Whole genome sequencing implicates genes leading to risk of suicide death

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Background

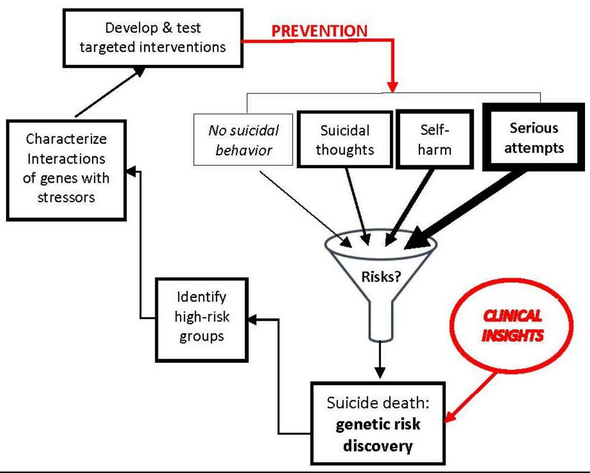
Public health impact of suicide death: Suicide results in >48,000 preventable deaths in the US annually, and the rate has risen over 33% since 1999.[1]
Genetic risk of suicide death: The estimates of heritability of suicide deaths is ~50% from aggregated studies.[2] Specific genetic risks remain largely unknown.

Why study suicide death?

Prediction of suicide attempt is improving ***…but accuracy of suicide death prediction remains near zero.***

Best predictor of suicide is prior attempt.

BUT < 10% of attempters go on to die by suicide. > 50% suicide deaths occur w/o prior attempt.



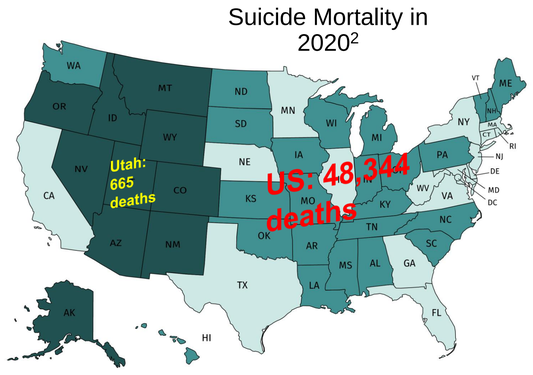
Understanding risks of suicide death will direct scarce resources to aid those most in need.

Why Utah?

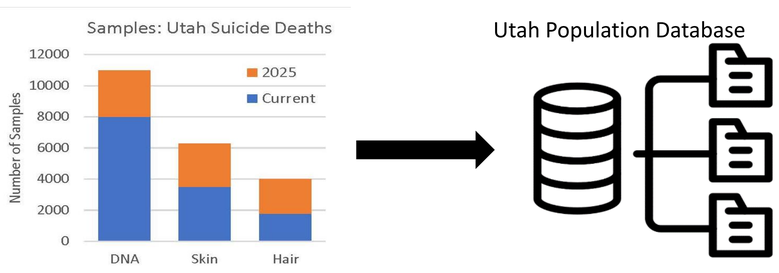
Utah is 6th in US for age-adjusted suicide rate[2]

Utah suicide cause of death rankings:
Ages 10-24: 1st
Ages 25-44: 2nd
Ages 45-54: 4th
Ages 55-64: 5th

Suicide Mortality in 2020[2]



Utah Suicide Genetics Research Study: Unmatched resources



World's largest ongoing collection of suicide death biosamples; > 10,000 with DNA by 2025[3]

Connected to state-wide population data: demographics, longitudinal medical records, exposures, genealogical records[4]

Collaborative expertise

Current collaborative studies span areas: genetics, animal models, statistics, imaging, epidemiology, exposures, clinical outcomes, ethics, social policy

Our "Round Table" approach: collaborative opportunities

Collegial: Prioritize investigator independence and early-stage investigator support

Nimble: Quickly pivot to meet diverse research opportunities and shift priorities based on new findings

Adaptable: Easily expand into new areas with new collaborative partners

Sustainable: Carried by combined successes across all elements

Translatable: Prioritize connections between research and clinical prevention efforts

