MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Genetics of Substance Use Disorders

Robert Althoff, MD, PhD

Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

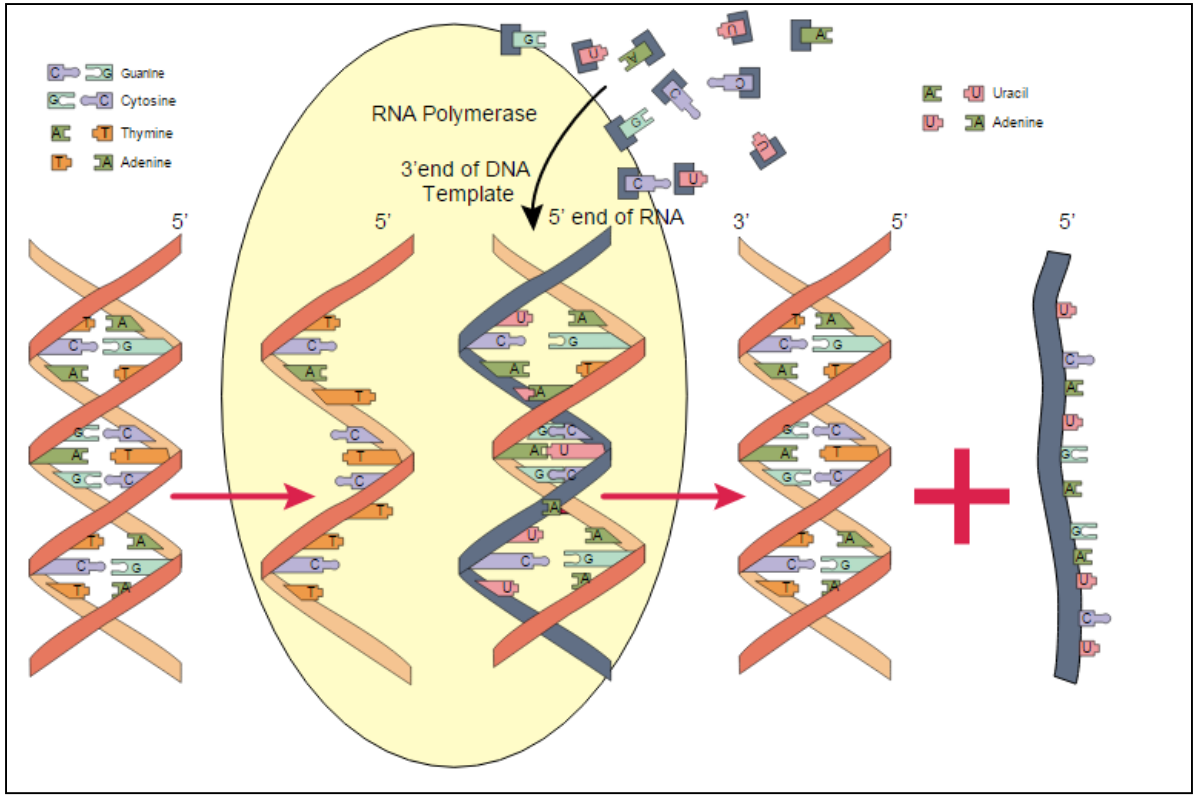
- I receive or have received research support from NIMH, NIDA, and the Klingenstein Third Generation Foundation
- I have ownership equity in WISER Systems, LLC as a partner.

Agenda

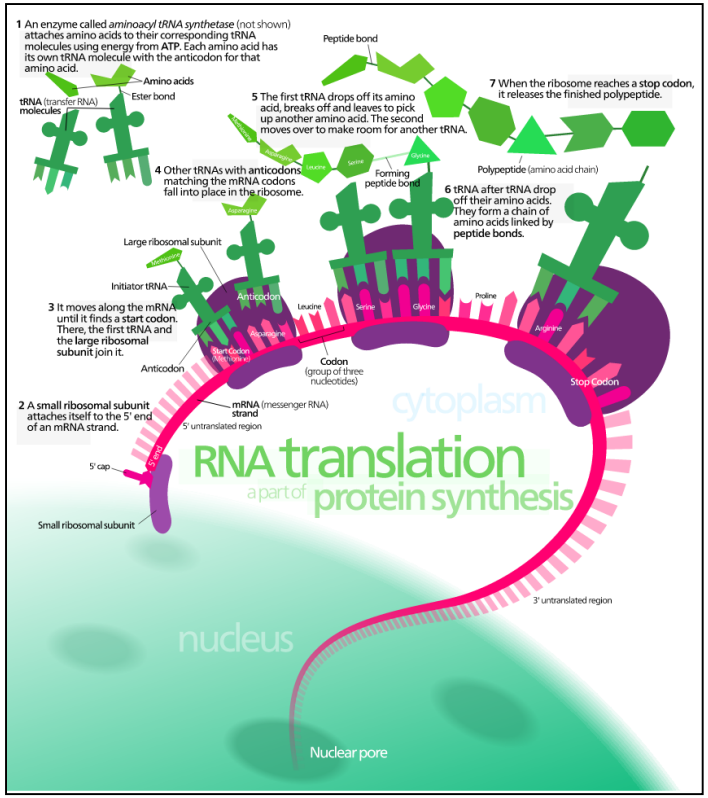
- Briefly review the concepts of genetics and genetic epidemiology
- Discuss heritability of substance use disorders
- Discuss gene x environment interactions and substance use disorders
- Discuss specific genes associated with substance use disorders

