phenotype behind the psychosis, pointing at 22q11.2**	Chromosomal microarray (or targeted FISH/MLPA for 22q11.2); refer to clinical genetics
4. Three-generation pedigree plus CYP2D6 poor-metaboliser report	Pedigree analysis + pharmacokinetic pharmacogenetics	**Familial-but-not-Mendelian pattern; genotype-confirmed poor metaboliser with toxicity**	Choose association/GWAS for the polygenic pattern; reduce dose or switch off the CYP2D6 substrate

Four tools, four discriminators: an empirical recurrence risk, a pharmacogenomic HLA screen, a copy-number-variant assay, and a pedigree read alongside a CYP genotype. In every row the discriminator names the tool and the tool forces the first move.

HOLD THIS

Name the tool the moment the stem lands and the answer is already written. The discriminator in the stem (a probability requested, an at-risk ancestry, a dysmorphic phenotype, a metaboliser report) names the genetic tool, and the tool forces the first move.

GOOD TO REMEMBER

- **Bipolar disorder (ICD-11 6A60):** most heritable major psychiatric disorder, heritability ~0.85 (up to ~0.9 for narrow BP-I); MZ concordance conventionally ~60%; empirical offspring recurrence risk ~10 to 15% with one affected parent (verify), higher for any mood disorder and ~40 to 50% if both parents affected.
- **HLA-B*15:02:** risk allele for carbamazepine-induced Stevens-Johnson syndrome / toxic epidermal necrolysis; frequent in Han-Chinese, Thai and South/South-East Asian populations, rare in Europeans; screen before starting carbamazepine, avoid if positive; cross-risk with phenytoin and oxcarbazepine.
- **HLA-A*31:01:** linked to a broader carbamazepine hypersensitivity spectrum (DRESS, maculopapular rash) across other ancestries including Europeans.
- **22q11.2 deletion syndrome:** velocardiofacial / DiGeorge syndrome; recurrent microdeletion on chromosome 22q; one of the strongest CNV risks for schizophrenia (a substantial minority of carriers develop psychosis); developmental delay, dysmorphism, conotruncal cardiac lesion, immune and palatal features.
- **Detection assay:** chromosomal microarray (CMA) is first-line for genome-wide CNV detection; FISH or MLPA is the targeted confirmatory test for 22q11.2; a standard karyotype misses microdeletions of this size.
- **CYP2D6 poor metaboliser:** two non-functional alleles (activity score 0, e.g. CYP2D6*4 homozygote); high plasma levels and toxicity at standard dose of CYP2D6-dependent drugs, so reduce dose or switch; ultrarapid metaboliser (gene duplication) under-responds and needs a higher dose or a switch.
- **Counselling principle:** genetic counselling is non-directive, gives population-level empirical probabilities without implying determinism, and never names a diagnosis to a family in a stigmatising way.
- **Study-design rule:** classical (parametric) linkage suits rare Mendelian traits with a known model; association / genome-wide association studies (and non-parametric or affected-sib-pair linkage) suit the common, polygenic, non-Mendelian psychiatric disorders.

16 · Consolidate: mnemonic total, retrieval and synthesis

This closing block is not new material; it is a **consolidation device** for the whole of these notes. The material has run one long circuit through psychiatric genetics: the methods ladder from twins to biobanks, the inheritance models and the liability-threshold idea, the twin and adoption designs, parametric linkage and the LOD score, the GWAS and CNV and polygenic-risk era, the newer sequencing and gene-therapy approaches, epigenetics and imprinting, endophenotypes, the neurodevelopmental and pleiotropy picture that dissolves the Kraepelinian line, the heritability league table across disorders, the worked example of schizophrenia genetics, pharmacogenetics, and finally the counselling clinic where all of it becomes a recurrence-risk figure spoken to a family. **Study by producing, not by re-reading.** Durable learning comes from spaced *active recall* (self-testing from memory) rather than repeated passive review, the testing effect that Roediger and Karpicke (2006) demonstrated directly. The three subtopics below give you the loop to run it: one master mnemonic that chains the smaller mnemonics into a single spine, a set of answer-free retrieval prompts, and a one-page synthesis map to redraw from memory.

