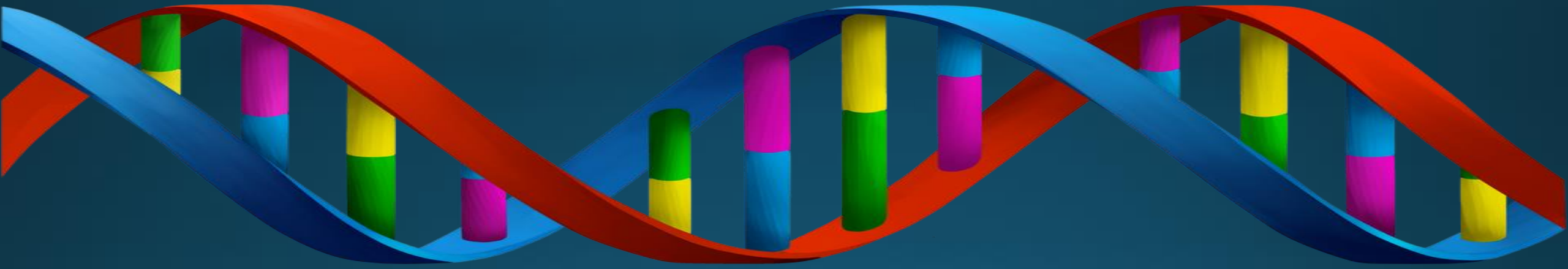
Behavior genetics across the psychology curriculum



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Why BG across the curriculum?

- Accelerating rate of discovery
- Increasing availability of behavior genetic information
  - Few are prepared to interpret it
- Every area of psychology contains behavior genetic content
- Presenting behavior genetic concepts, methods, and findings in psychology courses will benefit students
  - Adding biological information enriches understanding
- Students are curious about it

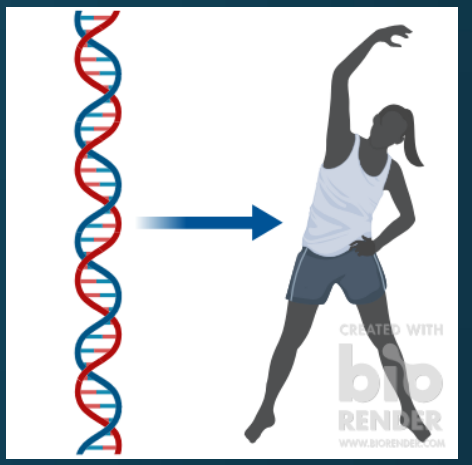
Overview

- Introduction to Behavior Genetics
  - Research method overview
  - Heritability
  - Polygenic
  - Candidate Genes
  - GWAS
- Examples for particular psychology courses
  - Abnormal
  - Developmental
  - Social
- Genetic Essentialism
- Conclusion

Goals

- Stimulate interest in presenting behavior genetics material
- Provide useful information on concepts, study designs, and findings
- Provide examples that may be useful in a variety of courses
- Provide perspective for interpreting BG findings

What is behavior genetics?

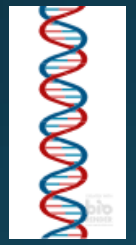


- Main questions
  1. Are **genetic *differences*** associated with ***individual differences*** in behavior?
  2. Which genes are involved?
  3. What are the mechanisms and pathways that mediate gene-behavior relations?
- Any behavior that **differs** among individuals is of interest

Basic research methods

- Non-human animal
  - Strain comparisons
  - Hybridization
  - Selective Breeding
  - Quantitative Trait Loci (QTL) studies
  - Mutagenesis
  - Genetic engineering

Use DNA

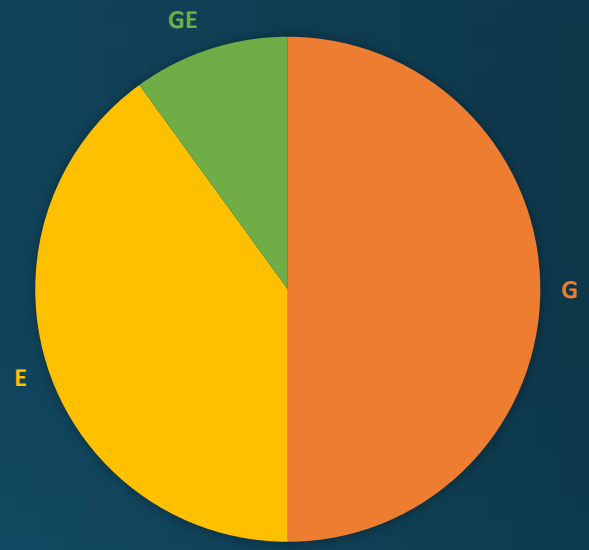


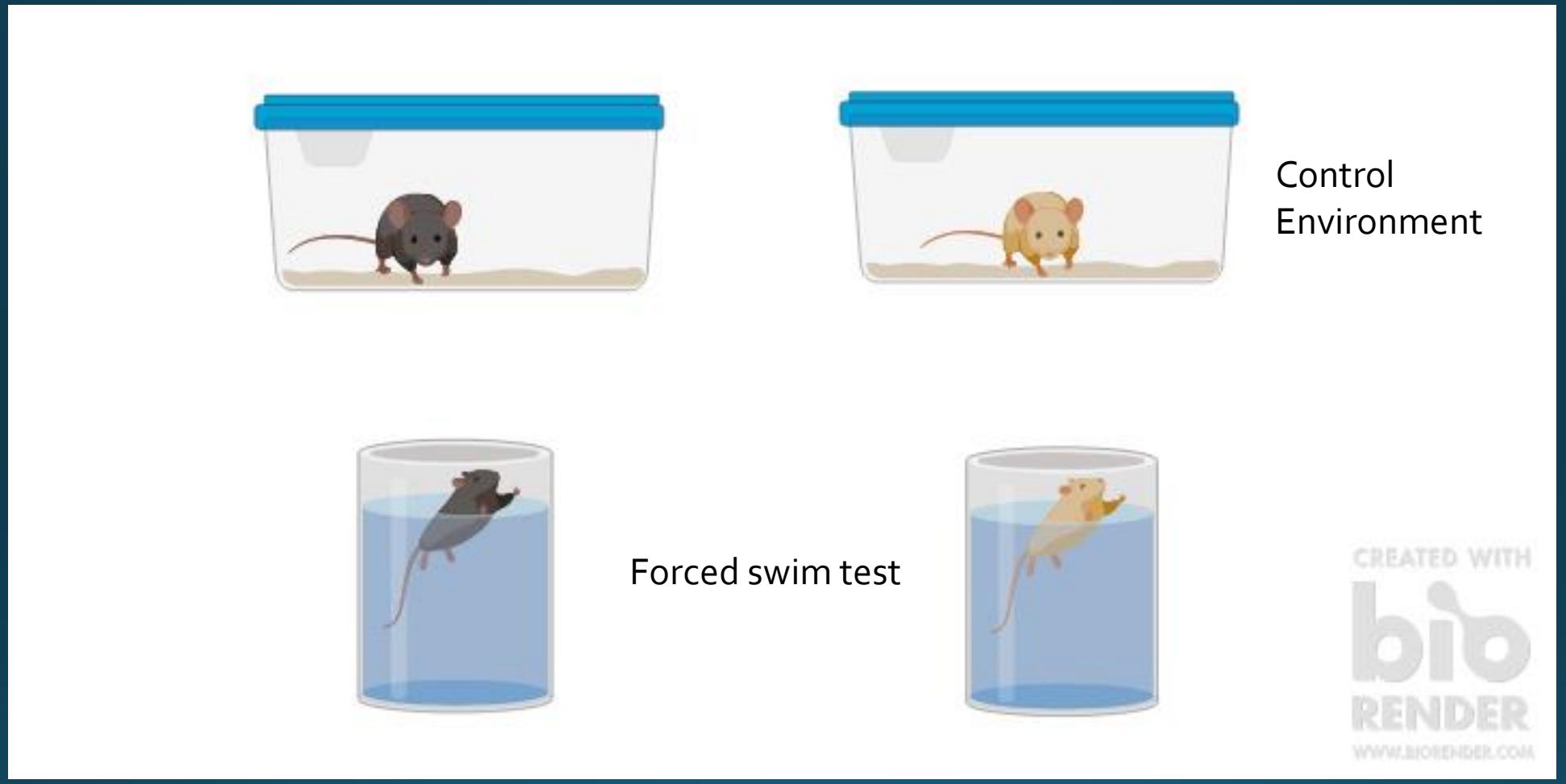
- Human
  - Family studies
  - Heritability estimation
    - Twin and adoption studies
  - Candidate gene association studies
  - Genome-wide association studies

GOAL: To understand how *genetic differences* are related to *individual differences in behavior*

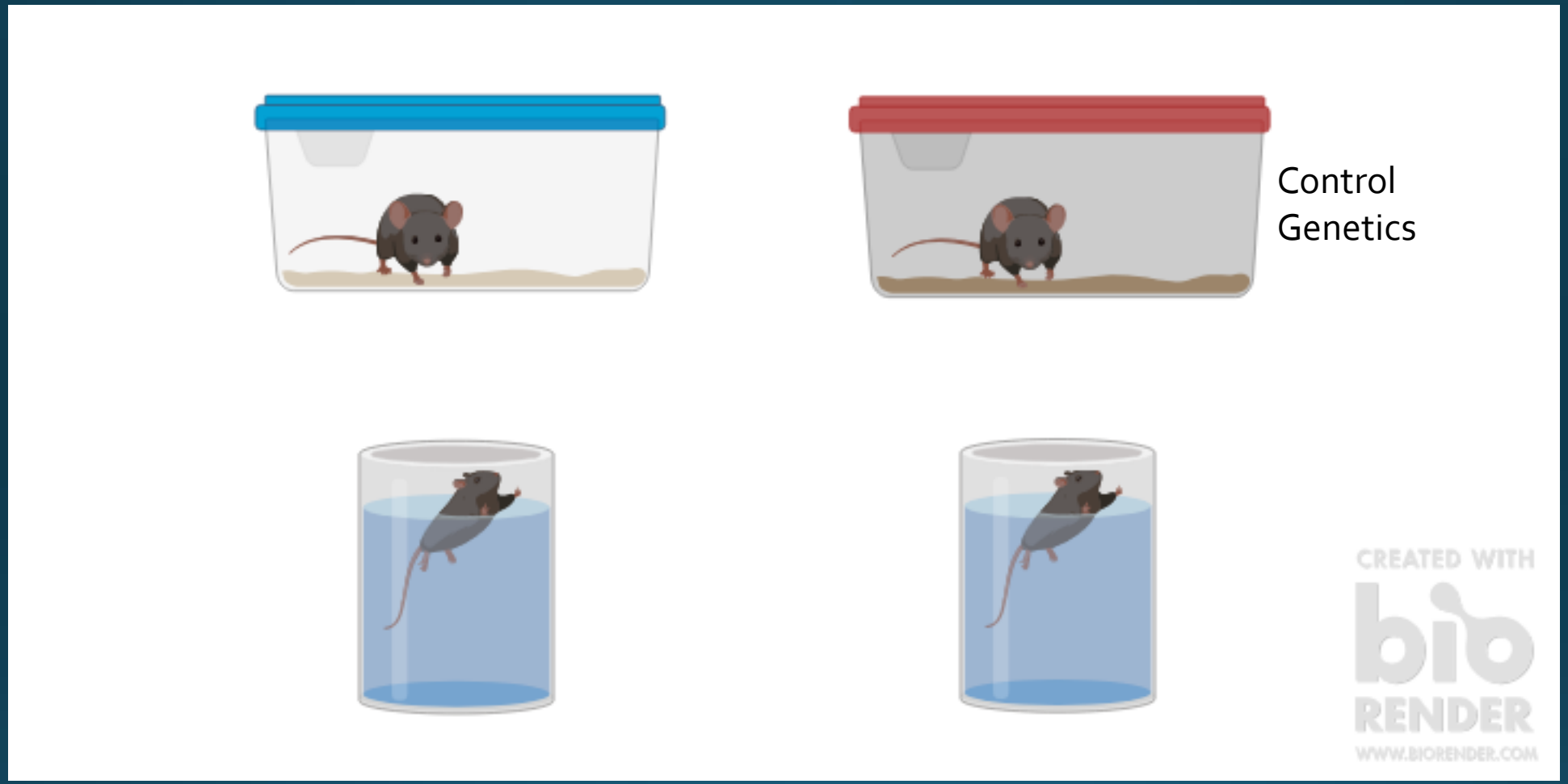
Heritability (h^2)

