HHS Public Access

Author manuscript

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2023 February 06.

Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2022 October ; 189(7-8): 221–246. doi:10.1002/ajmg.b.32917.

Genetics and epigenetics of self-injurious thoughts and behaviors: Systematic review of the suicide literature and methodological considerations

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Abstract

Suicide is a multifaceted and poorly understood clinical outcome, and there is an urgent need to advance research on its phenomenology and etiology. Epidemiological studies have demonstrated that suicidal behavior is heritable, suggesting that genetic and epigenetic information may serve as biomarkers for suicide risk. Here we systematically review the literature on genetic and epigenetic alterations observed in phenotypes across the full range of self-injurious thoughts and behaviors (SITB). We included 577 studies focused on genome-wide and epigenome-wide associations, candidate genes (SNP and methylation), noncoding RNAs, and histones. Convergence of specific genes is limited across units of analysis, although pathway-based analyses do indicate nervous system development and function and immunity/inflammation as potential underlying mechanisms of SITB. We provide suggestions for future work on the genetic and epigenetic correlates of SITB with a specific focus on measurement issues.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Keywords

suicide; genetics; epigenetics; DNA methylation; single nucleotide polymorphism; biomarker

1 | INTRODUCTION

Suicide is a leading cause of death worldwide and was reported as the tenth leading cause of death in the United States in 2019, claiming the lives of over 47,500 people (CDC, 2020). Importantly, suicide does not afflict all age groups proportionately, and it was the second leading cause of death for ages 10–34 in the same year. Beyond the death rate of suicide itself, an estimated 1.4 million US adults attempted suicide in 2019, and 12.0 million had thoughts of suicide (SAMHSA, 2020). These are likely underestimates given tendencies not to disclose self-injurious thoughts and behaviors (SITB) (Mayer et al., 2020). Although many efforts have been taken to improve the prediction and prevention of suicide, there is still a considerable degree of uncertainty with respect to who will attempt and die of suicide (Franklin et al., 2017), especially when considering those at risk for attempt and death among suicide ideators specifically (May & Klonsky, 2016).

Risk assessment typically includes a combination of self-reported items and clinician interview including a clinical history, which can present many limitations. For one, longitudinal studies have demonstrated that about one-third of people who report a suicidal history do not report that past history at a second assessment (Klimes-Dougan, Mirza, Babkin, & Lanning, 2022). Patients might also be motivated to conceal suicidal histories and intentions, especially considering perceived threats such as forced hospitalization (Blanchard & Farber, 2020). A meta-analysis of putative longitudinal risk factors for SITB, derived predominantly from self-reported and clinician-derived information, identified no strong or accurate predictors (Franklin et al., 2017). Greater explanatory power may emerge from a complementary line of research investigating the biological underpinnings of SITB when considered in conjunction with established psychometric assessments. Specifically, epidemiological studies have shown that suicide phenotypes are moderately heritable, with estimated heritability proportions of up to 43%, 55%, and 47% for ideation, attempt, and death, respectively (Edwards et al., 2021; Statham et al., 1998; Zai, de Luca, Strauss, et al., 2012). Further, the familial transmission of suicidal behavior can be separated from the contribution of psychiatric diagnosis itself (Brent & Mann, 2005). These findings have suggested a genetic component specific to suicide and motivated investigation of DNA sequence-level variants which may confer a trait-like risk for SITB (Bondy, Buettner, & Zill, 2006). Recently, investigations have expanded to explore epigenetics, the nonsequence level modifications which affect gene expression and have shown to be important in the across-level interplay between environmental experience and gene expression (Labonte & Turecki, 2010).

Despite a large research basis on genetics and epigenetics of SITB, there has been less attention to common findings between studies and methodological concerns. There has also been the challenge of addressing the widespread heterogeneity in SITB phenotypes, such as reconciling findings regarding ideation and attempt, or understanding the place

of self-injurious behaviors without suicidal intent. Here we undertook a systematic review of all available literature on the genetics and epigenetics of SITB, which we defined to include a broad range of suicide-related outcomes including suicide attempt (SA, including lethality), death by suicide (SD), suicide ideation (SI), and other self-injurious behaviors including nonsuicidal self-injury (NSSI). While recent studies have been published on this topic (Cheung, Woo, Maes, & Zai, 2020; DiBlasi et al., 2021), we believe that none have comprehensively summarized the extant literature while also addressing replicability and methodology.

To our knowledge, this is the largest and most comprehensive systematic review to date on the genetics and epigenetics of SITB, which allows for a critical evaluation of the field as a whole. We high-light issues beyond the usual criticism of candidate gene designs and present specific measurement-related challenges. In addition, we provide our insight to these measurement issues and also recommend potential future pathways which could contribute to greater understanding of the genetic and epigenetic underpinnings of SITB, ultimately leading to enhanced identification of at-risk individuals and prevention of additional deaths by suicide.

2 | METHOD

2.1 | Search strategy

We conducted a systematic search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). We searched the MEDLINE database for the following terms: ([epigenet*] OR [genet*] OR [DNA] OR [RNA] OR [miRNA] OR [mRNA] OR [genome] OR [RNA-seq] OR [methylat*] OR [polygenic] OR [GWAS]) AND ([suicid*] OR [self-injur*]), in March 2021, with updated searches in October 2021 and May 2022. We limited our search to peer-reviewed publications in English. We included studies which (a) assessed one or more of the following genetic/epigenetic metrics: DNA sequence-level variation (e.g., single-nucleotide polymorphisms [SNP], genome-wide association studies [GWAS], polygenic risk, copy number variants [CNV]), DNA methylation, histone modifications, noncoding RNAs (microRNAs and long noncoding RNAs [lncRNAs]), and (b) one or more of the following outcomes: SD, SA (including severity/lethality and impulsive nature), SI (passive or active), NSSI, and self-harm.

We did not include genetic epidemiological studies (e.g., twin and adoption studies, family risk) which did not conduct molecular genetic-specific analyses, or pharmacological treatment emergent suicidality studies. We also excluded studies which did not explicitly assess one of the suicidal phenotypes noted above as an outcome, such as studies which explored the association between a particular genetic/epigenetic metric and aspects of personality, perhaps in populations with elevated rates of suicidality. Only studies in human samples were included. Furthermore, studies had to include a reference to compare against the suicidal condition (e.g., control group, continuous measure of severity, within-subjects analysis). This criterion was implemented to exclude datasets in SITB populations without inferential statistical analyses (e.g., posted datasets). All ages and populations with relevant study design were included, with the exception of developmental delay due to concerns that

self-injurious behavior in contexts of pediatric developmental delay is distinct even from adolescent NSSI.

3 | RESULTS

3.1 | Search outcome

Our initial, broad search yielded 9,371 results. After removal of duplicates, title/abstract screening, and failed retrievals, 817 publications remained for full text screening. The October 2021 updated search revealed 272 new articles after duplication removal, of which 20 were selected for full text screening. The May 2022 updated search revealed 268 new articles after duplication removal, of which 29 were selected for full text screening. The full text screening was carried out in accordance with the exclusion criteria and yielded 577 full text publications to be included in this systematic review. Figure 1 illustrates the systematic screening process according to PRISMA guidelines. There were 31 GWAS studies; 7 genome-wide CNV studies; 4 whole exome/rare variant studies; 39 polygenic risk studies; 4 linkage studies; 438 studies focused on variations in candidate genes, 53 of which considered interaction with environment (GxE); 7 Mendelian randomization studies; 16 epigenome-wide association studies (EWAS); 36 candidate gene DNA methylation studies; 13 noncoding RNA studies; and 6 histone modification studies. Studies often fit in multiple categories and the relevant aims were included in each category.

3.2 | Genome-wide association studies and genome-wide CNV

Our search revealed thirty-one GWAS studies for SITB (Table 1), of which nineteen were focused exclusively on suicidal behavior (SA/SD). Some studies which included SI did so by considering continuous suicidality scales ranging from no suicidality to SI to SA (i.e., no reference group; Lybech et al., 2021; Schosser et al., 2011; Strawbridge et al., 2019; Zai et al., 2015; Zai et al., 2021), and only six studies assessed SI independently of suicidal behavior (Brick et al., 2019; Campos et al., 2020; Kimbrel et al., 2018; Mullins et al., 2014; Polimanti et al., 2021; Shen et al., 2020). In most cases, the large sample size needed for GWAS required a combination of multiple cohorts for analysis. Therefore, there were often multiple instruments used to determine the SITB phenotype within the same study (Supplementary Table S1).

Of all identified GWAS published to date, nine (Bani-Fatemi et al., 2016; Lybech et al., 2021; Mullins et al., 2019; Perlis et al., 2010; Rao et al., 2020; Schosser et al., 2011; Willour et al., 2012; Zai et al., 2015; Zai et al., 2021) focused on specific diagnostic groups, such as bipolar disorder (BD) and major depressive disorder (MDD), with some including multiple psychiatric disorder groups assessed separately. There was one GWAS focused on SI in youth (Brick et al., 2019), with no GWAS reports on suicidal behavior in youth. Estimates for SNP-based heritability (Supplementary Table S1) ranged from 0% (nonsignificant) to 48%, with the highest estimate coming from a study of SD in the Japanese population (Otsuka et al., 2019).

Genome-wide significant SNPs reported for SITB are listed in Table 1. Two genome-wide significant SNPs identified in the UK Bio-Bank ordinal suicidality association study

(Strawbridge et al., 2019) emerged in subsequent GWAS: rs7989250 (not annotated) was replicated at $p < .05$ in a study on SD in the Japanese population (Otsuka et al., 2019), and rs589046 reached "borderline significance" in the study of suicide attempt in the Dutch population (Erlangsen et al., 2020). Moreover, SNPs within the *ABI3BP* gene were significantly associated with SA in an initial study (Perlis et al., 2010) and nominally associated with SA and SI in a later study (Kimbrel et al., 2018). A female-specific genome-wide linkage and association study (Willour et al., 2012) identified region 2p12 for SA, while the SA association study by Mullins et al. (2014) identified a signal at rs17010519 within this region, as well.

