

GENETIC RISK FACTORS OF SUICIDAL RISK AMONG THE GENERAL POPULATION COHORT FROM SOUTHWESTERN UGANDA

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Background

- **Suicide** is the act of ending one's life.
- Uganda suicide rate for 2019 was **4.60%**.

7.6 males; 1.7 females per 100k population (World Population Review, 2000–2023).

- Suicidal behavior demonstrates a **significant genetic** influence (Brent et al., 1996; Mirkovic et al., 2016).

Suicide affects us all...

800,000
people die by
suicide each year

One person
dies by suicide
every 40 seconds

Suicide is
the 18th leading cause
of death in the world
*(It's the leading cause
in the 15-29 age range.)*

For every
completed suicide,
there are 20 attempts

thebestbrainpossible.com

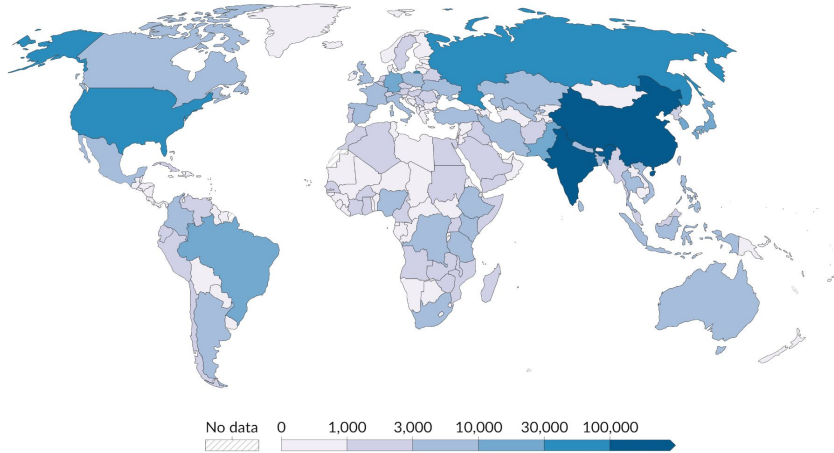
source: World Health Organization 2016

Background

Number of suicides, 2021

Estimated annual number of deaths from suicide. Suicide deaths are underreported in many countries due to social stigma and cultural or legal concerns. This data is based on modeling of global suicide patterns, and includes adjustments that aim to account for missing data and underreporting.

