



Suicide Prevention Across the Educational Continuum

6-Part Webinar Series



Mountain Plains (HHS Region 8)

MHTTC

Mental Health Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration



Mountain Plains (HHS Region 8)

PTTC

Prevention Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration

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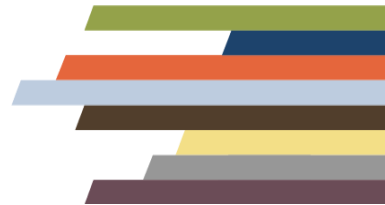
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World Class Resources to Discover Genetic Risks for Suicide Death

Hilary Coon, PhD

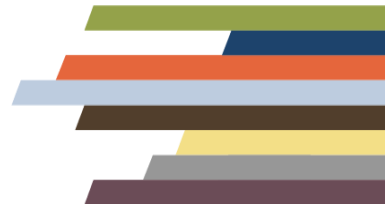
Professor

Department of Psychiatry

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SAMHSA

Substance Abuse and Mental Health
Services Administration



Suicide: A Public Health Crisis

Suicide is the
10th
leading cause of
death in the US

#2 for ages 25-34
#3 for ages 10-24

In 2017,
47,173
Americans died
by suicide

>800,000
deaths
worldwide

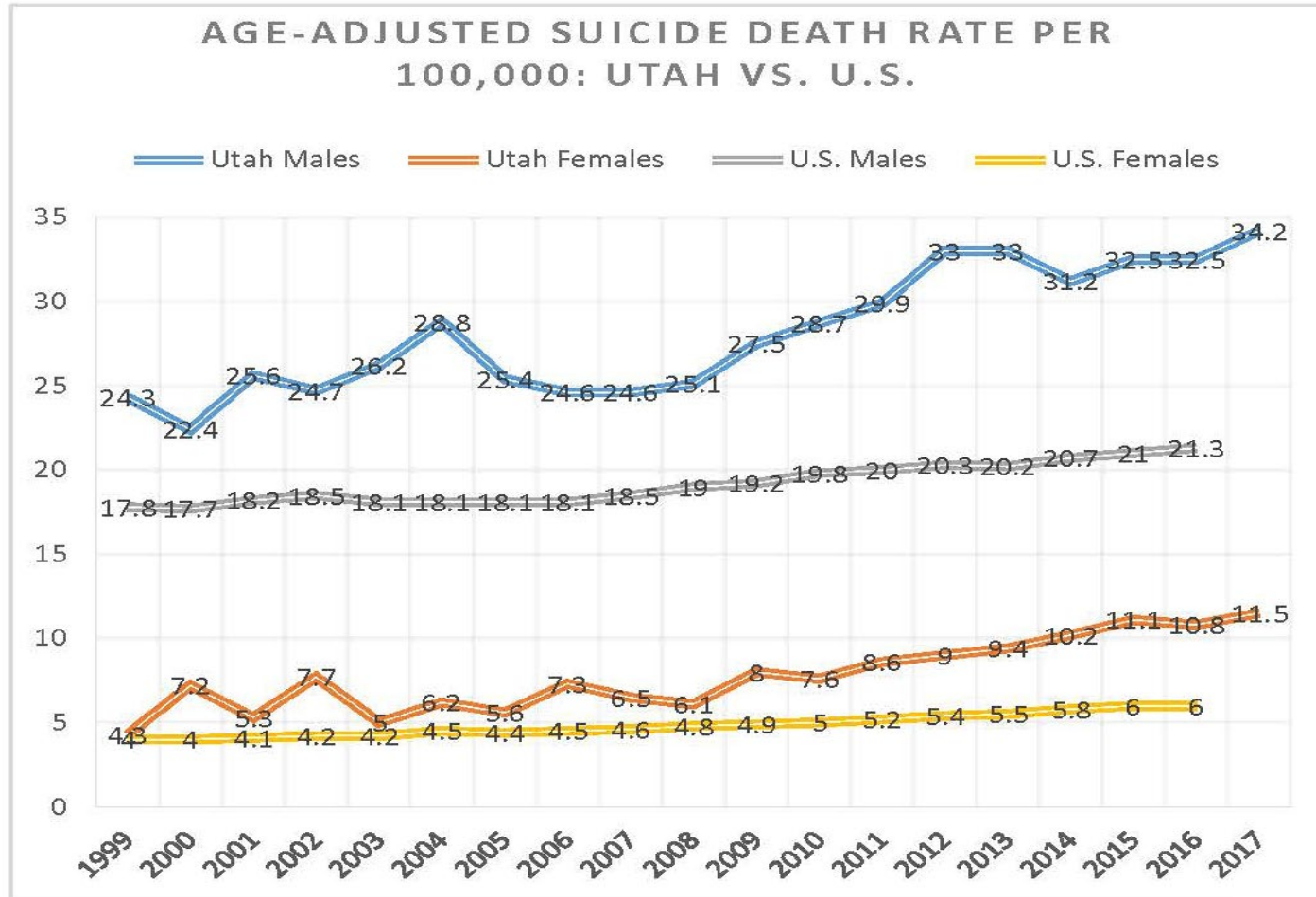
For every
suicide,
25-30
attempt

1,400,000
attempts in
2017 in the US

www.afsp.org

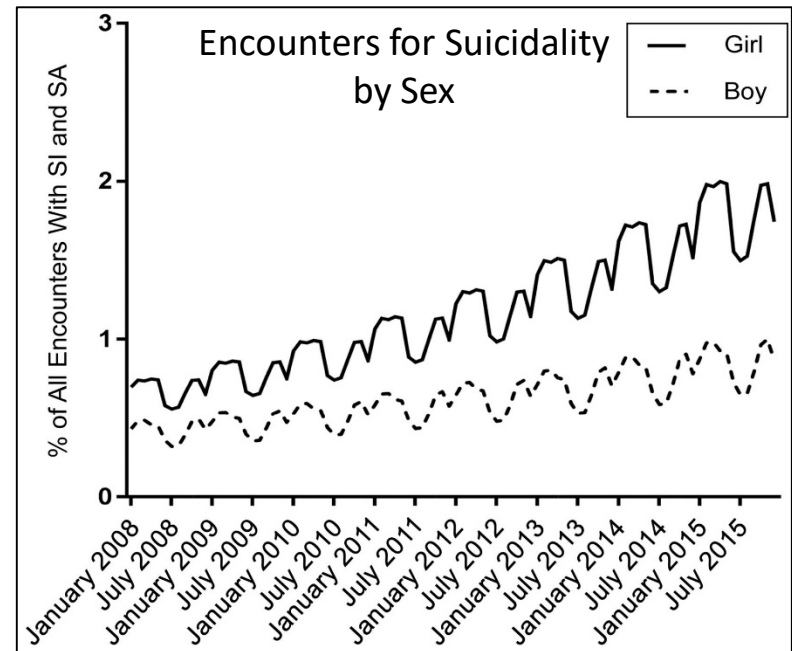
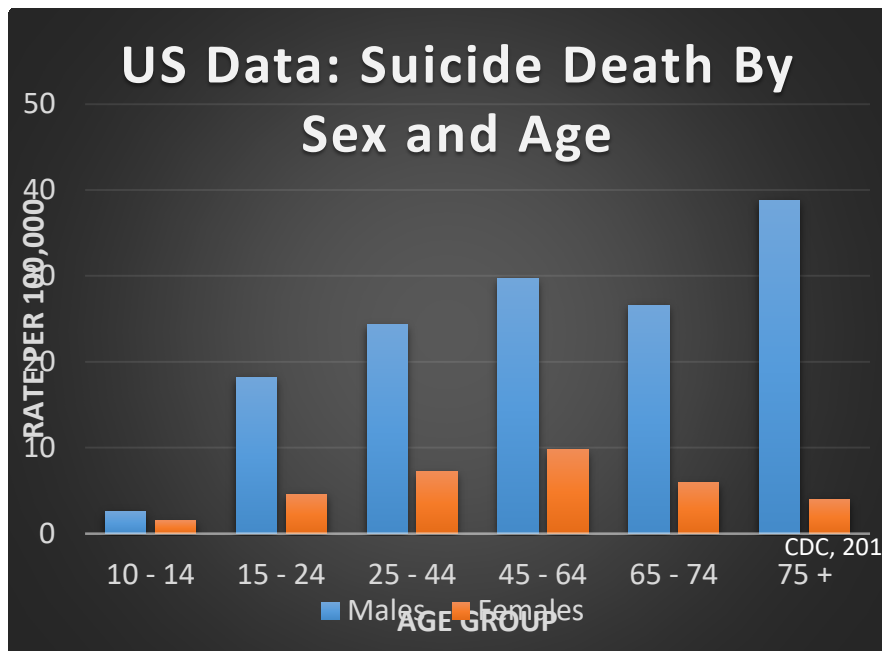
Rising Suicide Death Rates

- Incidence of suicide death has increased 33% in the US since 1999
- In this same time period, the increase has been 46% in Utah; dramatic increase in female suicide



Epidemiology: Suicide Death Vs. Attempt

- RATE: Suicide death: ~2/10,000 per year; attempts 25-30 times more common
- SEX DISTRIBUTION:
 - Suicide death: male:female ratio=3.8:1;
 - Attempts: more difficult to count accurately, but ~twice as common in females, especially in youth



Plemmons et al., Pediatrics, 2018

Suicide Death: Psychopathology & Familial Risk

- Many individuals who die by suicide struggle with mental illness

- BUT most individuals who have mental illness do not die by suicide
- AND suicide risk is significantly familial¹
- Familial risk is **independent** of psychopathology²
- Risk factors unique to suicide?

