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Genetic contributions to suicidal thoughts and behaviors

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Abstract

Suicidal ideation, suicide attempt (SA) and suicide are significantly heritable phenotypes. However, the extent to which these phenotypes share genetic architecture is unclear. This question is of great relevance to determining key risk factors for suicide, and to alleviate the societal burden of suicidal thoughts and behaviors (STBs). To help address the question of heterogeneity, consortia efforts have recently shifted from a focus on suicide within the context of major psychopathology (e.g. major depressive disorder, schizophrenia) to suicide as an independent entity. Recent molecular studies of suicide risk by members of the Psychiatric Genomics Consortium and the International Suicide Genetics Consortium have identified genome-wide significant loci associated with SA and with suicide death, and have examined these phenotypes within and outside of the context of major psychopathology. This review summarizes important insights from epidemiological and biometrical research on suicide, and discusses key empirical findings from molecular genetic examinations of STBs. Polygenic risk scores for these phenotypes have been observed to be associated with case−control status and other risk phenotypes. In addition, estimated shared genetic covariance with other phenotypes suggests specific medical and psychiatric risks beyond major depressive disorder. Broadly, molecular studies suggest a complexity of suicide etiology that cannot simply be accounted for by depression. Discussion of the state of suicide genetics, a growing field, also includes important ethical and clinical implications of studying the genetic risk of suicide.

Introduction

Suicide is a leading cause of death worldwide. Suicidal thoughts and behaviors (STBs) cause significant health and financial burden, and STBs cost the US alone over $70 billion per year (CDC, 2020). Major economic costs associated with STBs (Kinchin & Doran, 2017; Shepard, Gurewich, Lwin, Reed, & Silverman, 2016) are comprised of both direct medical costs and indirect costs, including lost productivity to households and employers. National suicide prevention programs are able to reduce these costs and save lives (Lewitzka, Sauer, Bauer, & Felber, 2019) but only 38 countries currently have a national strategy for suicide prevention (World Health Organization, 2014). In addition, research on STBs that informs these programs is challenging, because individual vulnerability to suicide appears to be complex and multidimensional, with many contributing sociodemographic, genetic and environmental factors (For recent reviews of this complexity, we refer the reader to Fazel & Runeson, 2020 Mann & Rizk, 2020; Turecki et al., 2019).

STBs in this review include suicidal ideation (SI), suicide attempt (SA), and suicide death. These phenotypes are each moderately heritable, with a significant proportion of risk attributed to genetic variation. Still, relatively little is known about causal genetic risk factors and the underlying biology of vulnerability to suicide (Lengvenyte, Conejero, Courtet, & Olié, 2019). One advantage of psychiatric genetics approaches over the last decade has been the quick estimation of shared molecular genetic covariances across many phenotypes. This allows for the examination of potential causes of heterogeneity relative to epidemiological observations. We have the view that the discovery of genetic risk factors contributing to suicide may lead the field to better identification of appropriate interventions, and early administration of such interventions. Below, we summarize important insights from epidemiological and biometrical research on STBs and we discuss the primary emerging empirical findings from molecular genetic research. Finally, we provide commentary on the state of the field and ongoing and future studies.

Defining STBs

STBs are unique with respect to psychiatry and medicine because they co-occur with multiple psychiatric and medical conditions and cross many diagnostic boundaries. Currently, STBs are

not defined or conceptualized as a discrete psychiatric disorder, and diagnostic criteria only exist within the context of major depressive and borderline personality disorders (Sisti, Mann, & Oquendo, 2020). Despite the importance of decreasing STBs to improving public health, the multifaceted nature of STBs has led to a historical heterogeneity of both suicide terminology and suicide risk measures, making it difficult to compare findings across epidemiological studies (Klonsky, May, & Saffer, 2016). This relative lack of distinction across outcomes has a complicated interpretation of results.

In this review of the genetic literature, we consider the three primary phenotypes comprising STBs – SI, SA, and suicide – both individually and together when possible. We use definitions that we believe are most consistent with accepted terminology. *SI* is defined as thoughts about ending one's own life, *SA* is defined as self-injurious, non-fatal behavior with the intent to die, and *suicide* is defined as a fatal behavior with intent to die (Turecki et al., 2019).

