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PERSPECTIVE

Convergence of recent GWAS data for suicidality with previous blood biomarkers: independent reproducibility using independent methodologies in independent cohorts

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Abstract

Recent genetic studies for suicidality, including four independent GWAS, have not reproduced each other's top implicated genes. While arguments of heterogeneity, methodology, and sample sizes can be invoked, heterogeneity is a feature, not a "bug" (as is well understood in biology and in personalized medicine). A comprehensive body of work on blood biomarkers for suicidality has previously been published by our group. We examine the issue of reproducibility using these different approaches, and provide reassuring evidence for convergence of findings, as well as some generalizable insights.

"To know things as they are is better than to believe things as they seem"

- Tom Wicker

Our group has published a series of papers in Molecular Psychiatry identifying blood gene expression biomarkers that track suicidal ideation in a discovery cohort, are validated in a suicide completers cohort, and predict suicidal ideation state, and future hospitalizations for suicidality, in independent cohorts [1–3].

Since our last publication in 2017, a series of 4 GWAS of suicidality (ideation, attempts) [4–7], as well as a family based genetic study of suicide completers [8] and a family based genetic study in suicide attempters [9], have been published, in Molecular Psychiatry and other journals.

We endeavored to examine the issue of convergence of those studies with our previous work (Table 1). Of note, there was no overlap between the top genes implicated by these different recent genetic studies, which raises the issue of apparent lack of reproducibility in the field. We compared the list of top genes implicated by each of the recent genetic studies (genes that were associated with loci/SNPs that were statistically significant and/or were highlighted/discussed by the authors in their paper) [4–9], with the list of candidate biomarkers that survived the initial whole-genome discovery step in our previous published studies, before any literature-based prioritization. We sought to see if any of the top genes from the recent genetic studies have functional evidence of tracking suicidal ideation in our blood gene expression biomarker discovery studies.

As illustrated in Table 1, there is a remarkable overlap with the universal candidate biomarkers described in our 2017 study (where we combined gender and psychiatric diagnosis). The overlap is even greater when we include all of our previous studies/analyses, conducted separately in males, females, and male bipolars. While statistical calculations could be made, the over-representation in the overlaps shown in Table 1 is self-evident (as a small number of genetic findings are highlighted in each genetic study, and a fraction of the genome has gene expression changes tracking suicidality in each of the biomarker studies). The important points are biological (functional evidence), and methodological (reproducibility). Reproducibility of findings, across independent laboratories, using independent cohorts, and different methodologies, is the litmus test in science [10]. These results are thus reassuring for the field.

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Table 1 Overlap of recent genetic studies for suicidality with previous biomarker studies

