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High polygenic burden is associated with blood DNA methylation changes in individuals with suicidal behavior

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ABSTRACT

Suicidal behavior is result of the interaction of several contributors, including genetic and environmental factors. The integration of approaches considering the polygenic component of suicidal behavior, such as polygenic risk scores (PRS) and DNA methylation is promising for improving our understanding of the complex interplay between genetic and environmental factors in this behavior. The aim of this study was the evaluation of DNA methylation differences between individuals with high and low genetic burden for suicidality. The present study was divided into two phases. In the first phase, genotyping with the Psycharray chip was performed in a discovery sample of 568 Mexican individuals, of which 149 had suicidal behavior (64 individuals with suicidal ideation, 50 with suicide attempt and 35 with completed suicide). Then, a PRS analysis based on summary statistics from the Psychiatric Genomic Consortium was performed in the discovery sample. In a second phase, we evaluated DNA methylation differences between individuals with high and low genetic burden for suicidality in a sub-sample of the discovery sample (target sample) of 94 subjects. We identified 153 differentially methylated sites between individuals with low and high-PRS. Among genes mapped to differentially methylated sites, we found genes involved in neurodevelopment (*CHD7, RFX4, KCNA1, PLCB1, PITX1, NUMBL*) and ATP binding (*KIF7, NUBP2, KIF6, ATP8B1, ATP11A, CLCN7, MYLK, MAP2K5*). Our results suggest that genetic variants might increase the predisposition to epigenetic variations in genes involved in neurodevelopment. This study highlights the possible implication of polygenic burden in the alteration of epigenetic changes in suicidal behavior.

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1. Introduction

Suicide is one of the leading death causes worldwide and it is considered a public health problem (Saxena et al., 2014). Suicide behavior (SB) is a complex phenomenon where social, environmental and biological factors interact (Haw et al., 2013). SB may be divided into completed suicide, suicide attempts and suicidal ideation (Turecki and Brent, 2016). It has been suggested that suicidal behaviors represent a continuum spectrum and shared several risk factors (Have et al., 2009). Furthermore, a transition among suicidal behavior forms has been identified, i.e., a cross-national study reported that 60% of the transitions from suicidal ideation to suicide attempt occurred within the first year of the ideation onset (Nock et al., 2008).

Several factors contributing to SB etiology have been identified, including environmental and genetic factors (Mann, 2003). The genetic bases of SB have been explored in twin studies, which have estimated a heritability of 43% for suicide attempt/completion, and 36% for suicidal ideation (McGuffin et al., 2010; Fu et al., 2002). Furthermore, only few significant findings have been identified in genome-wide association studies (GWAS) for SB, for review, see González-Castro et al. (2019b). Among significant associations observed in recent studies we can find rs138689899 for suicide attempt in mood disorders, as well as genes related with ATPase activity (*ATP10A*), pseudogenes (*SOGA2P1*) and long non-coding RNA (*LINC00348*) for death by suicide (Docherty et al., 2019; Mullins et al., 2019). Therefore, it can be said that SB has a polygenic architecture, represented by the interaction of numerous loci (Bondy et al., 2006).

On the other hand, environmental factors may exert their influence through epigenetic modifications, such as DNA methylation. Previous studies suggest that DNA methylation alterations are implicated in the etiology of SB (Turecki, 2014). Alongside with environmental stimuli, DNA methylation might be influenced by genetic modifications. In the same way, DNA methylation might mediate genetic risk, i.e., genetic variations may lead to abnormal methylation and subsequent misexpression of a relevant gene for a specific disorder (Ladd-Acosta and Fallin, 2016).

As it is known from the analysis of common genetic variation by GWAS, most psychiatric diseases have a polygenic structure (Horwitz et al., 2019; Wang et al., 2017; Collins and Sullivan, 2013). Recently, methods to summarize this polygenic risk have been developed, like polygenic risk scores (PRS). Thus, the integration of approaches considering the polygenic component of SB, such as polygenic risk scores (PRS) and DNA methylation is promising for improving our understanding of the complex interplay between genetic and epigenomic factors in this behavior.

In this study, we conducted a PRS analysis in a discovery sample of 568 Mexican individuals with SB (suicidal ideation, suicide attempt and completed suicide). Then, we identified the DNA methylation differences between individuals with high and low PRS in a sub-sample of 94 subjects from the discovery sample.

