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The Role of Epigenetic Dysregulation in Suicidal Behaviors

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Abstract

Suicidal behaviors have been associated with both heritable genetic variables and environmental risk factors. Epigenetic processes, such as DNA methylation, have important roles in mediating the effects of the environment on behavior. Dysregulation of these processes has been observed in many psychiatric disorders, and evidence suggests that they may also be involved in suicidal behaviors. Herein, we have summarized candidate gene and epigenome-wide studies which have investigated DNA methylation in relation to suicidal behaviors, as well as discussed some of the limitations of the field to date.

Keywords

Suicide; suicidal behaviors; epigenetics; DNA methylation; EWAS

Introduction

Nearly one million people die by suicide each year (Saxena et al., 2014), with considerably higher numbers attempting suicide or experiencing suicidal ideation. While a history of psychiatric disorders is present in the majority of people who display suicidal behaviors, their transmission is independent, indicating that suicidal behaviors represent a distinct phenotype (Turecki and Brent, 2016). That suicidal behaviors possess a genetic component has been demonstrated through numerous studies, with heritability estimated between 30-50% (Statham et al., 1998; McGuffin et al., 2001; Fu et al., 2002; Turecki and Brent, 2016). Although efforts to identify biological pathways underlying the genetic risk for suicidal behaviors have been ongoing for decades, it has become clear that the etiology and pathology of these behaviors are the result of a complex relationship between genetic factors and the environment. Epigenetic processes play an important role in mediating the relationship between genetics and the environment, and their relationship to both behavior and psychopathology has been well established (Weaver et al., 2004; McGowan et al., 2009; Turecki, 2014).

Epigenetics refer to molecular processes that alter gene expression without altering the underlying genomic sequence. The most commonly-investigated epigenetic mechanisms are DNA methylation, post-translational histone modifications, and non-coding RNA-mediated gene repression by microRNAs (miRNA). Each of these have been examined for their role in various psychiatric disorders, particularly mood disorders, anxiety disorders, and schizophrenia (for recent reviews, see (Hoffmann et al., 2017; Dwivedi, 2018; Punzi et al., 2018; Schiele and Domschke, 2018; Brown et al., 2019). Although the environmental exposures responsible for the majority of these epigenetic differences have not been identified, one environmental factor which has been shown to be associated with psychopathology-related epigenetic alterations is early life adversity (ELA). Specifically, ELA, defined as childhood abuse and parental neglect, is associated with increased rates of anxiety, depression, and suicidal behaviors (McCauley et al., 1997; Gilbert et al., 2009; McLaughlin et al., 2010), as well as specific epigenetic alterations (for examples see (McGowan et al., 2009; Jawahar et al., 2015; Lutz et al., 2015; Turecki and Meaney, 2016).

The most thoroughly investigated epigenetic mechanism is DNA methylation. DNA methylation involves the covalent addition of a methyl group to the 5’ position of cytosine nucleotides. In mammals, the majority of methylated cytosines are found at cytosine-guanine dinucleotides (CpG) (Maunakea et al., 2010b). When found within gene promoter regions, DNA methylation is typically associated with repression of gene expression (Jones et al., 1998; Klose and Bird, 2006), whereas gene body methylation can be linked to elevated levels of gene expression, and the use of alternative promoters (Maunakea et al., 2010a; Zemach et al., 2010; Jjingo et al., 2012). In addition to CpG methylation, non-CpG methylation and hydroxymethylation are important marks which display enriched levels in the brain, and appear to play important roles in synaptic development (Lister et al., 2013). Moreover, it must be noted that while the relationship between methylation and expression can often be predicted based on genomic location, the actual relationship between methylation and gene expression is far more complex, both in terms of the location of methylated sites (Spainhour et al., 2019), and the timing of expression changes (Pacis et al., 2019). Furthermore, as methylation patterns can be influenced by the underlying genetic sequence (Do et al., 2017), correlations between gene expression and methylation may not reflect a causal relationship.

