# IDENTIFYING EPIGENETIC BIOMARKERS OF RESILIENCE

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ABSTRACT

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Early-life exposure to disadvantage predicts a number of health and academic disparities. Even so, 40-60% of youth reared in disadvantaged contexts evidence resilient outcomes. Although these youth provide an important model of successful adaptation to adversity, we know relatively little about the origins of their positive outcomes, particularly the role of biological mechanisms. The current study sought to identify methylomic biomarkers of resilience in a unique sample of 135 twin pairs residing in disadvantaged neighborhoods. We conducted a Methylome Wide Association Study (MWAS) across the entire sample to uncover differentially methylated probes (DMPs) for psychiatric, academic, and social resilience, as well as resilience across domains. We uncovered methylome-wide significant DMPs for social and academic resilience and suggestive DMPs for each of the four resilience phenotypes. Pathway analyses suggested that methylation in pathways related to DNA repair and transcription and initiation of RNA Polymerase III are implicated in academic resilience while those related to T cell receptor signaling are implicated in social resilience. These analyses also highlight the role of the *BRF1* gene and the HLA region in academic and social resilience, respectively. To narrow in on DMPs that were specifically environmental in origin, we then conducted twin difference analyses with the discordant MZ twin pairs for each corresponding resilience phenotype. The methylome-wide significant DMPs did not differ significantly across discordant MZ twin pairs. Our findings predominantly highlight the role of biological mechanisms in resilience, providing support for the structural organizational model of resilience.

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# INTRODUCTION

Disadvantage refers to a spectrum of circumstances linked to systemic inequity. These include low familial socio-economic status (SES), disadvantaged neighborhoods (community violence, low cohesion), and scholastic disadvantage (high student-teacher ratios, limited resources, and inadequate buildings) (Wodtke, Harding, & Elwert, 2011). These forms of disadvantage are known to predict lower levels of a number of key health (Alvarado, 2016; Campbell, Shaw, & Gilliom, 2000; Duncan & Murnane, 2011; Raposa, Hammen, Brennan, O'Callaghan, & Najman, 2014) and academic outcomes (Campbell et al., 2000; Duncan & Murnane, 2011; Wodtke et al., 2011), including school readiness, academic performance, and attention skills. In doing so, they also serve to perpetuate systemic inequality across generations (Duncan & Murnane, 2011). Even so, not all youth reared in disadvantaged contexts suffer these consequences. Indeed, resilient outcomes are in fact quite common (40-62% of exposed youth; Luthar, 2015; Masten, 2001; Vanderbilt-Adriance & Shaw, 2008a). Resilience refers to an individual's positive adjustment and competent functioning within the context of adversity (Luthar, Cicchetti, & Becker, 2000). Resilient youth provide a model of successful adaptation to adversity and thus understanding how environmental and biological factors may enable these positive outcomes is of great importance.

Of note, while much of the early literature in the field conceptualized resilience as an individual trait that a given person does or does not possess, this conceptualization has since been viewed as problematic, since resilience is often domain-specific and can develop over time. More recent work has thus explicitly reconceptualized resilience as a dynamic outcome that is influenced by the individual's attributes, as well as their familial and community-level context (Luthar, et al., 2000; Masten, 2001; Rutter, 2006). A handful of theoretical frameworks of

resilience have been developed, with several researchers advocating for an integrative model that incorporates an ecological-transactional perspective (Curtis & Cicchetti, 2003; Luthar et al., 2000). The ecological-transactional model (Cicchetti & Lynch, 1993) incorporates multiple levels of ecology, including culture, community, family, and previous development, each of which contain potentiating and compensatory factors that shape outcomes. Potentiating factors refer to those that decrease the probability of resilience, while compensatory factors refer to those that increase the probability of resilience. The model specifically suggests that there are transactions between potentiating and compensatory factors, and that adaptation or maladaptation in response to adversity is dependent on how the child handles potentiating factors at each level, as well as the presence of compensatory factors.

Extant empirical literature on resilience has largely taken their cue from the ecological-transactional model of resilience, focusing all but exclusively on behavioral and psycho-social factors that promote or constrain resilience (Curtis & Cicchetti, 2003). Researchers have noted the protective role of parental warmth and monitoring for child outcomes following economic hardship (McLoyd, 1998) and divorce (Forgatch & DeGarmo, 1999). Similarly, cognitive functioning and warm parenting have been found to moderate the relationship between adversity and rule-governed, prosocial behavior (Conger & Conger, 2002; Kolvin, Miller, Fleeting, & Kolvin, 1988; Vanderbilt-Adriance & Shaw, 2008b). Emotion regulation has also been found to buffer against adversity in the development of positive social relationships, and cognitive and socioemotional competence (Alvord & Grados, 2005). Additionally, family warmth and cohesion were shown to predict academic achievement in disadvantaged youth (Orthner, Jones-Sanpei, & Williamson, 2004). Overall, parental warmth and monitoring, cognitive functioning, socio-economic status, emotion regulation, family warmth and cohesion, and self-perceptions

have been linked to academic achievement, prosocial behavior, self-confidence, positive mental health, and positive peer relationships (Conger & Conger, 2002; Curtis & Cicchetti, 2003).

These findings regarding behavioral and psycho-social factors that promote resilience have already contributed much to our knowledge base. Even so, some have questioned why the vast majority of resilience research omits meaningful consideration of biological factors, as these may well be an important part of the process of resilience (Curtis & Cicchetti, 2003). Indeed, the structural-organizational model of resilience (Cicchetti & Cannon, 1999) was developed in response to research reconceptualizing the brain as 'plastic', or comprised of groups of neurons that are interconnected in part as a function of experiential demands. The structural-organizational model builds on the ecological-transactional model of resilience, but argues that both biological and environmental factors exist within a cycle of reciprocal feedback and influence, and that developmental organization evolves through both top-down and bottom-up processes. In this way, the structural-organizational model incorporates both biological and psychological mechanisms, and does so across multiple levels of analyses.

A growing number of studies have taken up this call arguing for research that informs our understanding of the role of biological mechanisms in the development of resilience (Burt, 2017; Curtis & Cicchetti, 2003; Karatsoreos & McEwen, 2013; Luthar et al., 2000; McEwen, Gray, & Nasca, 2015; Panter-Brick & Leckman, 2013). One key possibility in this regard relates to epigenetics and the biological embedding of stress via the methylation (e.g., silencing or activation) of genes. Several epigenetic studies have found evidence of methylation resulting from environmental stressors, predicting outcomes ranging from stress-response (Smith, Zhao, Wang, Ratliff, Mukherjee, Kardia, ... & Needham, 2017) to physical health (Notterman & Mitchell, 2015) and depression (Sun, Kennedy, & Nestler, 2013).

Given the growing literature examining the role of methylation in response to stressors, it is somewhat surprising to note that literature examining the role of methylation in resilience to stressors remains scarce. That said, there are a handful of relevant empirical studies, all using animal models (Szyf, Weaver, Champagne, Diorio, & Meaney, 2005; Weaver, Cervoni, Champagne, D'Alessio, Sharma, Seckl, ... & Meaney, 2004; Zhang, Hellstrom, Bagot, Wen, Diorio, & Meaney, 2010). Weaver et al., (2004), for example, utilized rats to model the impact of maternal care (specifically, pup licking and grooming (LG) and arched-back nursing (ABN)) on the epigenome. Analyses revealed that high levels of LG and ABN altered DNA methylation at the GR exon $1_7$ promoter site. A cross-foster design in which the biological offspring of low LG and ABN mothers received care from high LG and ABN mothers (and vice-versa) indicated that maternal behavior appears to directly program methylation at this site regardless of germ line transmission. Detailed measurement of methylation at several time points further revealed that these methylation differences in response to maternal care emerged over the first week of life and were maintained into adulthood. What's more, the use of a histone deacetylase (HDAC) inhibitor trichostatin A (TSA) was able to reverse this methylation in the adult (post-mitotic) offspring hippocampus, and to reverse the negative effects of low LG and ABN maternal behavior on GR expression and the HPA stress response (Weaver et al., 2004; Szyf et al., 2005). The latter findings bolster the conclusion that the effects of maternal behavior on offspring are a function of methylation alterations.

Elliot and colleagues (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010) assessed changes in methylation in rats exposed to stress. They made use of an established social defeat protocol in which mice are forced to "intrude into the space territorialized by a larger mouse of a more aggressive genetic strain, leading to an agonistic encounter that ultimately

results in intruder subordination" (Krishnan, Han, Graham, Berton, Renthal, Russo, ... & Ghose, 2007). This protocol was established for 10 consecutive days to induce anhedonia and social avoidance. For the days that followed, the mice were assessed during a social interaction with an unfamiliar mouse in a neighboring chamber. Researchers discovered that while most mice avoided the neighbor, a subset of the mice exhibited behavioral resiliency to the social defeat and interacted with the mouse. Analyses revealed that the resilient mice had significantly increased methylation of the *Crf* promoter as compared to other mice.

In sum, although research is still limited, there is reason to expect that the methylome may be an important component of resilience to adversity. Meaningfully extending this line of work to understand resilience in living humans will be trickier than it might seem, however. Although usually discussed as a product of the environment only, the DNA methylome is also known to be genetically-influenced (Grundberg, Meduri, Sandling, Hedman, Keildson, Buil, ... & Wilk, 2013; Van Dongen, Nivard, Willemsen, Hottenga, Helmer, Dolan, ... & Beck, 2016; Zhang, Moen, Liu, Mu, Gamazon, Delaney, ... & Zhang, 2014). As such, what may appear to be environmentally-induced methylomic biomarkers for a given outcome could in fact reflect genetic effects, a potential confound that undercuts the conclusions of human methylation studies. Discordant monozygotic (MZ) twin designs are considered the gold standard for overcoming this uncertainty in living humans (Burt, McGue, Iacono, & Krueger, 2006). MZ twins are genetically identical and yet can and do have different methylomes as a result of their unique environmental experiences (Fraga, Ballestar, Paz, Ropero, Setien, Ballestar, ... & Boix-Chornet, 2005). Unfortunately, most twin studies are population-based and include relatively few youths exposed to adversity (and even fewer who demonstrate resilience to that adversity). The utilization of a sample enriched for disadvantage to study the role of methylation in resilience

would thus offer significant promise for our understanding of differences in adaptability to adversity.

