Epigenetics & CVD Risk Prediction

Myriam Fornage, PhD

University of Texas Health Science Center at Houston

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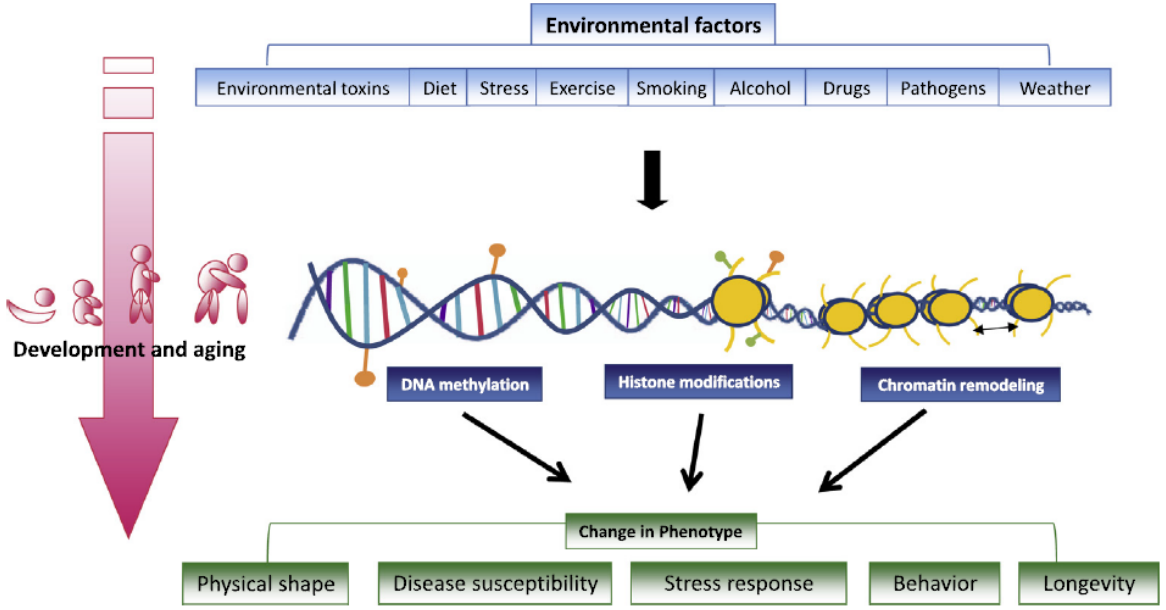
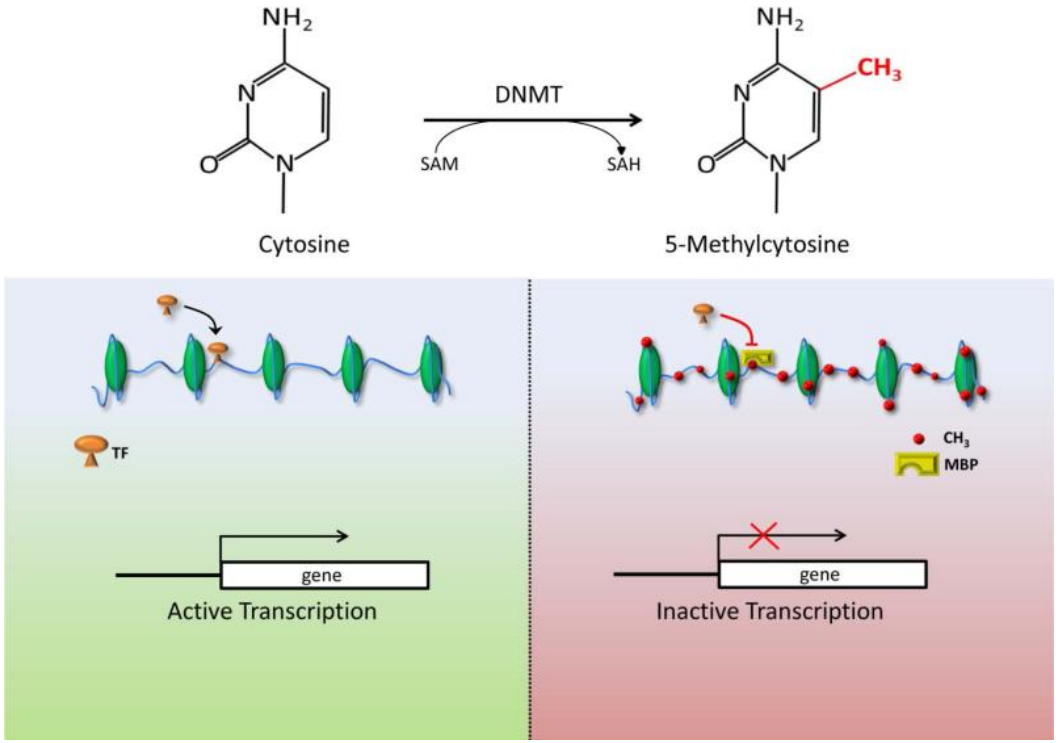
The Epigenome in Health and Disease

