Introduction to Psychiatric Genetics

Timothy Dellenbaugh, M.D.

UMKC Department of Psychiatry

Residency Director
UMKC School of Medicine
Associate Dean representing Center for Behavioral Medicine
Associate Professor of Psychiatry
University of Missouri-Kansas City
Center for Behavioral Medicine
Assistant Medical Director

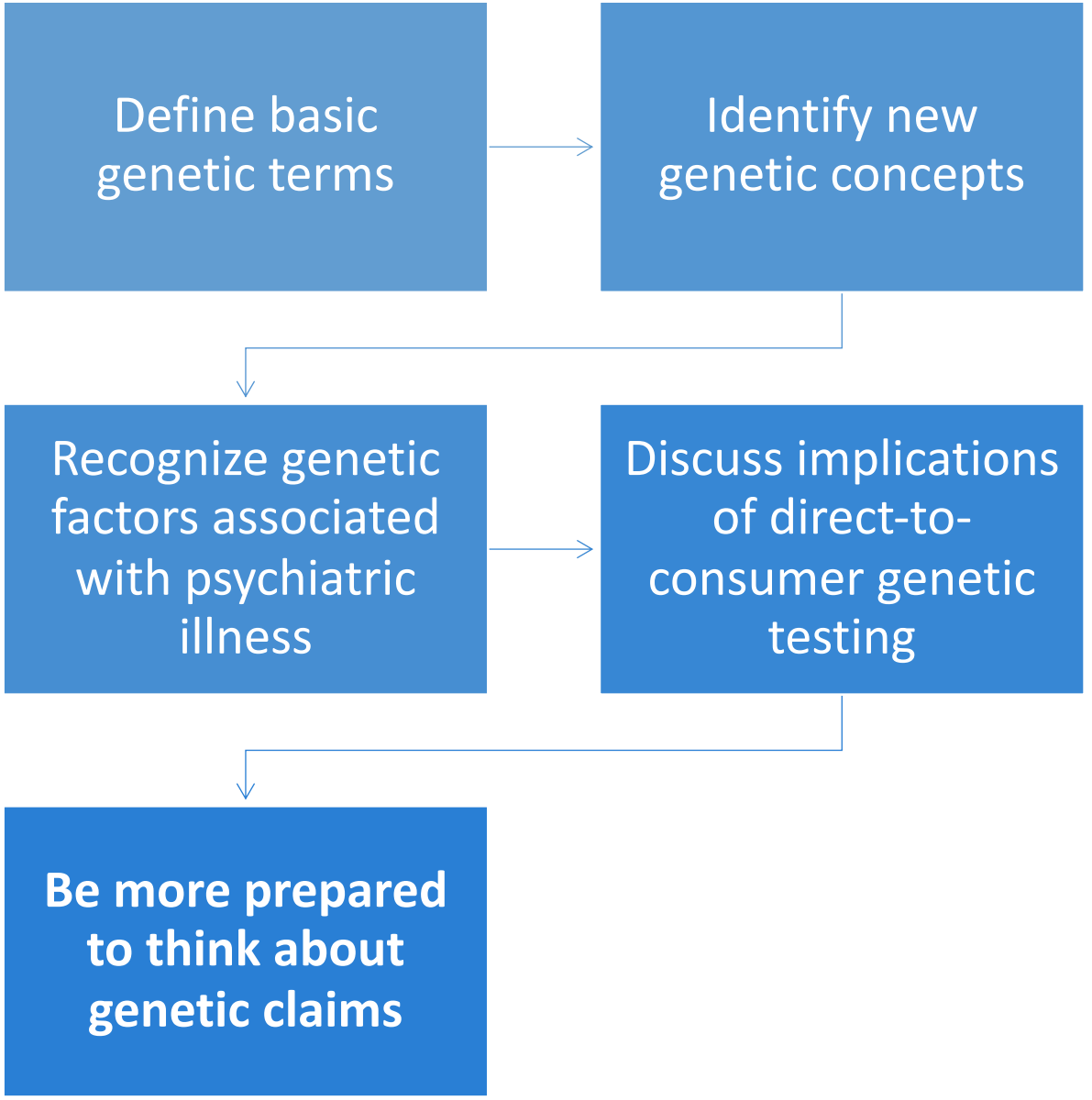
Disclosures:

No financial Disclosures

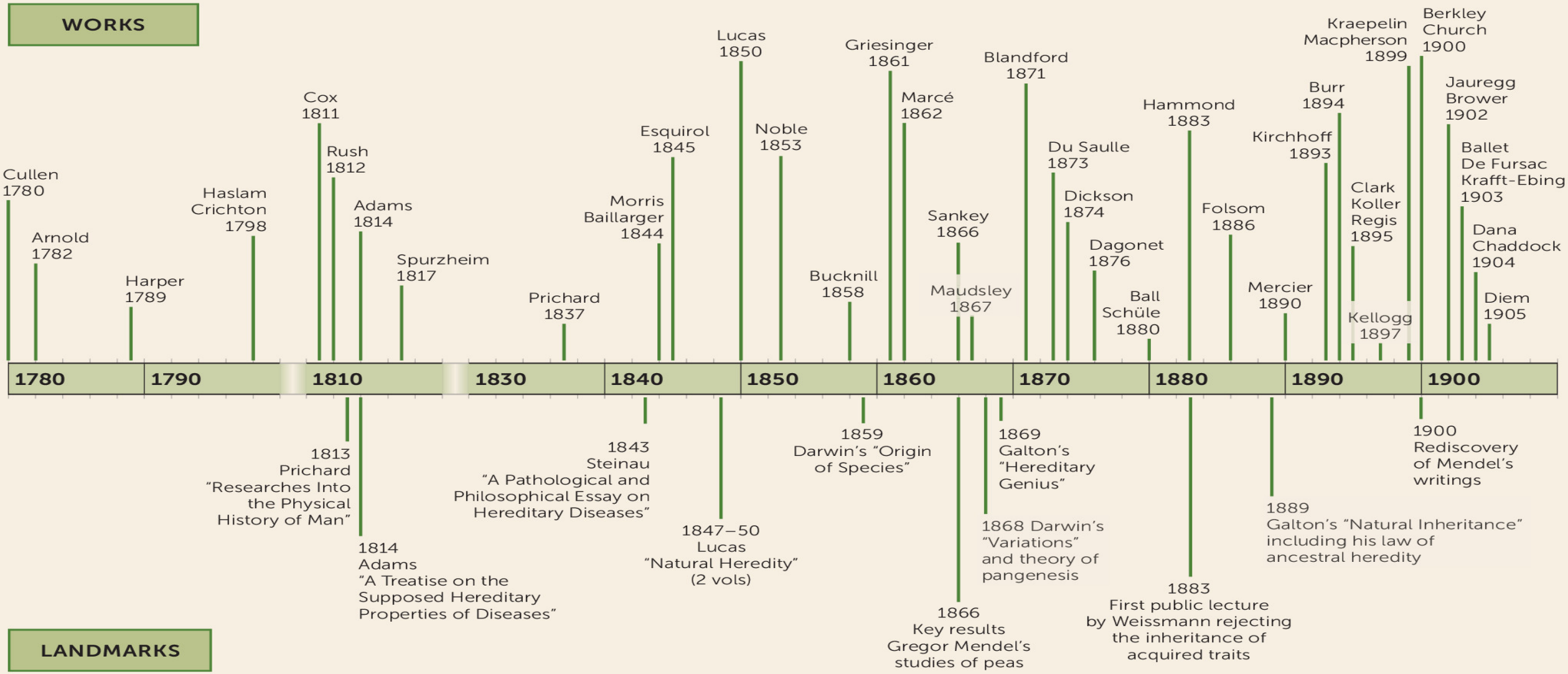
I am no expert, just curious

Learning Objectives

At the conclusion of this activity the participant will be able to:



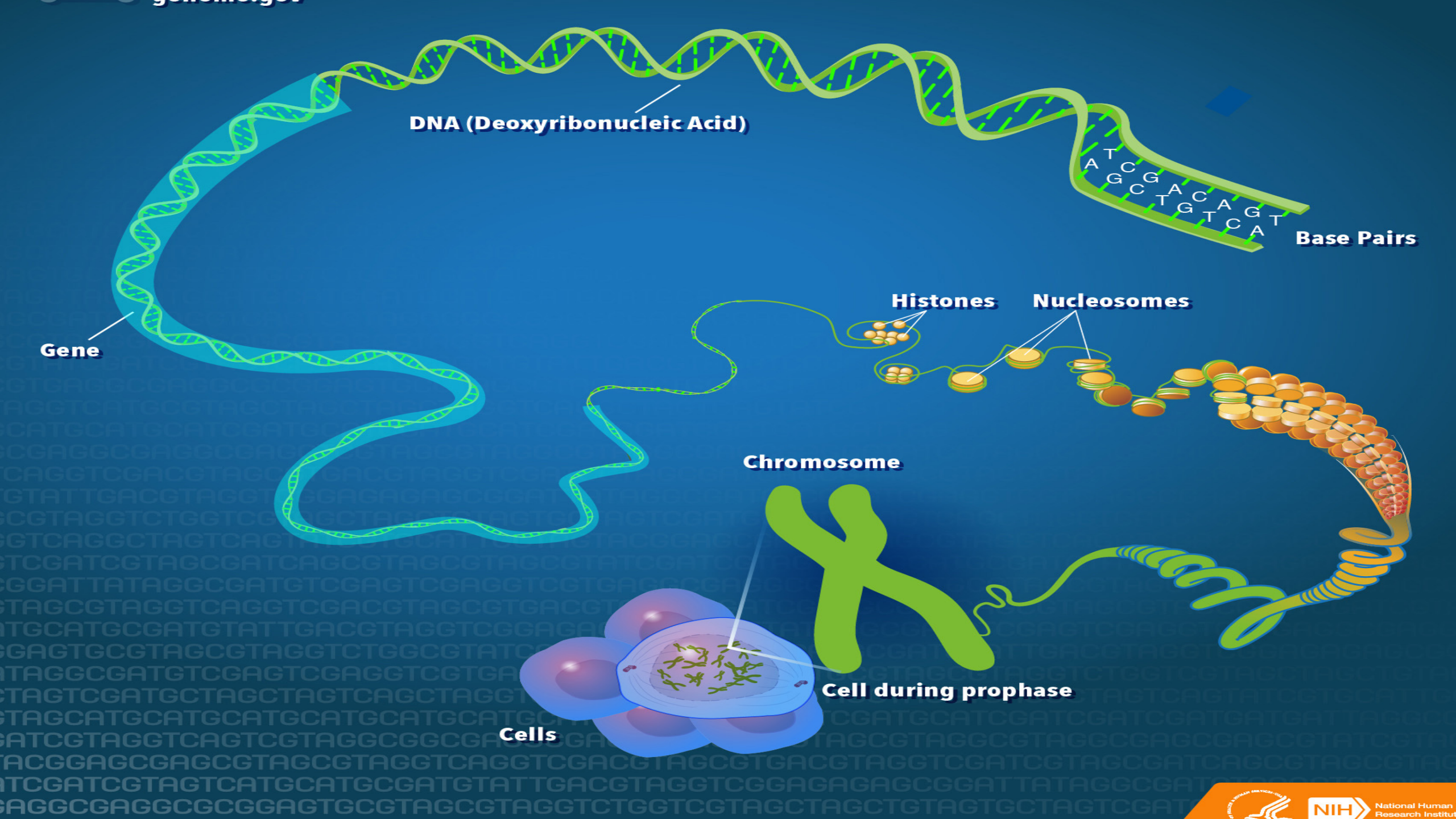
The Prehistory of Psychiatric Genetics: 1780-1910