**Current Study**

The current study will do just this, identifying epigenetic biomarkers of resilience in a unique sample of twins enriched for disadvantage. We will specifically identify epigenetic biomarkers (i.e., methylated probes) predicting academic resilience, social resilience, psychiatric resilience, and resilience across domains. Analyses will first be conducted across the entire sample of twins, allowing us to identify general epigenetic biomarkers of resilience. We will then conduct twin difference analyses in only discordant MZ pairs, allowing us to narrow in on those epigenetic biomarkers that are specifically environmental in origin. Based on the animal literature reviewed above, we specifically hypothesize that we will find evidence of methylated sites that predict resilience (i.e., academic, social, psychiatric, and across domains) to disadvantage and that differences in methylation between discordant MZ twins will predict differences in their resilience, strengthening causal inferences.

# METHODS

## Participants

Participants were recruited as part of the Twin Study of Behavioral and Emotional Development in Children (TBED-C), a study within the population-based Michigan State University Twin Registry (MSUTR; Burt & Klump, 2013; Klump & Burt, 2006). The TBED-C includes two independent samples collected between 2008 and 2015: a population-based sample of 1,054 twins from 528 families recruited from across lower Michigan and an "at-risk" sample of 1,000 twins from 502 families residing in modestly-to-severely disadvantaged neighborhoods in the same recruitment area. Participating twins were screened for cognitive or physical conditions that would impede completion of the assessment (e.g., a significant developmental delay). Children provided informed assent, and informed consent was obtained from parents. Zygosity was determined using physical similarity questionnaires administered to the twins' primary caregiver (Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998).

Recruitment procedures are detailed at length in prior work (Burt & Klump, in press). In brief, families were recruited directly from birth records, or from a population-based registry that was itself recruited via birth records, via anonymous recruitment mailings in conjunction with the Michigan Department of Health and Human Services. Recruitment procedures for the "at-risk" sample were restricted to those families residing in neighborhoods where 10.5% or more of households were living below the poverty line (the median for Michigan neighborhoods in 2008) according to census-level data. The response rate for the population-based and "at-risk" samples were 62% and 57%, respectively. The at-risk sample was significantly more racially diverse (15% Black, 75% White) than the population-based sample, reported lower family income (the means were $72,027 and $57,281, respectively; Cohen's d = –0.38), and had higher paternal

felony convictions (d = 0.30). The final "at-risk" sample appears representative of the full sample of families we attempted to recruit as indexed via a brief questionnaire administered to approximately 85% of nonparticipating families (Burt & Klump, 2013).

Participants in the current study were pulled primarily from the "at-risk" sample, although we also include those in the population-based sample who would have met criteria for the "at-risk" sample (N=266 of the 528 families). This yielded a total of 768 twin pairs residing in disadvantaged neighborhood contexts, of which saliva assays were completed for 144 twin pairs. Saliva assays had previously been completed for 48 DZ male-male twin pairs as part of Dr. S. Alexandra Burt's UH3 grant proposal. To supplement this sample, 96 additional MZ twin pairs were selected from available pairs for assaying. All MZ twin pairs discordant for resilience across domains were selected, and an equal number of resilient and non-resilient concordant pairs were selected who matched the gender and poverty level demographics of the discordant pairs. Following assay quality control procedures and exclusion of participants with insufficient informant data to compute outcomes of interest, 270 participants from 135 full twin pairs (115 MZ; 20 DZ) and six singletons formed the primary sample for the current study (total N = 276). All 20 DZ pairs were male-male, whereas among MZ pairs, 69 were male-male and 46 were female-female. The remaining singletons included 5 males and 1 female. All twins ranged in age from 6 to 11 years old at the time their questionnaires and saliva samples were collected.

**Measures**

Maternal reports on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), particularly the competency and psychopathology subscales, served as our primary measure of resilience. The CBCL is one of the most commonly used instruments for assessing academic and

social competence, as well as internalizing and externalizing problems prior to adulthood (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009).

**Academic Resilience.** The School Competency subscale of the CBCL served as our measure of academic resilience. Mothers responded to a four-part question about academic performance on a 4-point scale ranging from "Failing" to "Above Average", as well as 3 binary (yes/no) questions. This subscale includes items that assess school performance across subject domains, special education services received, repeated classes, and academic or other school related problems (e.g., Does your child receive special education or remedial services or attend a special class or special school?).

**Social Resilience.** The Social Competency subscale of the CBCL served as our measure of social resilience. Mothers responded to six questions assessing the child's involvement in organizations, number of friends, contact with friends, behavior with others, and behavior alone (e.g., About how many times a week does your child do things with any friends outside of regular school hours?).

**Psychiatric Resilience.** An absence of psychopathology score served as our measure of psychiatric resilience. Mothers rated the extent to which a series of statements described their child's behavior during the past 6 months; responses were made on a 3-point scale ranging from 0 (never) to 2 (often/mostly true). We examined all eight psychopathology scales in the CBCL: Anxious/Depressed (e.g., Fears certain animals, situations, or places, other than school), Withdrawn/Depressed (e.g., There is very little he/she enjoys), Somatic Complaints (e.g., Constipated, doesn't move bowels), Social Problems (e.g., Complains of loneliness), Thought Problems (e.g., Hears sounds or voices that aren't there), Attention Problems (e.g., Can't concentrate, can't pay attention for long), Rule-Breaking (e.g., Breaks rules at home, school, or

elsewhere), and Aggressive Behavior (e.g., Destroys things belonging to his/her family or others). For the current study, we recoded each of these eight subscales as binary variables that indicate whether the child was at or above (1) or below (0) the borderline clinical significance cut-point for that scale (Achenbach & Rescorla, 2001). The eight dichotomous variables were then summed and reverse scored to form an absence of psychopathology score ranging from 0 to 8, where a higher score reflects less psychopathology.

**Resilience across domains.** Consistent with state-of-the-science studies of socio-emotional resilience, we are defining overarching resilience in the face of disadvantage as both the absence of psychopathology and the presence of social and academic competencies (Luthar, et al., 2000; Masten, 2001; Rutter, 2006). Therefore, a dichotomous indicator of resilience across domains was computed with individuals above the CBCL social and academic competency subscale cut points (t-score = 40; Achenbach & Rescorla, 2001) and below the CBCL internalizing and externalizing score borderline cut points (t-score = 60; Achenbach & Rescorla, 2001) considered "resilient" (N = 135), whereas all others were considered "non-resilient" (N = 141) in at least one domain. Seventy-five twin pairs were concordant for resilience, while 60 pairs were discordant for resilience.

**Assaying the Methylome**

Saliva samples were collected during the twin-family's assessment using Oragene collection kits (DNA Genotek). DNA was extracted using the Oragene Laboratory Protocol Manual Purification of DNA. Extracted DNA was then sodium bisulfite converted and methylation was assessed in the converted DNA using the Infinium Human Methylation EPIC Bead Chip (Illumina). DNA conversion and methylation measurement were performed by the University of Michigan Sequencing Core.

**Data Processing and Methylation Score Calculation**

Thorough quality control and intra-sample normalization procedures were employed using the Chip Analysis Methylation Pipeline for Illumina HumanMethylation450 and EPIC (ChAMP) Bioconductor package (Butcher & Beck, 2015; Morris, Butcher, Feber, Teschendorff, Chakravarthy, Wojdacz, & Beck, 2014) in R version 3.6.3 (R Core Team, 2014). Samples with a high proportion of failed probes (≥10%) were removed (n=1). Poorly performing probes were removed if their detection p-value was above 0.01 (n=86415 probes), if the bead count was greater than 3 in at least 5% of samples (n=3608 probes), if probes aligned to multiple locations (cross-hybridizing probes; Nordlund, Bäcklin, Wahlberg, Busche, Berglund, Eloranta, & Heyman, 2013), or if probes were not located at CpG sites (n=2242). Filtering was also conducted for probes that overlapped with single nucleotide polymorphisms (SNPs; a common polymorphism in which single base pairs of a nucleotide vary) using the Infinium HD Methylation SNP List (n=88382 probes removed) (Zhou, Laird, & Shen, 2016). We then removed probes located on sex chromosomes (n=12610) as our analyses were conducted across sex. Furthermore, in order to detect any sample switches that may have occurred, parent-reported sex was compared with the overall amount of methylation detected on both sex chromosomes. These two measures were consistent and therefore no sample were removed due to sex mismatches. In order to correct for probe design bias, we used the champ.norm function (Teschendorff, Marabita, Lechner, Bartlett, Tegner, Gomez-Cabrero, & Beck, 2013) of the ChAMP package. The COMBAT function of the Surrogate Variable Analysis Bioconductor package was then used to correct for batch effects by slide and then array (Leek, Johnson, Parker, Fertig, Jaffe, Zhang, Storey, Torres, 2020). Finally, cell type proportions were estimated for the most common cell types in saliva using the Epigenetic Dissection of Intra-Sample-

Heterogeneity (EpiDISH) Bioconductor package (Zheng, Breeze, Beck, & Teschendorff, 2018). These procedures yielded methylation values (log2 methylated/unmethylated DNA at a specific probe) across 728,396 CpG sites for 276 participants.

**Methylome-Wide Association Study (MWAS)**

The MWAS was performed using regression to identify batch-adjusted methylation sites that predicted resilience (i.e., social, academic, psychiatric, and across domains), so-called differentially methylated probes (DMPs). Specifically, we fit logistic and ordinary least squares (OLS) regression models in R, version 3.6.3 (R Core Team, 2014) for our dichotomous and continuous outcomes, respectively. To account for the non-independence of twins within pairs, we corrected for the standard errors by fitting our models within a heteroskedasticity-consistent covariance matrix estimator using the sandwich package in R (Zeileis, 2006). Moreover, because there are heterogenous mixtures of cells in complex tissues such as those in saliva, variation in cell-type proportions can confound MWAS studies and inflate results. To control for potential confounders, we included gender, age, zygosity, ethnicity, and three cell types (i.e., epithelial, fibroblast, and natural killer cells) as covariates in our models. A p-value threshold of $P<9x10^{-8}$ was used to declare a DMP methylome-wide significant (Mansell, Gorrie-Stone, Bao, Kumari, Schalkwyk, Mill, & Hannon, 2019) and $P<1x10^{-5}$ for suggestive DMPs.