Investigating the role of epigenetic factors in suicidal behaviors follows one of two strategies. Classically, researchers have used hypothesis-driven candidate gene approaches focusing on genes and/or pathways of interest to suicidal behaviors. More recently, large scale

approaches, investigating methylation across the whole genome, have revealed additional genes and pathways not previously implicated in this phenotype. In this chapter, we will first highlight the major findings resulting from candidate gene studies (Table 1), focusing on studies examining stress response pathways, neurotrophic factor signaling, and neurotransmitter signaling. Secondly, we will summarize findings from larger, epigenome-wide association studies (EWAS) (Table 2). Finally, we will discuss some of the limitations and implications of the studies to date.

Stress Response Pathways

Stress response systems are essential for survival. They initiate numerous behavioral and physiological changes in response to environmental stressors. Not surprisingly, dysregulated functioning of stress response systems can be highly detrimental. The stress-diathesis interaction is widely used to conceptualize risk for suicide. The model assumes that suicide results from a combination of stressors and predisposing factors. As such, two molecular systems related to stress response, the hypothalamic-pituitary-adrenal (HPA) axis and the polyamine system, have been investigated at the epigenetic level for their role in suicide.

Corticotrophin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus activates the HPA axis, in turn, stimulating the release of adrenocorticotropic hormone from the pituitary gland, resulting in the release of glucocorticoids from the adrenal gland (Herman et al., 2003). These hormones travel systemically, acting to increase the expression of genes involved in metabolism and inflammation, resulting in numerous effects in the central nervous system. Dysregulation of this pathway has been found to play an important role in suicidal behaviors (Pfennig et al., 2005; O'Connor et al., 2016; Melhem et al., 2017). Moreover, numerous studies have shown that the early life environment can modify the reactivity of this stress system, leading to lifelong behavioral changes (Liu et al., 1997; Francis et al., 1999; Meaney and Szyf, 2005). Consequentially, the relationship between the epigenetic effects of ELA, and functioning of the HPA axis, has been the focus of a number of studies of suicide.

The polyamine system is important for all organisms playing a key role in numerous cell functions including growth, division, and signalling cascades. It is also a crucial system for stress responses, both at the cellular and behavioral levels (Tabor and Tabor, 1984; Gilad and Gilad, 2003; Minguet et al., 2008). The polyamine stress response (PSR) is activated after exposure to stressful stimuli, resulting in elevated levels of putrescine and agmatine in the brain and periphery (Fiori and Turecki, 2008; Turecki, 2014; Limon et al., 2016). Interestingly, the PSR appears to be developmentally regulated, and the emergence of the adult PSR is correlated with the cessation of the hyporesponsive period of the HPA system (Gilad, Gilad, Eliyayev, & Rabey, 1998). As with the HPA axis, dysregulation of this system has been observed in a number of psychiatric disorders, including mood disorders, anxiety, and schizophrenia (Fiori and Turecki, 2008). While the HPA and polyamine systems have distinct molecular effects on their biological targets, there is evidence for cross-talk at several levels (Cousin et al., 1982; Ientile et al., 1988; Gilad et al., 1998).

Suicidal behaviors in abused individuals has been investigated in three studies of glucocorticoid receptor (GR, NR3C1) promoter methylation (variable exon 1). Two studies, performed in the hippocampus of individuals who died by suicide, identified abuse-specific methylation differences associated with the expression of different GR isoforms (McGowan et al., 2009; Labonte et al., 2012a). The third study examined GR promoter methylation in the blood of individuals with bulimia nervosa finding that specific promoter methylation was

associated with suicidal behavior, but not childhood abuse (Steiger et al., 2013). It is unclear if these differences are related to differences in tissue (brain, blood), severity of suicidal behavior (suicide vs attempt), or other factors. Nonetheless, altogether these three studies reinforce the importance of this gene in psychopathology.

Moving beyond GR, two studies have examined larger sets of stress- and HPA-related genes in the blood. The first examined suicidal ideation in individuals with major depressive disorder (MDD), and its relationship to methylation and expression of five stress-related genes in the blood (Roy et al., 2017). Four genes displayed hypermethylation related to suicidal ideation: GR, corticotropin releasing hormone binding protein (CRHBP), FK506 binding protein 5 (FKBP5), and the neurotrophin brain-derived neurotrophic factor (BDNF). The increased methylation was inversely correlated with expression of BDNF, FKBP5, and NR3C1. The fifth gene, corticotropin releasing hormone receptor 1 (CRHR1), did not display differential methylation or expression in this cohort. A second study investigated methylation of CRH, CRHBP, CRHR1, CRHR2, FKBP5, and NR3C1 in the blood of individuals who had attempted suicide, and found hypomethylation of two sites within CRH in relation to higher severity of suicide attempts (Jokinen et al., 2018). Interestly, one of these sites was hypermethylated in adolescents with a high risk of psychiatric disorders, suggesting a complex relationship between this gene and psychopathology.

