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Identification of genetic variants influencing methylation in brain with pleiotropic effects on psychiatric disorders

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ABSTRACT

Psychiatric disorders affect 29% of the global population at least once in the lifespan, and genetic studies have proved a shared genetic basis among them, although the underlying molecular mechanisms remain largely unknown. DNA methylation plays an important role in complex disorders and, remarkably, enrichment of common genetic variants influencing allele-specific methylation (ASM) has been reported among variants associated with specific psychiatric disorders.

In the present study we assessed the contribution of ASM to a set of eight psychiatric disorders by combining genetic, epigenetic and expression data. We interrogated a list of 3896 ASM tagSNPs in the brain in the summary statistics of a cross-disorder GWAS meta-analysis of eight psychiatric disorders from the Psychiatric Genomics Consortium, including more than 162,000 cases and 276,000 controls. We identified 80 SNPs with pleiotropic effects on psychiatric disorders that show an opposite directional effect on methylation and gene expression. These SNPs converge on eight candidate genes: *ZSCAN29, ZSCAN31, BTN3A2*, *DDAH2*, *HAPLN4*, *ARTN, FAM109B* and *NAGA*. *ZSCAN29* shows the broadest pleiotropic effects, showing associations with five out of eight psychiatric disorders considered, followed by *ZSCAN31* and *BTN3A2*, associated with three disorders. All these genes overlap with CNVs related to cognitive phenotypes and psychiatric traits, they are expressed in the brain, and seven of them have previously been associated with specific psychiatric disorders, supporting our results. To sum up, our integrative functional genomics analysis identified eight psychiatric disease risk genes that impact a broad list of disorders and highlight an etiologic role of SNPs that influence DNA methylation and gene expression in the brain.

1. Introduction

Psychiatric disorders are complex disorders that encompass multiple neurologic conditions characterized by changes in mood, thinking and/or behavior that affect over 29% of the worldwide population at least once in lifetime (Steel et al., 2014). The classification and diagnostic criteria for all psychiatric disorders are collected in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Psychiatric disorders show in general a high heritability, and they share part of the underlying genetic basis, as proven by family,

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twin and more recently, genome-wide association studies (GWAS) (Brainstorm Consortium et al., 2018; Smoller et al., 2019). A recent GWAS meta-analysis performed across eight psychiatric disorders has detected 146 risk loci, 109 of them associated with at least two psychiatric disorders, confirming a pleiotropic effect of genetic risk variants. This study also reports significant genetic correlations between most pairs of the studied disorders, highlighting the closest genetic relationship between schizophrenia (SCZ) and bipolar disorder (BIP) ($r_g = 0.70 \pm 0.02$, *p*-value <1E−06) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). However, most of the underlying genetic basis of these conditions still remains undetermined, collectively known as missing heritability (Maher, 2008). The omnigenic model proposes that sub-threshold variants reported in GWAS can explain part of this missing heritability of complex disorders (Boyle et al., 2017; Liu et al., 2019). Interestingly, genetic variants associated with different complex disorders (either with genome-wide significance or sub-threshold) are enriched in active chromatin regions, including promoters and enhancers (Maurano et al., 2012; Roadmap Epigenomics Consortium, 2015; Wang et al., 2016), stressing the importance of considering the functional effect of identified variants.

Epigenetic mechanisms play an important role in complex disorders like psychiatric conditions, as it mediates the interaction between genetics and the environment. DNA methylation is the most stable epigenetic mechanism and it is influenced by multiple environmental exposures (e.g. pollution, tobacco smoke, or nutritional factors, among others) that lead to new DNA methylation patterns (Li and Zhang, 2014; Martin and Fry, 2018). Allele-specific methylation (ASM) occurs when the different alleles of one single nucleotide polymorphism (SNP) are associated with differential levels of methylation at a CpG site, which may lead to changes in gene expression (Meaburn et al., 2010). ASM is heritable, dynamic and remarkably, enriched in regulatory regions associated with histone marks indexing potential promoter and enhancer elements (Benton et al., 2019; Gagliano et al., 2016; Hannon et al., 2015). Furthermore, multiple studies have assessed the contribution of ASM to the susceptibility to specific psychiatric disorders using various approaches (Andrews et al., 2017; Chuang et al., 2013; Gagliano et al., 2016; Hannon et al., 2015; Pineda-Cirera et al., 2019, 2021; Wu and Pan, 2019), and interestingly, some of them have reported enrichment of ASM variants in GWAS data for attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and SCZ (Andrews et al., 2017; Gagliano et al., 2016; Hannon et al., 2015; Pineda-Cirera et al., 2019).

Considering the importance of ASM in specific psychiatric disorders and its impact on gene expression, the aim of the present study is to assess the contribution of ASM to the underlying genetics shared across a set of eight psychiatric disorders by using a systematic approach that combines genetic, epigenetic, and expression data.

2. Material and methods

2.1. Selection of allele-specific methylation SNPs

The SNP selection is fully described in a previous study of our group in which we assessed the contribution of ASM to ADHD susceptibility (Pineda-Cirera et al., 2019). Briefly, we combined the information from two previous studies in *postmortem* brain samples (Gibbs et al., 2010; Zhang et al., 2010) that describe ASM in four areas (cerebellum, frontal cortex, caudal pons and temporal cortex) and obtained 43,132 SNP-CpG pairs involving 33,944 different SNPs and 5,306 CpG sites (Figs. S1-S2). As we observed redundancy between studies and areas (Fig. S2), as well as between SNPs (in linkage disequilibrium; LD), we followed a SNP selection process ending up with 3896 tagSNPs that influence methylation in brain (Figs. S1 and S3). The SNP selection criteria and process is described in Fig. S1, further details can be found in our previous paper (Pineda-Cirera et al., 2019).

