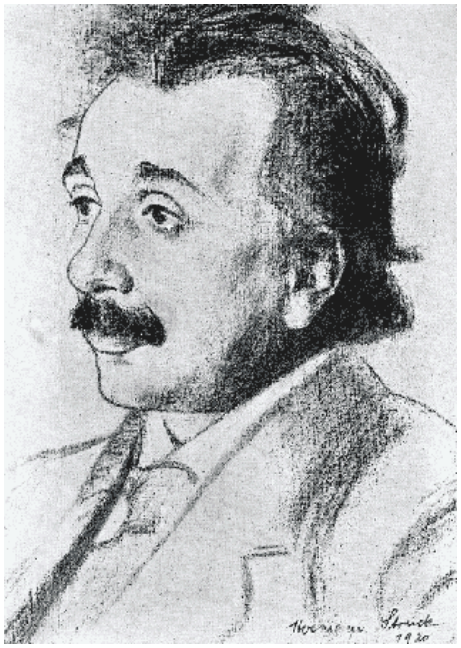
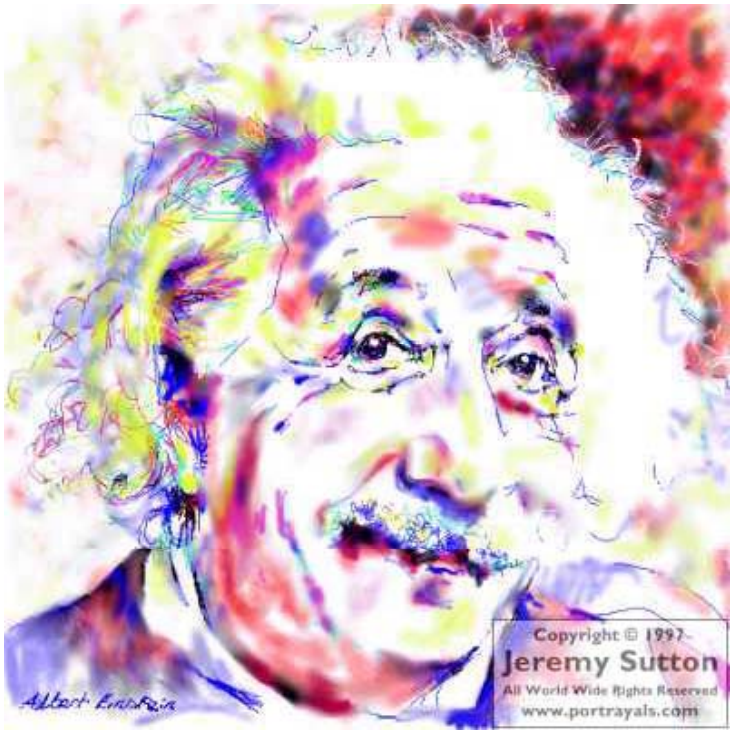
Nature, nurture and complex phenotypes

Andrey Rzhetsky

James Joyce




Albert Einstein
Copyright © 1997
Jeremy Sutton
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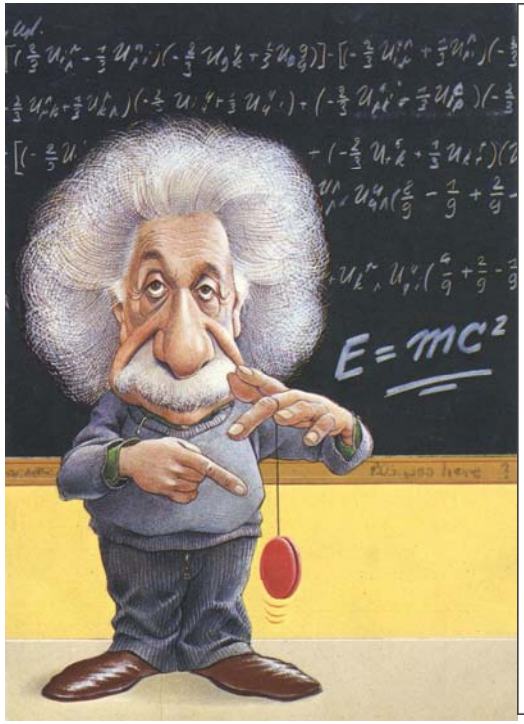
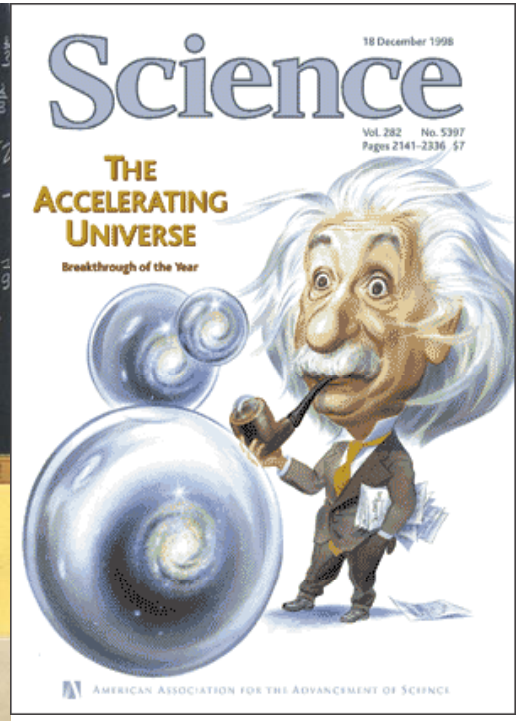
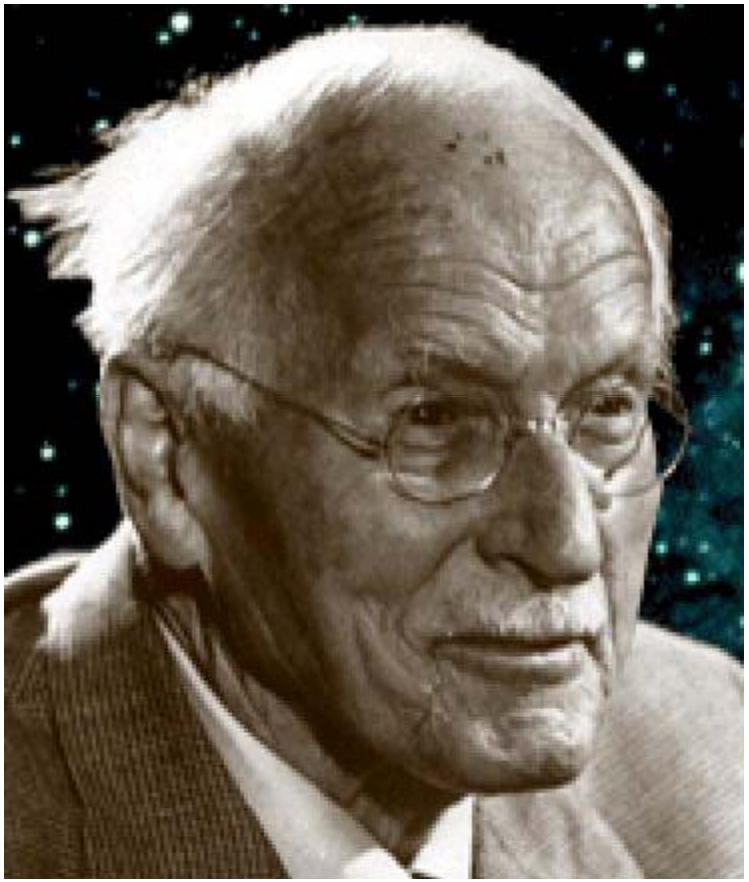
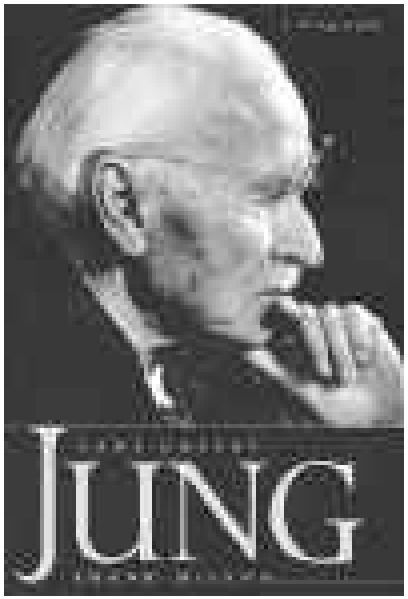
www.portrayals.com

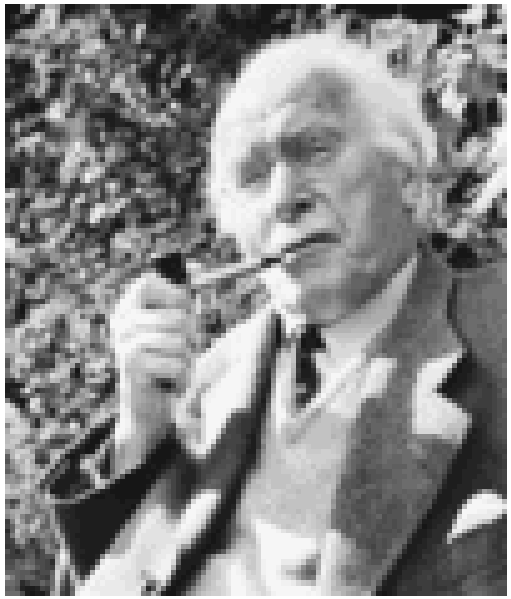

E = mc²


Science
18 December 1998
Vol. 282 No. 5397
Pages 2141–2336 $7
THE ACCELERATING UNIVERSE
Breakthrough of the Year
American Association for the Advancement of Science

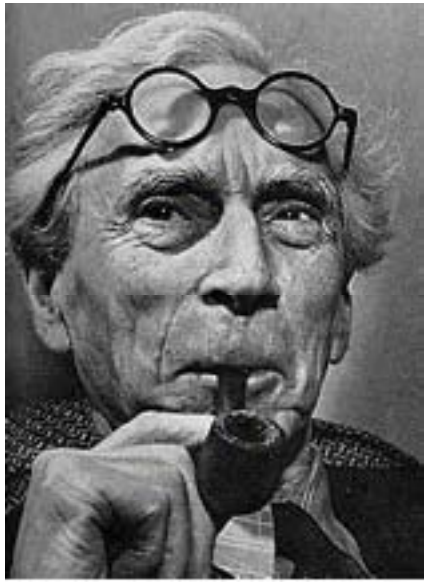


Carl Gustav Jung

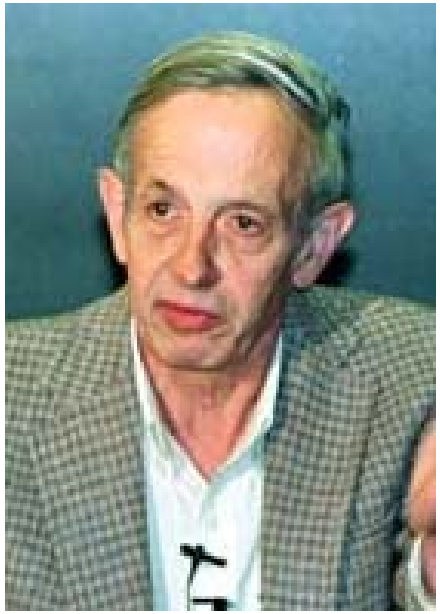


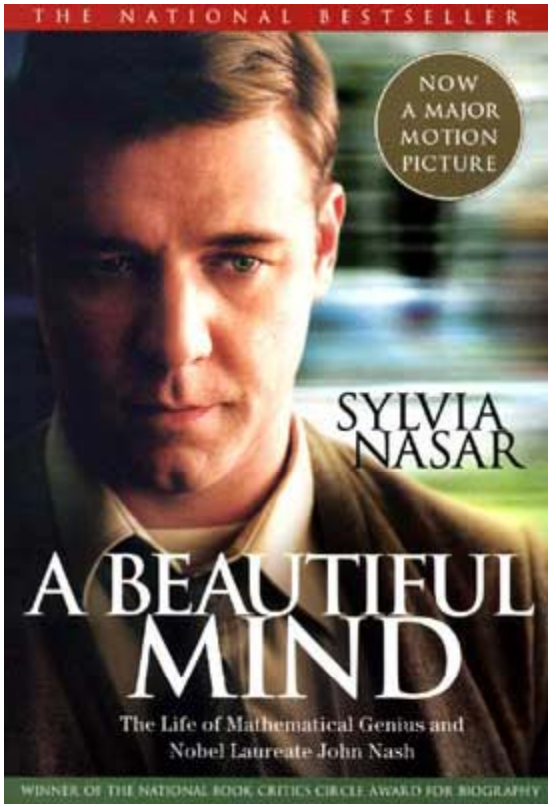


Bertrand Russell



What is common among them?



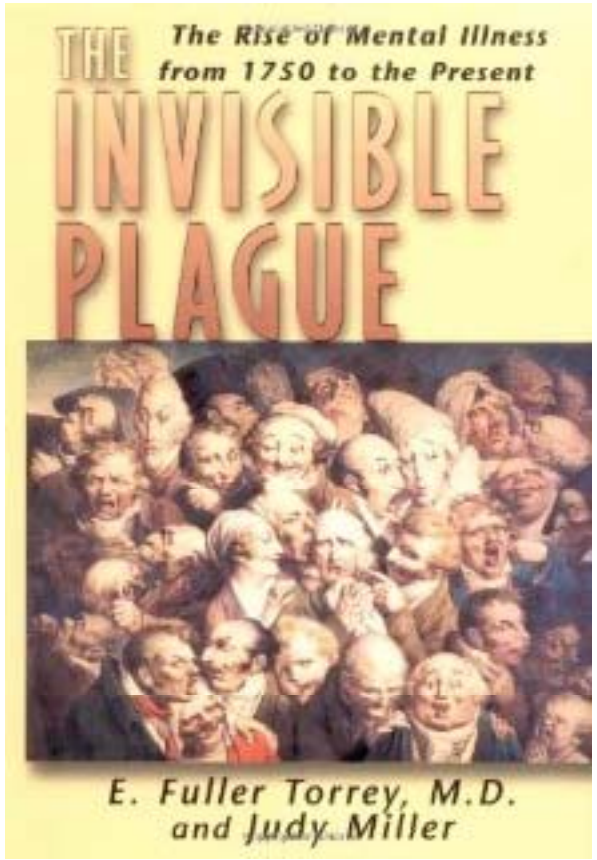

THE NATIONAL BESTSELLER
NOW A MAJOR MOTION PICTURE
SYLVIA NASAR
A BEAUTIFUL MIND
The Life of Mathematical Genius and Nobel Laureate John Nash
WINNER OF THE NATIONAL BOOK CRITICS CIRCLE AWARD FOR BIOGRAPHY

…Schizophrenia affecting one of the close relatives

The invisible plague

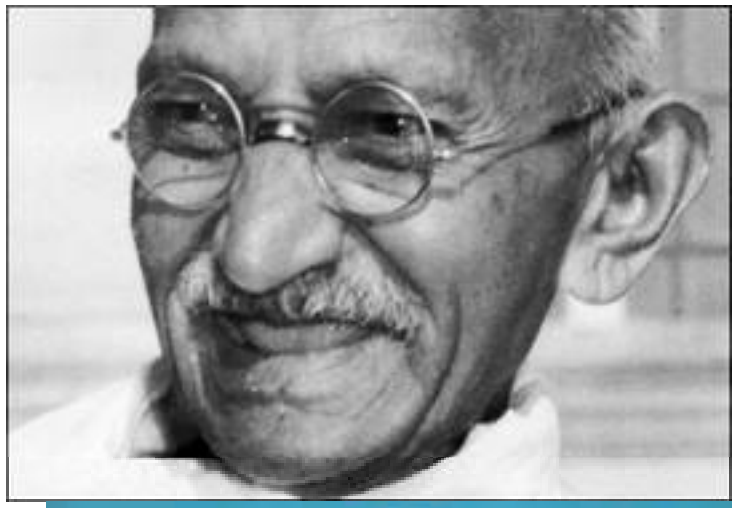
Steady rise
of prevalence
of neurodevelopmental
disorders during
the last 260
years

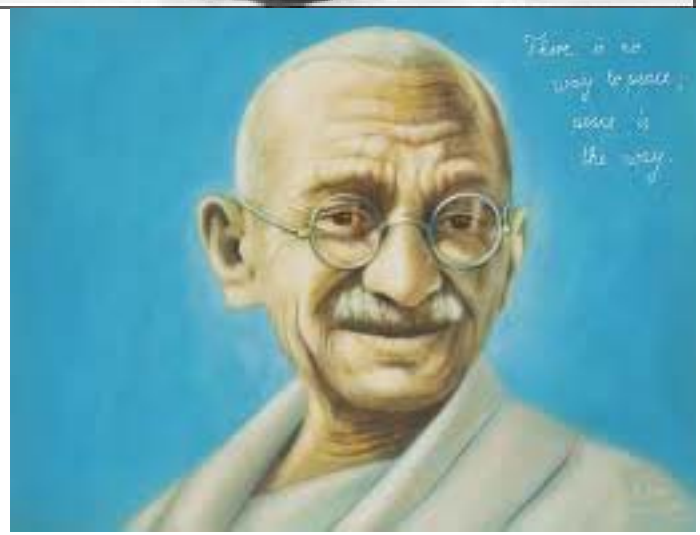
Autism
Bipolar disorder
Schizophrenia



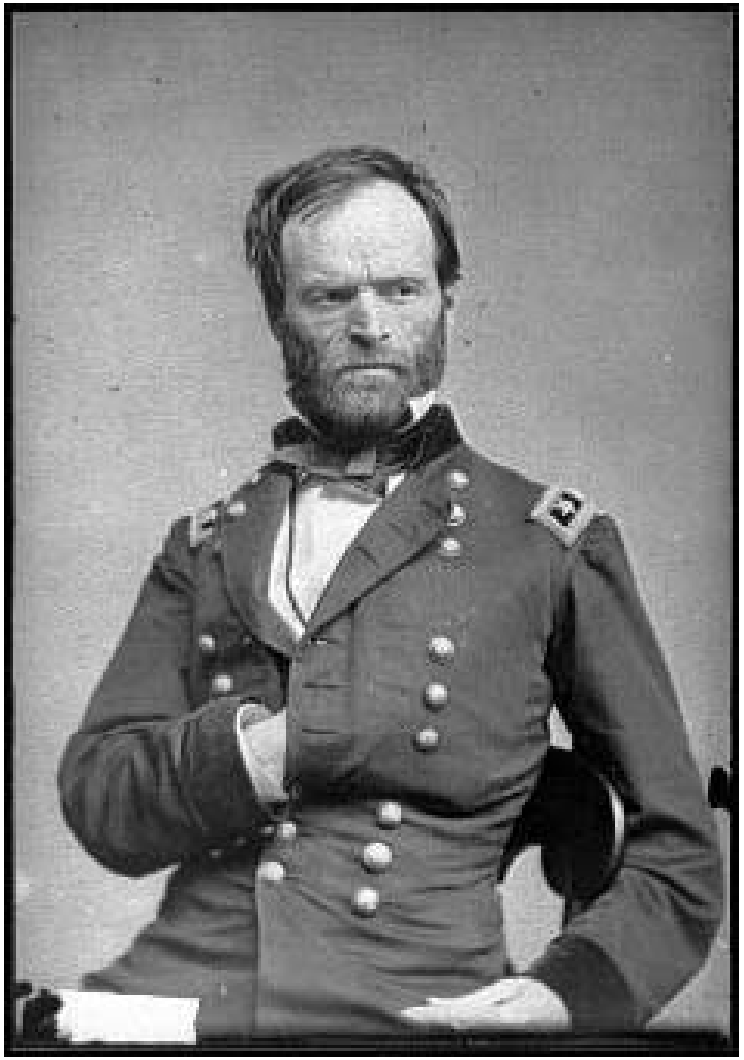
Hypertimic,
autoimmune Addison's disease,
steroid-induced bipolar disorder

Depression





Bipolar

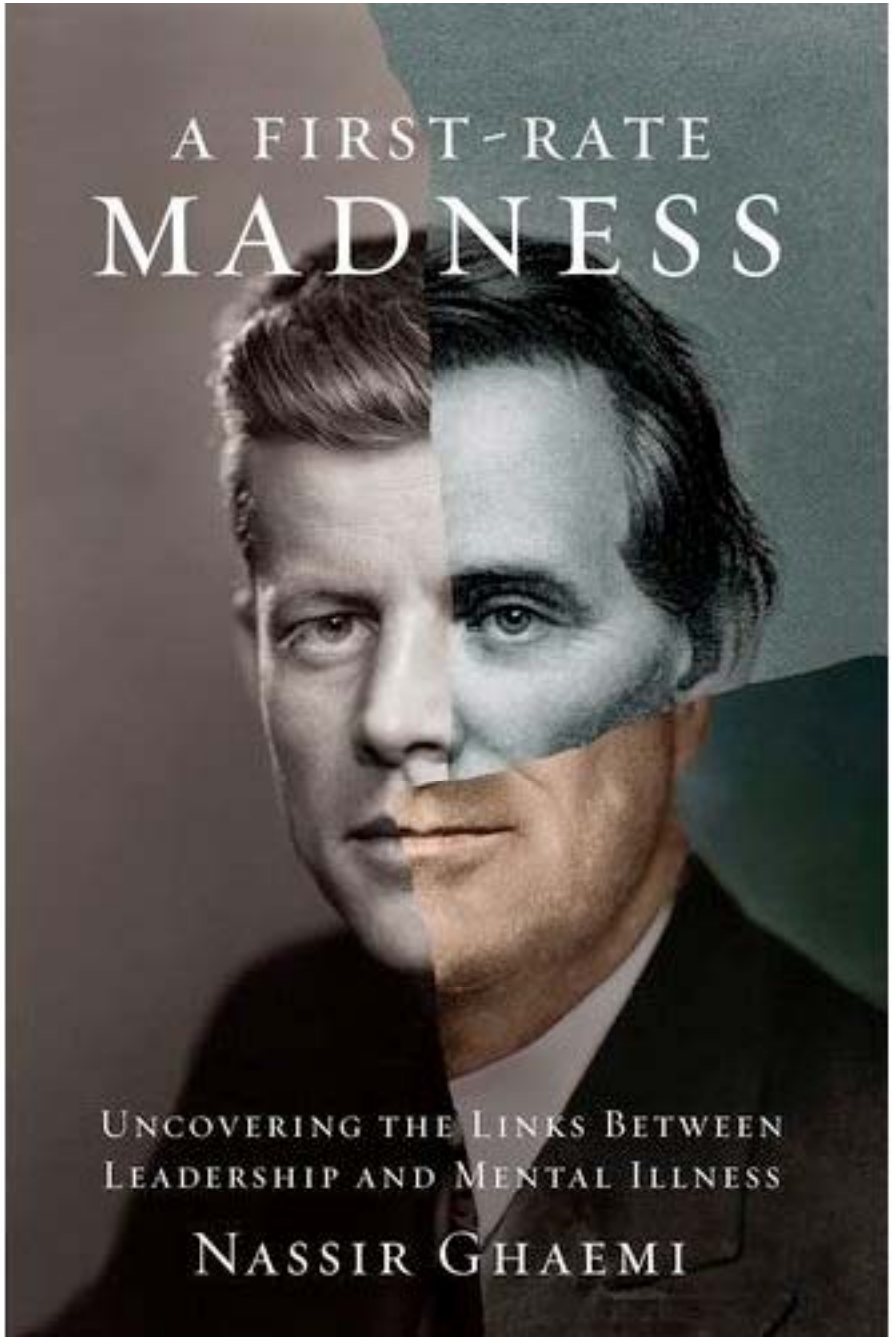


Depression/bipolar

Depression

Bipolar disorder

Hounted by a “black dog” of depression


A FIRST-RATE
MADNESS
Uncovering the Links Between
Leadership and Mental Illness
Nassir Ghaemi