One of the most consistent findings emerging from epigenetic studies of suicidal behavior has been alterated methylation in a polymorphic methylation site in the 3' untranslated region of spindle and kinetochore associated complex subunit 2 (SKA2), which is involved in GR signaling (Rice et al., 2008). The importance of this site was first identified in an EWAS examining the prefrontal cortex of individuals who died by suicide (Guintivano et al., 2014). This site was found to be hypermethylated and correlated with expression in both the brain and blood. Methylation at this site was increased in the blood in relation to suicidal ideation, interacted with anxiety to influence suicidal ideation and attempts, and was associated with waking cortisol levels. A follow-up study found that methylation at this site, in both blood and saliva, interacted with trauma exposure to predict lifetime suicide attempts, and mediated cortisol suppression in the dexamethasone suppression test (Kaminsky et al., 2015). Another group found that SKA2 methylation was associated with current, but not past, suicidal behaviors, as well as current and lifetime internalizing symptoms (Sadeh et al., 2016). Finally, a biosignature comprised of methylated sites in discoidin domain receptor tyrosine kinase 1 (DDR1), rho guanine nucleotide exchange factor 10 (ARHGEF10), and protein tyrosine phosphatase, non-receptor type 6 (SHP1), was found to interact with SKA2 methylation to predict suicidal ideation (Clive et al., 2016).

In the original study identifying SKA2 methylation in suicidal behavior, methylation at the 3' UTR site in SKA2 was also found to interact with methylation at a GR-binding site in the spermidine/spermine N1-acetyltransferase (SAT1) promoter to associate with suicidal ideation, suggesting that epigenetic regulation of SAT1 may be stress-related (Guintivano et al., 2014). The involvement of SAT1 in suicidal behavior was first demonstrated in a gene expression study showing widespread downregulation of this catabolic enzyme in the brains of individuals who died by suicide (Sequeira et al., 2006). However, two studies examining methylation of the promoter region of SAT1 in the brain found no differences in relation to suicide (Guipponi et al., 2009; Fiori and Turecki, 2011).

Additional polyamine-related genes have demonstrated differential expression in suicide (Fiori et al., 2011) and have been further assessed for epigenetic differences related to suicide. The first study examined two catabolic enzymes, spermine synthase (SMS) and spermine oxidase (SMOX), and found no signficant differences in individuals who died by suicide (Fiori and Turecki, 2010). However, a second study examining anabolic enzymes ornithine decarboxylase

antizymes 1 (OAZ1) and 2 (OAZ2), arginase II (ARG2) and S-adenosylmethionine decarboxylase (AMD1) found differential promoter methylation, with methylation of ARG2 and AMD1 being significantly correlated with gene expression (Gross et al., 2013).

Neurotrophic Factor Signalling

Neurotrophins are a class of peptide growth factors secreted by specific cells to increase the growth and survival of neurons, and include nerve growth factor (NGF), neurotrophin 3 (NT-3), neurotrophin 4 (NT-4), and brain-derived neurotrophic factor (BDNF). Both the expression of these growth factors, as well as the BDNF receptor TrkB, demonstrate dysregulated expression in suicide (Dwivedi et al., 2005; Pandey et al., 2008; Ernst et al., 2009; Sheldrick et al., 2017). To date, epigenetic studies examining neurotrophic factors have focused on BDNF and TrkB, and along with SKA2, have been the most consistent epigenetic findings related to suicidal behavior.

