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DNA methylation as a biomarker for disease, behavior and environment

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[1]VU Amsterdam, [2]The Biobank-based Integrative Omics Study (BIOS) Consortium, financed by BBRMI-NL (NWO 184.021.007), [3]Aggression in Children: Unraveling gene-environment interplay to inform Treatment and InterventiON strategies. The ACTION study received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602768.

Introduction

Epigenome-wide association studies (EWASs) have identified disease-associated DNA methylation differences for a range of conditions in various tissues. DNA methylation in peripheral tissues such as blood may provide insight into disease pathogenesis or may be utilized as a disease biomarker, which, in contrast to genetic scores, captures information on life-long exposure to environmental triggers of a disease.

Methods

Heritability of DNA methylation based on twin-family data and genome-wide SNPs

As part of the BBMRI-NL BIOS consortium, we established a catalogue of between-individual variation in DNA methylation (Illumina 450k array; van Dongen et al 2016 Nat Commun). Using data from 3089 blood samples from twin families, we estimated the contribution of environmental and genetic effects to individual differences in DNA methylation at 411,169 sites. We also identified interactions with age and sex. These results are available at http://bbmri.researchlumc.nl/atlas/.

Disease- and trait enrichment for methylation sites with sex- or age-specific environmental variance

We used the EWAS atlas (http://bigd.big.ac.cn/ewas/index) to examine the overlap with methylation sites detected in 333 EWASs of diseases and traits on January 14 2018.

Results

Figure 1: The main sources of variation in DNA methylation are additive genetic effects and unique environment. Means: a^2=20%, e^2=80%, c^2=3%, d^2 =8%.

Figure 2: Four exemplary CpGs with high or low heritability.

Figure 3: Single Nucleotide Polymorphisms (SNPs) explain on average 37% of total heritability.

Figure 4: 10% of CpGs shows significant interaction of genes or environment with age. For 82% of these CpGs, the environmental variance increases with age and heritability decreases (in this cross-sectional study) .

Figure 5: Many CpGs associated with cigarette smoking show an increase of environmental variance with age. Monozygotic twins discordant for smoking show less similar methylation levels.

Table 1: Top 10 enriched traits/ontologies among 2,034 methylation sites with a sex difference in environmental variance. In total, enrichment was seen for 15 traits. Top enriched traits are allergy- and immune system-related.

Table 2: Top 10 enriched traits/ontologies among 32,234 methylation sites with age-dependent environmental variance. In total, significant enrichment was seen for 58 traits. Top enriched traits are related to rare genetic disorders, cancer, and smoking.

Conclusion

Our catalogue holds valuable information on locations in the genome where methylation variation between people may reflect disease-relevant environmental exposures or genetic variation, and whether this variation is sex- or age-specific.