- Behavioral variance in a population can be partitioned into components
  - Genetic
  - Environmental
  - Gene by environment interplay (GE correlation and GxE interaction)
- Heritability is a statistic that estimates the proportion of trait variation in a population that is attributed to genetic variation
  - Ranges between 0 and 1





If **genetically different strains** of mice are raised in **identical conditions**, any differences in a trait are due to genetic differences (i.e. $h^2 = 1$)

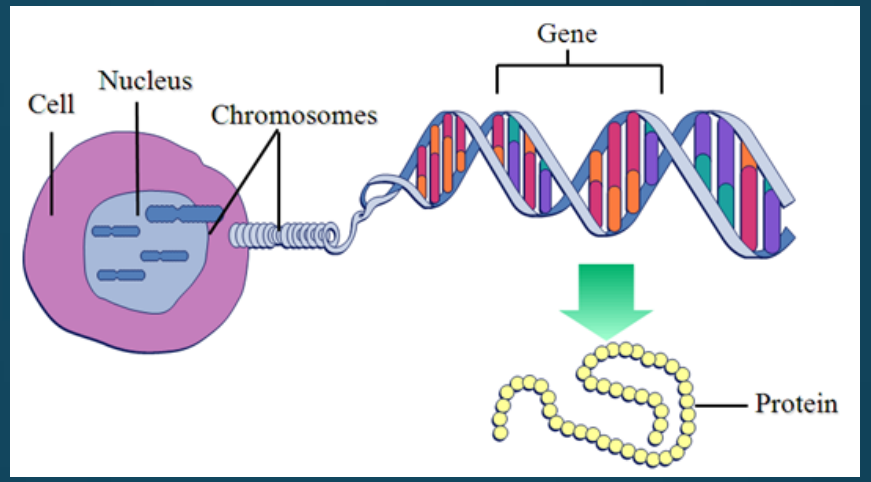


If **genetically identical** (i.e. *isogenic*) mice are raised in **different** conditions, behavioral differences are due to environmental differences ($h^2 = 0$)

Twin studies

- Heritability is estimated using trait similarity of individuals with **known relatedness**
- Studies comparing **behavioral similarity among twin pairs** are most common type to estimate heritability
  - Monozygotic (MZ) twins share 100% of their genes
  - Dizygotic (DZ) twins share 50% of their genes on average
- If differences in a trait are at least partially due to genetic differences, then MZ twin pairs should be more similar to each other than are DZ twin pairs (i.e. $h^2>0$)

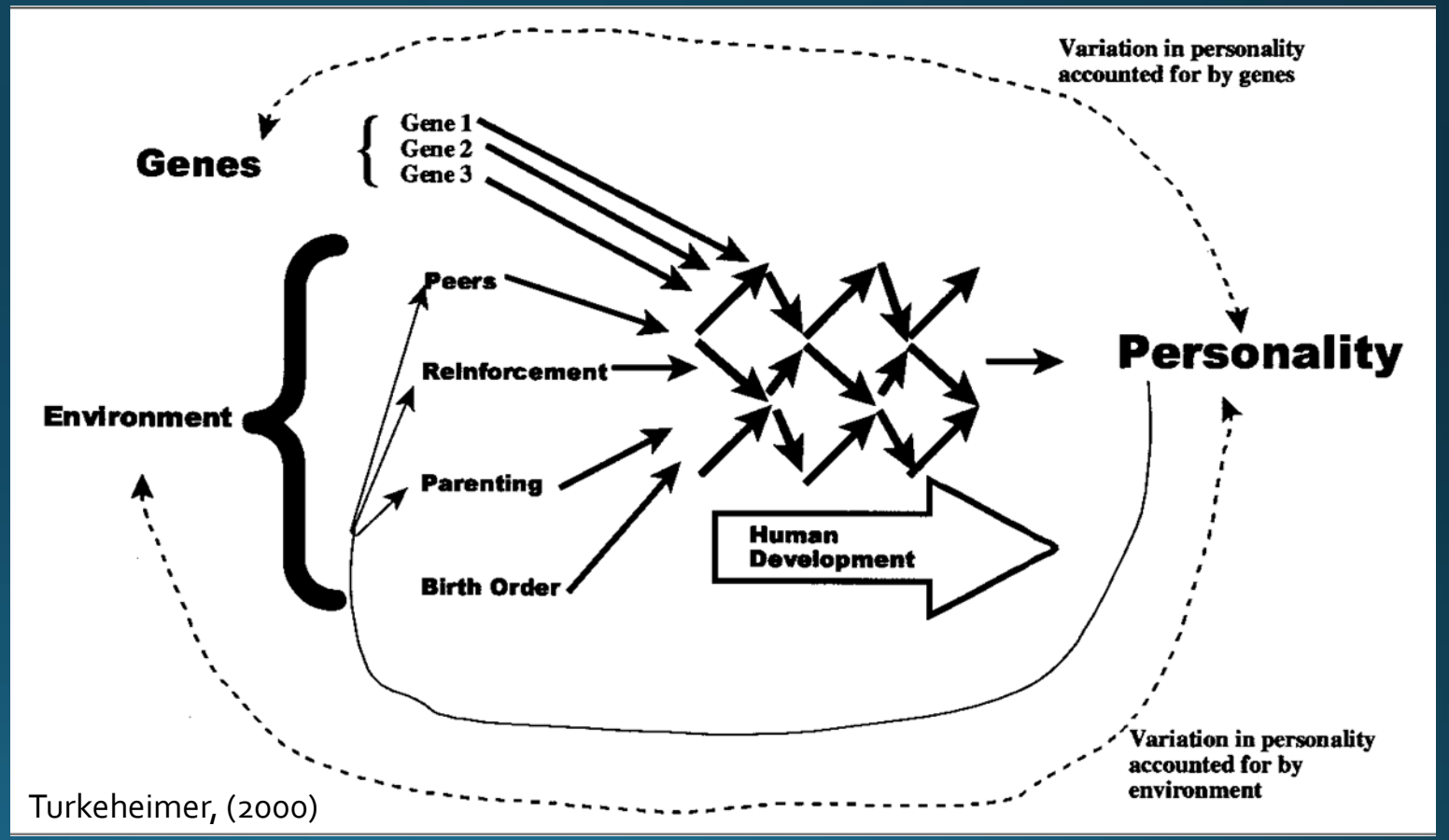
Genes



- The human genome contains about 20,500 genes and 3 billion DNA base pairs (i.e. A, T, C, G)
- Each person's genome contains about 4-5 million single nucleotide polymorphisms (SNPs)
- Such DNA sequence variations can affect
  - Structure and function of proteins
  - Gene expression (i.e. amount of protein produced)
- Proteins are the building blocks of biology
  - Varying structure, function or amount of proteins can have major impact on the function of cells, biological circuits, organ systems