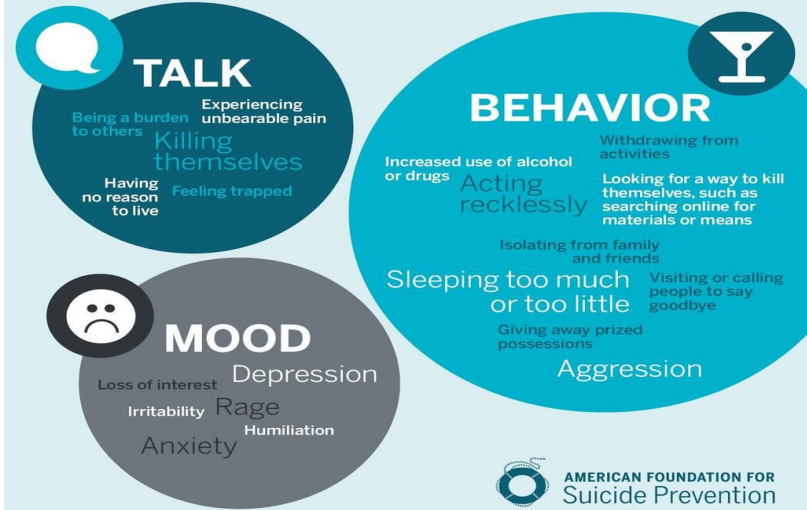
Our World
in Data



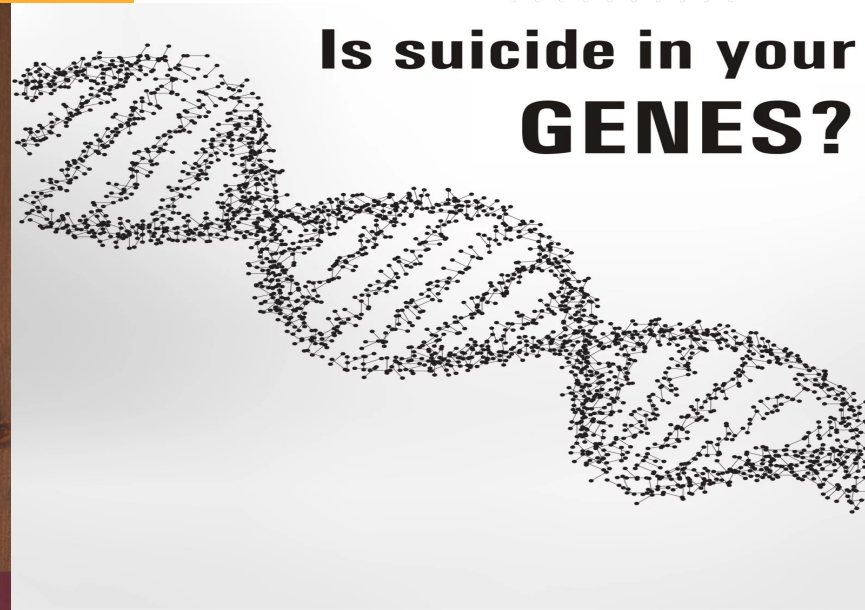
Data source: IHME, Global Burden of Disease (2024)

OurWorldInData.org/suicide | CC BY

SUICIDE WARNING SIGNS



Background



TWIN STUDIES: Using correlational research to establish a genetic argument for the origin of human behaviour.

- Provide substantial support for the contribution of genetic risk factors to suicidal behavior (Brent et al., 1996). Heritability estimates for suicidal thoughts and behaviors from twin and family studies range from 30% to 55%.

Why is study this important?

- Many individuals within the **Uganda Genome Resource** (UGR) have common mental disorders including **suicidal risk** (Kalungi et al., 2023).
- **Genomic studies:** Populations of European descent.

A black and white photograph of a hand holding a piece of torn, lined paper. The paper has handwritten text in cursive: 'Every 40 seconds someone commits SUICIDE.' The background is dark and out of focus.

FACT

77% of suicides take place in low-and middle income countries as reported by WHO.

- **Gap persists** in understanding the **genetic determinants of suicidal risk** among Africans.
- Aim of **uncovering specific genetic factors** that influence suicidal risk.

Objectives



Main Objective: Investigate host genetic impact on suicidal risk among the GPC.

Specific Objectives

1. To identify SNPs associated with suicidal tendencies(GWAS).
2. To refine association signals(fine mapping).
3. To validate association findings(replication).

Methods

- Study population



Genotype data from the Uganda Genome Resource (UGR)

- Genotype data from **approximately 5,000 individuals and whole-genome sequence data from around 2,000 individuals** representing 10 ethnolinguistic groups.
- Includes data of the **general population cohort (GPC)** an ongoing cohort consisting of approximately 22,000 participants residing in 25 villages within a sub-county in Kalungu district in Southwestern Uganda.