2.2. Case-control GWAS datasets

We explored the selection of 3896 ASM tagSNPs in the summary statistics from a GWAS meta-analysis performed by the Cross-Disorder Group of the Psychiatric Genomics Consortium that includes data of eight psychiatric disorders: ADHD (Demontis et al., 2019), anorexia nervosa (ANO) (Duncan et al., 2017), ASD (Grove et al., 2019), BIP (Stahl et al., 2019), major depression (MD) (Wray and The Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2018), obsessive-compulsive disorder (OCD) (Arnold et al., 2018), SCZ (Ripke et al., 2014) and Tourette's syndrome (TS) (Yu et al., 2019). This GWAS meta-analysis consists of 6,786,994 autosomal SNPs, representing a combined sample of 162,151 cases (11.8% ADHD, 2.2% ANO, 11.3% ASD, 12.6% BIP, 36.9% MD, 1.7% OCD, 20.7% SCZ and 2.9% OCD) and 276,846 controls with European ancestry. Diagnose criteria for each of the psychiatric disorders is detailed in a manuscript by the Cross-Disorder Group of the Psychiatric Genomics Consortium (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). The publicly available summary statistics that we used do not include 23andMe data.

2.3. Statistical analysis

First, we performed an enrichment analysis using the Fisher's exact test in R (R Core Team, 2014) to assess whether ASM SNPs are over-represented among the identified risk variants in the cross-disorder GWAS meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). We considered *p*-value thresholds ranging from 5E-02 to 5E-08 and the total number of ASM SNPs present in the cross-disorder meta-analysis (31,486 out of 33,944 SNPs) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

We then explored the contribution of ASM SNPs to different psychiatric disorders by following a sequence of steps (Fig. 1). First, we inspected in the summary statistics of the cross-disorder GWAS meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) the selection of 3896 ASM tagSNPs out of the 33,944 ASM variants described in previous works (Gibbs et al., 2010; Zhang et al., 2010). 302 of these SNPs were not present in the GWAS data, so we applied the Bonferroni correction for multiple testing considering 3594 SNPs ($p \leq$ 1.39E-05, 0.05/3594 tagSNPs). We then discarded possible artifacts in the results by removing those CpG sites that were detected by probes that lie in genomic regions with SNPs variants. We then retrieved tagged ASM SNPs in high LD ($r^2 \geq 0.85$) with the selected SNPs (obtained after applying the Bonferroni correction and discarding probe artifacts) that also correlated in *cis* with the methylation levels of the same CpG sites ($R^2 \geq 0.2$). From all those ASM SNPs, we selected only the ones that show association with at least two psychiatric disorders by using the posterior probability of association with each disorder (m-value ≥0.9; Fig. 1) (Han and Eskin, 2012). Finally, from the associated ASM SNPs obtained through the previous steps we selected only those ASM SNPs that are eQTLs in the brain for genes containing at least one of our selected CpG sites within their possible promoter region (-5Kb to +1Kb from the transcription start site; TSS) and which risk allele shows opposite effects on methylation and gene expression (Fig. 1). To do that, we used GTEx data (Release V8) to assess whether the associated ASM SNPs were described to be eQTLs in any of the available brain areas (The GTEx Consortium, 2020).

2.4. Functional annotation

We assessed functional annotations of the identified ASM SNPs using three methods. First, we inspected if the associated ASM SNPs lie in regions enriched in histone marks related to enhancer (H3K4me1 and H3K27ac) or promoter regions (H3K4me3 and H3K9ac) using the Haploreg v4.1. tool in the available brain areas (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php)(Ward and Kellis, 2016).