(Kendler 2020)

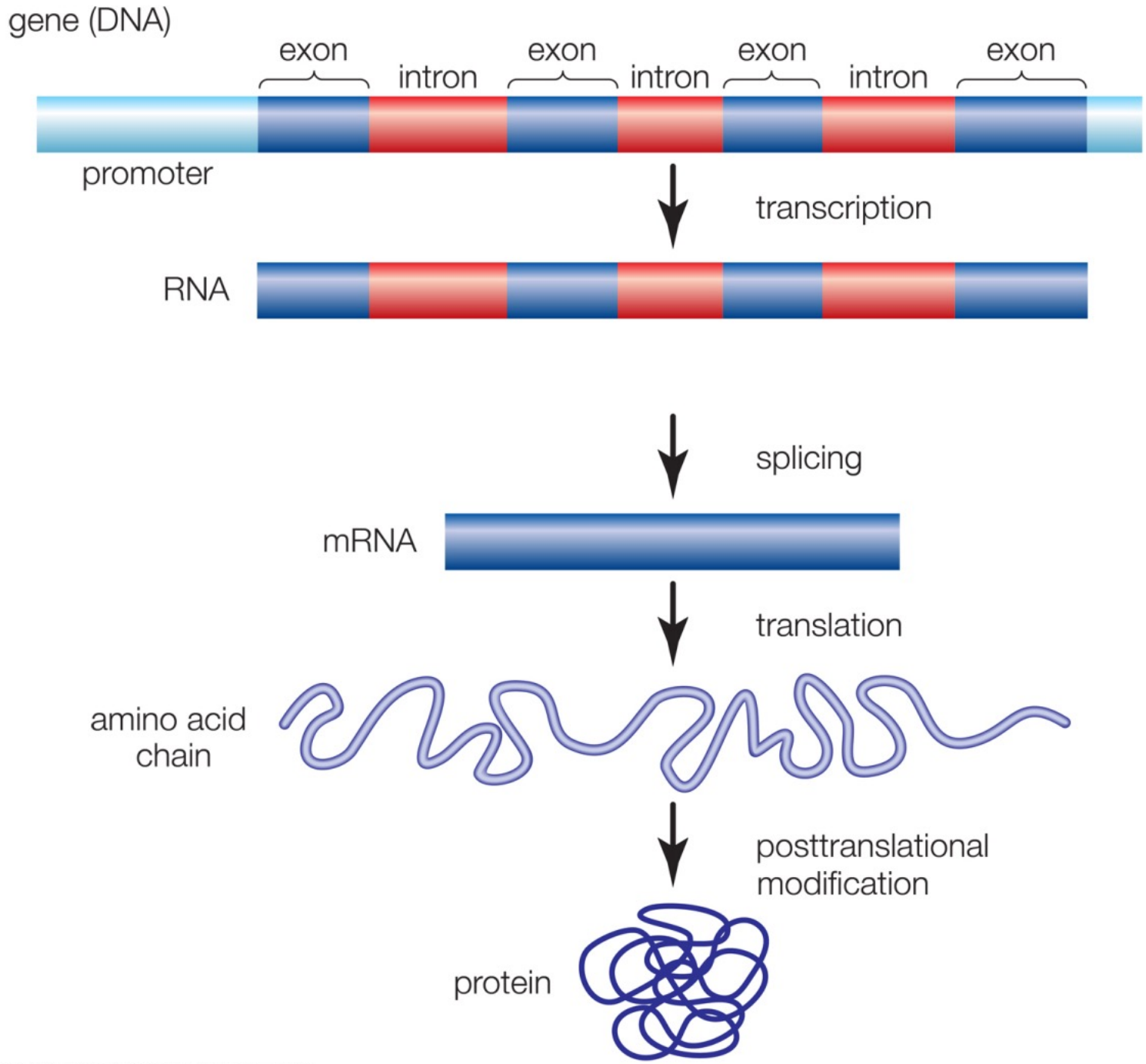
Genes influence:

- metabolism of medications
- risk of developing illness
- response to treatment
- side effects


DNA (Deoxyribonucleic Acid)
Base Pairs
Gene
Histones
Nucleosomes
Chromosome
Cell during prophase
Cells