Book's main thesis:

"Insanity" was strength of great leaders, rather than weakness, directly contributing to their success

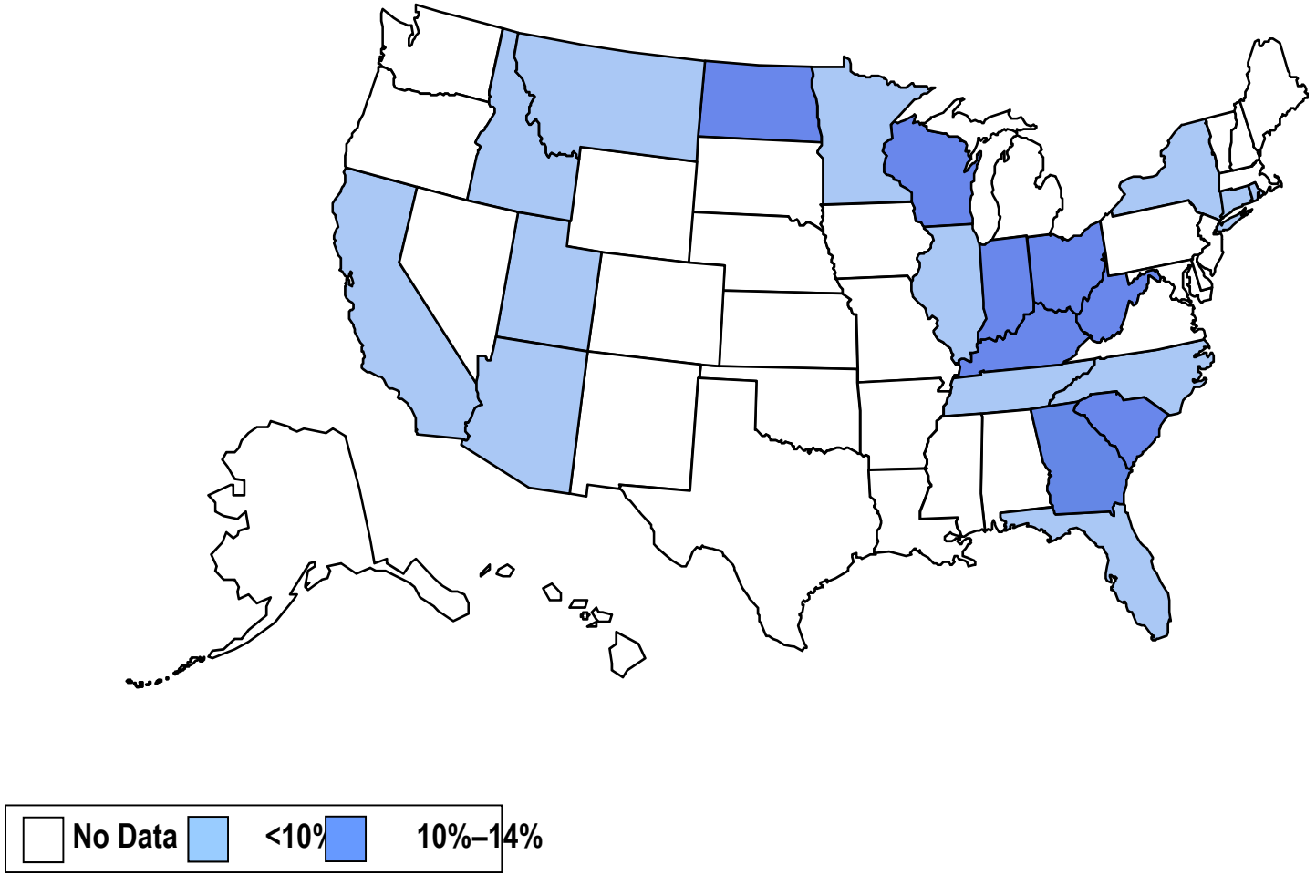
Genetics?

(OBESITY TRENDS in the USA
Source: CDC)

Obesity Trends* Among U.S. Adults

BRFSS, 1985

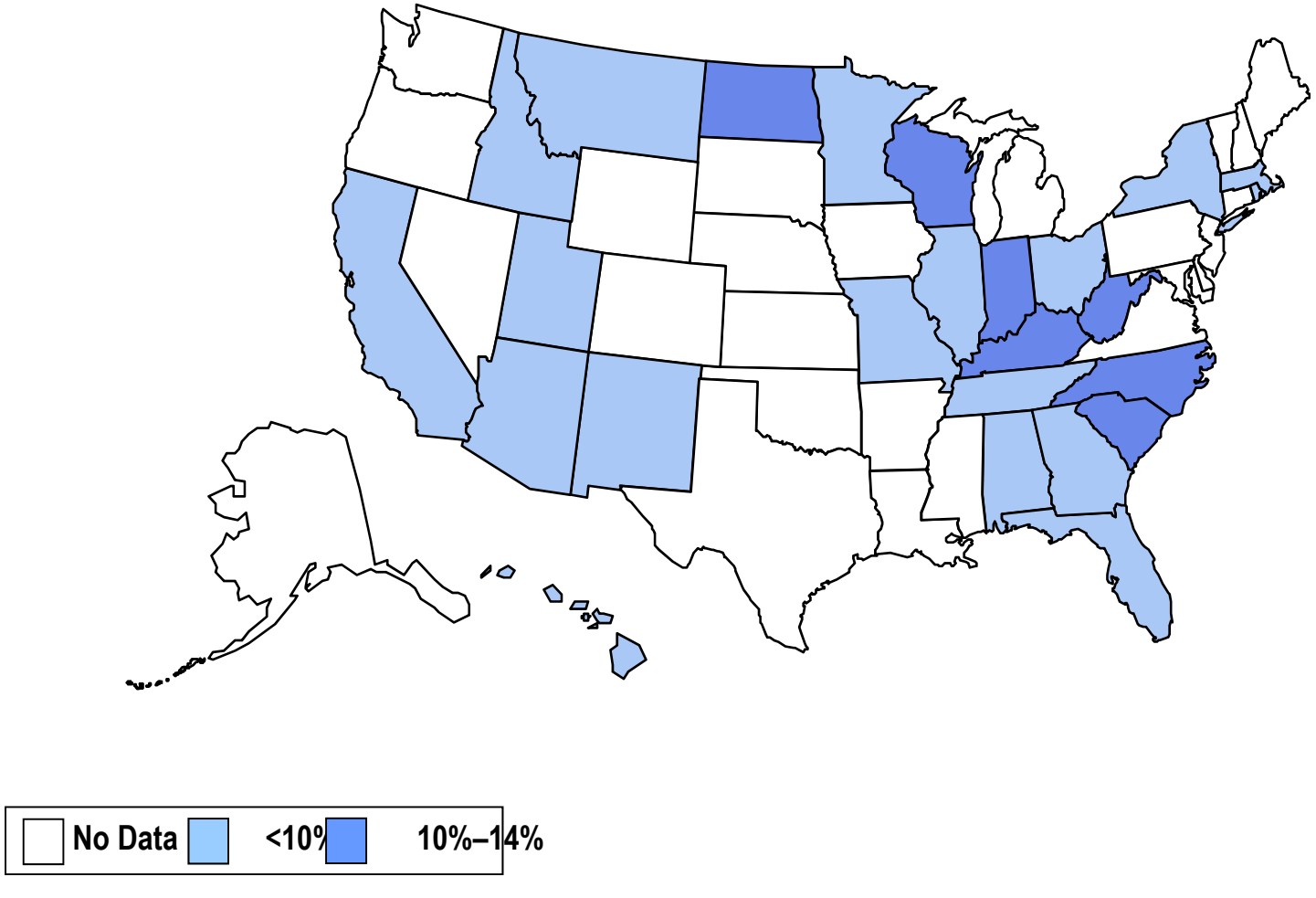
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1986

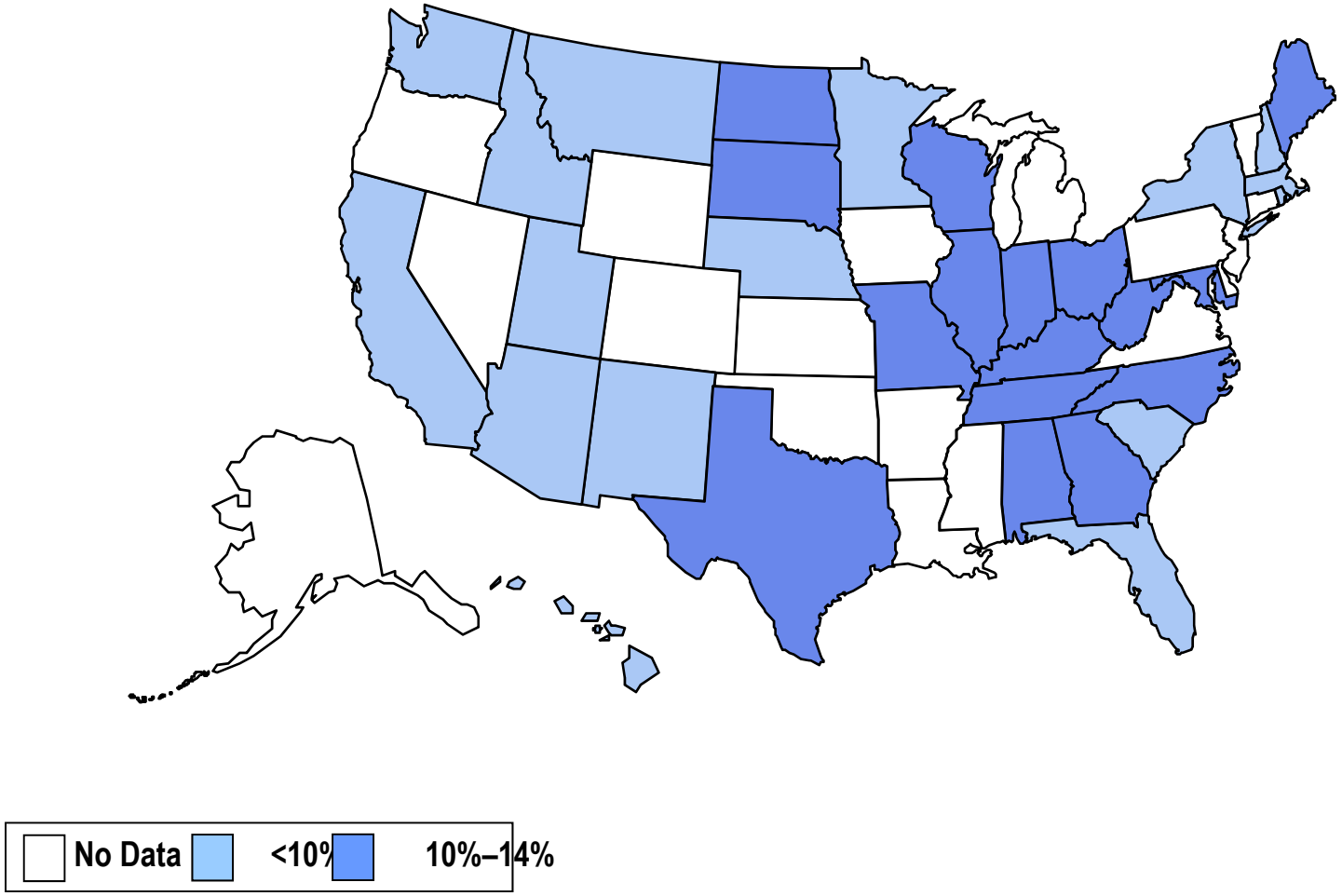
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1987

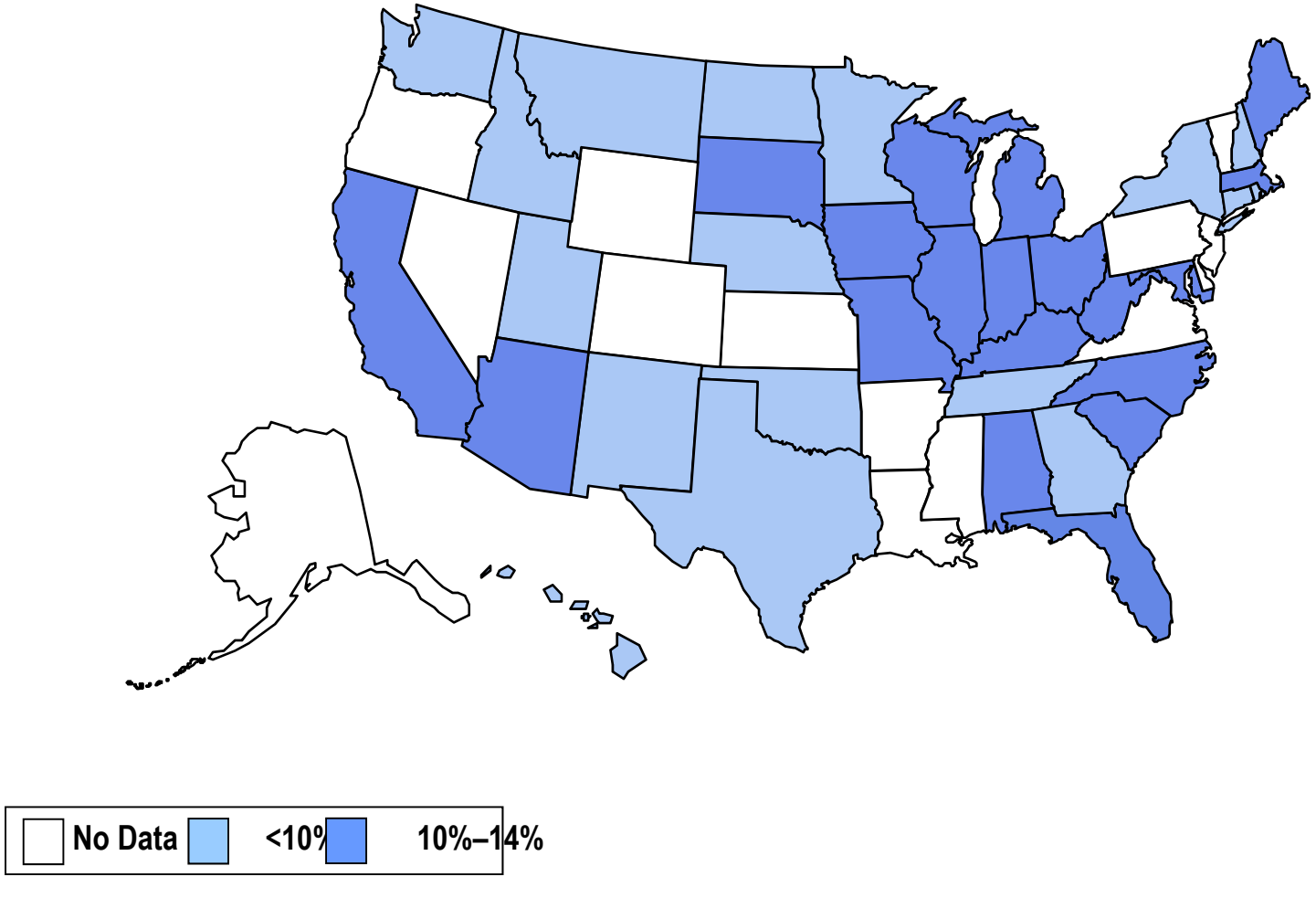
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1988

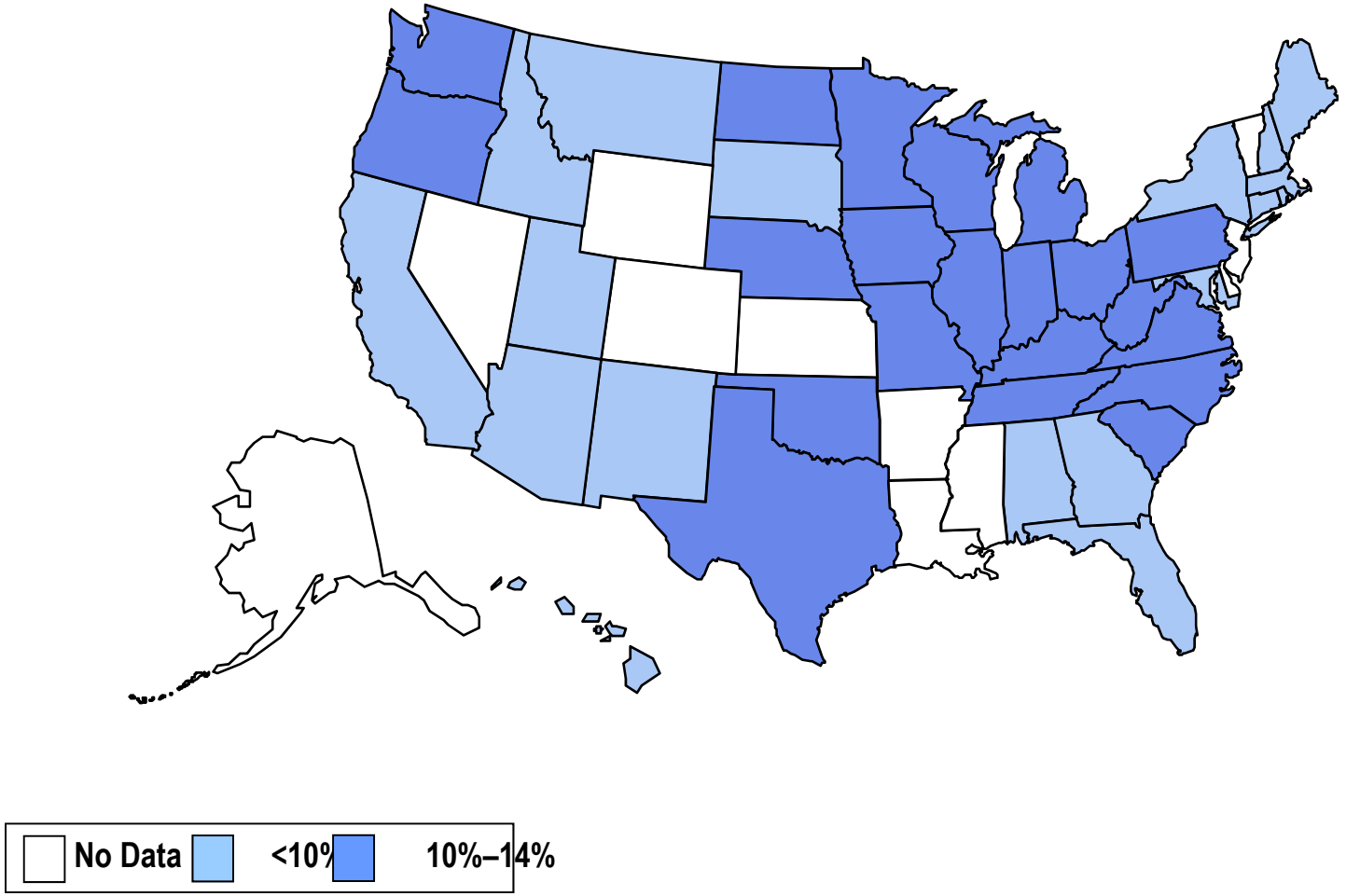
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1989

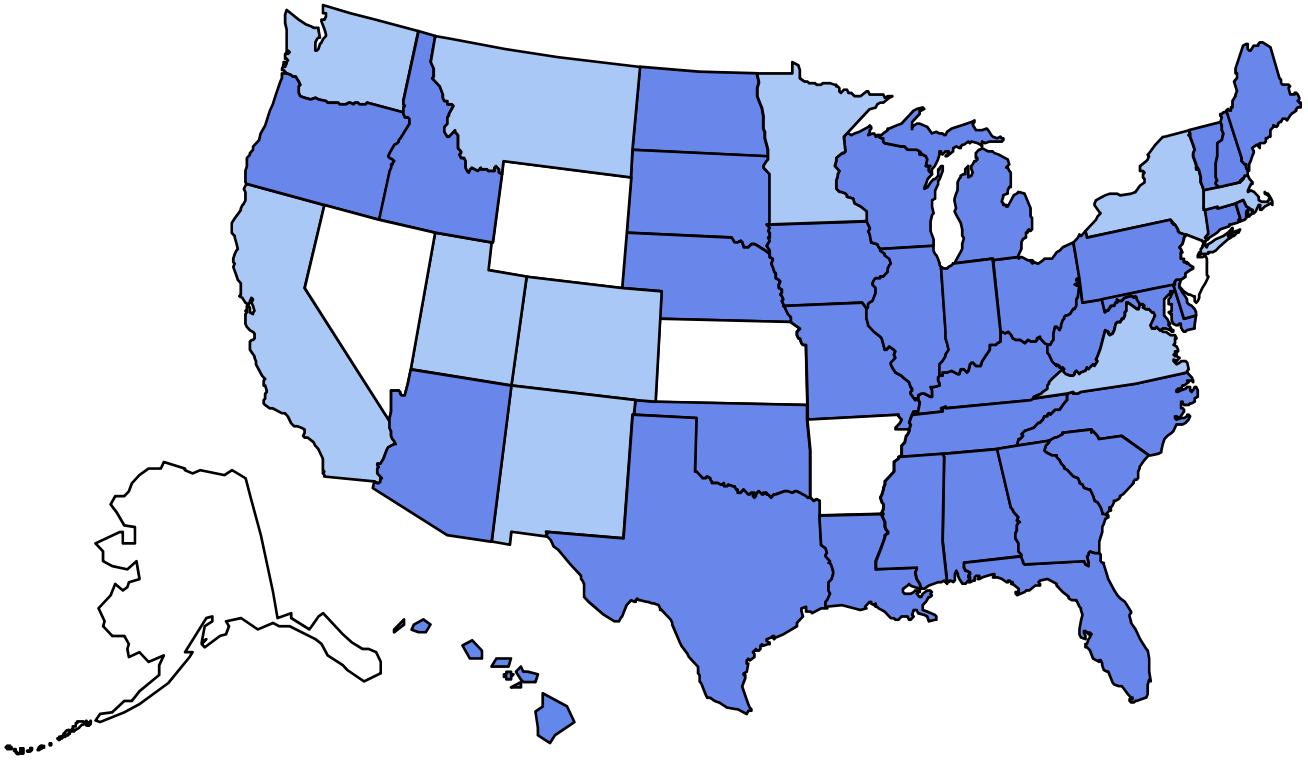
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