2. Material and methods

2.1. Study overview

The aim of the present study was to evaluate the DNA methylation differences between individuals with high and low genetic burden for suicidality. For this, we took a two-phases approach. In phase one we conducted a PRS analysis in a discovery sample of 568 Mexican individuals with SB (suicidal ideation, suicide attempt and completed suicide). The PRS analysis is based on summary statistics (effect alleles and odds ratios) from the Psychiatric Genomic Consortium (PGC) GWAS results. Then, we identified the PRS with the highest association with SB in the discovery sample. In a second phase, we evaluated whether the PRS differences could promote changes in blood DNA methylation patterns. For this, single nucleotide polymorphisms (SNPs) associated with SB in the discovery sample were used for PRS calculation, in a sub-sample from the discovery sample comprising 94 subjects, hereinafter referred to as 'target sample'. Then, we evaluated the DNA methylation differences between individuals with high and low PRS in the target sample. All samples were collected by the Psychiatric Disorders Research Group. An overview of the methods is shown in

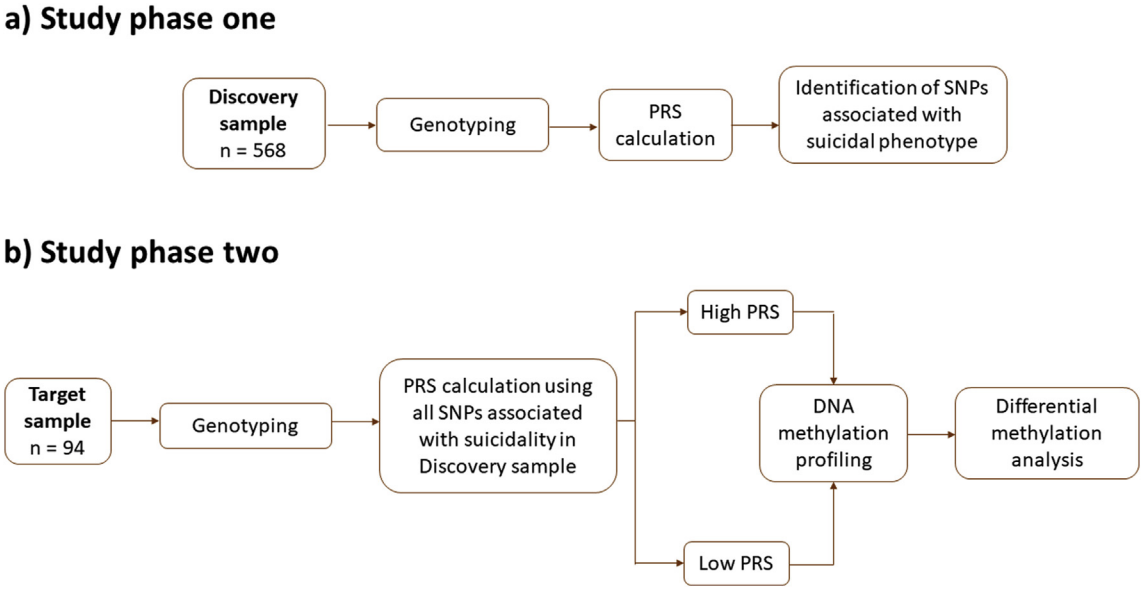

Fig. 1. Methods overview. a) Study phase one. In a discovery sample of individuals with different psychiatric disorders in comorbidity with suicidal behavior (suicidal ideation, attempt or completion), the polygenic risk score (PRS) was calculated in order to identify SNPs associated to SB. b) Study phase two. In the target sample, PRS was calculated considering only SNPs associated to SB in the discovery sample. Then, individuals were classified into high and low PRS groups; then, a differential methylation analysis between both groups was performed.

Fig. 1.

2.2. First phase: discovery sample

The discovery sample comprised a total of 568 Mexican individuals, of which 282 were males (48.79%) and 296 were females (51.21%). The discovery sample included 149 individuals with SB (64 individuals with suicidal ideation, 50 with suicide attempt and 35 with completed suicide). This sample included individuals with different psychiatric comorbidities such as eating disorders (Genis-Mendoza et al., 2019), suicide attempt (Genis-Mendoza et al., 2017), completed suicide (Cabrera et al., 2019) and neurocognitive disorder (Genis-Mendoza et al., 2018) from previously described samples. In addition, independent samples of individuals with bipolar disorder, first psychotic episode, obsessive compulsive disorder and schizophrenia were included. The complete sample recruitment and evaluation are described in Supplementary Material 1. The mean age of the discovery sample was 28.93 ± 20.25 years old. A summary of clinical information from the Discovery sample is shown in Supplementary Table 1.

2.3. Association of psychiatric PRS with SB in the discovery sample

Peripheral blood, buccal swab and brain samples were analyzed in the discovery sample. Genotyping is described in Supplementary Material 1. A PRS is a single value that predicts genetic predisposition to a certain phenotype (Dudbridge, 2016; Marees et al., 2018). This score is the result of adding the genetic variants weighted by their corresponding effect sizes (Choi et al., 2018). The effect sizes are usually estimated from GWAS results (Euesden et al., 2015). In this study, PRS in the discovery sample was calculated estimating effect sizes using GWAS summary statistics data from the Psychiatric Genetics Consortium (PGC) of different psychiatric disorders.