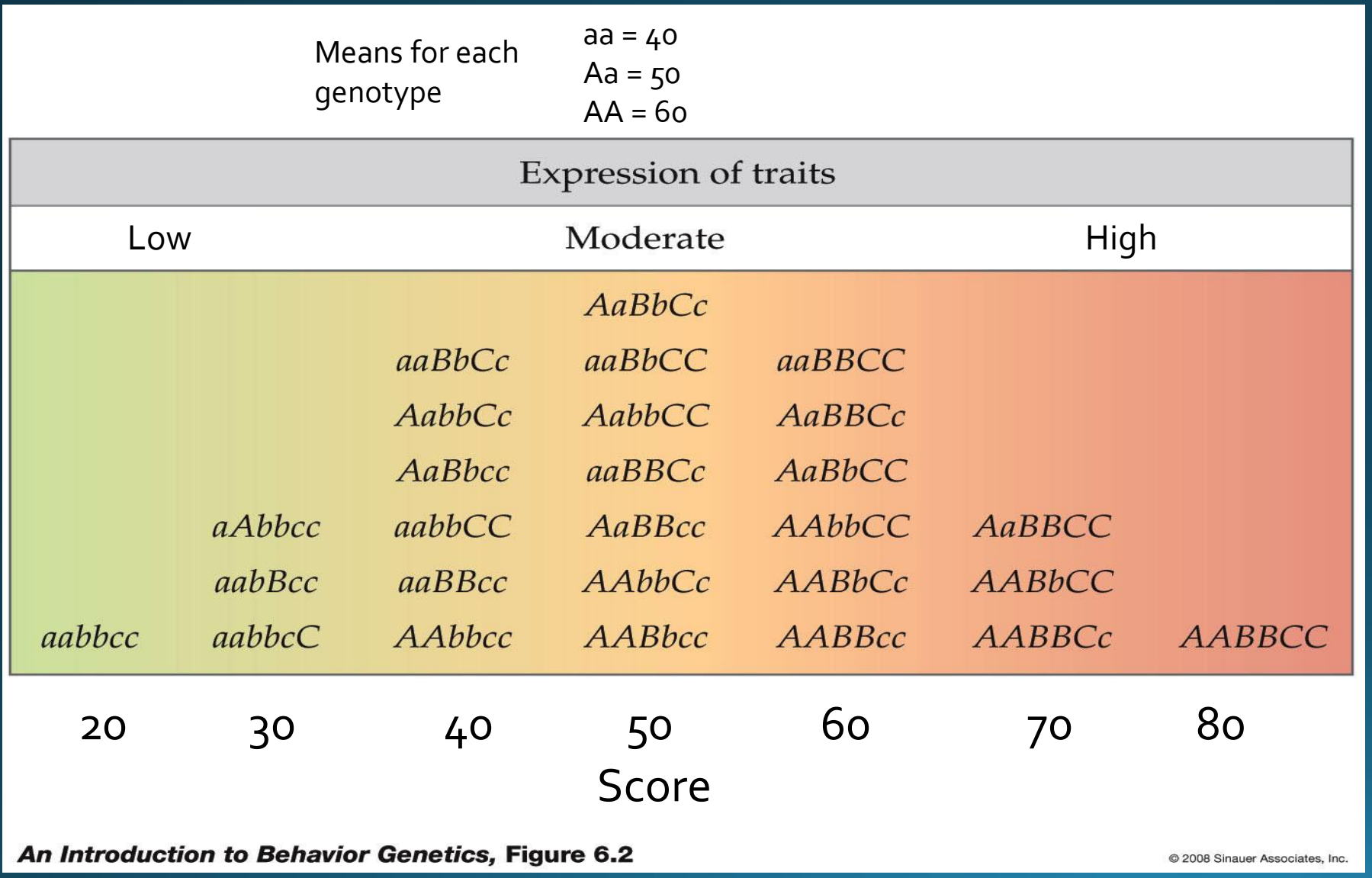
Strong vs. Weak Genetic Explanation

- Few behavioral disorders are caused by mutations in a single gene (e.g. Huntington disease)
  - Strong genetic explanation
- Most behaviors appear to the product of a complex pathway involving many genes, each with a small effect (i.e. polygenic), as well as many other factors
  - Weak genetic explanation



Turkeheimer, (2000)

Polygenic Effects



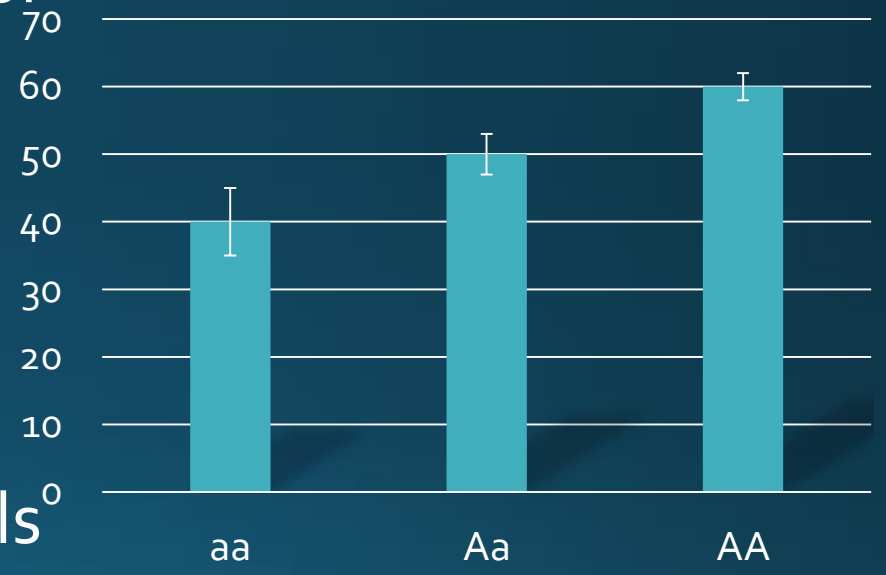
An Introduction to Behavior Genetics, Figure 6.2

Polygenic effects are hypothesized to be **additive**, with certain variants *increasing* (i.e. upper case letters) trait expression, others *decreasing* (i.e. lower case).

As the number of gene variants impacting the trait grows, the more the trait distribution approximates normality.

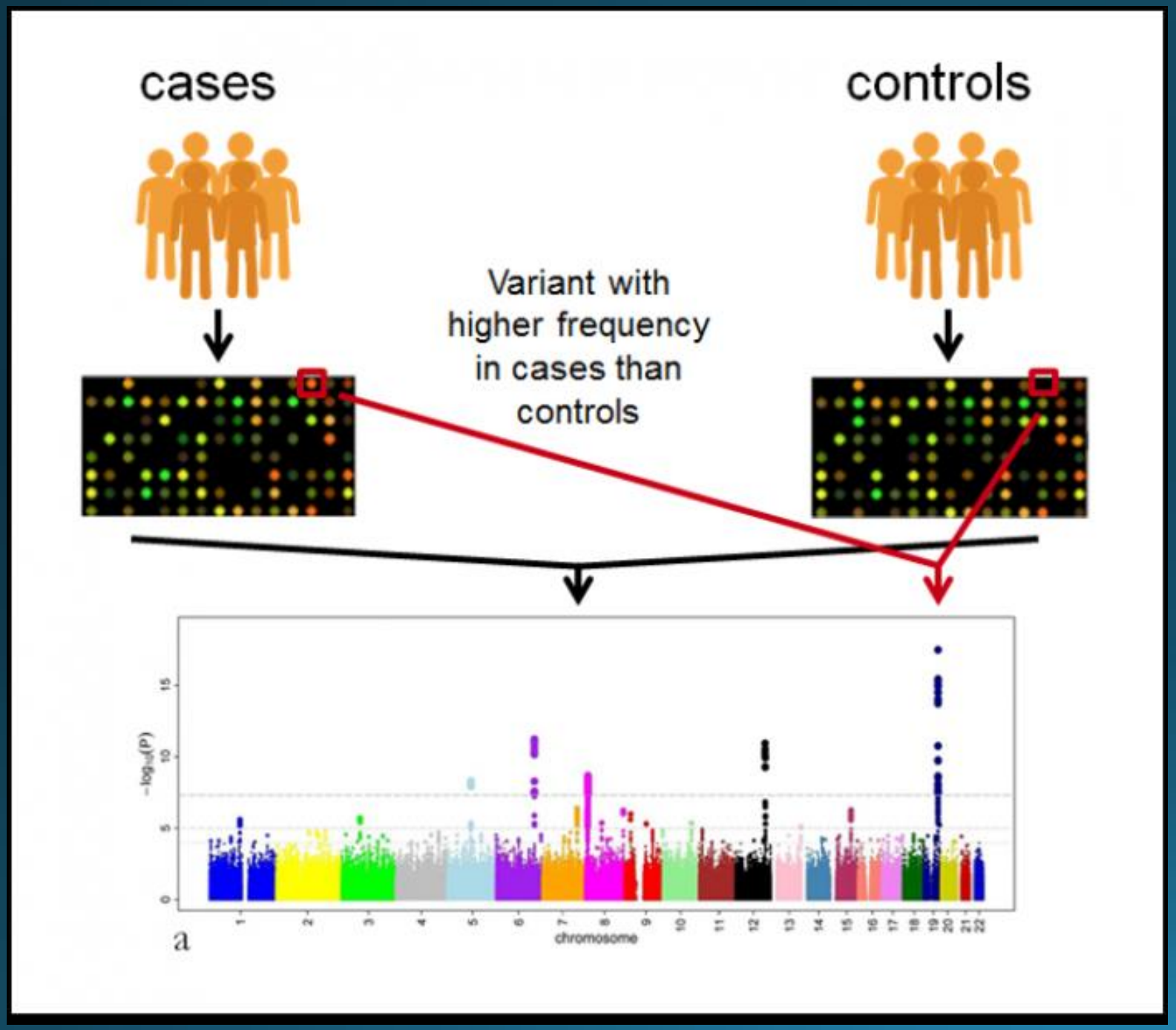
Candidate gene association studies

- Certain genes are hypothesized to be good candidates for involvement in pathways to behavior
  - Previous research
  - Theory
- Genetic variants that affect structure, function or expression of those genes are considered good candidates for testing
- Compare groups comprised of unrelated individuals with different genotypes on behavior of interest
- Out of favor because of failure to replicate findings of underpowered studies



Genome-wide association studies

- A genome-wide association study (GWAS)
  - "discovery-driven" (i.e. hypothesis free)
  - tests statistical associations between a particular outcome and genetic variants across the genome
- Genetic variants are selected for testing based on their known location in the genome
- Typical GWAS tests hundreds of thousands to 2M variants
  - Infinium PsychArray
    - Fixed markers: ~593,260
    - Custom marker add-on capacity: Up to 60,000
- Multiple comparisons increase risk of false positive, so adjustments to significance level are needed



- If certain genetic variants are found more frequently in people with the disease than in healthy controls, those variants are "associated" with the disease.
- A “Manhattan” plot presents significance levels of associations across chromosomes

Abnormal Psychology

- Courses in Abnormal Psychology typically cover risk factors for developing psychopathology
- Alcohol use disorder (AUD) is a problematic pattern of alcohol use leading to clinically significant impairment or distress
  - Impaired control over use
  - Continued use despite problems
  - Craving
  - Tolerance
  - Withdrawal
- In 2016, an estimated 283 million people aged 15+ years worldwide had either AUD or "harmful use" (representing 5.1% of adults).