Methods

GWAS, Replication and Fine Mapping

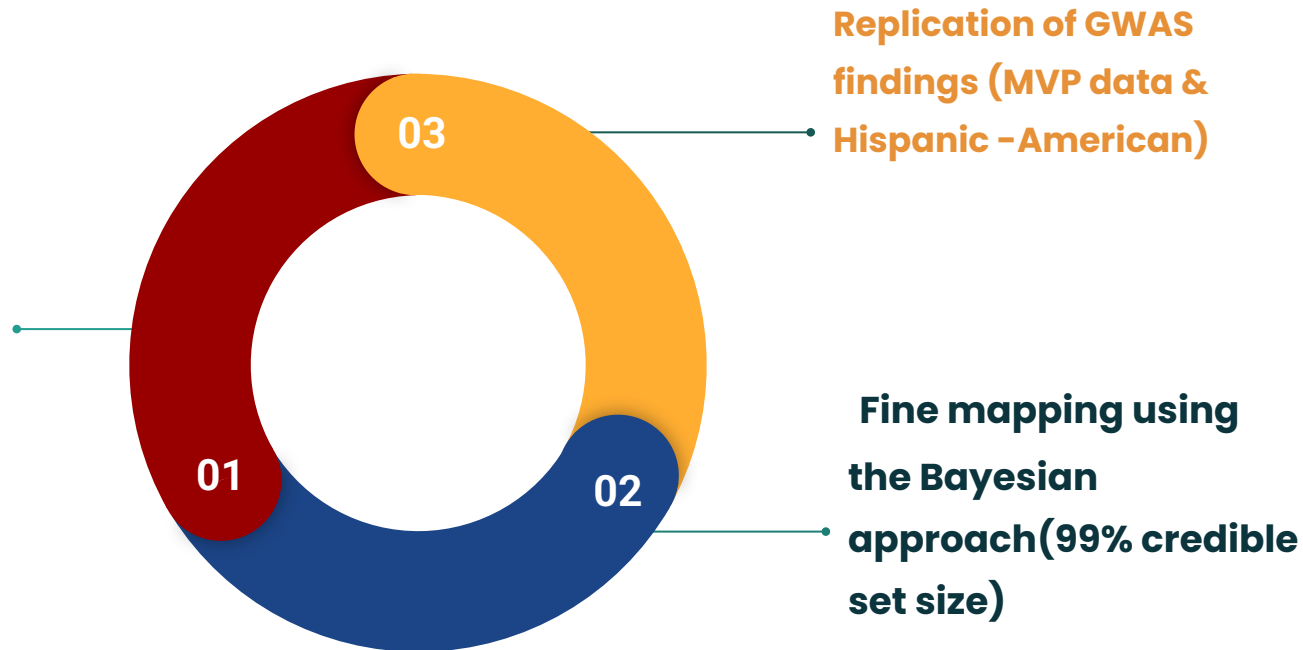
GWAS in fastGWAGLMM:

Generalized Linear Mixed Model

- 876 - Controls
 - 104 - Cases
- 980 individuals

Covariates

- Age
- Sex



● fastGWA-GLMM



- fastGWA-GLMM is a tool designed for ultra-fast **generalized linear mixed model-based association analysis**, specifically for binary traits.
- fast GWA-GLMM test-statistics of both common and rare variants are well-calibrated under the null, even for traits with an **extreme case-control ratio** (e.g., 0.1%).
- Uses a **sparse Genetic Relationship Matrix** (GRM) to conduct GWAS efficiently, accounting for population stratification.

● FASTGWA-GLMM



1: Obtaining my PLINK Files

I needed to generate **.bim**, **.bed**, and **.fam** files from the genotype URG data.

```
Code: ./plink --bfile UGR --keep output_suicide_ugrfam --make-bed --out  
GPC_result.suicide --noweb4
```

2: Created a GRM

Using GCTA/Complex traits

```
Code: ./gcta64 --bfile GPC_result.suicide --make-grm 0.05 --out suicide_data_grm
```

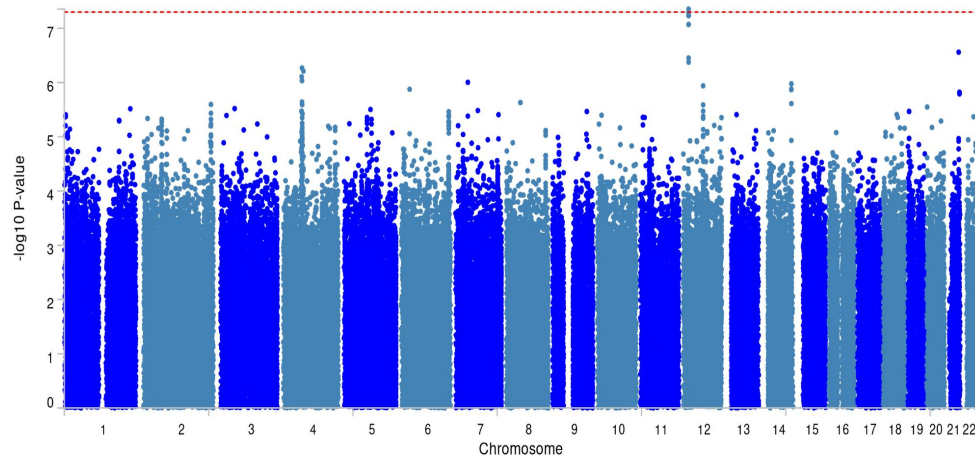
3: Generated a Sparse GRM

```
Code: ./gcta64 --grm suicide_data_grm --make-bK-sparse 0.05 --out GPC_sp_grm
```

