Suicide Prevention Across the Educational Continuum
6-Part Webinar Series
Disclaimer

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World Class Resources to Discover

Genetic Risks for Suicide Death

Hilary Coon, PhD
Professor
Department of Psychiatry
University of Utah School of Medicine
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

![Age-Adjusted Suicide Death Rate Per 100,000: Utah vs. U.S.](ibis.health.utah.gov)
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

![Graph showing suicide death rates by sex and age in the US](image1)

![Graph showing encounters for suicidality by sex](image2)

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 familial\(^1\)

\(^1\)Egeland et al., 1985
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 familial.¹

- Familial risk is **independent** of psychopathology.²

- Risk factors unique to suicide?

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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

Tidemalm et al., 2011; Zai et al., 2012; Pederson & Fiske, 2010; McGuffin et al., 2010; Baldessarini & Hennen, 2004; McGuffin et al., 2001; Roy & Segal 2001; Wender et al., 1986
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• **Adoption studies:**
  • Adopting relatives: no increased risk
  • Biological relatives: **4-5 times** the population rate

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

Tidemalm et al., 2011; Zai et al., 2012; Pederson & Fiske, 2010; McGuffin et al., 2010; Baldessarini & Hennen, 2004; McGuffin et al., 2001; Roy & Segal 2001; Wender et al., 1986
Health burden vs. research funding

- 47,173 suicide deaths
  - NIH suicide funding: $103 million
- 40,610 breast cancer deaths
  - NIH breast cancer funding: $690 million

For more information:
- mh.nih.gov/fundi
- 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
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

![Diagram showing relationships between Suicide Risk, Extreme subsets, demographics, diagnoses, Extended high-risk families, Genome-wide rare variants, and Exposures]
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
## 30 Significant Genomic Familial Regions

<table>
<thead>
<tr>
<th>Sharing Families</th>
<th>Chromosome</th>
<th>Region length</th>
<th>N sharing Cases</th>
<th>P-Value*</th>
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</table>
204 genes implicated by SGS regions

- Suicide (prior evidence)
- Psychiatric/Neuronal (39%)
- Inflammation/Immune (15%)
- Metabolic (5%)
- Cell growth/function (12%)
- Other/unknown (20%)
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.

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

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Chr</th>
<th>Associations</th>
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<tr>
<td>KLHL1</td>
<td>13q21.33</td>
<td>Actin: assoc. with dopamine metabolism</td>
</tr>
<tr>
<td>DACH1</td>
<td>13q21.33</td>
<td>Chromatin remodeling: neocortical development</td>
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<td>UBE3A</td>
<td>15q11.2</td>
<td>Ubiquitin; Angelman syndrome; intellectual disability</td>
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<td>ATP10A</td>
<td>15q11.2</td>
<td>Ubiquitin; synaptic plasticity; autism risk association</td>
</tr>
<tr>
<td>NDRG4</td>
<td>16q21</td>
<td>Cell cycle progression; response to cerebral ischemia</td>
</tr>
<tr>
<td>SETD6</td>
<td>16q21</td>
<td>Methylation (epigenetic); receptor signaling</td>
</tr>
<tr>
<td>CNOT1</td>
<td>16q21</td>
<td>Transcription regulation; neural development; GWAS SZ</td>
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<tr>
<td>GOT2</td>
<td>16q21</td>
<td>Mitochondrial glutamate transfer; Alzheimer’s association</td>
</tr>
<tr>
<td>HS3ST3B1</td>
<td>17p12</td>
<td>Membrane protein; inflammation; dementia</td>
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<td>COPRS</td>
<td>17q11.2</td>
<td>Histone binding (epigenetic)</td>
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<td>UTP6</td>
<td>17q11.2</td>
<td>Interaction between miRNA and methylation (epigenetic)</td>
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<tr>
<td>NCAN</td>
<td>19p13.11</td>
<td>Neurocan; cell adhesion; bipolar; SZ; mood; ADHD</td>
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<tr>
<td>HAPLN4</td>
<td>19p13.11</td>
<td>Formation of GABAergic synapses</td>
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<td>TM6SF2</td>
<td>19p13.11</td>
<td>Transmembrane; alcohol dependence, alcohol-liver disease</td>
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<td>SUGP1</td>
<td>19p13.11</td>
<td>Splice factor; alcoholic liver disease</td>
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<tr>
<td>MAU2</td>
<td>19p13.11</td>
<td>Chromatid cohesion factor; neuronal maturation</td>
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<td>GATAD2A</td>
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<td>Transcriptional repressor; SZ</td>
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<td>TSSK6</td>
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<td>Chromatin remodeling; fertility</td>
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<td>Mitochondrial membrane; Parkinson’s disease</td>
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<td>Y1EFN3</td>
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<td>Mitochondrial protein; unknown function</td>
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<tr>
<td>CILP2</td>
<td>19p13.11</td>
<td>Cartilage scaffolding; triglycerides; stroke association</td>
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</table>
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

- Depressive Symptoms
- Major Depressive Disorder
- Neuroticism
- Loneliness
- Autism
- Cognitive Performance
- Attention Deficit Hyperactive Disorder
- Subjective Well-Being

Legend:
- Suicide
- Generation
- Scotland
- UK10K

p-value threshold
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
<table>
<thead>
<tr>
<th>Psychiatric Genomics Consortium</th>
<th>Suicide Working Group</th>
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<td>Cohort</td>
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<td>Vanderbilt</td>
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<td>PGC MDD</td>
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<td>PGC SZ</td>
<td>1683</td>
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<td>PGC substance abuse</td>
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<td>PGC eating disorders</td>
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<td>deCode</td>
<td>800</td>
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<td><strong>Total</strong></td>
<td><strong>25,492</strong></td>
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</table>
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

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- John Anderson, BS

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- Todd Grey, MD (former Chief Medical Examiner)
- W. Brandon Callor, MS

- staff assisting with collection

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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
Thank you!

Presenter Contact Information:

Dr. Hilary Coon
Professor
Department of Psychiatry
University of Utah School of Medicine

hilary.coon@utah.edu
Suicide Prevention Across the Educational Continuum
6-Part Webinar Series
Thank You

Mountain Plains MHTTC:
mountainplains@mhttcnetwork.org

Mountain Plains PTTC:
mountainplains_ptttc@utah.edu