Genetic studies		Biomarker studies			
Study **Phenotype** (Discovery cohorts)	Top genes implicated	Niculescu et al. [3] Suicidal Ideation (Universal Within-subject $n = 66$)	Niculescu et al. [3] Suicidal Ideation (Male bipolar Within-subject $n = 20$)	Levey et al. [2] Suicidal Ideation (Females Within-subject $n = 12$)	Niculescu et al. Suicidal Ideation (Males [1] Within-subject $n = 37$)
GWAS					
Levey et al. [7] **Severity of suicide attempt** (Yale-Penn European Americans (EAs, $n = 2439$) and African Americans (AAs, $n = 3881$)	**LDHB** **ARNTL2-AS1** **FAH** **CTXND1** **PGBD5** **NARG2** **PHLDB2**	**LDHB** **PHLDB2** **PGBD5**	**PGBD5**	**FAH** **PHLDB2**	**PHLDB2**
Kimbrel et al. [5] **Suicide ideation**, **Suicide attempt** (US Military Veterans; Suicide ideation $n = 138/1433$; Suicide attempt $n = 122/1447$)	**KCNMB2** **ABI3BP** **LUZP2**	**KCNMB2** **ABI3BP**	**LUZP2**	**KCNMB2**	**ABI3BP** **LUZP2**
Erlangsen et al. [6] **Suicide attempt** (Danish population, $n = 6024/44{,}240$)	**PDE4B** **FAM114A2** **RBFOX2** **PREX1** **KIAA1549L**	**PDE4B** **FAM114A2** **RBFOX2**	**PDE4B** **FAM114A2** **RBFOX2**	**PDE4B**	**RBFOX2** **PREX1**
Stein et al. [4] **Suicide attempt** (US Military $n = 473/9778$)	**MRAP2** **CEP162**	**CEP162**		**CEP162**	**CEP162**
Family-based genetic studies					
Coon et al. [8] **Suicide completers** (43 Utah high-risk families, with an average of 6.2 suicides per family)	**207 genes**	72/207 (**34.8%**) **ACSL6** **LACTB** **PRKAG2** **AGBL2** **GIMAP1** **GIMAP7** **HTR2A** **al.**	63/207 (**30.4%**) **NUB1** **MTNR1A** **STAT1** **SP140** **ABCB8** **SLC7A1** **HTR2A** **al.**	89/207 (**43%**) **FNDC3A** **ETV2** **ADAM10** **RCBTB2** **CYP4V2** **GIMAP4** **HTR2A** **al.**	65/207 (**31.4%**) **SLC7A1** **GIMAP5** **AQP9** **ALDH1A2** **PRKAG2** **RHEB** **MSRA** **al.**
Sokolowski et al. [9] **Suicide attempt** (Ukraine population, family based study, trios, $N = 498$ offspring with medically severe suicide attempt)	**CACHD1** **CACNA1D** **CR1** **CRISPLD2** **GABRR2** **GNAS** **GRIN2B** **GSN** **MAP3K9** **PFN2** **PRSS3** **RALGPS1** **RETREG1** **RNASEH2B** **SYTL3** **TSPAN2** **UBE2H**	**CACNA1D** **CR1** **GRIN2B** **GSN** **RALGPS1** **RNASEH2B** **SYTL3** **UBE2H**	**CR1** **GNAS** **GSN** **MAP3K9** **RALGPS1** **RNASEH2B** **SYTL3** **TSPAN2** **UBE2H**	**PRSS3** **RALGPS1** **TSPAN2**	**CACNA1D** **CR1** **CRISPLD2** **GNAS** **GSN** **RALGPS1** **RNASEH2B** **SYTL3** **TSPAN2** **UBE2H**

On a methodological note, it is possible that different approaches have different sample size requirements, and different challenges in accruing those sample sizes. As we show here, our within-subject longitudinal gene expression studies tracking a quantitative phenotype (severity of suicidal ideation), conducted with dozens of subjects, are comparable to larger family based genetic studies for a strong categorical phenotype (suicide completion), with hundreds of subjects, and to case-control genetic (GWAS) studies conducted with thousands or tens of thousands of subjects.

Of interest, the genes that overlap between our biomarker studies and the genetic studies were by and large not among the top predictive biomarkers for suicidality identified by us at the end of our biomarker studies [1–3]. It is possible that SNP-level signal strength and reproducibility, as are

assessed in GWAS, tag genes that are more invariant and perhaps involved in less-specific, housekeeping type functions, as opposed to the genes identified by expression studies looking at functional ability to track and predict a phenotype. The latter may identify genes that are more specific for a phenotype and more variable at a SNP level due to evolutionary fine tuning and adaptation to the environment, especially in the case of complex behavioral phenotypes like suicidality.

Suicidality (ideation, attempts, completions) is a heterogeneous phenotype, likely on a spectrum of severity [3], with a strong environmental component, and with biological gender and diagnostic differences [1–3]. It is likely that our blood biomarkers reflect the effects of many different SNPs, are at the interface of genes and environment, and thus capture more of the biology. Beyond their practical applicability, they can serve as a Rosetta Stone and integrator of independent genetic studies [11].

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Author contributions ABN designed the analyses and wrote the manuscript. HLN analyzed the datasets. Both authors reviewed the final manuscript and agreed with it.

Compliance with ethical standards

Conflict of interest ABN is listed as inventor on a patent application being filed by Indiana University, and is a co-founder of MindX Sciences. The other author declares that he has no conflict of interest.

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