The first study investigating BDNF in suicide examined methylation of the promoter/exon IV regions in the brain Wernicke area of people who died by suicide, and found hypermethylation, which was inversely correlated with expression (Keller et al., 2010). Hypermethylation of BDNF has also been repeatedly shown in the blood: in individuals with MDD who had previously attempted suicide (Kang et al., 2013), as well as suicidal ideation in people with MDD (Kang et al., 2013; Roy et al., 2017), the elderly (Kim et al., 2014), patients with breast cancer (Kim et al., 2015), and people with acute coronary syndrome (Kang et al., 2018).

Two studies have also found significant methylation differences in the TrkB.T1 isoform in suicide. The first study found hypermethylation at specific promoter sites in the prefrontal cortex of suicides, which was associated with decreased expression of this transcript (Ernst et al., 2009). The second study identified hypermethylation at several sites in the 3' UTR of TrkB.T1, which correlated with expression in the prefrontal cortex (Maussion et al., 2014). However, hypermethylation of TrkB appears to be brain-region specific, as no differences were found in the cerebellum (Ernst et al., 2009) or the Wernicke area (Keller et al., 2011).

Neurotransmitter Systems

Neurotransmitter systems are the main target for the majority of psychopharmaceutical agents currently in use, and have been extensively explored in psychiatry. Serotonergic neurotransmission is the target of most antidepressants, and has been the focus of several epigenetic studies of suicidal behavior. Three studies have examined methylation of a specific CpG site in exon 1 of the serotonin 2A receptor (HTR2A). Although one study found increased levels of methylation at this site in the blood of patients with schizophrenia who had attempted suicide relative to non-attempters (De Luca et al., 2009), follow-up studies by the same group were not able to fully replicate these findings (Bani-Fatemi et al., 2016; Bani-Fatemi et al., 2017). Furthermore, no differences were found in suicide attempters with bipolar disorder, or in the brains of people who died by suicide (De Luca et al., 2009; Bani-Fatemi et al., 2017). Finally, one study examined tryptophan hydroxylase 2 (TPH2), and found hypermethylation in the blood of people with MDD who had previously attempted suicide relative to non-attempters (Zhang et al., 2015).

A few additional epigenetic studies of neurotransmitter systems have been performed, and have identified methylation differences in $GABA_A$ α1 receptor subunit (Poulter et al., 2008), kappa opioid receptor (Lutz et al., 2018), and components of galanin signaling (Barde et al., 2016). However, these findings have yet to be replicated.

Epigenome-Wide Association Studies (EWAS)

Although candidate gene studies have provided important insight into the role of specific genes and methylation marks in psychiatric disorders, it has become increasingly clear that epigenetic reprogramming in response to the environment occurs on a much larger scale, and that genome-wide patterns of altered methylation may be more relevant than quantifying levels at specific CpG sites. Furthermore, candidate gene studies lack the ability to assess relationships between altered methylation across different biological pathways, as well as how methylation at a specific locus may be influenced by that in nearby genomic regions. These issues can be better studied using epigenome-wide approaches, which also have the potential to identify genes and pathways not been previously implicated in suicide. A summary of EWAS examining suicidal behaviors is shown in Table 2.

Four EWAS have investigated suicidal behaviors within individuals diagnosed with mood disorders. The first study assessed methylation in the orbital prefrontal cortex of suicides with MDD relative to non-psychiatric controls (Haghighi et al., 2014). Their results showed a significant effect of age on methylation, with a significantly higher number of age-related CpGs in the depressed suicide group. Furthermore, these age-related genes were enriched for those associated with behavior, cell cycle, cell death and survival, and cellular and embryonic development. The second study also compared depressed suicides relative to non-psychiatric controls, and evaluated methylation in two regions: the orbitofrontal cortex, and the anterior cingulate cortex (Murphy et al., 2017). Three genes were found to be differentially methylated in both brain areas: psoriasis susceptibility 1 candidate 3 (PSORS1C3), TAP binding protein (TAPBP), and ATP synthase membrane subunit c locus 2 (ATP5G2). In an independent sample of depressed suicides, hypomethylation of PSORS1C3 was observed in sorted neuronal cells from the prefrontal cortex. Using a combination of polygenic risk scores (PRS) and weighted gene co-expression network analysis (WGCNA), they found enrichment for processes related to nervous system development and mitochondrial function. A third study examined methylation in the prefrontal cortex of an astrocytic-dysfunction sub-group of depressed suicides relative to non-psychiatric controls (Nagy et al., 2015). They found 115 differentially methylated regions, with the most significant findings in the genes glutamate ionotropic receptor kainate type subunit 2 (GRIK2), and brain enriched guanylate kinase associated (BEGAIN), which was inversely correlated with gene expression. Methylation differences in GRIK2 were maintained in both neuronal and non-neuronal cells, whereas hypermethylation of BEGAIN was found only in non-neuronal cells. An in vitro study showed that this region of BEGAIN has a regulatory function, which is impacted by methylation. Finally, one study examined methylation in the blood of people with bipolar disorder, and dichotomized their sample based on high or low levels of suicidal behaviors (Jeremian et al., 2017). They identified differential methylation in three genes: membrane palmitoylated protein 4 (MPP4), nucleoporin 133 (NUP133), and TBC1 domain family member 16 (TBC1D16). Additionally, they calculated DNA methylation age, and found a weaker correlation with tissue age in people in the high suicidal behaviors group.