Recently, the International Suicide Genetics Consortium (ISGC; total $N = 549,743$; 29,782 cases) identified two *loci* reaching genome-wide significance for SA on chromosomes 6 ($p = 1.97 \times 10^{-8}$) and 7 ($p = 1.91 \times 10^{-10}$) (Mullins et al., 2022). The locus on chromosome 7 remained significant after conditioning on psychiatric disorders, and was independently replicated within the Million Veteran Program (MVP; $p = 3.27 \times 10^{-3}$) cohort. A separate GWAS study with the MVP cohort (total $N = 409,153$; 14,089 cases) identified two genome-wide significant (GWS) multi-ancestry *loci* on chromosomes 20 ($p = 3.64 \times 10^{-9}$) and 1 ($p = 3.69 \times 10^{-8}$) (Kimbrel et al., 2022). A strong signal identified in the MVP at the Dopamine Receptor D2 (*DRD2*) locus ($p = 1.77 \times 10^{-7}$) was subsequently replicated in the ISGC cohort ($p = 7.97 \times 10^{-4}$) in the same study.

Most recently, the ISGC and MVP studies were merged into the largest GWAS meta-analysis of SA to date, which included both multi-ancestry and ancestry-specific GWAS of SA for African, Asian, and European ancestry admixtures. This study, presented at the 2021 World Congress for Psychiatric Genetics, included 22 cohorts with 43,871 SA cases and 915,025 ancestry-matched controls and identified 12 GWS *loci*, including eight in a multi-ancestry meta-analysis and four additional *loci* unique to European ancestry (Docherty et al., 2022).

In addition to the specific SNPs, gene-based analyses have identified *RETREG1* (*FAM134B*), *GSN*, *GNAS*, *CACNA1D* (SA; Sokolowski, Wasserman, & Wasserman, 2018), *HGF* (SI; Polimanti et al., 2021), *HEPACAM*, *CNTN5*, *PSMD14*, and *HEPN1* (ordinal suicidality; Wendt et al., 2021), and *BTN2A1* (SA/SD; Mullins et al., 2022) in association with SITB. Pathway analyses performed with significant genes have also implicated multiple biological processes in SITB, including growth hormone secretion, immune processes (SA; González-Castro et al., 2019), caspase pathway (SA severity; Levey et al., 2019), neurocircuitry (ordinal suicidality; Strawbridge et al., 2019), synaptic function and brain development (ordinal suicidality and SA, respectively; Lybech et al., 2021; Sokolowski et al., 2018), cellular assembly and organization, nervous system development, cell death and survival, immunological disease, infectious disease, inflammatory response (SA/SD; Galfalvy et al., 2015), CNS development, homophilic cell adhesion, regulation of cell proliferation, transmission of nerve impulse (SD; Galfalvy et al., 2013), oxytocin signaling, glutamatergic synapse, axon guidance, calcium signaling, circadian entrainment, cortisol synthesis and secretion, dopaminergic synapse, and circadian rhythm (SA; Kimbrel et al., 2022). A recent analysis on SD by Sokolowski and Wasserman (2021) pooled information from published GWAS and whole exome studies to group identified genes together, finding

evidence for contributions from chromosome 19 as well as a set of 54 “core” genes involved in synaptic and nervous system development.

Finally, the six genome-wide CNV studies (Gross et al., 2015; Melhem et al., 2017; Perlis, Ruderfer, Hamilton, & Ernst, 2012; Rao et al., 2020; Sokolowski, Wasserman, & Wasserman, 2016b; Tombácz et al., 2017) have conflicted on overall differences and specific genetic regions. Increases in both global rate of CNV and duplications >500 kb have been reported in SA (Melhem et al., 2017; Rao et al., 2020), although some studies have reported no overall differences in deletions or duplications in SITB samples (Gross et al., 2015; Perlis et al., 2012; Tombácz et al., 2017). With respect to specific genes, the 10q11.21 region (*ZNF33B*) was associated with SA in MDD (Rao et al., 2020), and 9p24.1 (*GLDC)* copy number may contribute to SA risk (Melhem et al., 2017). Rare CNVs implicated in neurodevelopment might also play a role in SA (Sokolowski, Wasserman, & Wasserman, 2016b).

3.3 | Whole exome/rare variants

Four studies have assessed rare variants (Coon et al., 2013; DiBlasi et al., 2021; Monson et al., 2017; Tombácz et al., 2017), all focused on suicidal behaviors. The most recent rare variant approach identified five high-impact rare variants associated with SD in the following genes: *SNAPC1*, *TNKS1BP1*, *ADGRF5*, *PER1*, and *ESS2* (DiBlasi, Kang, & Docherty, 2021). *SNAPC1* and *PER1* had previously been implicated in SITB. A study of SA in BD identified no individual variants that passed study-wide significance for association with SA, with the most significant variant being the common variant rs2215955 (*AMPH*) (Monson et al., 2017). The top gene-level results were *CFAP70* and *SLC6A13*, with an enrichment of rare variants in the *ALDH* genes. A study of SD in MDD found rare genetic variants associated with calcium ion channels (*CACNA1B*, *−1C*, *−2D4*) and *TGF-β* (Tombácz et al., 2017). One study took a high-risk pedigree approach to identify families with increased risk for SD (Coon et al., 2013). Rare variants identified in the SD pedigree members included those in genes coding for membrane proteins (e.g., *FAM38A*, *HRCT1*, *TMEM141*, *ANO5*). Other variants identified included those previously implicated in neurobiology and psychiatric illness (e.g., *CASP9* and BD, *PLXNB1* and neurocircuitry).

3.4 | Polygenic risk scoring

Thirty-nine studies, including 12 of the identified GWAS studies, included polygenic risk scoring (PRS) in their analyses (Supplementary Table S2). PRS for psychiatric disorders including MDD, BD, schizophrenia (SCZ), attention-deficit/hyperactivity disorder (ADHD), autism, cannabis use, post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and anxiety have all been associated with SITB outcomes. The highest percentage variance explained for a psychiatric PRS was for SCZ, explaining up to 11.8% of variability in child SA (Joo et al., 2022).

Some studies have built PRS for SITB from other samples and deployed them in independent datasets; for example, a PRS for SA in BD explained 10.3% of variability in a composite index of SI/SA/SD (Cabrera-Mendoza et al., 2020), an SD PRS differentiated BD SD and BD SA (Monson et al., 2021), an ordinal suicidality PRS predicted dynamics in

longitudinal SI trajectories which were moderated by social support (Na et al., 2022), and a PRS for SA explained 1.08% variability in SD (Mullins et al., 2022). Interestingly, PRS for SD identified SD cases of documented high-family risk (Coon et al., 2022).

An emerging body of work is deploying polygenic scores derived from adult GWAS samples in youth datasets (Daskalakis et al., 2021; Joo et al., 2022; Lee et al., 2021), as currently there are no large GWAS of SITB based in youth samples. These studies have identified significant associations between adult GWAS-derived PRS for various traits and child SITB.

Other studies have tested the cross-ancestry predictive capability of PRS which are built in European samples. For example, a combination of high PRS for risky behavior and low to moderate PRS for depression (both European-based) predicted lifetime SA in a cohort of young African Americans (Rabinowitz et al., 2021). A European-based PRS for depression predicted SITB only in Mexican adolescents, but not adults (Martinez-Levy et al., 2021). A European-based PRS for SA (Mullins et al., 2019) explained 2.73% variability in SA in Koreans with BD (Lee et al., 2022).

In addition, aside from psychiatric disorders, a multigenic score built with 750 neurodevelopmental genes explained 4.9% of variance in SA for Europeans (Sokolowski et al., 2016a), while a three-locus score for *HTR2A*, *TPH1* and *TPH2* explained 5% of variance in SA for Europeans (Pompili et al., 2017), and a four-locus score across *FKBP5*, *RORA*, *CHRNA5*, and *CRHR1* predicted SA or suicide plan in a largely European sample (Boscarino et al., 2022).

3.5 | Linkage

We identified four genome-wide linkage studies focused on SITB (Butler et al., 2010; Dick et al., 2010; Willour et al., 2007; Zubenko et al., 2004). SA in mood disorders was associated with 2p12, 6q12, 8p22-p21, and the Xq25–26.1 regions (Zubenko et al., 2004). The 2p12 region again arose as the strongest signal for SA in BD in a later study (Willour et al., 2007). The significant association of 2p12 with suicidal behavior (SD, SA, quantitative SI/SA) was replicated in a five sample meta-analysis (Butler et al., 2010). While 2p12 region has not robustly emerged in GWAS studies, there was a female-specific signal at rs10170138 (*LRRTM4*) in this region in one GWAS on SA (Willour et al., 2012), although this signal did not reach genome-wide significance. Chromosome 2 was similarly implicated in a linkage study of alcohol dependence and SA (Dick et al., 2010).

3.6 | Candidate gene variation and Mendelian randomization

We identified 438 candidate gene studies evaluating sequence variation (SNPs) in SITB samples (see Supplementary Table S3 for an over-view). Of these, 392 focused specifically on self-injurious behaviors rather than thoughts. Candidate gene studies have predominantly focused on monoamine systems including serotonergic (e.g., *TPH*, *SLC6A4*, *5-HT*, *N* = 206) and dopaminergic (e.g., *TH*, *DRD*, *DAT1*, *N* = *17*) systems, the hypothalamic–pituitary adrenal (HPA) axis (e.g., *CRH*, *FKBP5*, *NR3C1*, *SKA2*, *N* = 26), neurotrophic/neuroplastic functioning (e.g., *BDNF*, *NTRK2*, *HOMER1*, *NRXN1*, *N* = 39), and immune response/inflammation (e.g., *TNF alpha*, *IL-1*, *N* = 14). Fifty-three studies also included

GxE interaction analyses, with overall childhood trauma, sexual abuse, and stress levels as environmental factors.

Generally, positive and negative findings have been reported for each candidate gene/SNP, with little concordance and validation between independent studies. One possible approach to reconciling varying results across studies is meta-analysis. Our search identified 27 meta-analyses of candidate gene studies in SITB, 19 of which focused on serotonergic genes. Hits in meta-analyses have included SNPs within *FKBP5*, *NOS1*, *SLC6A4*, *TPH1*, *HTR1B*, and *BDNF* (Supplementary Table S3).

