

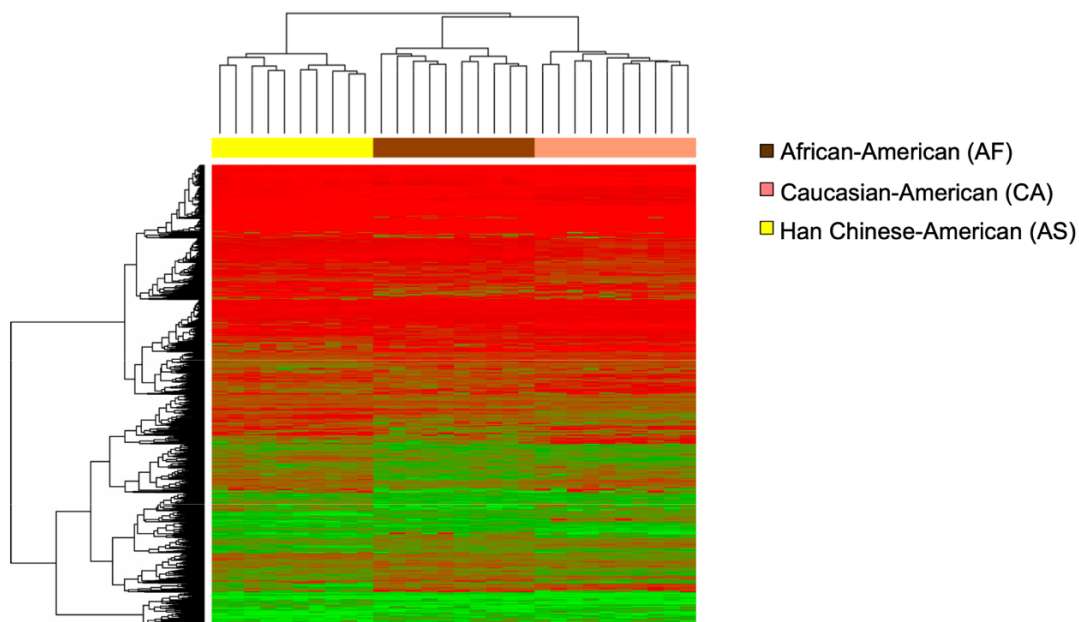
## DNA methylation contributes to natural human variation

Conventional wisdom and the central dogma of molecular biology (that DNA encodes the instructions for protein synthesis via RNA, and that these proteins lead to phenotypic traits) would lead you to believe that the natural phenotypic variations observed between different human populations are due to genetic differences – and you wouldn't be entirely wrong. However, we cannot attribute natural human variation solely to genetic mechanisms. For example, genetically identical individuals such as monozygotic twins, cloned animals, and Agouti mice have been shown to have DNA methylation and phenotypic differences.

So now we know that the natural variation we see between individuals isn't **only** due to genetic differences – epigenetic variations, especially DNA methylation, contribute to this variation. But does this only occur between individuals, or does DNA methylation play a role in the differences observed between entire populations too? And how does it do this? These are the questions that Heyn et al. set out to answer in this study.

In order to do this, a differential DNA methylation analysis of around 300 individuals from 3 human populations (Caucasian-American, African-American, Han Chinese-American) was performed. The B-lymphocytes of these individuals were analyzed at a genome-scale resolution of around 450 000 CpG sites. DNA methylation at distinct loci enabled the separation of samples with respect to geographic origin and a subsequent integration of genotype data enabled precise separation into genetically dependent and independent variation.

Using 439 CpG sites differentially methylated between Caucasian-American, African-American, and Han Chinese-American individuals, Heyn et al. were able to separate the distinct populations with respect to their geographical regions, as seen in Figure 1 below.



**Supplemental Figure 1.** Hierarchical cluster of naive blood samples (n=30) using DNA methylation levels of 1373 pop-CpG sites differentially methylated ( $\Delta$  mean  $\beta$ -values  $\geq 0.12$ ; ANOVA, FDR  $< 0.01$ ) between African (AF, brown), Asian (AS, yellow) and Caucasian (CA, pink) populations in LCLs. Displayed are absolute DNA methylation levels (low: green; high: red) and samples were clustered using the complete agglomeration method for Manhattan distances.

It was also possible to associate these sites with phenotypic characteristics such as appearance, drug metabolism, response to external stimuli, sensory perception, and disease susceptibility. Additionally, local selective pressure was shown to introduce the manifestation of epigenetic variants.

Two thirds of the population-specific CpG sites were directly associated with the underlying genetic background. This suggests that genetic context influences DNA methylation. Thus, DNA methylation acts as an intermediate regulatory event that leads to phenotypic differences between populations.

Heyn et al. were thus able to demonstrate DNA methylation differences that distinguish three major human ethnic groups. While many of these differences are associated with underlying genetic changes, which suggests a direct relationship between genetic and epigenetic codes, others stand alone as epigenetic markers and CpG methylation quantitative trait loci associated with natural variation in humans. DNA methylation therefore likely contributes to the different phenotypic characteristics (such as drug response and disease frequencies) that occur between human populations. Detecting distinct pop-CpG sites within populations suggests that divergence and selection pressure shape not only the genetic code, but also the DNA methylation landscape.