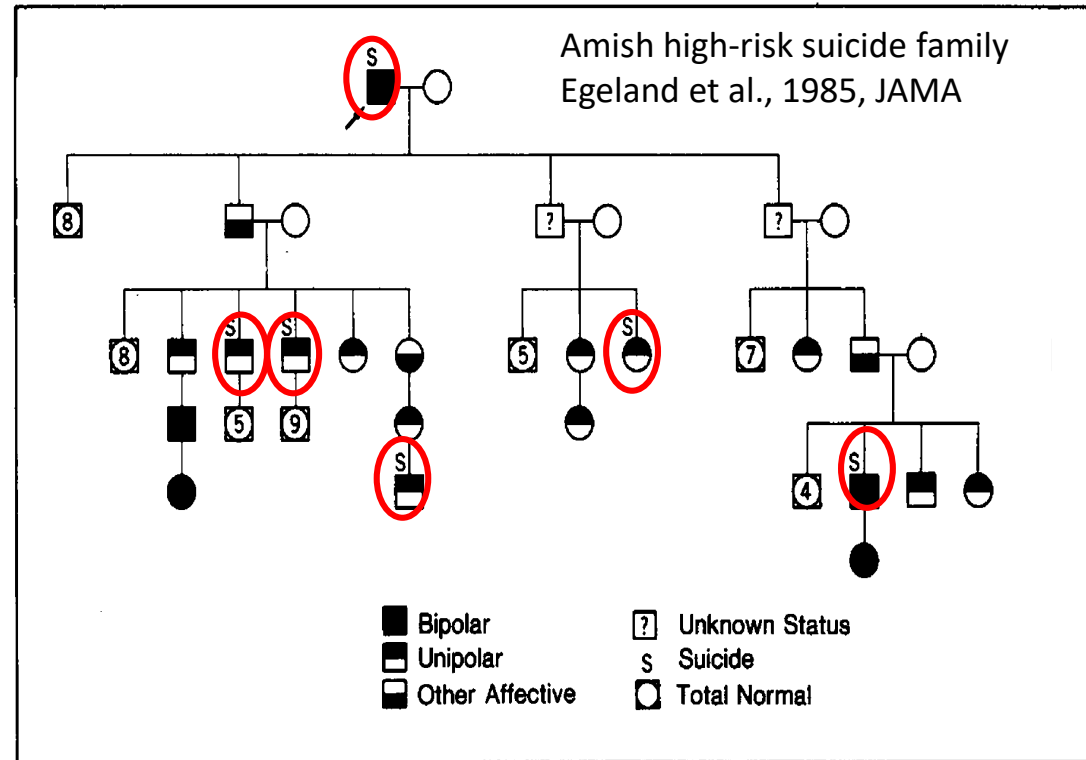


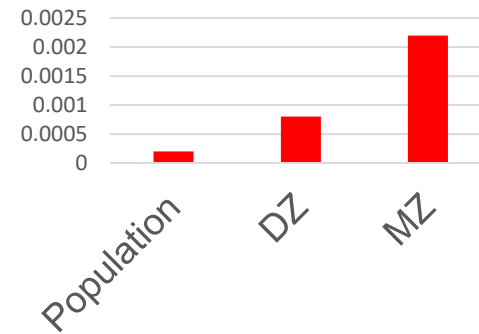
Fig 1.—Pedigree 214.

¹Egeland et al., 1985; ²Brent & Mann, 2005

Suicide Death: Aggregated Evidence for Genetic Risk

- **Twin studies:**

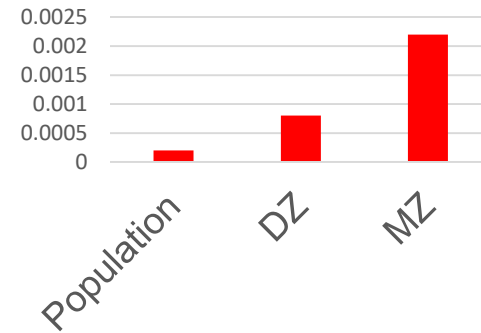
- Fraternal : **4 times** the population rate
- Identical : **11 times** the population rate



Suicide Death: Aggregated Evidence for Genetic Risk

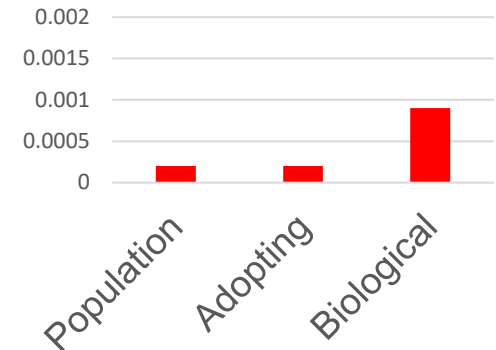
- **Twin studies:**

- Fraternal : **4 times** the population rate
- Identical : **11 times** the population rate



- **Adoption studies:**

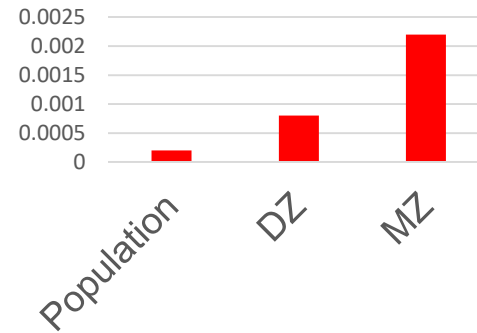
- Adopting relatives: no increased risk
- Biological relatives: **4-5 times** the population rate



Suicide Death: Aggregated Evidence for Genetic Risk

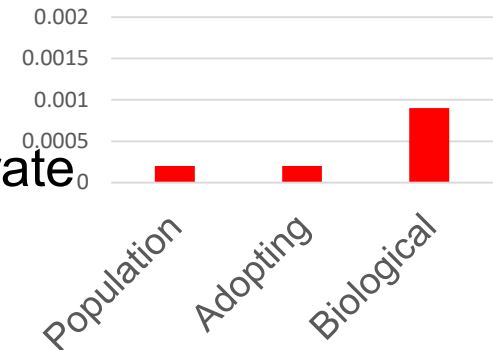
- **Twin studies:**

- Fraternal : **4 times** the population rate
- Identical : **11 times** the population rate



- **Adoption studies:**

- Adopting relatives: no increased risk
- Biological relatives: **4-5 times** the population rate



- **Evidence: genetic contribution to risk of suicide death = ~50%**

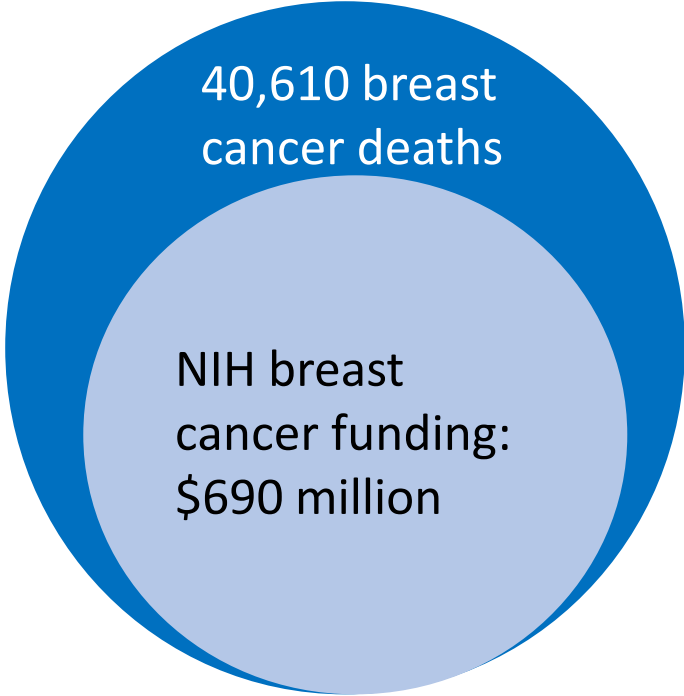
Health burden vs. research funding



47,173 suicide
deaths

NIH
suicide
funding:
\$103 million

mh.nih.gov/fundi



40,610 breast
cancer deaths

NIH breast
cancer funding:
\$690 million

cancer.gov/about-nci/budget

Suicide Risk Studies: Why Utah?

- Utah in the top 6 for suicide rate (MT currently highest, then AK, WY, NM, ID, UT).
- Suicide = leading cause of death for persons under age 25 in UT.

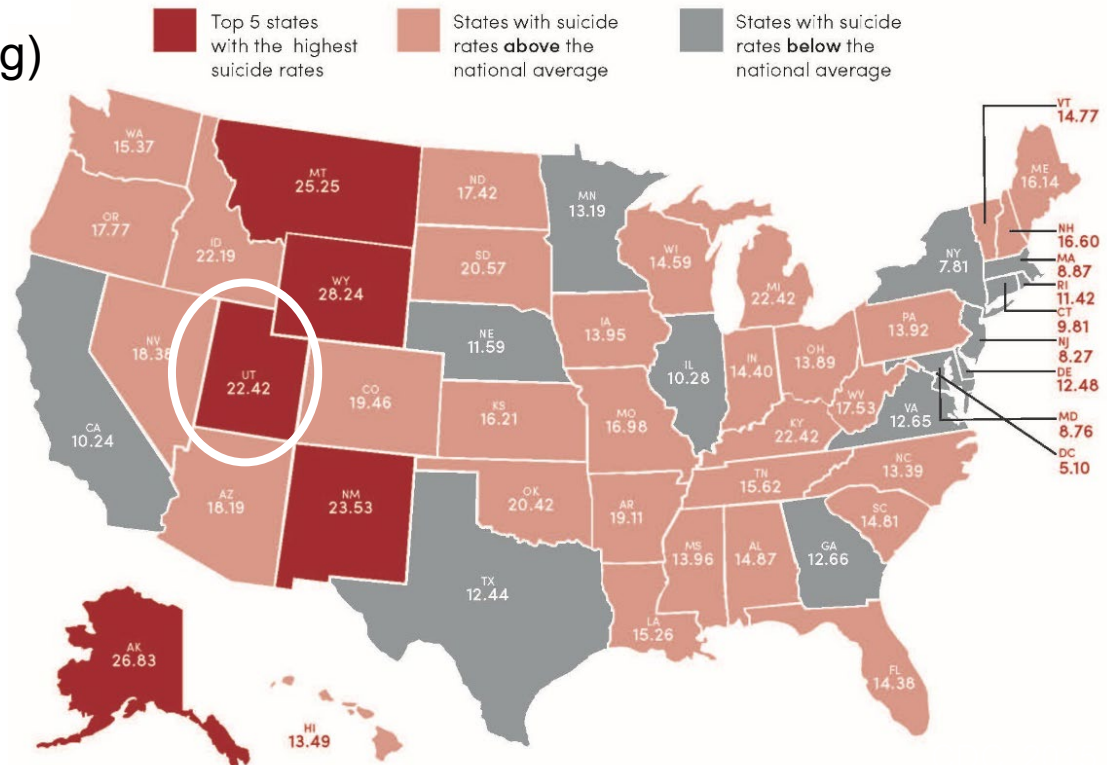
Utah Resources

- Central Medical Examiner
- >7,000 cases with DNA (growing)