Measured SI and SA are observed to be highly variable over time, with trait-like and state-like components depending on the population studied (Klonsky et al., 2016). However, a recent study in depressed individuals observed that individual SI variation did not change over a period of 2 years, suggesting that SI may be more trait-like in some individuals (Oquendo et al., 2020). Generally, genetic study designs have treated STBs as traits, with the goal of determining which genes and neurobiological pathways confer risk and protection.

Predicting STBs

Distinguishing the factors that predict each distinct phenotype, SI, SA and suicide, will be important for understanding targets for prevention and intervention. Previous research on the prediction of suicide has indicated that SI and SA predict future SI and SA, but that SI and SA are insufficient for predicting suicide. A recent meta-analysis of studies examining SI suggested that SI has a low positive predictive value for suicide (McHugh, Corderoy, Ryan, Hickie, & Large, 2019) and a recent review of attempt prediction models has indicated that positive predictive values for SA are very high (>0.8), while positive predictive values for suicide are almost completely null (Belsher et al., 2019). The low prevalence of suicide inherently reduces the positive predictive values for suicide relative to SI and SA. But that does not mean that we should not try to improve the prediction of suicide; on the contrary, the stakes of suicide are high, and we share the view that this makes efforts to improve prediction critical.

The poor prediction of suicide with current phenotyping, even in high-risk SA cohorts with ample clinical data, indicates that genetic information may be a necessary addition to current prediction efforts. One reason to examine genetic data, alongside epidemiological data on suicide, is its ability to provide risk metrics for multiple phenotypes as proxies for conditions that we cannot otherwise measure. We already observe genetic risks associated with suicide that with replication, may help us to better parse suicide risk phenotypes. Genetic risk metrics from population-based suicide research may provide predictive value to current models, and will certainly provide insights about risks unique to STB phenotypes.

Epidemiology

Decades of research have indicated that STBs have shared unique risk factors that vary by population and by individual. Two people

can manage STBs and yet share very few risk factors. This makes it difficult to characterize risks at a population level without also characterizing specific risk groups. And since STBs do not result in death for most individuals (Turecki & Brent, 2016), examining risk factors for SI, SA and suicide separately and together will help to differentiate risk factors for each phenotype.

Epidemiology of SI and SA

There have been more studies focusing on SI and SA than on suicide. Rates of SI and SA are higher than that of suicide, and obtaining clinical or genetic data on suicide death has been historically challenging. The stigma associated with dying by suicide has negatively influenced reporting rates (Nock, Borges, & Ono, 2012). Another challenge to collecting data specific to suicide has been the ethical and legal complexities of obtaining postmortem suicide data. Relatedly, many geographic locations cannot process postmortem examinations in a centralized fashion, compounding the difficulty of collecting and examining genetic data from large enough cohorts. Additionally, the low population base rate of suicide makes it difficult to obtain sufficient sample sizes. To provide some perspective on this base rate, for every suicide there are approximately 20 individuals with SAs, and many more with SIs (World Health Organization, 2014).

Lifetime prevalence rates are roughly 9.2% for SI and 2.7% for SA. However, sex ratios of suicide and SA differ dramatically, with a 4:1 ratio of males to females for suicide death and virtually the opposite pattern for SA (Nock et al., 2008), a significant epidemiological difference dividing SA from suicide. Among people who attempt suicide, only 10–15% eventually go on to die from suicide, with 1.6% of suicides occurring within 1 year and 3.9% within 5 years of an attempt (Olfson et al., 2017; Suominen et al., 2004). In other words, SA and SI can lead to an eventual suicide death, but for the vast majority of people, it does not. Within the realm of SI and SA, more research is needed that compares individuals with chronic SI who do not attempt suicide to those with SAs.