**Pathway Analysis**

To gain insight into the biological pathways affected by resilience, we used ConsensusPathDB (CPDB) (Kamburov, Christoph, Lehrach, & Herwig, 2009; Kamburov, Pentchev, Galicka, Wierling, Lehrach, & Herwig, 2011) to test for overrepresentation of top suggestive MWAS findings located within genes in the biological pathways in the Reactome (Croft, Mundo, Haw, Milacic, Weiser, Wu, & Jassal, 2014) database. For a pathway to be

considered enriched, a cut-point of P<.01 was utilized and at least two genes among the top MWAS findings had to be present.

**MZ Difference Analysis**

Finally, we conducted twin difference tests in R version 3.6.3 (R Core Team, 2014) in which we compared discordant MZ co-twins to strengthen causal inferences. Because MZ co-twins cannot differ in their epigenome as a consequence of genetic differences (as they are genetically-identical), any differences in the methylome of co-twins points towards environmental mediation. We computed differences in batch-adjusted methylation scores for the significant and suggestive DMPs from the MWAS as well as for the four resilience phenotypes. The sample for each analysis was restricted to twin pairs discordant on the corresponding outcome. We then regressed methylation difference scores for the DMPs and covariates (i.e., gender, age, and ethnicity, each on the twin pair level) on resilience (i.e., academic, social, psychiatric and across domains) difference scores. DMPs were then compared to a 95% significance threshold ($p \leq .05$).

# RESULTS

## Descriptive Statistics

Descriptive statistics for resilience across domains, psychiatric resilience, academic resilience, and social resilience are available in **Table 1**. Approximately half of participants were considered to be resilient across domains. Moreover, approximately half of MZ twin pairs were discordant for resilience across domains, whereas 61% were discordant for social resilience, 38% for academic resilience, and 30% for psychiatric resilience. The majority of participants exhibited high scores for psychiatric and academic resilience, however, social resilience scores were more variable. Finally, means and standard deviations of the four resilience phenotypes in MZ twins and DZ twins were equivalent.

**Table 1.** Descriptive Statistics

| | Monozygotic Twins (MZ) | | | | | Dizygotic Twins (DZ) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Construct** | **Mean** | **SD** | **Min** | **Max** | **N** | **Mean** | **SD** | **Min** | **Max** | **N** |
| **Resilience Across Domains** | 0.50 | .50 | .00 | 1.00 | 240 | 0.39 | .49 | .00 | 1.00 | 41 |
| **Psychiatric Resilience** | 5.52 | .93 | .00 | 6.00 | 237 | 5.51 | .98 | 2.00 | 6.00 | 41 |
| **Academic Resilience** | 4.85 | 1.12 | .00 | 6.00 | 238 | 4.54 | 1.17 | 1.50 | 6.00 | 40 |
| **Social Resilience** | 7.42 | 2.26 | 1.00 | 13.50 | 238 | 7.12 | 2.63 | 2.50 | 13.50 | 41 |

*Note.* Means, standard deviations (SD), minimums (Min), maximums (Max), and sample size (N) are presented for each of the four resilience phenotypes. On the left are the descriptive statistics across individuals who are in a monozygotic twin pair and on the right are the descriptive statistics across individuals who are in a dizygotic twin pair.

## Methylome-Wide Association Study (MWAS)

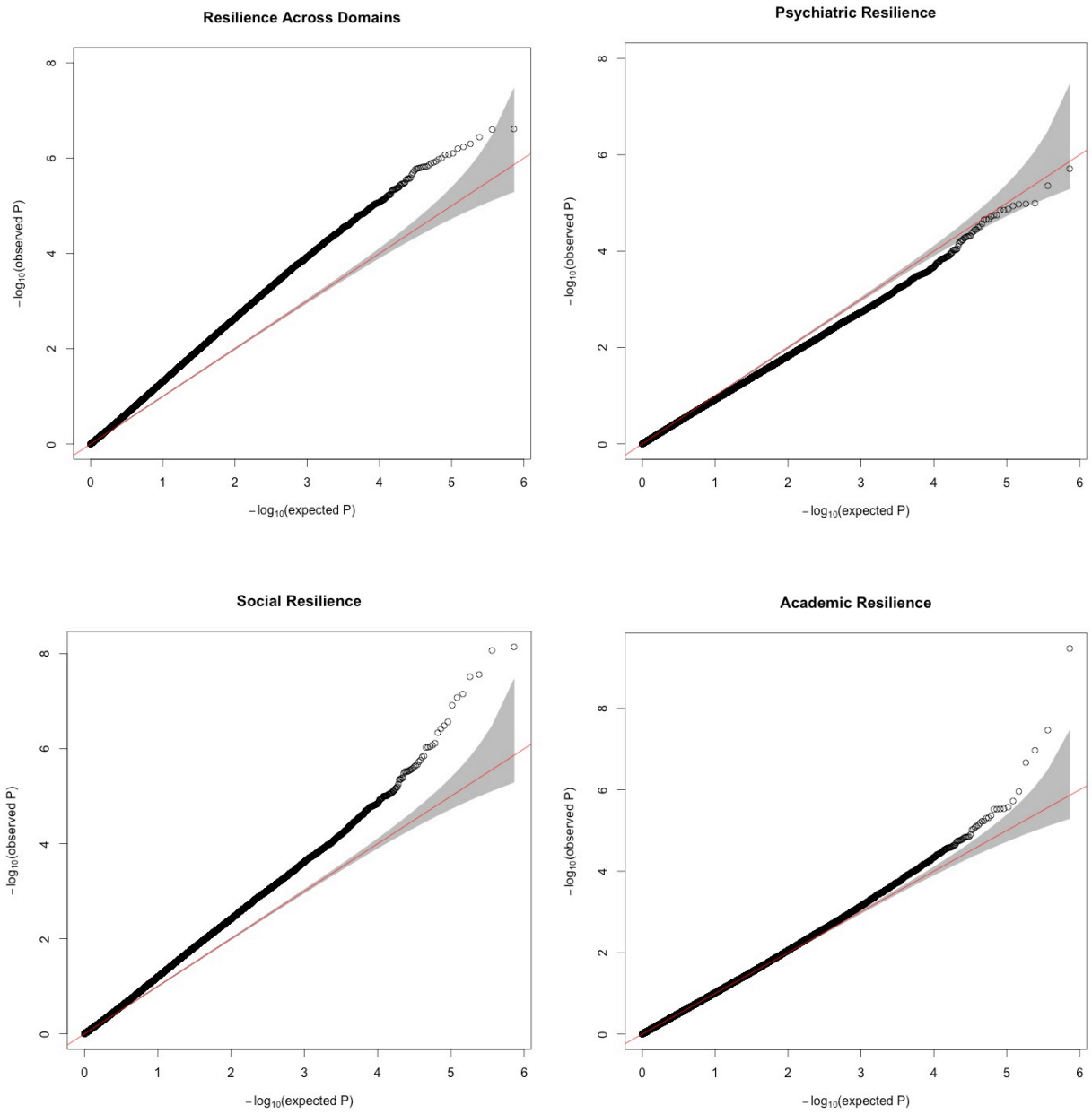
The quantile-quantile (QQ) plots for each of the resilience outcomes are shown in Figure 1. The number of points above the 95% confidence interval, deviating from the line of expected points according to the null hypothesis, indicates a considerable number of significant or

suggestive findings for resilience across domains, academic resilience, and social resilience. However, the plot for the psychiatric resilience does not depict points deviating from the line that are above the 95% confidence interval, suggesting that the results for this MWAS are consistent with the null expected values. The Manhattan plots in Figure 2 provide a visual of the location of methylome-wide significant ($P \leq 9 \times 10^{-8}$) and suggestive ($P \leq 1 \times 10^{-5}$) CpG sites associated with each of the four MWAS outcomes or DMPs. Figure 2 shows that associated CpG sites are spread across the methylome.

Information about the location of the top ten significant and/or suggestive MWAS DMPs and test statistics for each outcome are provided in Table 2 (this information is also provided for all MWAS results in Table 5 in the appendix). Table 2 also includes information about whether a DMP is in a potentially coding (exon or expressed sequence) or not coding (intron or intervening sequence) region of a gene, as well as whether it is in a region of the genome that has a large number of GC base pairs and CpG dinucleotide repeats (CpG island).