Two-bottle choice

Selective breeding

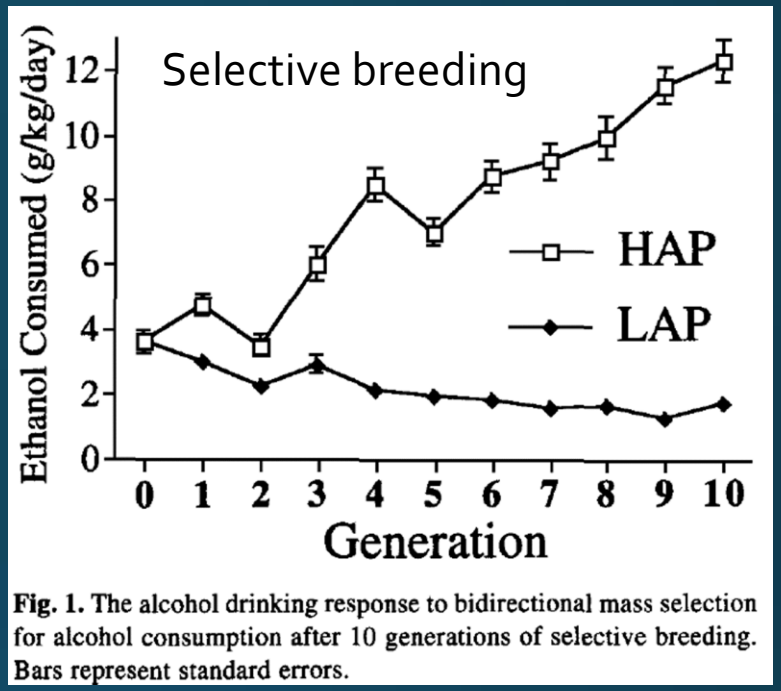
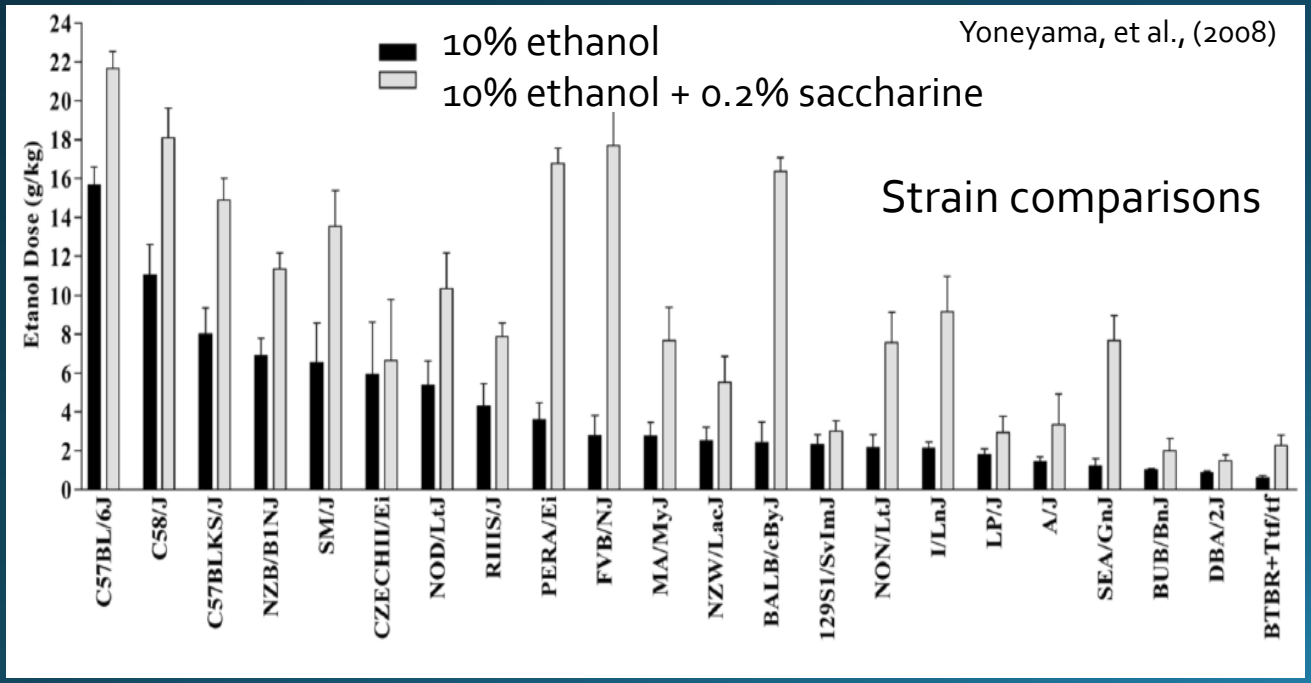
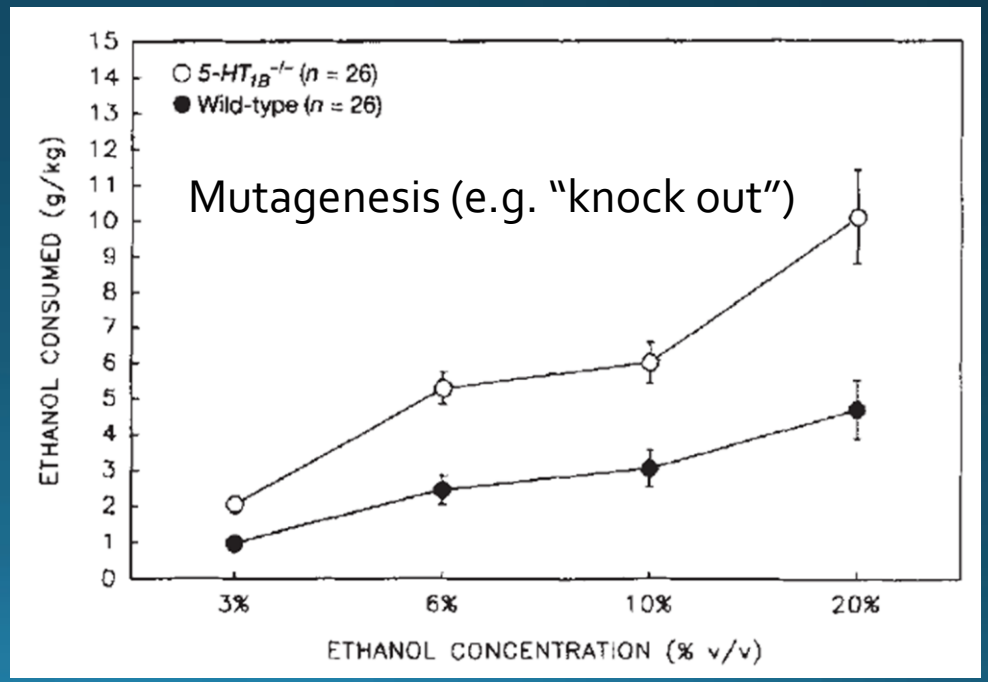


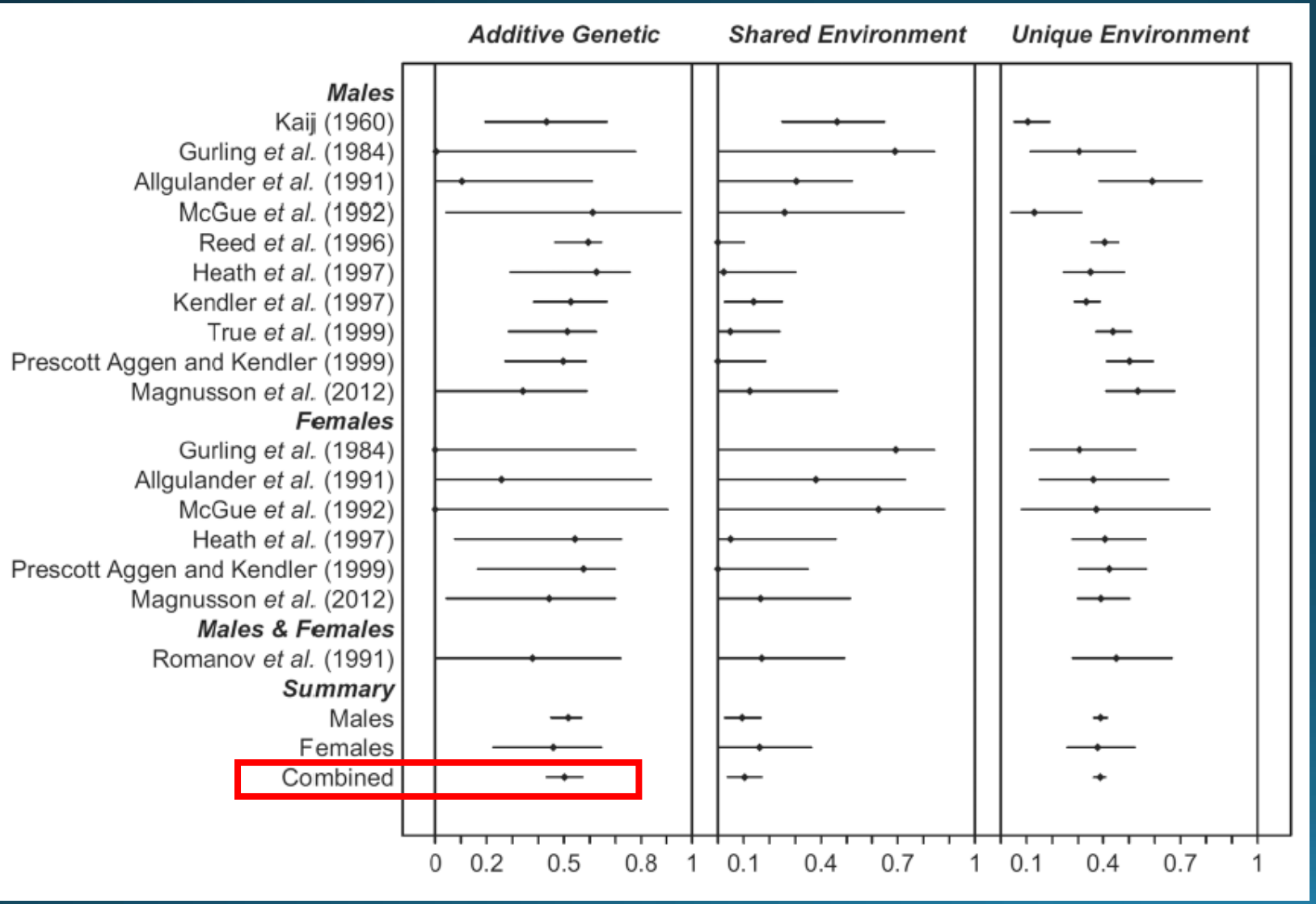
Fig. 1. The alcohol drinking response to bidirectional mass selection for alcohol consumption after 10 generations of selective breeding. Bars represent standard errors.

Yoneyama, et al., (2008)





Heritability estimates of alcohol use disorders



Genetic and environmental variance components for alcohol use disorders in twin studies by sex (Verhulst, et al., 2015)

Heritability estimate = 0.49 [95% CI 0.43–0.53]

Therefore, genetic similarity is statistically associated with behavioral similarity.