Use them in that order. Recite the mnemonic spine to confirm the scaffold is intact, close the notes and work the retrieval prompts aloud, then take a blank sheet and rebuild the whole-day

circuit from method through architecture to the disorders arrayed on it. Where a limb of the map will not come, that gap is the prediction error naming the exact topic to reopen, which is the entire point of the exercise.

HOLD THIS

One architecture of common and rare variation, differing in dose and neurodevelopmental timing, generates the whole spectrum. Recite the mnemonic spine, work the retrieval prompts aloud, then redraw the architecture plane from memory; the gaps name the topics to reopen.

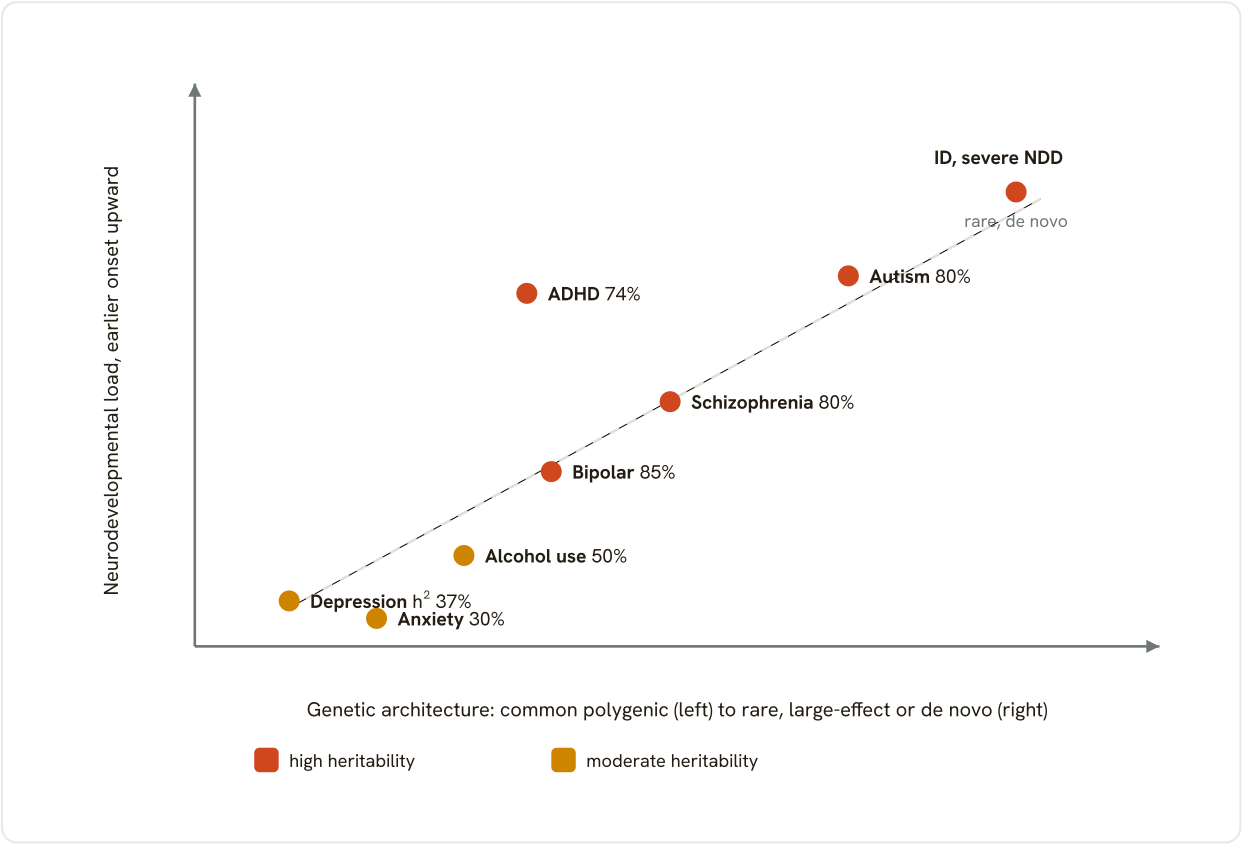


Fig 3.9 The whole subject on one map: major disorders placed by genetic architecture and neurodevelopmental load. Reading left to right, risk shifts from common-variant polygenic (depression, anxiety, much of bipolar and schizophrenia) toward an increasing contribution of rare, large-effect and de novo variants (autism and severe intellectual disability). Reading bottom to top, disorders carry more neurodevelopmental load and earlier onset. Colour marks heritability tier. Redraw this from memory as the synthesis of these notes: for any disorder, you should be able to place it and name the methods that would find its risk.

16.1 Master mnemonic total: chaining the whole subject into one spine

Every topic here already carries its own mnemonic. The problem at revision is not recalling any single one but retrieving the correct one under time pressure and in the right order. The device below is a *mnemonic of mnemonics*: a spine that indexes the methods ladder, the inheritance and threshold logic, the twin and adoption designs, the linkage-to-GWAS mapping tools, the polygenic and copy-number architecture, the newer approaches, epigenetics, endophenotypes, the pleiotropy story, the heritability league, the schizophrenia worked example, pharmacogenetics and counselling, so that recalling the spine pulls each sub-mnemonic up with it. Walk it in the order the material ran, from how we look, through what the architecture is, to what we do with it in clinic.