Utah Population Database

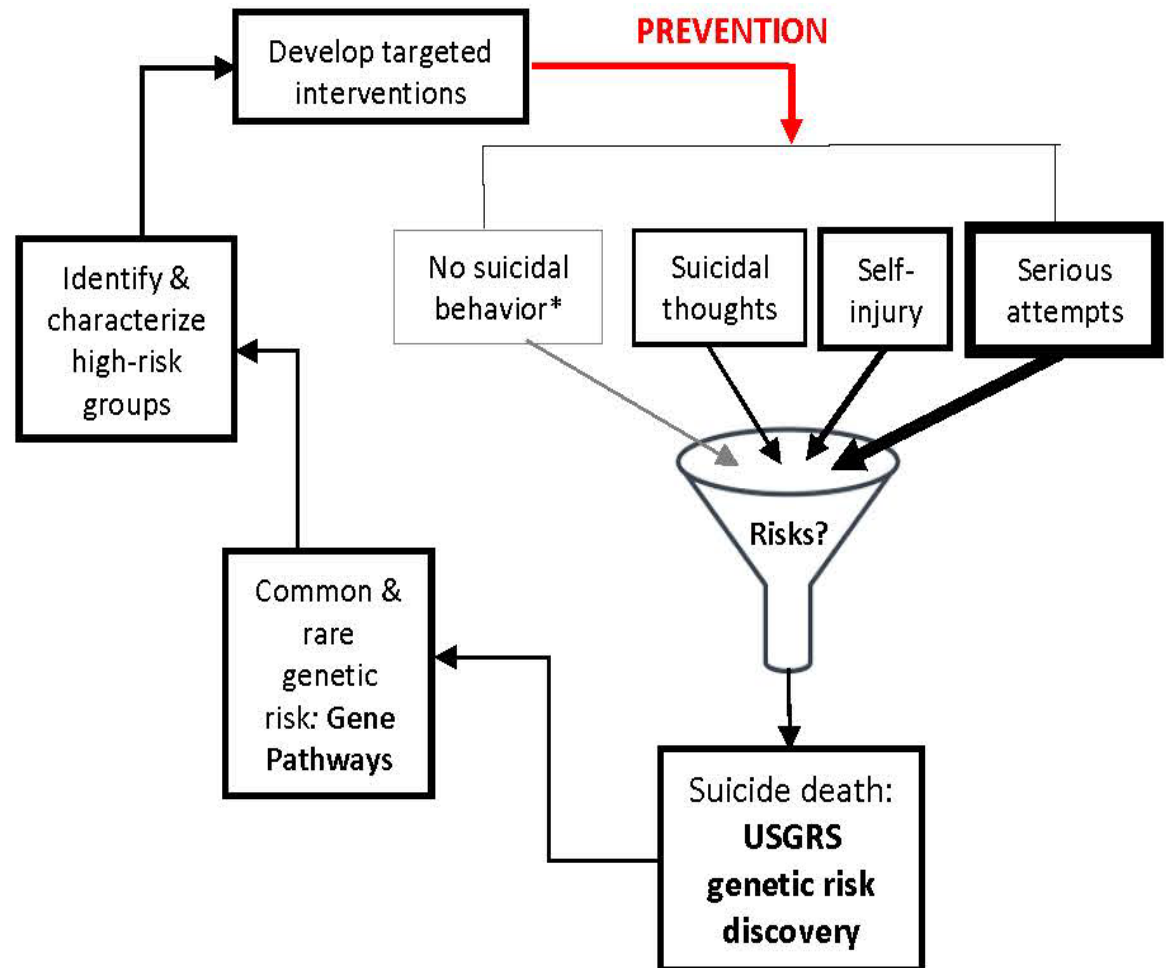
- Medical records
- Demographics
- Genealogical records
- Exposure data

AVERAGE SUICIDE RATE BY STATE
(National average 13.26 per 100,000)

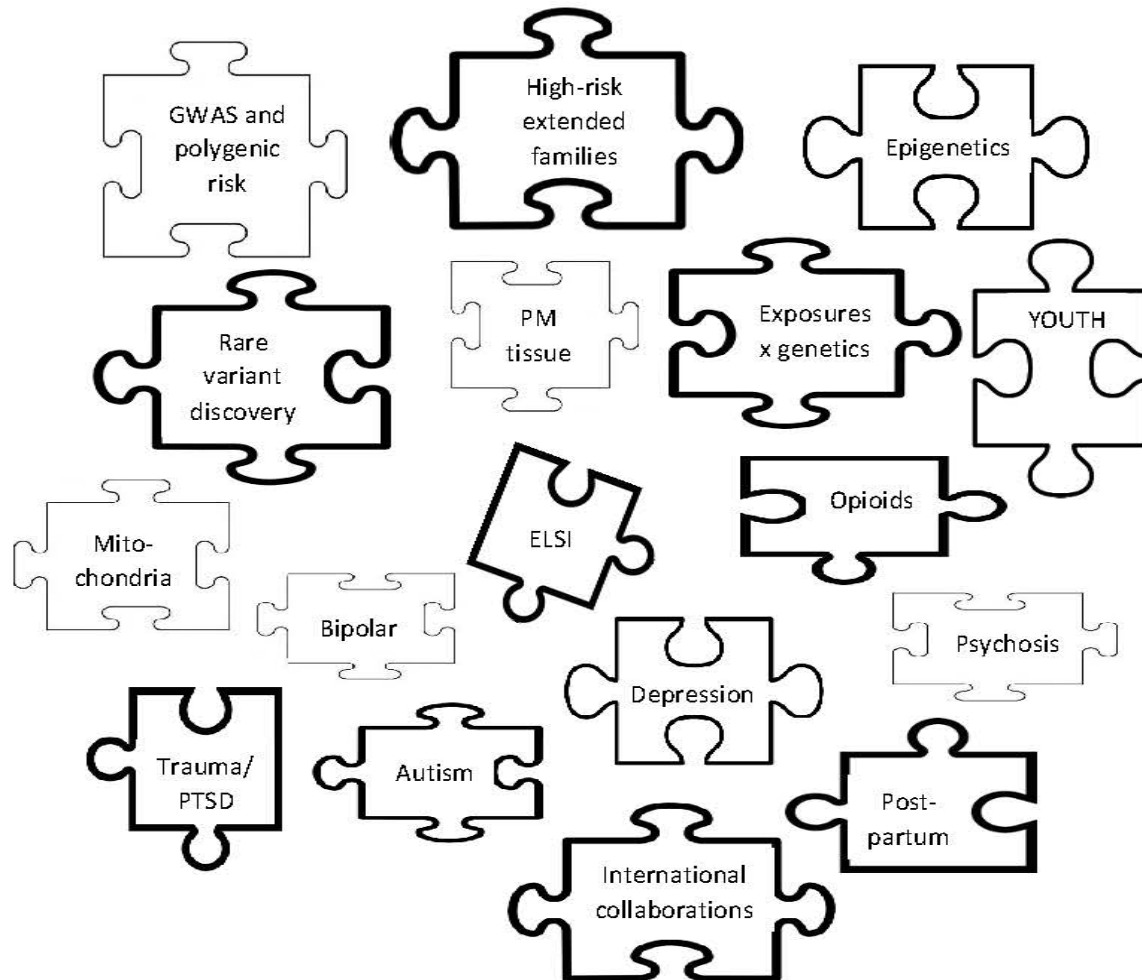


The need to study suicide death

- Risk prediction challenging:
- **>50% suicide deaths occur w/ no evidence of prior attempts**
- **Though suicide attempt is the best predictor of death, only ~7% of attempters go on to die by suicide**
- BUT: suicide death: ~50% heritable
- **Opportunity with a world class resource: Utah Suicide Genetic Risk Study (USGRS)**
 - OME: 10,000 with DNA by 2024
 - >95% link to UPDB



Objectives: Utah Suicide Genetic Risk Study



Find genetic risk factors for suicide.

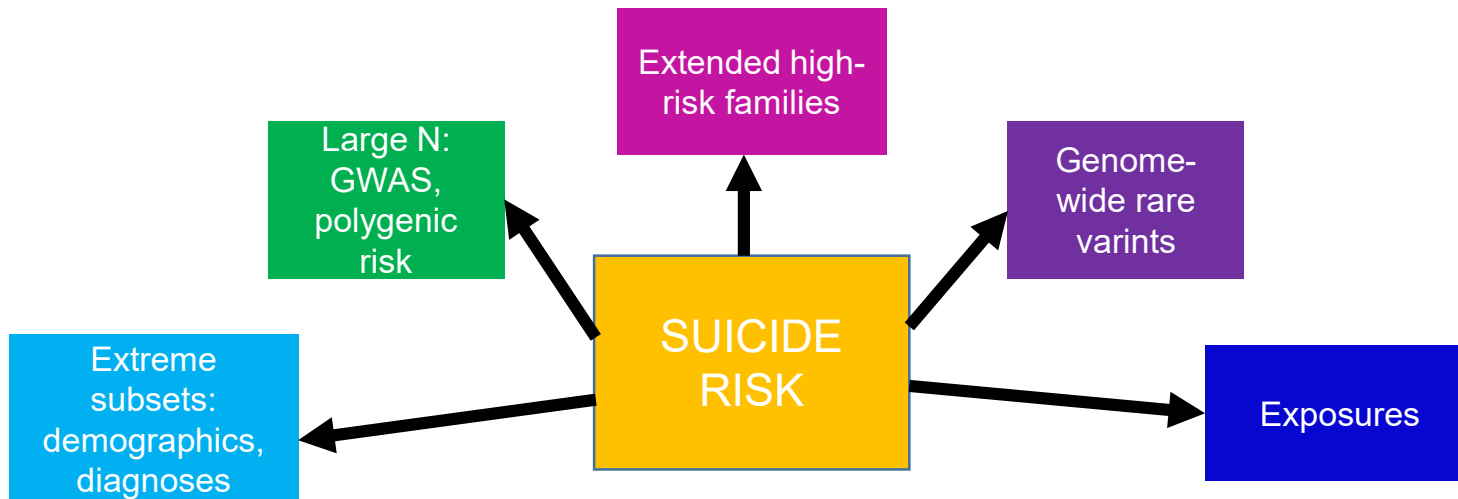
Characterize genetic risk subgroups.