Protein synthesis

https://www.britannica.com/science/gene

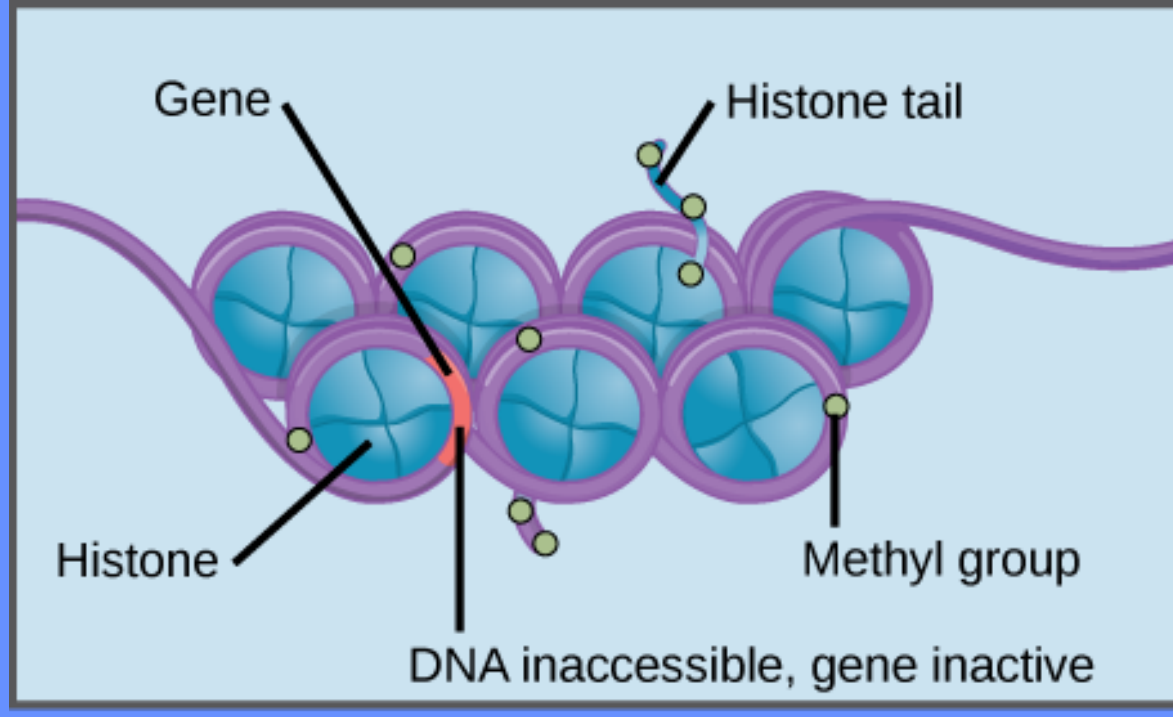


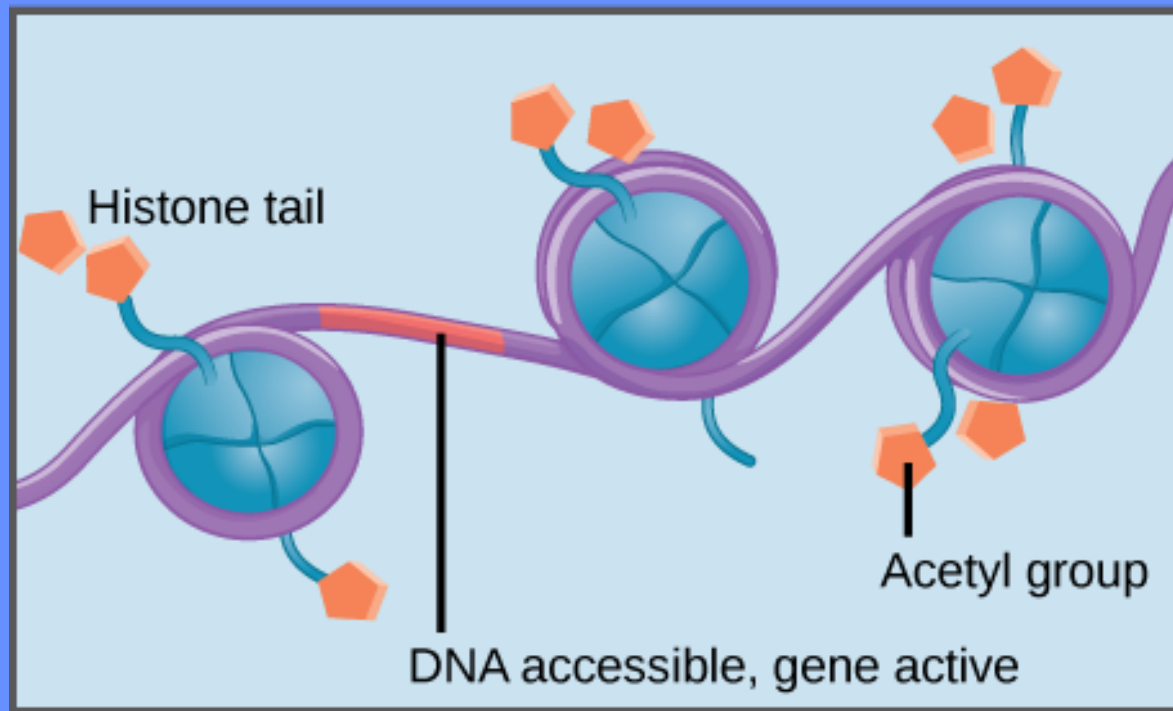
Epigenetics

- Regulating genes without changing DNA sequence

- DNA methylation
  - Mutes gene
- Histone acetylation
  - Gene accessible

https://commonfund.nih.gov/sites/default/files/epigeneticmechanisms.pdf

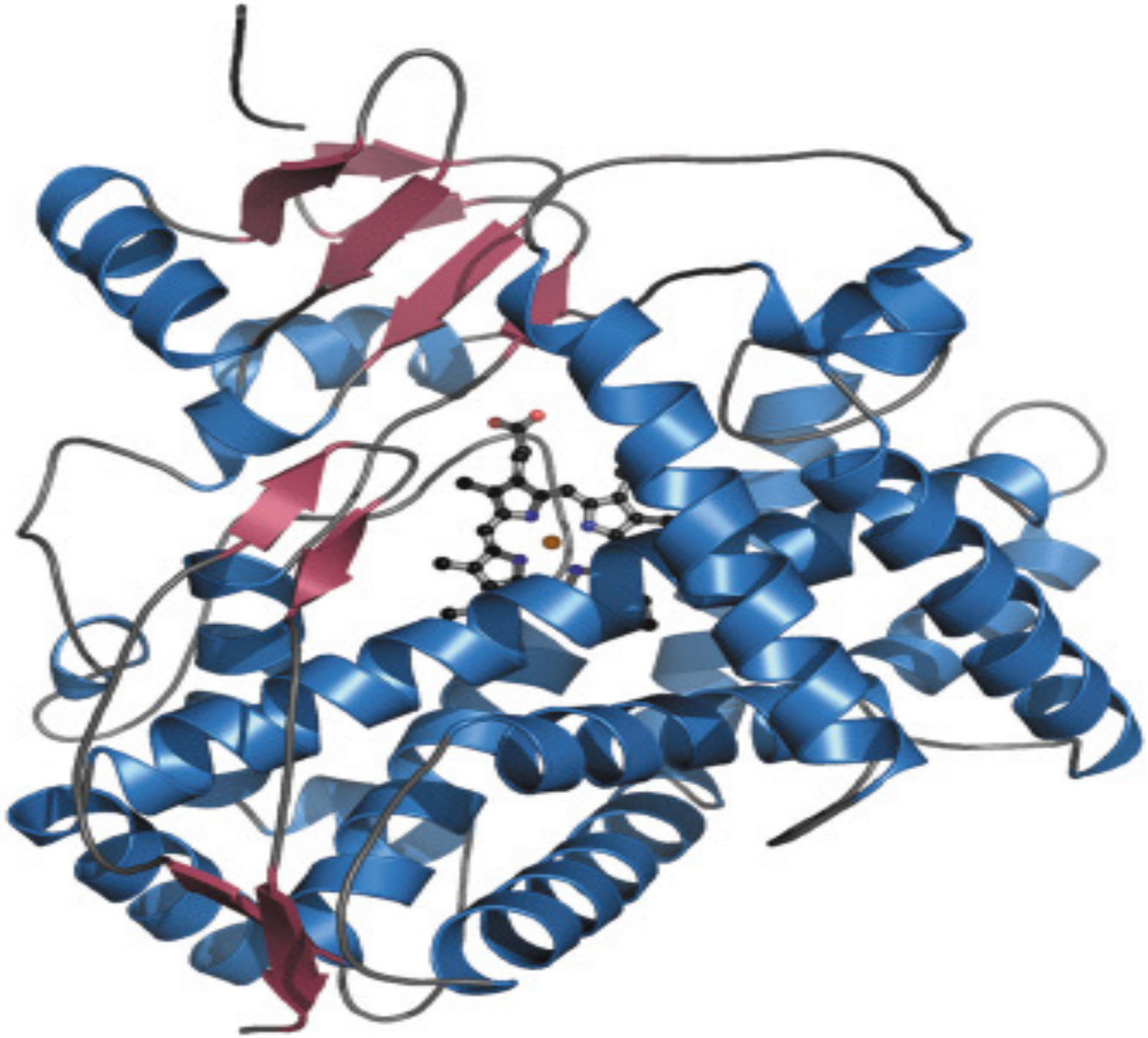




Cytochrome P450 2D6

~500 Amino acids

Heme group



(Rowland et al., 2006)

What is a Cytochrome?

What does it do?

- Transfer electrons
- Make molecules more polar and easier to excrete
- Why named P450?

Who has them?

- Mammals?
- All animals?
- Plants?
- Fungi?
- Bacteria?
- Viruses?

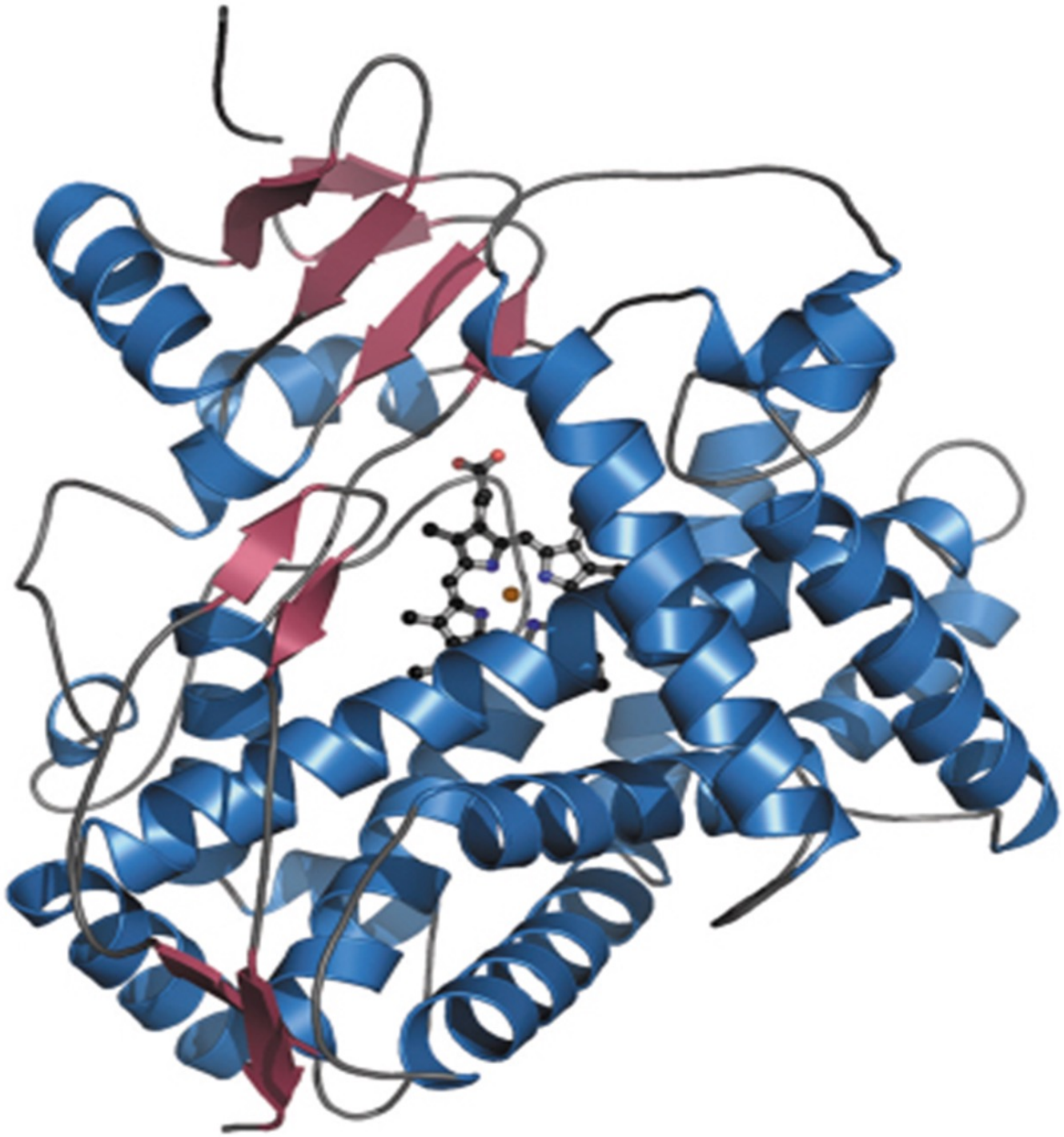
(Werck-Reichhart & Feyereisen, 2000)

(Ingelman-Sundberg, 2005)

CYP2D6

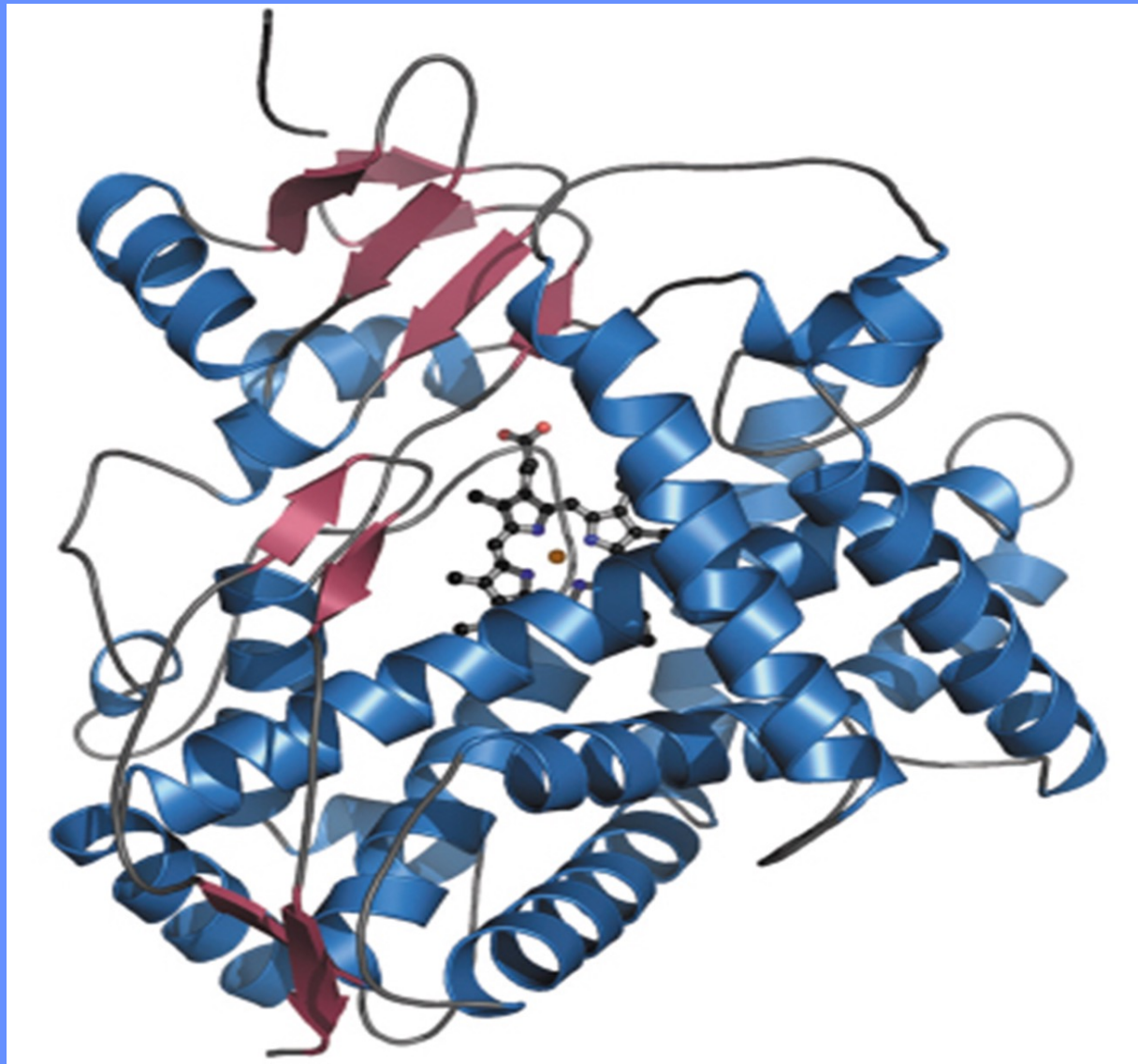
- Duplication
- Deletion
- Frame shift
- Splice defect
- Codon
  - SNP

(Taylor et al., 2020)