Central Dogma

- DNA →RNA →Protein

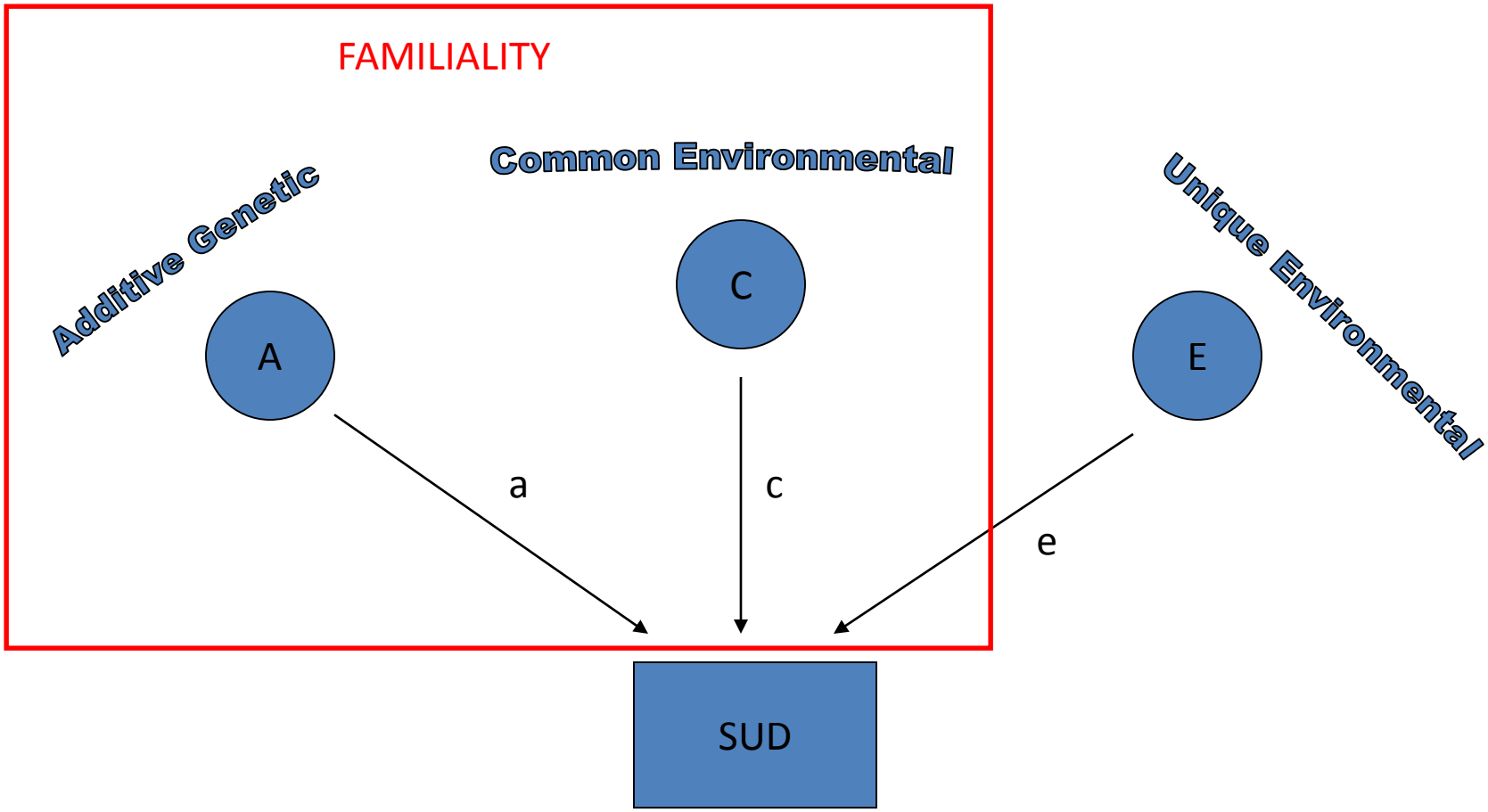


"Rna syn" by Fred the Oyster. The source code of this SVG is valid. This vector graphics image was created with Adobe Illustrator.. Licensed under GFDL via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Rna_syn.svg#/media/File:Rna_syn.svg