Six studies performed Mendelian randomizations focused on candidate genes involved with substance use disorders, insomnia, atopic dermatitis, inflammation, and blood lipids. There was no evidence that genes involved in substance use disorders contribute to self-harm, SA, or SD (Colbert et al., 2021). There was also no evidence that genes involved in atopic dermatitis contribute to SI or SA (Qi & Li, 2022). Evidence has emerged for significant risk effects of insomnia-related genes on suicidal behavior (SA/SD), which were especially robust in depressed samples (OR = 1.34) and replicated in an independent sample (Nassan et al., 2022). There also appears to be a protective effect of genes related to circulating C-reactive protein on deliberate self-harm (OR = 0.92; Russell et al., 2020), and a relatively robust relationship between triglyceride-related genes and deliberate self-harm (OR = 2.51; So, Chau, Cheng, & Sham, 2021). Genes related to MDD and SCZ appear to associate with self-harm (Lim et al., 2020). A seventh study indexed 1,520 traits for association with SA and tested causal roles by Mendelian randomization for three of them which had emerged as significant candidates by other methods (Campos et al., 2022). Genes related to any of these traits (hernia, vitamin D, reasons for glasses myopia) did not significantly relate to SA. So far, none of the canonical candidate genes investigated have emerged as significant hits in GWAS studies of SITB.

3.7 | Epigenome-wide association studies

Our search revealed 16 EWAS reports, of which 12 assessed either differential methylation of regions (DMRs) or positions (DMPs) in relation to SITB (Table 2; ancillary information in Supplementary Table S4). The remaining four studies did not report on specific positions or regions but did report comparison of global methylation levels between groups. Twelve genome-wide methylation studies were focused in post-mortem brain tissues (commonly studied areas include frontal cortex regions and hippocampus), with the remainder in blood (most commonly white blood cells, WBCs). Four studies focused on SITB in the context of specific psychiatric groupings (e.g., BD).

DMPs which reached genome-wide significance include hypomethylation of cg00963169 (*ELAVL4*) in the prefrontal cortex (PFC), cg14392966 (*PUS3*) in the cerebellum (Policicchio et al., 2020) and cg19647197 (*CCDC53*) in WBCs (Bani-Fatemi et al., 2018); and hypermethylation of cg24533989 (*ATP8A1*), cg13989295 (*SKA2*), cg15918259 (*LOC153328*), and cg17106415 (*KCNAB2*) in the PFC (with only *SKA2* remaining nominally significant after fluorescence-activated nuclei sorting for neuronal and nonneuronal fractions; Guintivano et al., 2014). Genome-wide significant DMRs include hypomethylated regions within the *WRB* gene in the PFC; *MPP4* 5′ UTR, *TBC1D1* intron

3 (WBC; Jeremian et al., 2017); *DNAJC15* (BA25 area), *SNAI3* (BA25), *PSORS1C3* (BA11/25), *TAPBP* (BA11/25), *ADYC9* in the BA 9 area (Romero-Pimentel et al., 2021), and *ATP5G2* (BA11/25) (Murphy et al., 2017), as well as hypermethylation of *PSORS1C3* in the PFC, *CERC2* in the cerebellum (Policicchio et al., 2020), *ZFP57* in BA 9 (Romero-Pimentel et al., 2021), and *NUP133 exon 1* in WBC (Jeremian et al., 2017). Of note, the *PSORS1C3* DMR was found to be genome-wide significant in two independent studies (Murphy et al., 2017; Policicchio et al., 2020).

The *PSORS1C3* finding was validated by bisulfite pyrosequencing, and the DMR hypomethylation was partially replicated in an independent subsample (Murphy et al., 2017). *GRIK2* hypomethylation and *BEGAIN* hypermethylation were both validated by bisulfite cloning and high-resolution melting (Nagy et al., 2015); the SD case group was selected for the additional requirement of astrocytic abnormality (downregulated astrocytic markers). *SKA2* cg13989295 hypermethylation in SD (shown by cell sorting to predominate in neuronal fraction) was replicated in two independent SD brain samples as well as peripheral blood in living people (SI), and interaction with genetic variation at rs7208505 in blood prospectively predicted SI and SA at about 80% (although other information such as self-report anxiety was included; Guintivano et al., 2014). Hypomethylation of *ADYC9* in PFC of SD was validated by bisulfite sequencing (Romero-Pimentel et al., 2021). Interestingly, this study also identified differential methylation of *CRH*, which has been studied as an *a priori* candidate gene for suicide due to its involvement in physiological stress response.

Pathway analyses of genes annotated to DMPs and DMRs have corroborated dysfunctions in biological pathways including long-term synaptic depression and brain development (Policicchio et al., 2020), synaptic plasticity, notochord cell differentiation, blood brain barrier, inflammation, cAMP responsive element modulator (CREM) and CRH pathways (Romero-Pimentel et al., 2021), opioid signaling (Gaine et al., 2019), plasma membrane (Kouter et al., 2019), nervous system development and mitochondrial function (Murphy et al., 2017), transcriptional regulation (Schneider et al., 2015), and cognition including learning and memory (Labonté et al., 2013).

Finally, regarding the average methylation level across the genome, two studies reported no difference between SITB and reference groups (Wernicke area, SD, Keller et al., 2010; hippocampus, SD, McGowan et al., 2008), while two studies found global hypermethylation in the SITB group (ventral PFC, SD, Haghighi et al., 2014; blood, SA, Murphy et al., 2013). Schneider et al. (2015), who found no significant DMRs/DMPs, reported global hypomethylation in PFC of SD, as did Kouter et al. (2019) in BA9 and hippocampus.

3.8 | Candidate gene methylation

Candidate gene methylation studies are far fewer in number than candidate SNP studies, with our search identifying 36 reports for inclusion (Supplementary Table S5). Twenty-eight of the thirty-six studies exclusively focused on self-injurious behaviors (i.e., SA, NSSI/SH, SD) rather than thoughts (SI).

The most commonly studied gene system was *BDNF* ($N = 10$, including two studies investigating the TrkB.T1 gene; Kang et al., 2018; Ropret, Kouter, Zupanc, & Videtic Paska, 2021; Roy, Shelton, & Dwivedi, 2017; Kim et al., 2015; Kim et al., 2014; Maussion et al., 2014; Kang et al., 2013; Keller et al., 2011; Keller et al., 2010; Ernst et al., 2009). Of the eight studies examining methylation specifically in the *BDNF* gene, six found *BDNF* hypermethylation to be implicated across a range of SITB outcomes, while one study of SI found no group differences (Roy, Wang, Palkovits, Faludi, & Dwivedi, 2017), and an SD study found hypomethylation (Ropret et al., 2021).

Seven studies focused on HPA axis-related genes (*SKA2*, *FKBP5*, *NR3C1*, *CRH* genes; Jokinen et al., 2018; Kouter, Zupanc, & Videtič Paska, 2022; Roy, Shelton, & Dwivedi, 2017; Clive et al., 2016; Sadeh et al., 2016; Kaminsky et al., 2015; Steiger, Labonté, Groleau, Turecki, & Israel, 2013). In general, findings on methylation of the HPA axis related genes are sparse as few genes have been extensively studied. Four studies (Clive et al., 2016; Kaminsky et al., 2015; Kouter et al., 2022; Sadeh et al., 2016) implicate methylation in the *SKA2* gene, first identified in EWAS, to be important in SI and SA, with prospective predictive capability and possible interaction with lifetime trauma history. However, other HPA axis candidate genes such as *CRH* and *NR3C1* have not been extensively studied by independent teams in the context of methylation and SITB.

Only two of the candidate methylation studies focused on adolescents (*POMC*, *SIRT1*; Zheng et al., 2020; Wang et al., 2021), and both were focused on self-injurious behaviors rather than thoughts. There were no candidate methylation studies of SI in youth.

3.9 | Noncoding RNAs

Nine studies reported on miRNA alterations in SITB, six of which pursued miRNome-wide, hypothesis-free approaches (Table 3; ancillary information in Supplementary Table S6). Most genome-wide miRNA studies (four of six) included case group sizes of fewer than ten individuals, with three studies focusing on MDD suicides, one focusing on BD suicides (Squassina et al., 2020), one focusing on mixed psychiatric disorder suicides (Smalheiser et al., 2014), and one focusing on a specific subgroup of SD with low TrkB.T1 mRNA expression (Maussion et al., 2012). Two candidate miRNA studies specifically investigated miRNAs involved in the TNF-α and *SAT1/SMOX* pathways (Wang et al., 2018; Lopez et al., 2014, respectively). These studies found a fivefold elevation of miR-19a-3p (*TNF-α* repressor) (DLPFC, Wang et al., 2018), and approximately twofold upregulation of miR-34c-5p, miR-139–5p, miR-195, and miR-320c (*SAT1/SMOX* targeting) in SD (PFC, Lopez et al., 2014). The third candidate miRNA study focused on seven miRNAs which were selected *in silico* based on their regulation of six candidate genes (*SLC6A4, HTR1A, BDNF, NR3C1, ZNF714, NRIP3*), finding a nonsignificant trend for increased expression of hsamiR-4,516 and hsa-miR-381–3p in SD (Videtič Paska et al., 2022). Although hypothesis-free approaches have identified many candidate miRNAs involved in SITB, there has been little overlap between findings by different teams. Enrichment analyses of miRNAs identified by genome-wide approaches reveal involvement of biological pathways related to insulin resistance (Squassina et al., 2020), GABAergic and dopaminergic neurotransmission (Roy, Wang, et al., 2017), alternative splicing and neurotransmission/plasticity (Smalheiser

et al., 2012), and neurotrophin (Maussion et al., 2012). Finally, one study considered general patterns in up- or down-regulation averaged across all miRNAs, and found a global downregulation in miRNA expression to be associated with SD (Smalheiser et al., 2012). While miRNAs are often considered potential blood biomarkers, only one genome-wide study quantified miRNA expression from peripheral sources (lymphoblastoid cell lines) rather than postmortem brain (Squassina et al., 2020), and no study has quantified miRNAs from multiple tissue sources within the same individuals.