Single Nucleotide Polymorphism

- Nonfunctional enzyme
- Decreased function enzyme
- Equivalent function enzyme
- Increased function enzyme
- Promoter change



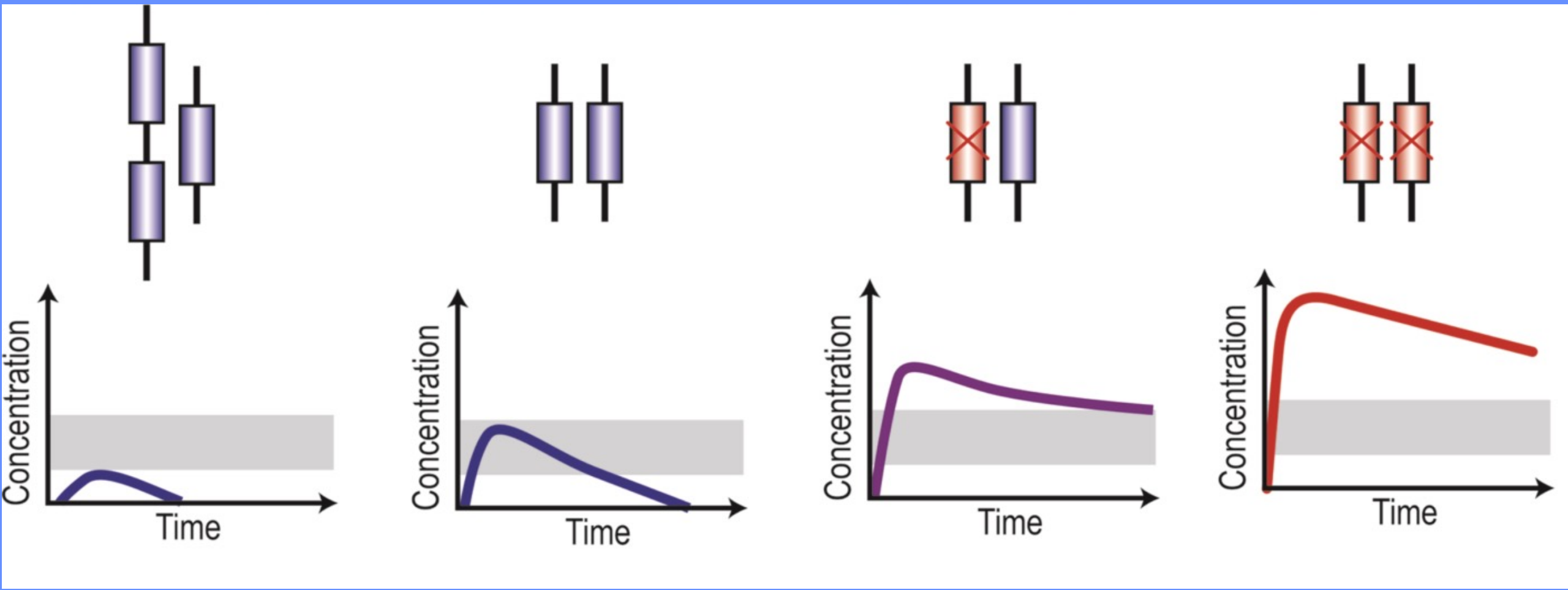
(Taylor et al., 2020)

How many genetic variants of cytochrome 2D6 have been identified in humans?

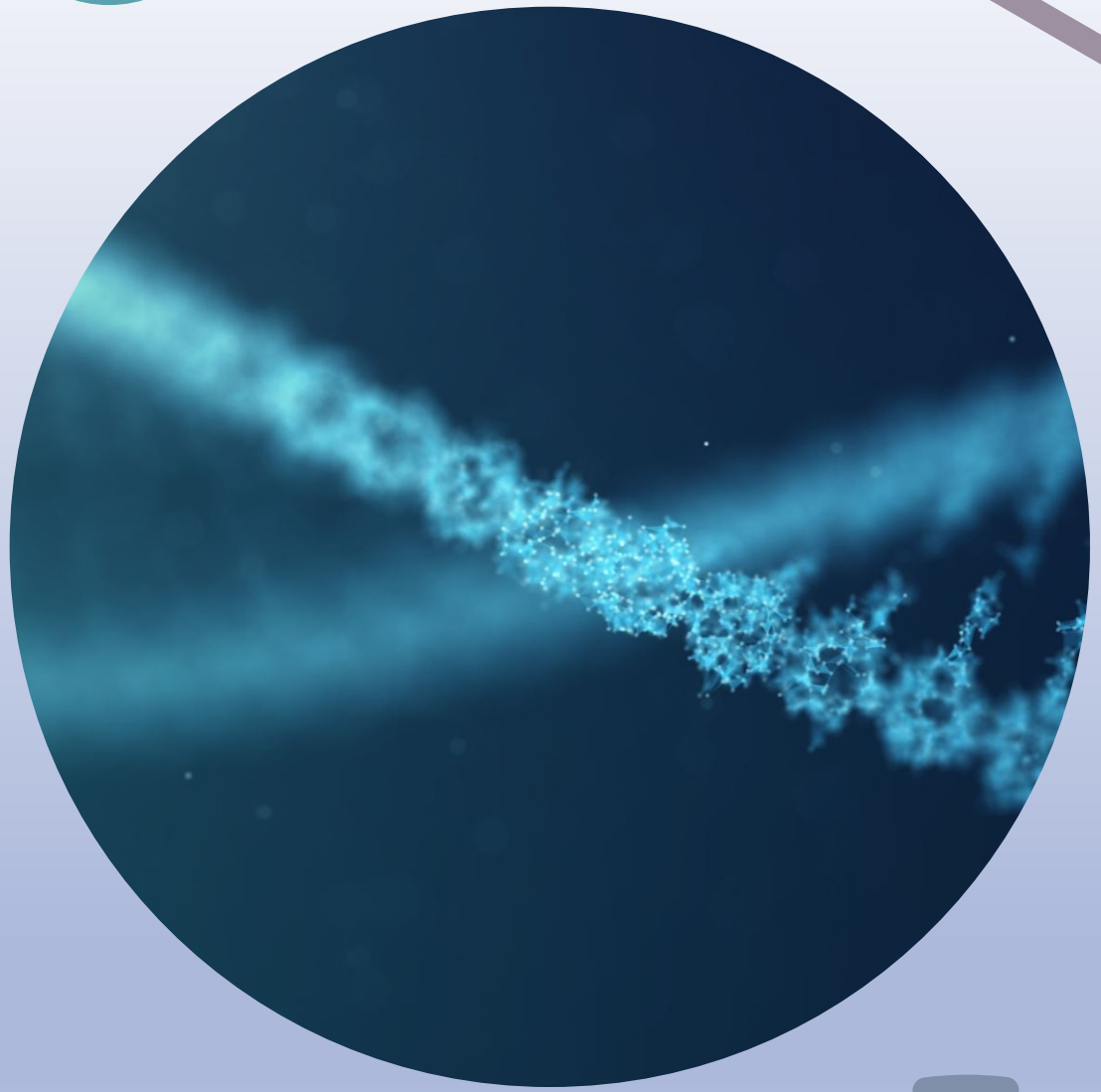
A. 10-25
B. 25-50
C. 50-100
D. >100

(Taylor et al., 2020)

Rapid Extensive Intermediate Poor



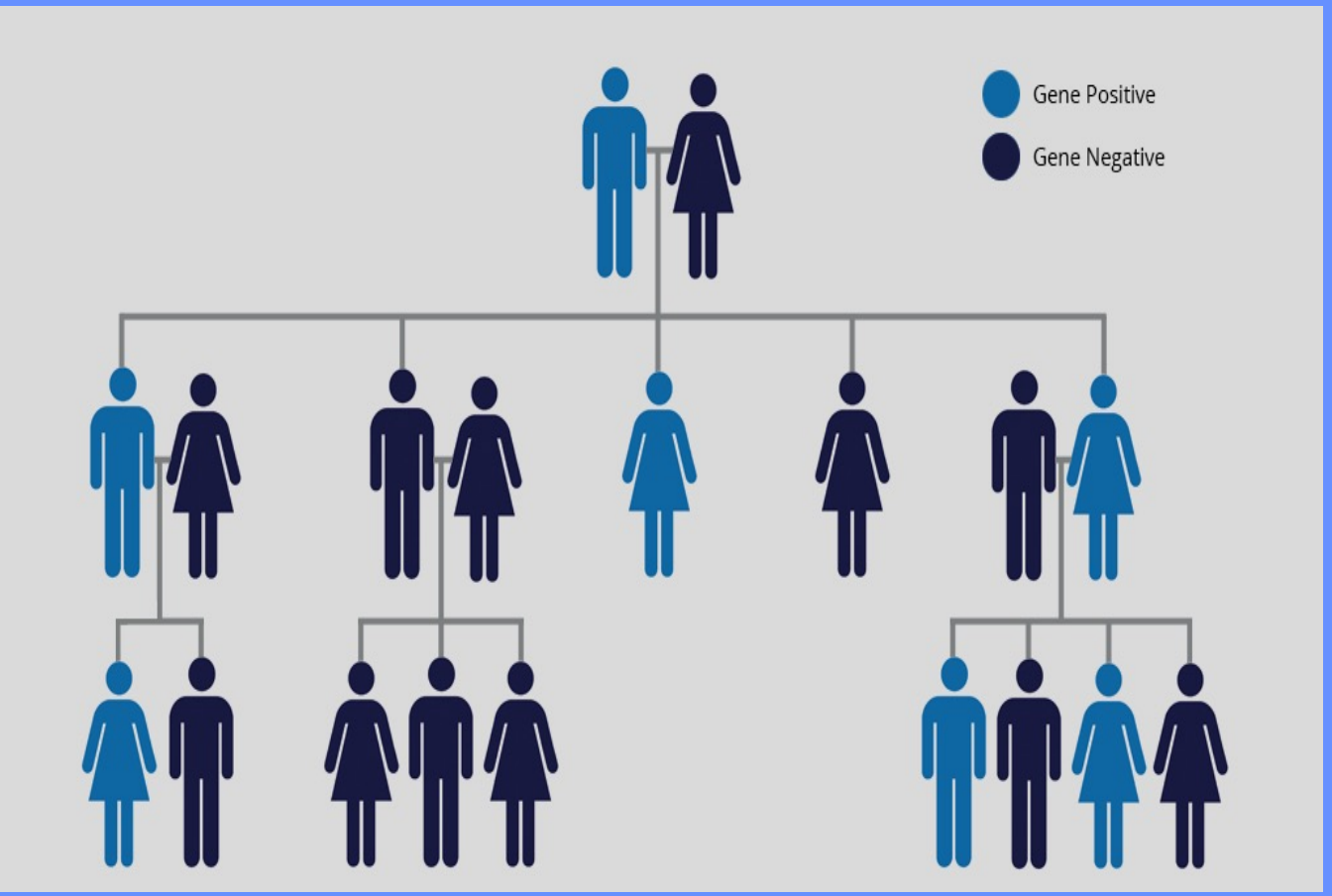
(Nagele & Liggett, 2011)



Genes and diagnoses

Simple and Complicated

Risk of developing Huntington's Disease



- **Autosomal Dominant**
- HTT gene codes for huntingtin protein
- CAG codon = Glutamine
  - Gets repeated excessively