Two studies have examined epigenome-wide methylation in groups with mixed psychiatric disorders, including MDD, bipolar disorder, or schizophrenia. The first study was described within the candidate gene studies earlier, and identified four differentially methylated regions: ATPase phospholipid transporting 8A1 (ATP8A1), potassium voltage-gated channel subfamily A regulatory beta subunit 2 (KCNAB2), LOC153328, and SKA2, in the prefrontal cortex of depressed suicides (Guintivano et al., 2014). Differential methylation of SKA2 in the prefrontal cortex was replicated in two cohorts, comprised of suicides with bipolar disorder or schizophrenia, as well as correlated with other important behavioral and physiological

measures, as described earlier. A second study assessed the prefrontal cortex and the hippocampus in a small group of suicides who died by hanging, and found differential methylation of a number of genes in both regions (Kouter et al., 2019). Two of these genes, nuclear receptor interacting protein 3 (NRIP3) and zinc finger protein 714 (ZNF714), were also differentially expressed in the prefrontal cortex.

Finally, three postmortem studies have used a three-group design to disentangle the effects of ELA and suicide, by comparing non-psychiatric controls to suicide completers with or without a history of ELA. Similar to the previous section, suicides within these three studies were diagnosed with various psychiatric disorders, including MDD, bipolar disorder, or schizophrenia. The first study was performed in the hippocampus, and examined genome-wide promoter methylation (Labonte et al., 2012b). They identified 362 promoters which were differentially methylated in abused suicides relative to non-psychiatric controls. Gene ontology analyses indicated that genes associated with neuronal plasticity were the most enriched among the differentially methylated regions, and highlighted alsin (ALS2) as being of particular importance. Methylation differences in this promoter were found to be specific to neuronal cells, and hypermethylated at a functional CpG site specifically in abused suicides relative to non-abused suicides and non-psychiatric controls. A follow-up study was performed using a larger sample, again examining promoter methylation in the hippocampus, specifically to identify suicide-related differences by controlling for a history of ELA (Labonte et al., 2013). Gene ontology analyses of differentially methylated promoters found enrichment for genes related to cognitive processes and neuronal communication, with the most significant differences in this cluster found within the genes nuclear receptor subfamily 2 group E member 1 (NR2E1), cholinergic receptor nicotinic beta 2 subunit (CHRNB2), glutamate metabotropic receptor 7, (GRM7), and dopamine beta-hydroxylase (DBH). Finally, a third study was performed in the anterior cingulate cortex, and assessed epigenome-wide differences in abused suicides relative to non-psychiatric controls (Lutz et al., 2017). Differential methylation was enriched in genes related to oligodendrocytes, and both an impairment in transcription of myelin-related genes, and a reduction in myelination, was observed in depressed suicides with a history of childhood abuse. The three most differentially methylated regions were in leucine rich repeat and Ig domain containing 3 (LINGO3), POU class 3 homeobox 1 (POU3F1), and integrin subunit beta 1 (ITGB1). Methylation differences in LINGO3 and POU3F1 were found to be specific to oligodendrocytes, with no changes in neuronal cells. Finally, suicides without a history of childhood abuse had similar methylation levels to non-suicides in these cells, indicating that these effects are specific to ELA, rather than suicide.