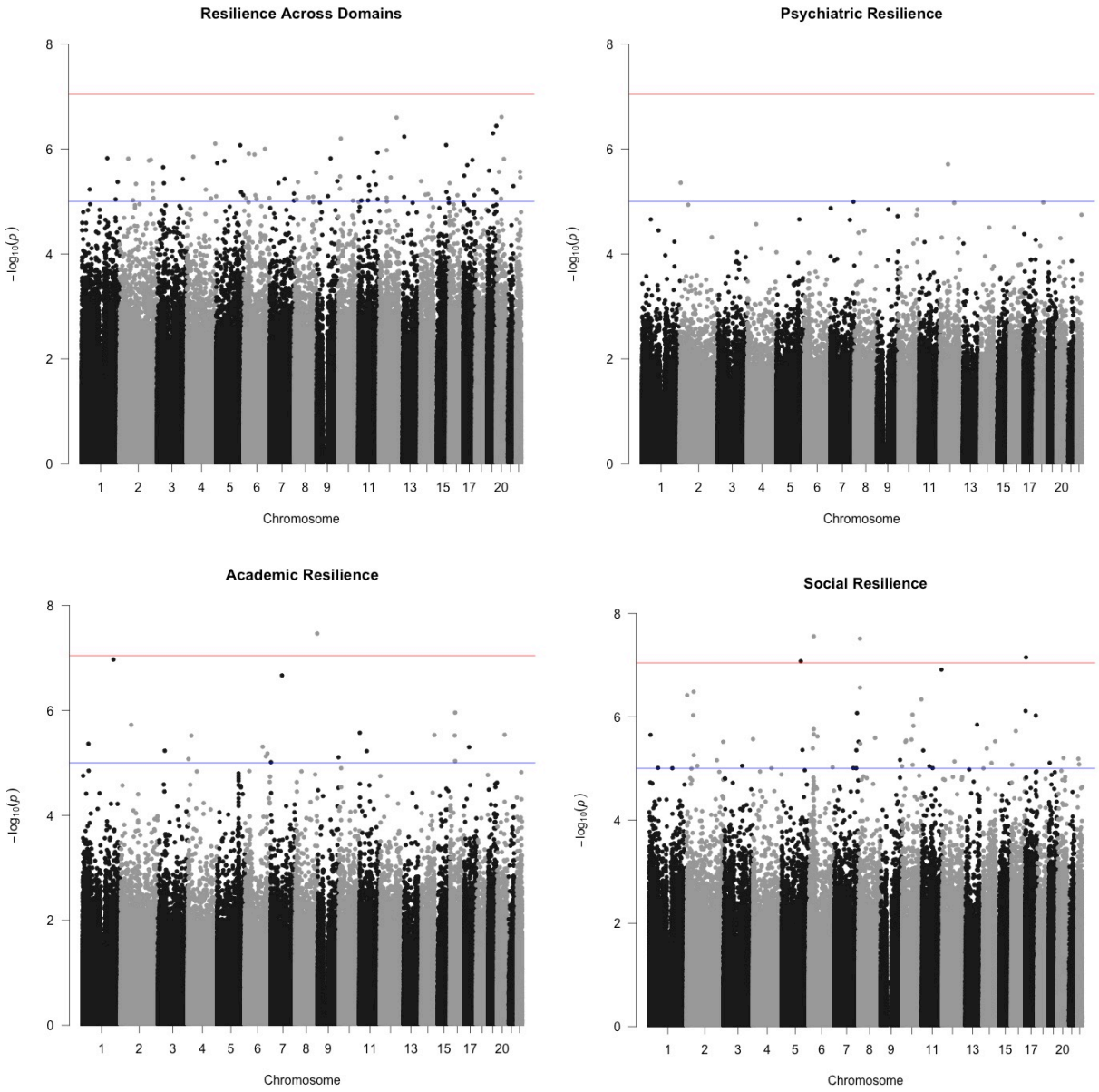
Results indicated that, although there were no methylome-wide significant DMPs associated with resilience across domains, there were 90 suggestive DMPs. One of the top suggestive DMPs was located in an intron of *SOX30,* which is a member of the SOX family of transcription factors involved in determining cell fate and regulating embryonic development (Osaki, Nishina, Inazawa, Copeland, Gilbert, Jenkins, ... & Semba, 1999). Another top DMP was located in an exon of *PSMB8* which encodes for a member of the proteasome B-type family and is associated with immune pathways (Muchamuel, Basler, Aujay, Suzuki, Kalim, Lauer, ... & Shwonek, 2009).

**Figure 1.** Methylation Wide Association Study Quantile-Quantile Plots




*Note.* Quantile-quantile (QQ) plots of observed CpG association P-values (y-axis) against p-values expected under the null hypothesis of no effect of the CpG (x-axis) for each of the four outcomes. The negative logarithm in base 10 of the association P-value is plotted. The red line depicts the expectation under the null hypothesis in which methylation is not associated with the outcome. Deviation of points above the 95% confidence interval (grey shaded areas) in the right upper corner are indicative of potentially significant and/or suggestive findings.

**Figure 2.** Methylation Wide Association Study Manhattan Plots




*Note.* Manhattan Plots of the -$\log_{10}$ P-values organized by chromosome. The red line is for methylome-wide significant (P< 9 x 10-8) and the blue line is for suggestive (P< 1 x 10-5) CpG sites associated with each of the four MWAS outcomes.

**Table 2.** Top Ten Significant and/or Suggestive Methylation Wide Association Study Differentially Methylated Probes

| Model | Probe | Chr | Start | Beta | Z/T-value | P-value | Gene | Genomic Features |
|---|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg08862567 | 20 | 33447234 | 80.275 | 5.161 | 2.452E-07 | *GGT7* | Intron; CpG island |
| | cg15869383 | 19 | 58258088 | -129.038 | -5.087 | 3.630E-07 | *ZNF776* | Intron; CpG island |
| | cg23044017 | 19 | 36822441 | -79.445 | -5.026 | 5.013E-07 | *LINC00665* | Exon; CpG island |
| | cg02536150 | 10 | 17754084 | 45.363 | 4.981 | 6.314E-07 | *STAM* | Intron |
| | cg24059404 | 4 | 184580365 | -193.388 | -4.937 | 7.929E-07 | *RWDD4* | Exon |
| | cg24221965 | 15 | 81422778 | 23.580 | 4.925 | 8.436E-07 | *C15orf26* | Intron |
| | cg16373426 | 5 | 157079899 | 88.290 | 4.924 | 8.499E-07 | *SOX30* | Intron |
| | cg09114799 | 12 | 48152514 | -242.566 | -4.881 | 1.056E-06 | *RAPGEF3* | Exon |
| | cg18056754 | 11 | 122955452 | 62.652 | 4.860 | 1.172E-06 | *CLMP* | Intron |
| | cg03078854 | 6 | 32810000 | 96.825 | 4.850 | 1.233E-06 | *PSMB8* | Exon |
| Psychiatric Resilience | cg00059246 | 12 | 54337928 | 3.673 | 4.866 | 1.957E-06 | *HOXC13* | Intron |
| | cg10674017 | 2 | 3201975 | -15.245 | -4.689 | 4.405E-06 | *TSSC1* | Intron |
| Academic Resilience | cg09169455 | 5 | 16843339 | -2.185 | -6.528 | 3.399E-10 | *MYO10* | Intron |
| | cg27413290 | 8 | 144552724 | -4.250 | -5.687 | 3.422E-08 | *ZC3H3* | Intron; CpG Island |
| | cg23901896 | 1 | 201976445 | -10.226 | -5.465 | 1.073E-07 | *ELF3* | Intron |
| | cg22018084 | 2 | 69038737 | -2.543 | -4.874 | 1.887E-06 | *ARHGAP25* | Intron |
| | cg03116740 | 11 | 841334 | 3.376 | 4.799 | 2.668E-06 | *POLR2L* | Intron |

*Note.* 'Probe' is the name of the CpG probe in the human reference genome hg19/GRCh37, 'Chr' is Chromosome, 'Start' is the base pair location of the probe (human reference genome hg19/GRCh37), 'Gene' is the gene the probe is located in, and 'Genomic Feature' indicates if the probe is located in an intron, exon, or CpG island. Also shown are the signed test statistic values for regression: 'Z-value' for the dichotomous outcome of resilience across domains, 'T-value' for the continuous outcomes, 'P-values', and 'Beta' or regression coefficient. The top ten methylome-wide significant ($P \leq 9 \times 10^{-8}$) and/or suggestive ($P \leq 1 \times 10^{-5}$) MWAS DMPs are displayed for each outcome.

**Table 2.** (cont'd)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Academic Resilience | cg20678377 | 20 | 47667339 | -2.715 | -4.780 | 2.909E-06 | *CSE1L* | Intron |
| | cg09895822 | 14 | 105738159 | 8.444 | 4.778 | 2.947E-06 | *BRF1* | Intron; CpG Island |
| | cg16444294 | 16 | 28925789 | 17.201 | 4.773 | 3.004E-06 | *RABEP2* | Exon |
| | cg00421032 | 4 | 22493280 | 9.058 | 4.772 | 3.025E-06 | *GPR125* | Intron |
| | cg08857221 | 1 | 37941360 | 4.155 | 4.694 | 4.315E-06 | *ZC3H12A* | Exon |
| Social Resilience | cg22321318 | 7 | 157294387 | 17.100 | 5.979 | 7.231E-09 | *AC006372.5* | Intron; CpG Island |
| | cg17416722 | 6 | 32554384 | 6.440 | 5.728 | 2.753E-08 | *HLA-DRB1* | Intron |
| | cg25960393 | 8 | 9106558 | 5.018 | 5.708 | 3.064E-08 | *RP11-115J16.1* | Exon |
| | cg14321269 | 17 | 6658197 | 17.674 | 5.546 | 7.061E-08 | *XAF1* | Exon |
| | cg25998860 | 5 | 126853953 | -114.782 | -5.512 | 8.389E-08 | *PRRC1* | Intron |
| | cg15559076 | 11 | 128109596 | 18.105 | 5.439 | 1.220E-07 | *RP11-702B10.1* | Intron |
| | cg11070274 | 8 | 9106609 | 5.106 | 5.278 | 2.721E-07 | *RP11-115J16.1* | Exon |
| | cg20424973 | 2 | 3045240 | 40.116 | 5.209 | 3.811E-07 | *LINC01250* | Intron |
| | cg10985094 | 17 | 3631481 | 23.115 | 5.064 | 7.701E-07 | *ITGAE* | Intron |
| | cg12738264 | 7 | 148725794 | -210.602 | -5.044 | 8.463E-07 | *PDIA4* | Exon; CpG island |

The psychiatric resilience MWAS yielded 2 suggestive DMPs and no methylome-wide significant DMP's. The top suggestive DMP was located in an intron of *HOXC13* which has been implicated in cancer prognosis and belongs to the homeobox family of genes that encode transcription factors involved in morphogenesis (Panagopoulos, Isaksson, Billström, Strömbeck, Mitelman, & Johansson, 2003). The second suggestive DMP was located in an intron of *TSSC1*, one of several genes in a tumor-suppressor gene region (Hu, Lee, Connors, Johnson, Burn, Su, ... & Feinberg, 1997).

