DNA methylation signatures of educational attainment

An epigenome-wide association study in four Dutch cohorts

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Biobank-based Integrative Omics (BIOS) Consortium

Large-scale infrastructure to analyse genetic (imputed SNPs), methylome (Illumina 450k array), transcriptome (RNA-seq), and phenotypic data on ~4000 individuals from 6 Dutch biobanks.

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|---|--|----------|--------|--|--|------------------|
| The Netherlands | Integrative genomics | | | Cited by | | |
| | | | | | All S | Bince 2015 |
| TITLE | | CITED BY | YEAR | Citations h-index i10-index | 5522 32 45 | 5298 32 45 |
| Systematic identifi HJ Westra, MJ Peters, Nature genetics 45 (10 | ication of trans eQTLs as putative drivers of known disease associations , T Esko, H Yaghootkar, C Schurmann, J Kettunen,)), 1238-1243 | 1329 | 2013 | | | 1400 |
| Epigenome-wide a adiposity S Wahl, A Drong, B Le Nature 541 (7635), 81 | association study of body mass index, and the adverse outcomes of the, M Loh, WR Scott, S Kunze, PC Tsai, JS Ried, $_{\rm 26}$ | 403 | 2017 | | лİ | 1050 |
| Genome-wide association study identifies 30 loci associated with bipolar disorder EA Stahl, G Breen, AJ Forstner, A McQuillin, S Ripke, V Trubetskoy, Nature genetics 51 (5), 793-803 | | | 2019 | 2013 2014 2015 | 2016 2017 2018 2019 | 350 |
| Heritability and ge FA Wright, PF Sullivan Nature genetics 46 (5) | nomics of gene expression in peripheral blood , Al Brooks, F Zou, W Sun, K Xia, V Madar, , 430-437 | 292 | 2014 | 2010 2014 2010 2010 2011 2010 2018 2020 | | |
| From promises to J Mill, BT Heijmans Nature Reviews Gene | practical strategies in epigenetic epidemiology tics 14 (8), 585-594 | 288 | 2013 | Co-authors | mans | |
| Trans-ancestry ge pressure and impl N Kato, M Loh, F Take Nature genetics 47 (11 | nome-wide association study identifies 12 genetic loci influencing blood icates a role for DNA methylation uchi, N Verweij, X Wang, W Zhang, TN Kelly,). 1282-1293 | 217 | 2015 | Lude Fra Professo | iniversity Medical Cen anke or of Functional Genon | nic |
| Disease variants a MJ Bonder, R Luijk, D' Nature genetics 49 (1) | alter transcription factor levels and methylation of their binding sites V Zhemakova, M Moed, P Deelen, M Vermaat, , 131-138 | 212 | 2017 | Rick Jan Assistan Peter A. Professo | isen t Professor, Departme C. ' t Hoen or Bioinformatics, Cent | nt) re) |
| Identification of co DV Zhernakova, P De Nature genetics 49 (1) | ntext-dependent expression quantitative trait loci in whole blood elen, M Vermaat, M Van Iterson, M Van Galen, , 139-145 | 198 | 2017 | | | |
| Shared genetic or MA Ferreira, JM Vonk, Nature genetics 49 (12 | igin of asthma, hay fever and eczema elucidates allergic disease biology H Baurecht, I Marenhoiz, C Tian, JD Hoffman, 2), 1752-1757 | 192 | 2017 | | | |
| Genetic and environme methylome J Van Dongen, MG Nin Nature communication | onmental influences interact with age and sex in shaping the human vard, G Willemsen, JJ Hottenga, Q Helmer, s 7 (1), 1-13 | 162 | 2016 | | | |
| Genome-wide ana | alysis identifies 12 loci influencing human reproductive behavior | 149 | 2016 | | | |

https://www.bbmri.nl/acquisition-use-analyze/bios Available data: https://omics-explorer.bbmri.nl.



Epigenome-wide association study

- Cohorts:
 - Netherlands Twin Register (NTR)
 - Leiden Longevity Study (LLS)
 - Rotterdam Study (RS)
 - Lifelines-Deep (LLD)

Approach: 1. EWAS in individual BIOS cohorts

2. Fixed-effects meta-analysis

Total sample size = 4179

| Cohort | NTR | LLS | RS | LLD | |
|---------------------|-----------|----------|-----------|-----------|--|
| | | | | | |
| Ν | 2199 | 668 | 608 | 704 | |
| % female | 68.6 | 52.5 | 57.7 | 57.67 | |
| Age, mean | 38.2 | 59.1 | 68.6 | 47.32 | |
| (sd) | (12.6) | (6.6) | (5.6) | (12.47) | |
| birth year, mean | 1968 | 1945 | 1943 | 1965 | |
| (range) | ('26-89') | ('25'74) | ('30-'60) | ('31-'87) | |

Tissue: peripheral whole blood (Illumina 450k methylation array)

van Dongen, Jenny, et al. "DNA methylation signatures of educational attainment." *npj Science of Learning* 3.1 (2018): 1-14.

