DNA Methylation and Health Outcome in an Aging Cohort

Alexandra Bartlett and Khyobeni Mozhui, Ph.D.

Introduction

DNA methylation is an epigenetic mechanism that involves the addition of a methyl group to to a cytosine base at CG dinucleotides (called CpG sites) and plays crucial role in regulating gene expression. DNA methylation undergoes extensive remodeling over the course of life, and is considered to be a biomarker of human age and potentially predictive of health and lifespan (Horvath et al. 2013; Marioni et al. 2015; Mozhui & Pandey 2017). Such epigenetic remodeling offers an explanation for the vast differences found in the epigenome of young individuals compared to the elderly. Here, we track changes in DNA methylation over time and its significance with regards to healthy aging.

Methods

DNA was sampled from 20 participants of the Health ABC study at baseline and follow-up year 6. Genome-wide DNA methylation was assayed on the the Illumina Infinium MethylaionEPIC microarray, which targets >850K CpG sites. Methylation is quantified as beta-value: ratio of methylated to total probes, ranging from 1 to 0. Data processing, quality check and normalization were performed in R. Major sources of variance were evaluated using principal component analysis (PCA) and the top 5 PCs were associated with baseline variable and cancer diagnosis.

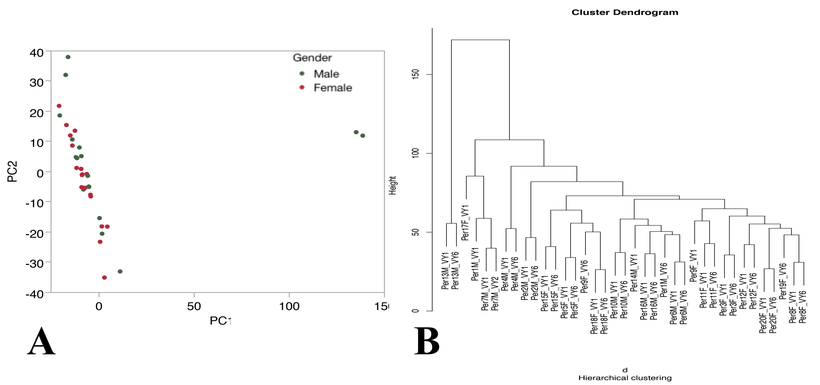

Figure 1. Data quality. (A) PCA identified two outlier samples that came from the same individual (person13) at visit years 1 and 6. **(B)** Hierarchical cluster dendrogram showed high data quality and most longitudinal samples paired with self.

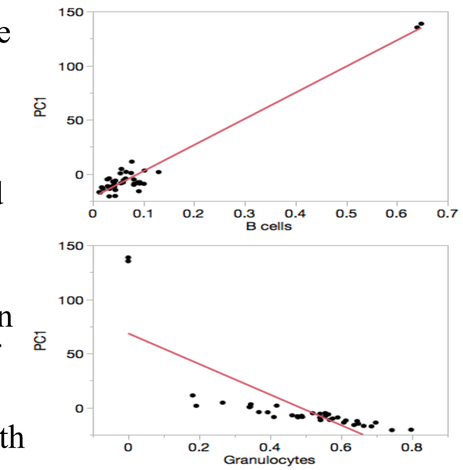

Figure 2. (A) Outlier identification. PC1 is strongly correlated with blood cell type. From this we identified person 13 as an outlier with high levels of B-lymphocytes.

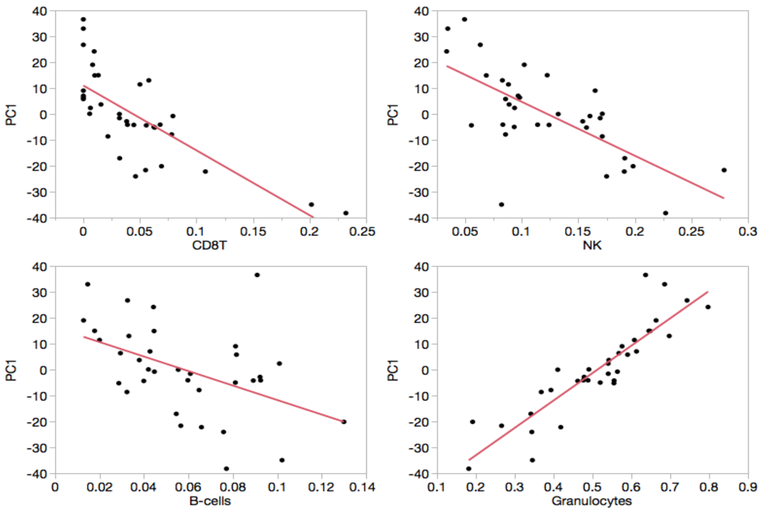

Figure 2. (B) Cellular heterogeneity signal. PC1 captures lymphoid and granulocyte signal and is robust and is specific to blood cell type

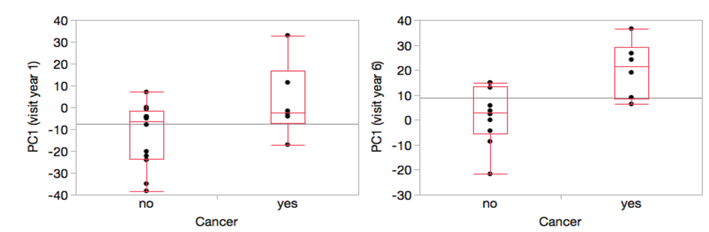

Figure 3. PC1 at VY1 and VY6. PC1 is significantly associated with cancer outcome at both visit years 1 and 6.

Results

Overall data was of high quality, with self-pairing for most participants; Person 13 was an outlier (**Figure 2A**). There was no obvious batch effect (**Figure 1A**). The largest source of variance, PC1, was due to cell composition. Person 13 had a high number of B-cells (**Figure 2B**), and was diagnosed with leukemia six months from baseline visit. Person 13 was therefore excluded and PCA repeated. PC1 to PC5 accounted for 45% of variance. PC1 was inversely correlated with lymphoid cells and positively correlated with granulocytes (**Figure 2B**). PC1 was was predictively of future cancer diagnosis at VY1 (X^2 (1) = 4.353, p <.05) and, this association became stronger at VY6 (X^2 (1) = 8.755, p <.05, **Figure 3**).

Primary cancer sites include: leukemia (including Person 13), prostate, colon, breast, stomach. There was no greater age acceleration in the cancer group, and the methylation age for all samples increased over time. While the methylation age appears significantly older than the actual chronological age, our analysis shows that the methylation age is sensitive enough to capture longitudinal age progression over the course of 5 years.

Conclusion

Our data demonstrates that we can derive information on cellular composition and change in cellular composition with age from global patterns in DNA methylation. The methylation pattern may also be predictive of future cancer diagnosis. However, given the small samples size, this needs to be replicated. It is also not clear whether the association with cancer diagnosis is related to differences in immune cells or other factors (e.g., medication use, lifestyle differences) and this warrants further investigation.

References

Marioni RE, Shah S, McRae AF, et al. “DNA methylation age of blood predicts all-cause mortality in later life.” *Genome biology* 16.1 (2015): 25-9.

Horvath S. "DNA methylation age of human tissues and cell types." *Genome Biology* 14.10 (2013):R115

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