(*https://hdsa.org/what-is-hd/history-and-genetics-of-huntingtons-disease/who-is-at-risk*)

Genome wide association study (GWAS)

(Demontis et al., 2019)

calculate

$$Z_{j,meta} = \frac{\sqrt{\tilde{N}_{1j}} Z_{1j} + \sqrt{\tilde{N}_{2j}} \tilde{Z}_{2j}}{\sqrt{\tilde{N}_{1j} + \tilde{N}_{2j}}}$$

where

$$\tilde{Z}_{2j} = sign\left(r_g\right) \frac{Z_{2j}}{\sqrt{1 + \left(1 - r_g^2\right) N_{2j} h_2^2 l_j / M}}$$

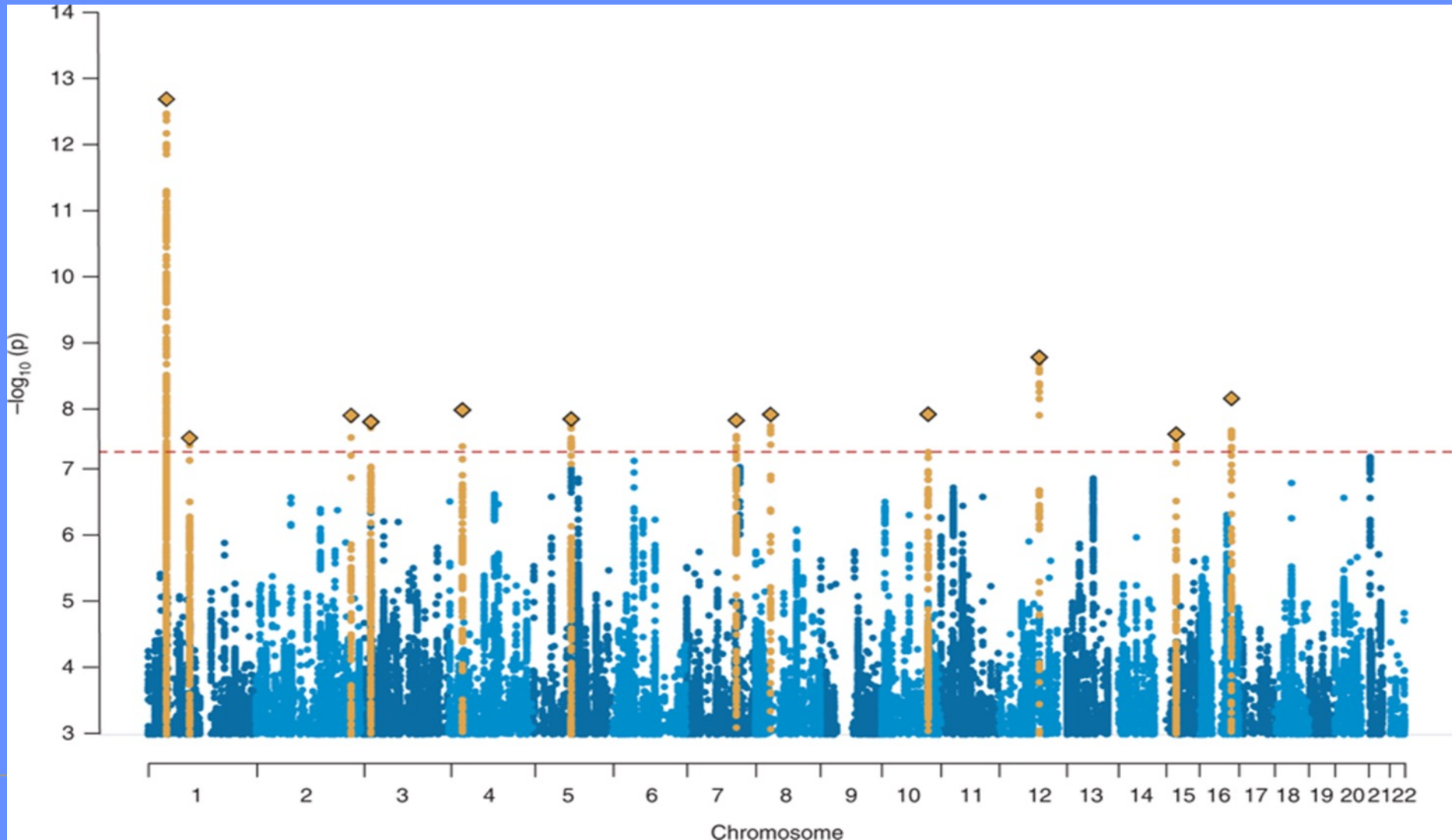
$$\tilde{N}_{1j} = N_{1j} \frac{P\left(1-P\right) \phi\left(\Phi^{-1}\left[K\right]\right)^2}{\left[K\left(1-K\right)\right]^2}$$

$$\tilde{N}_{2j} = N_{2j} \frac{r_g^2 h_2^2 / h_1^2}{1 + \left(1 - r_g^2\right) N_{2j} h_2^2 l_j / M}$$

Genome wide association study- ADHD

20K subjects
35K controls

12 loci found



(Demontis et al., 2019)

Genome wide association study- ADHD

- Heritability 70-80%

Genetic overlap with:

- Antisocial personality
- Cognitive impairment
- Autism spectrum disorder
- Schizophrenia
- Bipolar disorder
- Major depressive disorder

(Demontis et al., 2019)

Genes and treatment response in ADHD

Methylphenidate

- 36 studies (3647 children)
- 9 genes reviewed
  - 6 positive
  - 3 no effect

(Myer et al., 2018)

Atomoxetine

- Really likes 2D6
- Does not like any other cytochromes
- **10x** higher exposure in "poor metabolizers"

(Brown et al., 2019)

Polygenic risk scores

- **PRS=** Summary of a person's total genetic risk for that disorder
- How many risk variants are present x How strong is each one

(Lussier et al., 2020)

Genetics and Epigenetics of Suicide

GWAS of Suicide Attempt in major depressive disorder, bipolar disorder, and schizophrenia

	major depression	bipolar disorder	schizophrenia
10 SNPs for suicide attempt in mood disorders			**NO**
loci for suicide attempt	**Yes**	**Yes**	**NO**
Depression PRS associated with risk of suicide attempt	**Yes**	**Yes**	**Yes**
Counterpoints	**not replicated in other cohorts**		

(Allen and Dwivedi 2020)

Review of 52 studies of suicide epigenetics

- DNA methylation
- histone modifications
- microRNA (miRNA)

- **complex interplay of environmental risk factors with genetic risk factors**
- Hard to distinguish suicide specific effects from adverse childhood experiences and psych diagnosis

(Cheung et al., 2020)

MicroRNA may mediate Early Life Stress (ELS) vulnerability to depression and suicidal behavior

- MiRNAs influence:
  - gene expression
  - messenger RNA (mRNA)
    - altering protein production
  - individual miRNAs can have hundreds of targets
  - neuronal development and brain physiology
  - HPA axis

- **ELS may induce changes in miRNA function**

(Allen & Dwivedi, 2020)

What is the estimated genetic contribution to risk of developing autism?

A. <25%
B. 25-50%
C. 50-75%
D. >75%

Genetics of Autism

Etiology of Autism Spectrum Disorders and Autistic Traits Over Time

	Swedish Twin Registry (STR)	Child and Adolescent Twin Study in Sweden (CATSS)
Twin pairs	23K	15K
Participants born	1982-2008	1992-2008
Data	Dx from National Patient Register	Screening with a structured, parental telephone interview
Heritability	.88-.97	.75-93

- Highly Heritable
- **Contribution of environmental factors remained relative constant**

(Taylor et al., 2020)

All major psychiatric disorders have a heritable component

- **Heritability 20% to 45%**
- anxiety disorders
- obsessive-compulsive disorder
- posttraumatic stress disorder
- major depressive disorder

- **Heritability 50% to 60%**
- alcohol dependence
- anorexia nervosa

- **Heritability >75%**
- autism spectrum disorder (ASD)
- attention deficit hyperactivity disorder (ADHD)
- schizophrenia
- bipolar disorder

(Smoller, 2019)

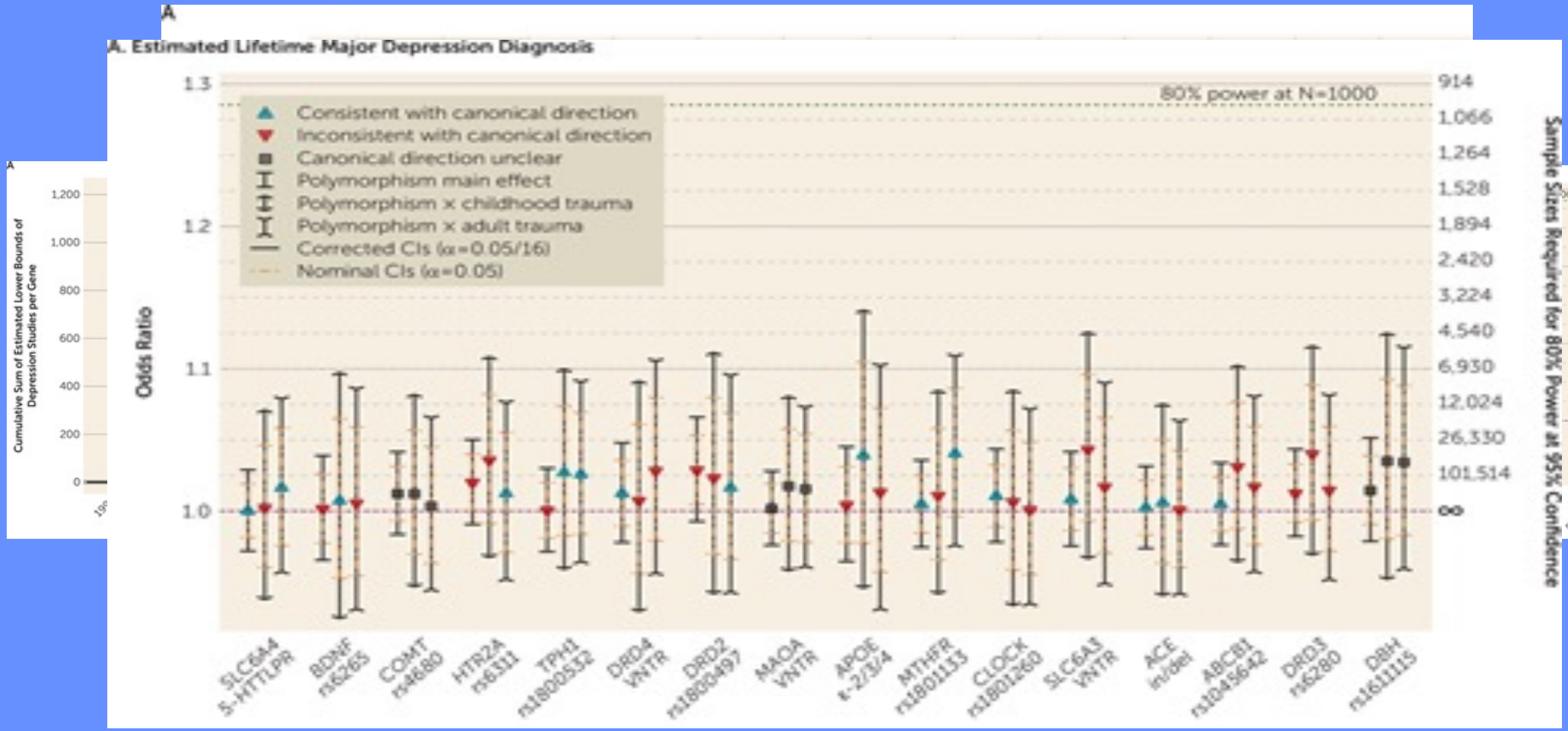
Depression Genetics

Development And Treatment

Which Gene shows a consistent association with risk of Depression?