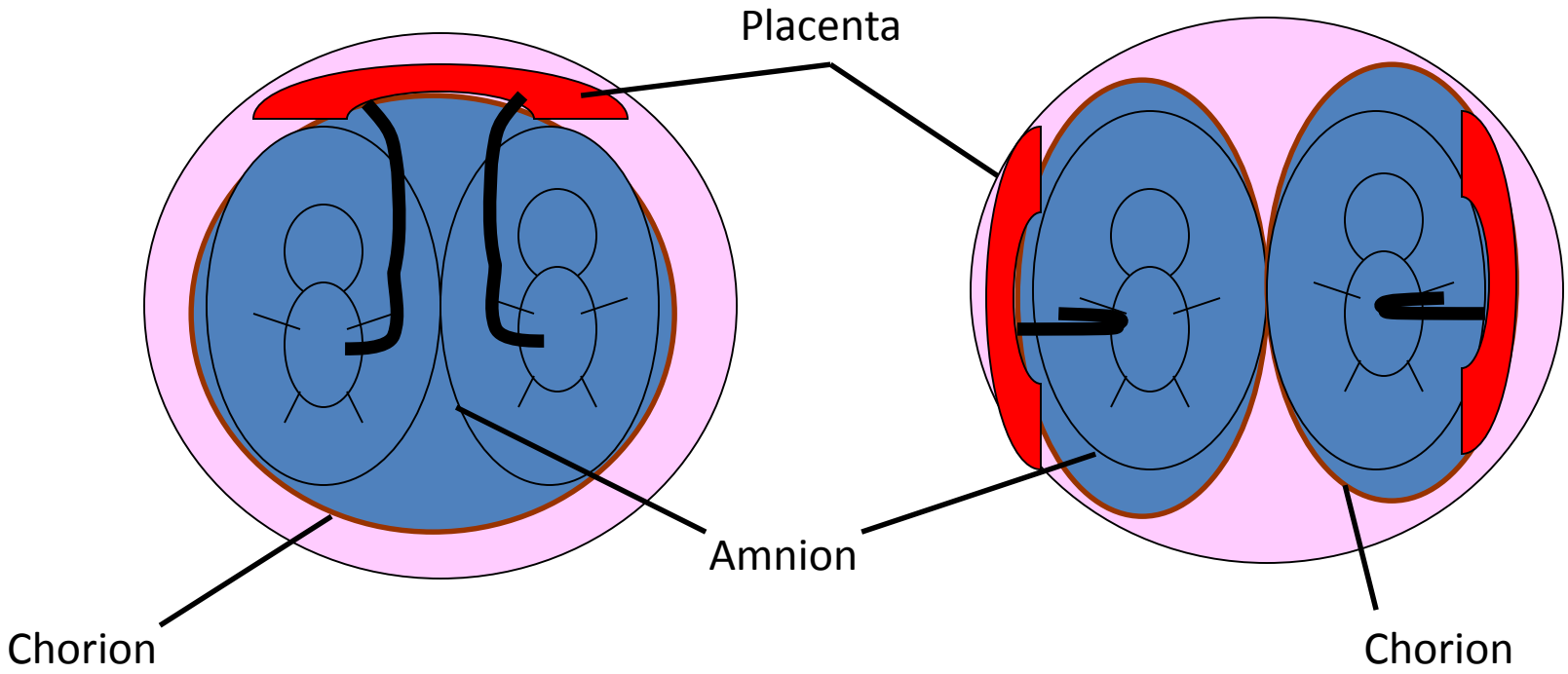


By Kelvinsong (Own work) [CC BY 3.0 (http://creativecommons.org/licenses/by/3.0)], via Wikimedia Commons