Educational attainment

Harmonization of the raw phenotype data:

1. Highest completed level of education at the age of 25 or higher – **7 categories**.

| 7 Levels | | | | |
|--|--|--|--|--|
| 1. primary school only | | | | |
| -lager onderwijs | | | | |
| 2. lower vocational schooling | | | | |
| -lager beroepsonderwijs (lbo) | | | | |
| 3. lower secondary schooling (general) | | | | |
| - middelbaar algemeen onderwijs (lavo, mavo) | | | | |
| 4. intermediate vocational schooling | | | | |
| - middelbaar beroepsonderwijs (mbo) | | | | |
| 5. intermediate/higher secondary schooling (general) | | | | |
| - voorgezet algemeen onderwijs (havo, vwo) | | | | |
| 6. higher vocational schooling | | | | |
| -hoger beroepsonderwijs (hbo) | | | | |
| 7. University | | | | |
| - wetenschannelijk onderwijs (wo) | | | | |

Educational attainment as a function of birth year



EWAS

- Linear relationship DNA methylation (outcome variable) education level (predictor)
- Covariates
 - Sex
 - Age
 - White blood cell counts
 - 96-wells plate, 450k row
- Additional analyses:
 + covariate smoking status

Relevance

Educational attainment

Important correlate/indicator of:

- Cognitive and personality characteristics (e.g. intelligence, attention, memory, reading ability, persistence, self-discipline)
 - Advantage : well-documented in many cohorts
 - Social environment in which the individual is born and raised-
 - Social outcomes of individual (occupation, income)
 - Health
 - Average life expectancy at birth: 79,1 Dutch men, 82,8
 Dutch women (RIVM reports 2012).
 - Difference in the Netherlands between high and loweducated groups:
 - 6.5 years for men
 - 6,1 years for women



Meta-analysis: 58 significant CpG sites



CNTNAP2: Contactin Associated Protein-Like 2- a neuronal transmembrane protein (neurexin family).

- *CNTNAP2* = target of transcription factor *foxp2*
- Genetic variants in *CNTNAP2* associated with neurodevelopmental phenotypes: language impairment, autism, intellectual disability, dyslexia, schizophrenia

PCDH9 : protocadherin 9.

- Copy-number variants: autism spectrum disorder
- knock-out mice: social and object recognition deficits.
- also described as a tumor-suppressor gene

AHRR (top site cg05575921).

- Aryl-Hydrocarbon Receptor Repressor
- One of the most strongly associated and best replicating hits in previous EWAS of smoking phenotypes

All 58 CpGs previously associated with smoking & 50% previously associated with prenatal maternal smoking

EWAS education, unadjusted for smoking status: 58 significant CpGs







25

Chromosome

Effect size: AHRR methylation – educational attainment in NTR

-0.025

No adjustment for smoking

Adjusted for smoking status

Adjusted for smoking status + smoking packyears

Adjusted for smoking status + maternal prenatal smoking

effect size in never smokers

effect size in never smokers, adjusted for maternal smoking



The AHR pathway

- AHR =Aryl-Hydrocarbon Receptor: binds to various environmental toxins (e.g dioxins, benzopyrene, PCBs) and endogenous substrates
- AHR is a transcription factor for:
 - Xenobiotic metabolism genes
 - Developmental genes
 - AHRR
- AHRR: represses the functioning of AHR (negative feedback)
- Increased expression of AHRR following prenatal and lactational dioxin exposure disturbs neural network formation in the developing mouse brain (Kimura et al 2015; 2016)



Nature Reviews | Cancer

Bernsten et al. bHLH–PAS proteins in cancer. Nature Reviews Cancer 13, 827–841 (2013) doi:10.1038/nrc3621

Follow-up: methylation level during fetal brain development

- 58 education associated sites
 - 18 show are dynamic in the fetal brain (significant after Bonferroni correction, 58 tests)



Dataset: Spiers, H. et al. Methylomic trajectories across human fetal brain development. *Genome Res.* 25, 338–352 (2015).

Cg25189904 (*GNG12*) r=-0.57,p= 7.1e-17 Top hit education (AHRR) r =0.27, p=2.5e-04 Cg21322436 (*CNTNAP2*) r = -0.19, p=9.6e-03

Follow-up: correlation methylation level blood – brain (postmortem)

- 58 education associated sites :
 - 10 significant correlation: blood one or multiple brain regions (Bonferroni correction 232 tests).
 - range: r = 0.36 to r = 0.63

Dataset: Hannon, E., Lunnon, K., Schalkwyk, L. & Mill, J. Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes. *Epigenetics* **10**, 1024–1032 (2015).

Blood EWAS of educational attainment shows epigenetic signatures of:



Dutch population (N=4152, adults)

Prenatal maternal plasma folate

Air pollution (fine matter)

Alcohol consumption (not significant)



ARTICLE

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Genetic and environmental influences interact with age and sex in shaping the human methylome

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Genetic influences on education-associated CpGs (mean heritability=58%)



Discussion

- Education closely related to health, Alzheimer's disease, societal inequality
- Cognition = brain / DNA methylation = blood
- Methylome: environmental and lifestyle differences



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Resources

Results

This website gives you access to the summary data of all association studies that have been performed by the <u>BBMRI-NL</u> consortium.

DNA methylation array QC and analysis pipelines

Streamlined workflow for the quality control, normalization, and analysis of Illumina methylation array data

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http://bbmri.researchlumc.nl/atlas/

nl/atlas/ https://molepi.github.io/DNAmArray_workflow/index.html