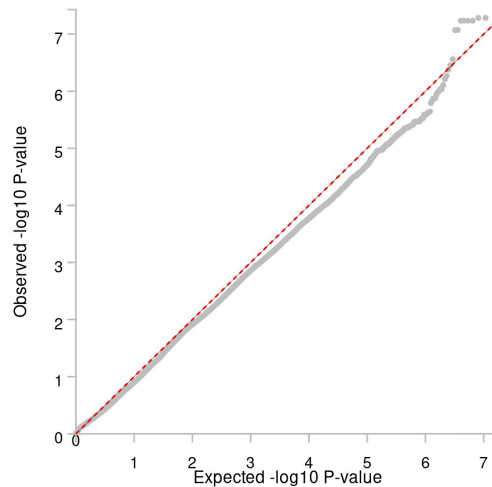
4: Submitted the Job Script

Results (FUMA)

- GWAS: Manhattan plot & QQplot



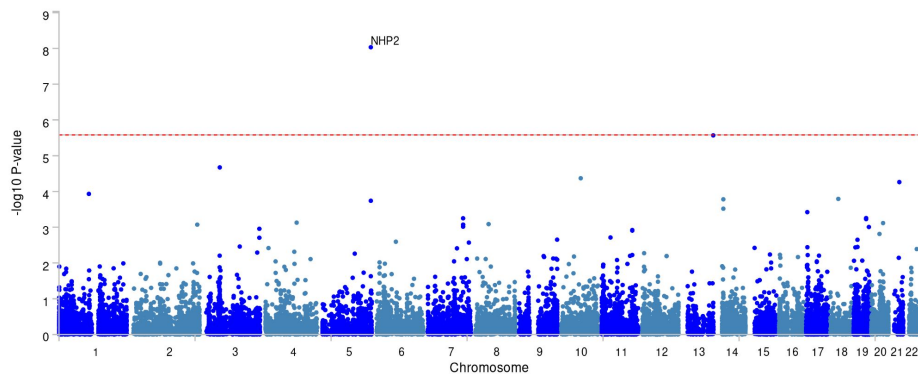
Manhattan plot



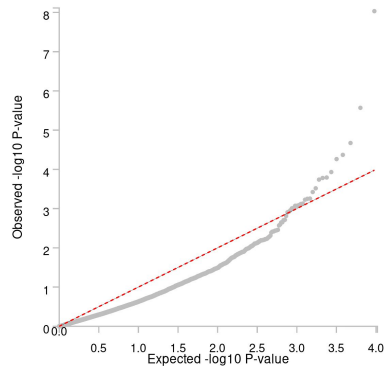
QQplot

Results

- GWAS: Gene plot & QQplot



Manhattan plot



QQplot

● SNPS



BP	rsID	p_value	beta	SE	EA	OA	Gene
12:19057031	rs369382779	4.41729e-08	2.64101	0.482526	C	T	CAPZA3