Genetic and Environmental Contributions to SUD



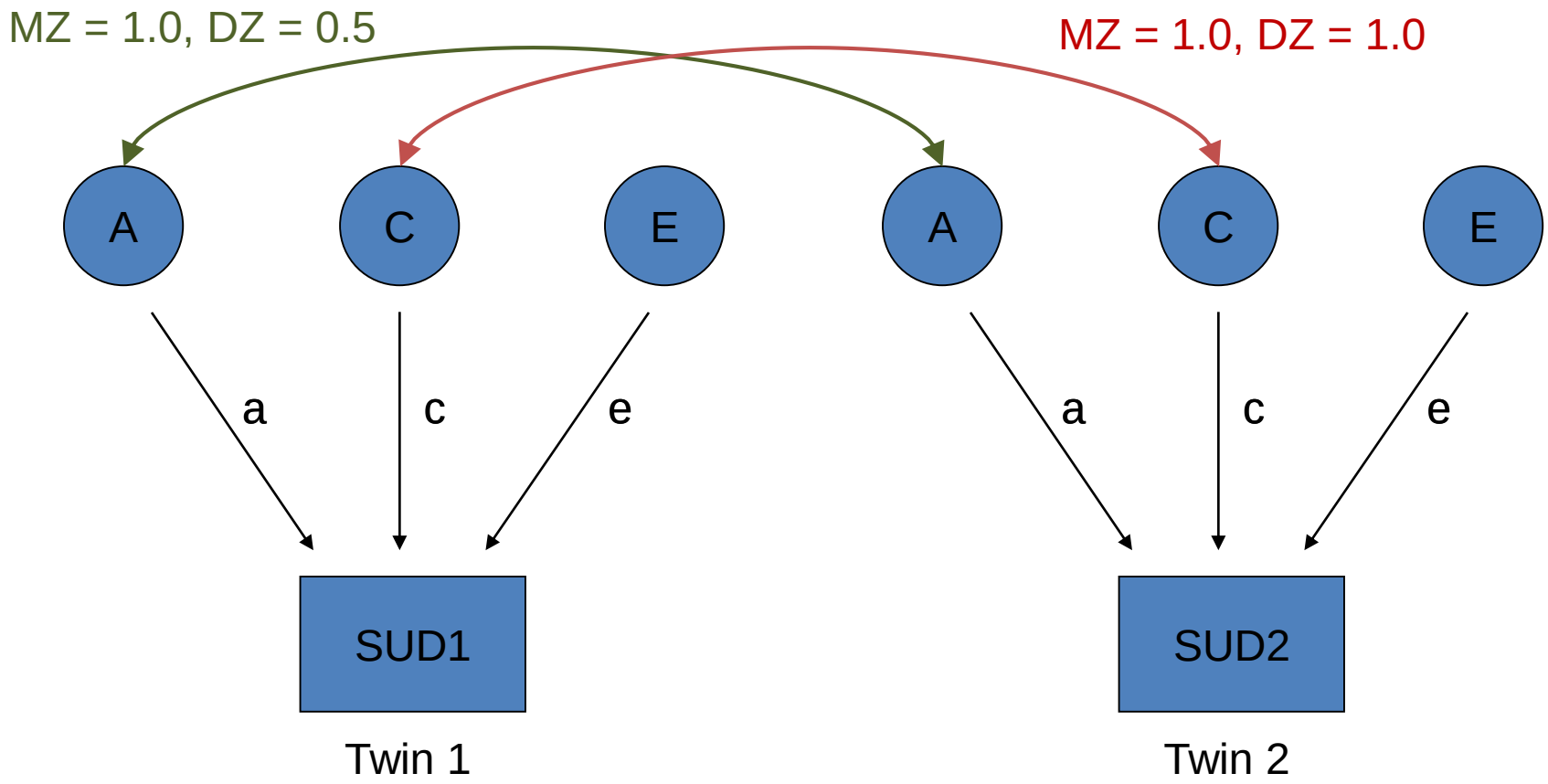
Twin Studies



Monozygotic (MZ) twins
Share 100% of DNA

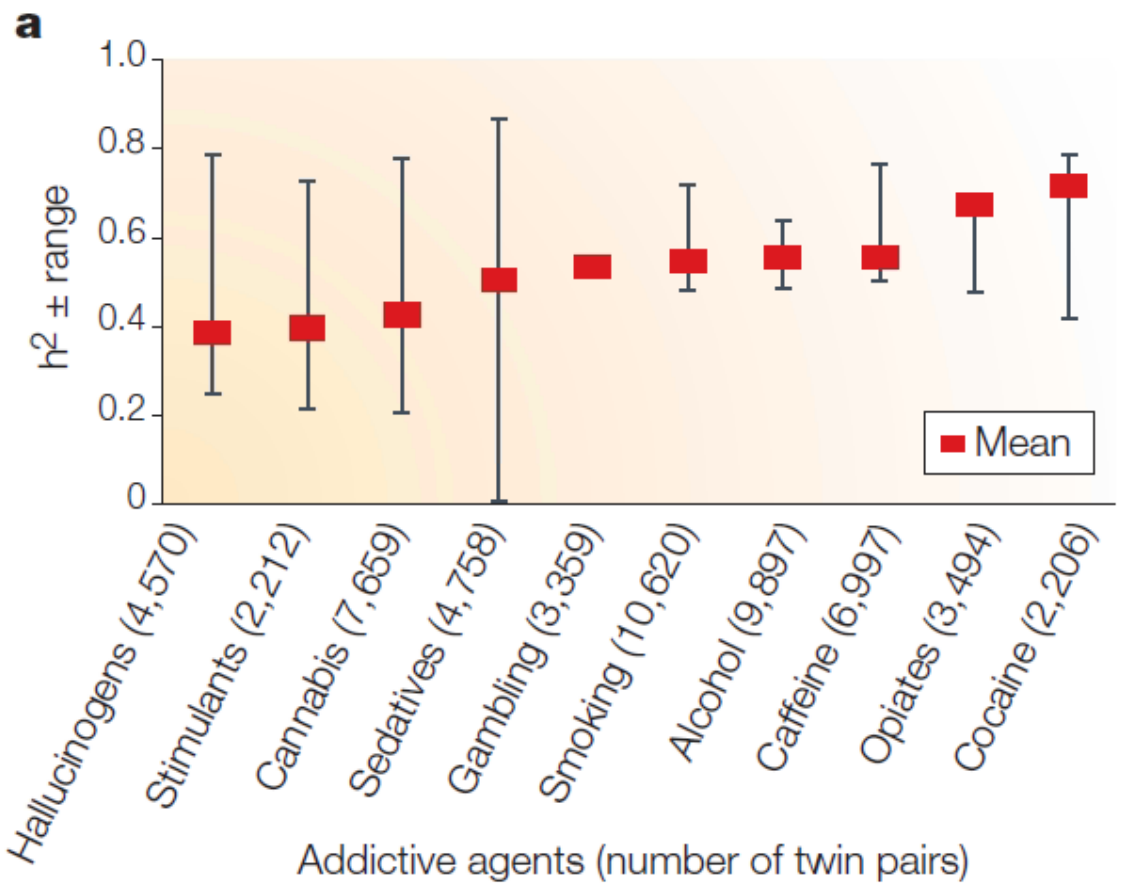
Dizygotic (DZ) twins
Share 50% of DNA

Twin Models



Heritability of SUDs

Heritabilities range from 40-70% for all substances, with the highest numbers being for cocaine abuse



From Goldman, Oroszi & Ducci (2005)

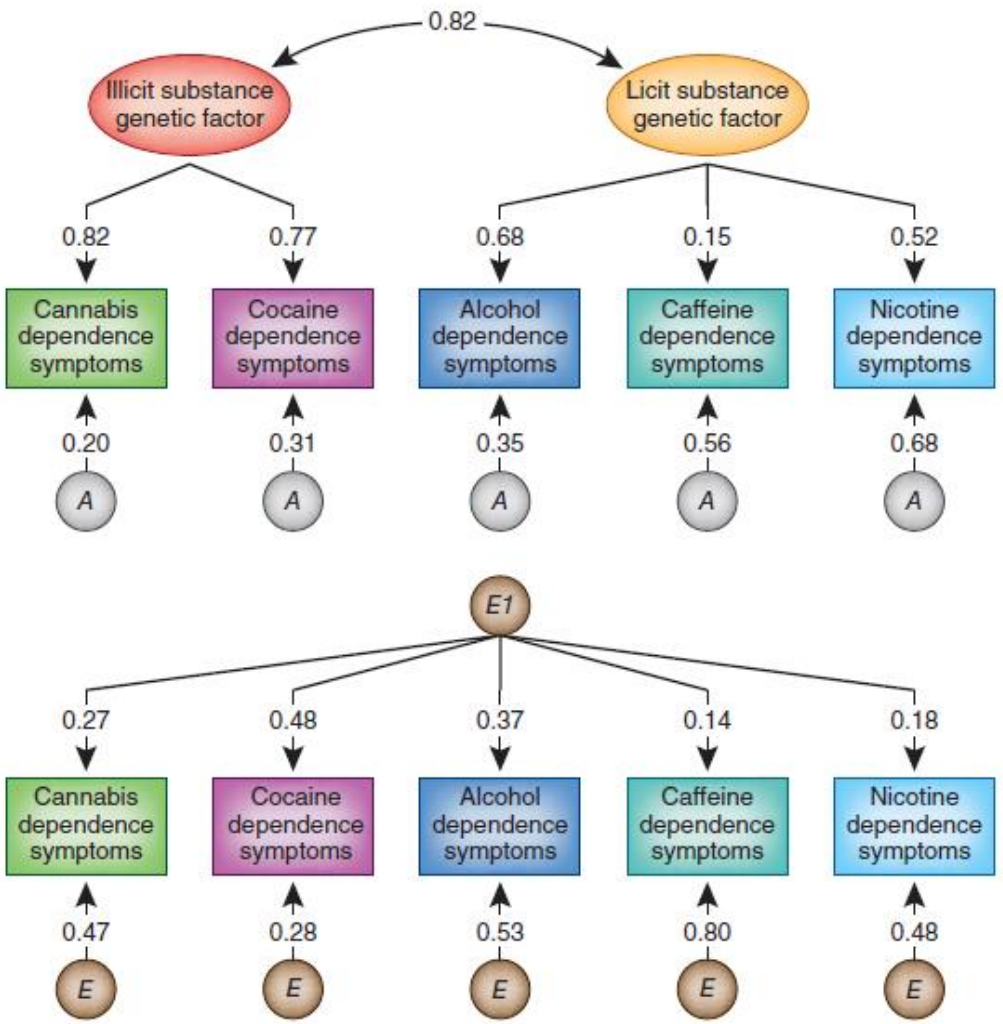
How Specific is the Heritability?