Epidemiology of Suicide

The lifetime prevalence of suicide is currently unknown, and only 80 countries have good quality data on suicide rates (World Health Organization, 2014). The World Health Organization (WHO) estimates that ∼ 800 000 individuals take their own life each year (World Health Organization, 2014). However, this estimate is conservative – suicide rates are often underreported due to stigma and the resulting misclassification of deaths (Klonsky et al., 2016). Broadly, suicide rates have been decreasing in many countries, with a notable increase in the United States (Hedegaard, Curtin, & Warner, 2020 increase in suicide mortality in the united states, 1999–2018. nchs data brief, 362. hyattsville, md: national center for health statistics.). In 2017, 1.4% of deaths globally were from suicide (Global Burden of Disease Collaborative Network., 2017) and in most countries, the suicide rate is higher than the homicide rate (Roth et al., 2018).

As discussed above, there are notable epidemiological differences between SA and suicide. Additionally, most people who do die by suicide actually do so on their first known attempt (DeJong, Overholser, & Stockmeier, 2010; Suominen et al., 2004). Thus, most suicides do not have any documented SA. Suicide rates also vary by age, sex, and location (Bachmann, 2018). In 2016, the global age-standardized suicide rate was 10.5

suicides per 100 000 persons, and the global suicide rate was higher for males than for females. This pattern is reversed in SA, where more women attempt suicide than do men.

With these differences in suicide – the limited number of suicides with previous SA and the reversed male to female ratio between SA and suicide – it would seem that observable risk factors for suicide would account for more variation in predictive models than is currently observed. No single risk factor or set of known risk factors appears to adequately explain suicide. Currently, risk factors with the strongest evidence of epidemiological association with suicide include drug and alcohol misuse, the presence of a neuropsychiatric disorder, and a family history of STBs. Other significant risk factors include access to lethal means, adverse life events, diagnoses of chronic and/or terminal illness, previous SAs, and adverse childhood experiences (Fazel & Runeson, 2020).

Notably, mental health conditions comprise an important risk factor for STBs, but they do not fully account for STBs. Most psychiatric disorders do carry an increased suicide risk (Yeh et al., 2019) and the most common mental health diagnoses in people who die by suicide include major depressive disorder, bipolar disorder, schizophrenia, or substance use disorders (Arsenault-Lapierre, Kim, & Turecki, 2004; Chesney, Goodwin, & Fazel, 2014; Yeh et al., 2019; Yoshimasu, Kiyohara, & Miyashita, 2008). After discharge from psychiatric hospitalization, the suicide rate among people with neuropsychiatric disorders is significantly higher, at 88 per 100 000 (Walter et al., 2019), declining slowly over time. This rate is much higher than that of the general population and represents an opportunity for potential targeted treatment and prevention. Yet overall, 98% of people with psychiatric disorders do not die by suicide (Nordentoft, Mortensen, & Pedersen, 2011). Thus, studying all suicide phenotypes, inside and outside the context of psychopathology, is going to be important for understanding the nature of suicide risk and related factors.

Recent events impacting epidemiological observations

Special consideration should also be given to suicide prevention in light of the coronavirus disease 2019 (COVID-19) pandemic (John, Pirkis, Gunnell, Appleby, & Morrissey, 2020). Suicide rates increased by 16% in the Japanese population from July to October of 2020, and the burden of COVID may have long-term effects on suicide risk in other populations (Tanaka & Okamoto, 2021). Financial stressors, social isolation and illness related to the pandemic, in combination with other risk factors, could exacerbate STBs in vulnerable groups (Gunnell et al., 2020). In the UK and US, STBs increased during the pandemic and were higher among ethnic minorities, unemployed people, essential workers, lower socioeconomic groups and people with mental and physical illnesses (Czeisler et al., 2020; Iob, Steptoe, & Fancourt, 2020).