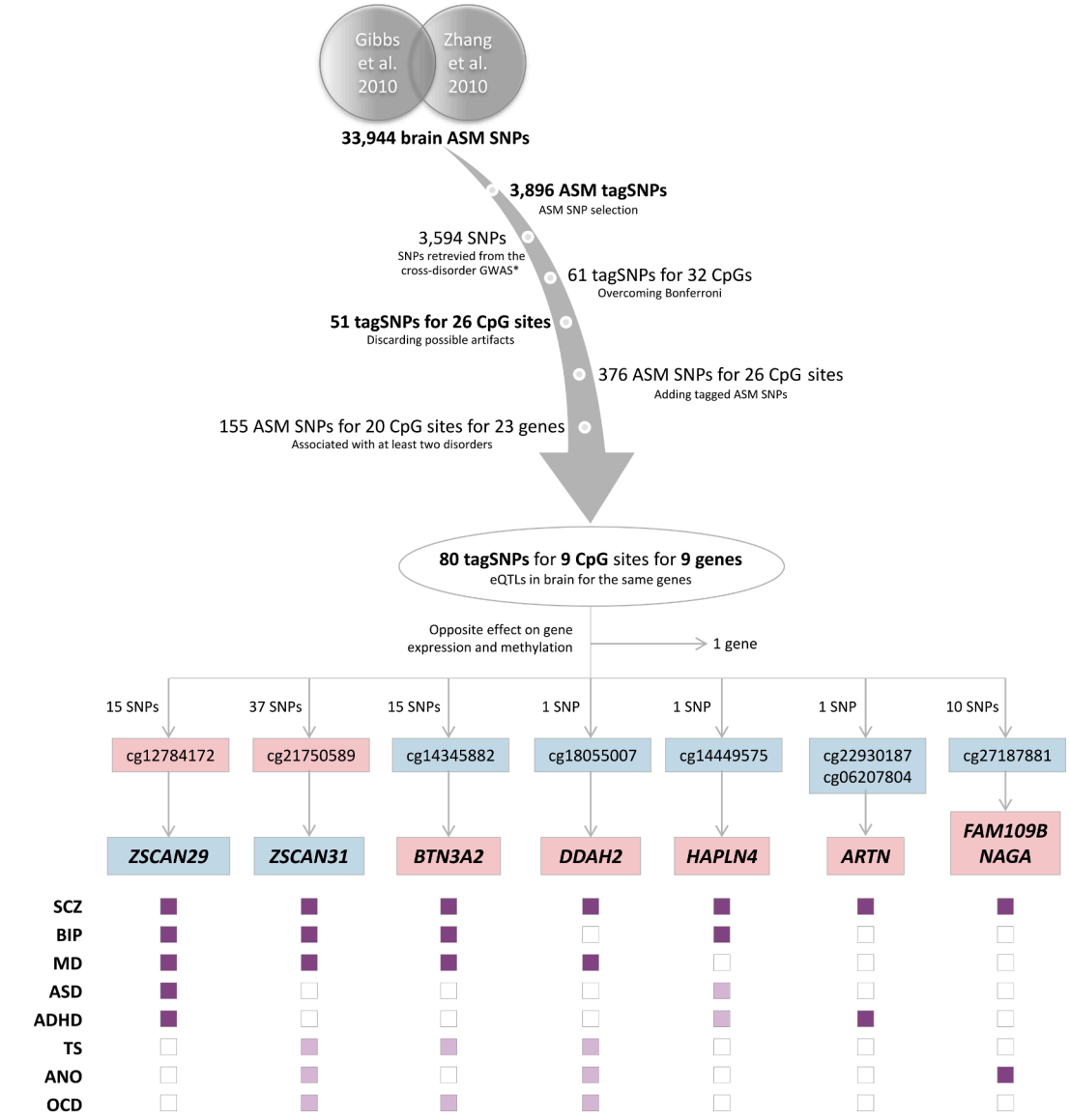

Fig. 1. Outline of the association study carried out from a selection of 3896 SNPs previously reported to display allele-specific methylation (ASM) in brain. The brain areas where ASM was assessed are cerebellum, caudal pons, frontal cortex and temporal cortex (Gibbs et al., 2010; Zhang et al., 2010). SNPs were tested in the summary statistics of the cross-disorder GWAS meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) and Bonferroni multiple testing correction was applied ($p \leq$ 1.39E-05, 0.05/3594 SNPs). The colour of CpG sites and genes indicate the effect of the risk allele on methylation or gene expression, respectively (red: increased, blue: decreased). The coloured squares indicate the probability of association with each disorder considering dark purple: m-value ≥0.9, light purple: 0.7 ≤ m-value <0.9 and white: m-value <0.7). SCZ: Schizophrenia; BIP: Bipolar Disorder; MD: Major Depression; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit/Hyperactivity Disorder; TS: Tourette's Syndrome; ANO: Anorexia Nervosa; OCD: Obsessive-Compulsive Disorder. *Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019 (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Second, we assessed whether the estimated expression of the candidate genes identified, modulated by the prioritized SNPs, is altered in the target phenotype using MetaXcan (Barbeira et al., 2018). Prediction models were constructed using the SNPs located within ±1 Mb from the TSS of the implicated genes and were trained with the RNA-Seq data of 13 GTEx brain tissues (GTEx Consortium et al., 2013). The SNP covariance matrices were generated using the data of European individuals of 1000 Genomes Project Phase 3 (The 1000 Genomes Project Consortium, 2015). Bonferroni correction was applied for multiple testing ($p \leq$ 9.25E-04; 0.05/54 tests (54 gene - brain area combinations)). Finally, we explored if the identified variants had previously been related to alterations on subcortical brain volumes using the summary statistics of a GWAS meta-analysis of seven magnetic resonance imaging (MRI) volumetric measures from the ENIGMA Consortium: Amygdala, Caudate nucleus, Hippocampus, Nucleus Accumbens, Pallidum, Putamen and Thalamus (Hibar, 2015). This GWAS meta-analysis consists of seven million markers inspected in 13,171 subjects of European ancestry (Hibar, 2015). We applied the Bonferroni correction ($p \leq$ 8.93E-05; 0.05/560 (80 SNPs and 7 brain areas)).

3. Results

In the present study we assessed the contribution of brain ASM to the etiology of psychiatric disorders. We first investigated whether the genetic risk variants identified in a GWAS meta-analysis of eight psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) are enriched in variants influencing methylation by

inspecting SNPs displaying ASM in *post-mortem* human brain samples (Gibbs et al., 2010; Zhang et al., 2010). Remarkably, we observed enrichment of ASM SNPs at all association thresholds we evaluated ($p <$ 2.2E-16), along with an increase of the odds ratios (OR) when imposing more stringent *p*-value thresholds (1.75 < OR < 8.90; Table S1).

We then inspected a selection of 3896 tagSNPs displaying ASM in the brain in the same cross-disorder GWAS meta-analysis retrieving the information of 3594 tagSNPs (92.2%). We obtained 61 ASM tagSNPs showing association with the phenotype after applying the Bonferroni correction for multiple testing that correlate with methylation levels of 32 CpG sites in *cis*. After discarding six CpG sites which methylation was detected with probes that recognize genomic regions with SNP variants, we ended up with 51 ASM tagSNPs that correlate with the methylation level of 26 CpG sites in *cis* (Fig. 1 and Table S2). As considering only tagSNPs may overlook true causal SNPs, we included in the analysis 328 additional ASM SNPs (LD, $r^2 \geq 0.85$), tagged by the initial 51 tagSNPs and correlating with the same 26 CpG sites, and retrieved the association *p*-values for 325 of them (99%) (Fig. 1). We then selected those ASM SNPs that were strongly associated with at least two psychiatric disorders (m-value ≥0.9), obtaining 155 ASM SNPs that correlate with the methylation levels of 20 CpG sites (Fig. 1).