MNEMONIC

"TWINS LADDER Climb the Threshold, LOD Maps the GWAS-CNV-PRS Triangle, New Genomes Cut and Splice, Marks Above the Genes, Endophenotypes Bridge, Pleiotropy Breaks the Dichotomy, Rank the Heritable, SZ is the Case, CYP-HLA Dose, and Counsel the Family"

TWINS LADDER Climb the Threshold fixes the opening two limbs. The methods ladder runs "Family, Twin, Adoption, Linkage, Association, biobank" as a rising sequence of resolution, each rung answering a sharper question than the last, from is-it-familial to which-variant-and-in-whom. The inheritance limb runs "Mendel is Simple, Psychiatry is Multifactorial: Liability crosses a Threshold": single-gene Mendelian rules give clean segregation ratios, but the common disorders are polygenic and multifactorial, modelled as a normally distributed underlying liability with an abrupt threshold above which the phenotype appears (Falconer). Two threshold corollaries carry exam weight: the more-often-affected sex sits at the lower threshold, so relatives of an affected member of the rarer, higher-threshold sex carry the higher recurrence risk (the Carter effect); and rising recurrence risk with more affected relatives or a more severe proband is the signature of multifactorial, not Mendelian, transmission.

LOD Maps the GWAS-CNV-PRS Triangle chains the mapping and architecture core. Parametric linkage runs on "Three to prove, minus Two to exclude": a LOD (logarithm of odds) of plus 3 (odds of 1000 to 1) proves linkage and minus 2 (odds of 100 to 1 against) excludes it, with the recombination fraction theta running from 0 (never separated, inside the gene) to 0.5 (unlinked). Association then runs on the GWAS threshold "Five times ten to the minus eight" (correcting for about a million independent common variants), and the architecture resolves into a triangle: common SNPs of tiny effect (odds ratios about 1 to 1.2), rare CNVs of large effect (odds ratios about 20 to 100), and the polygenic risk score (PRS) that sums the common alleles into one liability index. The single most useful discriminator for the whole field: "Common is small and many; Rare is large and few", the inverse relationship between allele frequency and effect size.