Discussion and Conclusions

As described above, a number of genes and biological pathways have now been shown to display altered methylation levels in relation to suicidal behaviors. However, many of these findings have been replicated across only a few studies, with relatively poor overlap between candidate gene studies and EWAS.

There are a number of factors which may explain the lack of consistency in epigenetic findings, and which represent important elements to address in future studies. Firstly, very diverse phenotypes have been used in the studies to date. Although suicidal behaviors are believed to represent a continuum between ideation and completed suicide, they may possess both distinct and shared epigenetic risk factors. Moreover, studies have used cohorts diagnosed with a variety of Axis 1 disorders. Although suicidal behaviors are considered to be trans-diagnostic, it seems likely that at a biological level, epigenetic changes related to suicidal

behaviors may interact with both epigenetic and genetic variations related to other psychopathologies. Additionally, epigenetic factors are susceptible to the underlying genetic sequence, as well as subtle environmental differences. As such, they can be easily confounded by socio-demographic variables such as age, gender, ethnicity, ELA, and smoking. Finally, the temporal relationship between environmental exposures, such as abuse, and the course of epigenetic alterations has not been clearly established. The stability of suicide-related epigenetic differences over time has yet to be addressed, nor has it been demonstrated that suicide-related epigenetic signatures in adulthood are identical to those that were present in childhood following adversity. Furthermore, there is some evidence that the age of experiencing abuse may be important in terms of defining the nature and extent of neurobiological alterations (Heim and Binder, 2012). The use of larger and better characterized cohorts, with more refined suicide phenotypes, and appropriate control populations, will enhance our ability to disentangle effects specifically related to suicidal behaviors.

Secondly, studies have investigated a variety of both central (frontal cortex, anterior cingulate cortex, hippocampus) and peripheral samples (whole blood, white blood cells, saliva). Brain regions have been selected based on evidence implicating their involvement in psychiatric disorders. However it remains unclear whether these regions are the most appropriate or meaningful sites for suicide-related epigenetic changes. Additionally, some of the studies described above have identified epigenetic changes specific to particular cell types (neuronal, non-neuronal, oligodendrocyte,…). As the majority of studies in the brain have used tissue homogenates, significant epigenetic effects found only within a few cell types may have been diluted and/or undetectable. The use of brain tissue is not an option to investigate suicide attempts or ideation. Accordingly, studies which have focused on these behaviors have relied on peripheral samples. The concordance between methylation patterns in the brain and peripheral tissues has not been fully established. A number of studies have found that DNA methylation variance is more closely linked to tissue-specificity than to individual-specificity, suggesting that variations in DNA methylation in blood do not necessarily capture variations in brain tissues (Hannon et al., 2015a; Hannon et al., 2015b; Schultz et al., 2015; Walton et al., 2015). Nonetheless, some findings, including those regarding SKA2, do appear to be present in both central and peripheral tissues, indicating that peripheral samples can be a viable option for some epigenetic marks. This consistency is very promising, as it indicates the presence of systemic changes in methylation which can be captured outside of the brain.

Future studies will be needed to determine the optimal cell-types and tissues to use in these investigations, and to identify and control for the most relevant clinical and socio-demographic variables. Further, both better-characterized cohorts, and larger scale epigenetic investigations, will be needed to fully delineate the extent of methylation differences specifically related to suicidal behaviors .

In spite of the issues described above, there have been some consistent findings with regards to genes displaying methylation differences in relation to suicidal behaviors. What is particularly promising are studies which have demonstrated that epigenetic processes, including those targeting suicide-related genes, can be modified by antidepressant treatment. Specifically, differential methylation and histone modifications have been found in the promoter regions of BDNF following antidepressant treatment (D'Addario et al., 2013; Lopez et al., 2013; Tadic et al., 2014). Additionally, levels of histone modification enzymes have been found to be altered by antidepressant treatment (Iga et al., 2007), and a number of miRNAs have been shown to be altered by treatment and involved in clinical response (Fiori et al., 2017; Lopez et al., 2017). Finally, treatment with histone deacetylase inhibitors has been shown to elicit antidepressant-like effects in animals (Tsankova et al., 2006; Covington et al., 2009; Hobara et al., 2010). As

such, while studies have definitively demonstrated the adverse effects of early childhood experiences, it appears that these environmental influences have the potential to be reversed, thus representing potential new targets for treatment of suicidal behaviors.