Four reports evaluated lncRNAs in SITB samples, one of which pursued a transcriptome-wide approach (Table 3; ancillary information in Supplementary Table S6). The remaining three studies selected candidate lncRNAs based on prior associations with SD (Punzi et al., 2019), association with MDD (Cui et al., 2017), and previous differential mRNA expression of a proximal gene (*MARCKS*; Punzi et al., 2014). Two reports (Punzi et al., 2014; Punzi et al., 2019) found elevated expression of *LINC01268* in DLPFC, with the more recent report attributing the elevation to violent SD specifically. Six lncRNAs that had previously been found to be downregulated in MDD were also downregulated in peripheral blood mononuclear cells of MDD patients with SI or SA (Cui et al., 2017). This result could suggest that there is some unique relationship between these lncRNAs and SITB above and beyond their correlation to MDD. Network analyses from the transcriptome-wide results, which reported 23 differentially expressed lncRNAs (Zhou et al., 2018), suggest involvement of immune signaling in suicide, especially that modulated by interferon.

3.10 | Histone modifications

Six studies considered histone protein alterations and their association with SITB (all SD), one of which involved a genome-wide approach (Misztak, Pańczyszyn-Trzewik, Nowak, & Sowa-Kućma, 2020); the remaining five studies investigated histones in candidate, prespecified regions of the genome (Table 4; ancillary information in Supplementary Table S7). Of the five candidate gene studies, which targeted the *Cx30*, *Cx43* (Nagy et al., 2017), *AMD1*, *ARG2*, *OAZ1*, *OAZ2* (Fiori et al., 2012), *SAT1* (Fiori & Turecki, 2011), *SMS*, *SMOX* (Fiori & Turecki, 2010), and *TrkB.T1* (Ernst, Chen, & Turecki, 2009) genes, none overlapped in targeted genes. All five candidate gene studies employed chromatin immunoprecipitation (ChIP) sequencing approaches. The genome-wide histone study (Misztak et al., 2020) identified downregulation of H3K9/14 ac and upregulation of HDAC3 and H3K27me2 in both frontal cortex and hippocampus of SD. All of the included reports measured histone proteins in postmortem brain tissue, with three of six being Brodmann Areas (BA) 8/9.

Histone studies, aside from considering group differences, also explored the downstream functional effects of this variation. For example, enrichment of H3K9me3 in *CX30* inversely correlated with gene expression (Nagy et al., 2017). The SD-associated increase in H3K4me3 in *OAZ1*, a regulator of polyamine biosynthesis, positively associated with expressions of this gene, consistent with the hypothesis of H3K4me3 transcriptional activation (Fiori et al., 2012). H3K27me3 within *SAT1*, a gene repression-related modification, did not relate to SD or gene expression (Fiori & Turecki, 2011), nor did H3K27me3 within *SMS* and *SMOX* genes (Fiori & Turecki, 2010). H3K27me3 was

enriched within the *TrkB* gene in BA10 of SD cases but not cerebellum, and a high degree of methylation was necessary for observable gene expression changes.

4 | DISCUSSION

There have been widespread reports of genetic and epigenetic alterations in SITB subjects, including variants within candidate genes, genome-wide associations, candidate and epigenome-wide methylation associations, noncoding RNAs, and histone protein modifications. We begin by discussing what can be learned from the existing literature with respect to the biological pathways involved in SITB outcomes. We then follow up our discussion with attention to methodological details that we believe will be important for future studies.

4.1 | Biological pathways implicated in SITB

It is important to note that, in most of medicine, single variant and candidate gene studies have often not replicated in GWAS. Suicide phenotypes are no exception. None of the most popular genes studied in suicide, such as monoamine genes and *BDNF*, have passed genome-wide significance thresholds in existing GWAS. The candidate gene literature on SITB is extensive, yet difficult to summarize outside of meta-analyses, which are prone to file drawer issues.

The SNP-based heritability estimates of SITB in the most recent GWAS are relatively low compared to other psychiatric disorders such as BD (20%; Mullins et al., 2021), MDD (9%; Howard et al., 2019), and alcohol dependence (9%; Walters et al., 2018), with estimates of 1%–3% in the Psychiatric Genomics Consortium (PGC) for SA (Mullins et al., 2019) and more recent GWAS estimating heritabilities from 5% to 7% for SA/SD (Mullins et al., 2022; Docherty et al., 2022). This SNP-based heritability is lower than the 30%–55% heritability for SA estimated from twin studies (Brent & Mann, 2005), which indicates that environmental factors likely play a critical role in the expression of the phenotype. So far, the vast number of PRS studies have largely explained very little variability in SITB outcomes. Higher impact rare variants, which are not indexed by common GWAS studies, may explain more variability when aggregated. Another possibility is that some of the heritability for suicidal behavior lies in epigenetic alterations influenced by experiences yet not captured by GWAS.

Indeed, many CpG positions and genomic regions have been found to be significantly different between suicide and nonsuicide subjects. Of these, two genes stand out as particularly well validated. *SKA2* (Spindle and kinetochore-associated protein 2) first emerged in an EWAS from Guintivano et al. (2014), and its association with suicidal outcomes has been documented across multiple levels since this first report (e.g., Clive et al., 2016; Kaminsky et al., 2015; Pandey, Rizavi, Zhang, Bhaumik, & Ren, 2016). Specifically, variation in *SKA2* function being related to suicidal outcomes is also consistent with a literature that implicates physiological stress response as a potential biomarker (Berardelli et al., 2020), given that the SKA2 protein is thought to interact with glucocorticoid receptor to modulate cortisol release (Boks et al., 2016). In addition to *SKA2*, hypomethylation near the *PSORS1C3* (Psoriasis Susceptibility 1 Candidate 3) gene has been identified in two EWAS

by the same research team (Murphy et al., 2017; Policicchio et al., 2020). While the function of this non-protein coding gene remains uncertain, there is evidence to suggest that it may be involved in immune signaling (Nair et al., 2006).

Noncoding RNA and histone studies in suicide are fewer in number. Generally, miRNA studies have not overlapped much, though the majority of studies did find significant differences in expression levels. One potential explanation is that the studies have varied in tissue location; however, even when comparing the two BA 9 studies (Pantazatos et al., 2017; Smalheiser et al., 2012) and the two BA 10 studies (Maussion et al., 2012; Smalheiser et al., 2014), there was no overlap in significantly differentially expressed miRNAs. Another possible explanation is the assay methodology, as substantial heterogeneity can be observed in Supplementary Table S5.

With respect to histone studies, most have been conducted in the context of specific candidate genes, with few efforts to replicate initial findings. Generally, these candidate histones have shown relation to candidate gene expression levels, although more effort will be needed in the future to establish the place of histones in suicide risk. Specifically, upon expansion of the number of novel candidates identified in unbiased approaches, it will be important to characterize these genes in terms of SNPs, methylation, and noncoding RNA/histone regulatory pathways.

One insight to convergence across units of analysis arises from biological pathway analyses. GWAS, EWAS, and noncoding RNA studies especially implicate nervous system development and function and immune function/inflammation in enrichment analyses. Previous studies using different approaches have already implicated immune dysfunction in suicide (e.g., Brundin, Bryleva, & Thirtamara Rajamani, 2017; Pandey, Rizavi, Bhaumik, & Ren, 2019), and findings may suggest an important role for (epi)genetic mechanisms in regulating these mechanisms. However, one limitation is that biological pathway analyses do not offer specific intervention targets and are often quite general. Further, although there might be a broader theme of (epi)genetically mediated neurocircuitry alteration and neuroinflammation in suicide, methodological variability renders these generalizations preliminary.

4.2 | Methodological considerations

Although there have been multiple reports of (epi)genomic findings associated with SITB outcomes, these results generally replicate poorly across studies. Furthermore, even in rare cases where a system is consistently implicated as dysregulated in suicide, methodological variability may be preventing definite conclusions. Here, we discuss some of the most prominent limitations of the current suicide (epi) genomics literature, which we pair with advice for future endeavors.

A primary consideration is the issue of measurement. The instruments used to establish the suicide-related phenotypes have greatly varied across studies. Importantly, some studies collapsed suicide phenotypes together, which may obscure important patterns given the substantial heterogeneity between phenotypes, and we observed an under-emphasis of suicidal thoughts (SI) compared to behaviors. Aside from being risk factors for behaviors,

suicidal thoughts themselves are sources of profound distress and despair. Therefore, understanding how the underlying biological mechanisms for SI might converge/diverge with those for behaviors such as SA and SD is an important aim for the field. Overall, there is an incomplete understanding of how much is shared vs. distinct between SITB outcomes, and attempts to address this question have been made by genetic correlations approaches within GWAS, although with limitations. For example, Campos et al. (2020) found a genetic correlation of 0.85 between “self-harm ideation” and “self-harm behavior”; however, this study did not define the “self-harm ideation” group as pure ideators (i.e., requirement of no self-harm behavior), so these groups likely overlapped.

Relatedly, past research has shown that the characteristics of the assessment tool are important in suicide risk assessment (Hom, Joiner, & Bernert, 2016). Of note, many studies included instruments with only one or a few items related to suicide, potentially leading to inaccurate estimates of suicide phenotypes. Even when only one particular phenotype is the outcome of interest, SITBs co-occur, and other outcomes (e.g., SA when studying SI) may be useful information for inclusion as covariates in analysis.

Measurement of (epi)genetic factors is also an issue. While genetic analyses are increasingly scalable and generally applicable across tissues, epigenetic projects require special attention to the source tissue. Methylation signature and noncoding RNA expression vary by cell and tissue type, with correlations between methylation in saliva, blood, and brain ranging from 0.85 to 0.90 (Braun et al., 2019). Even different regions of the brain can differ in gene expression and methylation patterns (Houston et al., 2013). The type of SITB analyzed may be confounded with tissue source, as brain tissue is only accessible in SD samples and saliva is more commonly assessed *in vivo*. There is emerging work on neuron-derived extracellular vesicles (exosomes) as potential peripheral markers of neural function (Saeedi, Israel, Nagy, & Turecki, 2019), but our review did not capture any such studies on SITB (epi)genetics.

Furthermore, analyses on bulk tissue can yield results which are confounded, as methylation is known to depend significantly on cell type composition (Jaffe & Irizarry, 2014). Therefore, while analysis on bulk tissue may be useful for identifying preliminary “hits”, it is advised that follow-up analyses either physically separate cell type fractions or computationally account for variation (Guintivano, Aryee, & Kaminsky, 2013). Moreover, the 5-hydroxymethylcytosine (5hmc) epigenetic alteration is typically indistinguishable from 5-methylcytosine (5mc) by most popular analytic methods (Kumar, Chinnusamy, & Mohapatra, 2018), and there is evidence that 5hmc may be important and provide complementary information in the context of psychiatric disorders (Madrid, Papale, & Alisch, 2016).