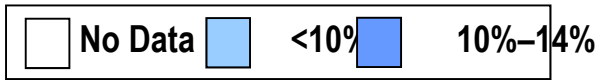


Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

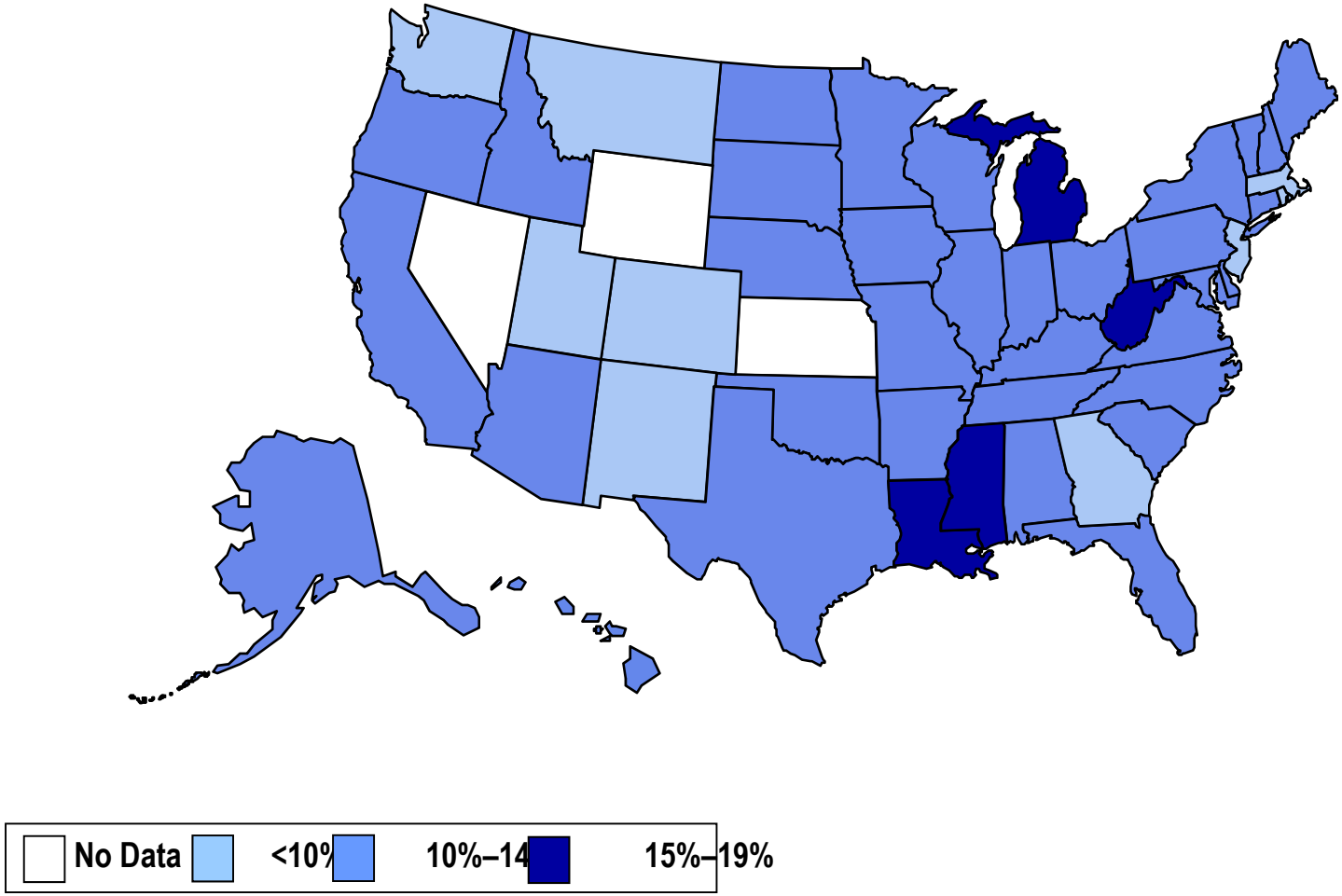




Obesity Trends* Among U.S. Adults

BRFSS, 1991

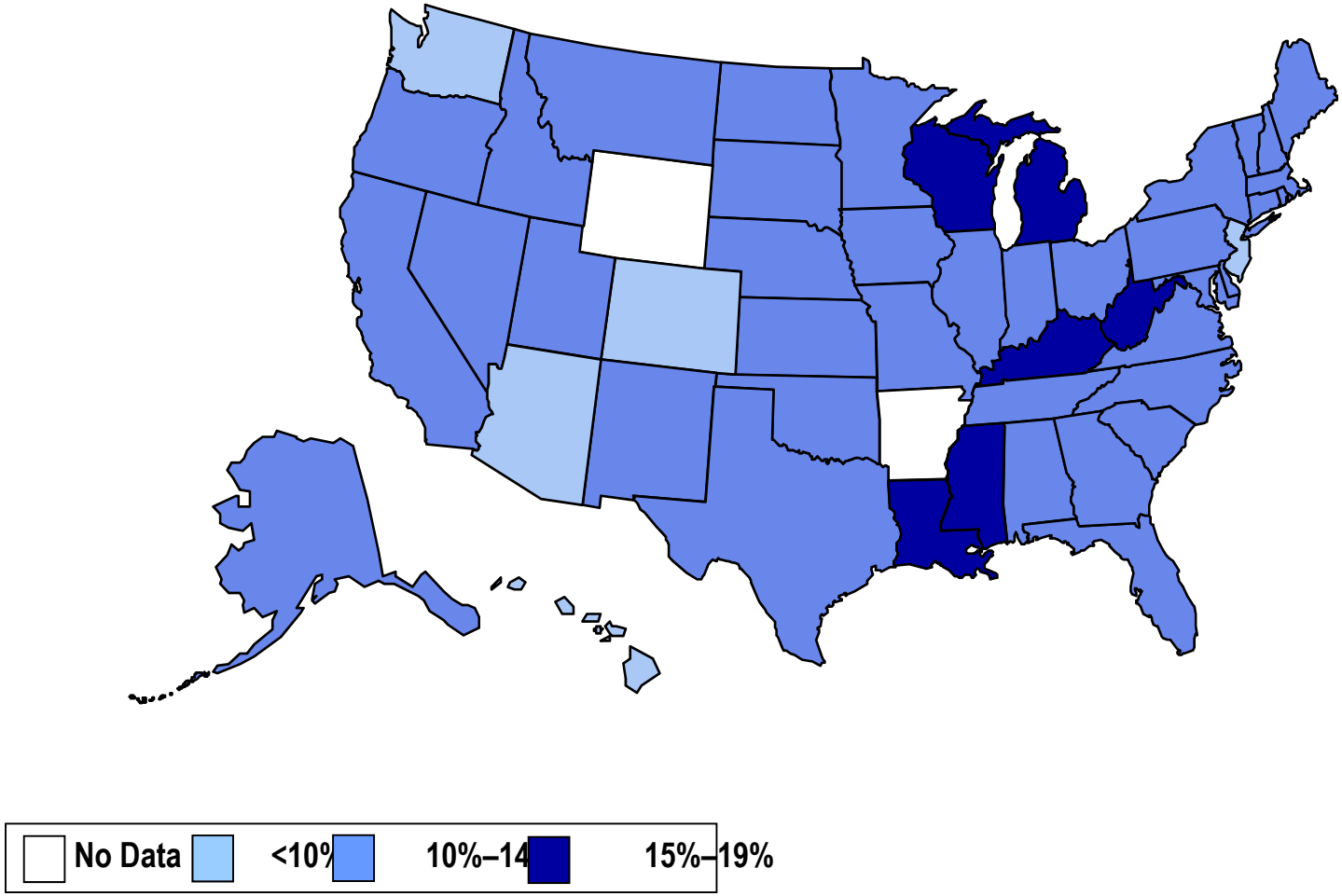
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1992

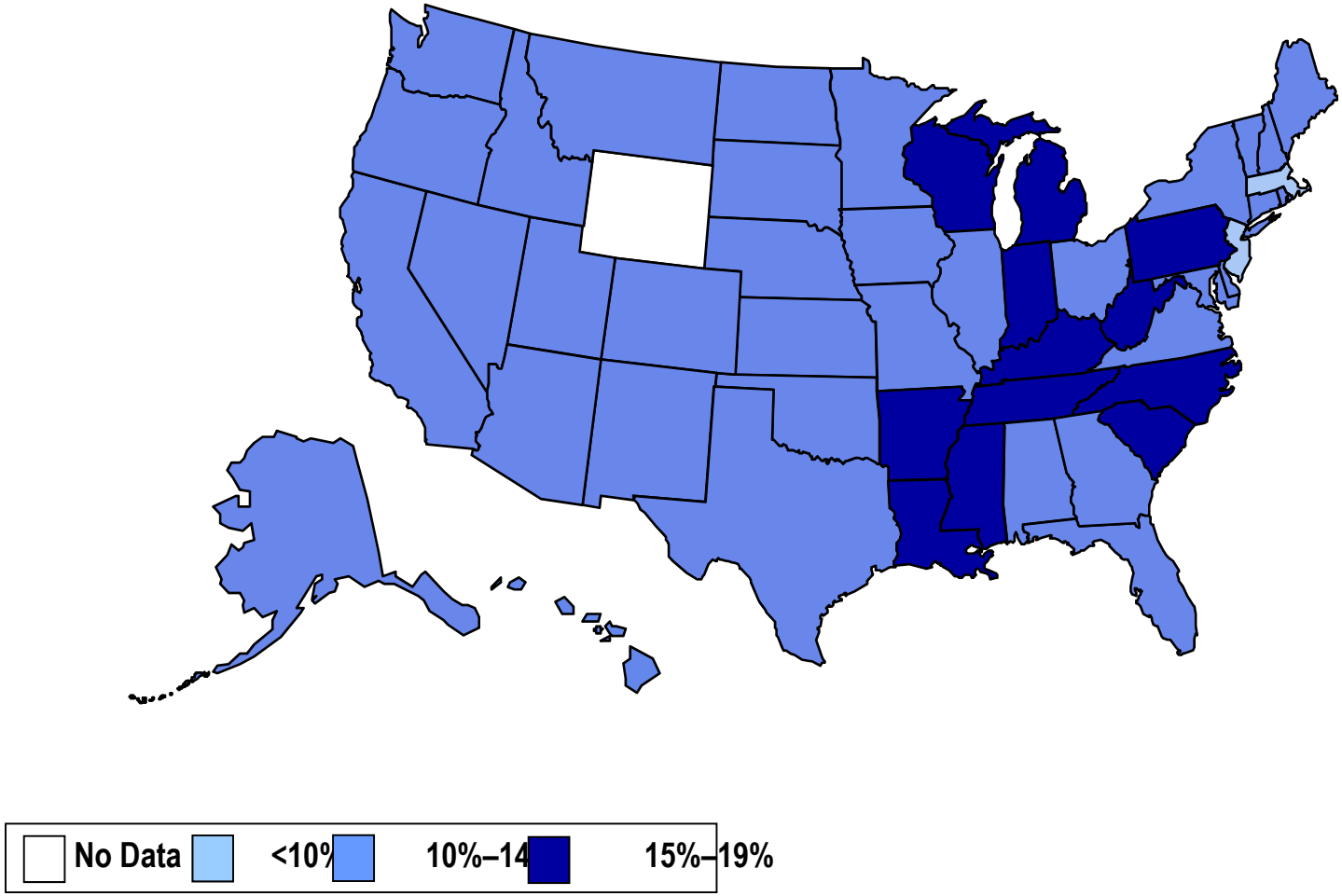
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1993

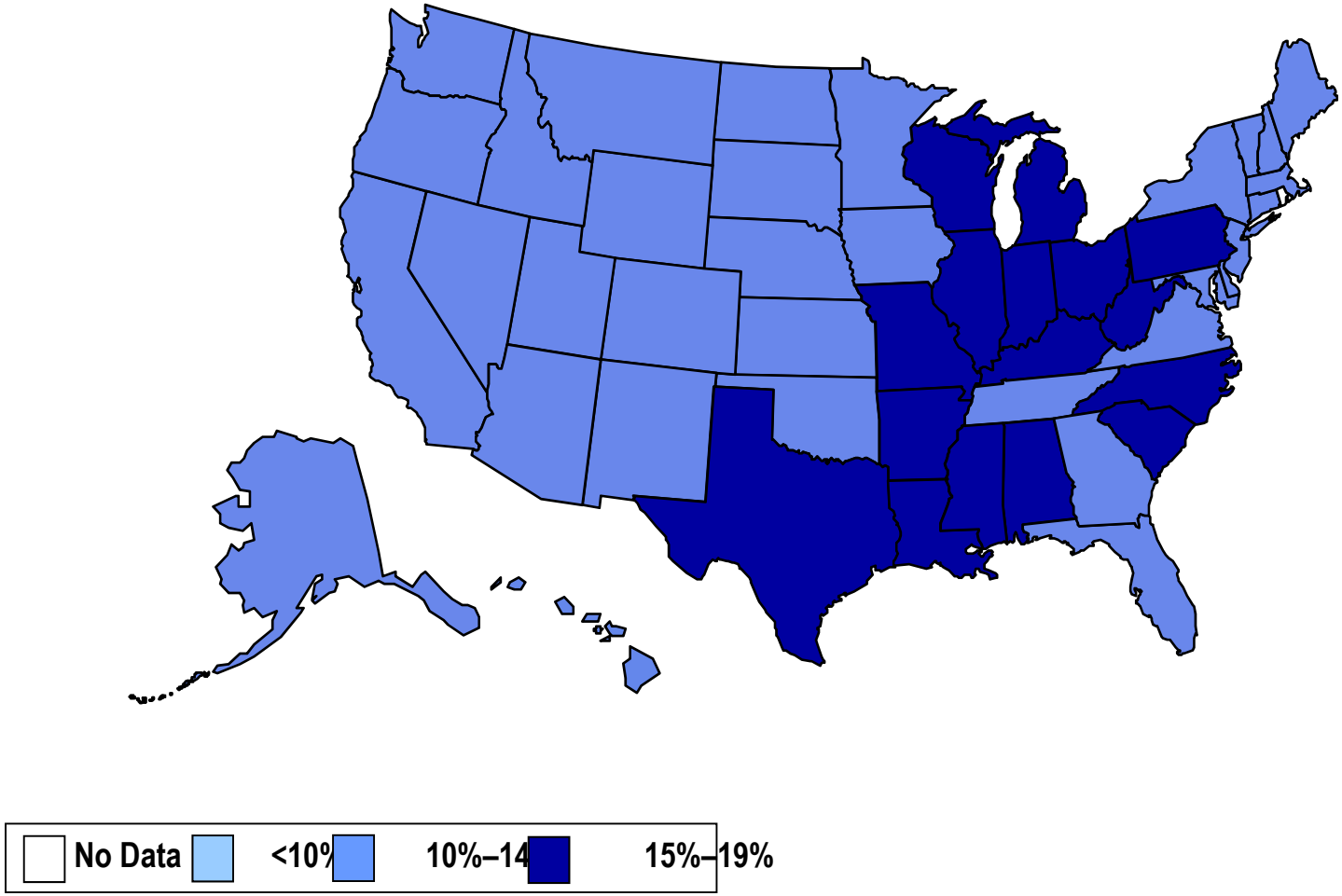
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1994

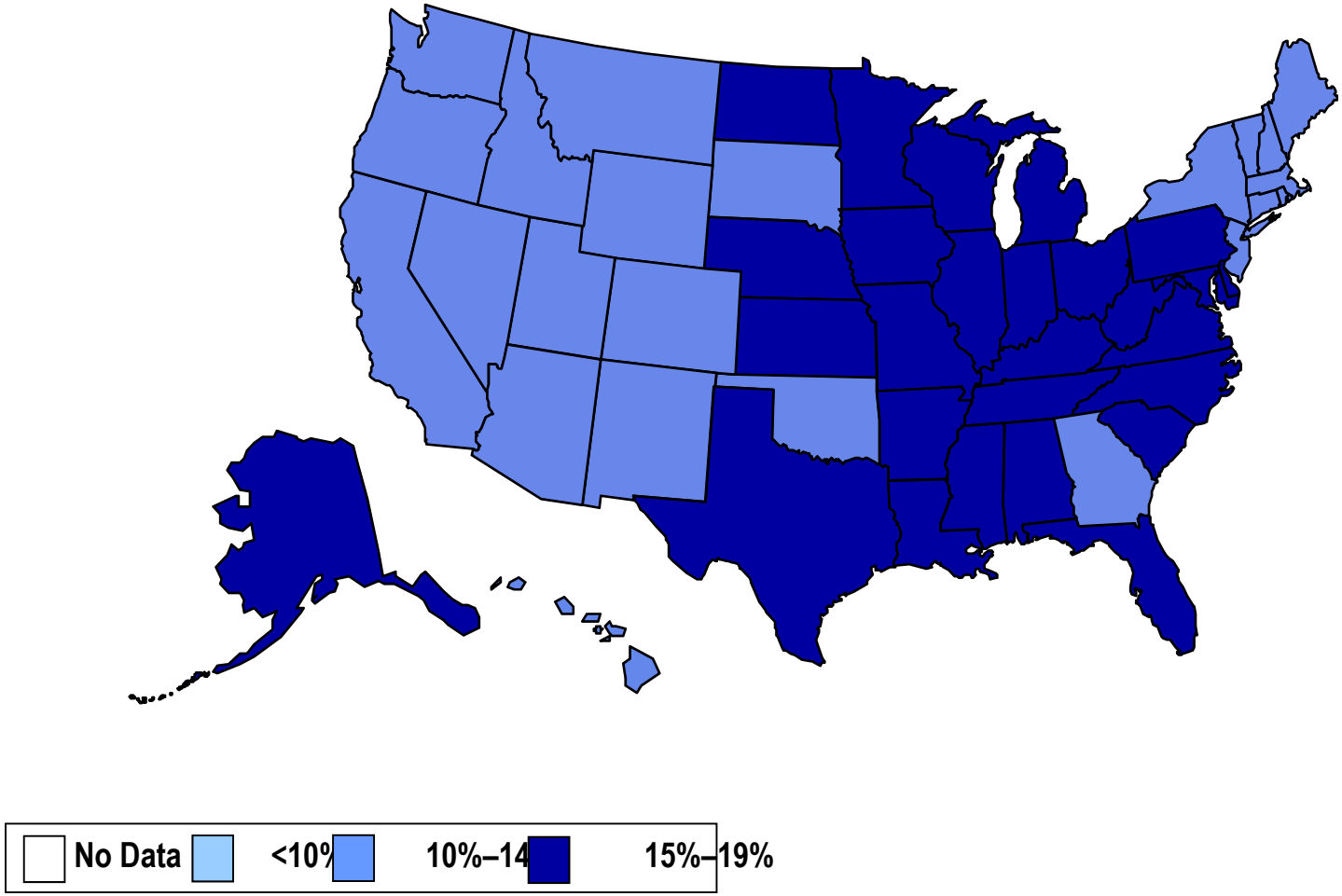
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1995

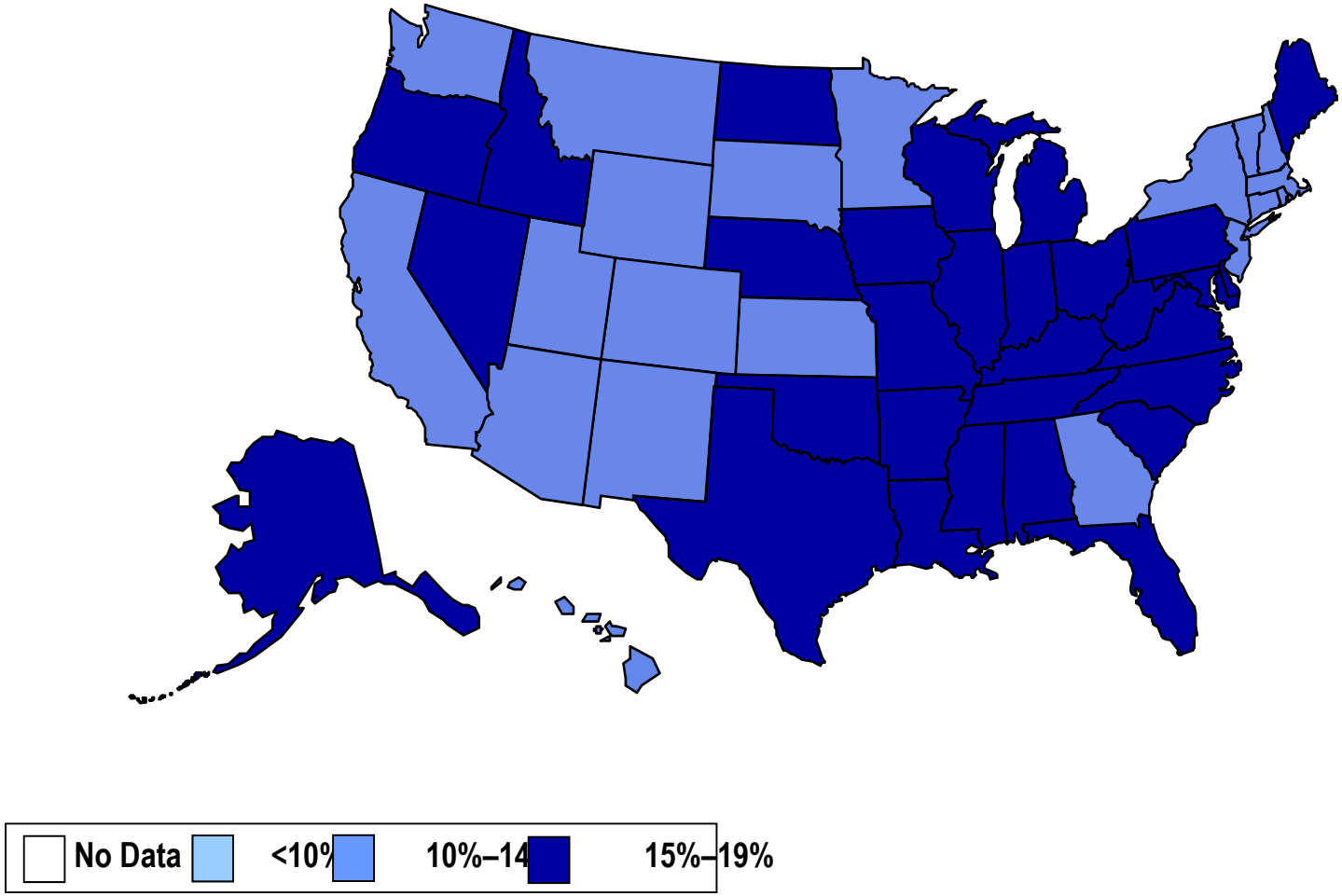
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1996