Understand biological mechanisms.

Recognize ELSI impacts.

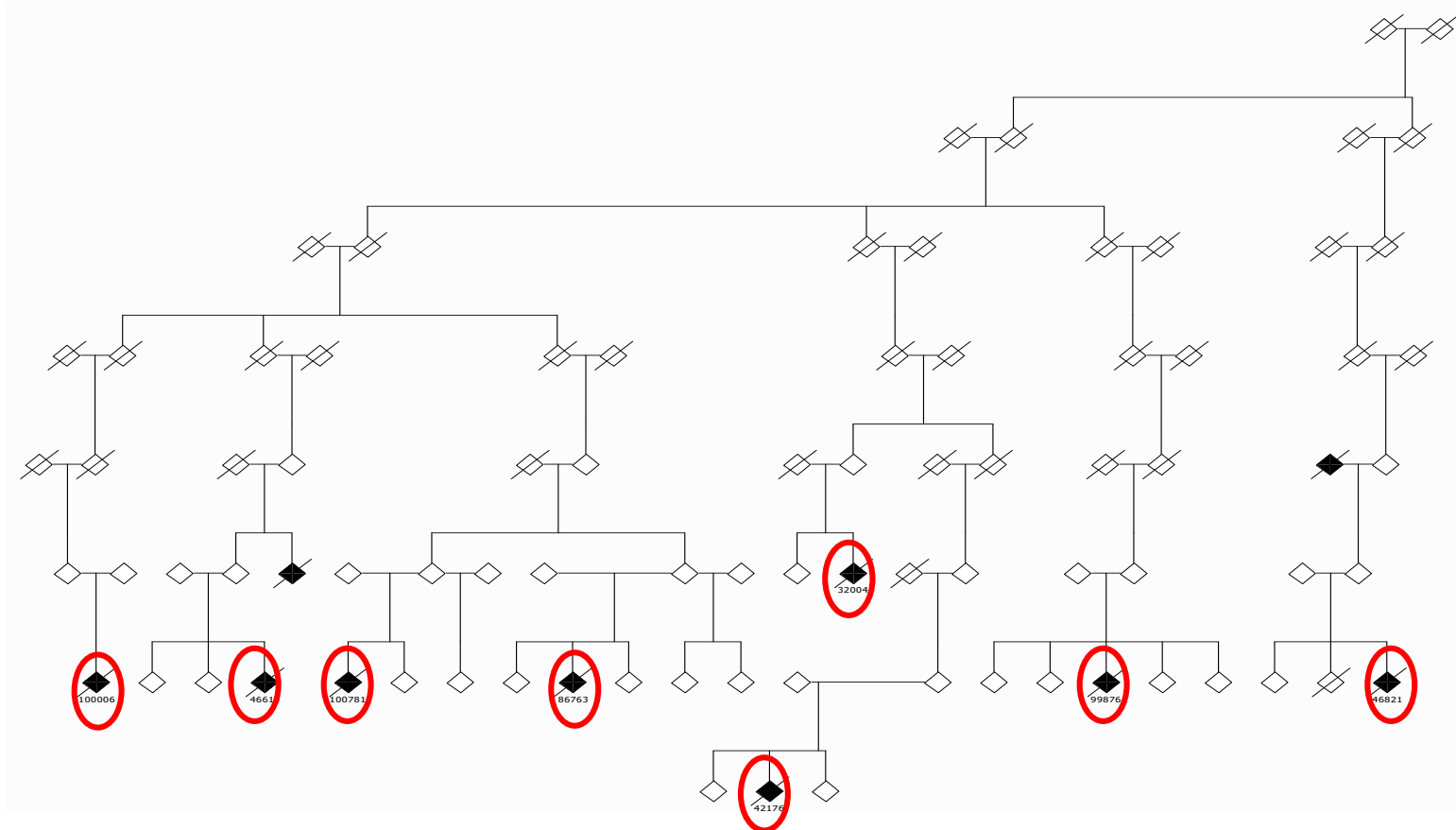
Utah Suicide Genetics Project: linking to phenotype data

- Link to Utah Population Database; de-identification
- Studies in high-risk family clusters
 - power to detect possible genes; increase in genetic homogeneity
 - Distant relatives of very large families minimize shared environmental risk: focus on genetics



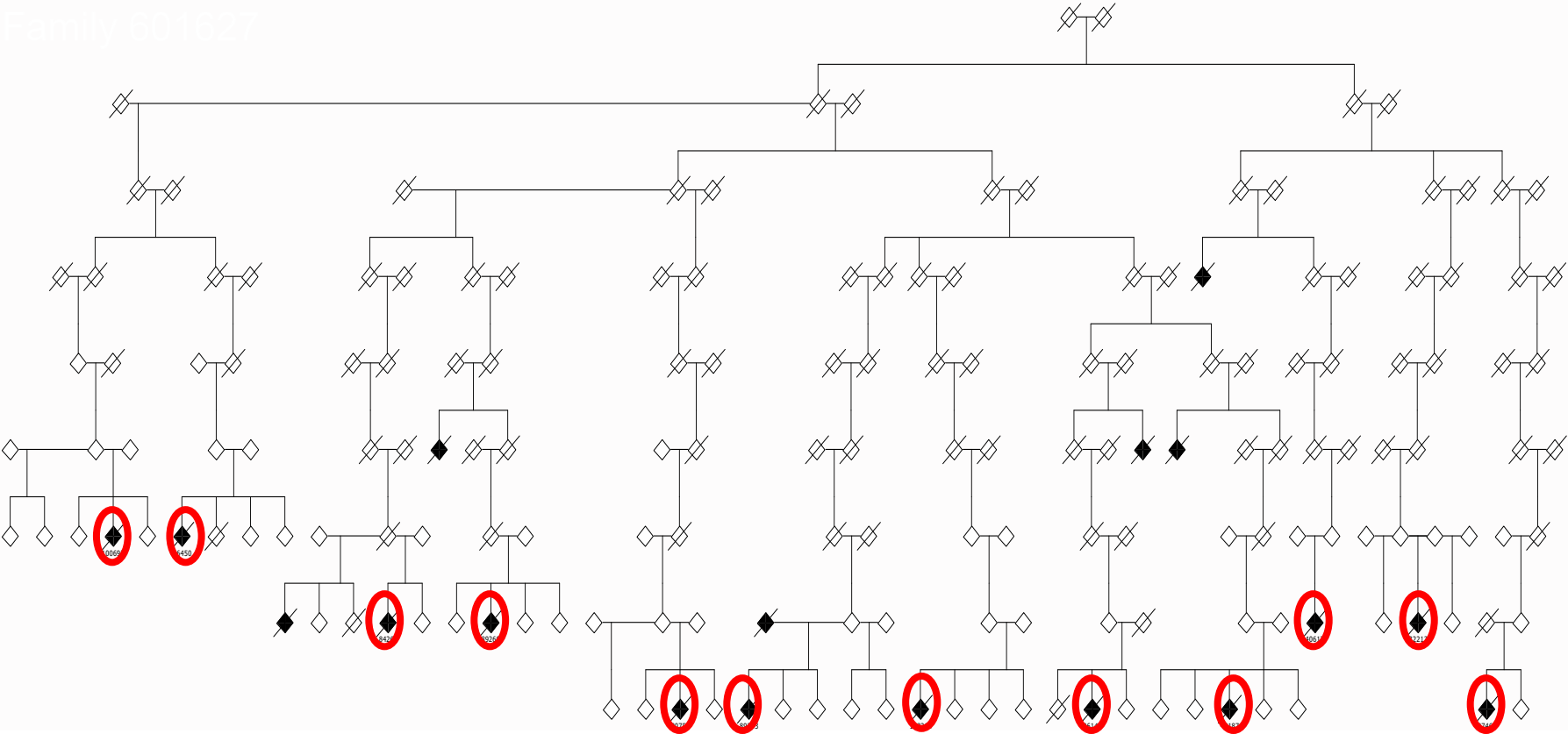
Large High-Risk Utah Families

- Select 43 highest risk families with most cases with DNA
 - Mean age at death=34.3 years (**~8 years younger than overall cohort mean**)
 - Genome-wide genotyping data: look for shared genomic regions
 - Prioritize: genes/variants