PRS was used for testing the genetic association between SB in the discovery sample and the following psychiatric disorders: schizophrenia (SZ) (Schizophrenia Working Group of the Psychiatric Genomics, 2014), major depression disorder (MDD) (23andMe Research Team et al., 2019), bipolar disorder (BD) (Stahl et al., 2019), attention deficit/hyperactivity disorder (ADHD) (Demontis et al., 2019), autism spectrum disorder (ASD) (Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017), anorexia nervosa (Watson et al., 2019), smoking behavior (Tobacco and Genetics Consortium, 2010), alcohol use disorder (Sanchez-Roige et al., 2019), cross-disorder (ASD, ADHD, BD, MDD, and SZ) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and suicide attempt in individuals with three different psychiatric disorders (MDD, BD and SZ) (Mullins et al., 2019). None of the individuals in our sample were included in the PGC GWAS data used to calculate PRS. Quality control and PRS calculation for each psychiatric trait are described in Supplementary Material 1.

2.4. Second phase: analysis of DNA methylation differences between individuals with low-PRS and high-PRS

Once we determined the PRS with the highest association to SB in the discovery sample, we evaluated if the PRS differences could promote changes in blood DNA methylation patterns. For this, we performed a PRS analysis in the target sample, which was a subsample from the discovery sample. A total of 94 subjects were included in the target sample. The target sample is described in Supplementary Material 1.

2.5. Polygenic risk score calculation in the target sample

Then, PRS was calculated using all the SNPs included in the PRS with the highest association with the suicidal phenotype in the discovery sample (Dudbridge, 2013). According to the results we obtained in the PRS calculation, individuals were classified in high and low PRS depending on whether their PRS was above or below the mean PRS for the target sample, respectively. High and low-PRS groups are described in Supplementary Material 1.

2.6. Differential DNA methylation changes in the target sample

We evaluated the methylation profile in individuals from the target subset. The microarray processing and differential methylation analysis between high and low-PRS groups are described in Supplementary Material 1.

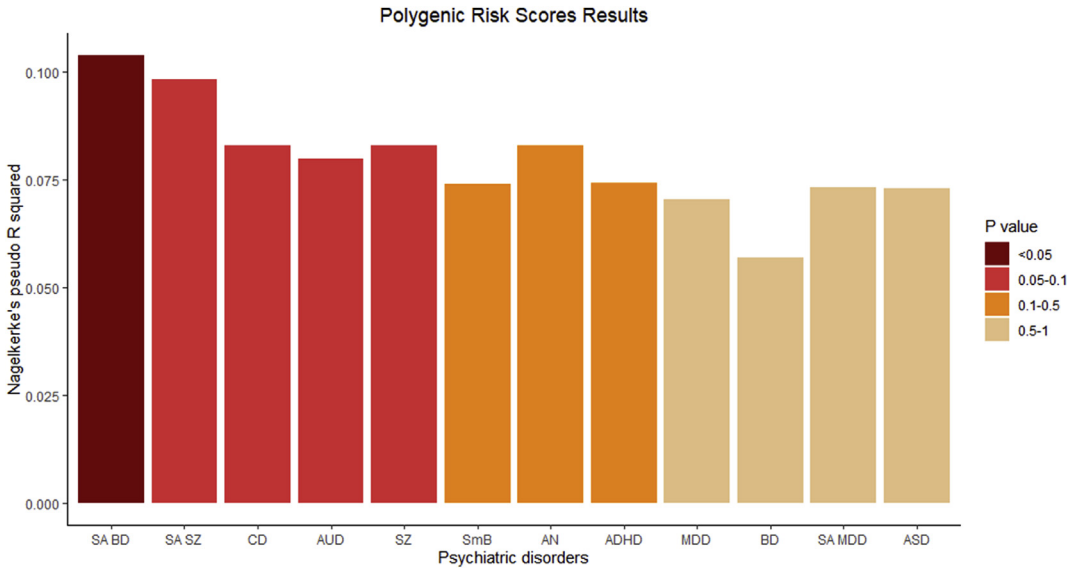

Fig. 2. Polygenic risk score results for different psychiatric traits in the discovery sample. The y-axis indicates R2 value for the PRS fit model. Abbreviations: Suicide attempt in bipolar disorder (SA BD); Suicide attempt in schizophrenia (SA SZ); Schizophrenia (SZ); Smoking behavior (SmB); Anorexia Nervosa (AN); Attention deficit/hyperactivity disorder (ADHD); Major depression disorder (MDD); Suicide attempt in major depression disorder (SA MDD); autism spectrum disorder (ASD); Bipolar disorder (BD).

2.7. Association analysis of SNPs included in PRS and DNA methylation patterns

In order to evaluate whether any of the SNPs associated to SB in the PRS analysis had a direct influence on the observed DNA methylation patterns in high and low-PRS individuals, a *cis* methylation quantitative trait loci (mQTL) analysis was performed. This analysis is described in Supplementary Material 1.

3. Results

3.1. Suicide attempt in bipolar disorder was the only PRS associated to SB in the discovery sample

PRS was calculated in the discovery sample using GWAS summary statistics of different psychiatric disorders. Suicide attempt in bipolar disorder was significantly associated to suicidal phenotype in the discovery sample (R^2 = 0.103) p-value = 0.0029). In addition, a significant difference in the PRS for suicide attempt in bipolar disorder was found between individuals with and without SB (p-value = 0.0007). We failed to find any association between SB and other psychiatric traits. Following the PRS for suicide attempt in bipolar disorder, the PRS for suicide attempt in schizophrenia and cross disorder had the highest association with SB in the discovery sample. However, we did not find significant differences for these PRS between individuals with and without SB in our sample (Supplementary Table 3). The results of PRS analyses are shown in Fig. 2 and detailed in Supplementary Table 2.