New Genomes Cut and Splice encodes the novel-approaches limb. Sequencing runs on "Exome for the coding 2 percent, Genome for everything", with trio designs catching de novo mutations that carry large effect (prominent in autism). Therapy runs on "Cut, Splice or Replace": genome editing (CRISPR) cuts, antisense oligonucleotides (ASOs) modify splicing or lower transcript, and viral (AAV) vectors replace a gene, the three exemplified by the spinal muscular atrophy precedents (the SMN2-splice-modifying ASO nusinersen and the AAV SMN1 replacement) and the huntingtin-lowering ASO trials in psychiatry-adjacent neurology.

Marks Above the Genes is the epigenetics line, "Methylation Silences, Acetylation Opens; Imprinting is Parent-of-origin": DNA methylation (laid by the DNMT enzymes) generally silences, histone acetylation generally opens chromatin, and imprinting means expression depends on the parent of origin, the exemplar being the single 15q11-q13 locus that yields Prader-Willi from paternal loss and Angelman from maternal loss (of UBE3A). The gene-by-environment epigenetic mediator to remember is FKBP5, where a risk allele plus childhood trauma demethylates a regulatory element and yields glucocorticoid-receptor resistance (Klengel 2013).

Endophenotypes Bridge, Pleiotropy Breaks the Dichotomy chains two conceptual limbs. Endophenotypes run on the Gottesman and Gould (2003) criteria "Heritable, State-independent,

Co-segregates, seen in unaffected Relatives, and disease-Associated", the measurable intermediate markers (P50 gating, prepulse inhibition, mismatch negativity, antisaccade, smooth pursuit) meant to sit closer to the genes than the diagnosis. Pleiotropy then runs on "One variant, Many disorders": the high cross-disorder genetic correlations (schizophrenia to bipolar rg about 0.68, the highest pair) and shared loci such as CACNA1C and the 22q11.2 deletion collapse the categorical boundaries into a shared cross-disorder architecture, the genetic basis of the p-factor.

Rank the Heritable, SZ is the Case is the quantitative payload. The heritability league runs top to bottom on "Bipolar and Autism High, Schizophrenia and ADHD Next, Depression and Anxiety Low": bipolar about 0.85 and autism about 0.80 at the top, schizophrenia about 0.80 and ADHD about 0.75 next, major depression about 0.37 and the anxiety and stress disorders about 0.30 at the floor. Schizophrenia is then the worked case that ties it all together: high heritability but a polygenic architecture (108 loci in the 2014 PGC GWAS), the MHC / complement C4A signal driving excess synaptic pruning, DRD2 closing the genetics-to-pharmacology loop, and the 22q11.2 deletion as the single largest known genetic risk.

CYP-HLA Dose, and Counsel the Family closes on the two clinical limbs. Pharmacogenetics runs on "CYP for the Dose, HLA for the Danger": the CYP2D6 and CYP2C19 metaboliser phenotypes (poor to ultrarapid, captured as an activity score) set drug exposure and dose, while the HLA alleles flag life-threatening reactions, HLA-B*15:02 for carbamazepine-induced Stevens-Johnson syndrome (screen in Han-Chinese and South and South-East Asian ancestry) and HLA-A*31:01 across broader ancestries. Counselling then runs on "Empiric risk, Non-directive, Genetics-clinic referral for the syndromic and the predictive": most psychiatric counselling gives empiric recurrence figures non-directively, reserving formal clinical-genetics referral for syndromic CNVs (22q11.2, 3q29) and true presymptomatic testing (the Huntington disease model), with PRS explicitly not yet clinically actionable and less valid in non-European (including Indian) populations.

The table restates the spine so you can quiz yourself on any single link. Cover the right two columns and recall the sub-mnemonic and its content from the cue phrase alone.