There were two methylome-wide significant and 20 suggestive DMPs associated with academic resilience. The top methylome wide significant DMP was located in an intron of *MYO10* which encodes a member of the myosin superfamily proteins and is associated with increased risk for childhood apraxia of speech (Peter, Wijsman, Nato Jr, University of Washington Center for Mendelian Genomics, Matsushita, Chapman, ... & Raskind, 2016). The second methylome-wide significant DMP was located in an intron and CpG island of *ZC3H3*, a gene that plays a critical role in the export of polyadenylated mRNAs from the nucleus and is involved in RNA cleavage (Hurt, Obar, Zhai, Farny, Gygi, & Silver, 2009). A top suggestive DMP was located in an intron and CpG island of *BRF1,* which encodes a subunit of the RNA Polymerase III transcription initiation factor and has been associated with neurodevelopmental abnormalities (Borck, Hög, Dentici, Tan, Sowada, Medeira, ... & Wenzeck, 2015).

Finally, there were six methylome-wide significant and 54 suggestive DMPs associated with social resilience. The top methylome-wide significant DMP was located in an intron and CpG island of *AC006372.5*, also known as *LOC101927914*, an uncharacterized RNA gene. The second top methylome-wide significant DMP, as well as a suggestive DMP, were located in an intron of *HLA-DRB1*. In addition, another suggestive DMP was located in an intron of *HLA-*

*DQB2*. *HLA-DRB1* and *HLA-DQB2* are located in the HLA region on chromosome 6, a large region of linkage disequilibrium indicating that these may not be independent signals (Simmonds & Gough, 2007).

**Enriched Pathways**

The majority of significant or suggestive DMPs were located in unique genes; 76 of 90 for resilience across domains, 2 of 2 for psychiatric resilience, 16 of 22 for academic resilience, and 47 of 60 for social resilience. Using a list of unique genes for each resilience outcome, we examined enrichment of pathways in the Reactome database using ConsensusPathDB (CPDB). All of the significantly enriched pathways are provided in Table 3. Resilience across domains yielded four significantly enriched pathways. The top significant pathway was the 'Listeria Monocytogenes Entry into Host Cells', which is involved in regulating the entry of bacterium that cause the majority of food-borne outbreaks. No prominent theme emerged among these results. There were no significant enriched pathways for psychiatric resilience, likely due to the small number of significant or suggestive DMPs for this outcome.

For academic resilience, we observed eight significantly enriched pathways. The *POLR2L* and *BRF1* genes overlapped in five pathways implicated in transcription or initiation of RNA Polymerase III. RNA Polymerase III serves as a catalyst for the synthesis of small RNAs (e.g., *tRNAs, 5S rRNA, snRNA)* considered to be essential for various cellular functions (Abascal-Palacios, Ramsay, Beuron, Morris, & Vannini, 2018). The *POLR2L* gene encodes a subunit of RNA Polymerase I, II, and III, and is therefore heavily involved in synthesizing messenger RNAs (Acker, Murroni, Mattei, Kedinger, & Vigneron, 1996). In addition, the *POLR2L* and LI*G3* genes overlapped in three pathways involved in gap-filling and nucleotide excision DNA repairs. As a member of the DNA ligase family, the *LIG3* gene is involved in excision repairs

**Table 3.** Enriched Pathways

| Model | Pathway | p-value | q-value | Effective Size | Gene Overlap |
|---|---|---|---|---|---|
| Resilience Across Domains | Listeria Monocytogenes Entry into Host Cells | 0.002 | 0.085 | 19 | *CTNNB1; STAM* |
| | BBSome-Mediated Cargo-Targeting to Cilium | 0.003 | 0.085 | 23 | *BBS7; LZTFL1* |
| | Endosomal Sorting Complex Required for Transport (ESCRT) | 0.005 | 0.109 | 32 | *STAM; VPS37C* |
| | Organelle Biogenesis and Maintenance | 0.009 | 0.126 | 240 | *PRKAG1; TMEM67; BBS7; LZTFL1* |
| Academic Resilience | RNA Polymerase III Transcription Initiation from Type 2 Promoter | 0.000 | 0.002 | 27 | *POLR2L; BRF1* |
| | RNA Polymerase III Transcription Initiation from Type 1 Promoter | 0.000 | 0.002 | 28 | *POLR2L; BRF1* |
| | RNA Polymerase III Transcription Initiation | 0.000 | 0.002 | 36 | *POLR2L; BRF1* |
| | RNA Polymerase III Abortive and Retractive Initiation | 0.001 | 0.002 | 41 | *POLR2L; BRF1* |
| | RNA Polymerase III Transcription | 0.001 | 0.002 | 41 | *POLR2L; BRF1* |
| | Gap-Filling DNA Repair Synthesis and Ligation in TC-NER | 0.002 | 0.003 | 68 | *POLR2L; LIG3* |
| | Transcription-Coupled Nucleotide Excision Repair (TC-NER) | 0.002 | 0.004 | 81 | *POLR2L; LIG3* |
| | Nucleotide Excision Repair | 0.005 | 0.007 | 113 | *POLR2L; LIG3* |
| Social Resilience | Phosphorylation of CD3 and TCR Zeta Chains | 0.000 | 0.002 | 30 | *HLA-DRB1; PTPRJ; HLA-DQB2* |
| | TCR Signaling | 0.000 | 0.016 | 72 | *HLA-DRB1; PTPRJ; HLA-DQB2* |
| | Translocation of ZAP-70 to Immunological Synapse | 0.002 | 0.033 | 27 | *HLA-DRB1; HLA-DQB2* |

*Note*. 'Pathway' is the name of the significantly enriched pathway from the Reactome database, 'Effective Size' is the number of genes involved in the corresponding pathway, and 'Gene Overlap' provides the names of genes from the MWAS that are present in the pathway. Also shown are the signed test statistic values for the pathway analyses: 'p-value' and 'q-value'.

**Table 3.** (cont'd)

| | | | | |
|---|---|---|---|---|
| PD-1 Signaling | 0.002 | 0.033 | 31 | *HLA-DRB1; HLA-DQB2* |
| Generation of Second Messenger Molecules | 0.003 | 0.039 | 41 | *HLA-DRB1; HLA-DQB2* |
| Interferon Signaling | 0.005 | 0.039 | 158 | *XAF1; HLA-DRB1; HLA-DQB2* |
| Downstream TCR Signaling | 0.005 | 0.039 | 51 | *HLA-DRB1; HLA-DQB2* |
| Neurexins and Neuroligins | 0.007 | 0.039 | 57 | *SYT9; SYT1* |
| MHC Class II Antigen Presentation | 0.007 | 0.039 | 59 | *HLA-DRB1; HLA-DQB2* |

and has been linked to increased risk for cancer (Li, Suzuki, Liu, Morris, Liu, Okazaki, ... & Abbruzzese, 2009; Li, Wang, Wang, Guan, Guo, Wang, ... & Yang, 2018), neural tube defects (Li, et al., 2018), Alzheimer's disease (Kwiatkowski, Czarny, Toma, Korycinska, Sowinska, Galecki, ... & Sliwinski, 2016), and recurrent depression (Czarny, Kwiatkowski, Toma, Kubiak, Sliwinska, Talarowska, ... & Sliwinski, 2017).

Social resilience evidenced nine significantly enriched pathways. The *HLA-DRB1* and *HLA-DQB2* genes appeared in 8 of these pathways, most of which are involved in T-cell receptor (TCR) signaling. These results appear to be driven by the HLA region on chromosome 6—a large region of linkage disequilibrium. The HLA region includes several genes—such as the *HLA-DRB1* and *HLA-DQB2* genes—that play a central role in immune system functioning (Simmonds & Gough, 2007). The HLA region is associated with longevity (Joshi, Pirastu, Kentistou, Fischer, Hofer, Schraut, ... & Shen, 2017), cognitive ability (Payton, Van Den Boogerd, Davidson, Gibbons, Ollier, Rabbitt, ... & Pendleton, 2006), and mental health disorders (e.g., Schizophrenia, Autism; Bennabi, Gaman, Delorme, Boukouaci, Manier, Scheid, ... & Leboyer, 2018; Halley, Doherty, Megson, McNamara, Gadja, & Wei, 2013).

**MZ Differences**

For our final analyses, we sought to evaluate the extent to which the significant and suggestive DMPs from each of the MWAS models above were environmental in origin via MZ differences analyses. Results are provided in Table 4. Four DMPs for resilience across domains differed significantly across discordant MZ pairs. The top DMP was located in an intron of *RNASET2*, a member of the Rh/T2/S-glycoprotein class of extracellular ribonucleases. The second top DMP was located in an intron and CpG island of *CD247*, which encodes a T-cell receptor zeta that contributes to the T-cell receptor-CD3 complex (Weissman, Samelson, & Klausner, 1986).

Three DMPs for social resilience also differed significantly across discordant MZ pairs. The top DMP was located in an intron of *ARID1B*, a gene that encodes an AT-rich DNA interacting domain-containing protein and is associated with intellectual disability and Autism Spectrum Disorder (Halgren, Kjaergaard, Bak, Hansen, El-Schich, Anderson, ... & Nielsen, 2012). The second top DMP was located in an exon and CpG island of the *GPR37* gene, which is a member of the G protein-coupled receptor gene family and is associated with Autism Spectrum Disorder (Fujita-Jimbo, Yu, Li, Yamagata, Mori, Momoi, & Momoi, 2012). DMPs for psychiatric and academic resilience did not differ across discordant MZ pairs.

**Table 4.** Significant Monozygotic Twin Difference Differentially Methylated Probes

| Model | Probe | Chr | Start | Beta | Z/T-value | P-value | Gene | Genomic Features |
|---|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg14257632 | 6 | 167351815 | 42.151 | 2.486 | 0.016 | *RNASET2* | Intron |
| | cg02648847 | 1 | 167408734 | 40.735 | 2.204 | 0.032 | *CD247* | Intron; CpG island |
| | cg02981663 | 13 | 28232082 | 25.182 | 2.108 | 0.040 | *POLR1D* | Intron |
| | cg01316433 | 9 | 92000900 | 31.966 | 2.027 | 0.048 | *SEMA4D* | Intron |
| Social Resilience | cg03384047 | 6 | 157357516 | -4.382 | -2.250 | 0.027 | *ARID1B* | Intron |
| | cg23847172 | 7 | 124406111 | -59.288 | -2.150 | 0.035 | *GPR37* | Exon; CpG Island |
| | cg04989255 | 8 | 110094904 | -6.863 | -2.130 | 0.036 | | |

*Note.* 'Probe' is the name of the probe in the human reference genome hg19/GRCh37, 'Chr' is Chromosome, 'Start' is the base pair location of the probe (human reference genome hg19/GRCh37), 'Gene' is the gene the probe is located in, and 'Genomic Feature' indicates if the probe overlaps with introns, exons, or CpG islands. Also shown are the signed test statistic values for regression: 'Z-value' for the dichotomous outcome of resilience across domains, 'T-value' for the continuous outcomes, 'P-values', and 'Beta' or regression coefficient. All significant ($P \leq .05$) DMPs are provided for each of the outcomes.