A. Serotonin reuptake pump
B. Serotonin receptors
C. Brain Derived Neurotrophic Factor
D. None of the above

Genetics of Depression Risk



(Border et al., 2019)

Genetics of Depression Risk

- **No evidence** was found for:
  - any candidate gene
  - any gene-by-environment effects
- Early hypotheses about depression candidate genes were incorrect

(Border et al., 2019)

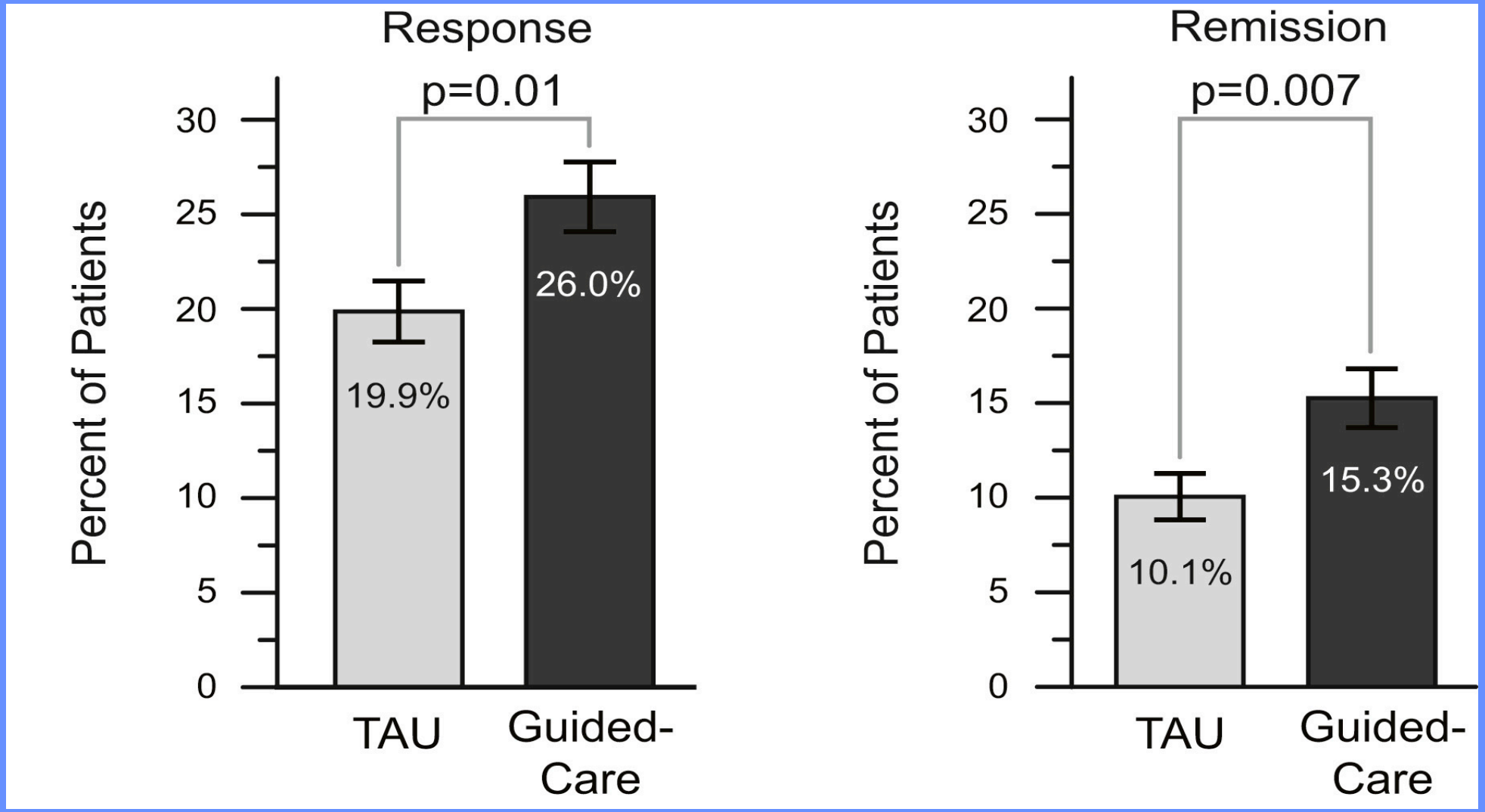
Letter to Editor and Author's response

- They mismeasured environments, so they are wrong
  - Vrshek-Schallhorn et al.

- We did not mismeasure environments and even if we did it would not change the results
  - Border et al

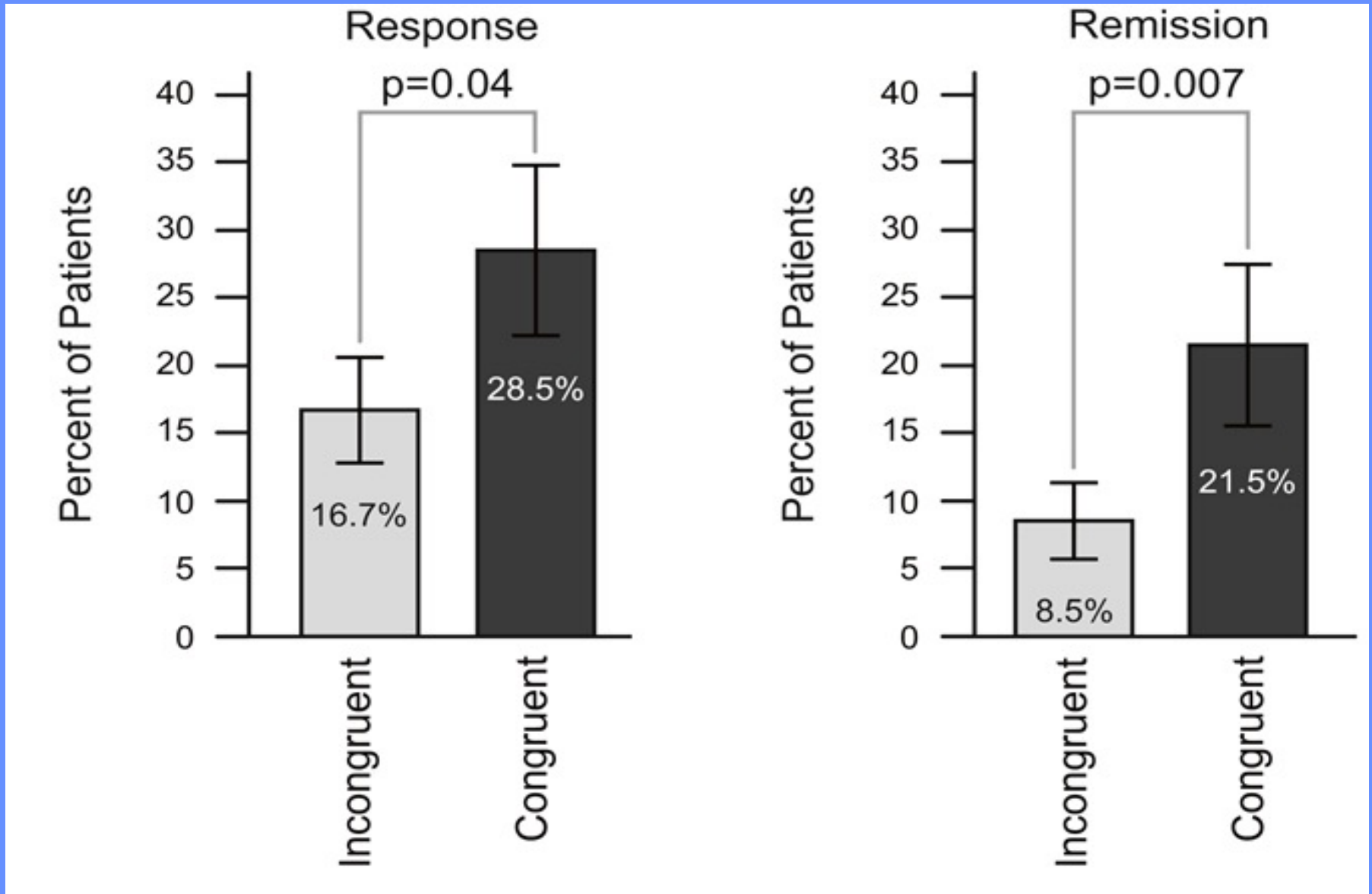
(Vrshek-Schallhorn et al., 2019)
(Border et al., 2019)

Genetic-Guided Depression Treatment



(Greden et al., 2019)

Genetic-Guided Depression Treatment



Pharmacogenomic test-guided treatment versus treatment as usual for major depressive disorder