Genetic epidemiology

Familial research has indicated that genetic variation significantly contributes to the occurrence of STBs. Combined evidence from family, twin, and adoption studies have heritability estimates of STBs that range from 30% to 55% (Voracek & Loibl, 2007). STBs run in families and can be transmitted independently of psychiatric comorbidities (Brent & Mann, 2005; Pedersen & Fiske, 2010; Tidemalm et al., 2011). The risk of SA is increased 5-fold in offspring whose parents have a history of SA (Brent et al., 2015). Recent biometrical studies of population-based registry data in Sweden are beginning to quantify the impact of genetic and environmental factors in the familial aggregation of STBs. In one analysis of Swedish registry data of offspring born between 1973 and 2001 (*N* = 2 762 883), genetic factors were observed to be the *primary* factor involved in the intergenerational transmission of STBs (O'Reilly et al., 2020). Another seminal study using the Sweden registry data reported that the transmission of SA results equally from genetic and environmental influences and that parental psychiatric and substance use disorders explain up to 40% of the genetic transmission effects (Kendler, Ohlsson, Sundquist, Sundquist, & Edwards, 2020). This study also examined the cross-generational genetic correlation between SA and suicide, and found estimates to be substantial (0.84), while also indicating important differences between transmitted genetic liability in the two phenotypes. This suggests that SA and suicide are partially distinct and that SA is not simply a milder form of suicide.

Genetics

Molecular genetics and genome-wide association studies

The discovery of genetic loci has the potential for improving our understanding of biological mechanisms, model systems, and drug targets. Genome-wide association studies (GWAS) have fueled genetic discovery in psychiatry, and international efforts have helped to establish that hundreds to thousands of common genetic variants contribute to psychiatric disorders (polygenicity), to varying degrees (Sullivan & Geschwind, 2019). Moreover, pleiotropy, where one gene influences multiple traits, is often observed across many psychiatric disorders (Anttila et al., 2018; Gandal et al., 2018).

Since STBs span all psychiatric disorders, polygenic approaches will be increasingly informative for modeling shared genetic covariance of STBs with psychiatric phenotypes and understanding the potential pleiotropy of STBs (Li, Chen, Ritchie, & Moore, 2020; Torkamani, Wineinger, & Topol, 2018). Observed pleiotropy can also result from phenotypic non-specificity – unlike other areas of medicine, we do not have laboratory tests for psychiatric conditions, and we are forced to make our best effort at a comprehensive diagnostic system. Luckily, discovery GWAS can provide us with new information about the overlap of phenotypes across populations where we cannot measure every phenotype.

More than 20 GWASs of STBs have now been conducted with various populations, ancestries, primary phenotypes and study designs (González-Castro et al., 2019a; Mirkovic et al., 2016). However, most of these GWAS have been limited to European ancestry populations, and have been statistically underpowered to detect specific loci at genome-wide significance levels. The recent, most well-powered GWASs to date have identified genome-wide significant variants, but these signals still await replication. Currently, the low predictive power of STBs GWAS results has prevented suicide polygenic risk scores (PRS) from achieving any clinical utility. In the future, PRS for SI, SA or suicide may have a clinical impact by contributing to extant models predicting individuals at high risk for STBs. This requires studying a number of conditions, traits, and diagnoses in relation to suicide data and fully characterizing the unique and shared genetic variance of suicide with the phenome.

Additionally, STBs present a methodological challenge. Across a putative 'spectrum' of suicide – suicide, SA, SI – phenotypic

Table 1. Overview of GWAS efforts with genome-wide significant findings in STBs

Phenotype	Ascertainment	Samples	Genome-wide significant loci number, chromosome location and SNP identifier	Study
Suicidal ideation, self-harm and suicide attempt	Population-based, European ancestry	• 36 599 SI • 2498 self-harm; unknown suicidal intent • 2666 SA • 83 557 controls	3 Total Chr9:rs62535711; Chr11:rs598046; Chr13: rs7989250	Strawbridge et al. (2019)
Suicide attempt	Clinical cohorts with diagnoses of major depression, bipolar disorder, or schizophrenia, European ancestry	Major depressive disorder • 1622 SA • 8786 controls Bipolar disorder • 3264 SA • 5500 controls Schizophrenia • 1683 SA • 2946 controls	3 Total MDD: 1 Chr10:rs45593736 BPD: 1 Chr4:23273116_D MDD + BPD:1 Chr2:rs138689899	Mullins et al. (2019)
Suicide death	Population-based, European ancestry	• 3413 suicide deaths • 11 049 controls	2 Total Chr13:rs34399104; Chr15: rs35256367	Docherty et al. (2020)