Fairly specific for nicotine and caffeine.

Not as much for others.

So, there are some general factors associated with broad liability.

There are also broad genetic associations with other psychiatric disorders such as externalizing disorders.



From Kendler et al (2012)

The Environment

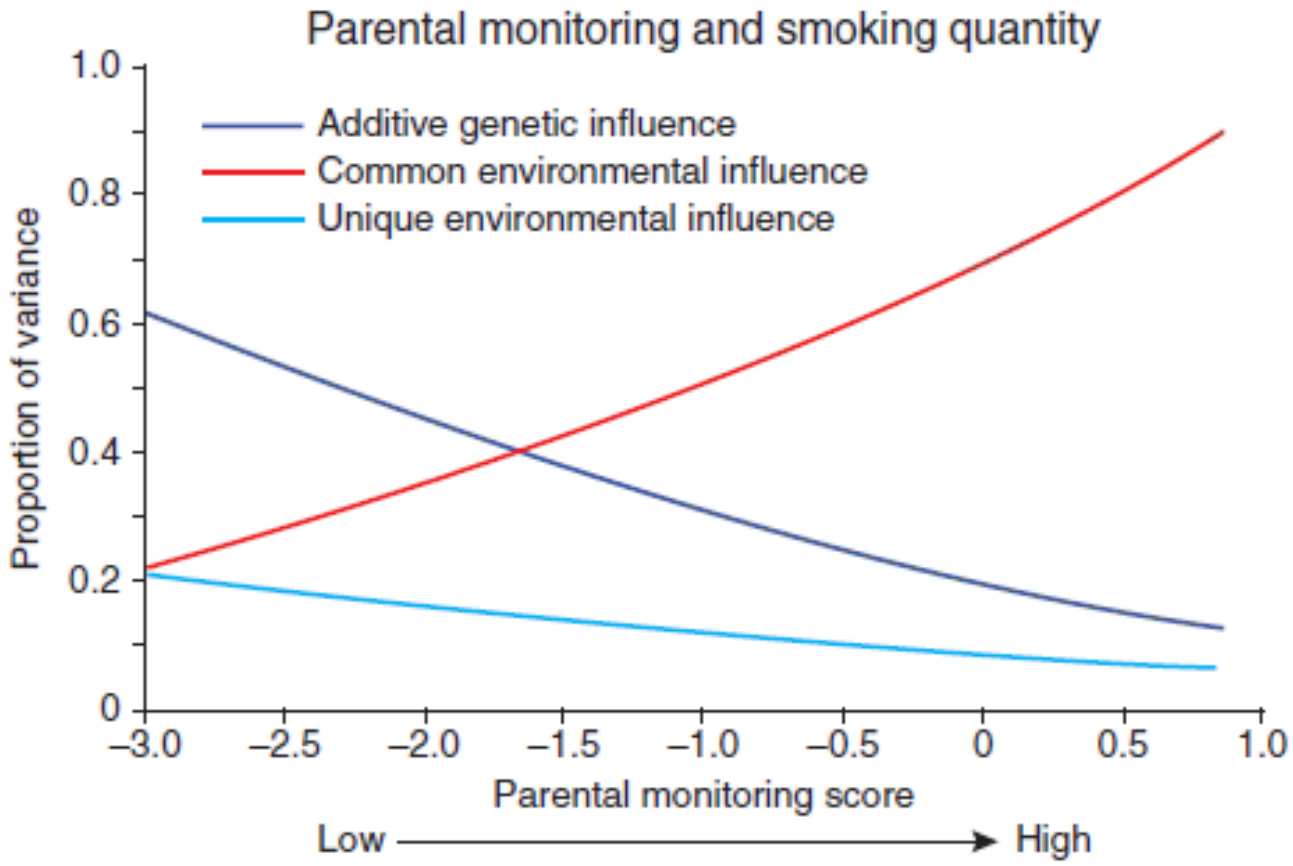
"What is inherited is the manner of reaction to a given environment"

- Dr. Elmer G. Heyne (1912 – 1997), Wheat Geneticist

Possible Roles for the Environment

- Direct effects on initiation and maintenance of SUDs
  - For example, heritability of smoking is almost zero at age 13, but increases with age
  - As twins age, genetic factors emerge
  - More on this in developmental precursors section
- Gene-environment correlation
  - Genetic factors associated with SUDs and with environments that promote them are correlated
  - For example, antisocial behavior
- Gene-environment interaction
  - Genetic risk only evident when placed in a fertile environment

Gene–Environment Interaction



Data from Dick et al (2007)

Gene–Environment Interaction

- Other factors that reduce genetic risk of SUD:
  - Religiosity
  - Rural settings, neighborhoods with less migration
  - High parental monitoring
  - Legislative restrictions
  - Social restrictions (eg. increased heritability of tobacco use disorders in women over the past half century)