- **Epigenome:** Set of stable alterations to the DNA and histone proteins that **alter gene expression** without change in the DNA sequence
- The epigenome as a link between the genome, the environment, and phenotypes of health & disease
  - May mediates the long-term impact of environmental exposures on disease risk



DNA Methylation

- is the most studied epigenetic mark
  - covalent binding of a methyl group to the 5' carbon of cytosines occurring mainly at CpG dinucleotide sequences
  - ~30 millions CpG across the human genome and 70% of them are methylated
- plays a critical role in the regulation of gene expression
  - modulates expression of genetic information by modifying DNA accessibility to the transcriptional machinery
- is dynamic, tissue- or cell-specific, and can be influenced by, both, genes and the environment
- can be measured reliably, quantitatively, in a cost-effective manner via DNAm array



Jia Zhong, et al. Circ Res. ;118(1):119-131

Pre-requisites for Risk Score Application

Epigenome-Wide DNA Methylation Studies (EWAS)

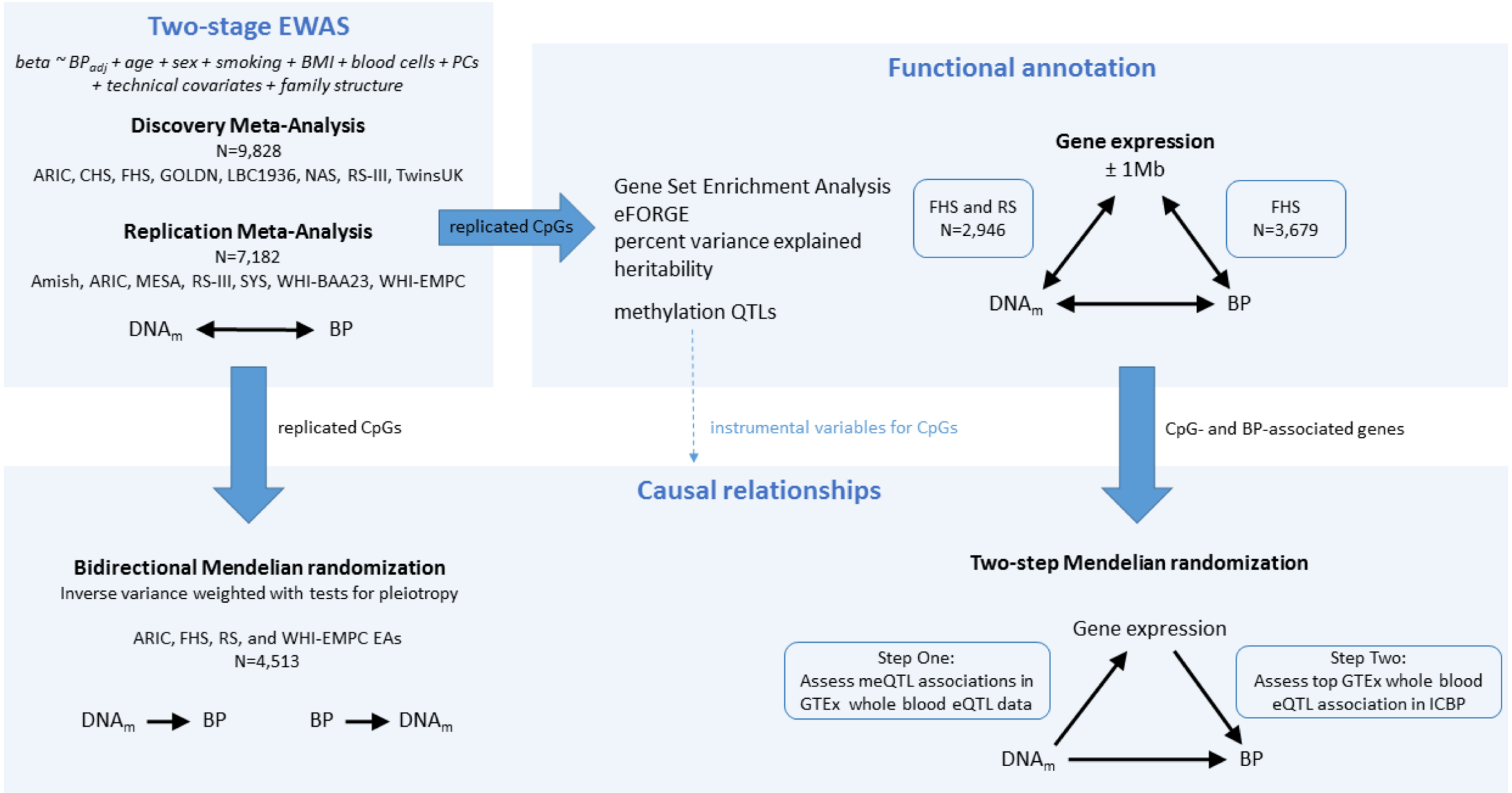
- **Goal**: The **integration** of DNA methylation data into our population-based research with the goal of **discovering relationships** between variation in **DNA methylation with environmental exposures, genetic variation,** and **disease risk** and disease-related traits
- Genome-wide association studies of DNAm and environmental exposures
  - DNA methylation signatures of cigarette smoking, alcohol intake, dietary vitamins intake, air pollution, dietary patterns
- Genome-wide association studies of DNAm and disease and disease-related traits
  - EWAS of blood pressure, circulating markers of inflammation, depressive symptoms, cognitive function, brain MRI traits
- GWAS of DNAm levels: Mapping of *cis* and *trans* meQTL