Moreover, we explored whether these 155 ASM SNPs are eQTLs for those genes which possible promoter region contains at least one of the highlighted CpG sites. We identified 80 eQTL SNPs in the brain for nine genes. Methylation in promoter regions usually correlates inversely with gene expression, and we observed this pattern for the risk alleles of all the 80 ASM SNPs in the following eight genes: *ZSCAN29, ZSCAN31, BTN3A2*, *DDAH2*, *HAPLN4*, *ARTN, FAM109B* and *NAGA,* pointing them as possible contributors to susceptibility to psychiatric disorders (Figs. 1-3 and S4-S8 and Table S3). Interestingly, 47 out of the 80 ASM SNPs lie in regions with histone marks related to promoter or enhancer regions (Table S4), and six out of the 80 SNPs show nominal associations with volume changes of pallidum (Table S5).

The risk alleles of the 80 ASM SNPs belong to 12 LD blocks, one of them associated with five disorders, two of them with three disorders and nine of them with two disorders (Table S3 and Figs. S9-S12). Considering that all the SNPs from each block are in high LD ($r^2 \geq 0.85$), we assessed the putative causal SNP at each LD block by selecting those variants showing more functional annotations (Table 1) and explored the effect of them on each psychiatric disorder (Figs. 3 and S13-S23). Convincingly, all SNPs from different LD blocks correlate with the same CpG site and have the same (opposite) effect on methylation and on gene expression. Four LD blocks correlate with increased methylation and diminished gene expression of *ZSCAN29* or *ZSCAN31* (Fig. 2 and Tables 1 and S3) and eight of them correlate with decreased methylation and increased gene expression of at least one of the following genes: *BTN3A2*, *DDAH2*, *HAPLN4*, *ARTN*, *FAM109B* and/or *NAGA* (Figs. S4-S8 and Tables 1 and S3). All the variants identified in *ZSCAN29*, *ZSCAN31, BTN3A2* and *DDAH2* show association with SCZ and BIP, the ones with the highest genetic correlation reported ($r_g = 0.70 \pm 0.02$, *p*-value <1E-06) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), and several variants in those genes but *DDAH2* are also associated with MD, with the same directional effects for all the associated disorders (Figs. 1-3, S5-S6, S13-S20, and Table S3). SCZ, BIP and MD are all included in the mood and psychotic disorders group as defined by factor analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Interestingly, most *ZSCAN29* variants also show associations with ASD and ADHD, with the same direction of effects (Fig. 2). These two conditions belong to the early-onset neurodevelopmental disorder group, making *ZSCAN29* the gene with broader pleiotropic effects in our study.

The SNP for *HAPLN4* is associated with SCZ and MD (Figs. 1, S7, S21, and Table S3). Finally, the SNP for *ARTN* is associated with SCZ and ADHD (Figs. 1, S4, S22, and Table S3) and the SNPs for *FAM109B* and *NAGA* to SCZ and ANO, disorders that belong to different groups (Figs. 1, S8 and S23, and Table S3).

Finally, we explored whether the eight genes identified in this study were predicted to be differentially expressed in cases versus controls when considering not only the ASM SNP but also all the SNPs located within ±1 MB from the TSS of each gene using the MetaXcan software (Barbeira et al., 2018). We obtained the same effect direction for *ZSCAN29* in hypothalamus (*Z*-score = −3.79), for *DDAH2* in frontal cortex (Z-score = 5.87), for *HAPLN4* in cerebellum (Z-score = 4.41) and for *NAGA* in caudate basal ganglia and cerebellum (Z-score = 3.53 and 3.62 respectively) (Table S6).

4. Discussion

In the present study we have evaluated the contribution of ASM variants to the genetic basis of eight psychiatric disorders (ADHD, ANO, ASD, BIP, MD, OCD, SCZ and TS). We identified 80 SNPs influencing methylation and gene expression in the brain with pleiotropic effects on at least two psychiatric disorders, which highlighted eight candidate genes: *ZSCAN29, ZSCAN31, BTN3A2*, *DDAH2*, *HAPLN4*, *ARTN, FAM109B* and *NAGA*.

We observed enrichment of ASM variants among the SNPs with broad cross-disorder effects on major psychiatric disorders. These results are consistent with previous studies in which enrichment of ASM variants was observed in a GWAS for ASD, ADHD and SCZ (Andrews et al., 2017; Gagliano et al., 2016; Hannon et al., 2015; Pineda-Cirera et al., 2019). Furthermore, regions with histone marks related to promoter and enhancer regions have previously been found enriched in ASM variants (Benton et al., 2019), and almost 60% of the identified variants in our study lie in regions with histone marks, either enhancers or promoters. All this evidence suggests that ASM is a key functional mechanism that helps to explain the causality of common variation related to complex disorders, identified through GWAS analyses.