Specific Molecular Genetic Risks

- Broad heritabilities not useful clinically
- Are there specific genes that place one at risk?
- Results from either:
  - Candidate gene studies: studies that examine specific genes thought to be associated
  - Genome-Wide Association Studies (GWAS): studies that look at markers across the entire genome
  - There have been 106 published studies using GWAS indexed in PubMed in just past 12 months
  - There has been one very large GWAS of alcohol and smoking (N = 1.2 Million) published in *Nature Genetics* in January, 2019
  - There was a large GWAS of cannabis use (N = ~384K) published in *Lancet Psychiatry* in December, 2020

Molecular Genetic Findings: Nicotine

- Single-nucleotide polymorphisms (SNPs) most likely to be involved have been associated with:
  - *CHRNA5, CHRNA3, CHRNB4* – all subunits of nicotine receptor
  - However, these may also be associated with risk for alcohol, cocaine, and opiate use/misuse.
  - Effect sizes are small (Odds Ratios ~1.2 - 1.4)

Molecular Genetic Findings: Alcohol

- Less convincing GWAS data. To date:
  - *GABRA2*- a GABAa receptor subunit gene
  - *PECR* – involved in fatty acid metabolism
  - question of *ALDH2, ADH1A, ADH1B, ADH1C* – alcohol dehydrogenase genes and *CDH13* – a cadherin
  - Certainly nothing that could be considered a biomarker
  - Heritability 60%, SNP heritability 33% (Mbarek et al 2015)

Molecular Findings Alcohol and Smoking

Table 1 | Non-synonymous sentinel variants

Phenotype	Gene	rsID	Chr	Position	REF	ALT	AF	Beta	*P*	*N*	*Q*
CigDay (SmkCes)	*CHRNA5*	rs16969968[a]	15	78,882,925	G	A	0.34	0.075	1.2×10^{-278}	330,721	0.34
CigDay	*HIST1H2BE*	rs7766641	6	26,184,102	G	A	0.27	−0.014	2.9×10^{-10}	335,553	0.78
CigDay (AgeSmk)	*GRK4*	rs1024323	4	3,006,043	C	T	0.38	−0.012	8.7×10^{-9}	337,334	0.17
SmkInit	*REV3L*	rs462779[a]	6	111,695,887	G	A	0.81	−0.019	4.5×10^{-29}	1,232,091	0.67
SmkInit (DrnkWk)	*BDNF*	rs6265	11	27,679,916	C	T	0.20	−0.016	2.8×10^{-19}	1,232,091	0.13
SmkInit	*RHOT2*	rs1139897	16	720,986	G	A	0.23	−0.012	1.8×10^{-15}	1,232,091	0.61
SmkInit (DrnkWk)	*ZNF789*	rs6962772[a]	7	99,081,730	A	G	0.15	−0.015	2.1×10^{-14}	1,232,091	0.92
SmkInit	*BRWD1*	rs4818005[a]	21	40,574,305	A	G	0.58	−0.010	3.9×10^{-14}	1,232,091	0.75
SmkInit	*ENTPD6*	rs6050446	20	25,195,509	A	G	0.97	0.035	8.8×10^{-13}	1,225,969	0.33
SmkInit	*RPS6KA4*	rs17857342[a]	11	64,138,905	T	G	0.38	−0.010	9.8×10^{-12}	1,232,091	0.16
SmkInit	*FAM163A*	rs147052174	1	179,783,167	G	T	0.02	0.037	2.3×10^{-10}	1,232,091	0.59
SmkInit	*PRRC2B*	rs34553878	9	134,907,263	A	G	0.11	0.016	1.2×10^{-9}	1,232,091	0.28
SmkInit	*ADAM15*	rs45444697[a]	1	155033918	C	T	0.21	0.010	5.3×10^{-9}	1,232,091	0.46
SmkInit	*MMS22L*	rs9481410[a]	6	97,677,118	G	A	0.76	0.010	1.1×10^{-8}	1,232,091	0.04
SmkInit	*QSER1*	rs62618693	11	32,956,492	C	T	0.04	−0.020	2.1×10^{-8}	1,232,091	1.00
DrnkWk	*ADH1B*	rs1229984	4	100,239,319	T	C	0.96	0.060	2.2×10^{-308}	941,280	0.05
DrnkWk	*GCKR*	rs1260326	2	27,730,940	T	C	0.60	0.008	8.1×10^{-45}	941,280	0.10
DrnkWk	*SLC39A8*	rs13107325	4	103,188,709	C	T	0.07	−0.009	1.5×10^{-22}	941,280	0.33
DrnkWk	*SERPINA1*	rs28929474	14	94,844,947	C	T	0.02	−0.012	1.3×10^{-11}	941,280	0.50
DrnkWk (SmkInit)	*ACTR1B*	rs11692465	2	98,275,354	G	A	0.09	0.008	2.5×10^{-11}	937,516	0.40
DrnkWk	*TNFSF12-13*	rs3803800	17	7,462,969	A	G	0.79	0.004	1.5×10^{-10}	941,280	0.67
DrnkWk	*HGFAC*	rs3748034	4	3,446,091	G	T	0.14	−0.005	1.7×10^{-8}	941,280	0.65

The sentinel variant in approximately 4% of loci was non-synonymous. Shown here are all non-synonymous sentinel variants, and all non-synonymous variants in near-perfect LD with a sentinel variant. If the listed gene was also associated (through single variant or gene-based test) with another phenotype, that phenotype is listed in parentheses. Several genes have been implicated in previous studies of substance use/addiction, including *CHRNA5*, *BDNF*, *GCKR*, and *ADH1B*. Phenotype abbreviations are defined in Fig. 1. Chr, chromosome; REF, reference allele; ALT, alternate allele; AF, allele frequency of ALT; *Q*, Cochrane's *Q* statistic *P* value. [a]These variants were not themselves sentinel, but were in near-perfect LD with a sentinel variant ($r^2 > 0.99$, from the 1000 Genomes European population). The scale of Beta is on the unit of the standard deviation of the phenotype. For binary phenotypes the standard deviation was calculated from the weighted average prevalence across all studies included in the meta-analysis (available in Supplementary Table 7).