In conclusion, the studies described in this chapter have demonstrated a number of epigenetic alterations associated with suicidal behaviors. Methylation differences in some genes, including SKA2, NR3C1, and BDNF, have shown excellent reproducibility across populations and phenotypes. It is clear that the epigenome is an integral system for mediating the effects of the environment on gene function. Understanding its involvement in suicidal behaviors represents a key step in elucidating the molecular mechanisms underlying their development, and for identifying new treatment targets and potential biomarkers for early diagnosis and prevention.

Table 1: Findings from targeted epigenetic studies in suicide. Genes displaying significant differences are in bolded type.

System	Gene(s) examined	Phenotype	Tissue	Significant Findings	Reference
Stress Response	**NR3C1**	Abuse and non-abuse, Suicide vs HC	Hippocampus	Hypermethylation in abused suicides	(McGowan et al., 2009)
	NR3C1	Abuse and non-abuse, Suicide vs HC	Hippocampus	Hypermethylation (exon 1B and 1C), hypomethylation (exon 1H)	(Labonte et al., 2012a)
	NR3C1	Bulimia with suicidality vs bulimia without suicidality vs HC	Whole blood	Hypermethylation of exon 1C in patients with suicidality	(Steiger et al., 2013)
	NR3C1, **BDNF**, **FKBP5**, **CRHBP**, CRHR1	Suicide ideation vs non-ideation, MDD	Peripheral blood mononuclear cells	Hypermethylation in suicide ideation	(Roy et al., 2017)
	CRH, CRHBP, CRHR1, CRHR2, FKBP5, and NR3C1	High-risk suicide attempt vs Low-risk attempt	Whole blood	Hypomethylation in high-risk attempters	(Jokinen et al., 2018)
	SKA2	Suicide attempts, suicide ideation	Saliva, whole blood	Methylation predicted suicide attempts	(Kaminsky et al., 2015)
	SKA2	Suicide ideation and attempts	Whole blood	Methylation predicted suicide attempts and ideation	(Sadeh et al., 2016)
	SAT1	Suicide vs HC	BA11	NS	(Guipponi et al., 2009)
	SAT1	Suicide vs HC	BA 8/9	NS	(Fiori and Turecki, 2011)
	SMS, SMOX	Suicide vs HC	BA 8/9	NS	(Fiori and Turecki, 2010)

	AMD1, ARG2, OAZ1, OAZ2	Suicide vs HC	BA44	Overall and site-specific differences in promoter methylation	(Gross et al., 2013)
Neurotrophins	**BDNF**	Suicide vs HC	Wernicke area	Hypermethylation in suicides	(Keller et al., 2010)
	BDNF	Suicide attempts, Suicide ideation	Whole blood	Hypermethylation in attempters and ideators	(Kang et al., 2013)
	BDNF	Suicide ideation, late life	Whole blood	Hypermethylation in suicidal ideation	(Kim et al., 2014)
	BDNF	Suicide ideation, breast cancer	Whole blood	Hypermethylation associated with suicidal ideation and depressive symptoms	(Kim et al., 2015)
	BDNF	Suicide ideation, acute coronary syndrome	Whole blood	Hypermethylation associated with suicidal ideation	(Kang et al., 2018)
	TrkB	Suicide vs HC	BA8/9	Hypermethylation in suicides	(Ernst et al., 2009)
	TrkB	Suicide vs HC	Wernicke area	NS	(Keller et al., 2011)
	TrkB	Suicide vs HC	BA8/9	Hypermethylation in suicides	(Maussion et al., 2014)
Neurotransmission	**HTR2A**	Schizophrenia and bipolar disorder, Suicide attempt vs Non-attempt	BA46, white blood cells	Hypermethylation in suicide attempters with schizophrenia	(De Luca et al., 2009)
	HTR2A	Schizophrenia, Suicide attempt vs	White blood cells	NS	(Bani-Fatemi et