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
Methods ladder	Family, Twin, Adoption, Linkage, Association, Biobank	**Rising resolution: is-it-familial to which-variant-in-whom; twins give heritability, adoption separates genes from rearing**
Inheritance / threshold	Mendel Simple, Psychiatry Multifactorial; Liability crosses a Threshold	Polygenic liability model; Carter effect (rarer-sex relatives higher risk); rising risk with load signals multifactorial
Linkage / LOD	Three to prove, minus Two to exclude; theta 0 to 0.5	**LOD +3 = 1000:1 for linkage, -2 = 100:1 against; recombination fraction; DISC1 from a translocation breakpoint**

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
GWAS / CNV / PRS	Five times ten to the minus eight; Common small, Rare large	Genome-wide significance; the frequency-effect-size triangle; PRS sums common alleles into one liability index
Novel approaches	Exome coding 2 percent, Genome everything; Cut, Splice, Replace	**WES vs WGS; de novo trios; CRISPR / ASO / AAV therapy, exemplified by the SMA and Huntington precedents**
Epigenetics	Methylation Silences, Acetylation Opens; Imprinting parent-of-origin	DNMTs and histone marks; 15q11-q13 gives Prader-Willi vs Angelman; FKBP5 gene-by-trauma mediator
Endophenotypes	Heritable, State-independent, Co-segregates, in Relatives, Associated	**Gottesman-Gould criteria; P50, prepulse inhibition, mismatch negativity, antisaccade, smooth pursuit**
Pleiotropy / cross-disorder	One variant, Many disorders	SCZ-BD rg about 0.68; CACNA1C and 22q11.2 shared; p-factor and the collapse of the Kraepelinian dichotomy
Heritability league	Bipolar and Autism High, SZ and ADHD Next, Depression and Anxiety Low	**BD about 0.85, ASD about 0.80, SCZ about 0.80, ADHD about 0.75, MDD about 0.37, anxiety about 0.30**
Schizophrenia case	High heritability, polygenic; C4A prunes, DRD2 loops, 22q11.2 biggest	108 PGC loci; complement-driven pruning; genetics-pharmacology loop; largest single CNV risk
Pharmacogenetics	CYP for the Dose, HLA for the Danger	**CYP2D6 / CYP2C19 metaboliser phenotype and activity score; HLA-B*15:02 and HLA-A*31:01 for carbamazepine reactions**
Counselling	Empiric risk, Non-directive, Genetics-clinic referral	Empiric recurrence figures given non-directively; syndromic-CNV and predictive-testing referral; PRS not yet actionable

The twelve-link master spine for this chapter, each row a cue phrase pointing to a topic mnemonic; recall the middle and right columns from the left cue alone.

16.2 Active-recall prompts: cover the page and answer aloud

These are retrieval questions, not a summary. They are deliberately answer-free, so that they force you to generate the answer from memory, which is where the testing effect does its work; printing a model answer here would defeat the device. This is the *retrieval practice* set for these notes: cover everything below the label, answer each aloud in a full sentence, then reopen the relevant topic only for the prompts you could not complete.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. State the six rungs of the genetic methods ladder in ascending order of resolution, and say precisely what question the twin design and the adoption design each answer that a family study cannot.
2. Define the liability-threshold model, explain the Carter effect in one sentence, and give the two features of a recurrence-risk pattern that point to multifactorial rather than Mendelian inheritance.
3. Write Falconer's formula for heritability from twin correlations and the ACE model, and explain the equal-environments assumption and why it is the design's load-bearing weakness.
4. Give the LOD score thresholds for proving and for excluding linkage with the odds each represents, and define the recombination fraction theta with its two limiting values.
5. State the GWAS genome-wide significance threshold and what it corrects for, then contrast the effect sizes of common SNPs against rare CNVs and state the general frequency-to-effect-size rule.
6. Explain what a polygenic risk score is, roughly how much schizophrenia liability it currently captures, and two reasons it is not yet used in clinical counselling.
7. Distinguish whole-exome from whole-genome sequencing, and explain why the trio design is the efficient way to detect the de novo mutations that matter in autism.
8. Name the three gene-therapy modalities (edit, splice-modify, replace) with one clinical exemplar each, and say which spinal muscular atrophy agent represents which modality.
9. Contrast the effects of DNA methylation and histone acetylation on transcription, then explain how a single imprinted 15q11-q13 locus produces two different syndromes.
10. State the five Gottesman and Gould criteria for an endophenotype, and name one candidate endophenotype together with the gene or receptor most associated with it.
11. Give the schizophrenia-to-bipolar genetic correlation and explain what such high cross-disorder correlations imply for the Kraepelinian dichotomy and the p-factor.
12. Rank bipolar disorder, autism, schizophrenia, ADHD, major depression and generalised anxiety by twin heritability from highest to lowest with an approximate figure for each.
13. For schizophrenia, name the most robust common-variant locus and its proposed synaptic mechanism, the locus that closes the genetics-pharmacology loop, and the single largest known genetic risk factor.
14. Distinguish the poor, intermediate, normal and ultrarapid metaboliser phenotypes, name the two CYP enzymes most relevant in psychiatry, and give one dosing consequence of each extreme.
15. Name the HLA allele that must be screened before carbamazepine and the ancestry group it is common in, and state what reaction it predicts.
16. Outline the principles of non-directive psychiatric genetic counselling, name two situations that warrant clinical-genetics referral, and state why polygenic risk scores are not yet part of counselling.