SNP Heritability

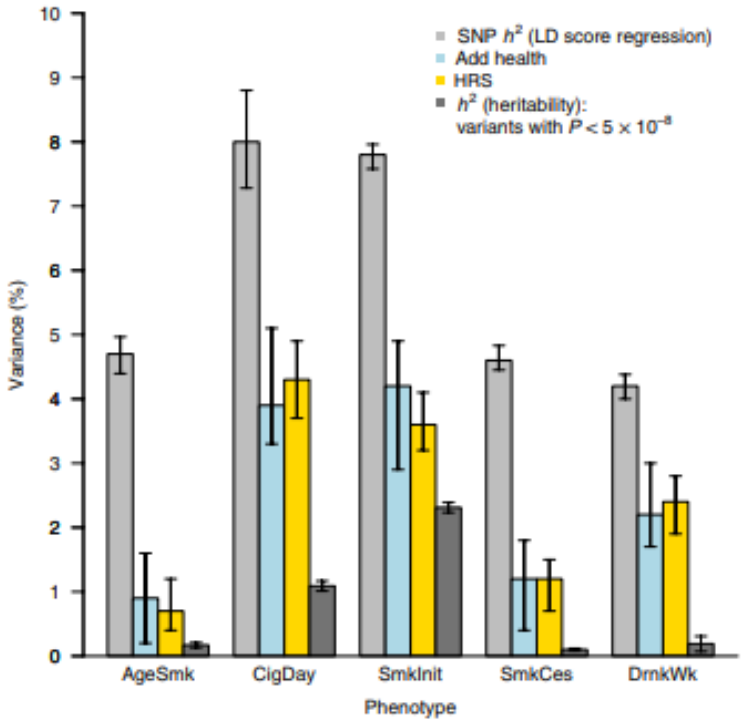


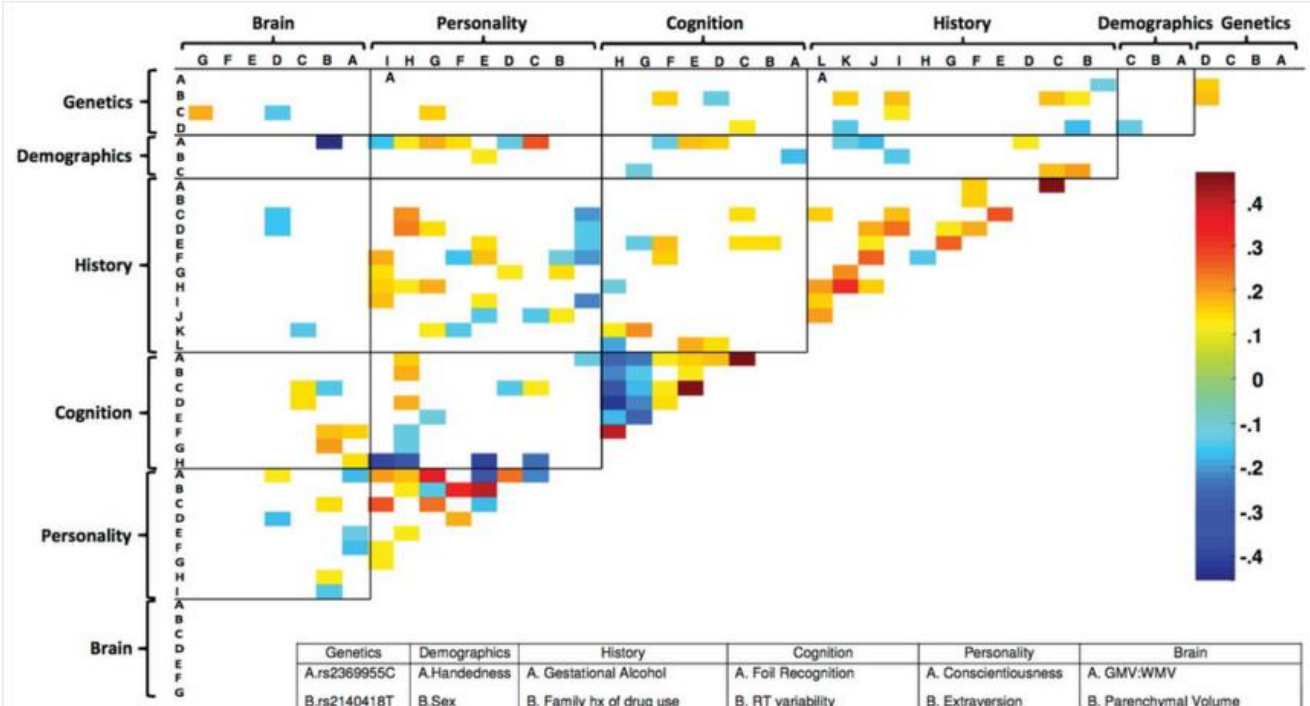
Fig. 3 | Heritability and polygenic prediction. The light gray bars reflect SNP heritability, estimated with LD score regression. The light blue and gold bars reflect the predictive power of a PRS in Add Health and the HRS, respectively. Despite the 41 year generational gap between participants from these two studies, and major tobacco-related policy changes during that time, the polygenic scores are similarly predictive in both samples. Error bars are 95% confidence intervals estimated with 1,000 bootstrapped repetitions. Dark gray bars represent the total phenotypic variance explained by only genome-wide significant SNPs.