		Non-attempt			al., 2016)
	HTR2A	Schizophrenia, Suicide attempt vs Non-attempt	Frontal cortex, saliva	NS	(Bani-Fatemi et al., 2017)
	TPH2	MDD, Suicide attempt vs Non-attempt	Whole blood	Hypermethylation in suicide attempters	(Zhang et al., 2015)
	GABAA	Suicide vs HC	BA10	Hypermethlation in suicide	(Poulter et al., 2008)
	Galanin, **GALR3**, GALR1, GALR2	MDD-Suicide vs HC	anterior cingulate cortex; dorsolateral prefrontal cortex; dorsal raphe nucleus; locus coeruleus; medullary raphe nucleus	Brain region- and gender-specific alterations in methylation	(Barde et al., 2016)
	KOR	Abuse and non-abuse Suicide vs HC	AI	Hypomethylation in abused suicides compared to non-abused suicides or controls	(Lutz et al., 2018)
Other	QKI	MDD suicide vs HC	BAs 4, 6, 8/9, 10, 11,20, 21, 24, 29, 38, 44, 45, 46, and 47, hippo-campus, amygdala, nucleus accumbens	NS	(Klempan et al., 2009)
	rRNA	Abused suicide vs HC	Hippocampus	Hypermethylation of rRNA promoters and 5' regulatory regions	(McGowan et al., 2008)
	CACNA1C	Suicide attempt vs Non-attempt	Whole blood	Significant differences in two	(Kim et al., 2017)

ERBB3	Suicide vs HC	Hippocampus	CpG sites in suicide attempters NS	(Mahar et al., 2017)
ELOVL5, FADS1, FADS2	MDD, Suicide attempt vs Non-attempt	Buffy coat	Hypomethylation in downstream region, hypermethylation in upstream region	(Haghighi et al., 2015)
TNFα	Suicide vs HC	Prefrontal cortex	Hypomethylation in suicide	(Wang et al., 2018)

BA: Brodmann area; HC: healthy control; MDD: major depressive disorder; NS: not significant

Table 2: EWAS investigating epigenetic differences related to suicidal behaviors.

Highlighted Genes	Phenotype	Tissue	Technology	Reference
ALS2, DGKZ, HIST2H2AB, NR1D1, TAF5L	Abuse and non-abuse Suicide vs HC	Hippocampus	MeDIP Promotor tiling array	(Labonte et al., 2012b)
NR2E1, CHRNB2, GRM7, DBH	Suicide vs HC	Hippocampus	MeDIP Promotor tiling array	(Labonte et al., 2013)
ATP8A1, KCNAB2, LOC153328, SKA2	Suicide, suicidal behaviors	BA9 BA10 BA46 White blood cells	HumanMethylation450K BeadChip	(Guintivano et al., 2014)
EYA2, MEGF11, LMNA, GLUD1, ERBB3, SLC18A2	MDD-Suicide vs HC	BA47	HumanMethylation27 BeadChip	(Haghighi et al., 2014)
BEGAIN, GRIK2	Suicide vs HC	BA8/9	MBD2 sequencing	(Nagy et al., 2015)
LINGO3, POU3F1, ITGB1	Abuse and non-abuse Suicide vs HC	BA24	Reduced representation bisulfite sequencing	(Lutz et al., 2017)
PSORS1C3, TAPBP, ATP5G2	MDD-Suicide vs HC	BA11 BA25	HumanMethylation450K BeadChip	(Murphy et al., 2017)
MPP4, TBC1D16, NUP133	BD-high suicidal behavior vs BD-low suicidal behavior	White blood cells	HumanMethylation450K BeadChip	(Jeremian et al., 2017)
NRIP3, ZNF714	Suicide vs HC	BA9 Hippocampus	Reduced representation bisulfite sequencing	(Kouter et al., 2019)
None	Suicide vs HC	BA10	HumanMethylation450K BeadChip	(Schneider et al., 2015)
None	Schizophrenia, Suicide attempt vs Non-attempt	White blood cells	HumanMethylation450K BeadChip	(Bani-Fatemi et al., 2018)

BA: Brodmann area; HC: healthy control; MDD: major depressive disorder

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