Example of one of the largest Utah extended families

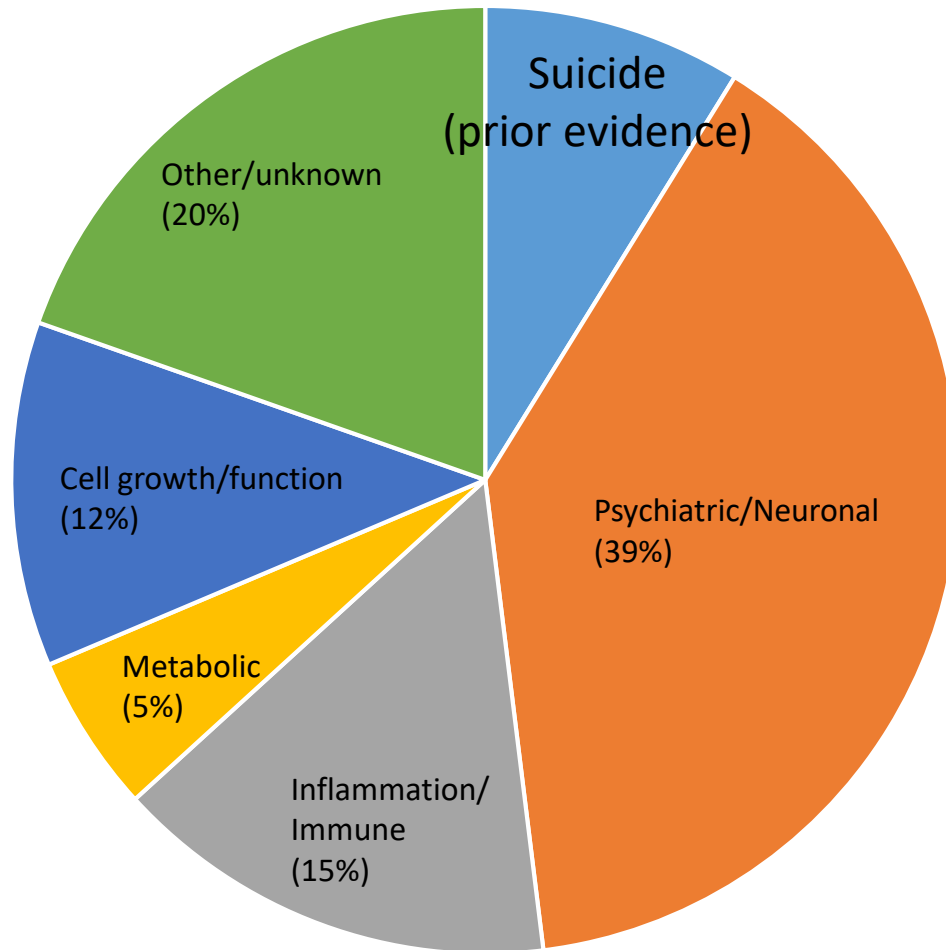
Family 501627



30 Significant Genomic Familial Regions

Sharing Families	Chromosome	Region length	N sharing Cases	P-Value ^a
709, 8556	1p34.2	121,550	6, 5	3.47E-12
791533, 540775	1q31.1-q31.2	895,549	3, 7	4.63E-09
601627	2p16.3	918,021	6	1.94E-10
176860, 11593	2q32.2 – q32.3	991,125	5, 6	4.31E-12
601627	2q36.3 – q37.1	554,589	6	2.39E-10
553615	3p14.1	553,999	8	8.87E-11
129334, 11593	3q26.33	155,082	4, 5	7.94E-12
603481	4q26	878,016	7	3.08E-08
807334	4q28.3	1,340,919	5	2.02E-07
8556, 66494	4q35.1 – q35.2	441,202	4, 5	1.82E-12
553615 ^b	5q23.3 – q31.1	2,620,770	9	2.39E-10
553615, 603481, 176860 ^c	5q23.3 – q31.1	2,135,012	7, 7, 7	1.30E-18
601627	5q33.3 – q34	694,644	7	5.47E-10
553615	6q11.1 – q12	1,576,180	8	1.34E-10
60205	6q24.3	459,602	5	4.02E-07
601627	7p21.2	856,645	6	2.04E-10
957634, 595955	7q36.1	883,853	3, 4	6.44E-11
587072, 595955	8p23.1	875,010	4, 5	4.71E-11
233769	10p15.3	472,479	7	1.11E-09
11593, 8556	10p12.33	184,567	4, 5	3.11E-11
27251, 233769	10q21.3	321,479	7, 5	8.22E-15
209487	11p11.2 – q12.1	9,206,070	6	6.60E-08
540775	11q13.3	451,605	7	6.20E-09
209487, 66494	12q.12	399,570	5, 5	2.14E-12
709	13q12.3	605,320	7	1.86E-08
27251, 41469	13q14.2	756,962	5, 4	2.93E-12
590241, 601627	14q23.1 – q23.2	1,660,713	5, 8	5.91E-14
709	15q21.3 – q22.2	1,045,187	6	2.74E-08
66494	15q22.2	772,162	6	5.44E-08
27251, 233769	18q11.2	79,657	8, 6	5.22E-15
27251, 622459	19q13.12	299,919	8,3	2.89E-12

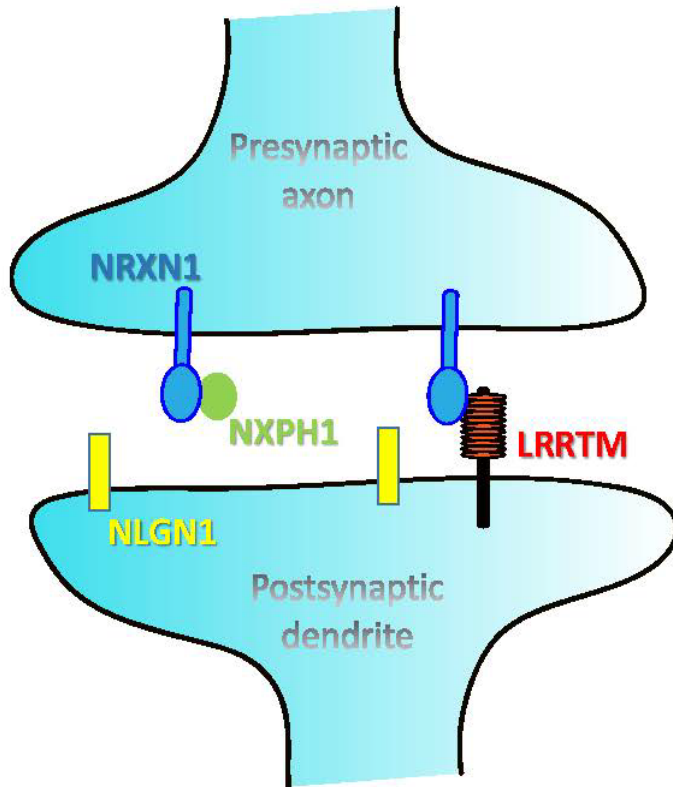
204 genes implicated by SGS regions



Follow-up Functional work: *NRXN1*

***NRXN1*: synaptic gene in a significant familial region**

- A key synapse organizing molecule
- Prior associations with psychopathology
- Two specific *NRXN1* genetic variants showed statistical association with suicide death



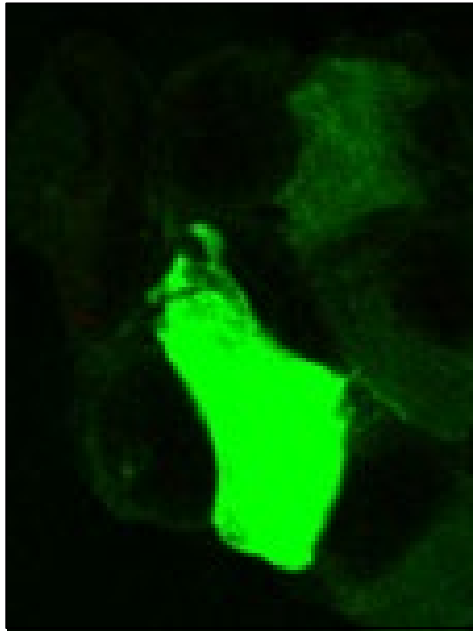
Tests of associated variants:

- Do variants interrupt binding with partners
- Do variants directly inhibit synapse formation

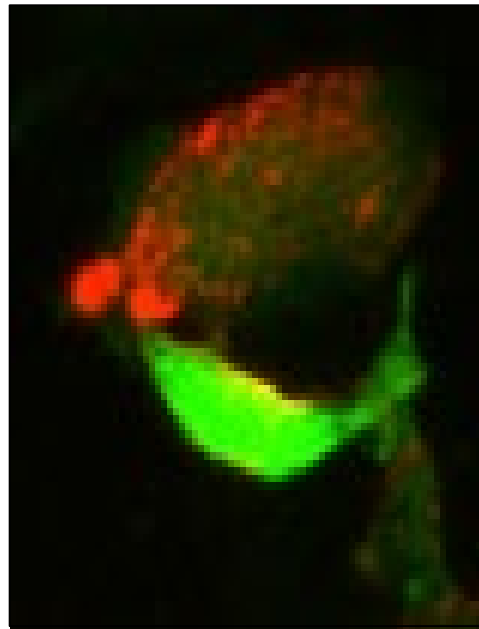
Evidence for functional impact: Neurexin Binding

Purify portion of *NRXN1* outside membrane; transfect with binding partner + fluorescent tag to visualize synaptic binding.

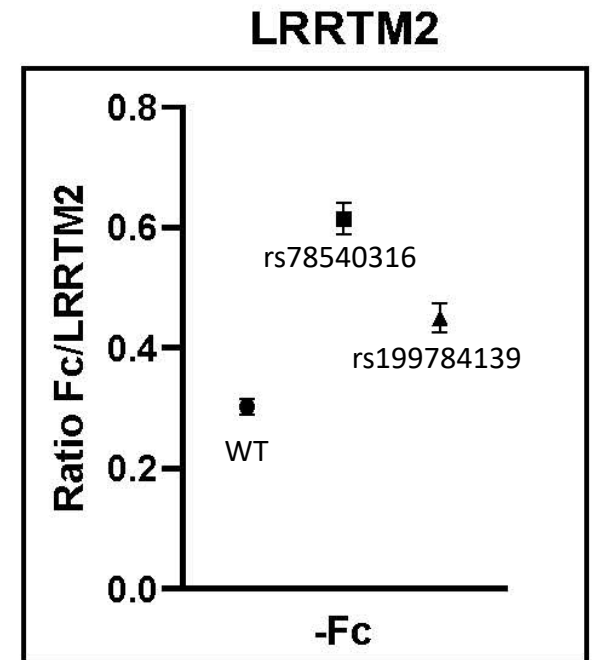
The associated variants showed increased binding to the postsynaptic binding partner, leucine-rich repeat transmembrane neuronal 2 *LRRTM2*