Other issues are related to practices regarding the participant sampling. Common reasons to exclude participants in the reviewed studies included presence of a neurological injury/disorder, substance use, and intellectual disability. While these criteria are usually in place to facilitate data collection and analysis, they may inadvertently eliminate important participants. As an example, there is a substantial overlap between substance use and suicide risk (Esang & Ahmed, 2018), and also the possibility that implicated gene networks are dependent on the presence of substance use (Cabrera-Mendoza et al., 2020). Likewise,

neurological injuries such as traumatic brain injuries are known risk factors for SD (Teasdale & Engberg, 2001). Moreover, most studies, especially post-mortem, focused on predominantly male samples. Even when sex was provided as a demographic variable and controlled for in analyses, it was rarely explicitly focused on as a source of biological variation. Overall, we noted little concern for sex differences in the existing studies of suicide (epi)genetics, which runs counter to well-established evidence that many aspects of SITB differ by biological sex (Bachmann, 2018).

Another common demographic limitation is age. Most research studies reported relatively high mean ages, and only one GWAS (no EWAS) focused on youth. Suicide is the second leading cause of death for ages 10–34 (CDC, 2020), yet developmental approaches to the (epi)genetics of suicide are understudied. This observation is strengthened by a paucity of longitudinal studies, which might be especially important for epigenetic studies (i.e., delineating whether dynamic epigenetic markers are predictors vs. correlates of suicidal states). No EWAS or transcriptome-wide noncoding RNAs studies available to date have included prospective predictive analyses. From a developmental systems perspective, the interplay between genes and the environment varies extensively by context, such that we cannot be confident that an interaction present in an older age group will explain a similar amount of variance in youth (D. S. Moore, 2016). A positive example by candidate gene studies is consideration of environmental interactions. While it is likely that the effect of a single gene is not completely moderated by a single type of experience (e.g., child maltreatment), these studies pave the way for considering how genome-wide liabilities are dependent on the context; risk effects might only be seen in conditions which are lacking in protective buffers. Novel approaches of GWAS (genome by environment-wide interaction studies; GxEWIS) and polygenic scores by environment interactions are interesting, although preliminary, in studies of suicide.

We identified only one GWAS of SITB in youth (Brick et al., 2019). It is unclear whether the risk variants identified in adult samples are similar to those for youth, considering that there is evidence that the nature of SITB is age- and development-dependent (Parellada et al., 2008), and that development entails substantial neurobiological reorganization (Casey, Heller, Gee, & Cohen, 2019). There is therefore potential in the literature for studies aiming to validate PRS of adult SITB in youth populations to determine if they explain a similar amount of variability in the youth SITB phenotypic outcomes. An interesting body of work is emerging testing adult-based polygenic scores in child samples (Daskalakis et al., 2021; Joo et al., 2022; Lee et al., 2021); these studies have generally shown that adult-based polygenic scores for complex traits such as psychiatric disorders do predict SITB outcomes in childhood, albeit weakly. However, none of these studies so far have tested polygenic scores for SITB and explained variance in children.

Ancestry is also a primary consideration in psychiatric genetics studies across all outcomes. Deploying PRS in target samples which markedly deviate from the base sample’s ancestral composition can bias performance and amplify inequities (Martin et al., 2019). Considering this issue in the context of suicide, the most well-powered unbiased studies, such as the large-scale PGC and ISGC consortia, are based of predominantly European ancestries. The added challenge of suicide death as a low base rate phenomenon means that it will

take intentional action to ensure that suicide genetics studies are representing all groups, especially considering that suicide rates cut across demographic lines and are particularly concerning in certain racial/ethnic groups such as Black and Hispanic people (Sheftall et al., 2022; Silva & Van Orden, 2018), who may currently be poised to benefit least from the findings of genetics studies. There are emerging approaches that may assist the field in improving PRS performance across ancestries, such as in highly admixed samples (Marnetto et al., 2020).

Aside from the overall composition of the sample, the issue of comparison within the sample is also important. Oftentimes, studies on suicide (epi)genomics implement case–control designs which require a reference group to compare the suicidal group against. Case–control studies varied widely on the selection of the reference group, and in many cases members of “suicide” groups were compared to nonpsychiatric controls. Of note, suicide and psychiatric diagnoses such as MDD and anxiety often cooccur (Nock, Hwang, Sampson, & Kessler, 2010). Furthermore, as demonstrated in the heterogeneity of suicide samples identified in the extant literature, this comorbidity is complex and not limited to a single psychiatric disorder. When a group of suicidal patients who are also confirmed for a psychiatric diagnosis are compared to a group without psychiatric diagnosis or suicidality, it becomes impossible to conclude whether the observed difference is attributable to the diagnosis or the suicidality *per se*. It would therefore be scientifically best to compare suicide cases to psychiatric controls who are as matched on diagnosis as possible, but this could be a challenge, particularly in postmortem studies, given that it could be difficult to amass enough samples from psychiatric controls which did not die by suicide. Furthermore, it could be anticipated that regardless, people with a psychiatric diagnosis who progress to suicidal behavior are experiencing a unique course of the disorder (Melhem et al., 2019), and psychiatric comorbidities further challenge group matching.

In studies of postmortem tissue in suicide decedents, a consideration of cause of death might also be necessary. One possibility is that biological differences between suicide decedents, who often die of otherwise atypical means such as shooting or hanging, and controls who die of natural causes (often required to have minimal to no medical intervention at the time of death) are confounded with differences in suicidality. Cause of death may therefore drive observed biological alterations. This issue is difficult to navigate as the manner of death could never be exactly matched between groups, but there are some examples in which it might be necessary to impose restrictions or more stringent controls, such as perhaps in cases in which suicide groups are overrepresented with drug overdose as cause of death, which is expected to alter biological networks (e.g., Moretti et al., 2019).

A particular question relevant to psychiatric diagnosis and SITB merits special consideration. Specifically, while self-injurious outcomes have been considered transdiagnostic, in that they are observed across a wide range of psychiatric phenotypes rather than being secondary symptoms of specific constellations (as has some-times been thought for MDD), there might also be some degree of disease type specificity. For example, suicide in BD has been suggested to exhibit some unique underlying mechanisms (Zakowicz et al., 2021). Genetic correlations approaches and PRS studies that were included in this review have associated SITB to some extent with many varied psychiatric disorders, but

the question still remains whether in further studies it is advantageous to stratify SITB by psychiatric diagnosis (e.g., suicide in BD, suicide in SCZ, suicide in MDD) vs. take a wholly transdiagnostic, or diagnosis-blind, approach which hypothesizes that the underlying mechanisms for SITB are largely resistant to other aspects of individual constitution.

Aside from these methodological challenges, there are also broader areas which remain underemphasized in suicide (epi)genetics and might be promising frontiers for further investigation. As an example, no genome-wide or epigenome-wide studies explicitly considered nonsuicidal self-injurious behaviors, also known as NSSI, as an outcome, although in some cases the more ambiguous definition of deliberate self-harm (which may include SA) was explored. NSSI is self-directed tissue destruction with a clear lack of suicidal intent, and its prevalence has been measured to be 17.2% in adolescents (Swannell, Martin, Page, Hasking, & St John, 2014). Moreover, NSSI has been shown to be a potent risk factor for SA (Chesin et al., 2017). Theoretically, it might be expected that biological mechanisms underlying NSSI and SA overlap given that both involve intentional damage to one's own tissue, but there are differences in the functional significance of the act as well as the general severity of the injuries. NSSI is often employed as a tool to regulate emotions in times of distress (Andover & Morris, 2014). There are no large-scale, unbiased studies of (epi)genetics of a rigorously defined NSSI, although some studies analyzed deliberate self-harm separately from SA (e.g., Russell et al., 2020). NSSI studies included were often focused on candidate genes and narrow in scope, but emerging polygenic scoring studies are beginning to consider NSSI as an outcome. It may be especially fruitful to explore differential polygenic score associations between NSSI and other SITB outcomes. Currently, research is limited in the ability to delineate the similarities and differences between NSSI and other suicidal outcomes with respect to (epi)genetic patterns, especially considering that NSSI often, but not always, evolves to SA (Plener, Schumacher, Munz, & Groschwitz, 2015).

Another promising future direction for the field is within-person design. Case–control studies often approach suicidality as static traits as opposed to thoughts and behaviors which fluctuate. Genetic main effects may be sensitive to age given that a gene's relationship with the phenotype depends on the environmental context. For epigenetics studies, a consideration of within-person change may be critical, as epigenetic pathways are sensitive to environmental variation even in the short run. There is also potential in integrating studies of suicide genetics and epigenetics with other metrics in longitudinal studies, including gene expression (e.g., Cabrera-Mendoza, Martínez-Magaña, et al., 2020; Romero-Pimentel et al., 2021), neuroimaging, hormone assay, behavioral measure, self-report, etc., to better understand the multi-level crosstalks and reciprocal interactions in the development of SITB within individuals (e.g., Moore, Sawyers, Adkins, & Docherty, 2018). While there are no robust animal models of suicide, research in animals may also be important in characterizing biological pathways hypothesized to relate to suicide risk. For instance, animal outcomes can be considered in terms of endophenotypes such as impulsivity and aggression (Roy & Dwivedi, 2021).

Finally, treatment studies could provide insight to the underlying (epi)genetics of suicide, as well. For example, treatments under study for potential anti-suicidal effects (e.g., ketamine;

Witt et al., 2020) could also be studied in terms of their coordinated effects on genome-wide DNA methylation and SITB within person, and treatment studies need not be limited to pharmacogenetics given preliminary evidence that psychotherapeutic approaches also modulate (epi) genetic pathways (Jiménez et al., 2018). Identifying the downstream effects of emerging anti-suicidal treatments might reveal novel candidate pathways for suicidality.

5 | CONCLUSION

(Epi)genetic alterations have been noted across a wide spectrum of SITB, but convergence is limited both within and across units. Results suggest that while a significant amount of progress has been made in charting out the basic pathophysiology of SITB, there still remains the need to validate initial findings and begin to build a larger framework for understanding the biological patterns that are associated with SITB. Some of the challenges in building this framework include methodological limitations, as well as underemphasis of certain issues and approaches. However, we believe that there is great potential for the field of suicide (epi)genomics to better explain SITB as a multi-level phenomenon and ultimately improve preventive intervention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

S.M. would like to thank Drs. Bonnie Klimes-Dougan, Ph.D., and Kathryn Cullen, M.D., for providing him with foundational knowledge in suicide research. G.R.F is funded by the National Institute of Mental Health (NIMH, 5K01MH121580) and by the American Foundation for Suicide Prevention (AFSP, YIG-0–066-20).