Psychiatric disorders share genetic risk factors, and a recent study identified three groups of highly genetically-related disorders based on genetic correlations and factor analysis: mood and psychotic disorders (SCZ, BIP and MD), early-onset neurodevelopmental disorders (ASD, ADHD and TS) and disorders with compulsive behaviors (ANO, OCD and TS) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Most of the strong associations (m-value ≥0.9) detected in the present study belong to the mood and psychotic disorders group, that also correspond to the disorders with larger sample sizes. Interestingly, the genes *ZSCAN31*, *BTN3A2*, *DDAH2* and *HAPLN4* are also associated with psychiatric disorders classified in another group if we apply a less strict threshold (0.7 ≤ m-value <0.9), mainly the disorders with compulsive behaviors (ANO, OCD and TS). This is possibly due to the limited sample sizes of the GWAS performed in these disorders, less than 5000 cases, which reduces the odds to detect significant associations. Further GWAS meta-analysis with larger sample sizes should be carried out to confirm these suggestive associations.

The 80 ASM SNPs we identified show opposite effects on methylation and expression for eight out of nine genes, as expected for methylation occurring in promoter regions, which is the case. Consistently, the direction of the effect on gene expression observed for the ASM SNPs is the same as that observed in the MetaXcan analysis, in which we considered not only ASM SNPs but also all the SNPs located within ±1 MB from the TSS, for *ZSCAN29*, *DDAH2*, *HAPLN4* and *NAGA* in some of the evaluated brain areas, strengthening the results of the present study. Moreover, all eight genes are expressed in the brain (GTEx Consortium et al., 2013) and overlap with CNVs related to cognitive phenotypes or psychiatric traits like autism, intellectual disability or aggressive behavior among others (Firth et al., 2009) (Table S7).

The genes *ZSCAN29* (associated with five disorders: SCZ, BIP, MD, ASD and ADHD) and *ZSCAN31* (associated with three disorders: SCZ, BIP and MD) encode zinc finger transcription factor proteins that belong to the krueppel C2H2-type zinc-finger protein family. Zinc finger proteins are essential in multiple regulatory mechanisms and some have been associated with psychiatric disorders as reviewed by Squassina