# DISCUSSION

The goal of this study was to identify epigenetic correlates of resilience to neighborhood disadvantage in a sample of living humans. MWAS analyses conducted in 135 twin pairs revealed a handful of methylome-wide significant DMPs associated with academic as well as social resilience, and suggestive DMPs associated with each of the four resilience phenotypes we examined (i.e., psychiatric, academic, social, and across domains). Pathway analyses revealed significantly enriched pathways for academic and social resilience, as well as resilience across domains. Results for academic resilience to neighborhood disadvantage pointed to methylation in pathways related to DNA repair as well as the transcription and initiation of RNA Polymerase III. DNA damage typically triggers a response which includes DNA repair. Dysregulation of DNA damage responses can result in developmental and neurological defects (Lee, Choi, Kim, & Kim, 2016). As mentioned previously, RNA Polymerase III is involved in transcribing small RNAs. Misregulation of small RNAs is thought to be implicated in abnormal brain development (Chang, Wen, Chen, & Jin, 2009). Taken together, these findings suggest that methylation in these two pathways may alter or inhibit regulation of DNA damage responses and small RNAs, resulting in atypical cognitive development.

These enriched pathways also highlight the role of methylation of the *BRF1* gene in academic resilience. Mutations in *BRF1* have been shown to cause central nervous system and neurodevelopmental anomalies due to a reduction in protein activity. It has been suggested that RNA polymerase III transcription initiated by *BRF1* is necessary for typical cognitive development (Borck et al., 2015), a process that may be affected by methylation of *BRF1*. The current study extends this line of work by demonstrating that an increase in methylation of *BRF1*

is associated with academic resilience, a construct that is thought to be correlated with cognitive ability (Mayes et al., 2009; Tiet et al., 1998).

Results also suggest that methylation in genes located in the HLA region involved in T cell receptor (TCR) signaling may play a role in social resilience to neighborhood disadvantage. TCR signaling refers to cellular signaling cascades involved in determining cell fate, including cell survival, differentiation, and proliferation. TCRs typically bind to proteins involved in immune response. Recent studies have demonstrated that proteins involved in immune response are expressed in the central nervous system and play critical roles in synaptic transmission and plasticity as well as refinement of connections during brain development (Garay & McAllister, 2010). Thus, methylation of genes involved in TCR signaling may have downstream effects on brain development. Research on social cognition has demonstrated that the temporal lobe, amygdala and cingulate cortices are implicated in social behavior via their involvement in perception of social stimuli and the ability to link these stimuli to emotion, motivation, and cognition (Adolphs, 2001). Therefore, while additional research is needed to confirm that TCR signaling impacts these brain regions in particular, this may explain its relationship with interpersonal functioning and social resilience (Cook, Greenberg, & Kusche, 1994).

MZ difference analyses demonstrated that four suggestive DMPs for resilience across domains and three for social resilience differed across discordant MZ twins. While none of the top methylome-wide DMPs for social resilience differed across discordant MZ twins, two suggestive DMPs were significant and located in genes (i.e., *ARID1B* and *GPR37*) that have been associated with Autism Spectrum Disorder – a neurodevelopmental disorder characterized by social deficits that are thought to result from poor brain connectivity (Balsters, Apps, Bolis, Lehner, Gallagher, & Wenderoth, 2017; Supekar, Uddin, Khouzam, Phillips, Gaillard,

Kenworthy, ... & Menon, 2013). In fact, *ARID1B* has been implicated in abnormalities in the corpus callosum which impact brain connectivity. As mentioned previously, social cognition research has demonstrated that several brain regions are involved in processes related to social behavior. It therefore stands to reason that poor brain connectivity would impede communication between these brain regions and therein interpersonal functioning and social resilience.

Since MZ twins are genetically identical, significant findings clearly point towards environmentally engendered methylation in those cases. Alternatively, the absence of significant MZ differences in our top methylome-wide significant DMPs suggests that those DMPs are not likely to reflect causal environmental processes per se. Rather, the current MZ difference findings are more consistent with the possibility of genetic or developmental mediation of those methylomic effects.

**Limitations**

The unique twin design of this study coupled with the relatively high degree of disadvantage experienced by participants uniquely positioned us to detect DMPs for resilience that are environmental in origin. However, there are limitations of the current study that are important to consider. First, because methylation is predominantly tissue specific, etiological interpretations of saliva-based methylation must be made with caution, the minimum interpretation being that DMPs are biomarkers of resilience. However, there does exist overlap in methylation across different tissues, including saliva and brain (Smith, Kilaru, Klengel, Mercer, Bradley, Conneely, ... & Binder, 2015). This suggests that it is possible for our saliva-based methylation findings to mirror methylation in brain tissue. There are several factors that may lead to cross-tissue methylation concordance, such as epigenetic reprogramming events, systematic effects of disease processes (i.e., inflammation), and genetic polymorphisms which

are identical across tissues. Given that genes in our MWAS results as well as our top enriched pathways may have downstream effects on neurodevelopment, cross-tissue concordance in resilience-associated methylation is probable. Although peripheral tissue methylation of the top DMPs in our study must be experimentally confirmed, they do indeed suggest that methylation related to brain function is associated with resilience.

Also, our study did not contain a replication sample, and it is thus unclear whether these results will replicate more broadly. Additional studies that make use of independent samples for discovery as well as replication are needed. In addition, our current sample was both small and cross-sectional, limiting the ability of the current analyses to detect significant effects as well as the ability to evaluate the persistence of observed effects. Studies using a larger and longitudinal sample are needed as they may be able to detect additional methylome-wide significant DMPs not identified by this study, and to identify the extent to which observed associations between the DMPs and resilience persist over time. Next, although our sample is representative of racial demographics throughout the state of Michigan, the racial breakdown of the sample is still primarily White, thereby limiting the generalizability of our findings to communities of color. It would be critical for future methylomic studies of resilience to recruit racially diverse samples. Also, our analyses focused on detecting DMPs and evaluating whether they were environmental in origin, but did not examine specific environmental predictors of DMPs. Future work should consider methylation as a mediator in the relationship between environmental influences and resilience, exploring specific environmental factors (e.g., parenting style) that might predict DMPs. Lastly, while this study focuses specifically on resilience to neighborhood disadvantage, there are many other forms of resilience that may have distinct methylomic markers (e.g.,

resilience to trauma). Additional research on other forms of resilience would facilitate a comparison of methylomic markers across distinct forms of resilience.

**Implications**

Overall, this study is the first to uncover potential methylomic biomarkers of resilience in a sample of living humans. Our findings preliminarily highlight the role of biological mechanisms in resilient outcomes, in that we identified a handful of methylome-wide significant and suggestive methylation sites that predict resilience to neighborhood disadvantage. By demonstrating the potential role of biological factors in resilience, our study provides support for key elements of the structural organizational model of resilience (Cicchetti & Cannon, 1999). The etiologic inferences we can make about these DMPs and genes are more limited, however, since the strongest DMPs from the MWAS did not differ across MZ twins discordant for resilience. Such results argue against clear environmental mediation of these specific methylomic effects. Instead, our results were more consistent with the possibility of genetic or developmental mediation for those DMPs. That said, we did identify a handful of suggestive methylomic correlates of resilience that differed across discordant MZ twins. These environmental changes in the methylome are also at least nominally consistent with the structural organizational model's theory in that they point to the importance of environmental effects, as well as reciprocal feedback between biology and the environment.

# APPENDIX

**Table 5.** Methylome Wide Significant and Suggestive Differentially Methylated Probes

| Model | Probe | Chr | Start | Beta | Z/T-value | P-value | Gene |
|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg08862567 | 20 | 33447234 | 80.275 | 5.161 | 2.4517E-07 | *GGT7* |
| | cg18153279 | 12 | 112825215 | -107.720 | -5.157 | 2.5151E-07 | |
| | cg15869383 | 19 | 58258088 | -129.038 | -5.087 | 3.6303E-07 | *ZNF776* |
| | cg23044017 | 19 | 36822441 | -79.445 | -5.026 | 5.0127E-07 | *LINC00665* |
| | cg11787544 | 13 | 29257932 | 71.521 | 4.997 | 5.8137E-07 | |
| | cg02536150 | 10 | 17754084 | 45.363 | 4.981 | 6.3142E-07 | *STAM* |
| | cg24059404 | 4 | 184580365 | -193.388 | -4.937 | 7.9287E-07 | *RWDD4* |
| | cg24221965 | 15 | 81422778 | 23.580 | 4.925 | 8.4358E-07 | *C15orf26* |
| | cg16373426 | 5 | 157079899 | 88.290 | 4.924 | 8.4989E-07 | *SOX30* |
| | cg22500078 | 6 | 138104344 | 114.899 | 4.893 | 9.9525E-07 | |
| | cg09114799 | 12 | 48152514 | -242.566 | -4.881 | 1.0559E-06 | *RAPGEF3* |
| | cg18056754 | 11 | 122955452 | 62.652 | 4.860 | 1.1719E-06 | *CLMP* |
| | cg03078854 | 6 | 32810000 | 96.825 | 4.850 | 1.2329E-06 | *PSMB8* |
| | cg23032249 | 6 | 69942249 | 13.053 | 4.843 | 1.2777E-06 | *BAI3* |
| | cg01143804 | 4 | 40751844 | -112.256 | -4.824 | 1.406E-06 | *NSUN7* |
| | cg02648847 | 1 | 167408734 | -78.393 | -4.812 | 1.4973E-06 | *CD247* |
| | cg01316433 | 9 | 92000900 | 68.800 | 4.810 | 1.5095E-06 | *SEMA4D* |
| | cg04324126 | 2 | 55277571 | -116.261 | -4.808 | 1.5272E-06 | *RTN4* |
| | cg17779707 | 20 | 48807326 | -207.610 | -4.805 | 1.551E-06 | *CEBPB* |

*Note.* 'Probe' is the name of the CpG probe in the human reference genome hg19/GRCh37, 'Chr' is Chromosome, 'Start' is the base pair location of the probe (human reference genome hg19/GRCh37), 'Gene' is the gene the probe is located in, and 'Genomic Feature' indicates if the probe is located in an intron, exon, or CpG island. Also shown are the signed test statistic values for regression: 'Z-value' for the dichotomous outcome of resilience across domains, 'T-value' for the continuous outcomes, 'P-values', and 'Beta' or regression coefficient. All methylome-wide significant ($P \leq 9 \times 10^{-8}$) and suggestive ($P \leq 1 \times 10^{-5}$) MWAS DMPs are displayed for each outcome. These are also the DMPs that were used for the enrichment analyses.