The twenty SNPs included in the PRS for suicide attempt in bipolar disorder were used for PRS calculation in the target sample. The list of SNPs included in PRS for suicide attempt in bipolar disorder is shown in Table 1.

3.2. Individuals with low-PRS and high-PRS exhibited different DNA methylation profile

PRS was calculated in the target sample using the twenty SNPs found to be correlated with suicidal phenotype in the discovery sample. Next, we classified individuals in high and low PRS depending on whether their PRS was above or below the mean PRS in the target sample, which was 0.0839. The mean PRS in high and low-PRS was 0.1049 and 0.0669, respectively. A significant difference in PRS was found between both groups (p-value < 2.2 e −16). The PRS distribution in high and low-PRS groups is shown in Fig. 3A.

We identified 153 differentially methylated sites between individuals with high and low-PRS, as shown in Fig. 3B. From these, 91 sites were hypermethylated and 62 hypomethylated in the group of high PRS in comparison to low PRS. The top 10 significantly different methylated sites between both groups are listed in Table 2. The complete list of sites with differentially methylated regions between groups is available in the Supplementary Material 2.

Regarding the location of CpG sites relative to CpG islands, 23 sites (15%) were located inside CpG islands. Meanwhile, 26 CpG sites were located in island shores (17%), 12 were found in north and 14 in south shores; eight sites (5.2%) were located in island shelves (six in north and two in south shelf). Finally, 96 sites (62.7%) were found in Open Sea (non-CGI-related sites) (Fig. 4A).

Gene annotation indicated that hypermethylated sites were mapped to 69 genes. Meanwhile, hypomethylated genes were mapped to 42 genes. Regarding the location relative to genes, most of the CpG sites were located in gene bodies (38%). Twenty sites were located in untranslated regions of genes (5′UTR and 3′UTR) and 29 sites in transcription start site regions. (Fig. 4B). Chromosomal annotation indicated that the highest numbers of hypermethylated and hypomethylated sites were found in chromosomes 1 and 2, respectively. The chromosomal distribution of differentially methylated sites is shown in the Supplementary Fig. 2.

The gene ontology analysis with DAVID of genes related to all differentially methylated sites (including hyper- and hypomethylated) indicated enrichment in cell communication (p-value = 0.028, 41 genes including *GNA14, ARHGEF26, PFKFB2, COPS3, KCNA1, GABBR1, CACNB1*), cellular component organization (p-value = 0.03, 40 genes including *RAB3GAP2, ARHGEF26, RTP1, COPS3, TIMM17A, KCNA1*) and synapse (p-value = 0.006, 7 genes: *KCNAB2, STXBP5, TENM2, KCNA1, GABBR1, CYFIP2, DSCAM*), protein binding (p-value = 0.002, 63 genes including *GNA14, RAB3GAP2, LTBP3, COPS3, GABBR1, SLC22A11, PDCD4*). For the latter term additional GO categories indicated enrichment specifically in cytoskeletal protein binding (*FMN2, SYNE2, KIF7, TMEM201, KIF6, LIMCH1, CALD1, RAB14, PARK2, MYLK*).

GO term descriptions for genes related to hypermethylated CpG sites showed high enrichment for cell junction, forebrain development,

Table 1
SNPs correlated with suicidal behavior in discovery sample.

Chromosome	Base-pair position[a]	SNP	Overlapped or nearest genes[b]	A1	A2	Annotation[c]
1	90801258	rs7518543	*RNU6-695P; RP5-827O9.1*	T	C	
1	167445001	rs2995093	*CD247*	G	A	non-coding intronic, intronic
1	179471750	rs10913801	*AXDND1*	T	G	intronic,non-coding intronic
1	188172047	rs1906255	*RN7SKP156; RP11-201A3.1*	G	A	
2	78342416	rs1347723	*AC012494.1*	G	A	non-coding intronic
2	107329516	rs1006472	*EEF1A1P12*	G	T	
3	69432555	rs12330712	*FRMD4B*	C	A	intronic,non-coding intronic
4	23267131	rs16873417	*RP11-453O5.1*	T	C	non-coding intronic
4	117017017	rs701779	*RP11-659O3.1*	G	A	non-coding intronic,3downstream
5	162958461	rs7722476	*MAT2B; RP11-756G12.1*	C	T	
6	133447768	rs9389049	*LINC00326; MTCYBP4*	A	G	
7	123845784	rs6466898	*RP5-921G16.1*	T	C	non-coding intronic
8	130691025	rs6470757	*CCDC26*	A	G	non-coding intronic
10	97119049	rs7900095	*SORBS1*	T	C	intronic,non-coding intronic
11	87006224	rs1893005	*TMEM135*	A	G	intronic
12	47471439	rs2269828	*AMIGO2*	A	G	coding syn
13	70644890	rs299531	*KLHL1*	G	T	intronic
14	92959216	rs11623883	*SLC24A4*	A	G	intronic, coding nonsyn,non-coding intronic
15	34294637	rs603152	*AVEN*	A	C	intronic
18	21736933	rs1049683	*CABYR*	A	C	intronic, coding nonsyn,3downstream

[a] Base-pair position (bp units).
[b] Genes separated by semicolon indicate nearest upstream and downstream gene, respectively.
[c] Indicates the genomic regions of the various transcript isoforms of the annotated gene.