Alcohol Metabolism Genes

- Certain genetic variants affect the break down of alcohol in the liver, and are associated with risk for developing an alcohol use disorder

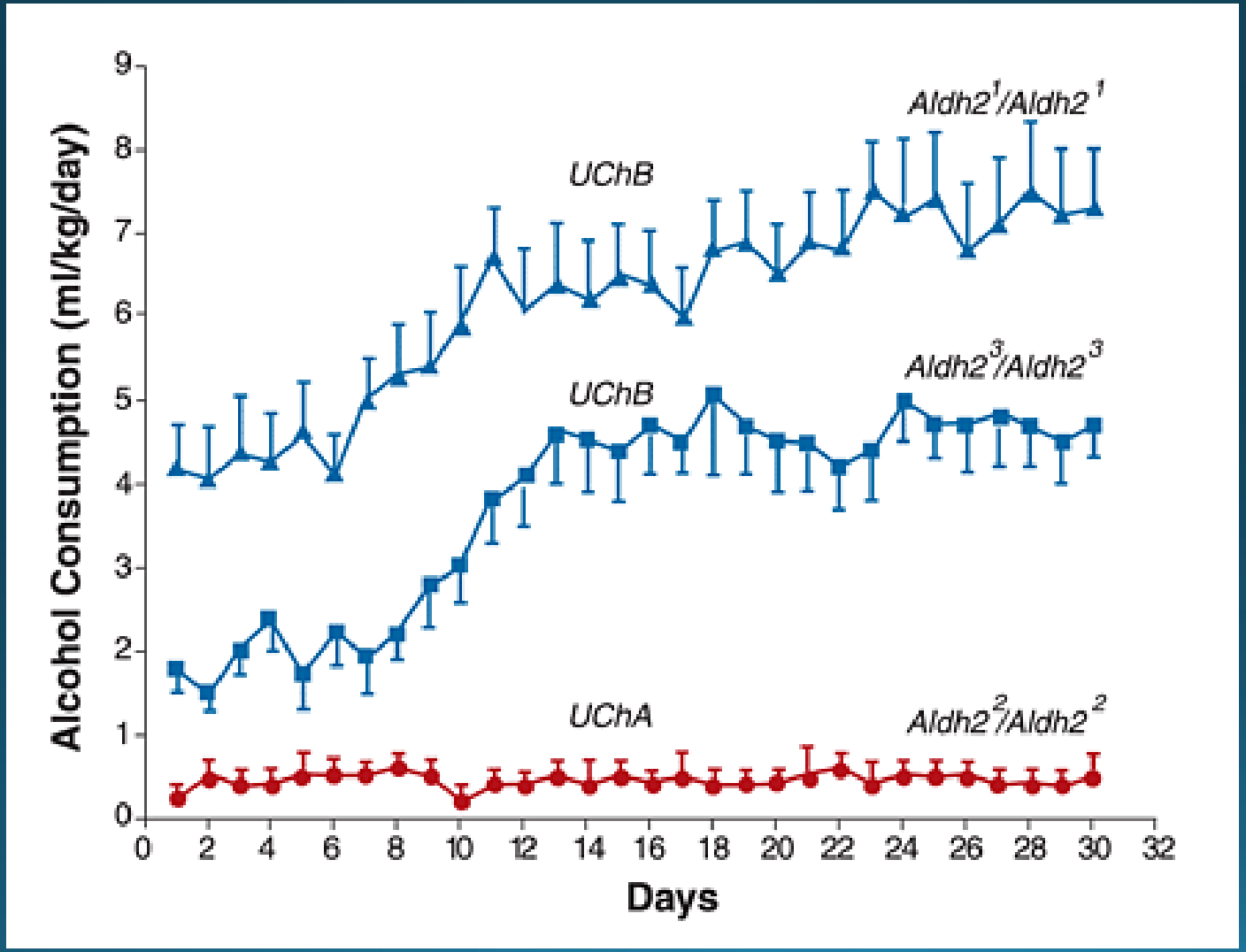
Alcohol Metabolism Genes

- Aldehyde dehydrogenase (ALDH2— rs671, chromosome 12q24.12)
  - A **loss of function** variant of ALDH2, found only in certain Asian populations, slows rate of acetaldehyde removal and reduces risk for alcohol dependence
  - Disulfiram (Antabuse®) inhibits alcohol metabolism by blocking acetaldehyde clearance, and is used to treat alcoholism

Alcohol-induced Facial Flushing

Brooks, et al., 2009

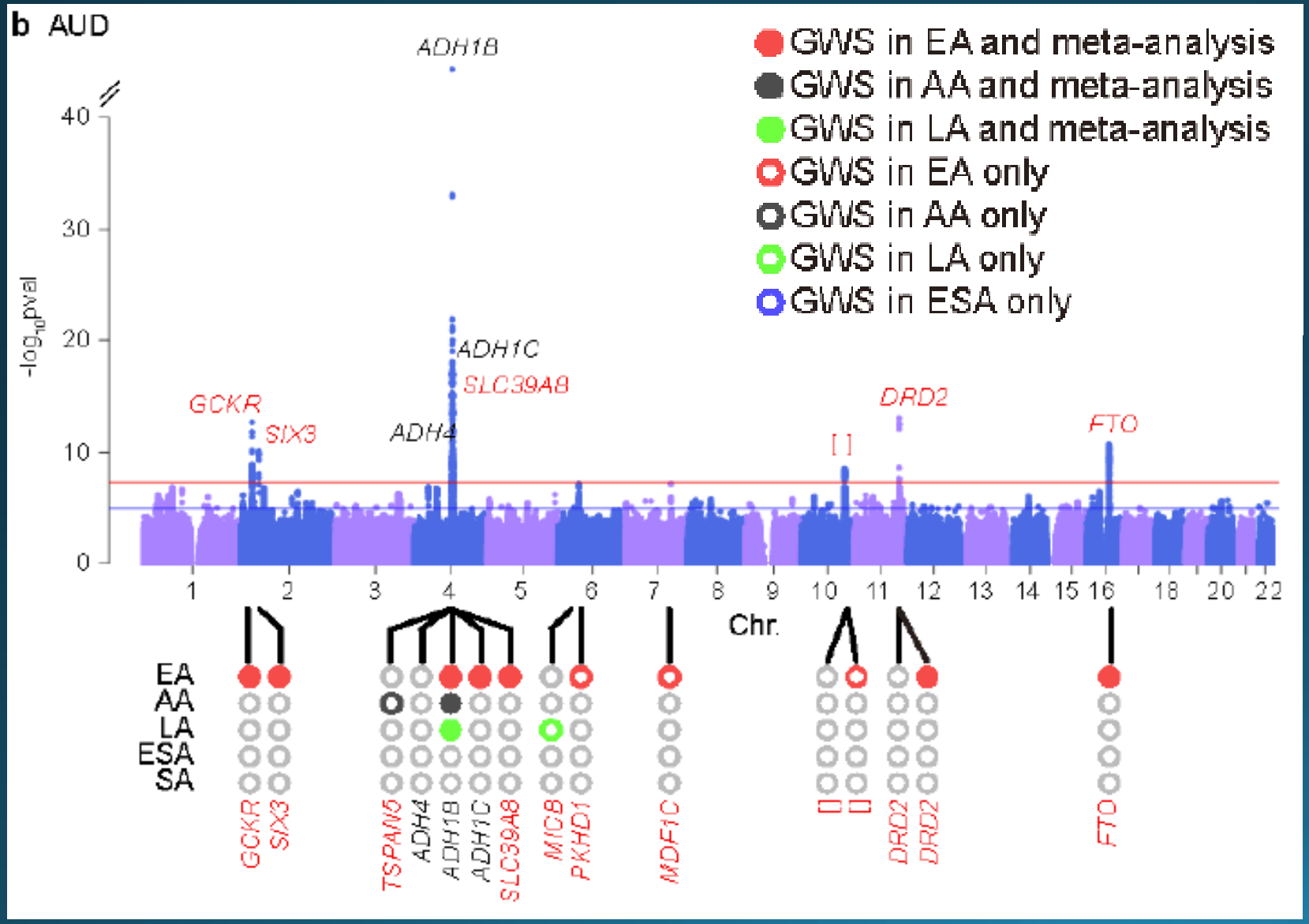
Voluntary ethanol consumption in selected lines of rats is associated with different versions of Aldh2 (Quintanilla, et al., 2006)



Alcohol Metabolism Genes

- Alcohol dehydrogenase (ADH1B— rs1229984, chromosome 4q23)
  - **Gain of function** ADH1B alleles produce ADH enzymes with rapid catalytic function, and are associated with **reduced risk for alcohol dependence**

Manhattan Plot for the GWAS on Alcohol use disorder across five populations (N= 55,985 cases and N=224,014 controls; Kranzler, et al., (2019) [preprint])



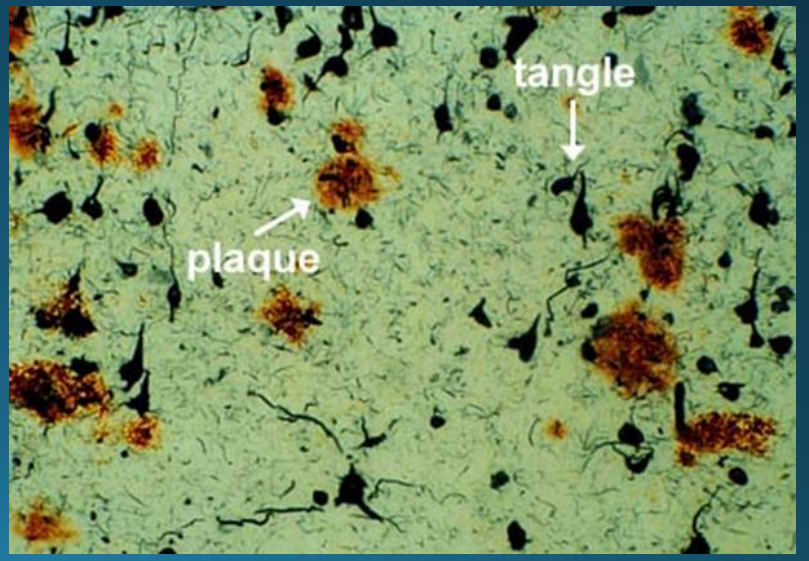
EA: European American;
AA: African American;
LA: Hispanic or Latino;
EAA: East Asian American;
SAA: South Asian American

Alcohol use disorder summary

- **Convergent evidence** indicates that genetic variation explains some of the risk for the development of alcohol use disorder
  - Runs in families
  - Non-zero heritability estimate
  - Non-human animal studies
  - Alcohol metabolism genes
- **Points to emphasize to students**
  - Risk for alcohol use disorders is
    - Polygenic
    - Moderated by environment
  - Genes do not **cause** alcoholism, but knowing your family history can help you make decisions

Developmental Psychology

- Courses in Developmental Psychology often cover disorders that have **age-related** expression
- 1% of those between age 60 and 65 have dementia
  - Forgetfulness, loss of concentration, mood changes, motor problems progressing to from mild to severe
- Percentage of individuals above age 65 with dementia doubles with every 5 years of age (over 1/3 of those over age 90 have dementia)
- **Alzheimer's disease** is the most common age-related dementia
  - Roughly 35 million people
- Characterized by neurofibrillary plaques and tangles
- Heritability estimates 0.60 to 0.80