SI, suicidal ideation; SA, suicide attempt; Chr, chromosome; MDD, major depressive disorder; BPD, bipolar disorder.

base rates rise while measurement becomes increasingly complex. For example, the rarer occurrence of suicide reflects a concrete, binary phenotype with virtually no measurement error, but a collection of such data is quite difficult. The more common occurrence of lifetime SA can vary in both frequency and intensity (i.e. intentionality, lethality). And the occurrence of SI reflects a symptom but not a behavior, and is typically assessed clinically by questionnaire or interview. Ideation also varies in frequency and intensity.

As more variation is introduced, efforts to harmonize data across large GWAS cohorts is exceedingly difficult. And naturally, the largest cohorts tend to be of those phenotypes with the highest base rates. In the following sections, we review GWAS efforts within each of these phenotype domains, moving from the more common to the more extreme.

Suicidal ideation

The largest GWAS of STBs examined self-report data from European ancestry individuals in the UK Biobank with a case−control design. This study used a broad definition of STBs, including some individuals with self-harm and unknown suicidal intent. This GWAS compared mostly individuals with SI/self-harm (7.2% of the cases were also SA cases) to controls without these thoughts and behaviors (see Table 1). This study identified three loci meeting criteria for genome-wide significance (see Table 1), and SNP-based heritability was estimated at 7.6% (Strawbridge et al., 2019). PRS of SI/SA were tested in an independent sample and associated with a higher risk of suicide at most significance thresholds. The strongest genetic correlations were observed between SI/SA and major depressive disorder, but since this study included both SI and SA individuals together, it will be important, when sample sizes increase, to further examine what genetic risk can be attributed to each distinct phenotype. Efforts are underway to parse genetic variance due to each phenotype in current consortia efforts involving the UK Biobank.

Suicide attempt

SNP-based heritability estimates of SA in Europeans have been significant and range from 3.5% to 4.6% (Erlangsen et al., 2018; Ruderfer et al., 2019). The largest GWAS of SA was conducted using diagnostic cohorts of Europeans from the Psychiatric Genomics Consortium and has provided three genome-wide significant loci associated with SA (Mullins et al., 2019) (see Table 1). Using a case−control design, attempters were compared with non-attempters across several PGC cohorts.

A meta-analysis was then also conducted across cohorts ascertained for specific psychiatric disorders. PRS of SA were derived to examine the genetic liability of SA within the context of major depressive disorder, bipolar disorder and schizophrenia. The PRS analyses indicated that genetic risk for major depressive disorder is associated with SA risk in people with major depression, bipolar disorder and schizophrenia. This suggested that SA genetic risk may not be attributable solely to a psychiatric disorder with which an individual is diagnosed, which may be intuitive given the strong overlap of depression, bipolar disorder, and schizophrenia. Three separate studies have also found a significant genetic overlap of SA with major depressive disorder using PRS methods (Levey et al., 2019; Lim et al., 2020; Ruderfer et al., 2019).

Suicide

The largest GWAS of suicide was recently conducted on population-ascertained cases in the US, collected at the University of Utah through the centralized Utah Office of the Medical Examiner. This study was limited to individuals of European ancestry because rates of other ancestries were too small, but efforts to incorporate all ancestries with larger samples are underway. This GWAS identified two genome-wide significant loci (Table 1), estimated significant SNP-based heritability of suicide at 25%, and used suicide PRS to predict case−control status, using training and test sets with two independent control cohorts (Docherty et al., 2020). Suicide cases were observed to

have elevated PRS for multiple psychiatric traits, with the largest effect sizes observed for behavioral disinhibition, major depressive disorder, and schizophrenia.

Another GWAS of suicide conducted in a Japanese population included two independent data sets (set 1 = 385 suicide cases and 7409 controls; set 2 = 357 suicide cases and 6560 controls) (Otsuka et al., 2019). Although this study did not identify significant loci, significant and relatively high SNP-based heritability estimates of 35–48% were observed. This study was also notable for being the first to predict case−control status in an independent case−control cohort from its GWAS-derived PRS. The variance explained for the PRS at the most significant *p*-value (2.7×10^{-13}) was 1.3–2.4%.