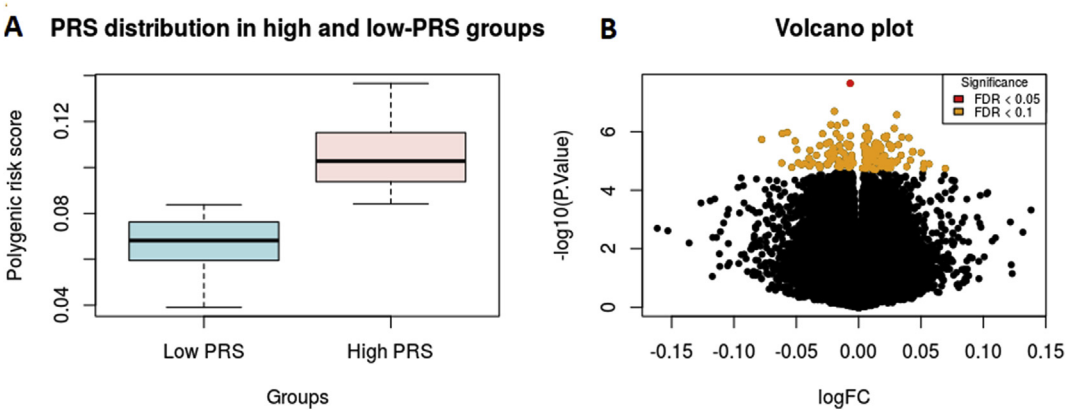

Fig. 3. A) Boxplot of PRS in high and low-PRS groups. The horizontal line in each box indicates the median, boxes indicate 25–75% interquartile ranges, whiskers indicate 1.5 (IQR) boundaries. The y-axis shows the PRS score. B) Volcano plot of DNA methylation differences between high and low-PRS individuals in the target sample. Each point represents a CpG site with mean DNA methylation between both groups on the x-axis and − log10 of the uncorrected P value from a paired test on the y-axis.

Table 2
Top 10 differentially methylated sites between high- and low PRS individuals.

Chromosome	Chromosomal coordinates[a]	CpG site	Gene[b]	logFC	p- value[c]
2	69969370	cg19269713*	*ANXA4*	−0.00684	2.25E-08
2	2.41E+08	cg25446612	*PP14571; GPC1*	0.020476	1.54E-06
4	75543224	cg25339818	–	0.022517	1.40E-06
5	1.34E+08	cg04702335	*PITX1; C5orf66*	0.007371	1.32E-06
6	1.69E+08	cg17802216	*SMOC2*	0.007729	1.64E-06
12	5018805	cg19651132	*KCNA1*	0.00608	7.07E-07
14	64339588	cg17309380	*SYNE2*	0.021672	1.68E-06
15	93442302	cg25875908	*CHD2*	0.008503	1.17E-06
20	42939972	cg27662220	*FITM2*	0.005157	1.40E-06
21	42212910	cg21701521	*DSCAM*	0.007545	1.23E-06

*This site was differentially methylated with a FDR corrected p-value < 0.05.
[a] Chromosomal coordinates: chromosomal coordinates of the CpG (Build 37).
[b] Gene: CpG related gene symbol according to annotation.
[c] Uncorrected p-value.