Figure 1

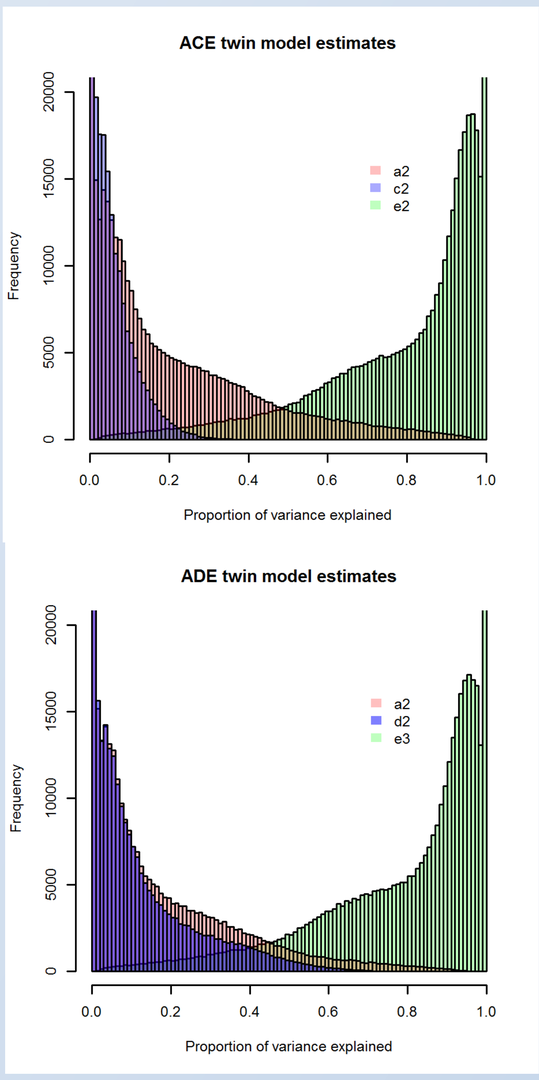

Figure 2

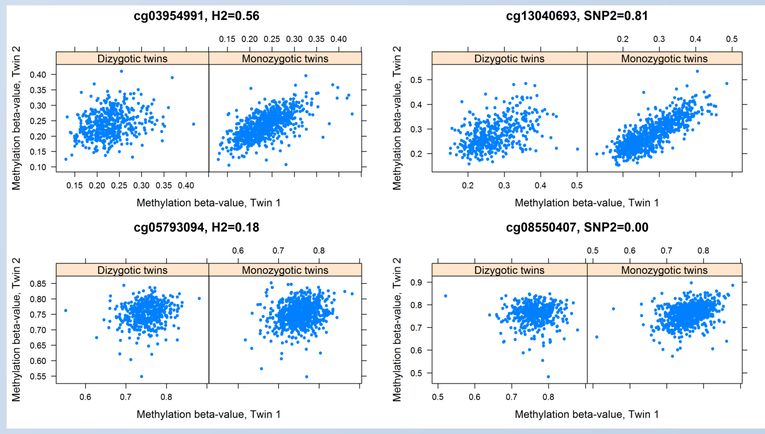

Figure 3

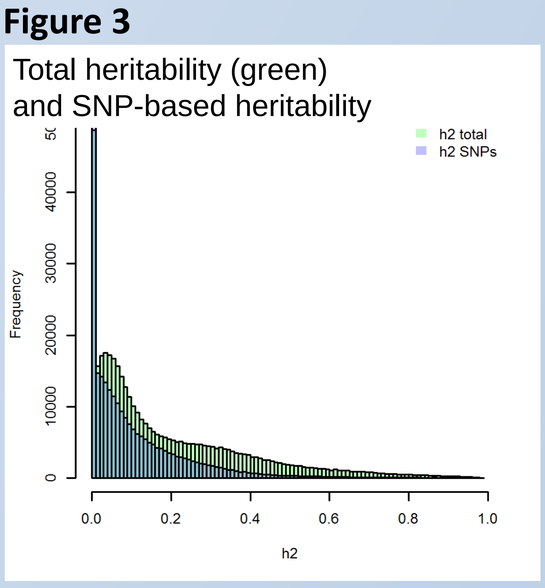

Figure 4

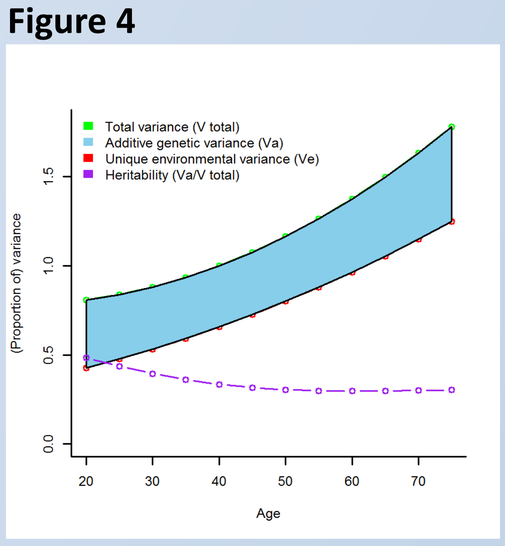

Figure 5

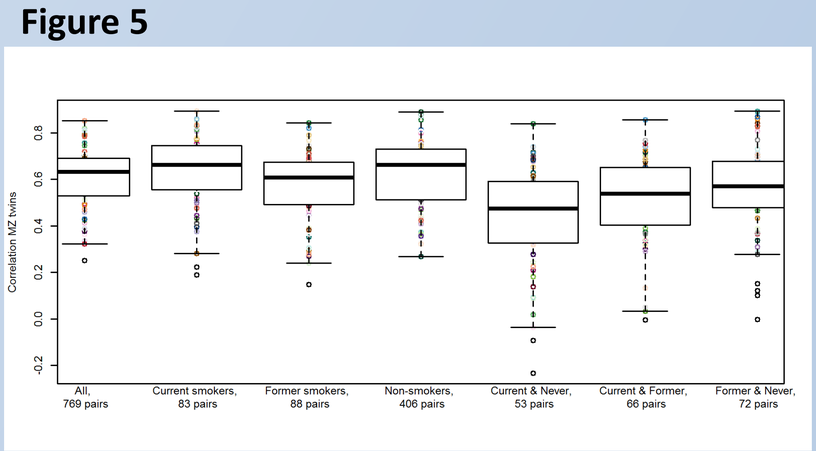

Table 1 Methylation sites with sex differences in environmental variance (Ve)