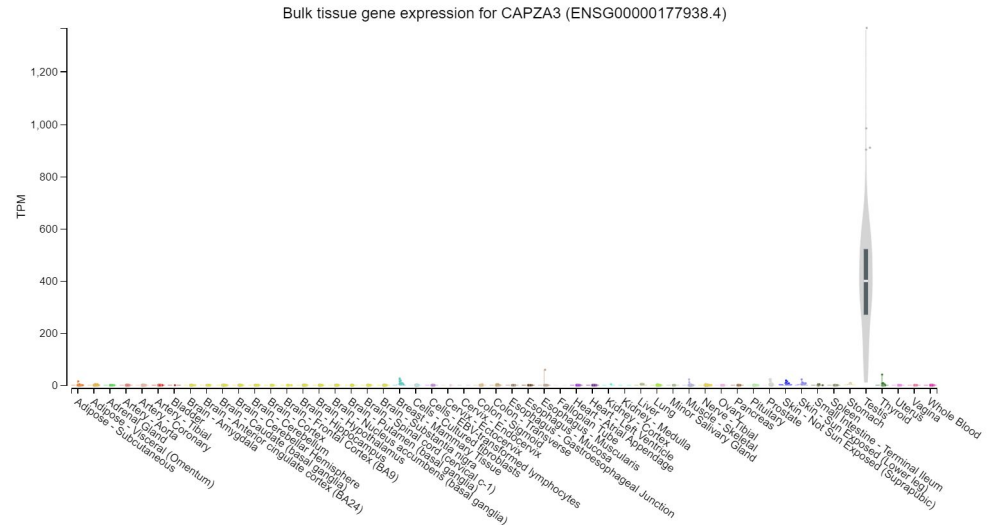
Annotated SNP in LD

BP	rsID	p_value	beta	SE	EA	OA	Gene
12:19556933	rs146295570				C	T	AEBP2

CAPZA53 intergenic

Genecards summary

- CAPZA53 (Capping Actin Protein Of Muscle Z-Line Subunit Alpha 3) is a Protein Coding gene.
- Diseases associated with CAPZA3 include **Male infertility Due To Globozoospermia** and Male infertility
- May be important in determining sperm architecture and male fertility.



Bulk tissue gene expression GTEX

AEBP2 (AE Binding Protein 2) is a Protein Coding gene.

Diseases associated with AEBP2 include **Adult Malignant Schwannoma** and **Weaver Syndrome**.

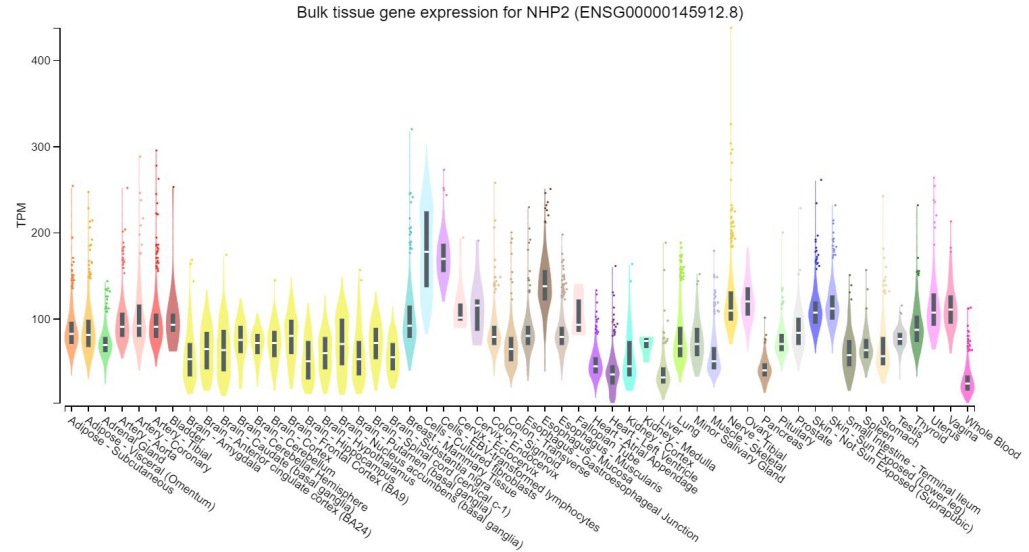
Predicted to enable transcriptional coregulator activity. Predicted to be involved in regulation of transcription by RNA polymerase II.



NHP2 on chr 5

Genecards summary

- NHP2 (NHP2 Ribonucleoprotein) is a Protein Coding gene.
- Diseases associated with NHP2 include Dyskeratosis Congenita, Autosomal Recessive 2 and Dyskeratosis Congenita.
- Among its related pathways are **rRNA processing** in the nucleus and cytosol and **Chromosome Maintenance**.