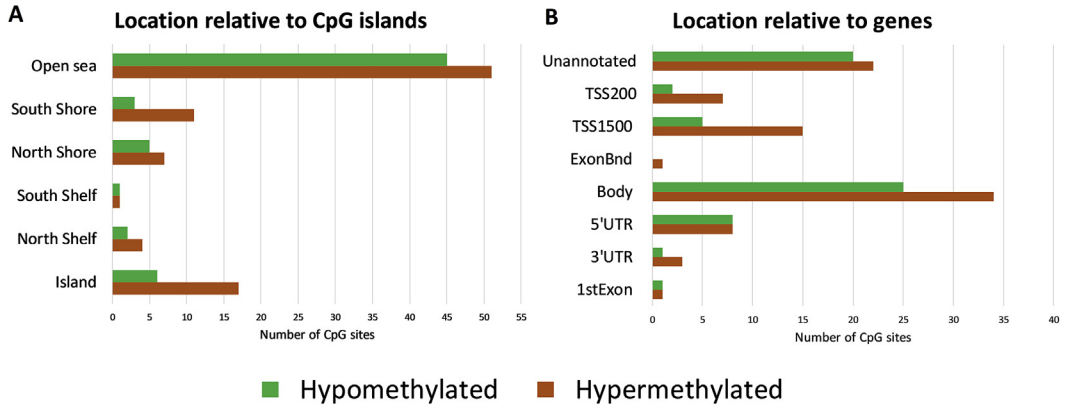

Fig. 4. A)Location relative to CpG islands. The graphic shows the proportion of all the identified CpG sites by their location relative to CpG islands. Island shores indicate flanking shore regions, < 2 kb up- and downstream of CpG islands; Island shelfs indicate sites found 2–4 kb up- and downstream of CpG islands), and open sea refers to sites not related to CpG islands. B) Location relative to genes. TSS1500 (200–1500 nucleotides upstream of transcription start site; TSS200 (up to 200 nucleotides upstream of transcription start site); 5′ UTR (5′ untranslated region); 1st exon; Body (gene body); ExonBnd (exon boundaries), and 3′ UTR (3′ untranslated region).

cell differentiation and cell projection. Regarding the latter term, additional GO terms indicated enrichment for neuron projection morphogenesis (*CTTN, TENM2, NFASC, PARK2, DSCAM, NUMBL*). Meanwhile, GO analysis for genes related to hypomethylated CpG sites indicated an association with ATP binding, ion transport, cell projection, cytoskeletal protein binding, and oxytocin signaling pathway. The GO terms associated to genes related to differentially methylated sites and the genes comprised under each GO term are shown in Fig. 5 and Supplementary Table 4, respectively.

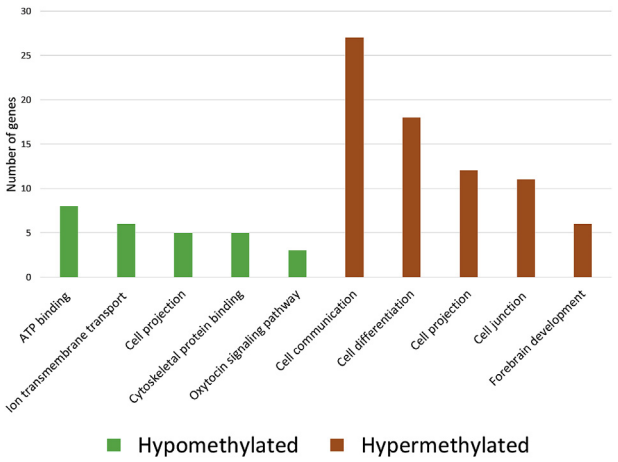

Fig. 5. Gene ontology analysis of genes mapped to differentially methylated CpGs. GO terms of genes related to hypermethylated (orange) and hypomethylated sites (green) in individuals with high PRS relative to individuals with low PRS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3. SNPs associated with SB do not act as cis mQTLs

After the association analysis, we obtained a total of six SNP-CpG pairs with a significant association (*rs10913801*-cg07769737, *rs1006472*-cg17300220, *rs1006472*-cg02025958, *rs1006472*-cg24751773, *rs1006472*-cg03216028, *rs1006472*-cg22402378). None of the identified *cis* mQTLs were found among the SNPs associated to SB in our sample. Functional annotation on mQTLs did not indicate any association with microRNA, miRNA, scaRNAs nor snoRNA targets sites.

4. Discussion

Recent studies have integrated PRS and epigenetic data in other complex psychiatric disorders, such as autism and schizophrenia (Hannon et al., 2016, 2018; Viana et al., 2017). Integrative approaches provide an insight on the genetic variants implicated in the predisposition to epigenetic variations in genes participating in complex disorders. To our knowledge, this is the first study integrating polygenic risk scores and DNA methylation in suicidality.

4.1. Relevant GO terms

One of the most remarkable findings in our results, was the different degree of DNA methylation between individuals with high and low-PRS in CpG sites located in neurodevelopmental genes. Of interest as well, were those differences found in genes involved in pathways contributing to neurodevelopment and brain remodeling, such as cell proliferation, cytoskeletal organization and formation of cell projection. These findings are in line with previous reports of alteration of these biological processes in suicide (Thalmeier et al., 2008; Zhurov et al., 2012; Turecki et al., 2012).

Regarding the neurodevelopment, there is evidence showing that this biological process is highly influenced by epigenetic modifications (including DNA methylation), that regulate cell differentiation and development during the lifetime (Meng et al., 2019; Gapp et al., 2014). It has been suggested that the interaction between predisposing genetic factors and environmental factors leads to those epigenetic changes. Then, these epigenetic changes could alter gene expression leading to morphological and functional alterations of brain circuits resulting in neurodevelopmental alterations (Jaffe et al., 2016).

Additionally, neurodevelopmental alterations have been implicated in the etiology of mental disorders, as it is postulated in the 'neurodevelopmental hypothesis' (Jaffe et al., 2016; McGrath et al., 2003). The neurodevelopmental hypothesis has been deeply explored in schizophrenia, where the interaction between genetic and environmental factors has been identified as a predisposing mechanism for the onset of this disorder (Matrisciano et al., 2018).