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg20346695 | 2 | 203776994 | -178.423 | -4.797 | 1.6083E-06 | *CARF* |
| | cg23013151 | 17 | 60864729 | 17.362 | 4.796 | 1.6195E-06 | *MARCH10* |
| | cg04710629 | 2 | 191045041 | -128.412 | -4.791 | 1.662E-06 | *C2orf88* |
| | cg00166213 | 5 | 53606451 | -122.841 | -4.787 | 1.6934E-06 | *ARL15* |
| | cg05879499 | 5 | 6668384 | 32.962 | 4.768 | 1.8605E-06 | *SRD5A1* |
| | cg17568035 | 17 | 27224810 | -211.214 | -4.750 | 2.0294E-06 | *DHRS13* |
| | cg22002948 | 3 | 41235823 | 43.192 | 4.732 | 2.225E-06 | *CTNNB1* |
| | cg19350812 | 19 | 10676863 | -41.641 | -4.701 | 2.5866E-06 | *KRI1* |
| | cg09220171 | 11 | 98704582 | 35.471 | 4.693 | 2.6941E-06 | |
| | cg16123583 | 22 | 43582883 | -55.324 | -4.692 | 2.705E-06 | *TTLL12* |
| | cg07387591 | 20 | 17208648 | 80.581 | 4.691 | 2.7222E-06 | *PCSK2* |
| | cg03411765 | 8 | 143484815 | -32.338 | -4.683 | 2.8315E-06 | |
| | cg10426797 | 17 | 7169573 | 89.509 | 4.656 | 3.2266E-06 | *Y_RNA* |
| | cg23917918 | 10 | 13385881 | 127.575 | 4.649 | 3.3293E-06 | *SEPHS1* |
| | cg20825216 | 11 | 2274399 | 31.154 | 4.642 | 3.4475E-06 | |
| | cg15679813 | 22 | 45405626 | -91.393 | -4.641 | 3.4694E-06 | *PHF21B* |
| | cg14637885 | 12 | 74416009 | 15.828 | 4.640 | 3.4768E-06 | |
| | cg21470464 | 7 | 95969817 | 20.612 | 4.627 | 3.7074E-06 | *RNU6-364P* |
| | cg12372632 | 3 | 170781530 | 45.948 | 4.625 | 3.7417E-06 | *TNIK* |
| | cg02207779 | 14 | 24701799 | -102.581 | -4.606 | 4.1025E-06 | *GMPR2* |
| | cg21783328 | 9 | 136243031 | -195.968 | -4.606 | 4.107E-06 | *SURF4* |
| | cg08008884 | 1 | 235377331 | 39.450 | 4.599 | 4.2451E-06 | *ARID4B* |
| | cg08964784 | 8 | 24769500 | 15.264 | 4.598 | 4.2677E-06 | *RP11-624C23.1* |
| | cg07917528 | 7 | 55412267 | 25.595 | 4.589 | 4.4622E-06 | *RP11-775L16.1* |
| | cg04482075 | 16 | 1991307 | 158.995 | 4.588 | 4.4793E-06 | *MSRB1* |
| | cg22850860 | 3 | 45902662 | 24.664 | 4.587 | 4.4944E-06 | *LZTFL1* |

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg10214933 | 2 | 216715261 | 79.068 | 4.585 | 4.5491E-06 | |
| | cg24457562 | 2 | 106212100 | -23.651 | -4.581 | 4.6264E-06 | |
| | cg07580827 | 11 | 111943185 | 32.149 | 4.575 | 4.7552E-06 | *PIH1D2* |
| | cg14019124 | 11 | 66611060 | -96.940 | -4.569 | 4.9014E-06 | *RCE1* |
| | cg02761287 | 21 | 47878739 | -90.314 | -4.561 | 5.0851E-06 | *DIP2A* |
| | cg16595404 | 10 | 12238159 | -91.628 | -4.537 | 5.7194E-06 | *CDC123* |
| | cg17997673 | 1 | 52082396 | 5.207 | 4.530 | 5.8866E-06 | *OSBPL9* |
| | cg18914514 | 18 | 18822122 | -80.556 | -4.529 | 5.9323E-06 | *GREB1L* |
| | cg13680184 | 4 | 122791313 | -65.253 | -4.529 | 5.9351E-06 | *BBS7* |
| | cg16635767 | 19 | 39574639 | -185.857 | -4.527 | 5.9777E-06 | *PAPL* |
| | cg05734400 | 2 | 216176659 | -73.706 | -4.520 | 6.1957E-06 | *ATIC* |
| | cg26247036 | 11 | 71814594 | -196.676 | -4.517 | 6.2642E-06 | *LRTOMT* |
| | cg09472203 | 15 | 83378613 | -167.882 | -4.507 | 6.5823E-06 | *AP3B2* |
| | cg14447399 | 5 | 162930289 | -67.934 | -4.505 | 6.6274E-06 | *MAT2B* |
| | cg09555914 | 19 | 58011308 | -225.180 | -4.502 | 6.7374E-06 | *ZNF773* |
| | cg12001456 | 7 | 157357802 | -114.115 | -4.492 | 7.0643E-06 | *PTPRN2* |
| | cg15358052 | 14 | 69865455 | -76.804 | -4.487 | 7.2378E-06 | *SLC39A9* |
| | cg19878597 | 14 | 53684326 | -50.856 | -4.481 | 7.4136E-06 | *AL163953.3* |
| | cg07160800 | 5 | 177018949 | -137.125 | -4.478 | 7.5356E-06 | *TMED9* |
| | cg09636406 | 17 | 73663133 | -100.133 | -4.477 | 7.572E-06 | *RECQL5* |
| | cg27276059 | 6 | 75829276 | 49.473 | 4.476 | 7.5936E-06 | *COL12A1* |
| | cg00011284 | 16 | 53469343 | -54.459 | -4.476 | 7.5958E-06 | *RBL2* |
| | cg08159120 | 9 | 75263370 | 20.716 | 4.468 | 7.898E-06 | *TMC1* |
| | cg14801164 | 4 | 190393518 | 17.673 | 4.466 | 7.9571E-06 | *HSP90AA4P* |
| | cg22232107 | 8 | 124194080 | 15.622 | 4.463 | 8.0952E-06 | *FAM83A* |
| | cg02981663 | 13 | 28232082 | 52.289 | 4.460 | 8.1854E-06 | *POLR1D* |

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Resilience Across Domains | cg22687346 | 8 | 94767371 | -174.067 | -4.456 | 8.3344E-06 | *TMEM67* |
| | cg06996254 | 12 | 47427790 | 65.076 | 4.453 | 8.4757E-06 | |
| | cg14257632 | 6 | 167351815 | 73.566 | 4.450 | 8.5993E-06 | *RNASET2* |
| | cg17610929 | 2 | 220379043 | -84.870 | -4.450 | 8.6036E-06 | *ASIC4* |
| | cg09532899 | 15 | 97007486 | 13.178 | 4.448 | 8.6863E-06 | |
| | cg15720223 | 6 | 15398117 | 53.213 | 4.446 | 8.7284E-06 | *JARID2* |
| | cg19226770 | 4 | 156921360 | 14.690 | 4.446 | 8.7477E-06 | |
| | cg02457826 | 20 | 30310732 | -60.153 | -4.444 | 8.8428E-06 | *BCL2L1* |
| | cg09808985 | 14 | 89704016 | 42.398 | 4.442 | 8.9163E-06 | *FOXN3* |
| | cg14465408 | 6 | 82980356 | 10.150 | 4.441 | 8.9379E-06 | |
| | cg09994724 | 11 | 123986110 | -78.918 | -4.439 | 9.056E-06 | *VWA5A* |
| | cg23173573 | 1 | 221916860 | -146.059 | -4.438 | 9.0883E-06 | *DUSP10* |
| | cg17689735 | 8 | 15095819 | 11.380 | 4.436 | 9.1722E-06 | *SGCZ* |
| | cg19139691 | 2 | 86668468 | -59.727 | -4.430 | 9.426E-06 | *KDM3A* |
| | cg22372439 | 11 | 60929244 | -48.029 | -4.428 | 9.4951E-06 | *VPS37C* |
| | cg09163686 | 11 | 17229661 | -148.562 | -4.427 | 9.5621E-06 | *NUCB2* |
| | cg01877778 | 7 | 157415537 | 85.967 | 4.426 | 9.6079E-06 | *PTPRN2* |
| | cg01089060 | 10 | 97050835 | -65.715 | -4.426 | 9.6158E-06 | *PDLIM1* |
| | cg21054179 | 12 | 49412580 | -116.318 | -4.417 | 9.9882E-06 | *PRKAG1* |
| Psychiatric Resilience | cg00059246 | 12 | 54337928 | 3.673 | 4.866 | 1.9571E-06 | *HOXC13* |
| | cg10674017 | 2 | 3201975 | -15.245 | -4.689 | 4.4048E-06 | *TSSC1* |
| Academic Resilience | cg09169455 | 5 | 16843339 | -2.185 | -6.528 | 3.3989E-10 | *MYO10* |
| | cg27413290 | 8 | 144552724 | -4.250 | -5.687 | 3.4215E-08 | *ZC3H3* |
| | cg23901896 | 1 | 201976445 | -10.226 | -5.465 | 1.0726E-07 | *ELF3* |
| | cg13598010 | 7 | 72838775 | -7.625 | -5.326 | 2.151E-07 | |
| | cg10091996 | 16 | 31548639 | -1.845 | -4.990 | 1.0988E-06 | |