Heyn, H., Moran, S., Hernando-Herraez, I., Sayols, S., Gomez, A., Sandoval, J., Monk, D., Hata, K., Marques-Bonet, T., Wang, L., & Esteller, M. (2013). DNA methylation contributes to natural human variation. *Genome Research*, 23(9), 1363–1372. <https://doi.org/10.1101/gr.154187.112>

# DNA METHYLATION CONTRIBUTES TO NATURAL HUMAN VARIATION

Heyn et al.

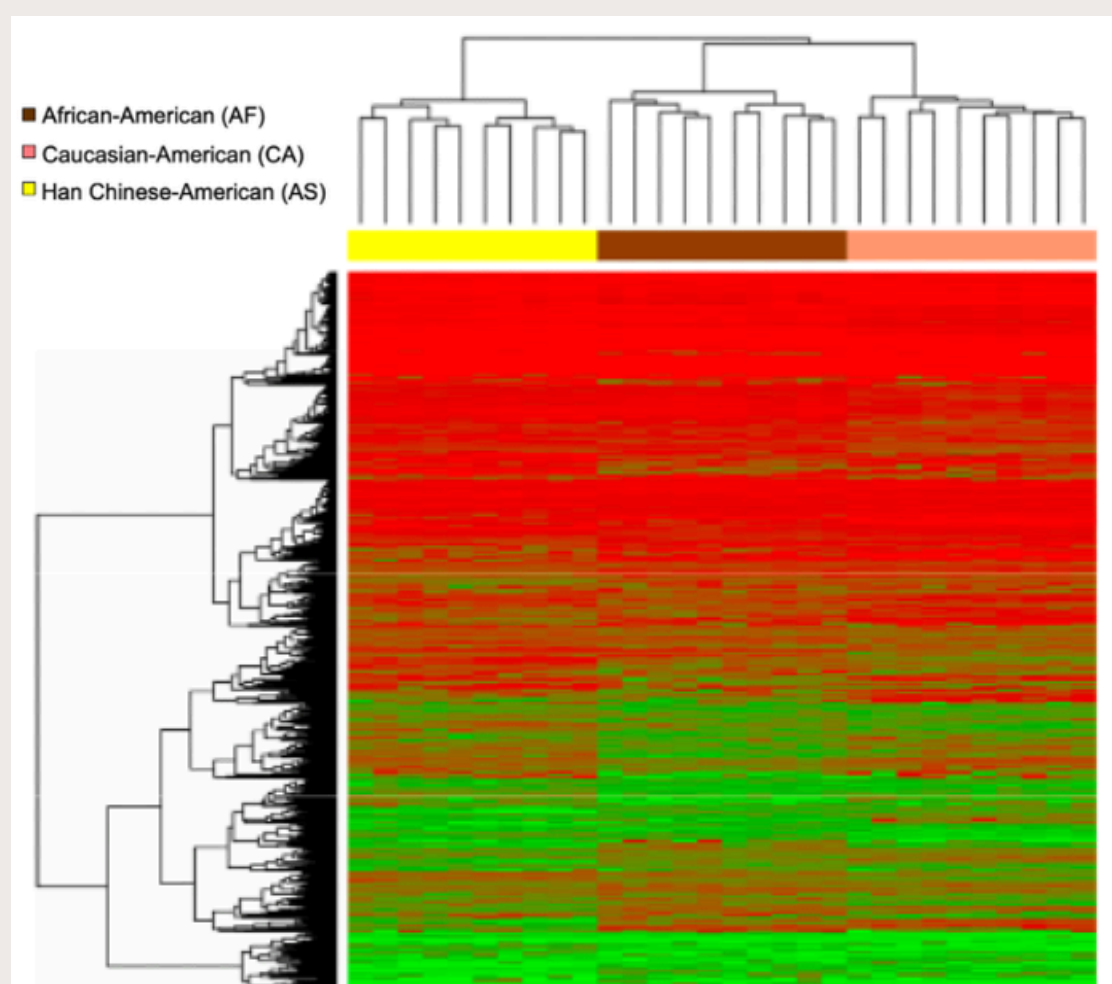
## Research Overview

This study examines whether DNA methylation contributes to the phenotypic variation observed between human populations, and how this is done.

## Research Question

Does DNA methylation play a role in the phenotypic differences observed between entire populations and how does it do this?

## Data Highlight



The distinct populations were able to be separated with respect to their geographical regions.

## Methodology

- Differential DNA methylation analysis
- 300 individuals
  - Caucasian-American
  - African-American
  - Han Chinese-American

## Key Insights

It is possible to associate differentially methylated regions with phenotypic characteristics.

- appearance
- drug metabolism
- response to external stimuli
- sensory perception
- disease susceptibility

Two thirds of sites were directly associated with the underlying genetic background, suggesting genetic context influences DNA methylation.

## Conclusion

DNA methylation contributes to different characteristics by acting as an intermediate regulatory event leading to phenotypic differences between populations.