Utah Suicide Genetic Research Study Data Highlight: Whole Genome Sequencing

WGS Sample

672 UT suicide deaths selected for whole genome sequencing
From 5500 suicides with current genome-wide array data:

- Evidence of familial risk from genealogical data back to 1700's: cases in very extended families (avg. relatedness=9th degree) where familial risk of suicide is *significantly elevated*
- Includes 18 relative pairs first cousin or closer (~5% of the WGS sample)
- Young age at death: avg=28.9 years; significantly lower than Utah average age at suicide death of 40.1, p<0.0001
- 75.8% male (not different from the Utah suicide cohort)
- WGS subset had more documented prior suicide attempts (p=0.03); more documented exposure to trauma (p=0.03).

WGS Methods and QC

Sequencing:

- Illumina platform; average read depth: 30X coverage
- Sequence calling pipeline based on Broad Institute methods developed and implemented by *Utah Center for Genomic Discovery (UCGD)*[5]
- 672 suicide samples attempted; joint calling with 429 unrelated Utah controls (additional comparisons are made in the analysis phase with publicly-available controls)[6]

Quality Control:

- Cases: two suicide samples deleted due to low quality; one unintentional duplicate suicide sample also deleted
- Controls: one Utah control deleted due to low quality; 8 Utah controls related to cases deleted (3 avuncular, 5 cousin)
- Ancestry from genotyping: 15 suicides with <90% European ancestry flagged for sensitivity analyses

Prioritization: Structural Variants (SVs)

Structural variants (SVs): deletions, duplications, inversions, translocations, other complex re-arrangements. Focus first on simple deletions (most reliably detected).

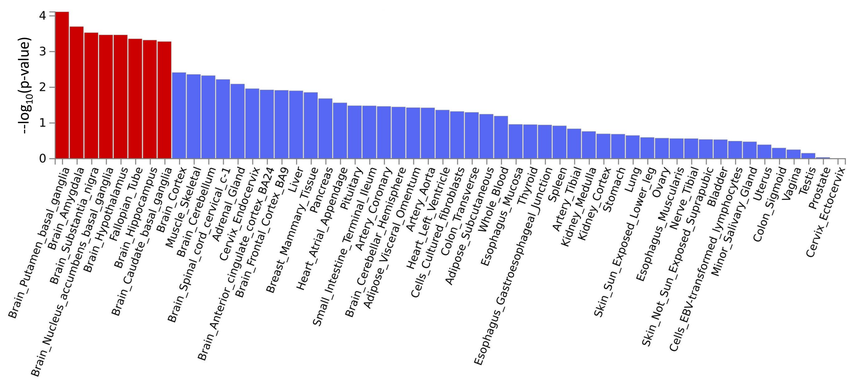
Pre-analysis filtering of deletions done blind to gene function:

- Additional quality filter for structural variants (SVs): Duphold quality software[7]
- Must span a coding region
- Must occur in at least 2 suicide deaths and must be relatively uncommon (<20%) in public control data (Utah controls; also large public databases such as GnomAD, https://gnomad.broadinstitute.org/)
- Omit deletions <100bp or greater that 1Mb as possible artifact

Final set for further study: 321 deletions
Of these, 64 had elevated frequency in suicide deaths with at least nominal significance compared to UT controls, public databases.

Deletions in Utah suicides: brain tissue specificity

Significant brain tissue specificity (shown in red) was found using FUMA[7] in a test of 64 genes associated deletions with nominally significant elevation in frequency.



Functional prioritization

Integrated PsychENCODE results from comprehensive brain transcriptome data in postmortem samples from patients with autism spectrum disorder (ASD), schizophrenia (SZ), bipolar disorder (BD)[8]

Final prioritization within 64 top deletions: associations with genes with neuronal function or psychiatric associations and/or FDR<0.05 altered brain expression in ASD/SZ/BD from PsychENCODE.