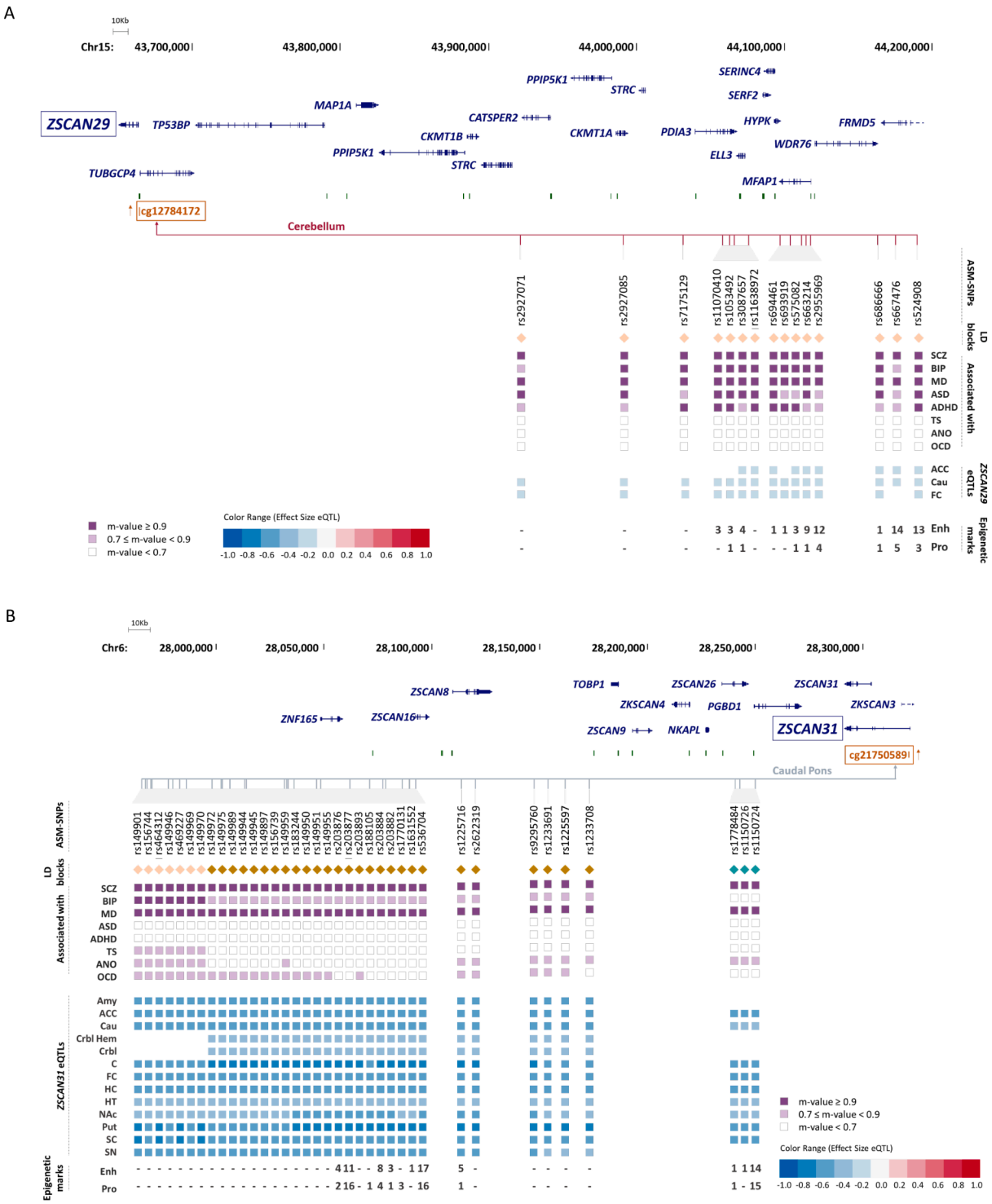

Fig. 2. Genomic context of allele-specific methylation (ASM) variants, methylation and eQTL information for the CpG site cg12784172 (A) and cg21750589 (B). Genes are depicted in dark blue, showing the direction of transcription with an arrow; CpG sites inspected in the reference studies appear in brown; framed CpG sites indicate those sites showing differential levels of methylation for the associated ASM SNPs, and brown arrows indicate the effect on methylation of the risk variants, with indication of the brain regions where the ASMs were described. The tagSNPs are underscored. The coloured rhombuses show the LD blocks present in each region. The framed squares indicate probability of association with each disorder considering dark purple: m-value ≥0.9, light purple: 0.7 ≤ m-value <0.9 and white: m-value <0.7. The coloured squares for eQTLs indicate the effect on gene expression of the risk allele, according to the legend (red: over-expression, blue: under-expression). Amy: Amygdala; ACC: anterior cingulate cortex; Cau: caudate basal ganglia; Crbl Hem: cerebellar hemisphere; Crbl: cerebellum; C: cortex; FC: frontal cortex; HC: hippocampus; HT: hypothalamus; NAc: nucleus accumbens basal ganglia; Put: putamen basal ganglia; SC: spinal cord; SN: substantia nigra. The number of enhancer (H3K4me1 and H3K27ac) and promoter (H3K4me3 and H3K9ac) histone marks found in the different brain areas are displayed for each SNP. '-' indicates no known enhancer or promoter histone marks. Enh: enhancer; Pro: promoter. SCZ: Schizophrenia; BIP: Bipolar Disorder; MD: Major Depression; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit/Hyperactivity Disorder; TS: Tourette's Syndrome; ANO: Anorexia Nervosa; OCD: Obsessive-Compulsive Disorder. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

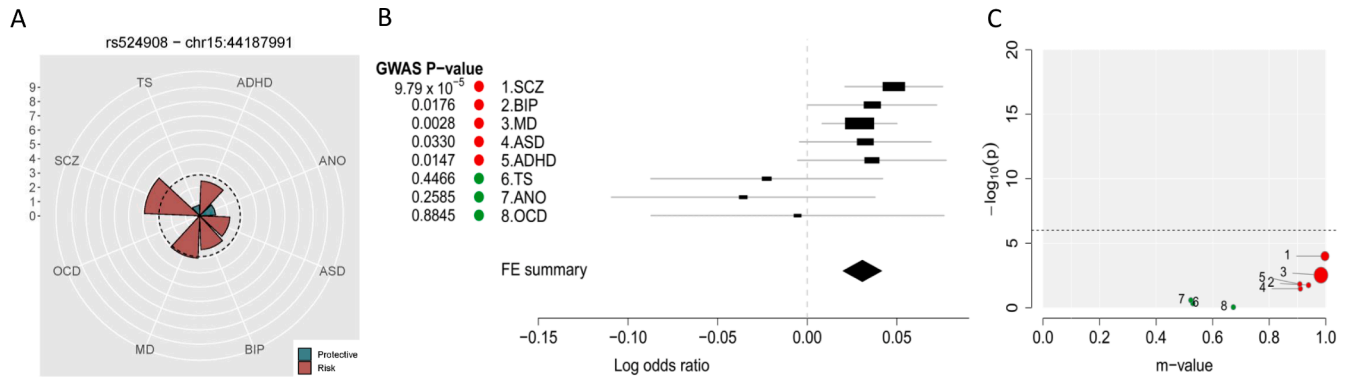

Fig. 3. Effects and associations of rs524908, near the *ZSCAN29* gene, on each psychiatric disorder. A) The radius of each wedge corresponds to the absolute values of *Z*-scores (log(ORs)/SE) obtained from association tests of the SNP for the studied disorders. The effect of the SNP, calculated for the allele A1, is indicated with the red colour (risk) or green colour (protective). The dotted line around the center indicates statistically significant SNP effects that account for Bonferroni multiple testing of 12 SNPs (*p*-value = 0.0041). B) Forest-plot displaying disorder-specific association *p*-values, log(ORs) and standard errors of rs524908. The meta-analysis p-value summary statistic is displayed in the bottom of the forest plot. C) PM-plot of the m-values (the posterior probability that the effect exists in each disorder) and -$\log_{10}$(p-value) of each disorder-specific association. Disorders are depicted as a dot, the size is proportional to the sample size of individual GWAS and the colour indicates the m-value, considering red: m-value ≥0.9, green: 0.2 ≤ m-value <0.9 and blue: m-value <0.2. SCZ/1: Schizophrenia; BIP/2: Bipolar Disorder; MD/3: Major Depression; ASD/4: Autism Spectrum Disorder; ADHD/5: Attention Deficit/Hyperactivity Disorder; TS/6: Tourette's Syndrome; ANO/7: Anorexia Nervosa; OCD/8: Obsessive-Compulsive Disorder. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2019, such as *ZNF804A* with SCZ and BIP (O'Donovan et al., 2008; Steinberg et al., 2011; Sun et al., 2015) or *ZEB2*, *ZKSCAN4* and *ZNF750* associated with SCZ (Guan et al., 2016; Khan et al., 2016; Ripke et al., 2013; Yue et al., 2011). Furthermore, *ZSCAN31* is located in the region of chromosome 6 known as major histocompatibility complex (MHC, 6p21.32-p22.1), enriched in histone-related genes and immune system genes that has previously been associated with SCZ in multiple GWAS (Mokhtari and Lachman, 2016). Remarkably, zinc finger genes have also been associated with response reactions to psychotropic drugs, which points to an interesting role to be further explored in the understanding of the contribution of these proteins to psychiatric disorders (Squassina et al., 2019).