No better when providers were **unconstrained** by the results

Was better when treatment was concordant with assay results

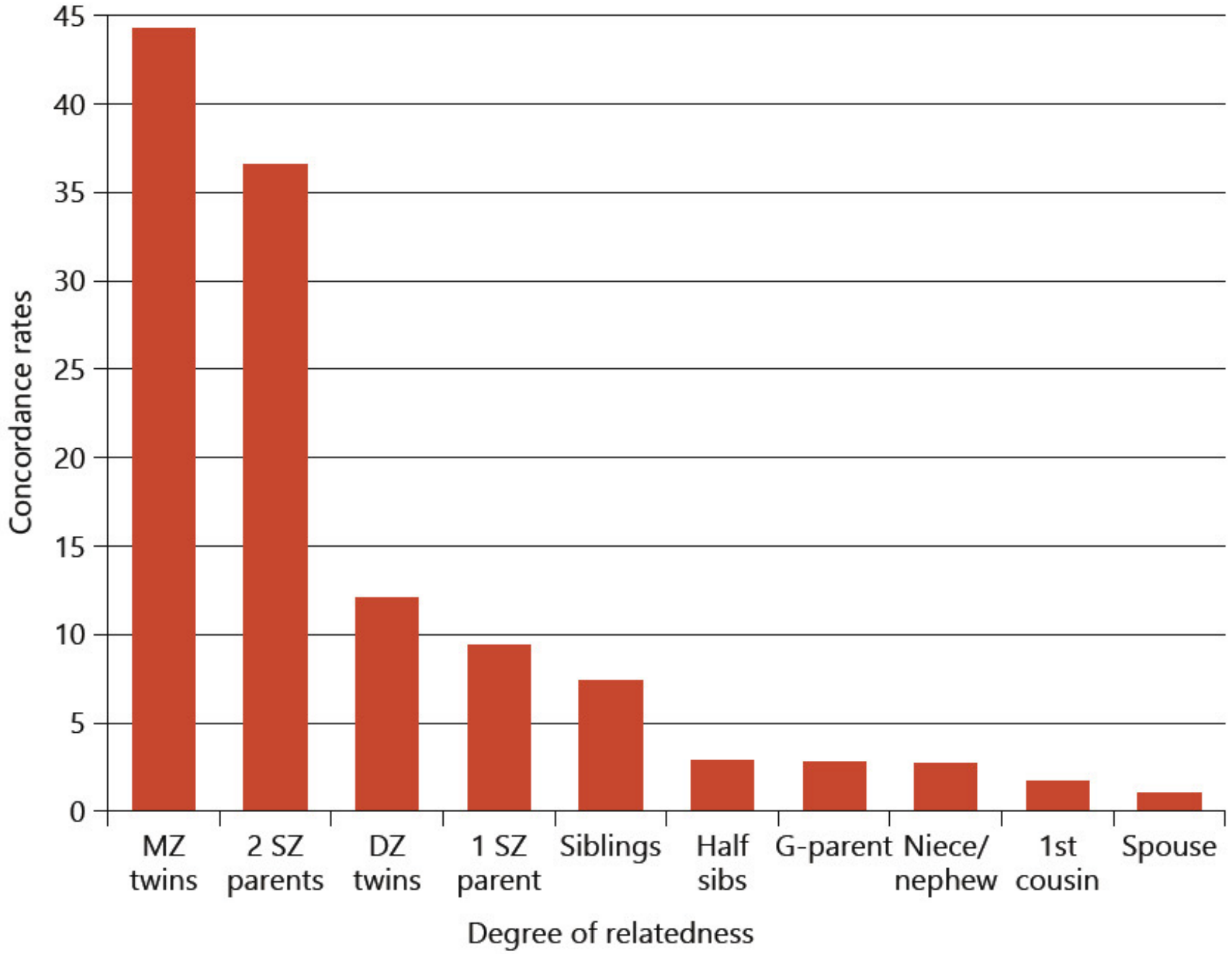
(Perlis et al., 2020)

Gene variants and antidepressant response

- 16 studies-2257 patients with MDD. Seven Asian. Nine Caucasian.
- 8 SNPs were analyzed:
  - 5-HTTLPR
  - 5HTR2A (rs6311, rs6314, rs7997012 and rs6313)
  - 5HTR1A (rs6295)
  - BDNF (rs6265)
  - 5HTTSTin2
- **None** associated with antidepressant response

(Du et al., 2020)

Schizophrenia Concordance



(Avramopoulos, 2018)

Genetics of Schizophrenia

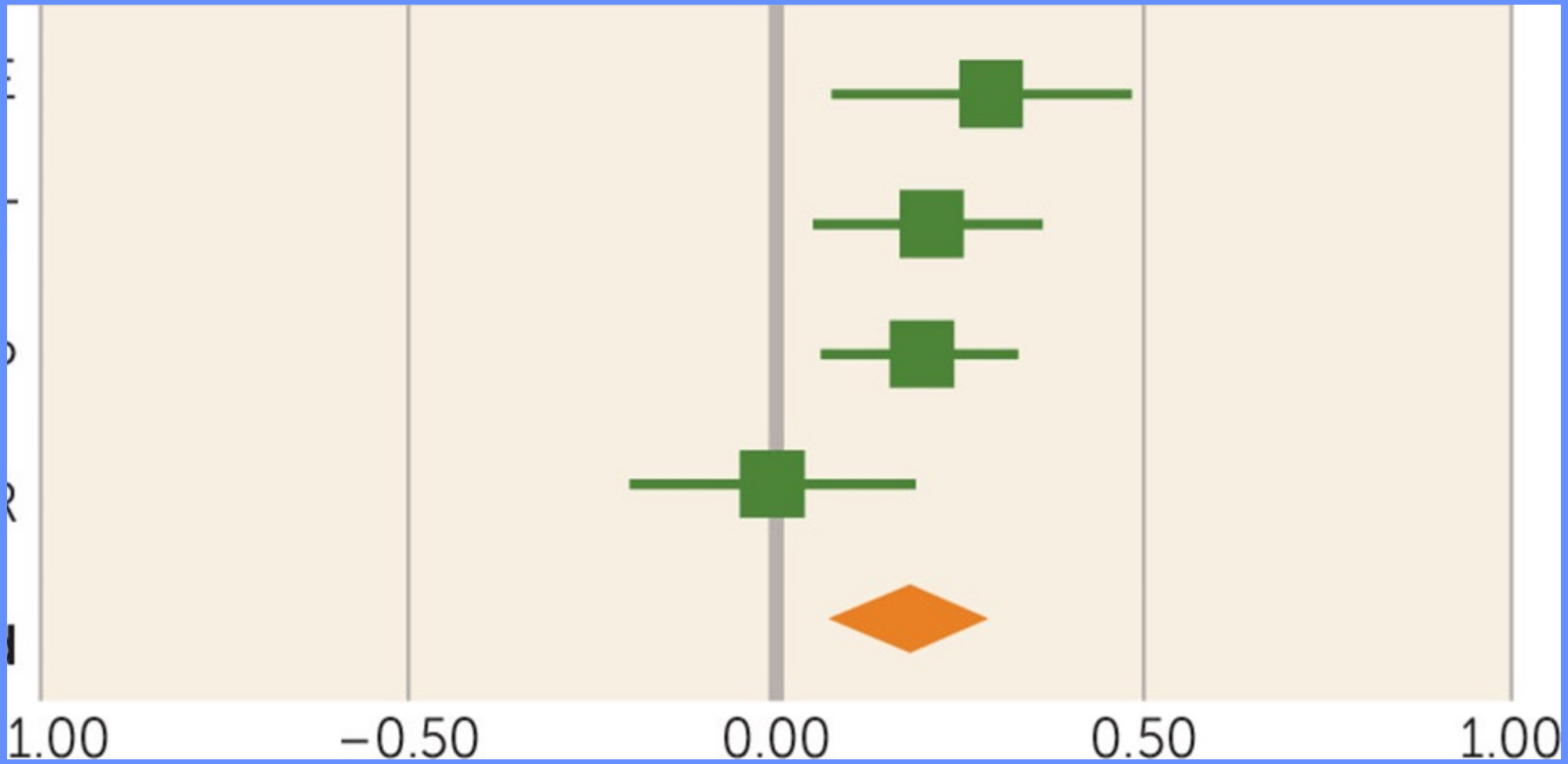
- Velo-Cardio-Facial Syndrome (VCFS)
  - deletion in chromosomal band 22q11.2
- deletion increases the risk of schizophrenia ≈ **70 times**
- present in 1 out of 300 individuals with schizophrenia

- GWAS- 248 genome-wide significant loci
- GWAS variants are mostly non-coding

(Avramopoulos, 2018)

Polygenic Risk score in first episode treatment

more genetic risk = less response to treatment



(Zhang et al., 2019)

Polygenic risk score for schizophrenia: Ancestry > Diagnosis

- Difference between some ancestral groups was 10 times the difference between European cases and controls
- PRS derived from Europeans cannot be applied to non-Europeans
- Limits potential usefulness in clinical settings

(Curtis, 2018)

A polygenic **resilience** score moderates the genetic risk for schizophrenia

- Some rare gene variants provide resistance to simple genetic disease
- Some gene variants protect from complex diseases (Chen)

- Resilience has been traditionally viewed as a psychological construct
- Genetic Resilience = heritable variation that promotes resistance to disease by reducing the impact of risk loci
- Resilience and risk loci operate independently

(Hess et al., 2019)

(Chen et al., 2016)

Genetics of Alzheimer's

Autosomal Dominant

- If you get **one** copy you get early Alzheimer's
  - APP-amyloid precursor protein
  - PSEN1
  - PSEN2

Polygenic Risk Score

- GWAS
- APOε and >20 others carry similar risk
- Heritability 80%

(Kim, 2018)

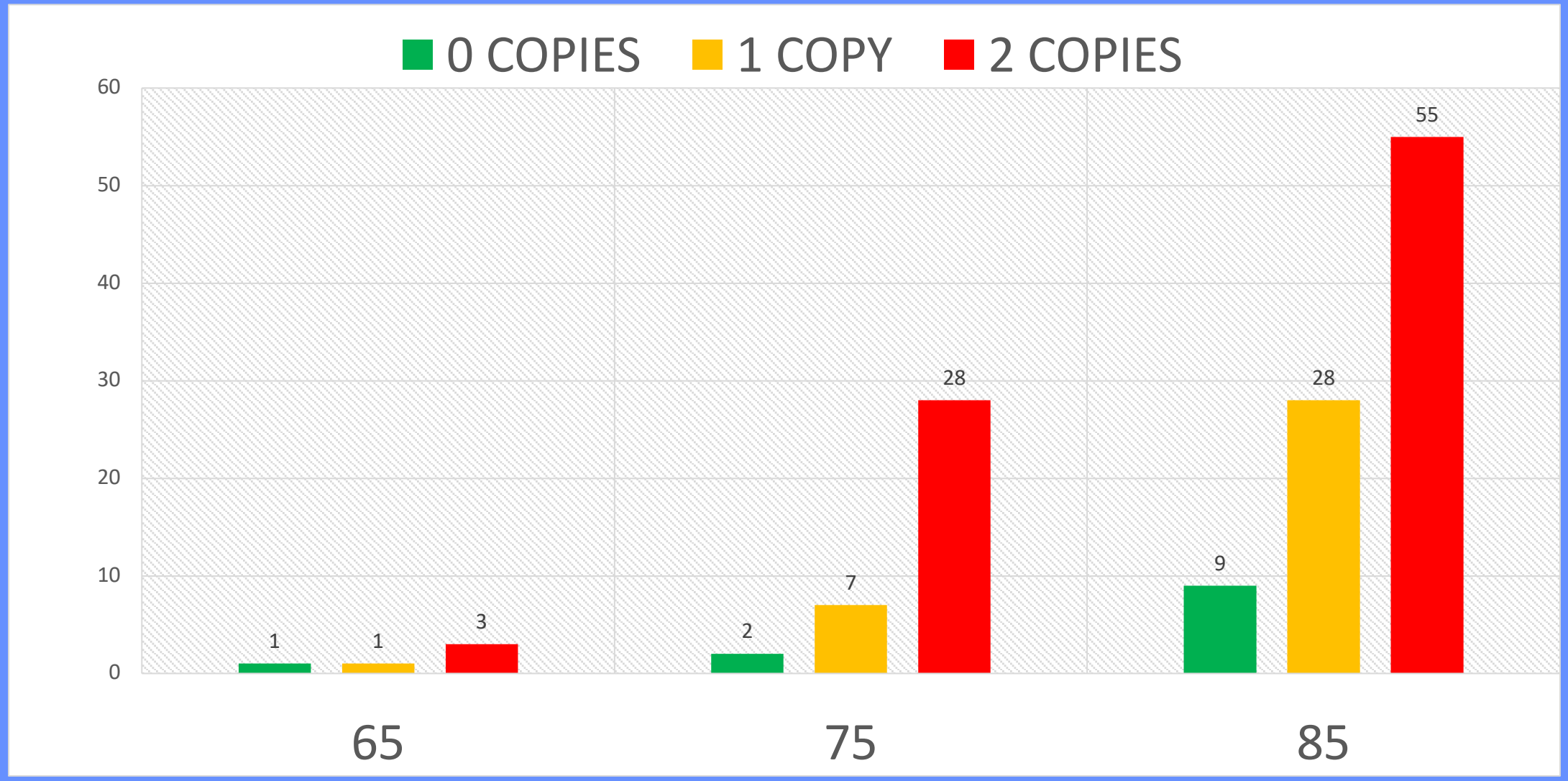
Genetics of Alzheimer's

23 and Me only examines APOε 4

- "Does **not** include all possible variants or genes associated with late-onset Alzheimer's disease.
- Does **not** include *any* variants or genes linked to early-onset Alzheimer's disease.
- Does **not** determine a person's full APOε genotype."