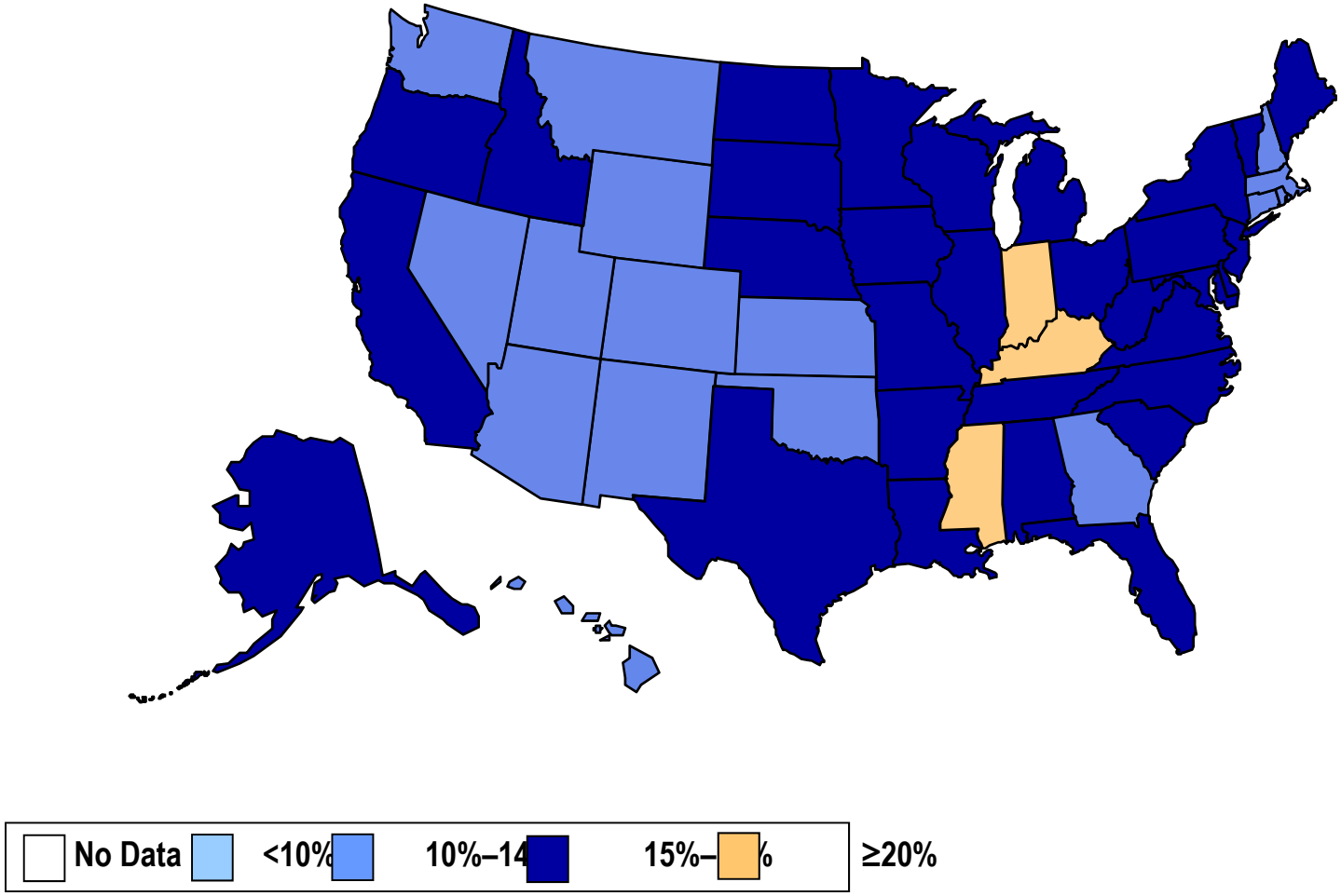
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1997

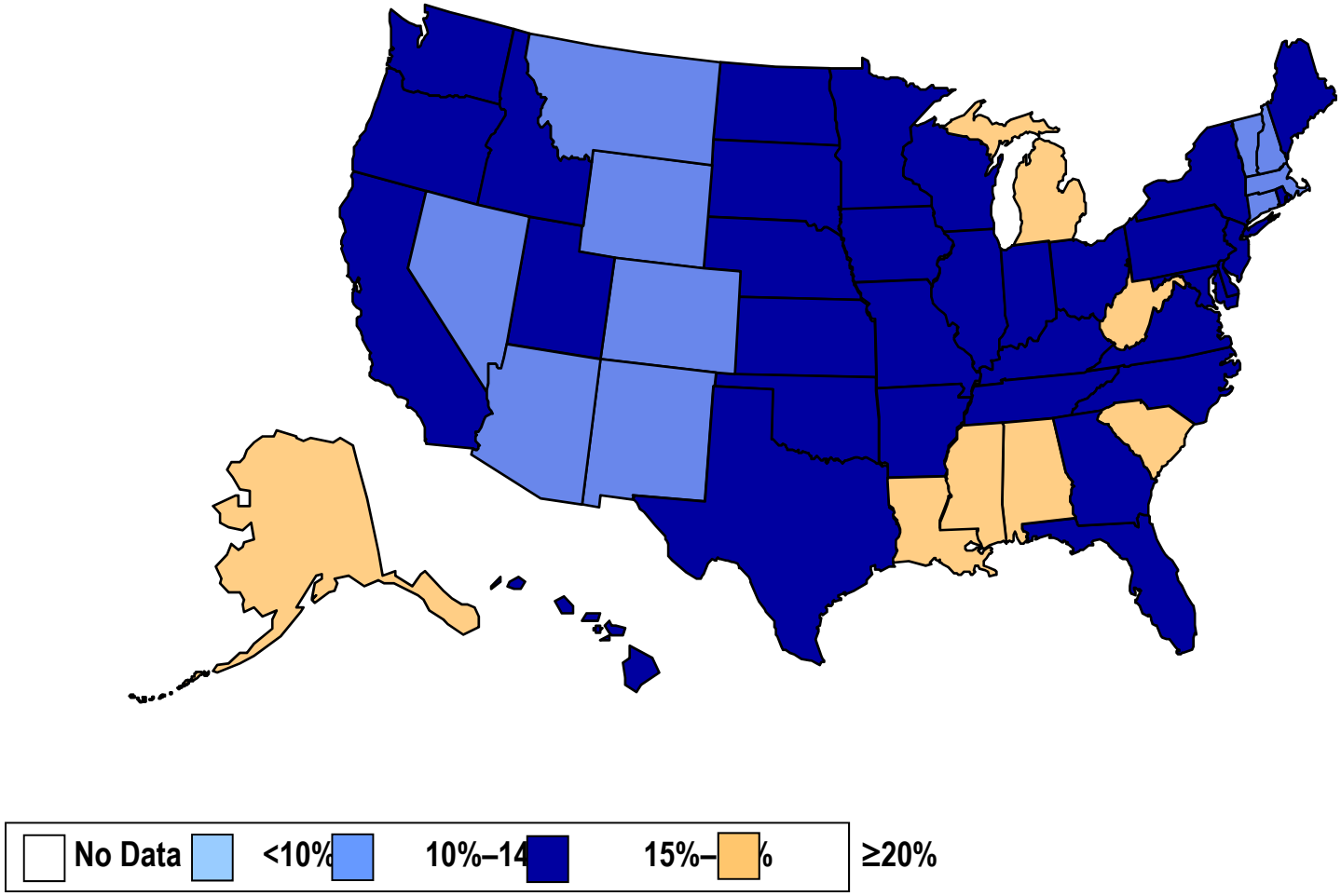
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1998

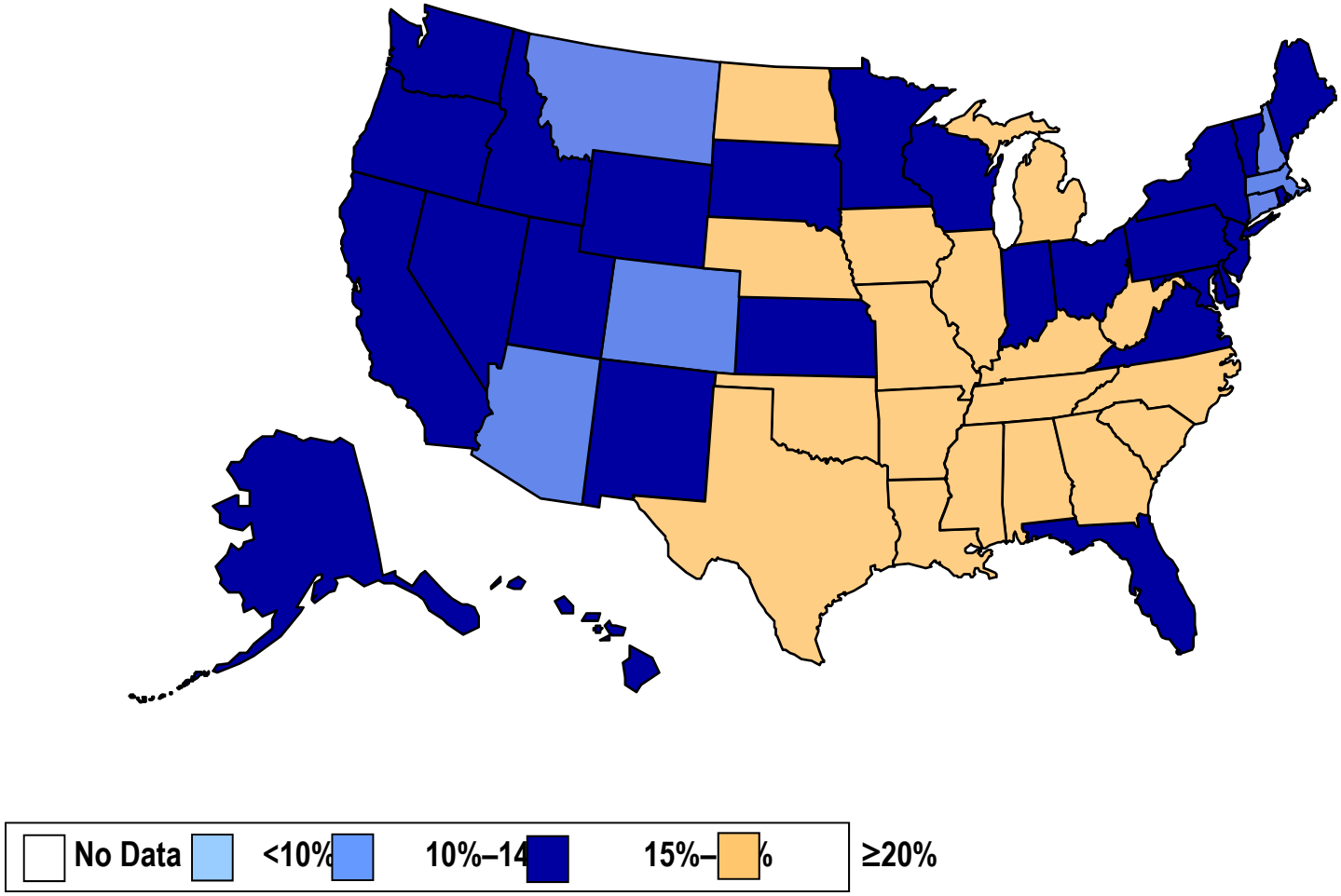
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1999

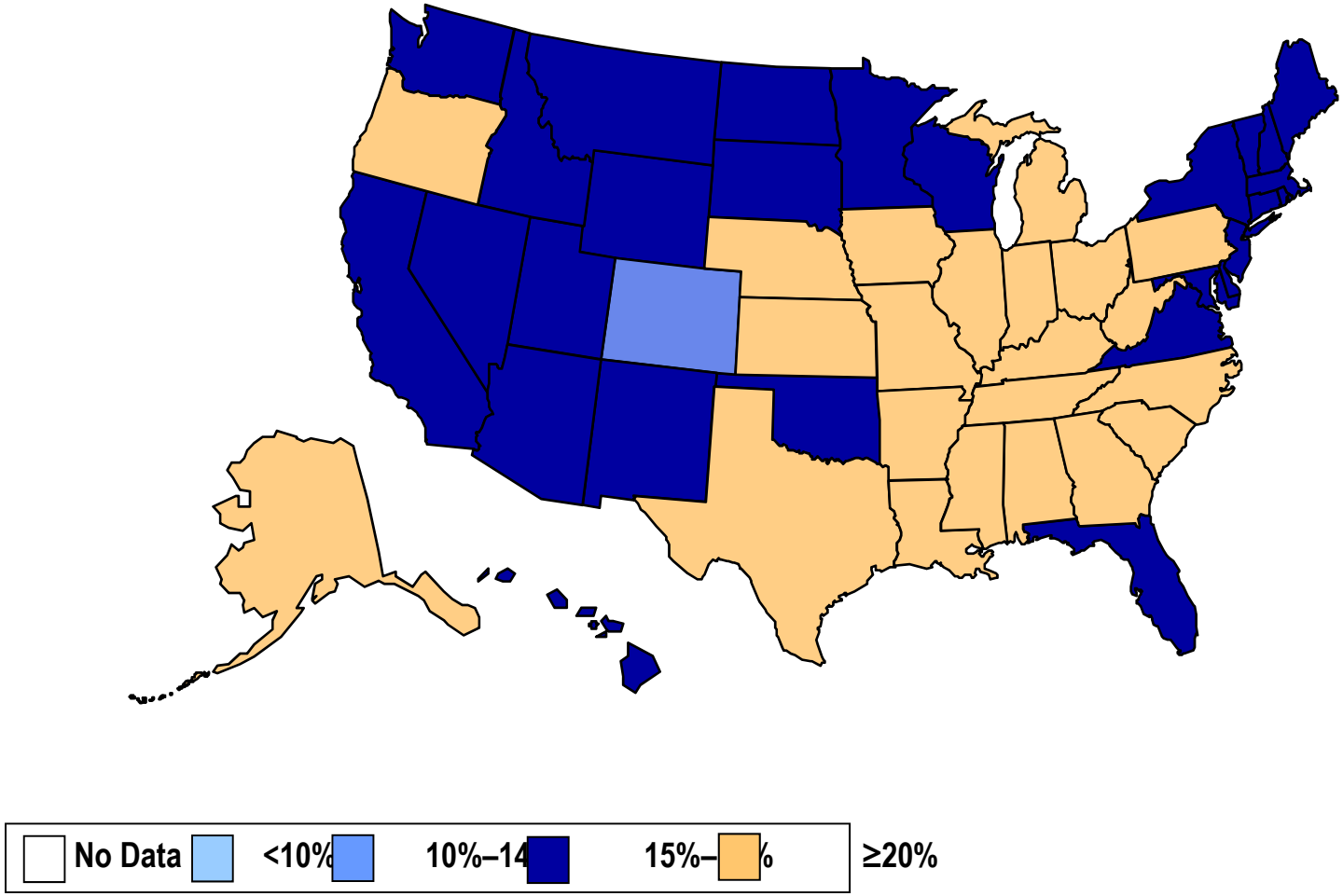
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2000

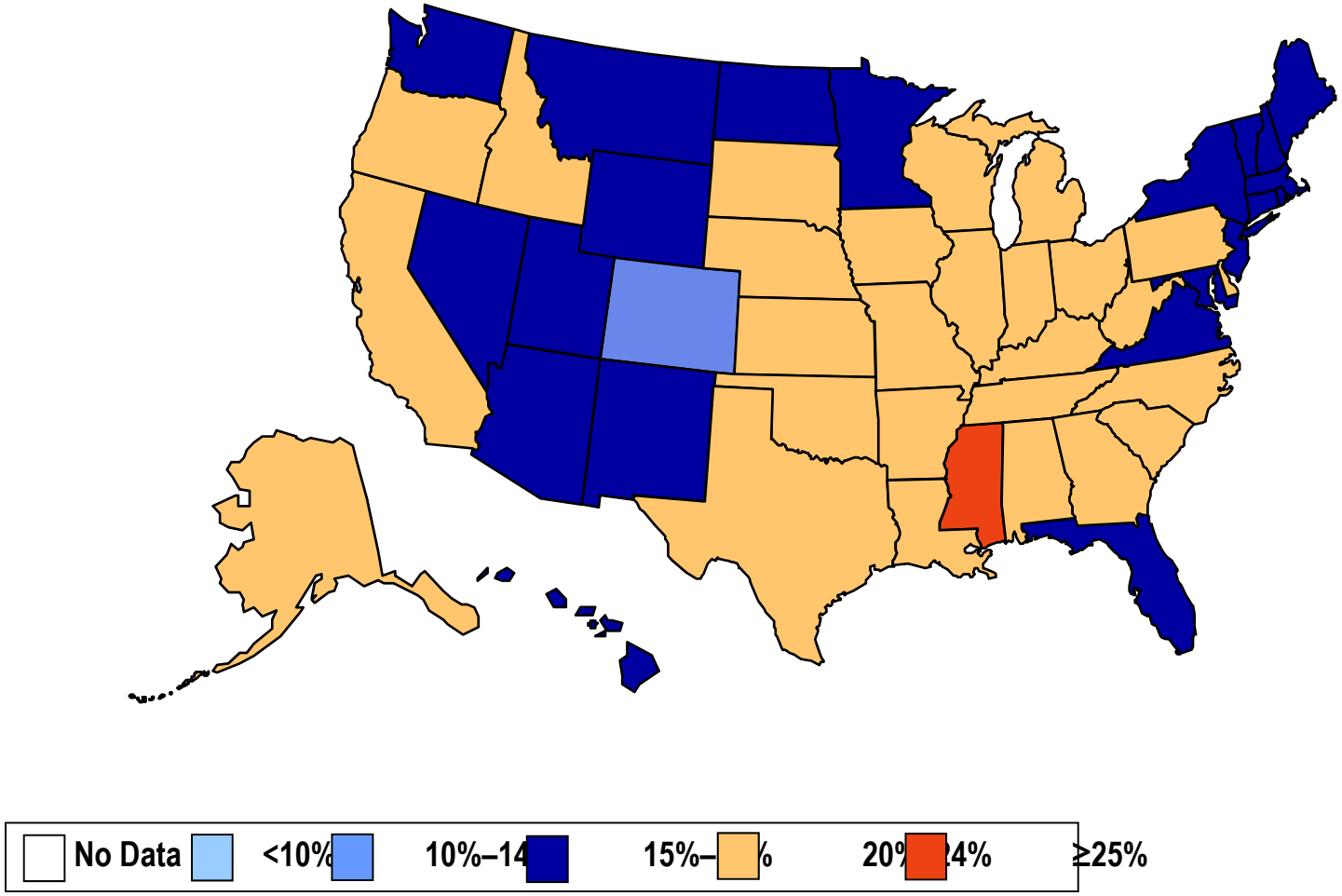
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

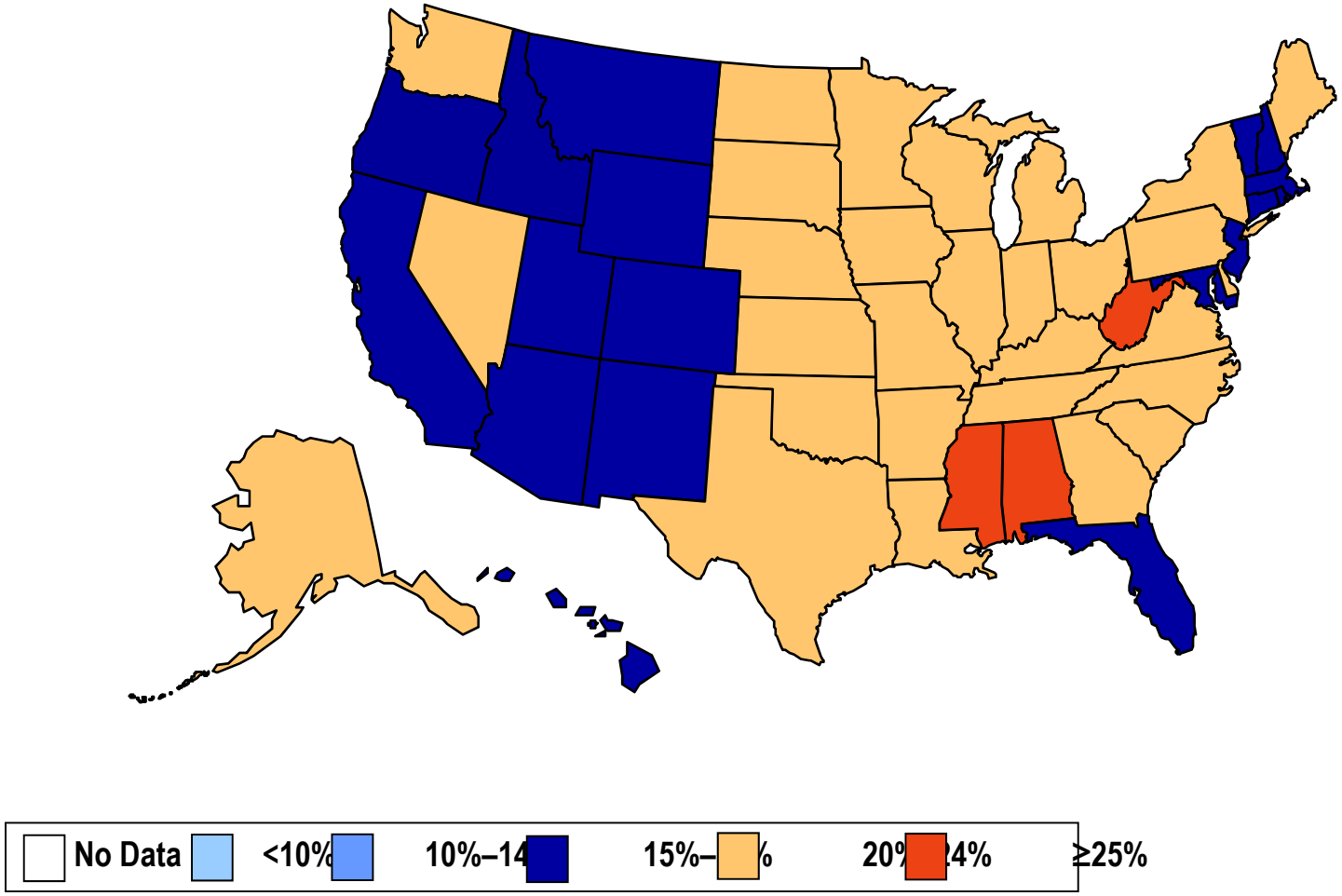
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults
BRFSS, 2002

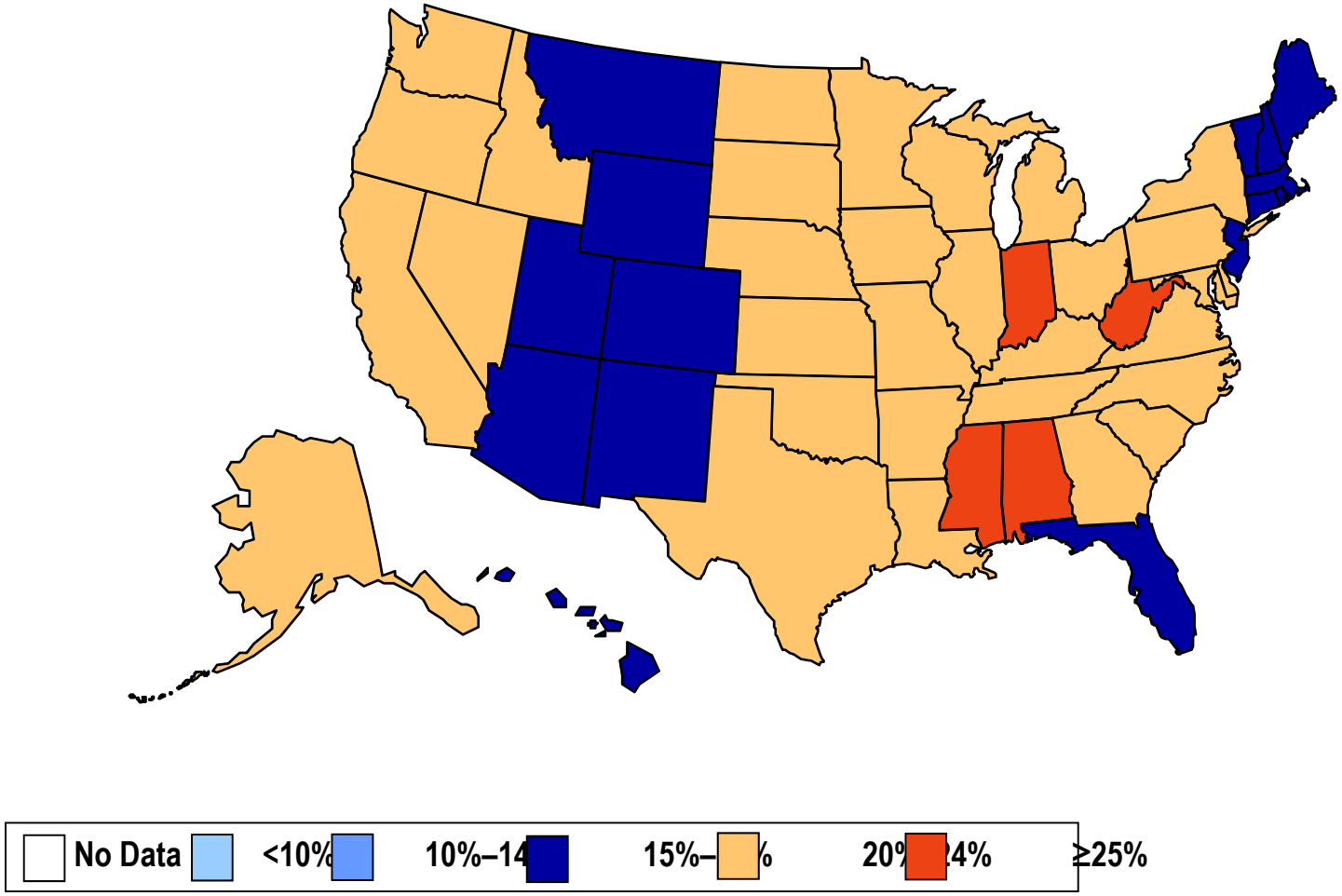
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2003