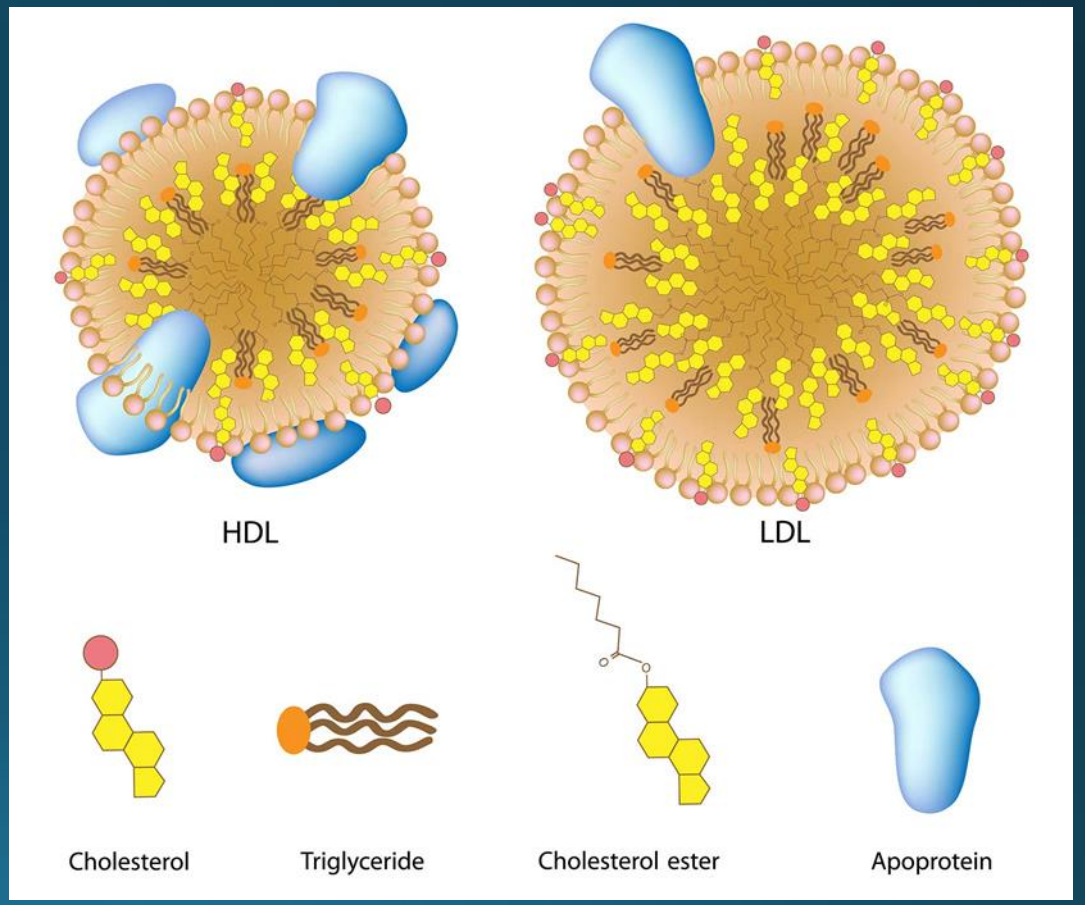


Early Onset Alzheimer's Disease

- **Familial**—Autosomal dominant inheritance
  - Early onset—diagnosis before age 65 (only ~5% of AD cases)
- Mutations in found in three genes cause EOAD
  - **APP** (amyloid precursor protein)
    - Found in many tissues and organs, including the brain and spinal cord
    - May bind to other proteins on the surface of cells or help cells attach to one another
  - **PSEN1** (presenilin 1) & **PSEN2** (presenilin 2)
    - Code for subunits of an enzyme (gamma-secretase) that chops up proteins as part of normal cellular function
    - Amyloid precursor protein is processed by gamma-secretase
- Improper processing of APP by gamma-secretase appears to be critical step in development of β-amyloid plaques in EAOD

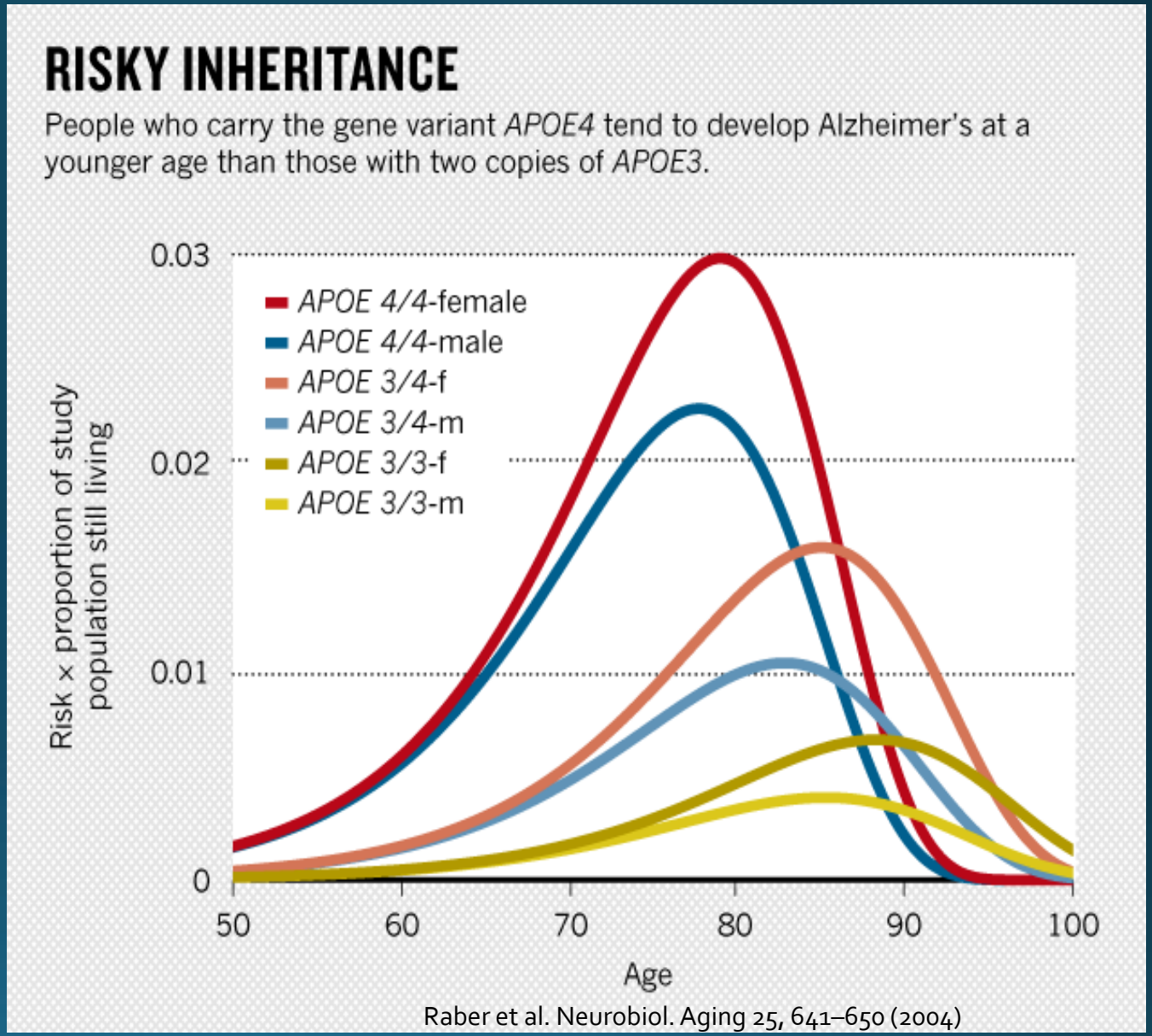
Late Onset Alzheimer's Disease

- **Sporadic**—Disease does not run in families
  - Symptom onset typically after age 65 (95% of AD cases)
  - Midlife smoking and high cholesterol may increase risk for dementia later in life
- Genetic variations in the apolipoprotein E gene (*ApoE*) are associated with risk of developing Alzheimer's disease
  - The apolipoprotein E (*ApoE*) gene makes a protein which, when combined with fat, becomes a lipoprotein.
  - The lipoprotein ApoE is a very low-density lipoprotein, responsible in part for removing cholesterol from the bloodstream.



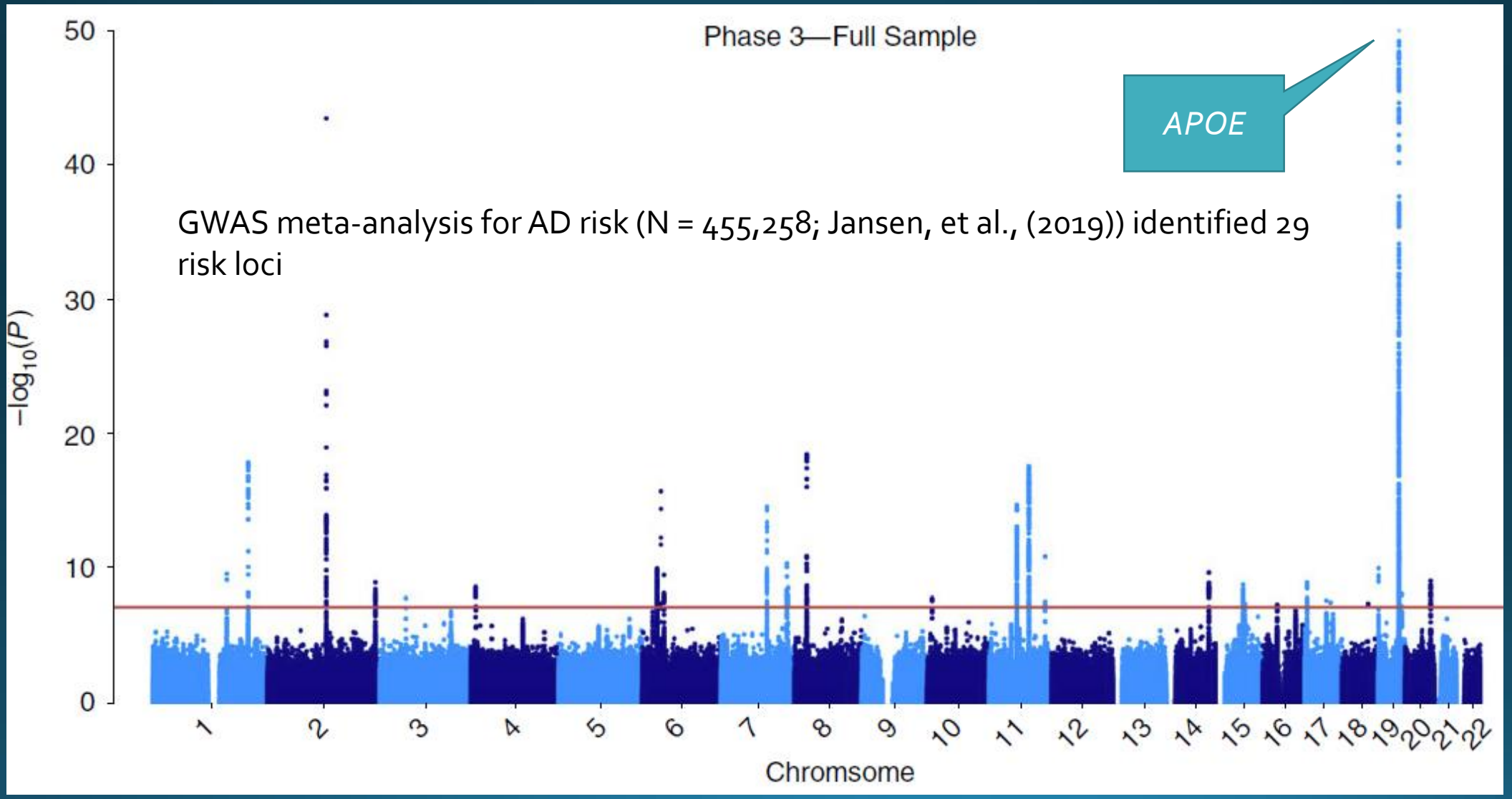
Risk for late onset Alzheimer's disease is associated with *APOE* genotype

rs429358	rs7412	Name	Frequency	Risk
C	T	ε1	Rare	?
T	T	ε2	8.4%	Decrease
T	C	ε3	77.9%	
C	C	ε4	13.7%	Increase