Trait(s)	-log10(p)	Count	Percentage	Ontology(s)	-log10(p)	Count	Percentage
respiratory allergies (RA)	61.73636	44	0.09072165	allergy (EFO:0003785)	23.31404	62	0.0118321
leukoaraiosis (LA)	11.459279	15	0.02824859	immune system disease (EFO:0000540)	17.22567	126	0.0073461
childhood stress	8.54759	16	0.02909091	white matter lesion progression measurement(EFO:0007746)	11.45928	15	0.0282486
aging	7.5549483	132	0.00718915	brain measurement (EFO:0004464)	11.45928	15	0.0282486
gestational diabetes mellitus	6.4427805	58	0.00889707	eye disease (EFO:0003966)	10.82877	56	0.0111665
primary Sjögren's Syndrome (pSS)	6.4389367	34	0.01144011	Rare genetic neurological disorder (Orphanet:71859)	8.959106	31	0.012731
Coffin-Siris syndrome (CSS)	6.3762193	10	0.03731343	Rare genetic intellectual disability with developmental anomaly (Orphanet:183763)	8.942227	31	0.0127101
Kabuki syndrome (KS)	5.842684	22	0.01163406	Rare genetic intellectual disability (Orphanet:183757)	8.942227	31	0.0127101
maternal Hepatitis B virus (HBV) infection	4.0209394	8	0.02409639	environmental stress (EFO:0000470)	8.044222	18	0.0233463
amygdala:hippocampal (AH) volume	3.112394	2	0.2	anxiety (EFO:0005230)	8.027139	18	0.0232859

Table 2 Methylation sites with age differences in environmental variance (Ve)

Trait(s)	-log10(p)	Count	Percentage	Ontology(s)	-log10(p)	Count	Percentage
aging	>309	2766	0.15064539	genetic disorder (EFO:0000508)	>309	2447	0.148285
maternal smoking	321.22342	869	0.26656443	Rare genetic intellectual disability with developmental anomaly (Orphanet:183763)	296.009	722	0.296023
follicular thyroid carcinoma	295.2026	1209	0.21686098	Rare genetic intellectual disability (Orphanet:183757)	296.009	722	0.296023
Kabuki syndrome (KS)	218.41418	545	0.2882073	Rare genetic neurological disorder (Orphanet:71859)	295.723	721	0.296099
Claes-Jensen syndrome	209.04805	420	0.4	follicular thyroid carcinoma (EFO:0000501)	295.203	1209	0.216861
down syndrome	165.63806	1881	0.12840466	smoking behavior (EFO:0004318)	291.919	2030	0.119849
B Acute Lymphoblastic Leukemia with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)	156.87471	2433	0.11531352	smoking status measurement (EFO:0006527)	286.187	1920	0.124336
thyroid lesion	114.26391	415	0.23673703	Rare genetic developmental defect during embryogenesis (Orphanet:183530)	277.707	753	0.269025
folic acid supplement during pregnancy	102.744606	198	0.4212766	carcinoma (EFO:0000313)	268.129	4610	0.111471
smoking	100.23674	1292	0.0908324	Genetic digestive tract malformation (Orphanet:183545)	220.624	575	0.277912

Ongoing work : aggressive behavior (ACTION project)

- The value of blood-based DNA methylation for identifying biomarkers or underlying mechanisms for behavioral and psychiatric traits is largely unclear.
- We are performing a meta-analysis of ~15.000 blood samples from 20 worldwide cohorts (age 0–80 years) to identify DNA methylation signatures in blood associated with aggressive behavior.
- We will also examine DNA methylation in buccal cells. Data from monozygotic twins will contribute to testing the utility of DNA methylation as a biomarker for complex traits and disease, and unravel its predictive value over and above genetic information.