Molecular Genetic Findings: Cannabis

- To date:
  - *FOXP2* – a gene regulator associated with cannabis use and speech/language delay
  - *Chromosome 8 locus* – near CHRNA2 and EPHX2
  - Certainly nothing that could be considered a biomarker
  - May be different for cannabis use vs. cannabis use disorder

What Does Predict Later Substance Use?

- Examined prediction of binge drinking 14→16
- Genetics played a small role compared to personality, history, and cognition

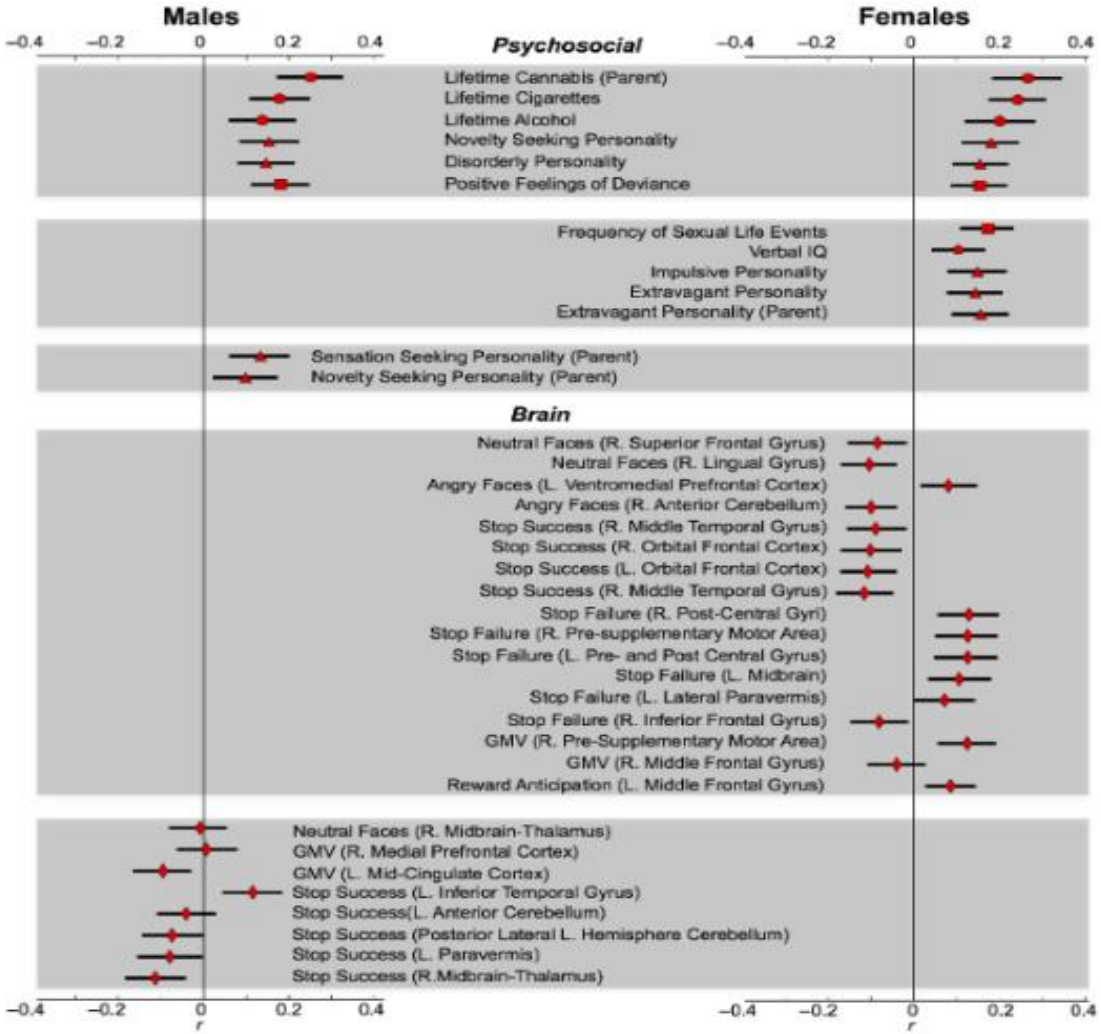


Genetics	Demographics	History	Cognition	Personality	Brain
A.rs2369955C	A.Handedness	A. Gestational Alcohol	A. Foil Recognition	A. Conscientiousness	A. GMV:WMV
B.rs2140418T	B.Sex	B. Family hx of drug use	B. RT variability	B. Extraversion	B. Parenchymal Volume
C.rs10893366T	C.Age	C. Family hx of alcohol use	C. RT mean	C. Neuroticism	C. Regional GMV
D.rs10758821T		D. 1-2 alcohol uses by age 14	D. SWM strategy	D. Sensation seeking	D. Emotional reactivity
		E. Smoking	E. SWM Errors	E. Hopelessness	E. Failed inhibition
		F. Family valence	F. AGN positive omissions	F. Anxiety sensitivity	F. Reward outcome
		G. Deviance valence	G. Verbal IQ	G. Excitability	G. Reward anticipation
		H. Autonomy valence	H. Performance IQ	H. Extravagance	
		I. Romantic history		I. Disorganization	
		J. Deviance history			
		K. Autonomy history			
		L. Accident history			

Data from Whelan et al (2014)

What Does Predict Later Substance Use?

- Examined prediction of cannabis onset 14→16
- Genetics played a very small role compared to personality, history, and cognition



Spechler et al (2018)

Summary

- Substance use disorders are heritable, but probably due to multiple genes with additive effects
- Twin heritabilities higher than SNP heritabilities suggest G x E or epigenetics
- Personality, life history, family history continue to be more reliable and cost-effective screens

Thank you!

Email me at: ralthoff@uvm.edu

Follow me on Facebook:
www.facebook.com/childpsychvt

Or Twitter:
@childpsychvt

Visit our website:
http://www.med.uvm.edu/vccyf

Image Credit: U.S. Department of Energy Human Genome Program