Funding information

American Foundation for Suicide Prevention, Grant/Award Number: YIG-0–066-20; National Institute of Mental Health, Grant/Award Number: 5K01MH121580

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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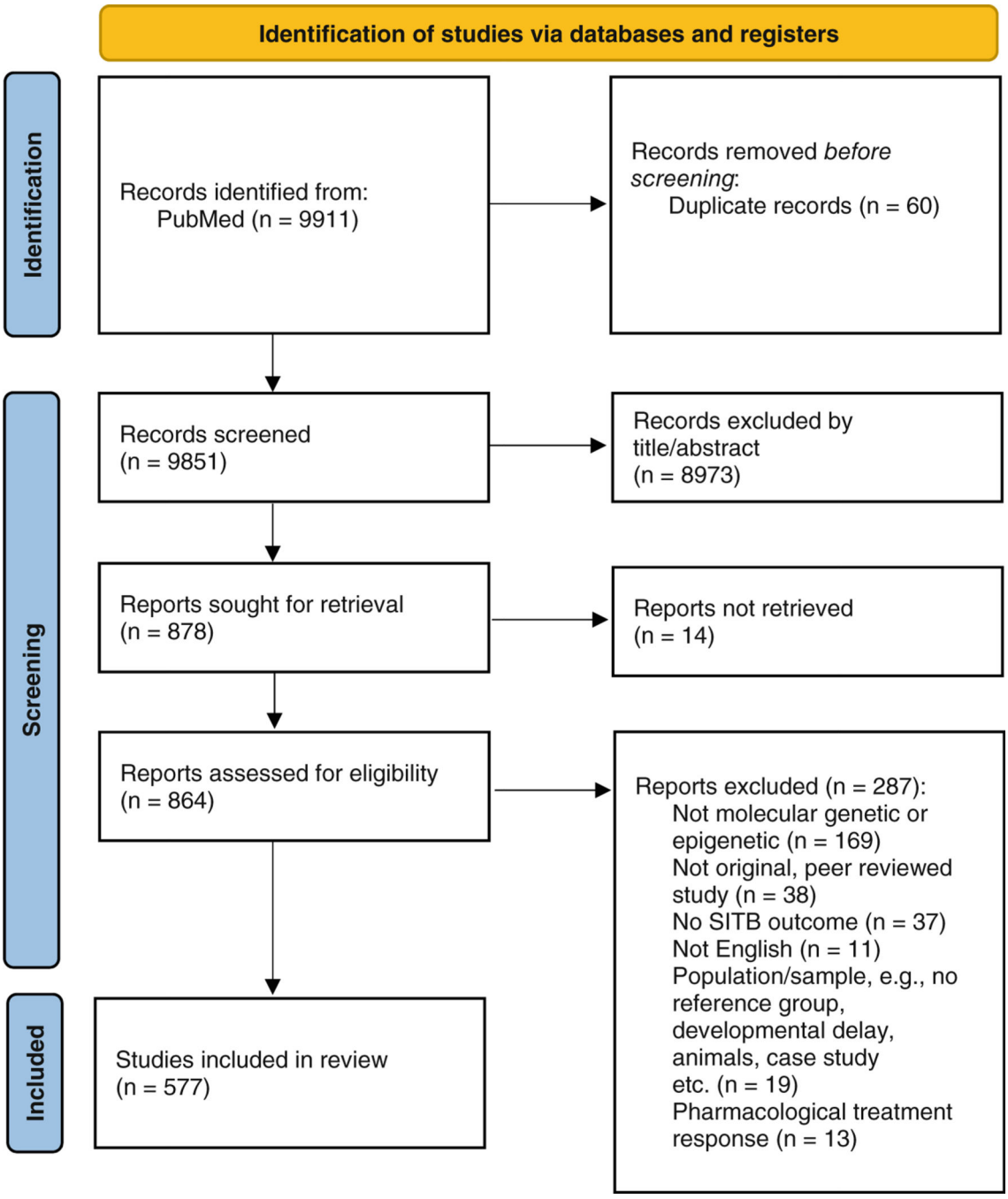

FIGURE 1.
PRISMA flow diagram for this systematic review.

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TABLE 1

Genome-wide association studies of suicidality which report differentially represented single nucleotide polymorphisms (SNPs)

SNPs	Gene-level results	Suicidal population	Suicide outcome	Ancestry	Reference
Pan-ancestry 2 *loci* on CHR 20 *(TSHZ2)* and CHR 1 *(SPATA17)* **EUR** rs4858820 (*ATRIP*) **AFR** rs56817213 (*TSHZ2*) **AS** rsl99633759, rs77378519, rs57790277 (*FBN1*) **HISP** rs34173987 (*CACNA2D3*), rs6907713 (*MIR3144, TBC1D32*), rs9596440 (*GUCY1B2*)	*SPATA17, DRD2*	*N* = 14,089 SA+ veterans (age M = 52.01, 15% F)	SA	EUR, AFR, AS, HISP	Kimbrel et al., 2022
NS (GxEWIS)	NR	*N* = 74,482 with range of self-harming responses (age M = @56, 52% F)	SH	White (British)	Li et al., 2022
Overall rs62474683 (CHR 7), rs71557378 *(MHC)* **Conditioning on MDD** rs62474683 (CHR 7) **Replication** rs62474683(CHR 7)	*PDE4B, SEMA6D, BTN2A1, DCC, LUZP2, TIAF1, FAM19A5*	*N* = 29,782 SA+/SD+ (age M = NR, %F NR)	SA/SD	EUR, AFR, EAS	Mullins et al., 2022
Overall NS **Suggestive** Within *STPG2, MCUR1, ARHGAP26, USP6NL*, and *TSPEAR* **Targeted replication of past GWAS** NS	**Overall** NS **Suggestive** *GFRA1, STPG2, ACE, IQCA1, DNASE2B*	*N* = 3,506 combined MDD/BD cohort members (age M = @45, 69% F)	Ordinal suicidality	EUR	Zai et al., 2021
Overall NS **Suggestive** rs2767403 *(AOPEP)*	NR	*N* = 1,155 BD patients (age M = 41.69, 42% F)	Ordinal suicidality	90% White/ Caucasian	Lybech, Calabró, Briuglia, Drago, & Crisafulli, 2021
Overall rsl2589041 *(RP6–65G23.1)* **Male-specific** rs2367967 *(CWC22)*, rs72619337 *(RP11–352E6.1)* and rs6854286 *(R P11–145E17.2)* **Female-specific** rsll8118557 *(CHST14)*	*HEPACAM, CNTN5, PSMD14, HEPN1*	*N* = 123,633 participants (age M = NR, %F NR)	Ordinal suicidality	EUR	Wendt et al., 2021
NR	**EUR** *LCAT, TSNAXIP1, CENPT, PARD6A* **AFR** *HGF* *SI in the context of substance use	*N* = @10,000 Yale Penn cohort participants (âge M = NR, %F NR)	SI	EUR, AFR	Polimanti et al., 2021

SNPs	Gene-level results	Suicidal population	Suicide outcome	Ancestry	Reference
SH rs567805973 (CHR 9) **SHI** rs4865733, rs7721698 (CHR 5)	**SH** *LING02, DCC, FBX02, WRB* **SHI** *SYT14, RPP14, FAM172A, SEMA3D, DCC, DDX27, ZNFX1*	*N* = 6,872 SH+ (total sample age M = 55.9, 69% F) *N* = 23,192 SHI+(total sample age M = 55.9, 65% F)	SH (includes SA), SHI (self-harm ideation)	EUR	Campos et al., 2020
Overall NS **Controlled for mental disorder** rs4809706 *(PREX1),* rs4810824 (CHR 20), and rs6019297 (CHR 20)	NR	*N* = 6,024 SA+ (age M = 24.3, 69% F)	SA	Born in Denmark	Erlangsen et al., 2020
rs34399104, rs35518298, rs34053895, rs66828456 *(UNC00348);* rs35502061 *(.SOGA2P1),* rs35256367 *(ATP10A)*	NR	*N* = 3,413 SD+ (age M = NR, %F NR)	SD	EUR	Docherty et al., 2020
NS	NR	*N* = 510 SI/SHI+ (age M = NR, 100% F)	SI/SHI	Peruvian (76% mestizo)	Shen et al., 2020
Overall NS **Suggestive** rs4863321; rs3844582 *(MSH2)*	**Overall** NS **Suggestive** *TPH2*	*N* = 122 MDD+/SA+ (age M = 42.2, 78% F)	SA	EAS	Rao et al., 2020
SH NS (193 suggestive concentrated on CHR 1) **SA** NS (15 suggestive)	NR	*N* = @6,711 SH+ (age M = NR, % F NR) *N* = @3,470 SA+ (age M = NR, % F NR)	SH, SA	EUR	Russell et al.,2020
Overall NS **Suggestive** rsl48870214, rsl46826470 *(SEMA3A)*	NR	*N* = 3,572 epidemiological youth (17% SI, age M = 13.7, 50% F)	SI	EUR	Brick et al., 2019
NR	*SCARA5*	*N* =37 SA+ (age M = 35.55, 46% F)	SA	Mexican	González-Castro et al., 2019
AFR rs683813 *(ARNTL2-AS1);* rs72740082 *(CTXND1, LINC01314, FAH);* rsll876255 *(CHR 18)* **EUR** 34 significant SNPs clustered on *LDHB* *no significant SNPs replicated in independent sample	**AFR** *NARG2* **EUR** *LDHB, PGBD5, PHLDB2*	*N* = 6,320 combined cohorts (age M = @40, @45% F)	SA severity	AFR, EUR	Levey et al., 2019
Overall NS **Suggestive** SNPs on *GRM1* and *CTPS2***Replication of past GWAS** rs7989250	NR	*N* = 746 SD+ (age M = @52, 34% F)	SD	EAS	Otsuka et al., 2019
Overall NS	NR	*N* = 6,569 psychiatric SA+(age M = NR, 60% F)	SA	EUR	Mullins et al., 2019