If more than a third of these will not come cleanly, do not push through the list a second time the same day; space the next attempt, because retrieval spaced across days is what builds durable

memory (Roediger and Karpicke 2006).

16.3 Synthesis map: the one page to redraw from memory

The final consolidation step is to build a single **synthesis map** and *redraw from memory* the whole of psychiatric genetics as one two-axis plane. Draw the **genetic-architecture plane**: the horizontal axis running from common-polygenic (many small-effect common variants) on the left to rare-large-effect (single CNVs and de novo mutations) on the right, and the vertical axis carrying neurodevelopmental load from low at the bottom to high at the top. Then place the major disorders onto it from memory: autism and intellectual disability high and toward the rare-large-effect right (de novo and CNV enriched, high neurodevelopmental load); schizophrenia high on neurodevelopmental load but sitting across the middle of the horizontal axis, with both a dense common-polygenic component (108 loci) and a rare tail (22q11.2, NRXN1); bipolar disorder mid-height, mostly common-polygenic and sharing much of its architecture with schizophrenia; ADHD toward the neurodevelopmental top but common-polygenic; and major depression and the anxiety and stress disorders low on both axes, common-polygenic with modest heritability. Annotate the plane with the frequency-to-effect-size gradient along the bottom (common small, rare large), the pleiotropy links drawn as arcs between the disorders that share loci (the schizophrenia-bipolar arc the thickest), and the clinical endpoints in the margin (PRS for the common-polygenic pole, clinical-genetics referral for the rare-large-effect pole, pharmacogenetic CYP and HLA testing as the treatment overlay). Redraw it once from memory, then check it against the figures above and fill only the gaps; the act of reconstructing the plane, not admiring a finished one, is what fixes the central claim, that a single architecture of common and rare variation, differing in dose and in neurodevelopmental timing, generates the whole spectrum of psychiatric disorder. The figure to rebuild is that two-axis plane, common-polygenic to rare-large-effect against neurodevelopmental load, with the disorders placed as points and the shared-locus pleiotropy drawn as connecting arcs. [FLAG concept_svg CF6]

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from the genetics territory.

LONG ESSAYS (25 MARKS)

- Describe the role of genetics, biological and psychological factors in the development of personality. MUHS 2018

SHORT NOTES (10 MARKS)

- Role of psychopharmacogenetics in psychiatry. MUHS 2013
- Gene mapping. MUHS 2012
- Neurogenetics. MUHS 2011

Genetics is a compact but recurring examiner favourite: pharmacogenetics, gene mapping and the broad "neurogenetics" note all appear, and genetics features inside integrative essays on personality and on individual disorders (schizophrenia genetics is the most examinable long answer). Prepare the methods well enough to define any one in three lines and to name the key findings.