• Fine mapping



BP	rsID	p_value	beta	EA	OA	Gene	PP	99%Credible set
12:19057031	rs369382779	4.41729e-08	2.64101	C	T	CAPZA3	59.7	5

A credible set of 5 variants.

BP: Basepair position
EA: Effect allele
OA: Other allele
PP: Posterior probability

● Replication



- Replication was attempted in African American ancestry participants from the **Million Veteran Programme** for a study on **attempted suicide**, though the replication was unsuccessful.

Conclusion



- Approximately **5 SNPs in LD** could be contributing to **suicidal risk** in the GPC.
- The GWAS method **fastGWAGLMM** conducted the GWAS efficiently and accounted for **accounted population stratification** and our low case control scenario.
- Potential for discovering genetic variants related to suicide in African populations if **more sequence data** from individuals of continental Africans is made available.

References



- Abou Chahla, M. N., Khalil, M. I., Comai, S., Brundin, L., Erhardt, S., & Guillemin, G. J. (2023). Biological factors underpinning suicidal behaviour: an update. *Brain sciences*, 13(3), 505.
- Brent, D. A., Bridge, J., Johnson, B. A., & Connolly, J. (1996). Suicidal behavior runs in families: a controlled family study of adolescent suicide victims. *Archives of general psychiatry*, 53(12), 1145–1152.
- Smeland, O.B., Wang, Y., Lo, M.T. et al. Identification of genetic loci shared between schizophrenia and the Big Five personality traits. *Sci Rep* 7, 2222 (2017). <https://doi.org/10.1038/s41598-017-02346-3>
- DiBlasi, E., Kang, J., & Docherty, A. R. (2021). Genetic contributions to suicidal thoughts and behaviors. *Psychological medicine*, 51(13), 2148–2155.
- Fatumo, S., Mugisha, J., Soremekun, O. S., Kalungi, A., Mayanja, R., Kintu, C., ... & Kaleebu, P. (2022). Uganda Genome Resource: A rich research database for genomic studies of communicable and non-communicable diseases in Africa. *Cell Genomics*, 2(11).
- Isometsä, E. (2014). Suicidal behaviour in mood disorders—who, when, and why? *The Canadian Journal of Psychiatry*, 59(3), 120–130.
- Kalungi, A., Kinyanda, E., Akena, D., Gelaye, B., Ssembajjwe, W., Mpango, R., Ongaria, T., Mugisha, J., Makanga, R., & Kakande, A. (2023). Prevalence and correlates of common mental disorders among participants of the Uganda Genome Resource: Opportunities for psychiatric genetics research.

References



Adams, M. J., Thorp, J. G., Jermy, B. S., Kwong, A. S. F., Kõiv, K., Grotzinger, A. D., Nivard, M. G., Marshall, S., Milaneschi, Y., Baune, B. T., Müller-Myhsok, B., Penninx, B. W., Boomsma, D. I., Levinson, D. F., Breen, G., Pistis, G., Grabe, H. J., Tiemeier, H., Berger, K., Rietschel, M., ... Derks, E. M. (2023). Genetic structure of major depression symptoms across clinical and community cohorts. *medRxiv : the preprint server for health sciences*, 2023.07.05.23292214. <https://doi.org/10.1101/2023.07.05.23292214>

Yamamoto, R., Li, X., Winter, S., Francke, U., Kilimann, M. W. **Primary structure of human amphiphysin, the dominant autoantigen of paraneoplastic Stiff-Man syndrome, and mapping of its gene (AMPH) to chromosome 7p13-p14.** *Hum. Molec. Genet.* 4: 265-268, 1995.


Lambert, J. C., Grenier-Boley, B., Harold, D., Zelenika, D., Chouraki, V., Kamatani, Y., ... & Amouyel, P. (2013). Genome-wide haplotype association study identifies the FRMD4A gene as a risk locus for Alzheimer's disease. *Molecular psychiatry*, 18(4), 461-470.

Schoenfeld, T., Cameron, H. Adult Neurogenesis and Mental Illness. *Neuropsychopharmacol* 40, 113–128 (2015).
<https://doi.org/10.1038/npp.2014.230>



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