The mechanism by which the *APOE* ε4 allele is related to the risk of LOAD is not well understood

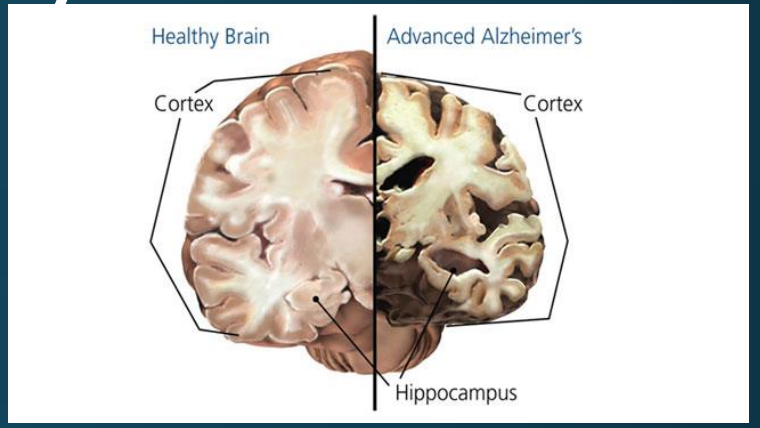
Alzheimer's disease risk GWAS



Mouse models of Alzheimer's Disease

- Over 150 different mouse models have been used to investigate the biological basis of AD
- Transgenic mice contain human genes
- **Transgenic** mouse models expressing high levels of mutant human amyloid precursor protein (APP) show symptoms and pathophysiological processes typical for early phase of Alzheimer's disease.

Alzheimer's disease summary



- Early onset Alzheimer's disease runs in families
  - Can be caused by mutations in three different genes
- Late onset Alzheimer's disease does not run in families
  - Risk factors include mid-life lifestyle and APOE genotype
  - Polygenic (at least 29 risk loci)
- Transgenic animal models are likely to be crucial in understanding the biology underlying AD pathology
- **Points to emphasize to students**
  - Risk for the most common type of Alzheimer's disease is
    - Polygenic
    - Moderated by environment
  - Both Genes and environment contribute to LOAD
  - APOE ε4 alleles are associated with increased risk, but it is possible that a healthy lifestyle can help to reduce risk

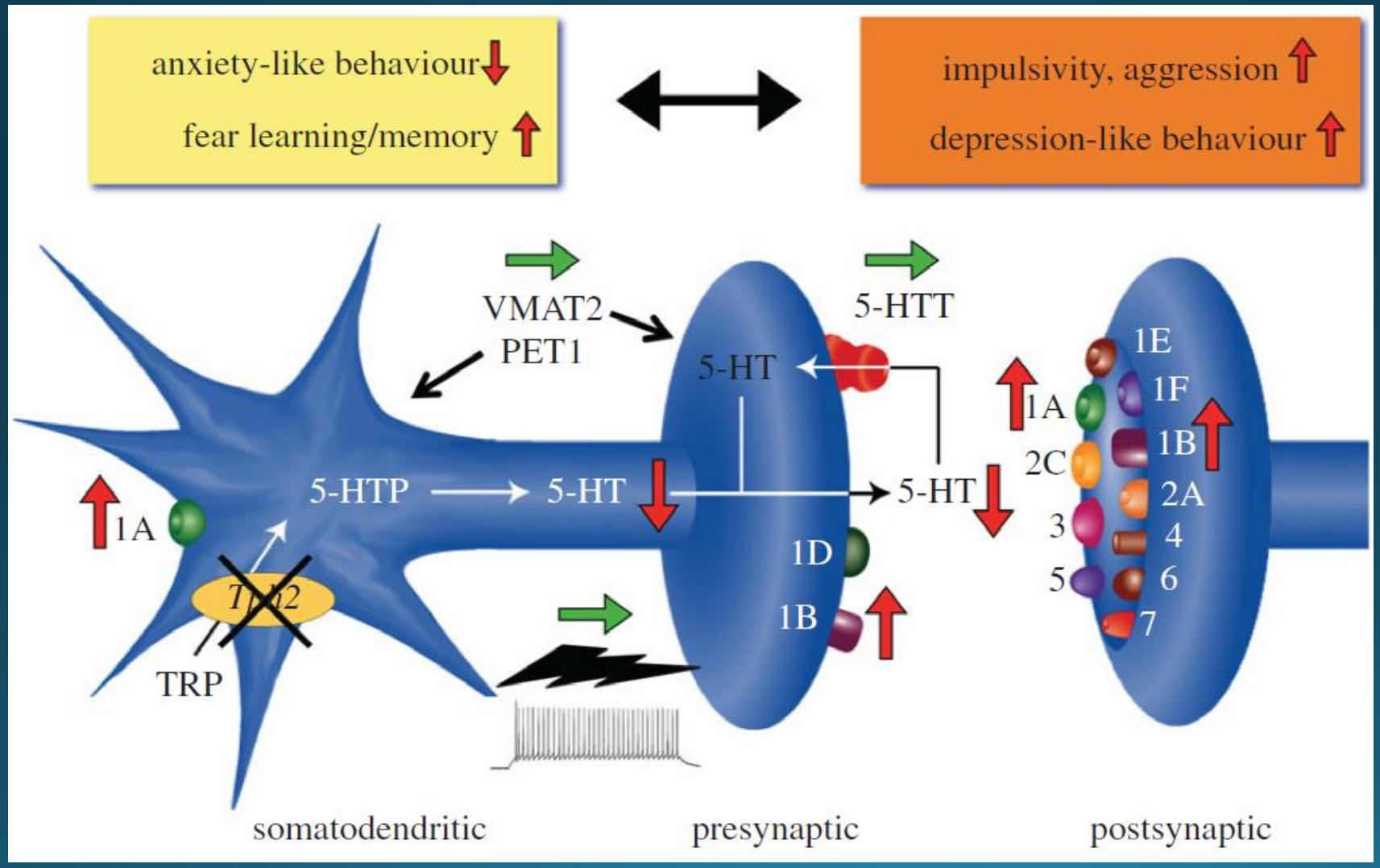
Social Psychology

- Courses in social psychology cover aspects of interactions among individuals
- **Aggression** is social behavior that is of great interest
  - Hostile or violent behavior or attitudes towards another
- Aggression is evolutionarily conserved and plays a role in survival and reproductive fitness
- Aggression is influenced by culture and context
- Heritability estimate of human aggression 0.50 (Tuvblad & Baker, 2011)

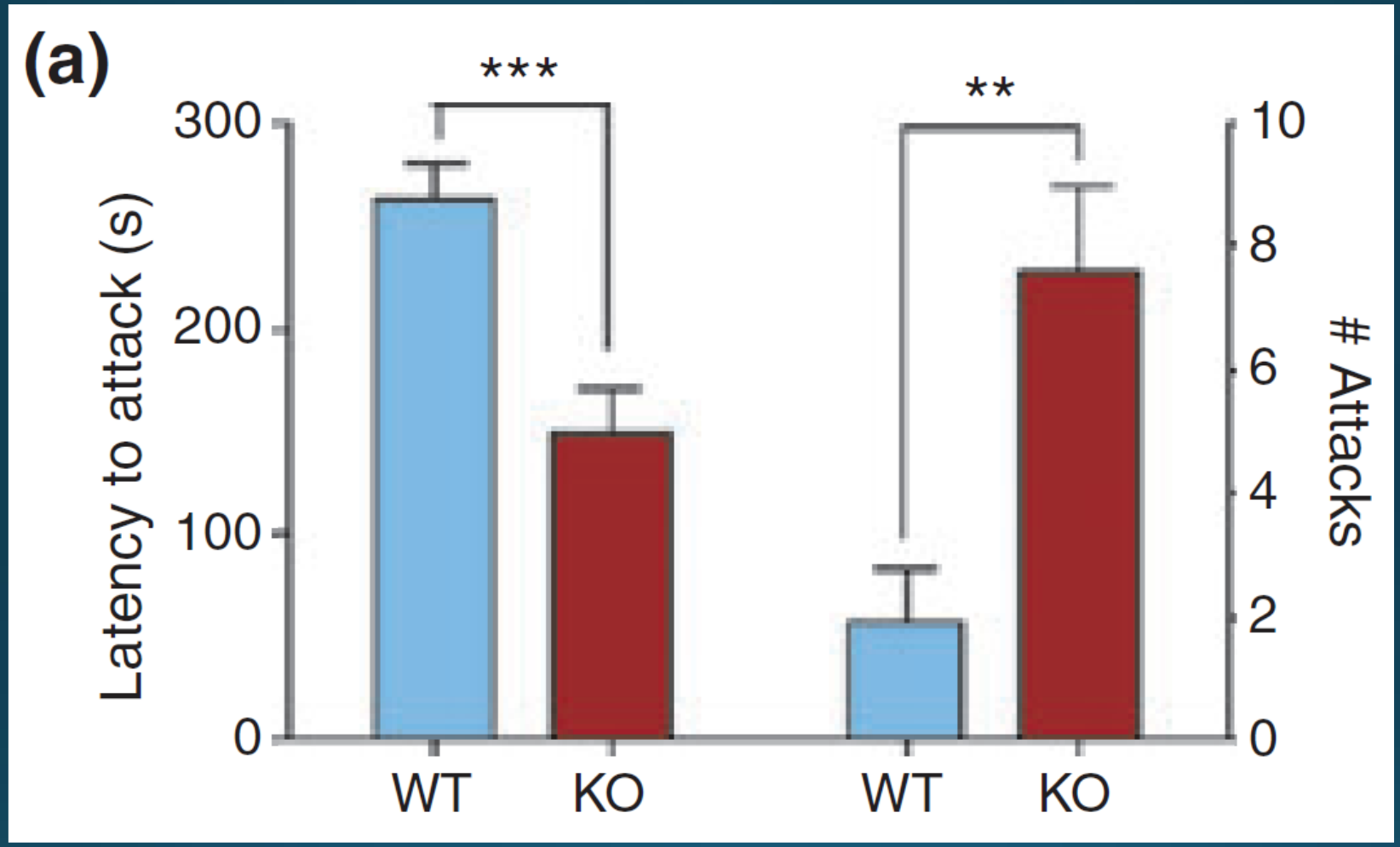
Knockout mice

- Strains of mice can be created where a single gene has been deactivated (i.e. knocked-out)
- Comparisons of knock-out (KO) mice with wild type (WT) mice that are genetically identical (except for the knock-out) enable testing of that gene's effect
- Resident-intruder test
  - Standardized test for aggression in mice
  - Male "resident" is housed with a female to establish territoriality
  - Female removed prior to test
  - Unfamiliar male "intruder" placed in cage
  - Observe and record offensive aggressive behavior of resident