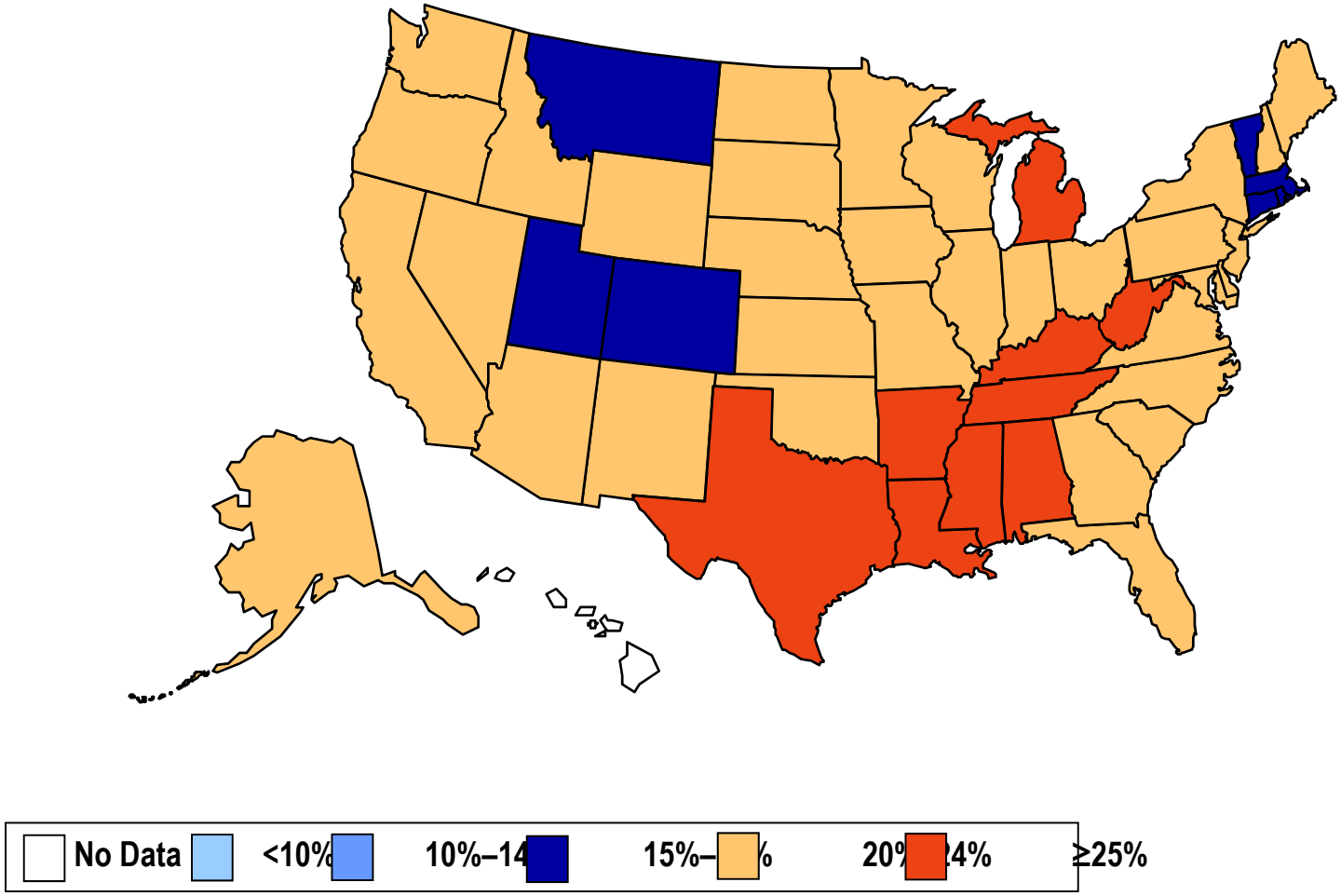
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2004

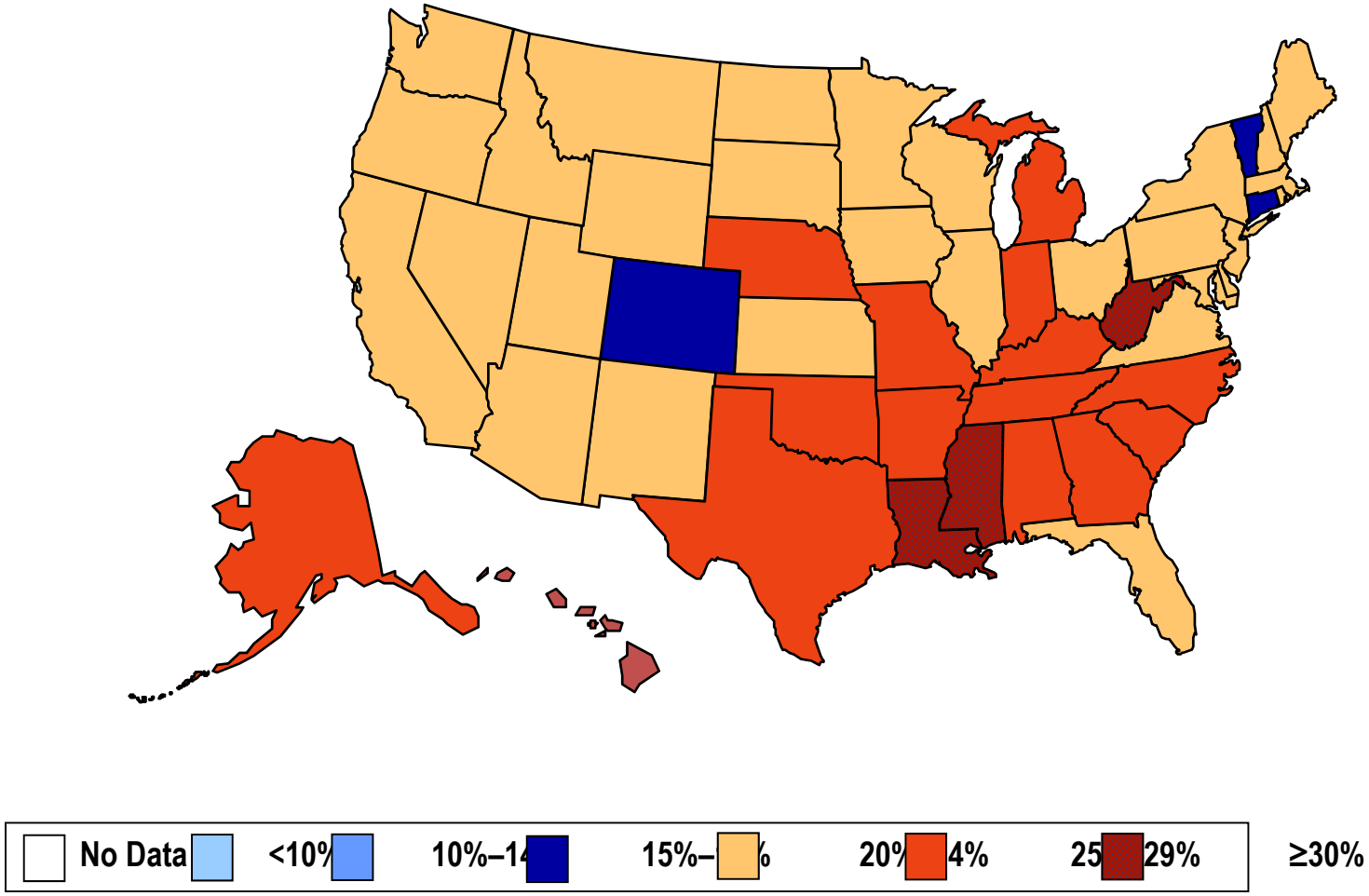
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2005

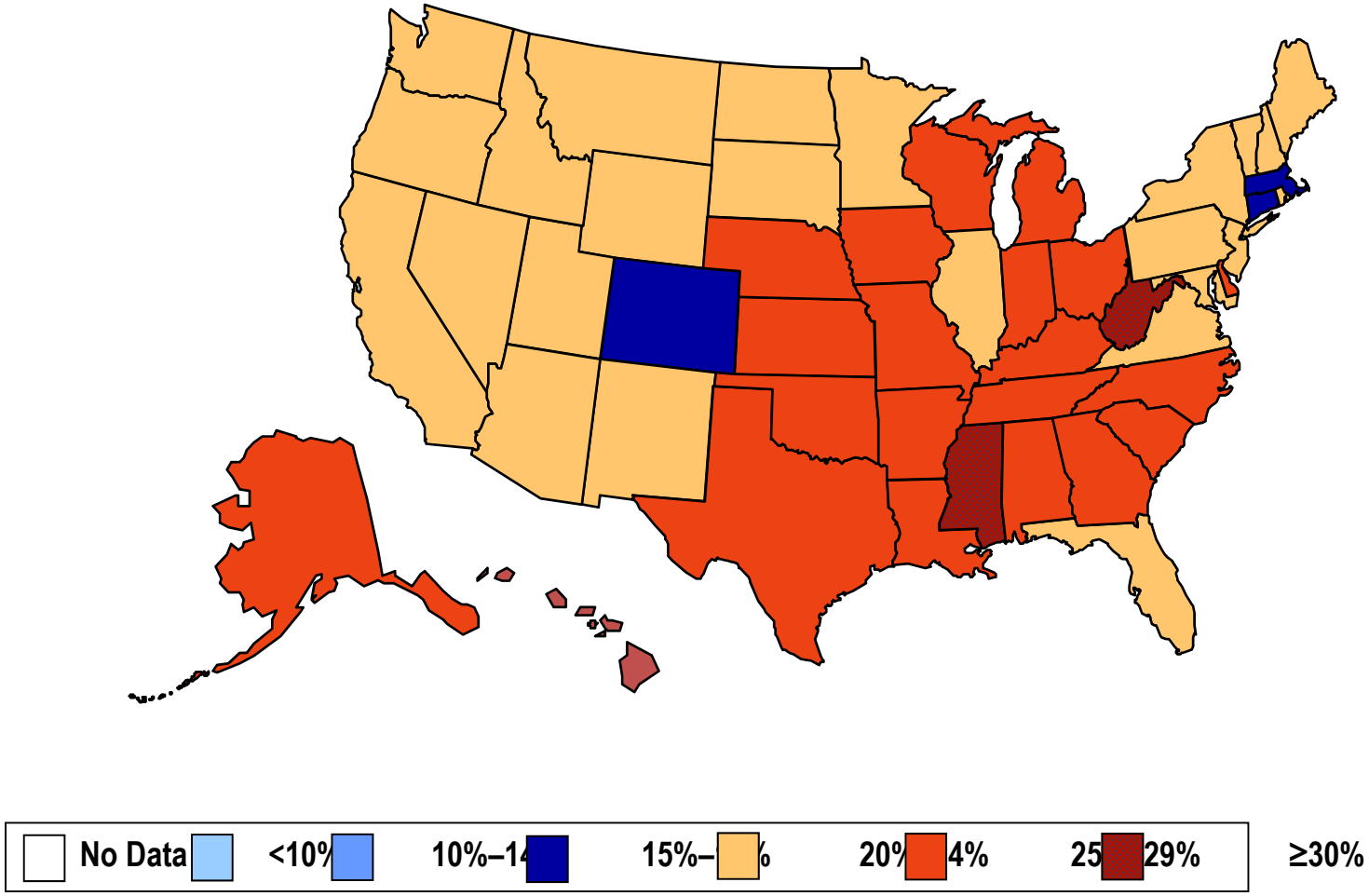
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2006

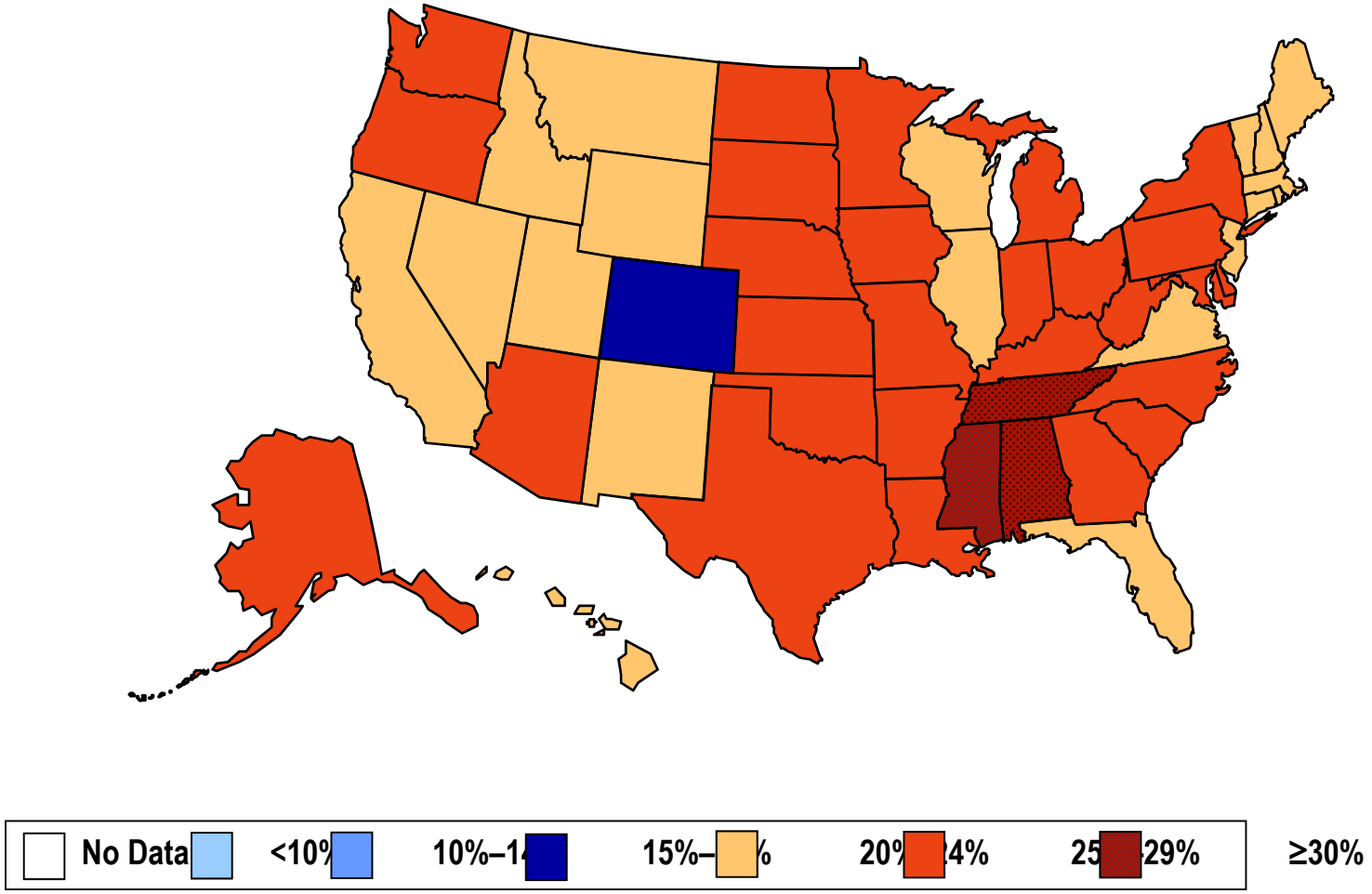
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2007

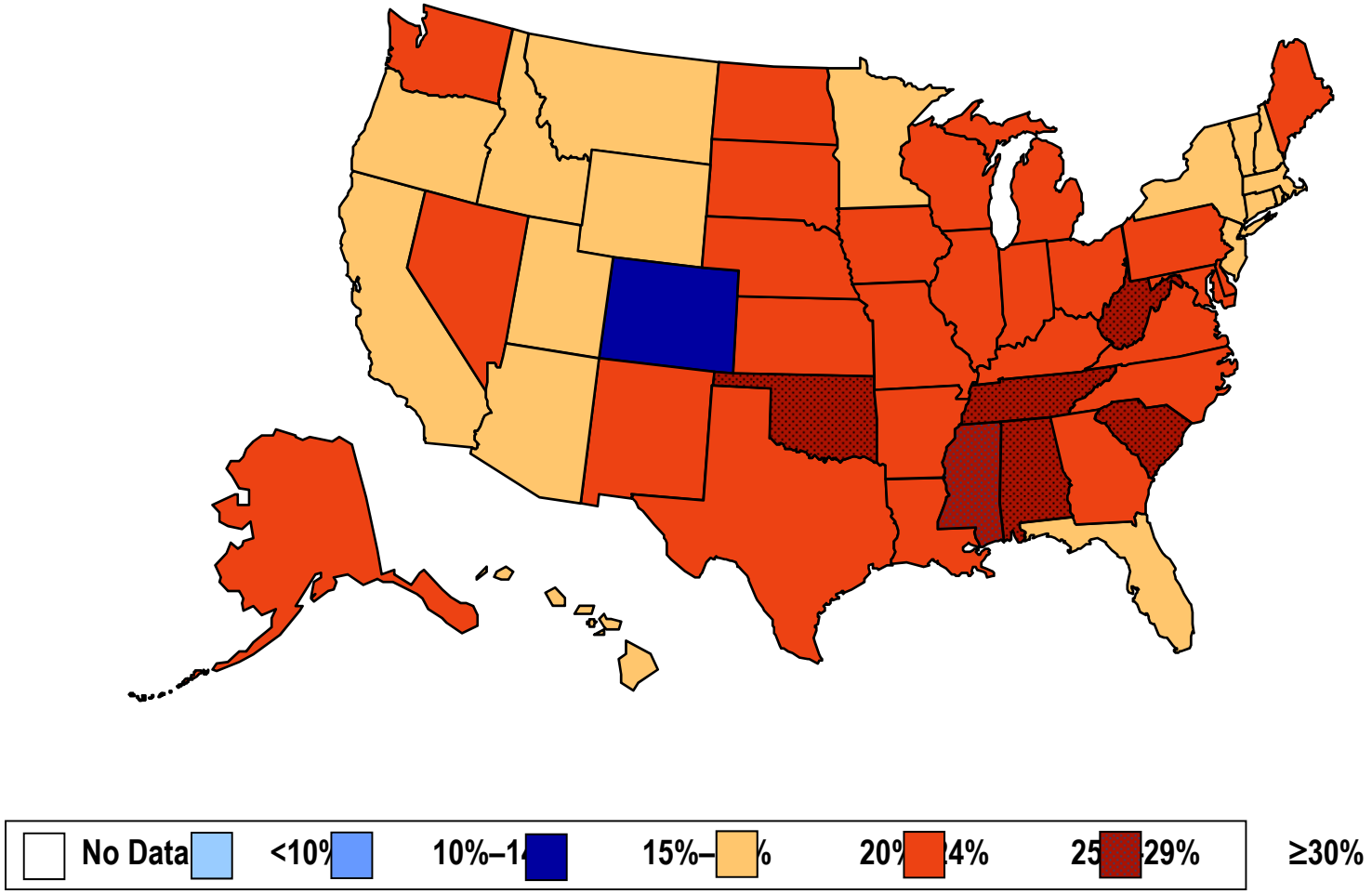
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2008

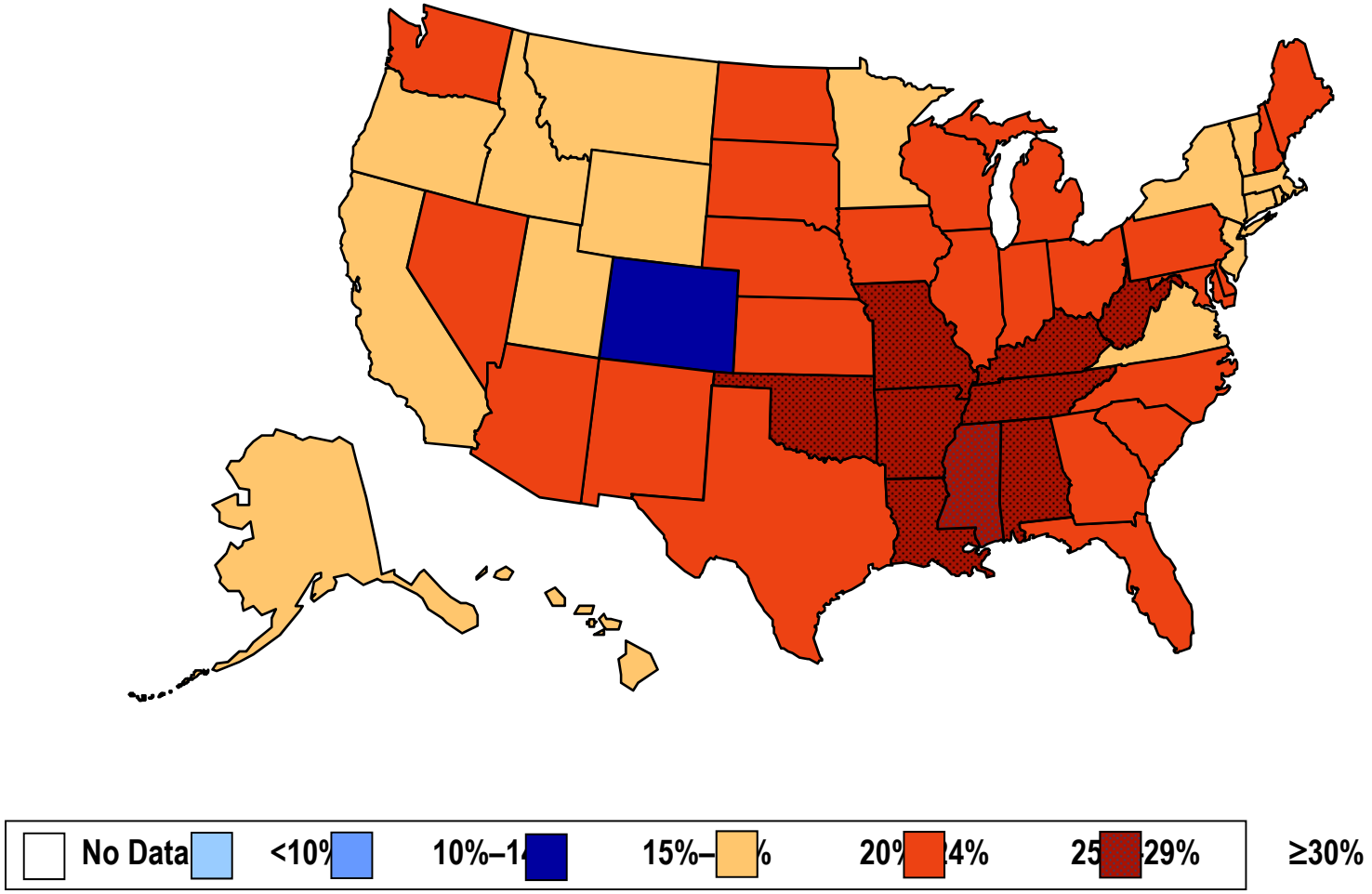
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2009

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Changes happen too fast!