NRXN1 only

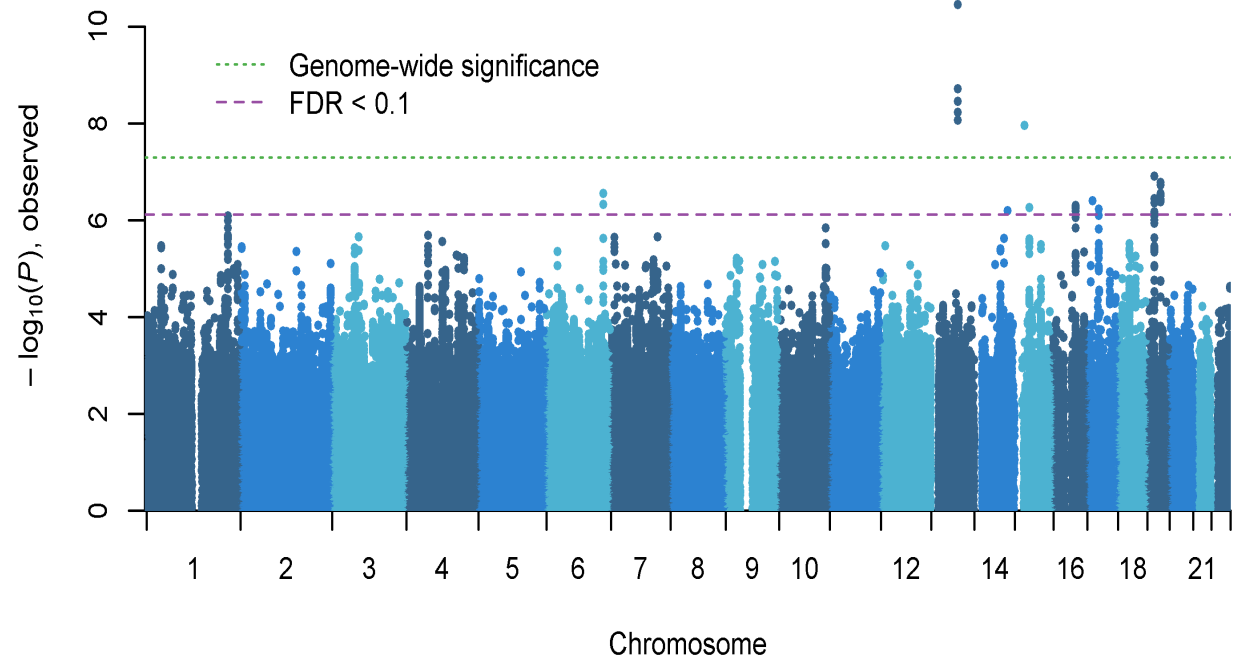
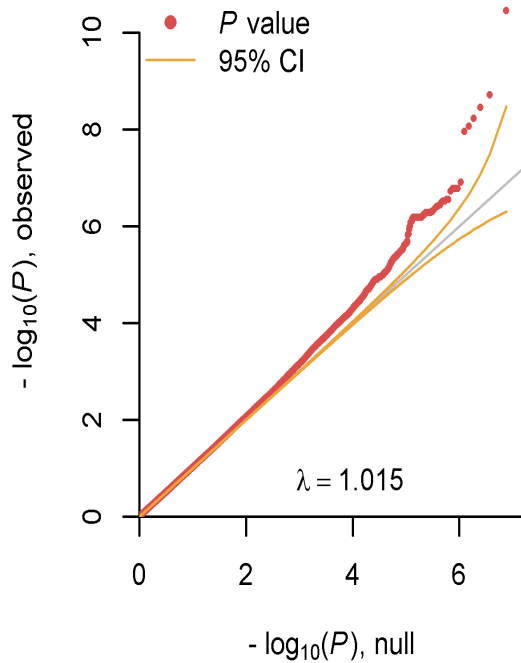


NRXN1 with
binding partner
LRRTM2

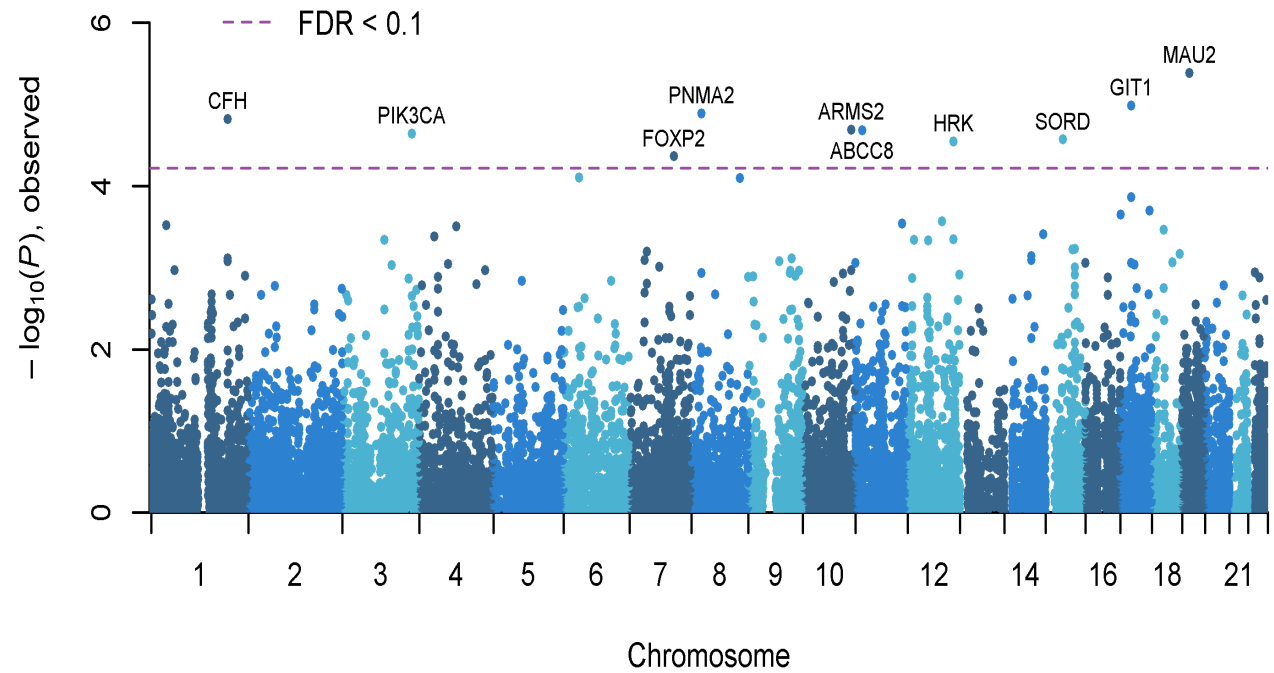
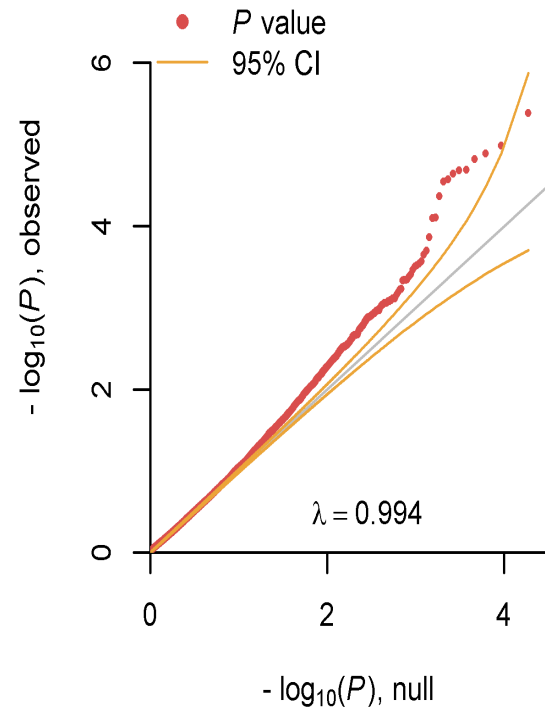


Evidence for significant **increase** in synapse binding in the presence of genetic changes associated with suicide risk

Genome-wide association (GWAS): 3,413 suicides, 14,810 controls, matched for ancestry



Additional 10 genes nominally significant from gene-based tests of >18,000 genes



GWAS: 21 genes implicated

Genes associated with significant genomic regions		
Symbol	Chr	Associations
<i>KLHL1</i>	13q21.33	Actin: assoc. with dopamine metabolism
<i>DACH1</i>	13q21.33	Chromatin remodeling; neocortical development
<i>UBE3A</i>	15q11.2	Ubiquitin; Angelman syndrome; intellectual disability
<i>ATP10A</i>	15q11.2	Ubiquitin; synaptic plasticity; autism risk association
<i>NDRG4</i>	16q21	Cell cycle progression; response to cerebral ischemia
<i>SETD6^d</i>	16q21	Methylation (epigenetic); receptor signaling
<i>CNOT1^b</i>	16q21	Transcription regulation; neural development; GWAS SZ
<i>GOT2</i>	16q21	Mitochondrial glutamate transfer; Alzheimer's association
<i>HS3ST3B1^c</i>	17p12	Membrane protein; inflammation; dementia
<i>COPRS^d</i>	17q11.2	Histone binding (epigenetic)
<i>UTP6</i>	17q11.2	Interaction between miRNA and methylation (epigenetic)
<i>NCAN^{a,b,c}</i>	19p13.11	Neurocan; cell adhesion; bipolar; SZ; mood; ADHD
<i>HAPLN4^{a,b}</i>	19p13.11	Formation of GABAergic synapses
<i>TM6SF2^b</i>	19p13.11	Transmembrane; alcohol dependence, alcohol-liver disease
<i>SUGP1^b</i>	19p13.11	Splice factor; alcoholic liver disease
<i>MAU2^b</i>	19p13.11	Chromatid cohesion factor; neuronal maturation
<i>GATAD2A^{b,d}</i>	19p13.11	Transcriptional repressor; SZ
<i>TSSK6^b</i>	19p13.11	Chromatin remodeling; fertility
<i>NDUFA13^b</i>	19p13.11	Mitochondrial membrane; Parkinson's disease
<i>YJEFN3^b</i>	19p13.11	Mitochondrial protein; unknown function
<i>CILP2^b</i>	19p13.11	Cartilage scaffolding; triglycerides; stroke association

Gene pathways, Genome-wide associations

Gene Ontology (GO) Functional Pathways:

Neuronal development (23%)

Metabolic (26%)

Mitochondrion (23%)

GWAS Catalog:

Schizophrenia (13%)

Alzheimers (10%)

Bipolar (7%)

PsychENCODE:

Differential gene expression in PM brain of those with SZ, AUT, BD (50%)

