DNA methylation as a biomarker for disease, behavior and environment

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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 BMBRI-NL BIOS consortium, we established a catalogue of between-individual variation in DNA methylation (Illumina 450k array; van Dongen et al 2016 Nat Commu). 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://bmbri.researchlumc.nl/atlas/.

Disease- and trait enrichment for methylation sites with sex- or age-specific environmental variance
We used the EWAS atlas (http://bind.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.

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.