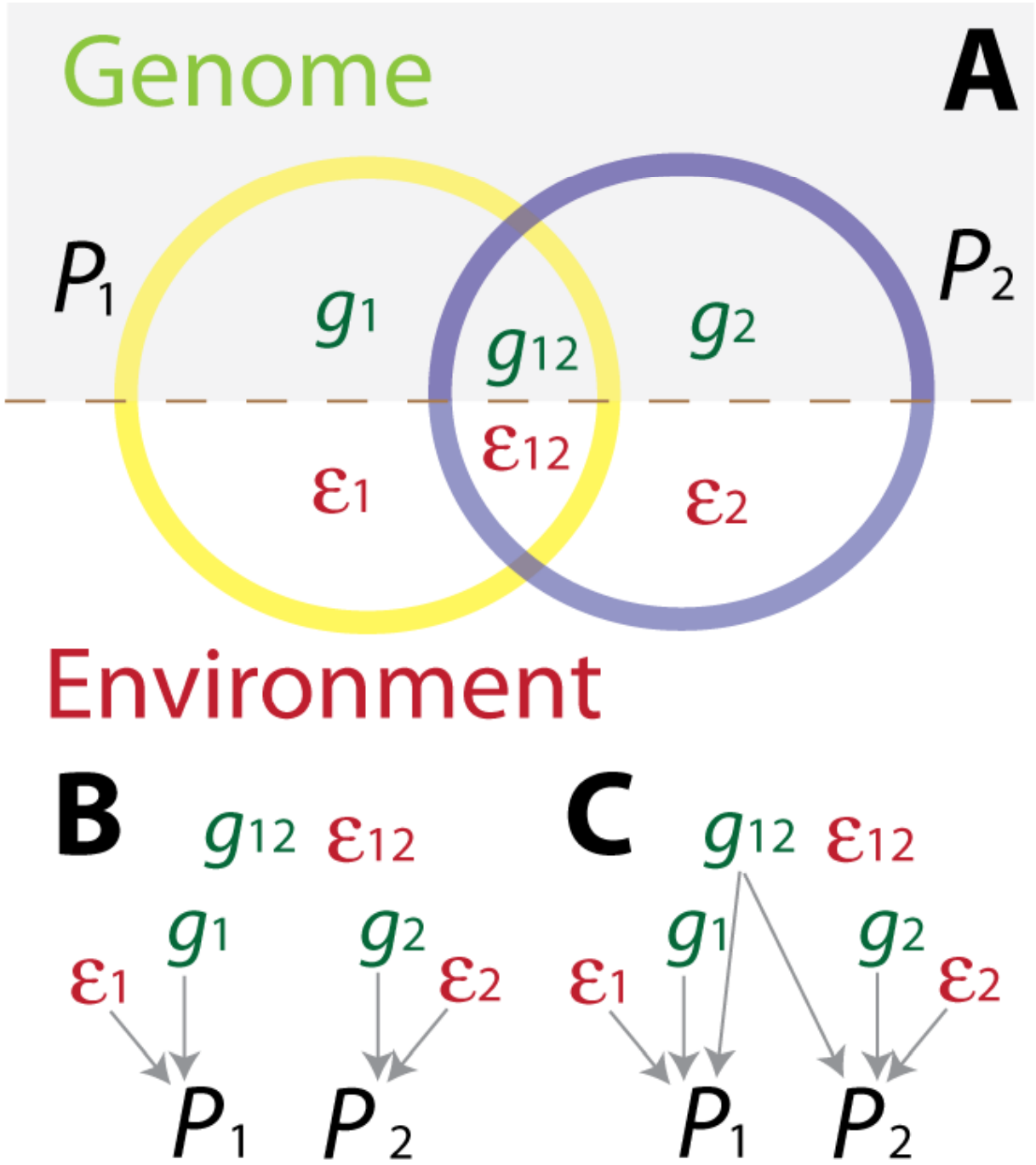
(Same story, for example, with autism and diabetes...)

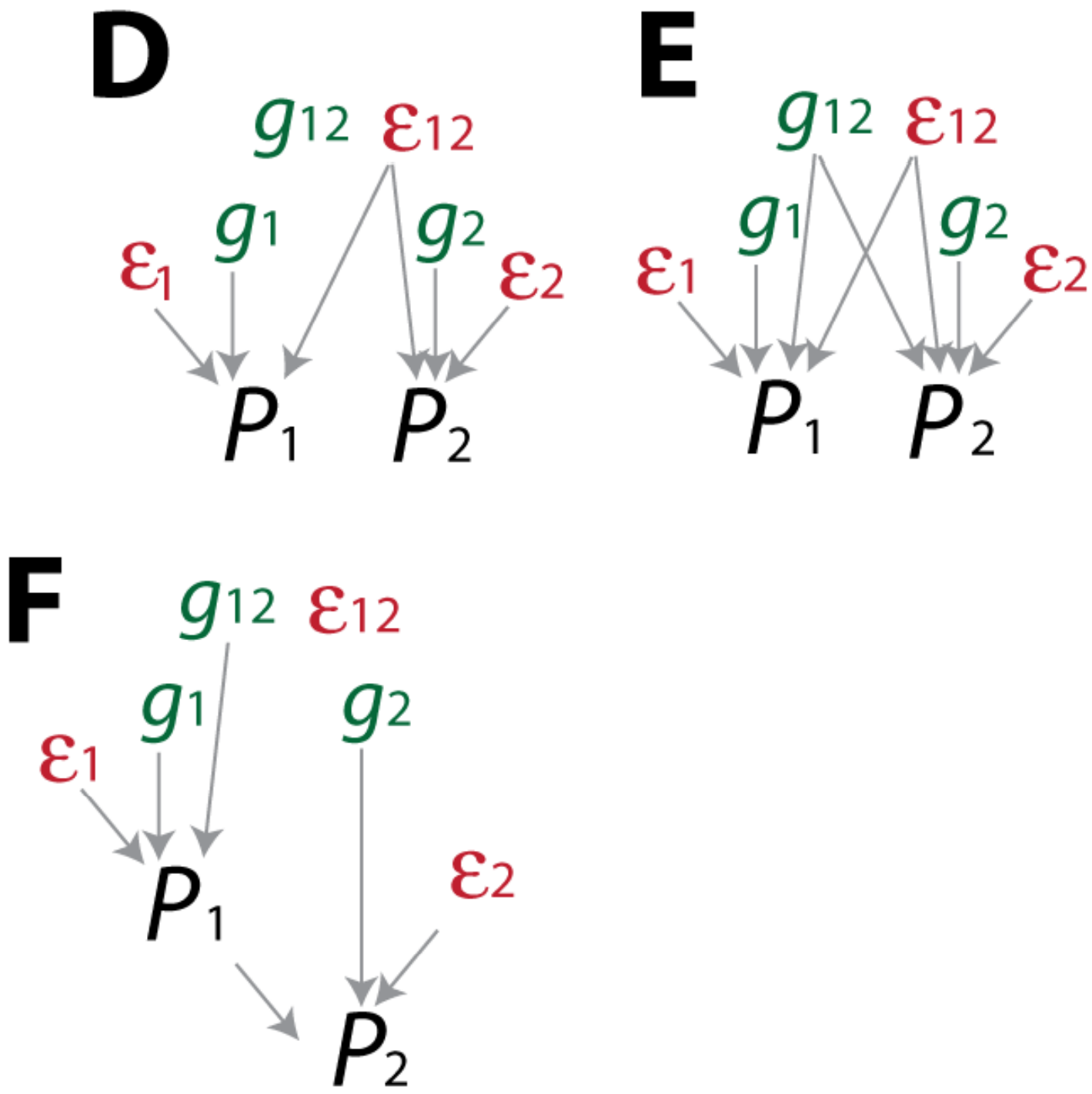
Should consider environment!

Environment?

Nature vs. Nurture

Genes or environment?


Genome
A
P_1
P_2
g_1
g_{12}
g_2
ε_{12}
ε_1
ε_2
Environment
B
g_{12} ε_{12}
g_1
g_2
ε_1
ε_2
P_1
P_2
C
g_{12} ε_{12}
g_1
g_2
ε_1
ε_2
P_1
P_2


D
g_{12} ε_{12}
g_1 g_2
ε_1 ε_2
P_1 P_2
E
g_{12} ε_{12}
g_1 g_2
ε_1 ε_2
P_1 P_2
F
g_{12} ε_{12}
g_1 g_2
ε_1
ε_2
P_1
P_2

Data: pedigrees + genetic variation + phenotypes (disease or healthy)

Genetic-linkage Mapping of Complex Hereditary Disorders to a Whole-genome Molecular-interaction Network

Tian Zheng Miron Baron T. Conrad Gilliam

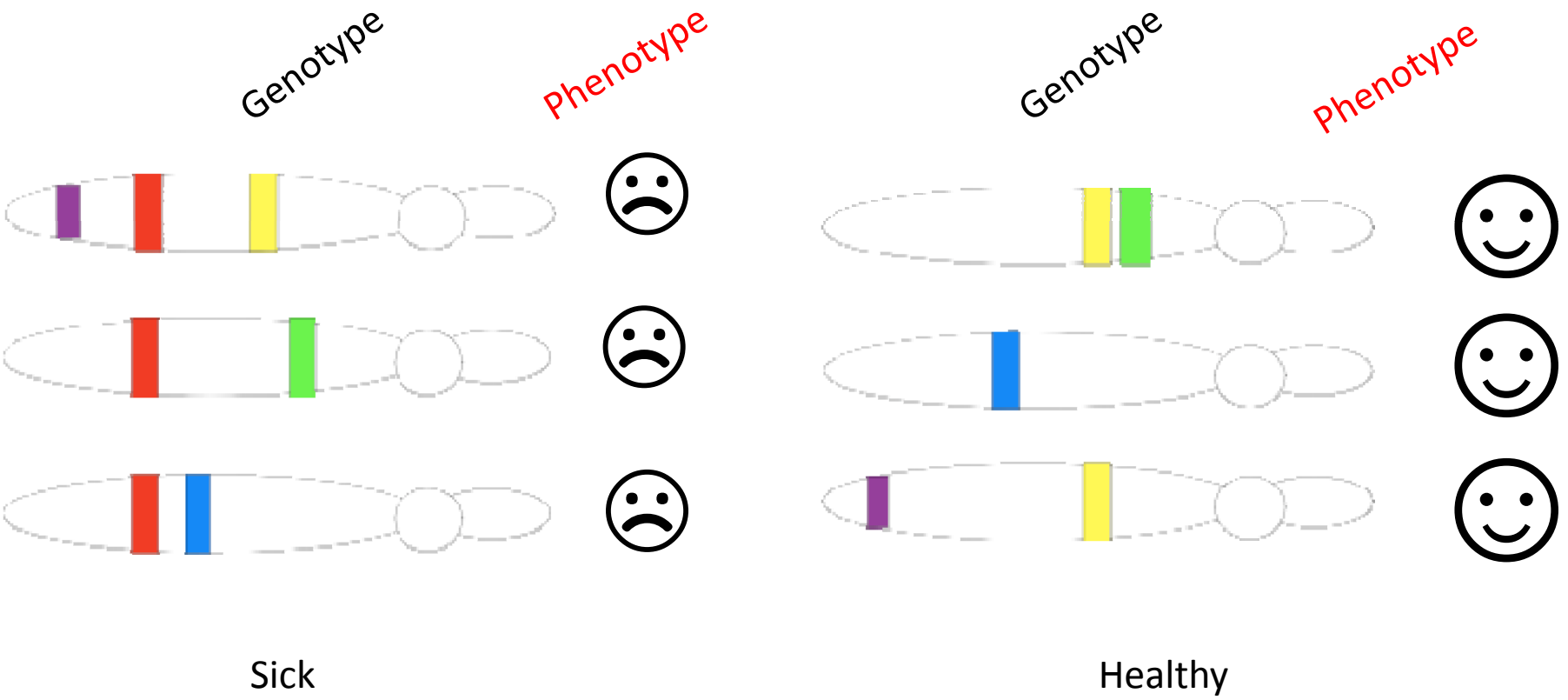
AR

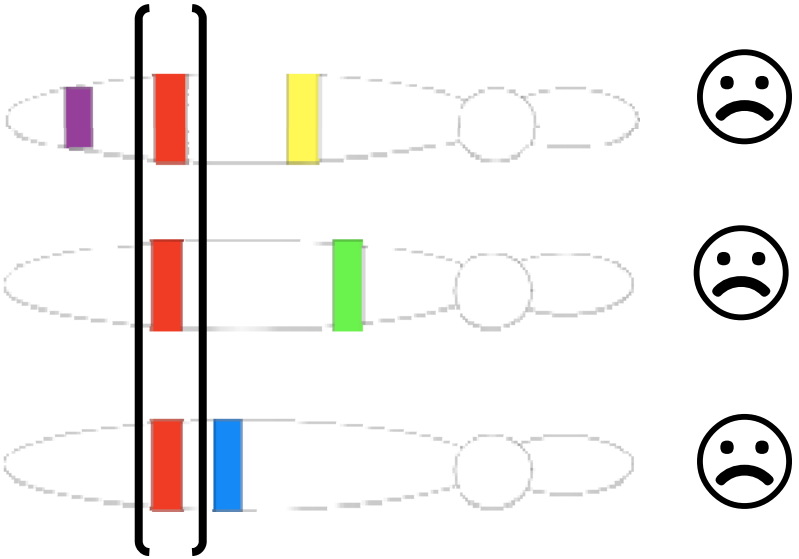
Genetic-linkage mapping of complex hereditary disorders to a whole-genome molecular-interaction network

Ivan Iossifov,[1] Tian Zheng,[2] Miron Baron,[3] T. Conrad Gilliam,[4] and Andrey Rzhetsky[4,5,6]

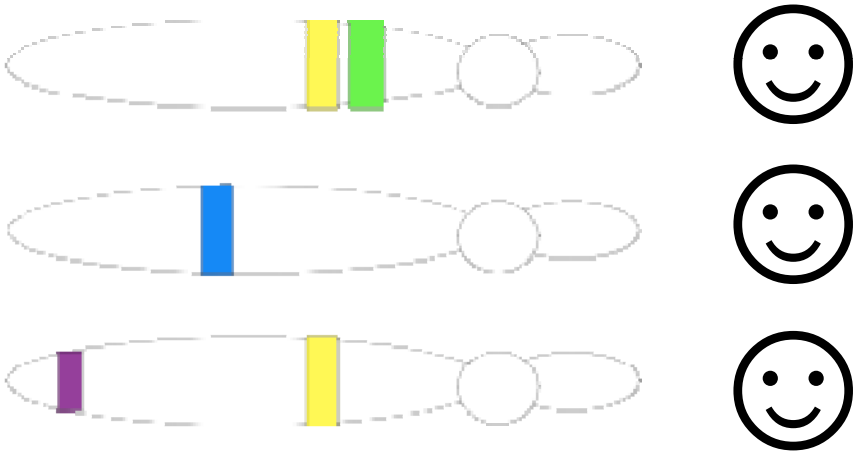
18:1150–1162 ©2008 by Cold Spring Harbor Laboratory Press; ISSN 1088-9051/08; www.genome.org

One-chromosome example





Sick



Healthy

Combinations of genes:

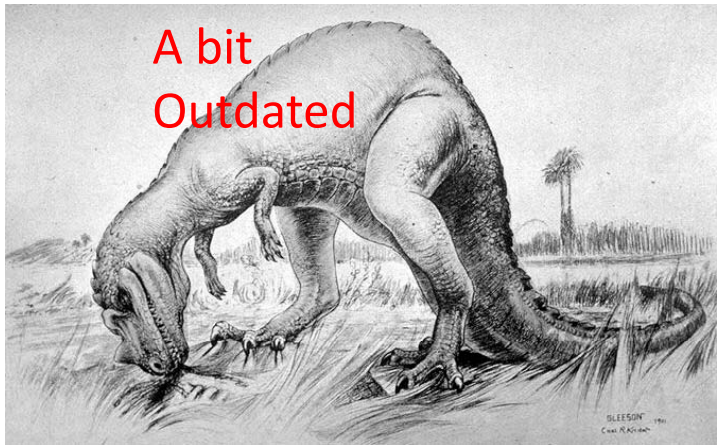
10^8 -- 2 genes

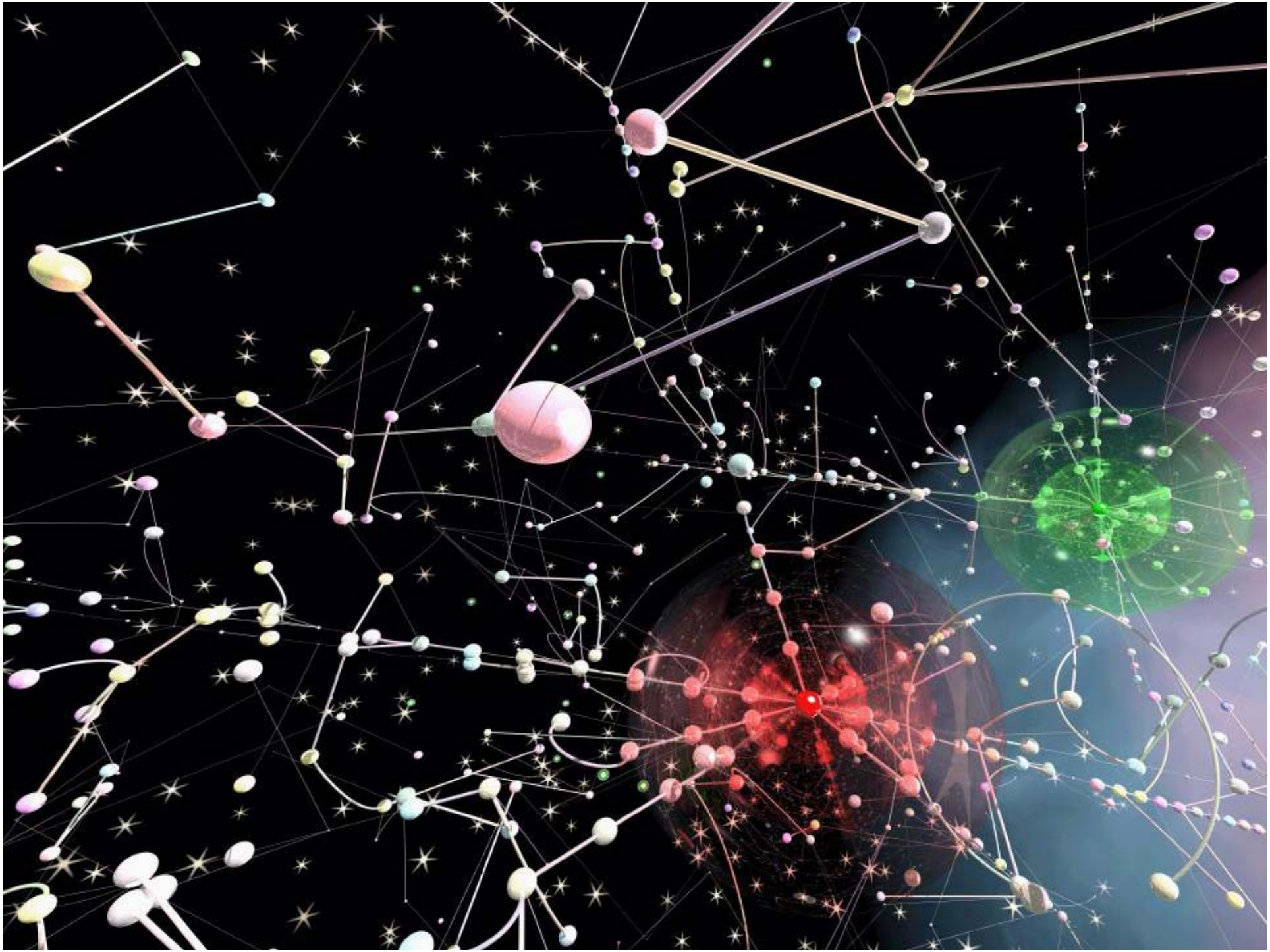
10^{12} -- 3 genes

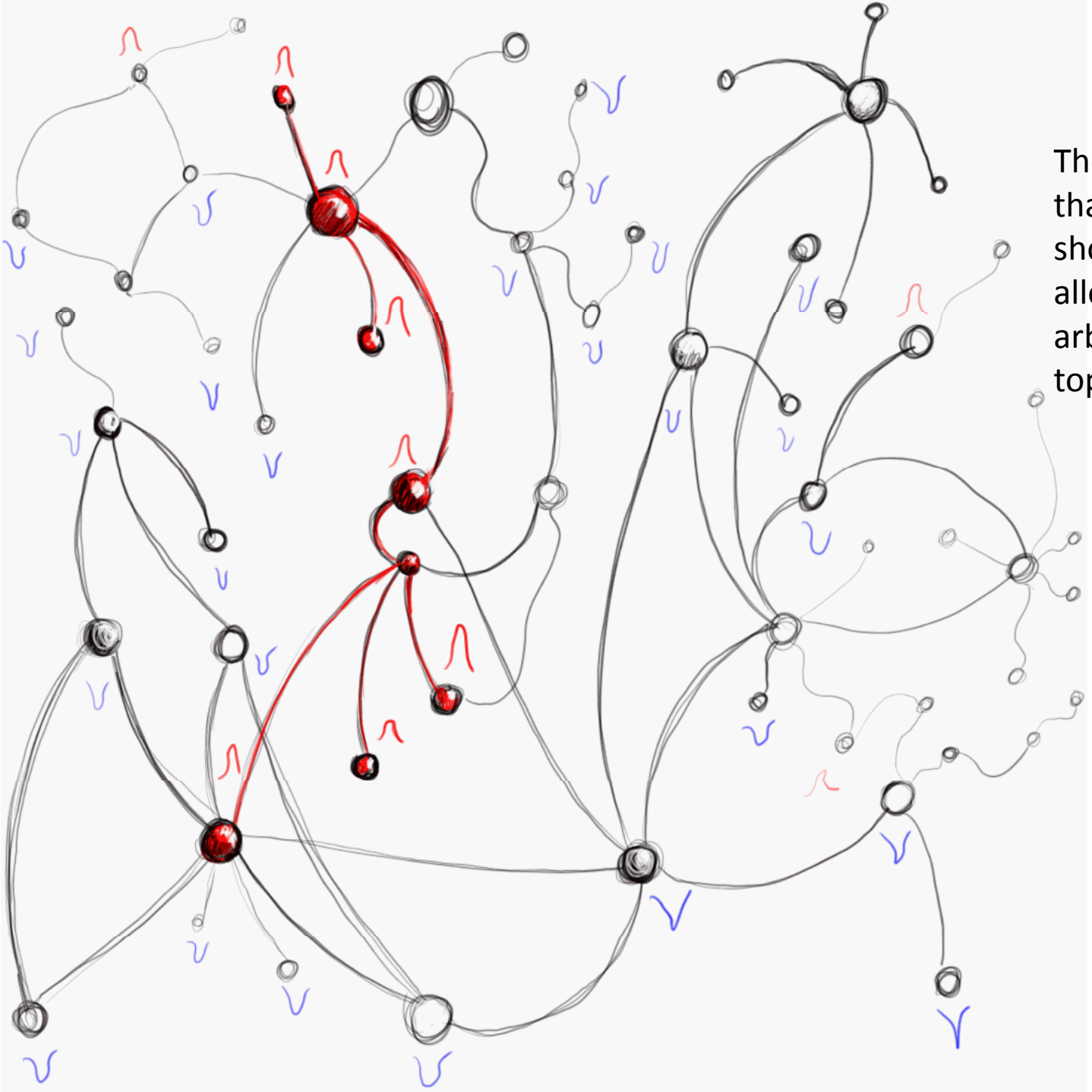
10^{16} -- 4 genes

10^{37} -- 10 genes

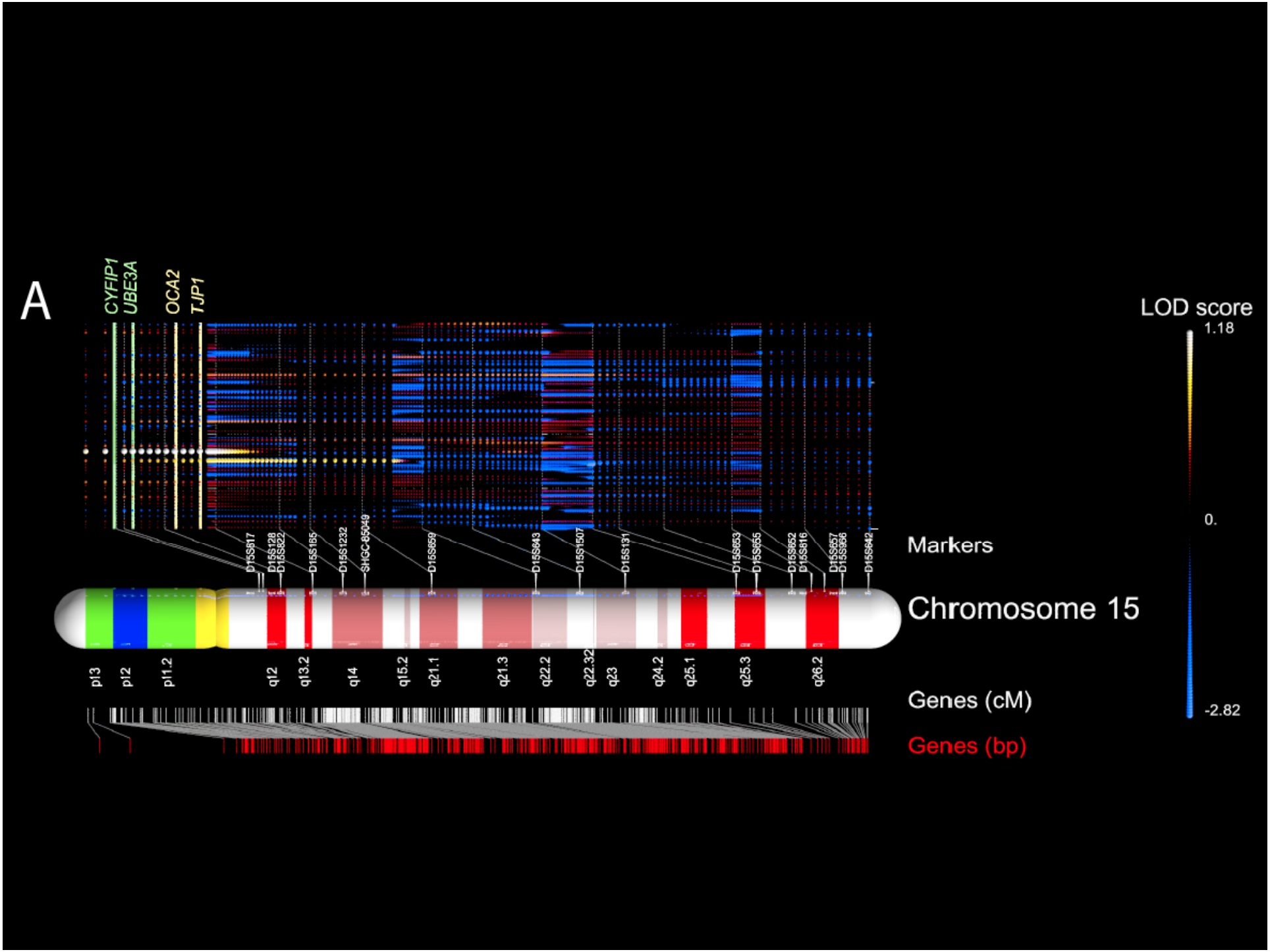
Now, we have 23 chromosomes in two copies,
~25,000 genes

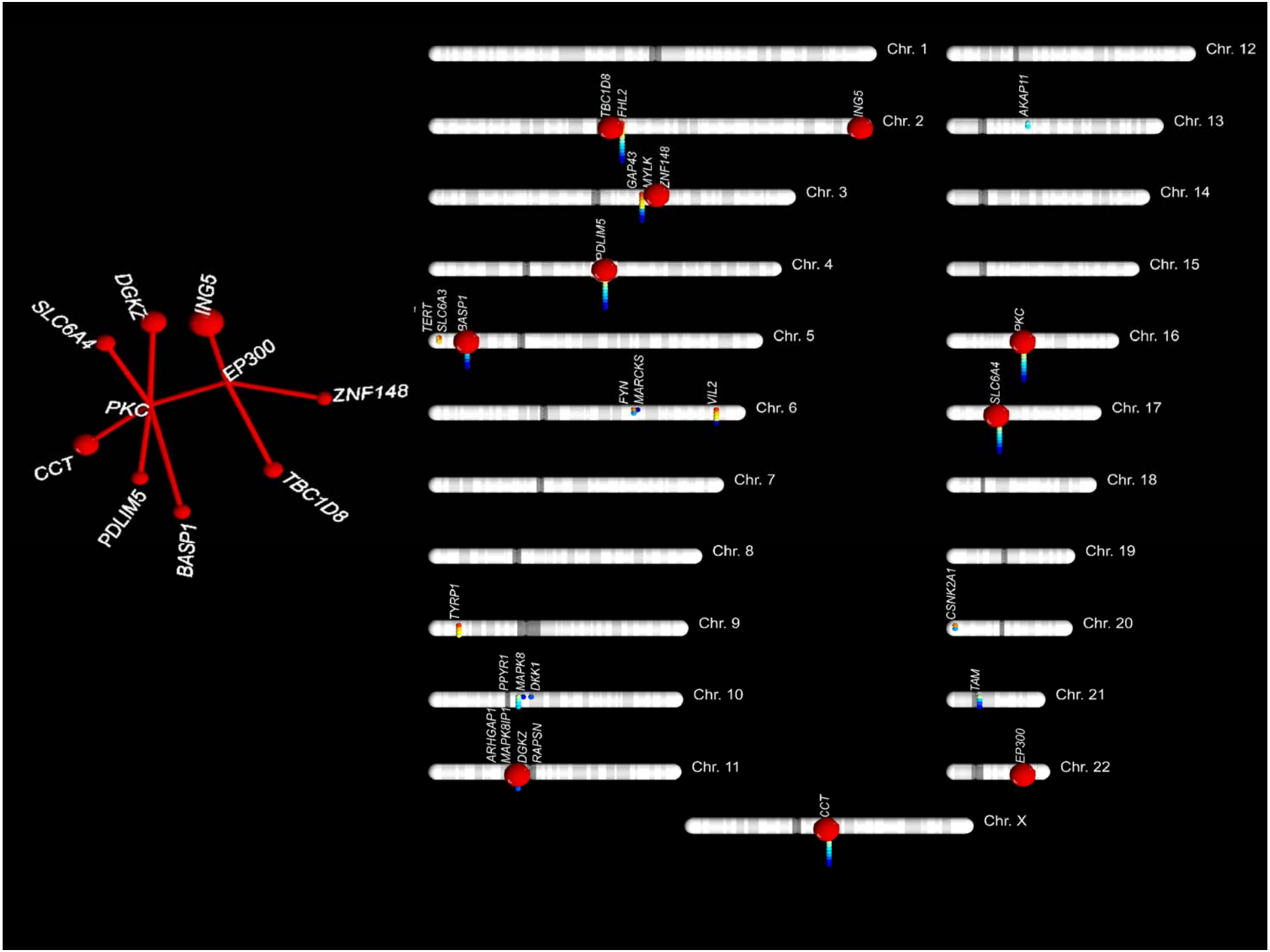


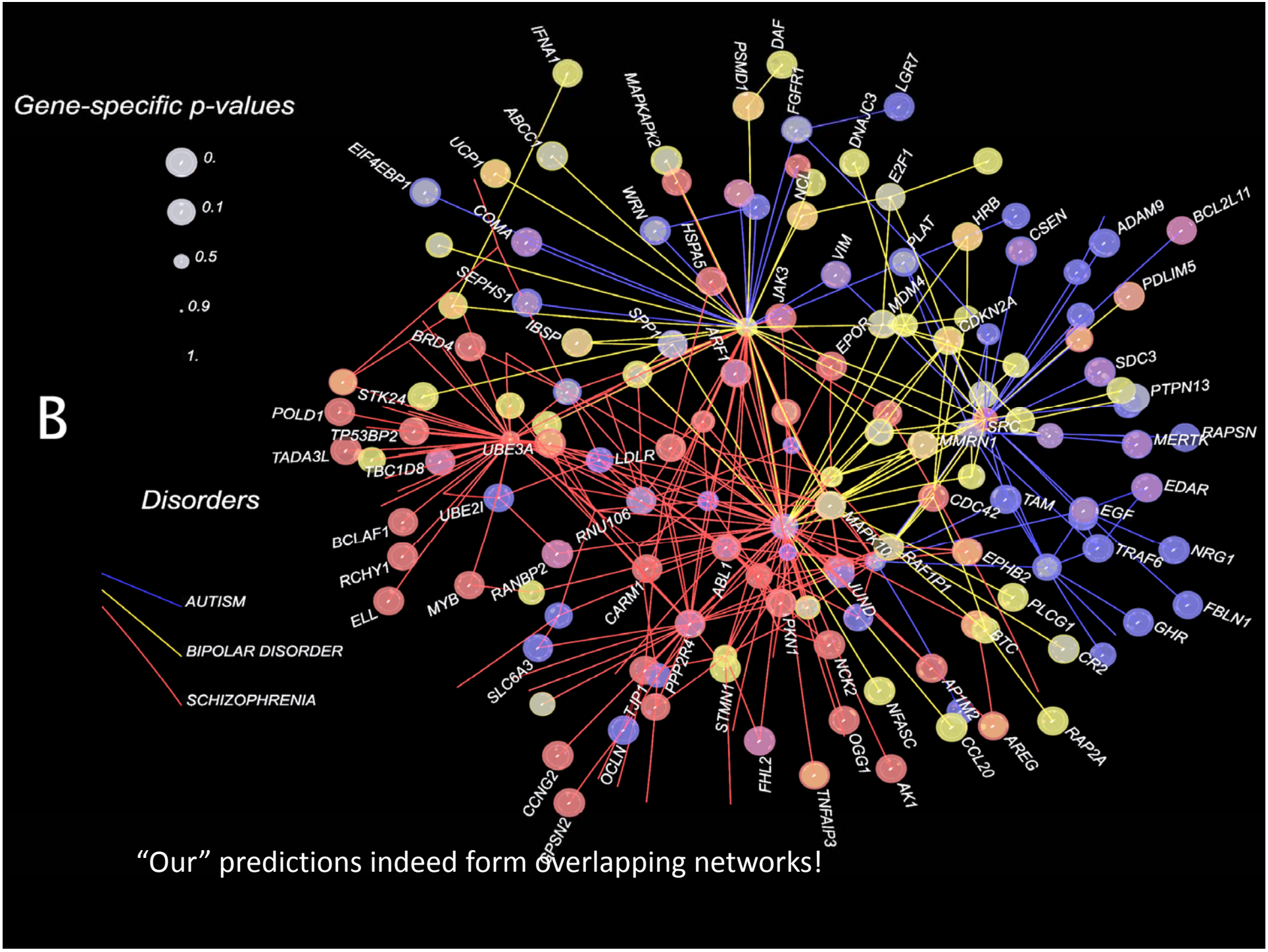




Then we realized that the clusters should be allowed to have arbitrary topology

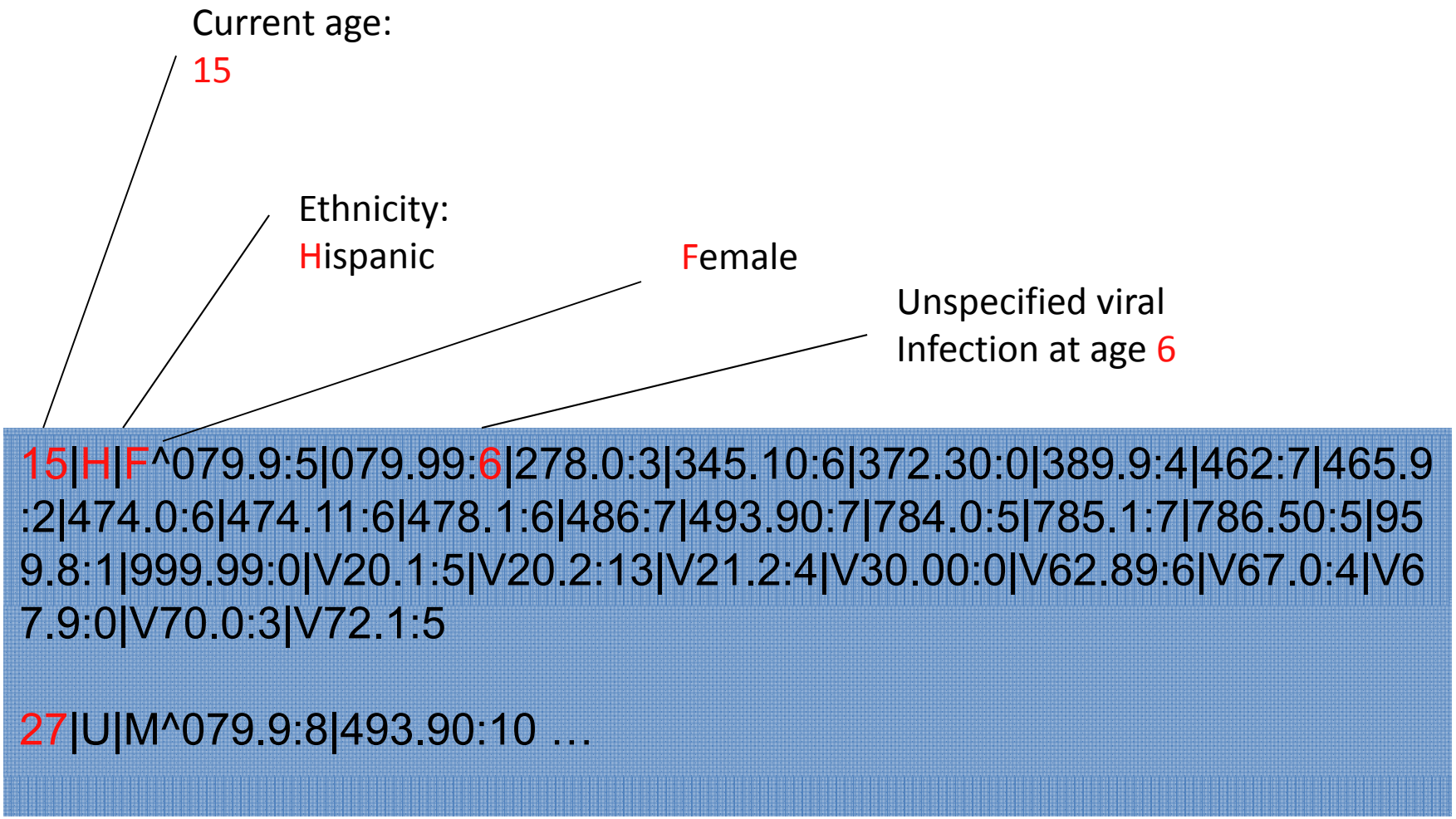

A
CYFIP1
UBE3A
OCA2
TJP1
LOD score
1.18
0.
-2.82
D15S817
D15S128
D15S822
D15S165
D15S1232
SHGC-85049
D15S659
D15S643
D15S1507
D15S131
D15S653
D15S655
D15S652
D15S816
D15S657
D15S956
D15S642
Markers
Chromosome 15
p13
p12
p11.2
q12
q13.2
q14
q15.2
q21.1
q21.3
q22.2
q22.32
q23
q24.2
q25.1
q25.3
q26.2
Genes (cM)
Genes (bp)


SLC6A4
DGKZ
ING5
EP300
ZNF148
PKC
CCT
PDLIM5
BASP1
TBC1D8
Chr. 1
Chr. 2
Chr. 3
Chr. 4
Chr. 5
Chr. 6
Chr. 7
Chr. 8
Chr. 9
Chr. 10
Chr. 11
Chr. X
Chr. 12
Chr. 13
Chr. 14
Chr. 15
Chr. 16
Chr. 17
Chr. 18
Chr. 19
Chr. 20
Chr. 21
Chr. 22
TBC1D8
FHL2
ING5
AKAP11
GAP43
MYLK
ZNF148
PDLIM5
TERT
SLC6A3
BASP1
PKC
FYN
MARCKS
VIL2
SLC6A4
TYRP1
CSNK2A1
PPYR1
MAPK8
DKK1
TAM
ARHGAP1
MAPK8IP1
DGKZ
RAPSN
EP300
CCT



"Our" predictions indeed form overlapping networks!

Completely different type of data
(the same problem)



Data: ICD9 codes in Columbia University clinical database

Data

$\sum = 1.5 \perp 10^6$ patient records

Probing genetic overlap among complex human phenotypes

Andrey Rzhetsky*†‡, David Wajngurt*, Naeun Park*, and Tian Zheng§

*Department of Biomedical Informatics, Center for Computational Biology and Bioinformatics and Joint Centers for Systems Biology, and †Judith P. Sulzberger, M.D., Columbia Genome Center, Columbia University, New York, NY 10032; and §Department of Statistics, Columbia University, New York, NY 10027

11694–11699 | PNAS | July 10, 2007 | vol. 104 | no. 28

AR

David Wajngurt

Naeun Park

Tian Zheng

Assumptions

1. If the same environmental effect triggers two (or more) different maladies, it typically does so through molecular mechanisms that are common between these two maladies.

In other words: *common environmental triggers of two phenotypes can be neglected.*

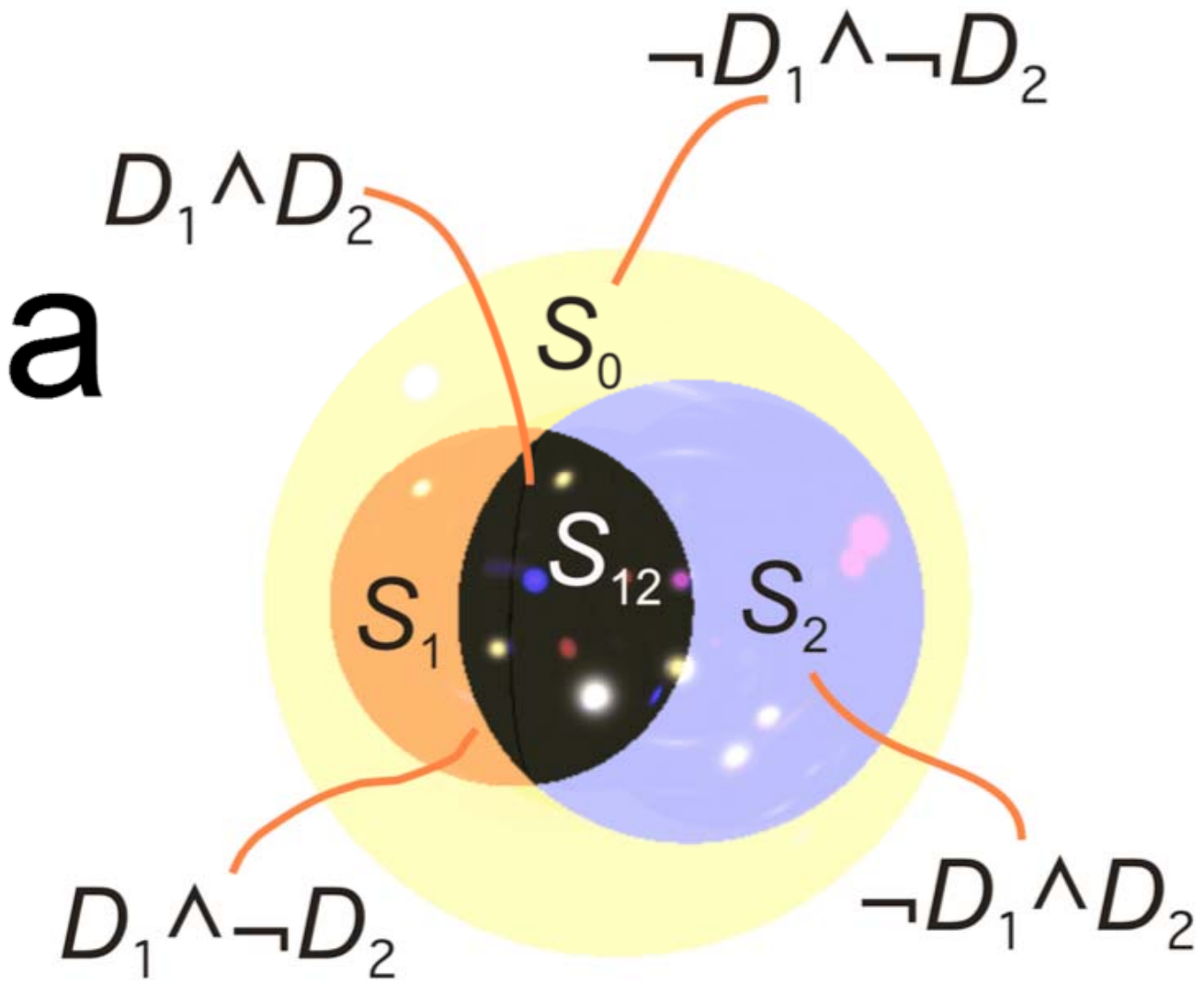
Although this assumption is likely to be violated for some pairs of disorders, it is a reasonable starting point for the model.