(*Alzheimer Disease. 23 and me*)

APOε4 and Alzheimer's risk by age



(Kim, 2018)

Direct-to-consumer genetic tests are sold for:

- Intelligence
- Diet
- Wine Preference
- Caffeine sensitivity
- Cancer risk
- Sunburn risk
- Selection of exercise
- Alzheimer risk
- Parkinson risk
- Drug metabolism
- Celiac disease
- Gut microbiome

Direct to consumer cancer genes

30 gene panel

- colorectal
- male breast
- prostate
- stomach
- melanoma
- pancreatic

"You tested negative, and 85-90% of all cancers have a **non-genetic** cause"

"Early detection improves survival"

(Color.com *Male Cancer genes*)

Is there Value in Knowing?

Knowing ***my*** genetic risk would change ***my*** behavior

T/F

Other people knowing ***their*** risk would change ***their*** behavior

T/F

All of these were *unchanged* with genetic information about risk:

- Smoking
- Diet
- Physical activity
- Alcohol use

- Little or no effect on risk-reducing health behavior

- If you expect that genetic information will play a major role in motivating behavior, prepare to be disappointed

(Hollands et al., 2016)


RNA, RNA
Where art thou?

non-coding RNAs (ncRNAs)

small RNAs (<200 nucleotides)		
microRNAs (miRNAs)	(~22 nucleotides)	modulating synaptic functions and neural structures
small interfering RNAs (siRNAs)	(~20-24 nucleotides)	double-stranded RNAs (dsRNAs) interfere in the translation of proteins
piwi-interacting RNAs (piRNAs)	(26–32 nucleotides)	regulation of *transposable elements* in germlines
small nuclear RNAs (snRNAs)	(~150 nucleotides)	snRNAs remove the pre-mRNA regions (intron)
small nucleolar RNAs (snoRNAs)	(~60-140 nucleotides)	modify rRNAs, tRNAs, and snRNAs

(Yoshino & Dwivedi, 2020)

long non-coding RNAs (LncRNAs) >200 nucleotides)

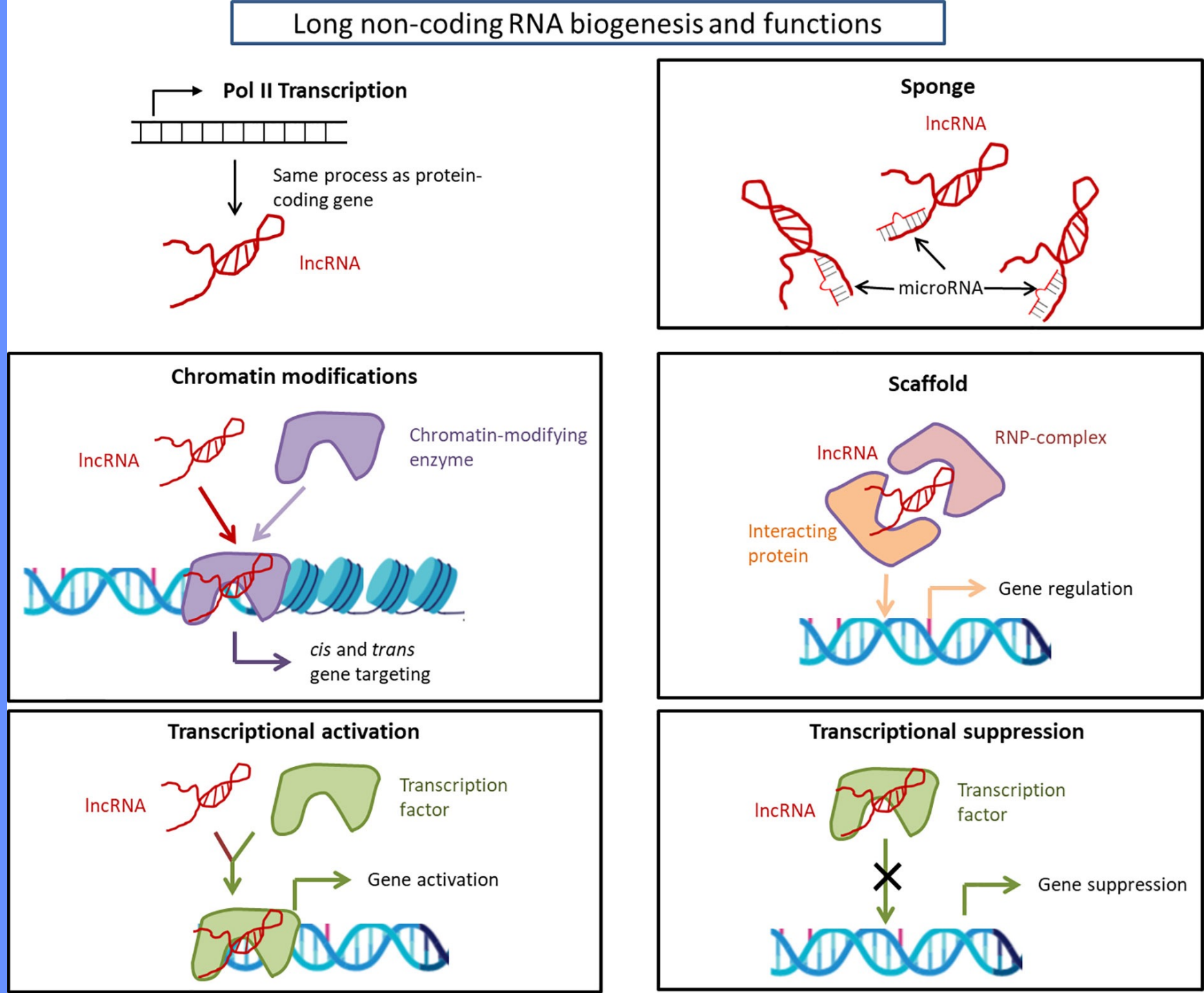
'sponges' that prevent miRNA functions

Modify chromatin

scaffolds that provide docking sites for proteins

activators and suppressors of mRNA transcription

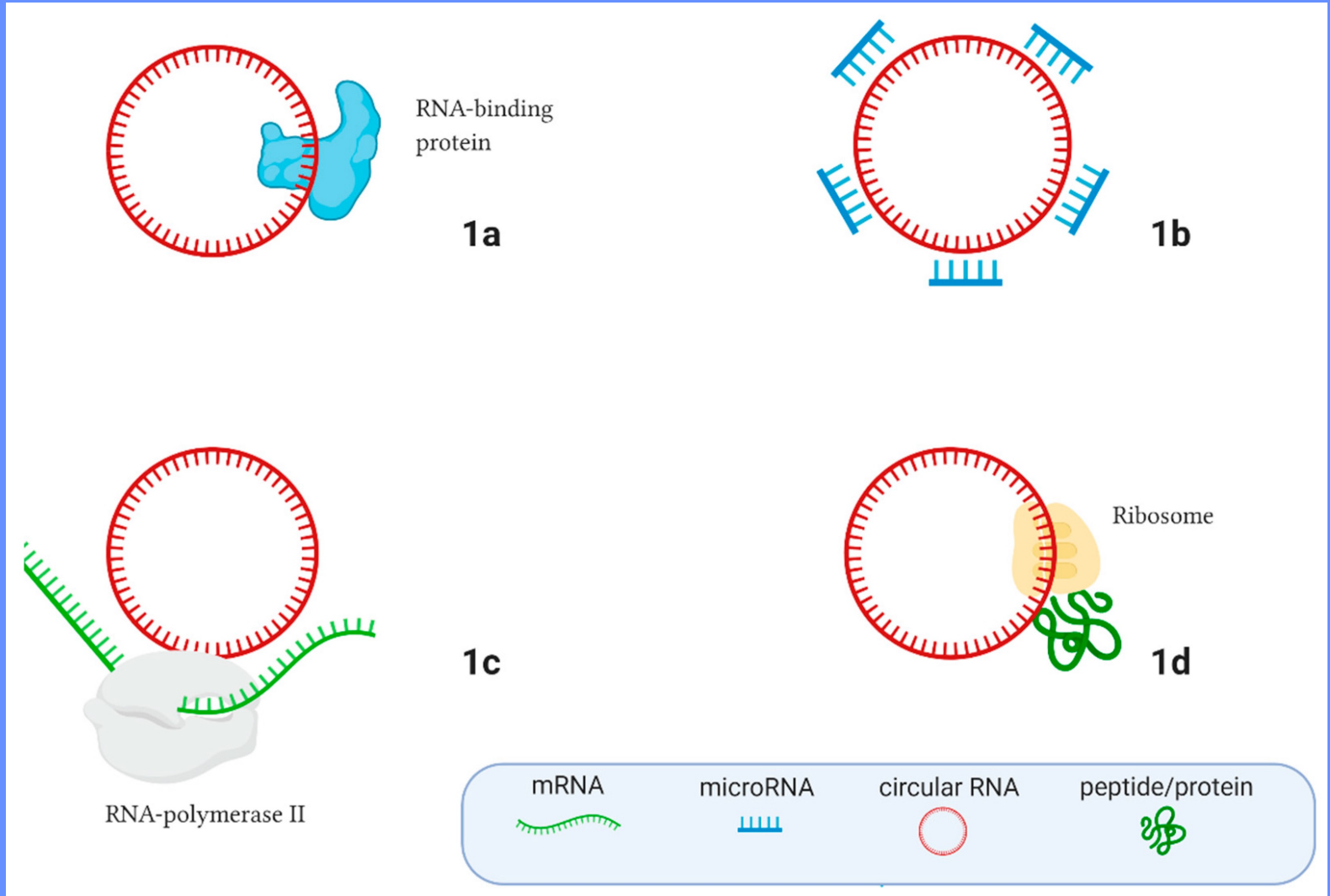
(Yoshino & Dwivedi, 2020)



Circular RNAs (circRNAs)

- are endogenous, single-stranded, non-coding RNA (ncRNA)
- interact with RNA-binding proteins (RBPs)
- affect microRNA
- modulate gene expression
- translate proteins by themselves

(Nedoluzhko et al., 2020)



Conclusions

1. Huge amount of new data being generated
2. Will influence our understanding of Psychiatric Disorders
3. It’s complicated and cool
4. Remember to temper enthusiasm with evidence

Which concept did you find most interesting?

A. Cytochromes
B. GWAS
C. Epigenetics
D. Polygenic Risk Score
E. Noncoding RNA

Questions?

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