Ancestry

GWASs of STBs, like most GWAS, have been conducted primarily with cohorts of European ancestry (Popejoy & Fullerton, 2016). The lack of ancestral diversity in psychiatric genetics to date limits the identification and generalizability of potential genetic risk factors and can contribute to health disparities (Kang & Ruderfer, 2020). Smaller studies of STBs have been conducted in cohorts of African American (Levey et al., 2019; *N* = 3238 cases with SA), Mexican (González-Castro et al., 2019b; *N* = 37 cases with SA), Peruvian (Shen et al., 2020, *N* = 522 cases with SI) and East Asian (Otsuka et al., 2019; *N* = 746 suicide cases) ancestries. Notably, polygenic analyses from the suicide GWAS in Japan were successful, in which a significant SNP-based genetic correlation of suicide was observed between two independent Japanese cohorts of suicide death (Otsuka et al., 2019). It remains unclear, and of great interest, whether significant genetic correlations can be observed across suicide case−control cohorts of different ancestries.

Rare variant genetic architecture studies

Most genetic studies of STBs have focused on common genetic variants, with only a small number of studies investigating rare genetic variation. Identification of rare genetic risk can more directly pinpoint genes of interest. Rare variation can include single-nucleotide variants (SNVs) as well as structural variation, like copy number variants (CNVs).

Two whole-exome sequencing studies have suggested that rare SNVs may be implicated in SA in bipolar disorder (Monson et al., 2017) and suicide in major depressive disorder (Monson et al., 2017; Tombácz et al., 2017). The largest examination of rare SNVs, in >2600 European ancestry suicide deaths, examined putatively functional SNVs present on genotyping arrays and identified five rare protein-coding SNVs significantly associated with suicide death (DiBlasi et al., 2021). CNV studies in SA have been underpowered, but also suggest a possible role for CNVs in STBs (Gross et al., 2015; Perlis, Ruderfer, Hamilton, & Ernst, 2012; Sokolowski, Wasserman, & Wasserman, 2016; Tombácz et al., 2017). All SNV and CNV results await replication, and ultimately more research is needed in the area of STBs and rare genetic variation to fully understand its impact.

Gene pathways and functional genomics

Risk genes and molecular pathways involved in suicide risk can also be identified with functional genomic approaches. Gene-expression studies and epigenetic studies are the most common functional genomic approaches used in research on STBs.

Gene-expression studies focus on the effect of gene structure, function and regulation on STBs, and have identified genes of interest, especially in studies of the postmortem brain (For a recent review see: Zhou et al., 2020). Other functional genomic research focuses on how genetic variation interacts with the environment to alter gene expression using a variety of epigenetic methods (For recent reviews, see: Cheung, Woo, Maes, & Zai, 2020; Fiori & Turecki, 2020). Similar to genetic architecture studies, we see few successful functional genomic replications, possibly due to heterogeneity of the phenotyping and methods across studies. However, it is increasingly evident that epigenetic alterations play an important role in STBs.

To date, over 2500 genes have been associated with suicide, with varying levels of statistical support (Sokolowski & Wasserman, 2020). Pathway enrichment results of 40 genes with multiple lines of evidence of association with STBs are related to the cell cycle and DNA repair – relatively large pathways comprised of many genes (Sokolowski & Wasserman, 2020). However, overall, these candidate genes lack statistical robustness and additional studies are needed to strengthen their associations with STBs. Preliminary gene ontology and pathway analyses of suggestive findings from GWAS studies on STBs suggest an association with the regulation of glucose, regulation of protein localization, and other cell cycle pathways (González-Castro et al., 2019a).

Current challenges to genetic research on STBs

Suicide is a complex phenotype, and a public health issue of urgent importance that is highly preventable (Gordon, Avenevoli, & Pearson, 2020). Genetic examination of the heritable phenotypes comprising STBs will help to better model the heterogeneity and understand the sequelae of STBs. However, as reviewed above, it is apparent that the low base rates of suicide and the complexity of measurement of STBs present significant challenges to suicide research.