BTN3A2 is associated with three mood and psychotic disorders (SCZ, BIP and MD), it is also located in the MHC region and it is involved in the immune response (Messal et al., 2011). Interestingly, several studies have highlighted an involvement of the immune system in psychiatric disorders (Bennett and Molofsky, 2019; Dantzer, 2018; Liberman et al., 2018) because of the crosstalk that exists between immunological function and the brain (Bennett and Molofsky, 2019). Furthermore, three of the variants located near *BTN3A2* had previously been associated with cognitive phenotypes or psychiatric disorders. Specifically, the rs9467714 and rs3799378 SNPs were associated with general cognitive function (*p*-value = 9.13E-11 and 2.24E-11, respectively) (Davies et al., 2018) and the rs3799380 SNP was associated with MD (p-value = 7.8E-09) (Nagel et al., 2018).

All the other highlighted genes are associated with two psychiatric disorders, schizophrenia being one of the two conditions (Fig. 1). The results presented in this work are concordant with previous SCZ GWAS (studies that are part of the cross-disorder GWAS meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019)) that also pointed out the *HAPLN4*, *FAM109B* and *NAGA* as candidate genes for the disorder (Ripke et al., 2014, 2013), and *DDAH2* is located in the MHC region, extensively associated with SCZ (Mokhtari and Lachman, 2016). The functions of *DDAH2* and *ARTN* are also of interest. *DDAH2* encodes an enzyme that regulates nitric oxide generation (Leiper et al., 1999). Nitric oxide has multiple well known functions in brain (Picón-Pagès et al., 2019) and it has been suggested to have a key role in psychotic disorders like SCZ (Maia-de-Oliveira et al., 2016; Nasyrova et al., 2015). *ARTN* encodes artemin, a protein that is necessary for sensory and sympathetic peripheral neuron survival in vitro and possibly also for the survival of dopaminergic neurons of the ventral mid-brain (Baloh et al., 1998). Furthermore, a knock-out mouse model for *ARTN* presents aberrations in the migration and axonal projections in the sympathetic nervous system (Honma et al., 2002). Lastly, the *ARTN* expression was altered in blood of MD patients (Otsuki et al., 2008) and was also associated with ADHD both in the largest GWAS performed on ADHD (Demontis et al., 2019) and in a work carried out by our group in which we studied the contribution of ASM to ADHD (Pineda-Cirera et al., 2019).

There are several strengths and limitations in the present study that should be discussed. Strengths: Although GWAS of psychiatric disorders have been quite successful in identifying novel associations, one of their major weaknesses has been the lack of knowledge on the functionality of the identified variants and so, the difficulty in deciphering the true causal genetic risk factors. In the present study we have overcome this major limitation by using SNPs influencing ASM, therefore focusing our attention only on variants with a possible functional effect. For instance, we highlight five genes (*ZSCAN31*, *HAPLN4*, *ARTN*, *NAGA* and/or *FAM109B*) that lie inside the 146 significant loci reported in the cross-disorder GWAS meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), however, only *ZSCAN31* was named in that study. Other studies have also used ASM to get new insights on the functional effect of SNPs reported in GWAS for specific psychiatric disorders (Andrews et al., 2017; Chuang et al., 2013; Gagliano et al., 2016; Hannon et al., 2015; Pineda-Cirera et al., 2019, 2021; Wu and Pan, 2019), with some results concordant with the ones described in the present study: 1) There is enrichment of brain ASM variants among sub-threshold and genome-wide significant variants identified in GWAS for specific psychiatric disorders (Andrews et al., 2017; Gagliano et al., 2016; Hannon et al., 2015; Pineda-Cirera et al., 2019); 2) ASM SNPs are overrepresented in regulatory regions (Gagliano et al., 2016; Hannon et al., 2015) and 60% of the reported variants lie in regions with histone marks related to enhancer and promoter regions; 3) Exploration of ASM SNPs has been useful in the assessment of the functional role of variants described in GWAS for psychiatric disorders (Andrews et al., 2017; Gagliano et al., 2016; Pineda-Cirera et al., 2019, 2021; Wu and Pan, 2019). Furthermore, three SNPs (rs9467704, rs9467714 and rs3799378) and multiple genes identified in the present study have previously been associated with specific cognitive phenotypes or psychiatric disorders. Limitations: We have not tested all possible ASM SNPs as the studies performed by Gibbs et al., 2010 and Zhang et al., 2010 were carried out by using genotyping platforms that do not include all the SNPs present in the genome. Furthermore, we only considered *cis* ASM variants and discarded from the study *trans* ASM variants (less

Table 1
Selection of putative causal allele-specific methylation (ASM) SNPs for each linkage disequilibrium (LD) block according to functional annotations.

