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EDITORIAL

What is the future of suicide genetics?

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Since the heritability of suicidal behaviors was established decades ago, investigators have sought to understand the precise molecular mechanisms which might drive familial clustering of suicides. Beginning with prespecified candidate gene targets, dozens to hundreds of potential "suicide genes" were advanced, although they tended to replicate poorly. The advent of genome-wide association studies (GWAS) recalibrated suicide genetics to comparing suicidal cases and controls on many single nucleotide polymorphisms (SNPs) without *a priori* hypotheses. Of note, the most recent GWAS studies of suicidal behaviors have identified significant *loci*, although the implicated SNPs and gene-level results conflict between independent studies, and the SNP-based heritability (a measure of variance explained by common genetic variation) is low (particularly for suicide attempt, estimated to be around 7% in the latest study).[1] It is likely that current studies are underpowered to identify replicable findings and that the heterogeneity of the suicide attempt phenotype may introduce greater noise, considering that a GWAS of suicide death identified a much higher SNP-based heritability of 16%.[2]

Despite significant progress in genetic analyses of suicide, there are presently limited clinical applications for existing results. On that note, it is a useful time to reflect on the beginnings of suicide genetics and also consider where the field is moving. In particular, it is important to reconsider the purpose of genetics studies and their potential for advancing an integrated understanding of suicide.

One important question is that of specificity. The significant findings identified in GWAS of suicidal outcomes are often mentioned in terms of their potential for detailed follow-up (e.g., preclinical experiments), with the ultimate goal of converting them into pharmacotherapeutic interventions. However, aside from the usual obstacles to translating basic science findings to such intervention, suicide presents even more unique challenges. For example, suicide is emergent among youth, but GWAS have so far been conducted in middle-aged and older cohorts, and genes are known to drive effects differentially across development.[3] Further, the spectrum of self-injurious thoughts and behaviors is incredibly heterogeneous, presenting an additional challenge for targeting specific biological pathways. Finally, there is an incomplete understanding of suicide's transdiagnostic nature. There is evidence that the presentation of suicide varies by disorder and that the associated SNPs do as well, but suicide clearly cuts across diagnostic boundaries.

One novel approach which may allow for immediate use of GWAS results is the polygenic risk score (PRS). PRS summates across risk variants as weighted by their effect sizes and allows for a global measurement of genetic liability for a particular phenotype in a sample unrelated to that of the GWAS. In other words, PRS moves away from the specificity of individual gene targets and instead allows for a consideration of how aggregate genetic risk might influence other systems. PRS for suicide might be theoretically useful when associated with measures of brain structure and function, peripheral markers, temperament, and anthropometric indicators, among others. These PRS might aid in assembling general mechanistic models of how genetic risk shapes development and suicide risk, but limitations abound, particularly in constraints of the GWAS sample, as well as trans-ancestral portability. There is particular danger in using PRS for clinical risk prediction, with the ethical implications of a PRS for suicide well detailed elsewhere.[4] At this stage, PRS for suicide are nascent, and if they are to ultimately be deployed in clinical settings, they will need to be built on better-powered GWAS as well as considered in tandem with other measures of suicide risk.

Reflecting on the origins of suicide genetics in family studies, we are now seeing large-scale case-control GWAS studies between unrelated individuals. Of note, there is still value in studying familial clustering of suicide, especially with exome-wide approaches. In particular, suicide death is rare, and while consortia have been able to assemble large sample sizes for studying this specific phenotype, studying families offers several advantages: not only does it reduce heterogeneity and issues of

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Box 1 Future directions in suicide genetics

- Within-person longitudinal studies of functional genomics
- Intergenerational studies
- Integration of genetic and psychosocial measures of risk
- Integration of multi-omics data (e.g., epigenomics, proteomics, metabolomics)
- Family studies, consanguineous families
- Polygenic risk score studies of mechanistic pathways to risk
- Larger and better-powered GWAS with ancestrally diverse populations
- GWAS of youth, specific self-injurious thoughts and behaviors, and other subgroups

population substructure, but such studies (including of consanguineous families) might be especially useful in identifying rare variants with larger effect sizes.[5]

Developmental psychopathology presents itself as a useful organizing framework for future genetic studies. While the case-control GWAS will continue (and should include younger ages and ancestrally diverse samples, whenever possible), special attention to multilevel dynamic patterns over time will assist in a more nuanced and robust understanding of suicide (Box 1). Within-person longitudinal studies which index across multiple levels not only of functional genomics but also broader levels, such as neural structure function, self-reported symptomatology, and observed behavior, will be important in clarifying the intraindividual and temporally specific processes which elevate or predict suicidal behavior risk. Intergenerational studies, which collect genetic and suicidal risk information from parents and offspring, could also outline genetic pathways to familial risk. Finally, molecular markers that arise from genome-wide approaches should be considered in terms of the additional variability they explain on top of established risk factors, such as past suicide attempt history and early life trauma, and genetic variant information should be integrated with other biological levels such as epigenomics and metabolomics. In summary, suicide genetics is an incipient field with great potential for clarifying risk patterns and informing model development, but careful consideration of context will be necessary in pushing the research forward to the ultimate goals of prevention and intervention.

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Disclosure

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