Epidemiological and biometrical research suggests that the three main phenotypes encompassing STBs (ideation, attempt and death) have distinct etiologies. The degree of pleiotropy in STBs phenotypes remains unclear. A large amount of clinical variability in defining STBs and the heterogenous etiologies of SI, SA, and suicide will require carefully planned genetic studies with well-defined primary phenotypes to elucidate the shared and unique risk factors between STBs. Large genetic studies examining SI, SA, and suicide are currently being facilitated through collaborations with the Psychiatric Genomics Consortium and the International Suicide Genetics Consortium to increase samples sizes, pending additional genotyping of new SI, SA, and suicide cohorts.

The primary goal of genetic studies of STBs is to identify genes and neurobiological pathways that confer risk and protection, to identify plausible intervention targets, and to ameliorate the suffering of individuals at risk. Recently, there has been demonstrable progress toward this end – a key finding being that STBs appear to be polygenic with many genetic loci of different effects contributing to risk. This allows genetic risk for suicide to be more easily modeled across phenotypes and populations, and also modeled conditional on other phenotypes. However, we are still at the beginning stages of genetic discovery in STBs, and thus far only a fraction of the genetic variation influencing STBs has been accounted for. Plausible genetic findings in STBs are starting to emerge, and we believe that they will enhance nosology, diagnosis, and treatment.

The sample size is a major factor in the genetic discovery of risk variants. The relatively small sample sizes of current genetic studies on STBs make genome-wide significant hits vulnerable to systematic biases. The complexity of phenotypes encompassing STBs, like most psychiatric traits, necessitates very large genetic discovery cohorts to achieve statistical power and for the successful discovery of risk variants.

It is critically important to model ancestry and ancestry admixture in genetic research on STBs to better understand ancestry-specific risk factors, to examine genetic risks that may be relevant to specific populations and locations, and to reduce health disparities. This has been historically difficult with the general lack of genetic data on suicide, but efforts are underway to increase access to diverse ancestry data resources as rapidly as possible (Docherty et al., 2020). Overall, the examination of ancestry will be essential to a comprehensive genetic discovery of STBs and will be a significant improvement to the field.

Examination of sex differences in STBs, likewise, has largely been limited to epidemiological observations and has not yet been examined with genetic data. With larger samples, it will be necessary to examine STBs within and across sex to better understand the genetic basis of these differences.

Genomic modeling of STBs is complex, and as discussed above, there is emerging evidence for significant genetic overlap with major psychiatric disorders. Genetic liability for major depressive disorder is increased in individuals who attempt suicide within a variety of psychiatric diagnoses. Major depressive disorder is the most prevalent psychiatric disorder (~16% prevalence) and STBs are prevalent within this diagnosis (Orsolini et al., 2020). Recognizing STBs as a distinct condition or set of behaviors, rather than a symptom of a given psychiatric diagnosis, allows researchers to look for risk factors involved in suicide beyond the confines of a particular psychiatric condition (Mann & Rizk, 2020; Salloum, 2017; Sisti et al., 2020). Yet there is some room for refinement of nosology and risk assessment by examining suicide within and across diagnostic groups.

Future directions

Genetic discovery of psychiatric risk generally increases with larger sample sizes (Sullivan & Geschwind, 2019). The International Suicide Genetics Consortium has recently merged efforts across STBs research. Currently, underway is the first collaborative GWAS meta-analysis including over 29 000 SA cases. This study will help to elucidate the genetic architecture of SA and examine its overlap with psychiatric disorders. In addition, only recently have suicide GWAS become large enough to derive estimates of molecular genetic correlations with other conditions. Comparing genetic correlations with those observed for SA will be particularly informative. Also underway by members of The International Suicide Genetics Consortium are efforts to link large genetic datasets of STBs with electronic health records (EHR). These efforts are expected to help improve accuracy when identifying individuals with STBs within the EHR at the highest risk.

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