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SNPs	Gene-level results	Suicidal population	Suicide outcome	Ancestry	Reference
MDD cohort rs45593736 *(ARL5B)* **BD cohort** chr4_23273116_D (LOC105374524) **SCZ cohort** NS **MDD/BD** 10 SNPs led by rsl38689899 *(IWS1, MY07B)*, rs28591567 *(LOC105374524)* *no significant SNPs replicated in independent sample					
Ordinal suicidality rs62535711 *(ZCCHC7);* rs598046 *(CNTN5);* rs7989250 (CHR 13) ***DSH* and ordinal SI/SA** *NS*	**Ordinal suicidality** *CNTN5, ADCK3/C,OQ8A, CEP57, FAM76B, DCC* **DSH** *EIF4A1, SENP3, DCC* **Ordinal SI/SA** *CDKAL1, CNTN5, ADCK3/COQ8A*	*N* = 122,935 UK Biobank cohort members (age M = NR, @60% F)	Ordinal suicidality	NR	Strawbridge et al., 2019
NR	207 genes	*N* = 216 SD+ from 43 high risk extended families (age M = NR, % F = NR)	SD	Predominantly northern EUR	Coon et al., 2020
Overall, SA and SI NS **Suggestive, SA** rs11762112 (CHR 7), rs79324256 *(KCNMB2)*, rs7931096 *(LUZP2)* **Suggestive, SI** rs2613142 (CHR4) **Replication of prior GWAS** Nominally significant SNPs within *ABI3BP*(Perlis et al., 2010)	NR	*N* = 122 US military veterans with lifetime SA (age M = 34.7, 41.8% F) *N* = 138 US military veterans with SI (age M = 36.11,19.57% F)	SI, SA	@50% non-Hispanic white	Kimbrel et al., 2018
NS	Most robust *RETREG1 (FAM134B), GSN, GNAS, CACNA1D*	*N* = 660 offspring with severe SA (age M = 24.2, 49% F)	SA	Cases 97.6% Russian/Ukrainian, controls; 99.5% Russian/Ukrainian	Sokolowski, Wasserman, & Wasserman, 2018
AFR rs144662392 **EUR** SNP cluster on *MRAP2, CEP162* **Replication of prior GWAS** NS	NS	*N* = 473 US military personnel with SA history (age M = NR, % F NR)	SA	AFR, EUR	Stein et al., 2017
Overall NS **Suggestive** rsl2895203 *(FUT8);* rs7897059 *(CAMK1D*, interaction with child trauma)	NR	*N = 53 SCZ+/SA+(age M = 45.3, 34.5% F)*	*SA*	@70% EUR	Bani-Fatemi, Graff, Zai, Strauss, & de Luca, 2016
Overall, SA/SD NS **Suggestive, SA/SD** 5 SNPs on *STK3, ADAMTS14, PSME2*, and *TBX20*	NR	*N* = 577 SD+/SA+ (combined cohorts; age M = NR, %F NR)	SA/SD (SI secondary)	Caucasian	Galfalvy et al., 2015

SNPs	Gene-level results	Suicidal population	Suicide outcome	Ancestry	Reference
Overall, SI NS **Suggestive, SI** 5 SNPs on *PLCB1.FAM5C*					
Overall, severity NS **Suggestive, severity** Region 8q12 *(LINC00968, PENK)*, region 10p11.2 *(CCDC7, C10orf68, ITGB1)* **Overall, SA in BD** NS **Suggestive, SA in BD** Region 8q12-q21 *(IL-7)*, region 18q22 *(TMX3)* **Replication of prior SA in BD GWAS** (Willour et al., 2012) NS	NR	*N* = 959 BD+ patients (age M = @40, @60% F)	Ordinal suicidality, SA in BD	NR	Zai et al., 2015
Overall NS **Suggestive** rs9351947 *(KCNQ5*; CHR 6), rsl7173608 *(RARRES2*; CHR 7), rsl7387100 *(PROM1*; CHR 4), rs3781878 *(NCAM1*; CHR 11)	NS (failed to replicate *ABI3BP*; Perlis et al., 2010)	*N* = 426 SA+ (total sample age M = 47.6, total sample 70% F)	SA	EUR	Mullins et al., 2014
rsl926123 (not annotated)	NR	*N* = 68 SD+ (age M = @43, 38% F, n = 45 mood disordered)	SD	Caucasian	Galfalvy et al., 2013
Overall 2,507 significant SNPs, led by rs300774 (2p25) **Male-specific** Most suggestive, rs5752388 (*AK026502*) **Female-specific** Most suggestive, rsl0170138 *(LRRTM4)* *no SNPs replicated in independent sample; in cross-sample meta-analysis, rs300774 (2p25) thresholded significance	NR	*N* = 1,201 BD+/SA+ (age M = NR, %F NR)	SA	NR	Willour et al., 2012
Overall, SSU and SA NS **SSU, suggestive** rs4751955 (*GFRA1*) **SA suggestive** rs203136 *(KIAA1244)* *not replicated in independent sample	NR	*N* =2,023 MDD+(251 SA) (age M = 46.3, 73% F)	Ordinal suicidality, SA	NR	Schosser et al., 2011
Overall, SA in BD NS **Overall, SA in MDD** s2576377 *(ABI3BP)* **Suggestive, SA in BD** rsl466846 (not annotated) *none replicated in independent sample	NR	*N* = 1,295 BD+/SA+ (age M = NR, %F NR) *N* = 176 MDD+/SA+ (age M = NR, %F NR)	SA	NR	Perlis et al., 2010

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Abbreviations: %F, percent female; @, estimated; AFR, African; age M, average age; AS, Asian; BD, bipolar disorder; BSSI, Beck Scale for Suicide Ideation; CHR, chromosome; C-SSRS, Columbia-Suicide Severity Rating Scale; DSH, deliberate self-harm; EAS, East Asian; EUR, European; GxEWIS, genome by environment wide interaction study; HISP, Hispanic; hsnp2, SNP-based heritability; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MDD, major depressive disorder; MINI, mini international neuropsychiatric interview; NR, not reported; NS, not significant; PHQ-9, Patient Health Questionnaire; SA, suicide attempt; SB, suicidal behavior; SCAN, suicide crisis assessment nurse; SCZ, schizophrenia; SD, suicide death; SH, self-harm; SHI, self-harm ideation; SI, suicide ideation; SIS, suicide intent scale; SNP, single nucleotide polymorphism; SSADA, semi-structured assessment for drug dependence and alcoholism; SSU, SCAN continuous suicidality score; UKB, UK Biobank.

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TABLE 2

Epigenome wide association studies of suicidality which report differentially methylated regions (DMRs) and positions (DMPs)

DMRs	DMPs	Suicidai population	Tissue	Suicide outcome	Ancestry	Reference
Overall 4,430 significant DMRs with > ± 0.01 fold change, led by *ZFP57* hypermethylation **Validation** *ADYC9* hypomethylated in bisulfite sequencing	NR	*N*=25 SD+ (age M = 30, 0% F)	BA 9	SD	Mexican	Romero-Pimentel et al., 2021
PFC *WRB* hypomethylated, *PSORS1C3, LGALS1* **CER** *CERC2* hypermethylated, *SLC44A4, WWTR1, MED13L* *results largely hold after controlling for psych, disorder	**PFC** cg00963169 *(ELAVL4,* hypomethylated) **CER** cgl4392966 *(PUS3)* hypomethylated, cgl7855963, cg25590492, cgl2284382, cgl0757978, cg04525580	*N*= 137 SD+ (age M = NR, %F NR)	PFC, CER	SD	NR	Policicchio et al., 2020
Overall NS **Suggestive** *SMPD2* distal promoter hypermethylation	**Overall** NS **Suggestive** cg06121808 (*SLC20A1,* hypermethylated)	*N*= 19 SCZ+/SI+ (age M = 44.58, 37% F)	WBC	Current SI	White EUR	Bani-Fatemi et al., 2020
Overall 330 DMRs (55.5% hypermethylated); none survived multiple test correction Suggestive *JRK/PSCA* hypermethylated	**Overall** **NS** **Suggestive** chrXp21.3 (intergenic, hypomethylated)	*N*=23 BD+/SD+ (age M = 45, 44% F)	BA 46	SD	Caucasian	Gaine et al., 2019
NR	**BA 9** 106 DMPs >25% methylation q-value <0.01, (63 hypo, 43 hyper, 86% intergenic, led by cg on *PLEKHA4*) **HIPP** 2,734 > 25% methylation q-value <0.01, (2,406 hypo, 328 hyper, 71% intergenic, led by cg on *AASDH).*	*N*= 9 SD+ (age M = 50.56 for BA 9, 53 for HIPP, 0% F)	BA 9, HIPP	SD	Slovenian	Kouter, Zupanc, & Videtič Paska, 2019
Overall NS **Suggestive** *PBK* hypomethylated	**Overall** NS **Suggestive** cgl9647197 *(CCDC53,* hypomethylated)	*N*= 54 SCZ+/SA+ (age M = NR, % F NR)	WBC	SA	EUR	Bani-Fatemi et al., 2018
5′ UTR *MPP4* hypomethylated, exon 1 *NUP133* hypermethylated, intron 3 *TBC1D16* hypomethylated	**Overall** NS **Suggestive** Leading NSHORE chr17:77965805–77,966,296	*N*= 24 BD+/highest suicidality (age M =48.1, %FNR)	WBC	SB (composite SA and SI)	Northern/ Western EUR	Jeremian et al., 2017

DMRs	DMPs	Suicidai population	Tissue	Suicide outcome	Ancestry	Reference
BA 25 *DNAJC15*, exon 3 *SNAI3* **BA 11** NS Cross tissue *PS0RS1C3* promoter hypomethylated, third intron of *TAPBP*,promoter region *ATP5G2* **Validation and replication** *PSORS1C3* hypomethylated	**Overall, BA 11 or BA 25** NS	*N*=20 MDD+/SD+ (age M = @49, @75% F)	BA 11, BA 25	SD	NR	Murphy et al., 2017
Overall 115 DMRs (59% of intragenic hypomethylated); led by chr10 and X chromosome **Validation** *GRIK2* hypomethylated, *BEGAIN* hypermethylated	NR	*N*=22 SD+/low astrocytic mRNA expression (age M = NR, 0% F)	PFC	SD	NR	Nagy et al., 2015
NS	NS	*N*= 6 SD+ (age M = 42.5, 0% F)	BA 10	SD	Caucasian	Schneider, el Hajj, Müller, Navarro, & Haaf, 2015
NR	**Overall** cg24533989 *(ATP8A1)*, cgl3989295 *(SKA2)*, cgl5918259 *(LOC153328)*, cgl7106415 *(KCNAB2)* **FACS sorting + replication** cgl3989295 (*SKA2*) nominally sig. In neuronal and nonneuronal	*N*= 7 SD+ (age M = NR, %F NR)	PFC	SD	Caucasian	Guintivano et al., 2014
Overall 273 hypermethylated probes, 93 hypomethylated probes	NR	*N*= 46 SD+ (age M = 38.8, 0% F)	HIPP	SD	French Canadian Caucasian	La bonté et al., 2013

Note: Studies which report genome-wide methylation percentage levels only are not included in the table, although they are discussed in text. Relative methylation (hypo/hyper) is referenced against the nonsuicidal group.