Similar to schizophrenia, neurodevelopmental variations have been identified in individuals with SB (Turecki et al., 2012). Recently, the polygenic basis of neurodevelopmental alterations in SB have been acknowledged (Sokolowski et al., 2016). Nevertheless, the effect of genetic background on neurodevelopmental alterations in SB has not been elucidated yet. In this regard, our results suggest that genetic variants in individuals with high suicidal burden might increase the predisposition to DNA methylation variations in genes involved in neurodevelopment and brain remodeling.

Another relevant finding related to brain function, was the representation of genes involved in synapses. Synapses related genes *KCNAB2, STXBP5, TENM2, KCNA1, CYFIP2,* and *DSCAM*, were not related to a specific neurotransmitter system, rather they implied some influence on general synaptic mechanisms (this was not observed with the gene *GABBR1*). This may suggest a global impairment of the synapse, which is relevant due to its potential impact on the disruption of neuronal circuits (van Spronsen and Hoogenraad, 2010). Regarding *GABBR1*, this gene encodes for gamma-aminobutyric acid type B receptor subunit 1; its up-regulation has been identified in the prefrontal cortex of individuals who died by suicide (Klempan et al., 2009; Sequeira et al., 2009). Our results suggest that *GABBR1* may be regulated by DNA-methylation.

Most of the genes that mapped to hypomethylated sites were related to ATP binding, including the gene related to the top differentially methylated CpG site, *ANXA4* as well as the genes coding for ATPases *ATP8B1* and *ATP11A*. An alteration in the expression of genes involved in ATPase activity has been observed in the brain of individuals who died by suicide (Klempan et al., 2009; Pantazatos et al., 2017). However, a misexpression of ATPase genes has not been reported in suicide attempt nor in ideation yet. A possible explanation is that an alteration in the expression of these genes could be brain-specific. Due to the crucial role of ATPases in energy production, further research regarding the role of these genes in other forms of suicidal behavior beside completed suicide is necessary.

4.2. Previous associations on top differentially methylated genes

Among the genes that mapped to top ten differentially methylated sites, we found genes previously linked to psychiatric or neurological disorders, such as epilepsy (*CHD2*) (Lamar and Carvill, 2018), schizophrenia (*GPC1*) (Kim et al., 2019), autism and bipolar disorder (*ANXA4*) (Harripaul et al., 2019; Kazuno et al., 2013). Interestingly, the SNP rs11907319 related to *FITM2* gene was found to be associated to ketamine response in patients with mood disorders (Guo et al., 2019). Since ketamine has shown to reduce suicide behavior in high risk populations as is the case of patients with treatment-resistant major depression disorder (Price et al., 2009; DiazGranados et al., 2010). The role of these genes in SB, particularly the factors influencing their methylation is worthy of exploring in future studies.

The effect of DNA methylation in gene expression varies according to the genomic region where it occurs, i.e., DNA methylation in promoter or enhancer regions is associated to gene repression; meanwhile, DNA methylation in the gene body could have the opposite effect (Jones, 2012). Most DNA methylation differences between high and low-PRS groups identified in the present study were located in gene bodies; therefore, this finding suggests a possible up-regulation of their associated genes.

4.3. Previous findings regarding SNPs associated with SB in our sample

Regarding the SNPs associated with SB in our sample, rs1906255 has been associated with language impairment (Villanueva et al., 2011)

and alcohol dependence (Yang et al., 2005). Due to the association between SB and alcohol use disorder (AUD), it has been proposed that both traits shared a common etiology and risk factors. Thus, the association of rs1906255 with SB in our sample suggests that this SNP may contribute to an increased suicidality reported in individuals with AUD (Wilcox et al., 2004), which makes it a possible candidate for future research in the association of both traits.

On the other hand, rs7900095 has been associated with late-onset Alzheimer (Grupe et al., 2006) and with suicide attempt in individuals with mood disorders (Perlis et al., 2010). The latter association is highly relevant, as the association found in our results provides evidence of the role that this SNP plays in suicidality. It also suggests that its association with SB is not limited to Caucasian population and it could be extended to other forms of SB, not only suicide attempt.

The SNPs associated with SB in the discovery sample did not show a direct influence on the observed methylation differences between high and low-PRS groups, as they were not identified as *cis* mQTLs. The mQTLs identified in our study have not been associated to any disorder yet. Therefore, their influence on the observed methylation differences might be linked to other regulatory mechanisms, such as *trans* mQTLs or transcription factor binding. Whether these mQTLs are implicated in SB should be further investigated.

4.4. Future research directions

Unlike the genome, DNA methylation varies across tissues and cell types (Pashayan et al., 2016). Although the suicidal pathology is localized in the brain, the assessment of DNA methylation changes in the brain of living subjects with SB is limited (El-Sayed et al., 2012). In our study, we identified DNA methylation alterations in genes implicated in brain functions in peripheral blood. Thus, these DNA methylation markers may reflect alterations in the central nervous system; in this case, they could potentially serve as biomarkers. However, the correlation of peripheral DNA markers associated to PRS with brain DNA methylation remains to be tested.