Quick review

The whole picture in one table	
THE GENETICS TOOLKIT	An evidence hierarchy, each method one question: family (does it run in families?), twin (genes vs shared environment?), adoption (genes vs rearing?), linkage (roughly where?), GWAS (which common variants?), CNV and sequencing (rare large-effect variants?), polygenic risk score (aggregate burden?). Risk is mostly common-variant polygenic plus a minority of rare large-effect variants; much heritability is still missing; risk is read out through neurodevelopment.
MODES OF INHERITANCE	Mendelian (autosomal dominant, autosomal recessive, X-linked) vs non-Mendelian (mitochondrial, genomic imprinting, anticipation via trinucleotide repeats). Psychiatric disorders are polygenic and multifactorial. The multifactorial-threshold (liability) model: liability is normally distributed, disease appears above a threshold; relatives are shifted right, so recurrence exceeds prevalence. Sex-specific thresholds give the Carter effect.
TWIN, FAMILY AND ADOPTION STUDIES	MZ vs DZ concordance; heritability approximately 2 times (rMZ minus rDZ); the ACE model splits variance into additive genetic, common environment and unique environment; the equal-environments assumption is the main critique. Adoption designs (adoptee, adoptee's-family, cross-fostering; Heston 1966; the Danish studies). Quantitative methods: segregation analysis, path analysis, variance-components. Gene-environment interaction and correlation.
LINKAGE, LOD SCORE, GENE MAPPING	Linkage tracks co-segregation within families; markers ran RFLP to microsatellite to SNP. LOD (logarithm of the odds) of 3 or more is significant, minus 2 excludes; affected sib-pair is the model-free version. Positional cloning, genetic vs physical maps, fine-mapping. Linkage largely failed for polygenic psychiatric traits (Lander and Kruglyak thresholds), which drove the move to genome-wide association.
GWAS, CANDIDATE GENES, CNVS, PRS	Candidate-gene studies (COMT, 5-HTTLPR, DISC1) mostly did not replicate. GWAS: genome-wide significance 5 x 10 to the minus 8, the Psychiatric Genomics Consortium, sample size the key. Schizophrenia: the complement C4 / MHC signal (Sekar 2016), 108 then 287 loci (Trubetskoy 2022). CNV syndromes: 22q11.2 (largest single risk), 16p11.2, 1q21.1, NRXN1. Polygenic risk scores sum common variants but are not yet individually predictive. Missing heritability.
NOVEL APPROACHES AND GENE THERAPY	Whole-exome and whole-genome sequencing; rare-variant burden; de novo mutations (paternal-age effect, large in autism). SCHEMA named ten genes (SETD1A, GRIN2A, others; Singh 2022). Functional genomics (eQTL, TWAS), iPSC neurons and organoids, Mendelian randomization, biobanks. Gene therapy (antisense oligonucleotides, AAV,