2. For each phenotype pair (D_1 and D_2), the whole human genome can be divided into four disjoint sets of nucleotide sites.

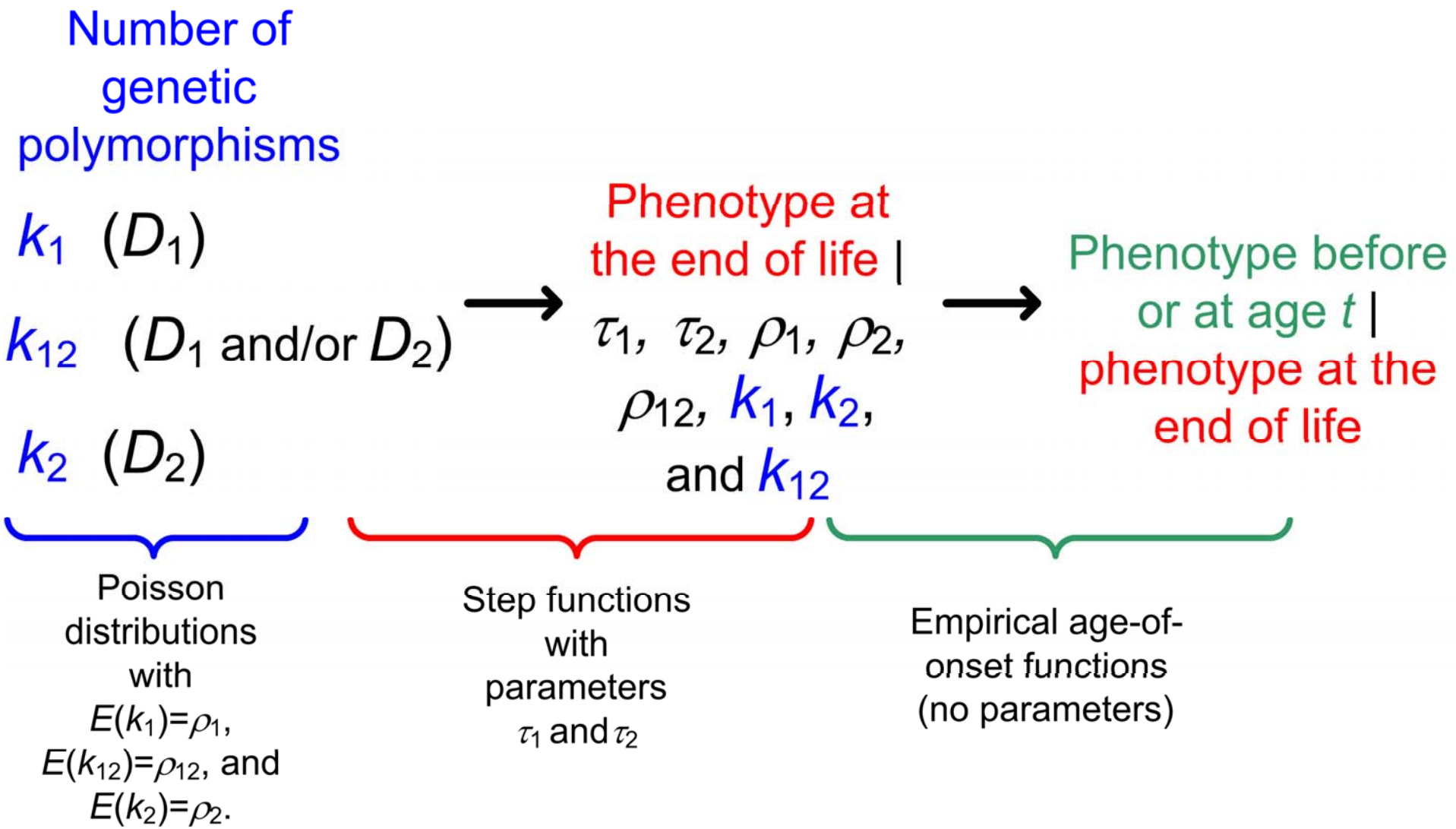
3. We assume a spectrum of hypothetical mechanisms that connect genetic variation within the four sets of nucleotide sites to the disease phenotype (genetic penetrance).

‘all models are wrong, some are useful’

4 sets of genomic sites

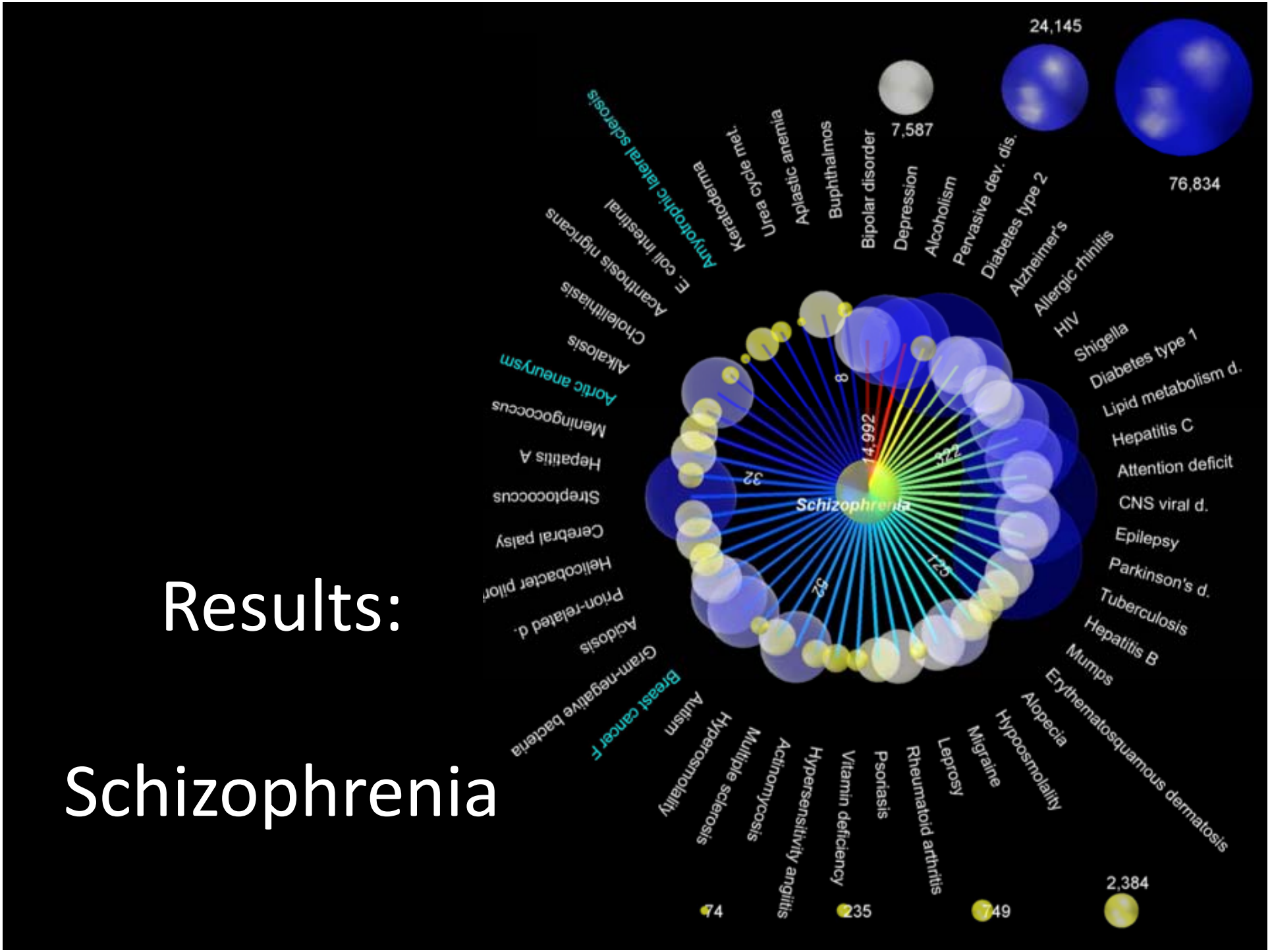


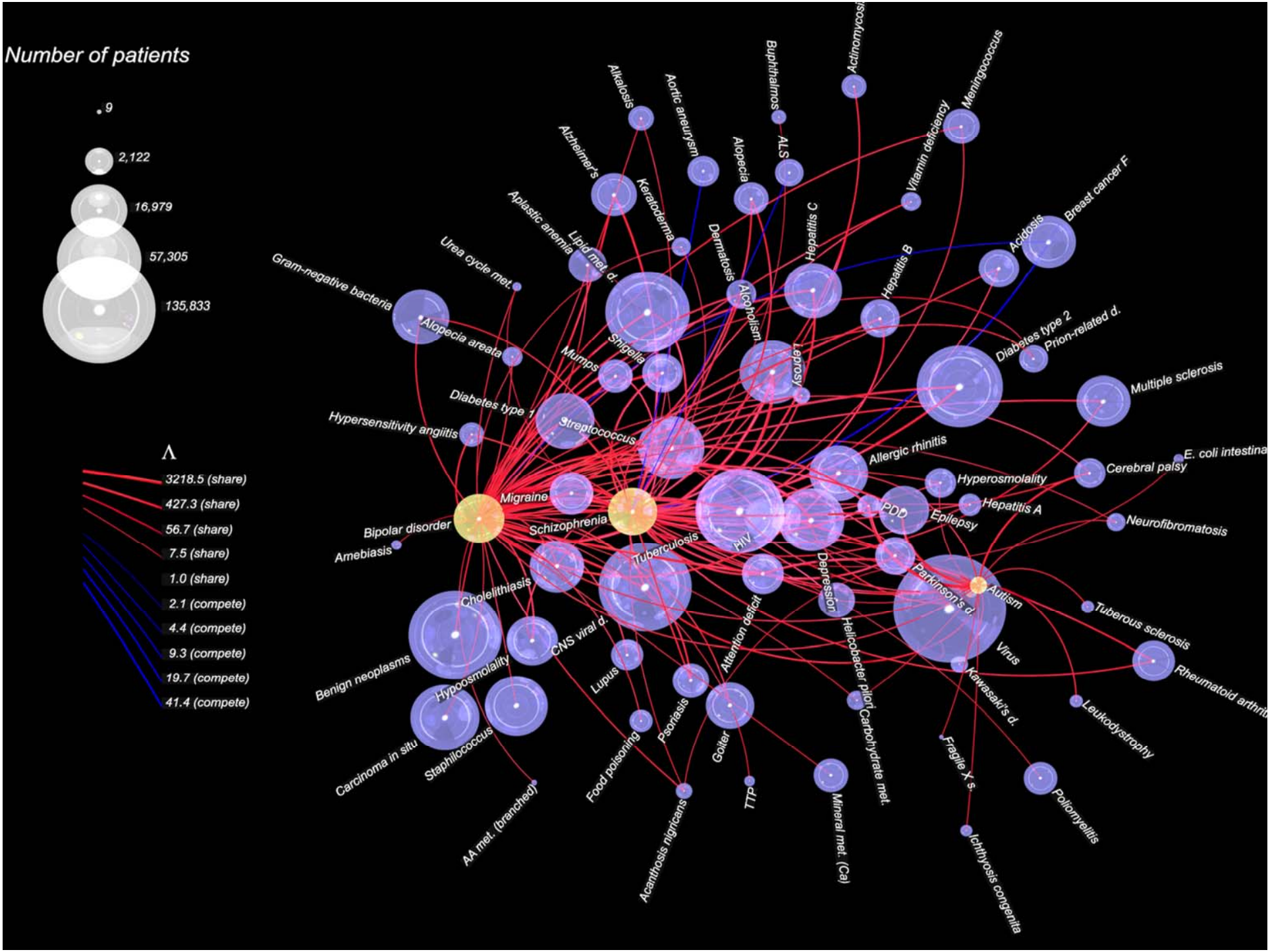
Model outline…

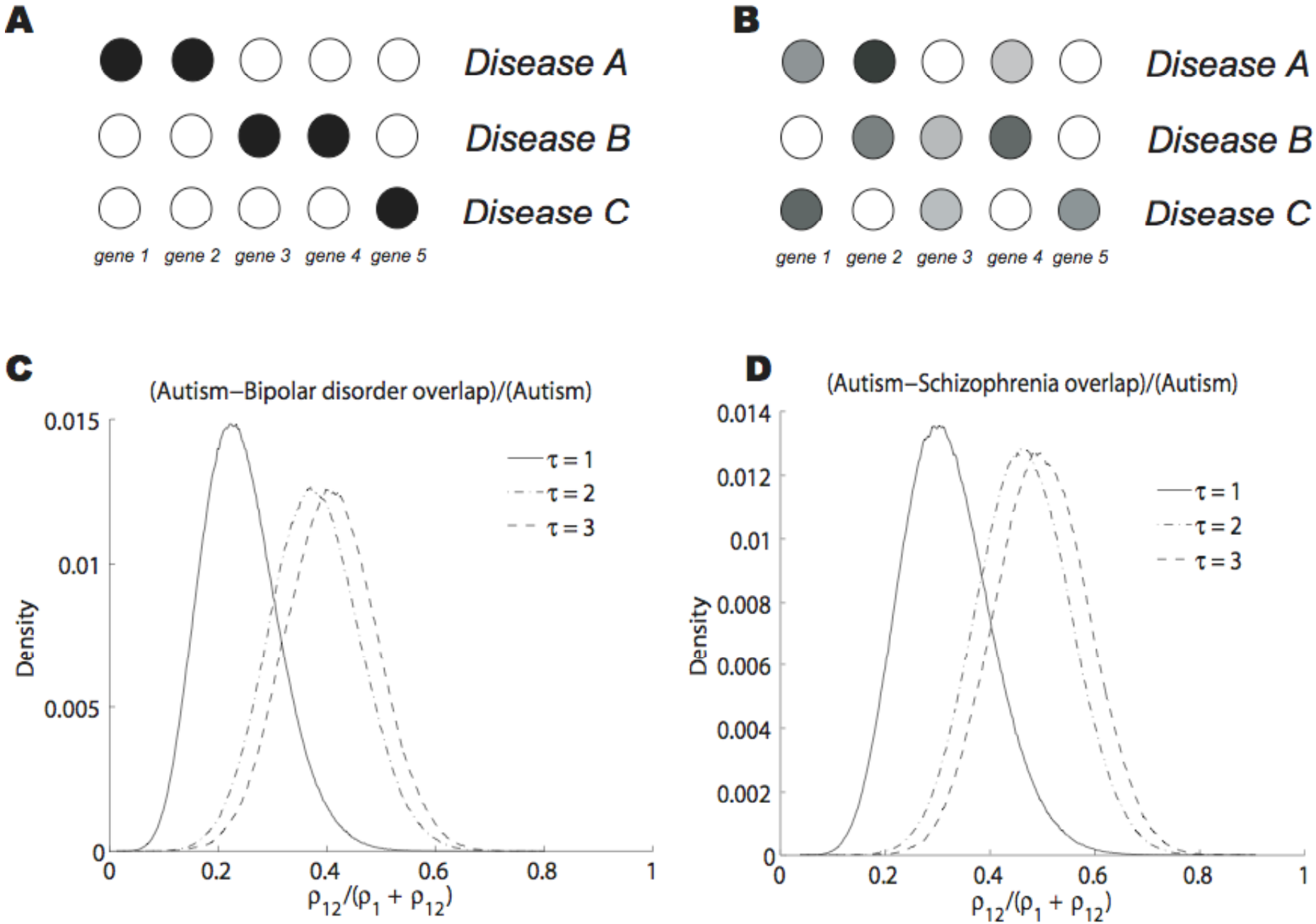


Results:

Schizophrenia




Number of patients
9
2,122
16,979
57,305
135,833
Λ
3218.5 (share)
427.3 (share)
56.7 (share)
7.5 (share)
1.0 (share)
2.1 (compete)
4.4 (compete)
9.3 (compete)
19.7 (compete)
41.4 (compete)
Actinomycosis
Meningococcus
Buphthalmos
Alkalosis
Aortic aneurysm
Alzheimer's
Alopecia
ALS
Vitamin deficiency
Aplastic anemia
Keratoderma
Dermatosis
Hepatitis C
Breast cancer F
Urea cycle met.
Lipid met. d.
Acidosis
Gram-negative bacteria
Alcoholism
Hepatitis B
Alopecia areata
Shigella
Leprosy
Diabetes type 2
Prion-related d.
Mumps
Multiple sclerosis
Diabetes type 1
Streptococcus
Hypersensitivity angiitis
Allergic rhinitis
E. coli intestina
Cerebral palsy
Hyperosmolality
Migraine
Hepatitis A
PDD
Epilepsy
Neurofibromatosis
Bipolar disorder
Schizophrenia
HIV
Amebiasis
Tuberculosis
Depression
Parkinson's d.
Autism
Cholelithiasis
Tuberous sclerosis
Helicobacter pilori
Virus
Benign neoplasms
CNS viral d.
Attention deficit
Rheumatoid arthriti
Hypoosmolality
Lupus
Kawasaki's d.
Leukodystrophy
Carbohydrate met.
Psoriasis
Goiter
Fragile X s.
Carcinoma in situ
Staphilococcus
Food poisoning
TTP
Mineral met. (Ca)
Poliomyelitis
AA met. (branched)
Acanthosis nigricans
Ichthyosis congenita


A
Disease A
Disease B
Disease C
gene 1
gene 2
gene 3
gene 4
gene 5
B
Disease A
Disease B
Disease C
gene 1
gene 2
gene 3
gene 4
gene 5
C
(Autism–Bipolar disorder overlap)/(Autism)
Density
0.015
0.01
0.005
0
τ = 1
τ = 2
τ = 3
0
0.2
0.4
0.6
0.8
1
ρ12/(ρ1 + ρ12)
D
(Autism–Schizophrenia overlap)/(Autism)
Density
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
τ = 1
τ = 2
τ = 3
0
0.2
0.4
0.6
0.8
1
ρ12/(ρ1 + ρ12)

This genetic overlap was only a hypothesis in 2007

Now it is confirmed experimentally in multiple independent studies

Some horn-blowing…

Technology Review
PUBLISHED BY MIT

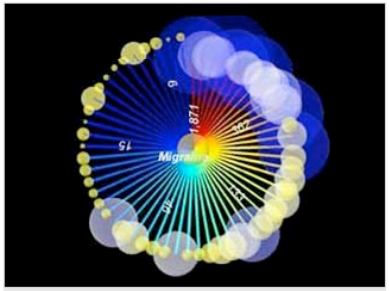
abcNEWS / Technology

Mapping Complex Diseases

A computer model of epidemiological data from 1.5 million people illuminates the genetic origins of many common diseases.

By KATHERINE BOURZAC
July 9, 2007

Researchers at Columbia University have mapped the overlap between 161 different diseases by studying epidemiological data from 1.5 million patients. Among their findings is a strong overlap between schizophrenia, bipolar disorder, and autism, suggesting that these three diseases may be caused by a shared group of genes. The researchers hope others will use their map to further investigate the genetic bases of the diseases they studied--genetics that in most cases are poorly understood.



The maps reveal connections between migraine and other diseases, such as infections.
(Andrey Rzhetsky)

Certain diseases caused by single genetic mutations are correlated with other conditions in well-known ways, says Andrey Rzhetsky, the leader of the mapping project, who is now a professor of genetic medicine at the University of Chicago. For example, the same mutation in the gene for hemoglobin, the protein that carries oxygen in the blood, causes sickle-cell anemia but protects against malaria. Unlike sickle-cell anemia, however, most diseases aren't caused by a single mutation. The genetic factors underlying most common diseases, such as diabetes, addiction, and heart disease, are complex and poorly understood. But Rzhetsky found connections between genetically complex diseases, too.

NEUROLOGY TODAY
AN OFFICIAL PUBLICATION OF THE AMERICAN ACADEMY OF NEUROLOGY
AMERICAN ACADEMY OF NEUROLOGY

Neurology Today:
7 August 2007 - Volume 7 - Issue 15 - pp 1,14-15
doi: 10.1097/01.NT.0000286902.40154.71
Article

A New Model for Mining Data on Shared Phenotypes for Autism, Schizophrenia, and Bipolar Illness

Talan, Jamie

Back to Top | Article Outline

ARTICLE IN BRIEF

✓ Biostatisticians used a complex mathematical formula to chart associations among disparate diseases, including autism, bipolar disorder, and schizophrenia.

Scientists have mined information from 1.5 million medical charts in an attempt to find shared genotypes that could explain groups of illnesses that either track together or put people at higher risk for multiple neurological and psychiatric problems, including autism, schizophrenia, migraine, and bipolar illness.

Andrey Rzhetsky, PhD, professor of medicine and human genetics at the University of Chicago, got the idea for this mathematical model while at Columbia University Medical Center. An expert biostatistician, he had access to 1.5 million patient records from the medical center over a 20-year period.

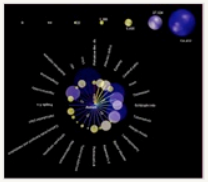
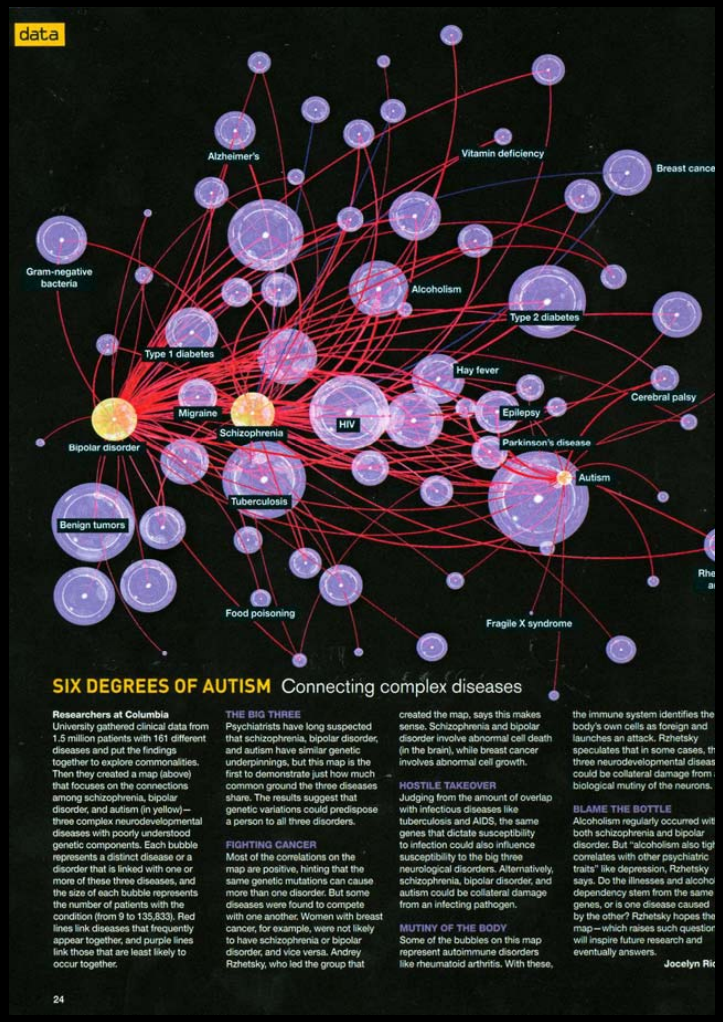


Figure. A mathematic...

Some horn-blowing…

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Thank you!