Abbreviations: @, estimated; Age M, mean age; BA, Brodmann area; BD, bipolar disorder; BSSI, Beck Scale for Suicide Ideation; CER, cerebellum; CSSRS, Columbia Suicide Severity Rating Scale; DMP, differentially methylated position; DMR, differentially methylated regions; EUR, European; FA, forensic autopsy; FACS, fluorescence activated cell sorting; HC, healthy control; HIPP, hippocampus; MDD, major depressive disorder; meDIP, methylated DNA immunoprecipitation; NR, not reported; NS, not significant; PA, psychological autopsy; PFC, prefrontal cortex; SCAN SSU, schedules for clinical assessment in neuropsychiatry suicidality score; SB, suicidal behavior; SCZ, schizophrenia; SD, suicide death; SI, suicide ideation; WBC, white blood cell.

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TABLE 3

Noncoding RNA (ncRNA) studies of SITB, including microRNA (miRNA) and long noncoding RNA (lncRNA) expression profiling

ncRNAs	Suicidal population	Tissue	Suicide outcome	Ancestry	Reference
miRNAs					
Overall NS **Suggestive** hsa-miR-4516 (↑), hsa-miR-381–3p (↑)	*N* = 20 SD+ (age M = 44.6, 0% F)	BA10	SD	NR	Videtič Paska, Alič, Zupanc, & Kouter, 2022
Overall, LCL miR-4286 (↑), miR-337–3p (↓) **qPCR validation, LCL** miR-4286 (↑) **BA 24** miR-4286 (↓, nonsignificant)	LCL *N* = 7 BD+/SD+ (age M = 40.6, 43% F) **BA 24** *N* =12 BD+/SD+ (age M = NR, %F NR)	LCL BA 24	SD	**LCL** Sardinian **BA 24** French Canadian	Squassina et al., 2020
DLPFC miR-19a-3p (↑), miR-20a-5p (↓), miR-92a-l-3p (↓) **PBMC** miR-19a-3p (↑)	**DLPFC** *N* = 43 SD+ (age M = @40, 16% F) **PBMC** *N* = 12 MDD+/SI+ (age M = 40.51, 50% F)	DLPFC PBMC	SD SI	**DLPFC** French Canadian **PBMC** 58% African American, 42% white	Wang, Roy, Turecki, Shelton, & Dwivedi, 2018
Overall NS	*N* = 9 MDD+/SD+ (age M = 59.2, 33% F)	BA 9	SD	NR	Pantazatos et al., 2017
Overall miR-17–5p (↓), miR-20b-5p (↑), miR-106a-5 (↑), miR-330–3p (↑), miR-409-bp (↑), miR-541–3p (↑), miR-582–5p (↑), miR-890 (↑), let-7 g-3p (↓), miR-99b-3p (↑), miR-550–5p (↑), miR-1179 (↑), miR-11197 (↑)	*N* = 9 MDD+/SD+ (age M = 45.22, 33% F)	LC	SD	NR	Roy, Wang, et al., 2017
Overall miR-34c-5p (↑), miR-139–5p (↑), miR-195 (↑), and miR-320c (↑)	*N* = 15 MDD+/SD+ (age M = 37.9, 0% F)	BA 44	SD	French Canadian	Lopez et al., 2014
Overall miR-152 (↓), miR-181a (↓), miR-330–3 (↓), miR-34a (↓), miR-224 (↓), miR-376a (↑), miR-133b (↓), miR-625 (↑)	*N* = 18 psychiatric SD+ (age M = NR, % F NR)	BA10	SD	NR	Smalheiser et al., 2014
Overall miR-142–5p (↓), miR-137 (↓), miR-489 (↓), miR-148b (↓), miR-101 (↓), miR-324–5p (↓),miR-301a (I), miR-146a (↓), miR-335 (↓), miR-494 (↓), miR 20b (↓), miR-376a (↓), miR-190 (↓), miR-155 (↓), miR-660 (↓), miR-130a (↓), miR-27a (↓), miR-497 (↓), miR-10a (↓), miR-20a (↓), miR-142–3p (↓)	*N* = 18 MDD+/SD+ (age M = 40.0, 11% F)	BA 9	SD	NR	Smalheiser et al., 2012
Overall hsa-miR-491–3P (↑),hsa-miR 185* (↑) **RT-PCR validation** hsa-miR 185* (↑)	*N* = 4 SD+with low TrkB-T1 (age M = 31, 0% F)	BA10	SD	French Canadian	Maussion et al., 2012
IncRNAs					

ncRNAs	Suicidal population	Tissue	Suicide outcome	Ancestry	Reference
Overall *LINC01268*/LOC285758 (↑); driven by violent SD	*N* = 127 SD+ (age M = @43, 35% F, 77 violent)	BA 9, BA 46	SD	Caucasian	Punzi et al., 2019
Overall 23 (15 ↑) **Validated with qPCR** CTC-487 M23.5 (↓), RP11–273G15.2 (↑), RP11–326I11.3 (↓), RP1–269 M15.3 (↑), RP11–96D1.10 (↓), CTD2647L4.4 (↓), RP11–453F18 B.l (↓), RP11–434C1.1 (↑), ZNF833P (↑)	*N* = 26 MDD+/SD+ (age M = 42.23, 27% F)	rACC	SD	NR	Zhou, Lutz, Wang, Ragoussis, & Turecki, 2018
SI TCONS_00019174 (↓), ENST00000566208 (↓), NONHSAG045500 (↓), ENST00000517573 (↓), NONHSAT034045 (↓), and NONHSAT142707 (↓) **SA** Same six IncRNAs (↓)	*N* = 57 MDD+/SI+ (age M = NR, %F NR) *N* = 19 MDD+/SA+ (age M = NR, %F NR)	PBMC	SI, SA	Chinese	Cui et al., 2017
Overall LOC285758/LINCQ1268 (↑)	*N* = 16 SCZ+/VSD+ (age M = NR) = NR, %F	DLPFC	Violent SD	59% Caucasian	Punzi et al., 2014

Abbreviations: %F, percent female; @, estimate; ↑, upregulated; ↓, downregulated; AD, Alzheimer's Disease; age M, mean age; BA, Brodmann Area; BD, bipolar disorder; CID-I/P, Structured Clinical Interview for DSM-IV, patient version; DLPFC, dorsolateral prefrontal cortex; FA, forensic autopsy; HAMD-24–24-item, Hamilton Rating Scale; HC, healthy control; LC, locus coeruleus; LCL, lymphoblastoid cell line; Li+, lithium medication; lncRNA, long noncoding RNA; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; miRNA, microRNA; NR, not reported; NS, not significant; PA, psychological autopsy; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; qRT-PCR, quantitative reverse transcription polymerase chain reaction; rACC, rostral anterior cingulate cortex; RT-PCR, reverse transcriptase polymerase chain reaction; SCZ, schizophrenia; SD, suicide death; SI, suicide ideation; SUD, substance use disorder; TLDA, TaqMan low density array; VSD, violent suicide death.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2023 February 06.

TABLE 4

Histones alterations related to SITB

Histones	Suicidal population	Tissue	Suicide outcome	Ancestry	Reference
BA 10 and HIPP H3K9/14 ac (↓), HDAC3 (↑), H3K27me2 (↑)	*N* = 14 no psychiatric disorder SD+ (age M = 29.21, 36% F)	HIPP, BA 10	SD	NR	Misztak et al., 2020
CX30 and CX43 H3K9me3 (↑)	*N* = 22 MDD+/SD+ (age M = 39.73,0% F)	BA 8/9	SD	NR	Nagy, Torres-Platas, Mechawar, &Turecki, 2017
OAZ1 H3K4me3 (↑)	*N* = 34 SD+ upregulated *AMD1, ARG2, OAZ1, OAZ2* (age M = NR, 0% F)	BA 44	SD	NR	Fiori, Gross, &Turecki, 2012
Overall NS	*N* = 10 SD+ (age M = 32.9,0% F)	BA 8/9	SD	NR	Fiori &Turecki, 2011
SMS and SMOX NS	*N* = 10 SD+ (age M = NR, 0% F)	BA 8/9	SD	French Canadian	Fiori &Turecki, 2010
BA 10, TrkB H3 lysine 27 methylation (↑) **CER, TrkB** NS	*N* = 20 SD+ (age M = 35.2, %F NR)	BA 10, CER	SD	French Canadian Caucasian	Ernst, Chen, &Turecki, 2009

Abbreviations: age M, mean age; AMD1, adenosylmethionine decarboxylase 1; ARG2, arginase 2; BA, Brodmann area; CER, cerebellum; ChIP, chromatin immunoprecipitation; CNS, central nervous system; Cx30, connexin 30; Cx43, connexin 43; FA, forensic autopsy; HC, healthy controls; HDAC, histone deacetylase; HIPP, hippocampus; MDD, major depressive disorder; NR, not reported; NS, not significant; OAZ1, ornithine decarboxylase antizyme 1; OAZ2, ornithine decarboxylase antizyme 2; PA, xx; SAT1, spermidine/spermine N1-acetyltransferase 1; SD, suicide death; SMOX, spermine oxidase; SMS, spermine synthase.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2023 February 06.