	SNP information				[1]Association values from the cross-disorder GWAS meta-analysis																	
			Alleles				m-value								[2]Correlation with methylation				[3]Epigenetic marks			
SNP	CHR	BP	A1	A2	OR	p-value	SCZ	BIP	MD	ASD	ADHD	TS	ANO	OCD	Effect on methylation	Tissue	p-value	R^2	Enhancer	Promoter	[4]Effect on gene expression	[5]Effect on brain volumes
rs2906458*	1	44,336,389	A	G	0.95	8.04E-07	**0.990**	0.509	0.234	0.612	**0.970**	0.374	0.514	0.421	↓ cg22930187	crbl[#]	5.55E-10	0.23	6	–	↑ *ARTN*	–
															↓ cg06207804	crbl[#]	1.10E-12	0.29				
rs9467704	6	26,319,486	T	C	0.91	3.11E-18	**1**	0.693	**0.930**	0.187	0.006	0.309	0.352	0.703	↓ cg14345882	pons[&]	2.77E-09	0.25	2	–	↑ *BTN3A2*	↑ Pallidum
																tctx[&]	7.62E-09	0.24				
rs9467714*	6	26,340,785	A	G	0.86	4.67E-17	**1**	0.880	**0.973**	0.455	0.032	0.731	0.639	0.899		tctx[&]	2.56E-08	0.22	1	2		↑ Pallidum
rs3799378*	6	26,404,374	A	G	1.06	2.64E-10	**1**	0.288	**0.984**	0.310	0.042	0.239	0.214	0.340		pons[&]	7.44E-09	0.24	8	6		↑ Pallidum
																tctx[&]	5.01E-08	0.21				
rs7773938	6	26,474,044	T	C	0.94	7.26E-18	**1**	**0.985**	**0.999**	0.119	0.016	0.264	0.580	0.642		pons[&]	2.35E-08	0.22	17	16		–
rs149946	6	27,970,031	T	G	0.95	1.94E-11	**1**	**0.959**	**1.000**	0.593	0.626	0.716	0.806	0.789	↑ cg21750589	pons[&]	1.03E-08	0.23	–	–	↓ *ZSCAN31*	↑ Pallidum
rs536704	6	28,092,603	T	G	1.06	7.45E-12	**1**	0.778	**1.000**	0.354	0.589	0.518	0.662	0.653		pons[&]	1.41E-10	0.29	17	16		–
rs1150724	6	28,250,236	T	C	0.95	1.31E-11	**1**	0.034	**0.926**	0.306	0.061	0.447	0.714	0.366		pons[&]	3.65E-08	0.22	14	15		–
rs1043618	6	31,783,507	C	G	0.95	1.05E-14	**1**	0.330	**0.986**	0.057	0.016	0.759	0.702	0.827	↓ cg18055007	crbl[&]	1.81E-08	0.26	7	16	↑ *DDAH2*	?
rs524908	15	44,187,991	A	C	1.04	5.11E-06	**0.997**	**0.939**	**0.983**	**0.910**	**0.908**	0.530	0.523	0.673	↑ cg12784172	crbl[&]	2.19E-09	0.29	13	3	↓*ZSCAN29*	–
rs2905421*	19	19,457,908	A	C	1.05	9.21E-08	**1**	**0.910**	0.000	0.819	0.832	0.122	0.385	0.366	↓ cg14449575	crbl[#]	6.74E-10	0.22	4	3	↑ *HAPLN4*	–
rs2143139	22	42,614,401	C	G	1.06	3.72E-07	**0.999**	0.051	0.007	0.023	0.164	0.026	**0.908**	0.313	↓ cg27187881	pons[&]	4.30E-10	0.27	16	6	↑ *NAGA*, ↑ *FAM109B*	?

ASM: Allele-specific methylation; [1]Data obtained from the GWAS meta-analysis of eight psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019); [2]Described in Zhang et al., 2010 and Gibbs et al., 2010; [3]eQTL information for brain tissues for the genes with a highlighted CpG site in their possible promoter region; [4]Histone marks found in brain areas; [5]Data from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (Hibar, 2015); SNP: Single Nucleotide Polymorphism; CHR: Chromosome; BP: Position (build hg19); A1: Allele 1; A2: Allele 2; All alleles are reported in the forward strand; OR: Odds Ratio (calculated on A1); SCZ: Schizophrenia; BIP: Bipolar Disorder; MD: Major Depression; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit Hyperactivity Disorder; TS:Tourette Syndrome; ANO: Anorexia Nervosa; OCD: Obssesive-Compulsive Disorder; Effect: Direction of the risk allele effect on DNA methylation levels; *: Significant tagSNPs overcoming Bonferroni multiple testing correction, the other SNPs are ASM SNPs in LD with these significant tagSNPs; Underlined allele: Risk allele; In bold: Significant associations between ASM tagSNPs and each psychiatric disoder (m-value ≥0.9); [#]Information from Zhang et al., 2010; [&]Information from Gibbs et al., 2010; crbl: Cerebellum; tctx: Temporal cortex.

common). In addition, the number of ASM SNPs described in cerebellum is higher compared to the other tissues studied. And lastly, there is an imbalance of the sample sizes used in the cross-disorder GWAS meta-analysis, and this could limit the power to detect associations for the disorders with smaller samples.

5. Conclusions

We used an integrative approach combining genetic, epigenetic and expression data that allowed us to highlight 80 SNPs influencing methylation and gene expression in brain and having pleiotropic effects on several psychiatric disorders. These SNPs point at eight genes, namely *ZSCAN29*, *ZSCAN31*, *BTN3A2*, *DDAH2*, *HAPLN4*, *ARTN*, *FAM109B* and *NAGA*. Among them, *ZSCAN*29 is associated with several mood and psychotic disorders and with early-onset neurodevelopmental disorders, turning it into the gene with the broadest pleiotropic effect followed by *ZSCAN31* and *BTN3A2,* associated with mood and psychotic disorders. Further investigation should be carried out to understand the specific role of these genes in the susceptibility to psychiatric disorders.

Declaration of interest

The authors declare no conflict of interest.

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Author contributions

LP-C and JC-D performed all the analyses included in this study; LP-C, JC-D, BC and NF-C designed the study; LP-C prepared the first draft of the manuscript; LP-C, JC-D and PHL prepared figures and tables; LP-C, JC-D, PHL, BC and NF-C reviewed and edited the manuscript. BC and NF-C coordinated the study and supervised the manuscript preparation. All authors contributed to and approved the final version of the manuscript.

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Appendix A. Supplementary data

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