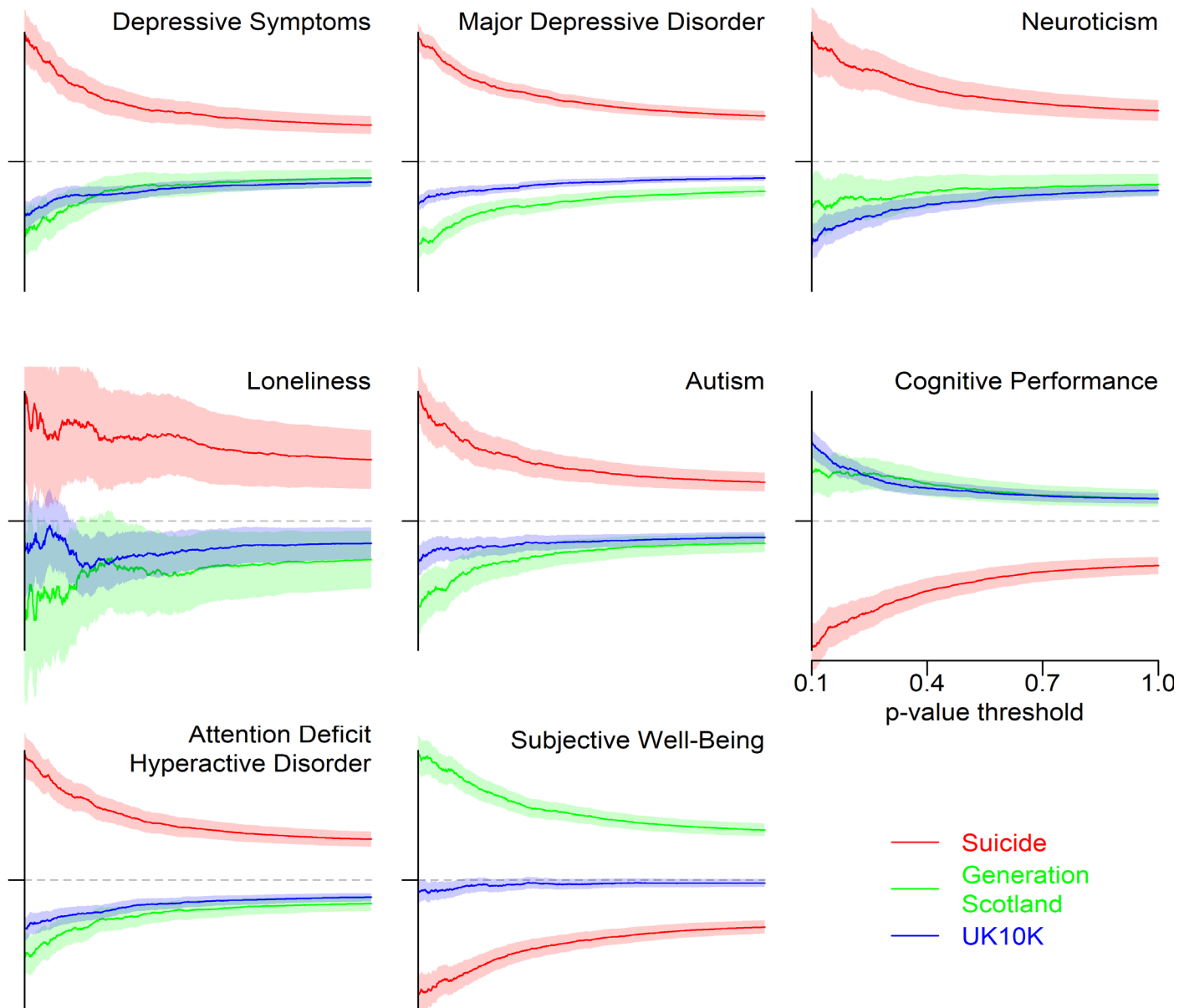
Polygenic risk scores of Utah suicides

What is a polygenic risk score?

- 1) Quantitative score reflecting background genetic risk of a trait
- 2) Take genome-wide p-values from an external, published study
- 3) Each p-value = association of genotype at that location to the trait
- 4) Apply p-values to genotypes in current study to create a score
- 5) This score = potential underlying biological risk of associated psychopathology.

Hundreds of polygenic risks can be computed for psychiatric, behavioral, and medical traits

Polygenic risk scores of Utah suicides



Genome-wide *rare functional variant* screen from genotyping data

- Try an efficient strategy: look for association with variants likely to affect gene function
- Kept 40,189 variants in the coding part of genes
- Compared frequencies between suicides and large, publicly-available resources of controls matched for ancestry

Genome-wide *rare functional variant* screen from genotyping data

5 genome-wide significant variants

- 1) *PER1* and *SNAPC1*: supporting postmortem evidence suicide death risk.
- 2) *PER1*: supporting association with bipolar disorder.
- 3) *PER1*, *TNKS1BP1*, *ESS2*: supporting association with schizophrenia.
- 4) *PER1*, *TNKS1BP1*, *ADGRF5*: other evidence of involvement with immune system, circadian rhythm, signal transduction processes.

These genes are immediate targets for investigation

They also target new gene pathways/mechanisms of risk:

- circadian rhythm
- neurodevelopment
- neurodegeneration

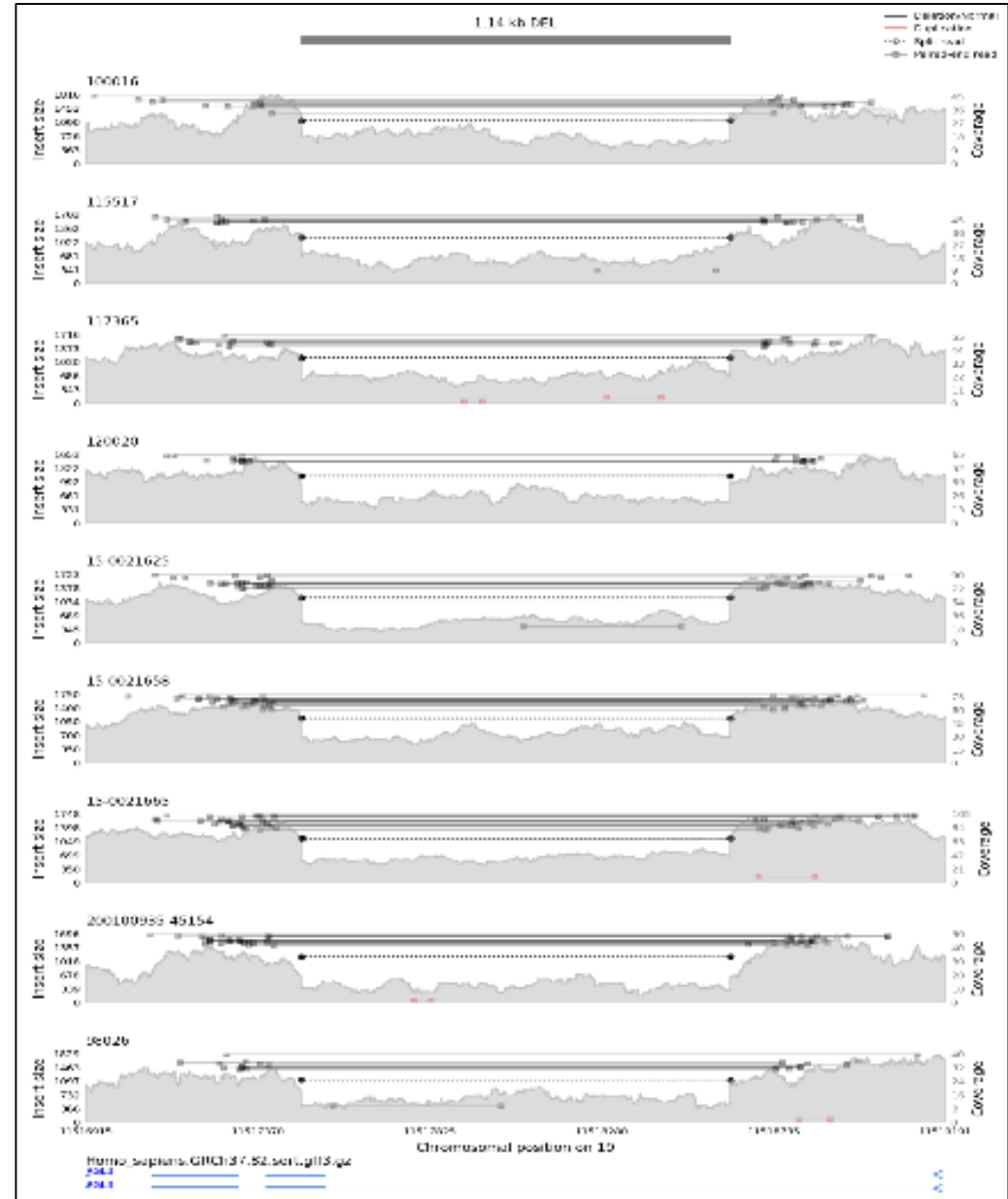
Rare structural variants (deletions, duplications, inversions)

DATA:

- 281 suicides with high-quality whole genome sequence (WGS) data;
- Jointly processed w/ 524 Utah controls (Utah longevity study, Utah CEPH)

ANALYSIS:

- LUMPY used to detect SVs (method with improved sensitivity; Quinlan lab; Layer et al., 2014)
- Compare to UT controls, and WashU control data (17,795 participants; *Abel et al., 2019*)



Structural variants (deletions, duplications, inversions)

Preliminary indication of enrichment of SVs in neuronal pathways; some overlap with GWAS gene pathways

To Do:

More analysis!

- Overlap with exons, other regulatory genomic features (TFBS, microRNAs, enhancers, epigenetic control)
- Validation
- Familial? Phenotypic associations?