RESULTS: Prioritized More Common Deletions (in >15 Suicides)

Chr	Length	gene	Suicide freq elevation	PsychENCODE FDR (disorder)	Functional associations	Relevant references
1	241	PLD5	0.08165	0.0000847 (SZ)	neurodevelopment	33270668
19	219	PLK5	0.07266	0.00585 (SZ)	neuronal differentiation; abuse, anxiety, depression, alcohol	27959334 31628824
6	193	PACSIN1	0.02100	NS	regulates synaptic inhibition	29028184
20	349	RTEL1	0.01873	0.00597 (SZ)	brain tissue expression/methylation	33831179
10	253	SKIDA1	0.01493	0.00332 (SZ)	brain connectivity	10502110
3	7117	ACAD11	0.01440	0.0000232 (SZ)	oxidation in brain	21237683
16	382	SYNGR3	0.01273	0.0135 (SZ)	interacts w/ dopamine; AD pathology	33472038
3	101	PLSCR5	0.00995	0.0000103 (SZ); 0.0261 (ASD)	MDD, BD, body weight	24348429

RESULTS: Prioritized Rarer Deletions (in <10 Suicides)

Chr	Length	gene	Suicide freq elevation	PsychENCODE FDR (disorder)	Functional sssociations	Relevant references
16	14764	IL4R	0.00599	0.0000188 (SZ)	neuroinflammation; response to early life stress	32499725
8	213	PLEC	0.00524	0.0145 (SZ)	epilepsy association	17515952
16	188	QPRT	0.00524	NS	neuronal exitotoxin; SZ association	21036897
10	125	MARCH8	0.00449	NS	mediates neuronal damage	31443122
17	313	NLGN2	0.00449	NS	synaptic transmission; many psychiatric associations	29339486 30573727
9	341	SHC3	0.00375	0.00343 (SZ)	signaling in cortical neurons; SZ, nicotine dependence	32933237 17179996
11	246	CD81	0.00375	0.000102 (SZ); 0.0289 (ASD)	neuron-derived exosome; TBI interactions; first-episode psychosis	31916313 33454965
17	351	FASN	0.00375	0.088 (ASD)	MDD association; energy balance in CNS	31706157 18776140
20	815	OSBPL2	0.00375	0.0190 (SZ)	neuronal interactions	32734583
11	291749	GPR83	0.00309	0.0855 (SZ); 0.0897 (BD)	pain sensitivity	33116307
12	702	SLC6A13	0.00302	0.00799 (SZ)	SZ association	20398908 21367462
10	354	NRP1	0.00301	NS	axon guidance; antidepressant response	25850031
21	369	C2CD2	0.00301	0.00000229 (SZ)	aging processes	29158487
16	381	RAB40C	0.00300	0.00693 (SZ)	enriched in glia; ubiquitination	18485483
16	494310	GINS2	0.00300	0.000615 (SZ); 0.0384 (BD)	alcohol use disorder	30513217
2	255	SP3	0.00284	NS	altered CpG sites in suicide	32488228
3	101	PLSCR5	0.00203	0.0000103 (SZ); 0.0261 (ASD)	MDD, BD, body weight	24348429
4	269000	PABPC4L	0.00177	0.00408 (ASD)	treatment resistant depression	24529801

Next Steps: ongoing work

Additional validation and prioritization

- **Manual validation**
- **Characterization of cases carrying deletions:** demographics, co-occurring diagnoses, exposures, background polygenic risks, familial risks
- **Association with gene-based results** from GWAS: our studies, consortium studies of suicidal behavior, psychopathology, other behaviors/conditions
- **Integration with burden tests of single nucleotide coding variants**
- **Integration with burden tests of regulatory variants**

Integration with other sample resources for functional studies

- **Studies in derived neuronal cells** in cases with skin biopsy samples
- **Studies of toxicology** in cases carrying variants with hair samples

Conclusions

Prioritization of deletions that span coding regions of genes found in WGS from suicide deaths selected for familiality and young age at death has identified:

- Genes with broad evidence for brain tissue specificity
- Genes with compelling published associations and with documented alterations in post-mortem brain tissue expression in psychiatric patients

Caveats: While our large sample has identified many potential genes of interest, considerable work remains to validate deletions, and to integrate with other ongoing work in our research group (e.g., polygenic risks, exposures, familial risks, studies of electronic heath records, epigenetics). We also continue to explore WGS risk associated with gene regulation using burden tests.

Clinical Perspective: While genetic factors are important for suicide risk, interactions with environmental factors, other genetic variants, and genetic background are of critical importance.

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Acknowledgments

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