The whole picture in one table	
	CRISPR) is real in monogenic neurological disease but not in polygenic psychiatric disorders.
EPIGENETICS	Stable change in expression without a sequence change: DNA methylation, histone modification, non-coding RNA. Genomic imprinting (Prader-Willi vs Angelman, 15q11-13). Early-life programming: FKBP5 demethylation with childhood trauma (Klengel 2013), Dutch-famine methylation (Heijmans 2008). Epigenetic clock (Horvath 2013) and accelerated ageing. Valproate is a histone-deacetylase inhibitor.
ENDOPHENOTYPES	Heritable intermediate traits closer to gene action. Gottesman and Gould (2003) criteria: associated with illness, heritable, state-independent, co-segregates in families, present in unaffected relatives. Examples: P50 sensory-gating deficit, prepulse inhibition deficit, smooth-pursuit and antisaccade abnormalities, mismatch negativity, working memory. They often proved no simpler genetically than the disorder (Flint and Munafo).
NEURODEVELOPMENTAL GENETICS AND PLEIOTROPY	Risk genes are enriched for synaptic, chromatin and FMRP-target functions and for early expression: risk acts through neurodevelopment. A continuum runs from intellectual disability through autism and ADHD to schizophrenia. De novo mutations and the paternal-age effect. Cross-disorder pleiotropy and the genetic p-factor: shared common-variant risk across disorders (Cross-Disorder PGC).
HERITABILITY ACROSS DISORDERS	Twin-based heritability (population variance ratio, not an individual statement, not immutable): schizophrenia about 80%, bipolar about 85%, autism about 80%, ADHD about 74%, major depression about 37%, generalised anxiety about 30%, alcohol use about 50%, OCD higher in child-onset. SNP-based heritability is lower than twin heritability (part of missing heritability).
SCHIZOPHRENIA GENETICS (FLAGSHIP)	Heritability about 80%; architecture is highly polygenic plus rare CNVs and de novo variants. GWAS and the C4 / synaptic-pruning story; 22q11.2 deletion the largest single risk; candidate-gene history (COMT, DISC1, NRG1, DTNBP1); endophenotypes (P50, PPI); gene-environment interaction (cannabis, urbanicity, migration, obstetric complications, paternal age); neurodevelopmental model; polygenic risk scores; genetic overlap with bipolar.
PHARMACOGENETICS AND PHARMACOGENOMICS	Pharmacogenetics is single-gene, pharmacogenomics is genome-wide drug response. CYP2D6 and CYP2C19 metaboliser phenotypes (poor, intermediate, normal, ultrarapid): CYP2D6 for risperidone, aripiprazole, tricyclics; CYP2C19 for escitalopram, clozapine. Immune-mediated: HLA-B*15:02 and carbamazepine Stevens-Johnson syndrome (screen first; frequent in South-East Asian and some Indian groups), HLA-A*31:01. Guidelines: CPIC, DPWG.

The whole picture in one table	
DISCRIMINATE: DESIGN AND PEDIGREE	Match the question to the design: familial? family study; genes vs shared environment? twin; genes vs rearing? adoption; roughly where? linkage; which common variants? GWAS; a rare cause in this patient? chromosomal microarray or sequencing; predict aggregate risk? polygenic score; drug response? pharmacogenetic test. Read a pedigree (squares male, circles female, filled affected, arrow proband). Pitfalls: assortative mating, phenocopy, incomplete penetrance, genetic heterogeneity.
GENETIC COUNSELLING	Non-directive; use empirical recurrence risks, not Mendelian ratios: offspring of one parent with schizophrenia about 10 to 13%, both parents about 40 to 46%, sibling about 9%; bipolar offspring about 10 to 15%. Refer to clinical genetics for dysmorphism, intellectual disability or a suspected CNV. Predictive and prenatal testing carry ethical weight; polygenic scores are not yet clinical. India: consanguinity, disclosure pressure, stigma.
APPLIED VIGNETTES	Counsel a couple (one parent with bipolar) with the empirical offspring risk, non-directively. Screen HLA-B*15:02 before carbamazepine in a patient of South or East Asian ancestry. A child with developmental delay, dysmorphism and later psychosis: order chromosomal microarray, consider 22q11.2, refer. Read a pedigree plus a CYP2D6 poor-metaboliser report and adjust.
CONSOLIDATE	The master mnemonic chains it all together. The retrieval prompts are answer-free (cover and recall). The synthesis map places each disorder on the genetic-architecture plane: common-polygenic to rare-large-effect on one axis, neurodevelopmental load on the other. For any disorder you should be able to place it and name the methods that would find its risk.

References

These notes are grounded in the standard texts (the source hierarchy below); landmark, contested and numeric claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and citations whose identifier did not resolve to the cited paper were corrected or dropped.

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