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Academic Resilience | cg22018084 | 2 | 69038737 | -2.543 | -4.874 | 1.8873E-06 | *ARHGAP25* |
| | cg03116740 | 11 | 841334 | 3.376 | 4.799 | 2.6679E-06 | *POLR2L* |
| | cg20678377 | 20 | 47667339 | -2.715 | -4.780 | 2.9094E-06 | *CSE1L* |
| | cg09895822 | 14 | 105738159 | 8.444 | 4.778 | 2.947E-06 | *BRF1* |
| | cg16444294 | 16 | 28925789 | 17.201 | 4.773 | 3.0042E-06 | *RABEP2* |
| | cg00421032 | 4 | 22493280 | 9.058 | 4.772 | 3.0255E-06 | *GPR125* |
| | cg08857221 | 1 | 37941360 | 4.155 | 4.694 | 4.3153E-06 | *ZC3H12A* |
| | cg06899313 | 6 | 117394044 | -3.045 | -4.665 | 4.9154E-06 | |
| | cg21207593 | 17 | 33310494 | 9.232 | 4.661 | 5.0047E-06 | *LIG3* |
| | cg11779551 | 3 | 45736062 | 4.226 | 4.626 | 5.8588E-06 | *SACM1L* |
| | cg24374161 | 11 | 46582057 | 6.554 | 4.622 | 5.9412E-06 | *AMBRA1* |
| | cg03706376 | 6 | 149093351 | 1.991 | 4.599 | 6.6064E-06 | *UST* |
| | cg19548912 | 6 | 138299067 | -1.079 | -4.570 | 7.4866E-06 | |
| | cg14377171 | 9 | 138022130 | 3.598 | 4.560 | 7.8217E-06 | |
| | cg19255656 | 4 | 2816364 | 10.344 | 4.543 | 8.4385E-06 | *SH3BP2* |
| | cg12777862 | 16 | 31548755 | -2.465 | -4.523 | 9.2109E-06 | |
| | cg01642827 | 7 | 925663 | 8.978 | 4.512 | 9.676E-06 | *GET4* |
| Social Resilience | cg22321318 | 7 | 157294387 | 17.100 | 5.979 | 7.2311E-09 | *AC006372.5* |
| | cg25950792 | 22 | 26797948 | 105.089 | 5.947 | 8.5823E-09 | |
| | cg17416722 | 6 | 32554384 | 6.440 | 5.728 | 2.7526E-08 | *HLA-DRB1* |
| | cg25960393 | 8 | 9106558 | 5.018 | 5.708 | 3.0643E-08 | *RP11-115J16.1* |
| | cg14321269 | 17 | 6658197 | 17.674 | 5.546 | 7.0609E-08 | *XAF1* |
| | cg25998860 | 5 | 126853953 | -114.782 | -5.512 | 8.3886E-08 | *PRRC1* |
| | cg15559076 | 11 | 128109596 | 18.105 | 5.439 | 1.2196E-07 | *RP11-702B10.1* |
| | cg11070274 | 8 | 9106609 | 5.106 | 5.278 | 2.721E-07 | *RP11-115J16.1* |
| | cg07273698 | 2 | 46636808 | 19.462 | 5.240 | 3.2738E-07 | |

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Social Resilience | cg20424973 | 2 | 3045240 | 40.116 | 5.209 | 3.8106E-07 | *LINC01250* |
| | cg19815792 | 10 | 130267642 | 26.874 | 5.171 | 4.6057E-07 | |
| | cg10985094 | 17 | 3631481 | 23.115 | 5.064 | 7.7009E-07 | *ITGAE* |
| | cg12738264 | 7 | 148725794 | -210.602 | -5.044 | 8.4631E-07 | *PDIA4* |
| | cg04141477 | 10 | 71502791 | 21.169 | 5.029 | 9.0758E-07 | |
| | cg07694621 | 2 | 43151937 | 14.740 | 5.024 | 9.3162E-07 | |
| | cg15856489 | 17 | 71687902 | 16.357 | 5.021 | 9.4378E-07 | |
| | cg02147339 | 13 | 96632986 | 19.975 | 4.934 | 1.4241E-06 | *UGGT2* |
| | cg06154432 | 10 | 77325337 | 12.938 | 4.924 | 1.4968E-06 | *C10orf11* |
| | cg24147543 | 6 | 32554480 | 4.661 | 4.892 | 1.7364E-06 | *HLA-DRB1* |
| | cg01085765 | 16 | 29139623 | 12.784 | 4.874 | 1.8835E-06 | *RP11-426C22.5* |
| | cg14255617 | 6 | 32729117 | 13.708 | 4.843 | 2.1816E-06 | *HLA-DQB2* |
| | cg20822540 | 1 | 9070126 | 11.551 | 4.837 | 2.2403E-06 | *SLC2A7* |
| | cg22867288 | 6 | 57086715 | -57.579 | -4.822 | 2.3965E-06 | *RAB23* |
| | cg04989255 | 8 | 110094904 | 19.688 | 4.807 | 2.5698E-06 | |
| | cg09826506 | 4 | 522635 | 41.146 | 4.796 | 2.7079E-06 | *PIGG* |
| | cg13256398 | 10 | 64579264 | 16.940 | 4.791 | 2.7608E-06 | *EGR2* |
| | cg09670566 | 10 | 28507576 | -95.315 | -4.782 | 2.8864E-06 | *MPP7* |
| | cg11726507 | 14 | 101155518 | 18.507 | 4.774 | 2.9897E-06 | |
| | cg10506179 | 7 | 158884942 | 67.823 | 4.771 | 3.0337E-06 | *VIPR2* |
| | cg19584551 | 10 | 24721828 | 19.546 | 4.769 | 3.0524E-06 | *KIAA1217* |
| | cg09990723 | 2 | 242691867 | 81.620 | 4.769 | 3.0537E-06 | *D2HGDH* |
| | cg12395012 | 8 | 11607385 | -32.546 | -4.753 | 3.2929E-06 | *GATA4* |
| | cg24036126 | 6 | 26234818 | -79.468 | -4.706 | 4.0821E-06 | *HIST1H1D* |
| | cg23104823 | 14 | 45553407 | -100.285 | -4.704 | 4.1139E-06 | *PRPF39* |
| | cg01926740 | 5 | 137911360 | -104.847 | -4.689 | 4.391E-06 | *HSPA9* |

**Table 5.** (cont'd)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Social Resilience | cg25105147 | 7 | 144474742 | 16.827 | 4.687 | 4.4442E-06 | *TPK1* |
| | cg08185661 | 11 | 7273497 | -73.812 | -4.685 | 4.482E-06 | *SYT9* |
| | cg23978866 | 2 | 47230406 | 13.203 | 4.638 | 5.5428E-06 | *TTC7A* |
| | cg10327502 | 20 | 37570621 | 38.265 | 4.609 | 6.2832E-06 | *FAM83D* |
| | cg20140488 | 22 | 25463865 | 12.812 | 4.601 | 6.5321E-06 | *KIAA1671* |
| | cg05148288 | 9 | 129319931 | 77.926 | 4.590 | 6.8552E-06 | |
| | cg00556742 | 2 | 200820714 | -132.159 | -4.587 | 6.9569E-06 | *C2orf47* |
| | cg25214900 | 12 | 79693301 | 26.200 | 4.574 | 7.3382E-06 | *SYT1* |
| | cg15457276 | 19 | 4832023 | -111.973 | -4.561 | 7.8039E-06 | *TICAM1* |
| | cg24607831 | 14 | 76975801 | 26.404 | 4.559 | 7.8588E-06 | *RP11-187O7.3* |
| | cg02384897 | 22 | 30214218 | 24.545 | 4.545 | 8.3512E-06 | *ASCC2* |
| | cg24945222 | 16 | 4395036 | 15.478 | 4.542 | 8.4858E-06 | *CORO7-PAM16* |
| | cg12312265 | 10 | 72546530 | 22.293 | 4.540 | 8.5565E-06 | *TBATA* |
| | cg10572362 | 3 | 125742863 | 38.532 | 4.530 | 8.9146E-06 | *SLC41A3* |
| | cg14402217 | 2 | 71222107 | -157.326 | -4.530 | 8.9202E-06 | *AC007040.6* |
| | cg10544696 | 10 | 1585344 | 11.113 | 4.526 | 9.0675E-06 | *ADARB2* |
| | cg00695187 | 11 | 48032703 | 16.950 | 4.526 | 9.0732E-06 | *PTPRJ* |
| | cg03384047 | 6 | 157357516 | 15.729 | 4.516 | 9.5091E-06 | *ARID1B* |
| | cg17933911 | 1 | 59248877 | 95.814 | 4.509 | 9.7689E-06 | *JUN* |
| | cg23847172 | 7 | 124406111 | -112.998 | -4.508 | 9.8334E-06 | *GPR37* |
| | cg13988209 | 11 | 69683042 | 16.937 | 4.507 | 9.8622E-06 | |
| | cg20332503 | 7 | 143081286 | 16.673 | 4.506 | 9.9191E-06 | *ZYX* |
| | cg10594585 | 1 | 153756108 | 21.460 | 4.506 | 9.9293E-06 | |
| | cg07674022 | 4 | 122854329 | 10.007 | 4.506 | 9.932E-06 | *TRPC3* |
| | cg23123972 | 14 | 23080612 | 51.672 | 4.504 | 9.9926E-06 | *ABHD4* |

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