NEW SEQUENCE DATA COMING SOON: ~400 more highly prioritized Utah suicide deaths

International Replication/Extension/Collaboration: PGC

Psychiatric Genomics Consortium Suicide Working Group		
Cohort	With attempt	No attempt
Vanderbilt	500	100,000
PGC MDD	1622	8786
PGC Bipolar	3264	5500
PGC SZ	1683	2946
PGC substance abuse	6320	--
PGC eating disorders	1000	--
UK Biobank	3300	35,000
iPsych	7003	19,559
deCode	800	--
Total	25,492	171,771

Progress

GWAS with 3,143 suicides
 Docherty et al., AJP, in revision

High-risk pedigrees
 Coon et al., Mol Psychiatry, 2018
 Nobre et al., IEEE Trans Vis Comput Graph, 2019
 Coon et al., Transl Psychiatry, 2013

Rare risk variants
 DiBlasi et al., Mol Psychiatry, submitted

Exposures
 Bakian et al., 2015

Ethics
 Shade et al., Am J Med Genet B Neuropsychiat Genet, 2019
 Kious et al., AJOB Empirical Bioethics, submitted

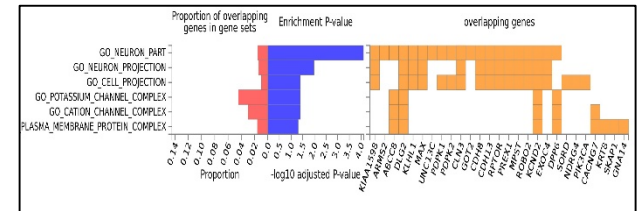
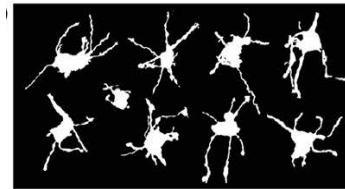
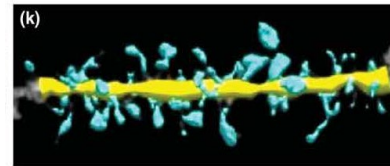
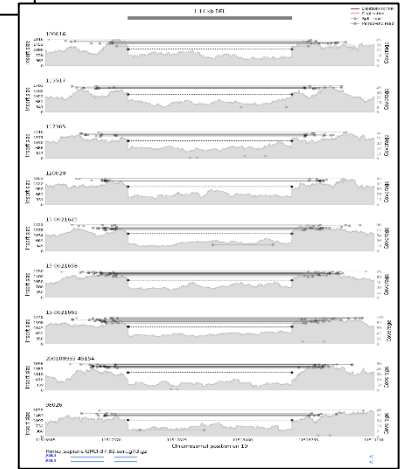
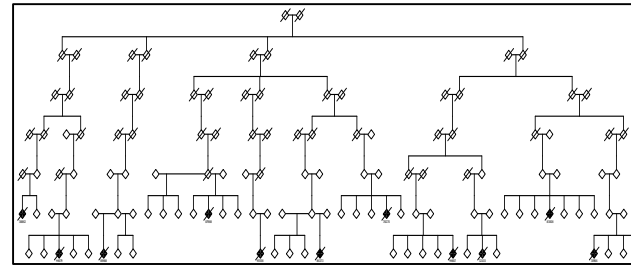
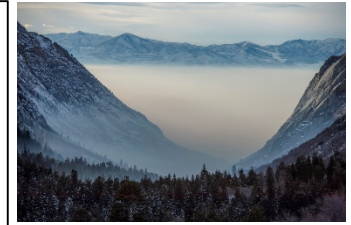
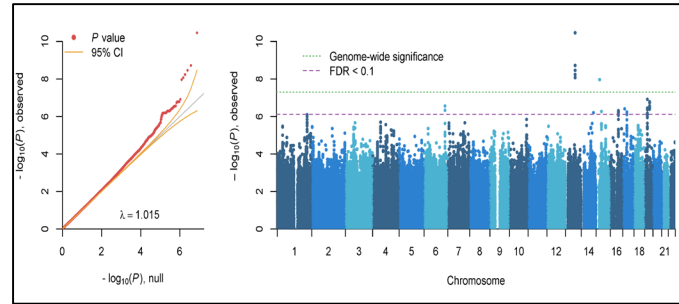
Suicide risk in demographic/clinical subgroups
 Kirby et al., Autism Res, 2019
 Keeshin et al., Suicide Life Threat Behav, 2018
 Darlington et al., Transl Psychiatry 2014
 Gray et al., Suicide Life Threat Behav, 2014

Tissue studies
 Das et al., J Comp Neurol, 2019

Whole Genome Sequence

Epigenetics

Mitochondria



Next Steps

Molecular data

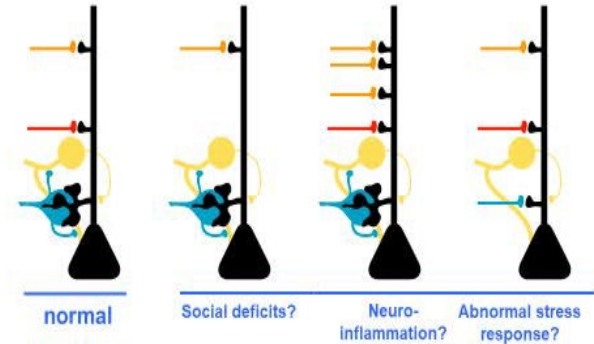
New genotyping: 5,500

New prioritized WGS: 400

Epigenetic analysis

Follow-up statistical modeling

Follow-up analyses of PM tissue



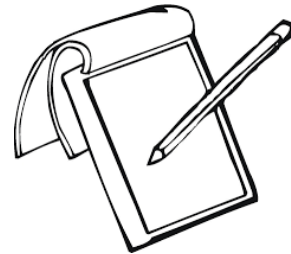
Phenotypes/biomarkers

Link to physician notes

Psychological autopsy in youth

Suicide and the opioid epidemic

Toxicology: hair samples



Ethics studies

New survivor groups
(rural, minorities)

Provider opinions



Collaborations

New local/regional:
collaborations
International

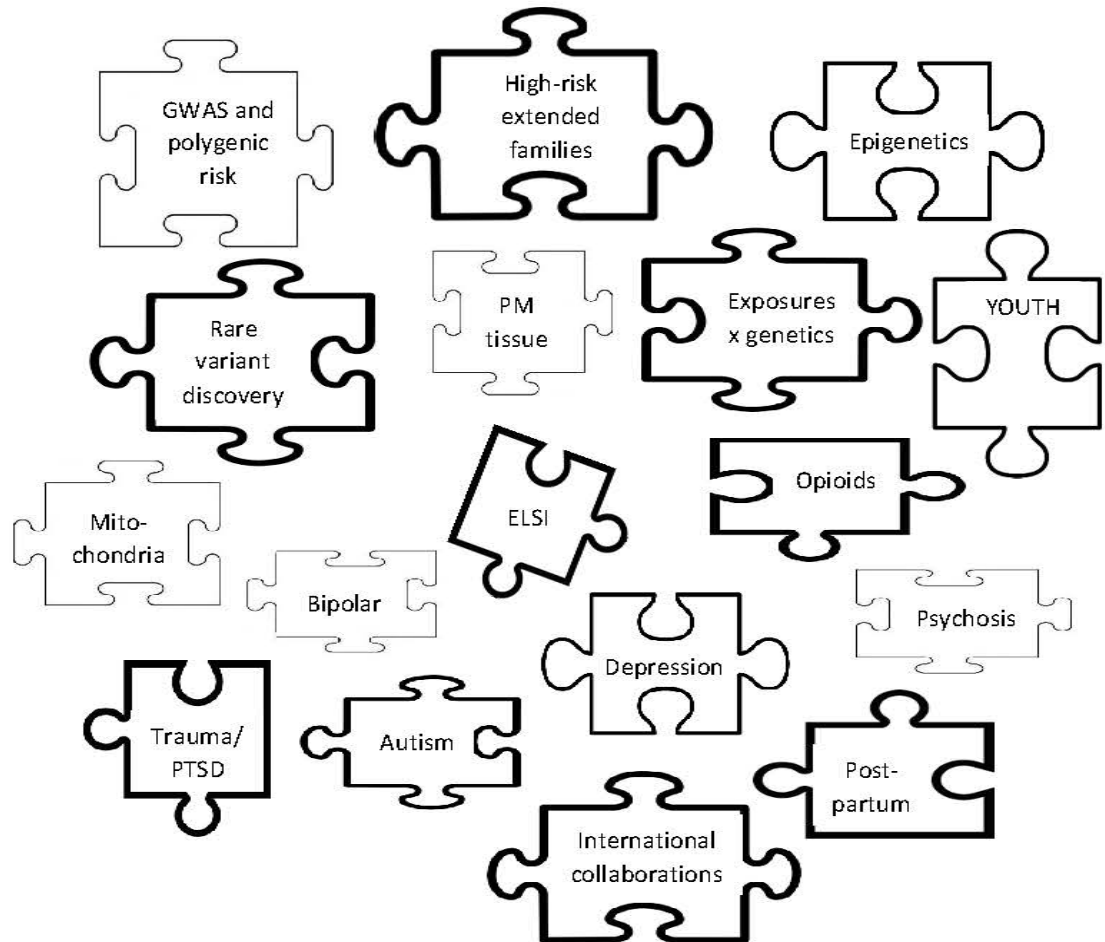


Reminder: suicide is COMPLEX

There are likely hundreds of genetic variants leading to suicide risk.

We are in a probabilistic universe, not a deterministic universe.

No one genetic change, in the absence of other genetics, and complex environmental risks/exposures can cause suicide.



Collaborators & Acknowledgments

Psychiatry

Douglas Gray, MD
Anna Docherty, PhD
Emily DiBlasi, PhD
Andrey Shabalin, PhD
Amanda Bakian, PhD
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Support

NIH; AFSP; Tanner Foundation;
Utah Genome Project; Janssen LLC;
Fund in Memory of Raymond Crump;
Nat.Ctr. Rsch Res.; HCI ; HMHI



National Institute
of Mental Health



HEALTH
UNIVERSITY OF UTAH



Suicide Risk Resources for Prevention and Research

PREVENTION, SERVICES

National Suicide Prevention 24-Hour Hotline: 1-800-273-8255 or text 838255

National Suicide Prevention website: <http://suicidepreventionlifeline.org/>

American Foundation for Suicide Prevention: <https://afsp.org/about-suicide/preventing-suicide/>

RESEARCH

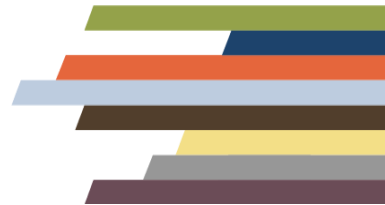
American Foundation for Suicide Prevention: <https://afsp.org/about-suicide/suicide-statistics/>

Centers for Disease Control:

<https://www.cdc.gov/nchs/pressroom/sosmap/suicide-mortality/suicide.htm>

National Alliance for the Mentally Ill (NAMI):

<https://www.nami.org/NAMI/media/NAMI-Media/Images/FactSheets/Suicide-FS.pdf>, <https://www.nami.org/learn-more/mental-health-conditions/related-conditions/risk-of-suicide>



Thank you!

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MHTTC

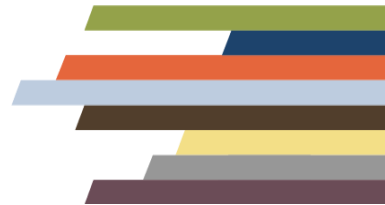
Mental Health Technology Transfer Center Network
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Suicide Prevention Across the Educational Continuum

6-Part Webinar Series



Mountain Plains (HHS Region 8)

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PTTC

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Thank You

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