Tryptophan hydroxylase (TPH2) is the rate-limiting enzyme of serotonin biosynthesis



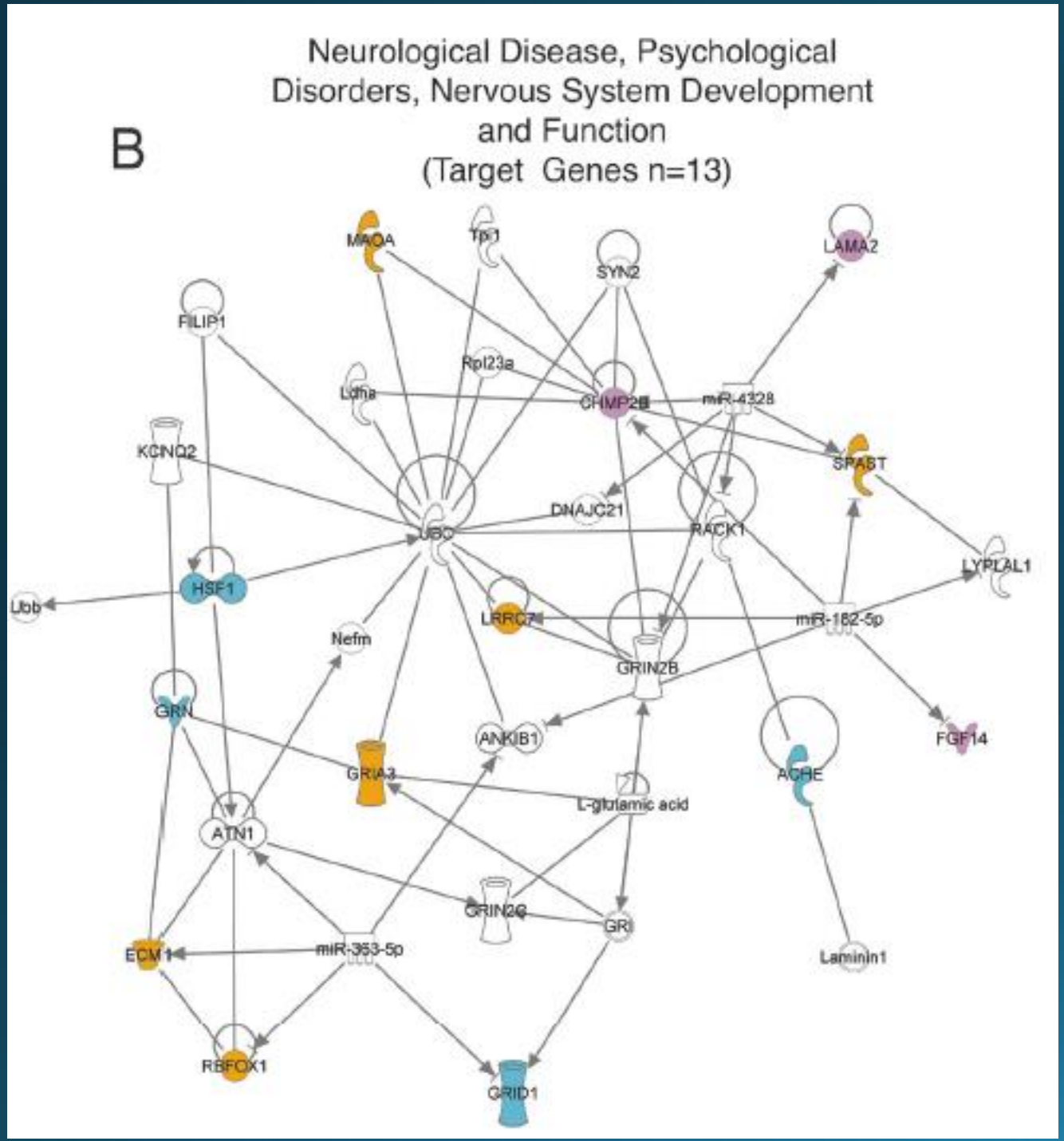
Lesch, et al., (2012)



Adult male Tph2 Knock out (KO) mice (n = 26) attack more quickly and more often when compared with adult male wild-type mice (WT, n=17) in the resident–intruder test (Angoa-Perez, et al., (2012)).

Top 40 genes associated with aggression are clustered in networks related to (A) nervous system development and function, (B) neurological disease and psychological disorders, and (C) cellular function and maintenance (Zhang-James, et al., (2018))

Gene symbol	Weighted ranking	Gene name	Gene symbol	Weighted ranking	Gene name
MAOA	4	Monoamine oxidase A	*ECM1*	2	Extracellular matrix protein 1
ERBB4	3	Erb-b2 receptor tyrosine kinase 4	*EEF1A2*	2	Eukaryotic translation elongation factor 1 alpha 2
GRIA3	3	Glutamate ionotropic receptor AMPA type subunit 3	*EHMT1*	2	Euchromatic histone lysine methyltransferase 1
MECP2	3	Methyl-CpG-binding protein 2	*GAD2*	2	Glutamate decarboxylase 2
PRNP	3	Prion protein	*GDI1*	2	GDP dissociation inhibitor 1
AVPR1A	2.5	Arginine vasopressin receptor 1A	*GRID1*	2	Glutamate ionotropic receptor delta type subunit 1
CHMP2B	2.5	Charged multivesicular body protein 2B	*GRN*	2	Granulin
EN2	2.5	Engrailed homeobox 2	*GSK3A*	2	Glycogen synthase kinase 3 alpha
FGF14	2.5	Fibroblast growth factor 14	*HSF1*	2	Heat shock transcription factor 1
HDAC4	2.5	Histone deacetylase 4	*LAMA2*	2	Laminin subunit alpha 2
KCNJ18	2.5	Potassium voltage-gated channel subfamily J member 18	*MAPK15*	2	Mitogen-activated protein kinase 15
LRRC7	2.5	Leucine rich repeat containing 7	*MME*	2	Membrane metalloendopeptidase
SERPINI1	2.5	Serpin family I member 1	*NFKB1*	2	Nuclear factor kappa B subunit 1
ACHE	2	Acetylcholinesterase (Cartwright blood group)	*NPY1R*	2	Neuropeptide Y receptor Y1
ALDH5A1	2	Aldehyde dehydrogenase 5 family member A1	*OSMR*	2	Oncostatin M receptor
ALK	2	Anaplastic lymphoma receptor tyrosine kinase	*PNOC*	2	Prepronociceptin
CACNB3	2	Calcium voltage-gated channel auxiliary subunit beta 3	*RBFOX1*	2	RNA-binding protein, fox-1 homolog 1
CADM1	2	Cell adhesion molecule 1	*SPAST*	2	Spastin
CRHR1	2	Corticotropin releasing hormone receptor 1	*SYN1*	2	Synapsin I
DNAJB5	2	DnaJ heat shock protein family (Hsp40) member B5	*WDR62*	2	WD repeat domain 62



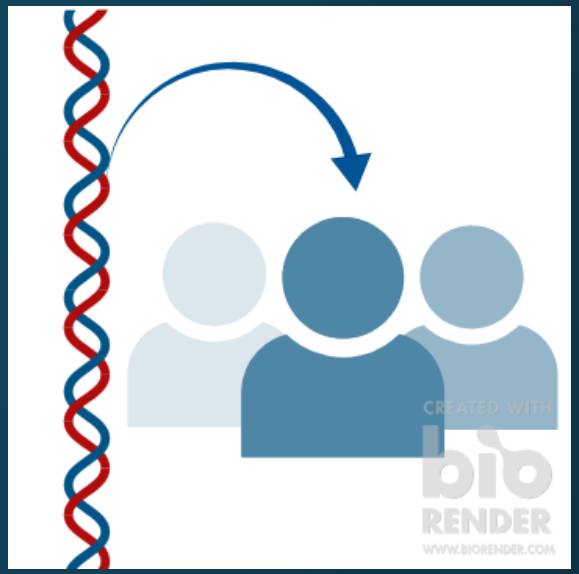
Networks were identified by ingenuity pathway analysis' network generation algorithm using direct relationships from the Ingenuity® Knowledge Base

Zhang-James, et al., (2018)

Aggression summary

- Knocking out the function of the rate-limiting enzyme for serotonin synthesis (Tph2) is associated with increased aggression in mice
- Studies of aggression genetics in humans have been equivocal due to small effect sizes and contributions of context and life history
- Genes associated with aggression produce proteins involved in complex networks of basic neural and cellular functions
- **Points to emphasize to students**
  - Risk for aggression appears to have a genetic component
    - Polygenic
    - Strongly moderated by environment
  - Genes do not **cause** aggression, people have substantial control over whether they act aggressively

Genetic Essentialism



- Bias that genetic attributions for human conditions such that those conditions are more likely to be perceived as:
  - Immutable, stable and inevitable
  - Having a specific etiology
  - Homogeneous and discrete
  - Natural or moral
- It is important to emphasize to students
  - Genetic association does not mean inevitable
  - Genes do not control behaviors, but act as members of biological networks
    - Genetic effects on behaviors are typically weak and indirect
  - Genes are not morality indicators

Conclusion

- Behavior genetic concepts and findings are relevant across the psychology curriculum
- A well-chosen example can help to introduce behavior genetics
- Although genes do not determine behaviors, genetic differences can help to explain individual differences in behavior

Questions?