It is worth mentioning that this is the first PRS study for suicidality in a Mexican population. Most genetic studies regarding SB have been performed in Caucasian populations (Zai et al., 2015; Menke et al., 2012; Bani-Fatemi et al., 2016). As genetic factors may vary across populations, the inclusion of Latino populations in future studies will provide valuable information regarding the diversity of genetic background in SB. Ongoing projects will provide more information on the genetic contributors in Mexican individuals with SB (González-Castro et al., 2019a). The inclusion of individuals with different psychiatric disorders and different forms of SB might improve the identification of alterations associated to suicidality independent of mental disorders.

The use of PRS offers the opportunity of using an individualized risk prediction based on personal profiles. PRS has shown clinical potential in different chronic conditions, such as breast cancer, coronary artery disease, obesity, and diabetes (Lambert et al., 2019). Therefore, its use in suicidal behavior might improve the identification of high-risk individuals and subsequently, the implementation of adequate suicide prevention measures. It is important to consider that clinical translational studies are required to assess the benefits of including the PRS in a clinical context, evaluating its performance alone and in combination with current screening tools for suicidal behavior (Mavaddat et al., 2019).

Furthermore, the association of PRS with other molecular traits, i.e., gene expression and protein expression, as well as clinical characteristics such as violent and non-violent suicide attempt, number of suicide attempts, etc. in SB are worthy of exploring in future research. It is important to keep in mind that SB is the result from the interplay of several contributors, including biological, social and environmental factors (Mann, 2003; Turecki et al., 2012). Thus, integrative studies considering more than one data dimension are crucial in the elucidation of the interactive relations between these factors.

4.5. Limitations

Limitations of the present study should be acknowledged. First, the use of microarrays restricted our analysis to probes available in the used platforms. Second, the sample size was relatively small in comparison with previous PRS studies in other populations. Thus, future research with larger samples is required to replicate our results. Third, our sample was highly heterogeneous in terms of psychiatric disorders. This heterogeneity may represent a confounder factor, as we cannot rule out the influence of mental disorders on the obtained results. Although suicidal behavior is a common feature in several mental disorders, characteristics of suicidal behavior may vary according to the comorbid mental disorder. Therefore, future studies including larger sample sizes of individuals with different mental disorders with and without suicidal behavior are necessary to identify disorder – specific alterations. The results obtained from a heterogeneous sample are more likely to be associated with suicidal behavior independently of comorbid mental disorders (Yin et al., 2016; Rodríguez-López et al., 2020). Even though our sample included individuals with different psychiatric disorders, individuals with other psychiatric comorbidities associated to SB were not represented in our sample, such as post-traumatic stress disorder.

In conclusion, our results suggest differences in DNA methylation between individuals with high and low PRS for suicidality. Findings in this study provide an insight regarding the molecular mechanisms underlying neurodevelopmental alterations in SB. Furthermore, this study highlights the promising use of PRS in combination with other molecular traits as a stratification tool in SB.

Contributors

Brenda Cabrera-Mendoza participated in data analysis and results interpretation. Also wrote the original draft of the present manuscript. José Jaime Martínez-Magaña contributed to project conception, supervision of data analysis, results interpretation and writing of the present manuscript. Alma Delia Genis-Mendoza participated in the design of the work, sample processing, and results interpretation. In addition, she revised the present manuscript providing essential ideas for its discussion. Emmanuel Sarmiento contributed to the evaluation and recruitment of patients with eating disorders and suicide attempt (adolescent sample). David Ruíz-Ramos contributed to the evaluation and recruitment of patients with eating disorders and methylation samples processing, Carlos Alfonso Tovilla-Zárate contributed to the evaluation and recruitment of patients with suicide attempt (adult sample). Thelma Beatriz González-Castro contributed to results interpretation. Isela Esther Juárez-Rojop contributed to the evaluation and recruitment of patients with suicide attempt (adult sample). Dulce Dajheanne García-de la Cruz, Michael Escamilla and Erasmo Saucedo-Uribe contributed to the evaluation and recruitment of patients with schizophrenia. Mauro López-Armenta and Fernando García-Dolores contributed to the evaluation and sample collection of individuals who died by suicide. Fernanda Real contributed to DNA isolation from brain samples. Gonzalo Flores and Rubén A. Vázquez-Roque contributed to nucleic acids isolation and results interpretation. Nuria Lanzagorta contributed to the evaluation and recruitment of patients with bipolar disorder. Oscar Rodríguez-Mayoral contributed to the evaluation and recruitment of patients with first psychotic episode. Janet Jiménez-Genchi, Carlos Castañeda-González and Andrés Roche-Bergua contributed to the evaluation and recruitment of patients with neurocognitive disorders. Humberto Nicolini contributed to the conception, design of the work and interpretation of the data. All the authors revised and approved the final version of this manuscript. We agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work.

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Appendix A. Supplementary data

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