EWAS vs. GWAS

- Genetic factors are fixed throughout the lifetime
  - No assumption about temporality of effects
  - No issue with time of sample collection
- Genetic factors can be assumed to be randomly assigned with respect to traits
  - Population stratification is identifiable and can be corrected
- Pattern of correlation (LD) well defined in genetic data

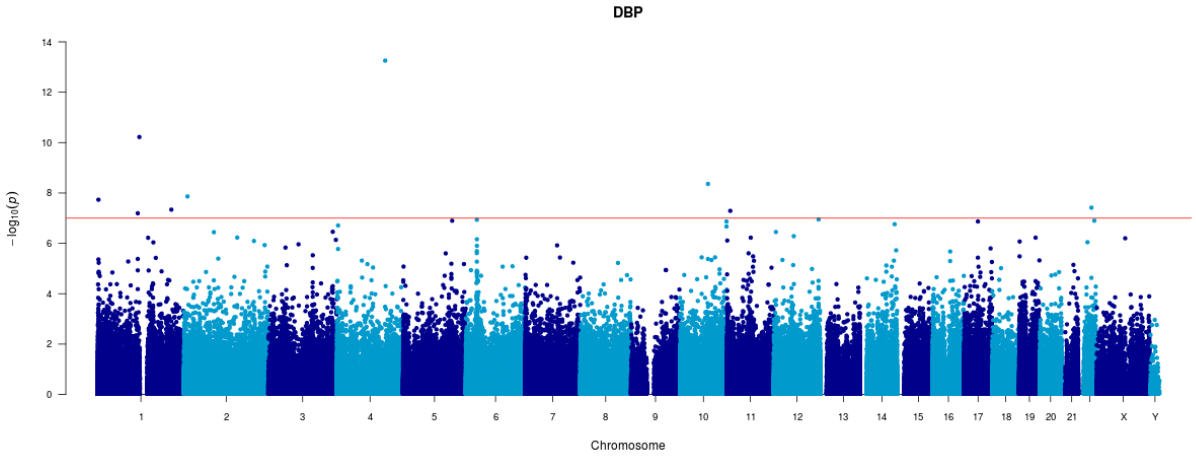
- DNA methylation is a dynamic process
  - Collection timing matter: Optimal timing of the measurement relative to outcome of interest?
  - Issues of reverse causation need to be carefully assessed
- Confounding is often present
  - Cellular heterogeneity
  - Measured and unmeasured environmental factors
- Inter-correlation of CpGs not well-defined or exploited
- DNAm is the dependent variable in EWAS studies

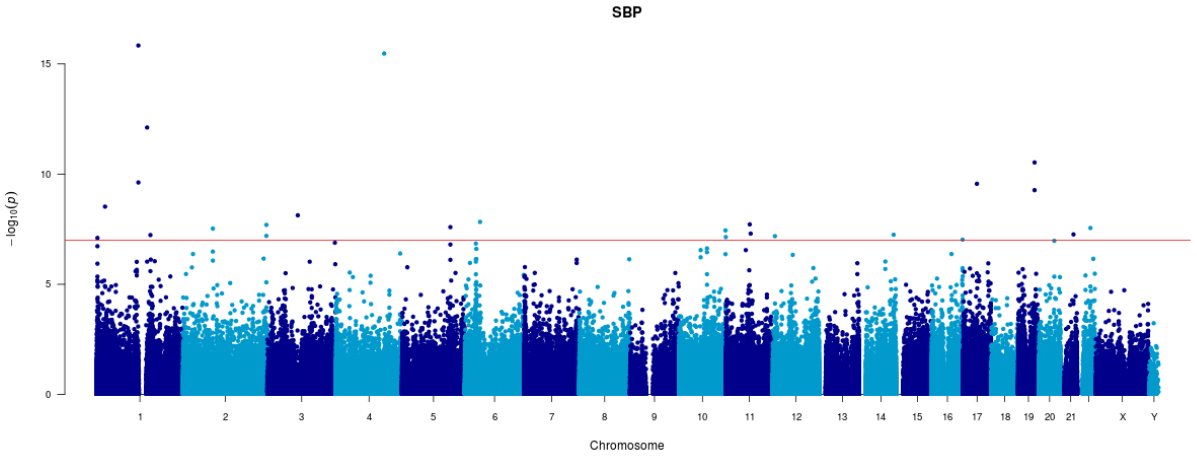
Study Design and Methodologies: Blood Pressure EWAS



EWAS of Blood Pressure – CHARGE Consortium

Discovery sample: 9,828 middle-aged to older adults (EA, N = 6650; AA, N = 3178) from 9 cohorts
Replication Sample: 7,182 middle-aged to older adults (EA, N = 4695; AA, N = 1458; HIS, N = 1029) from 7 cohorts

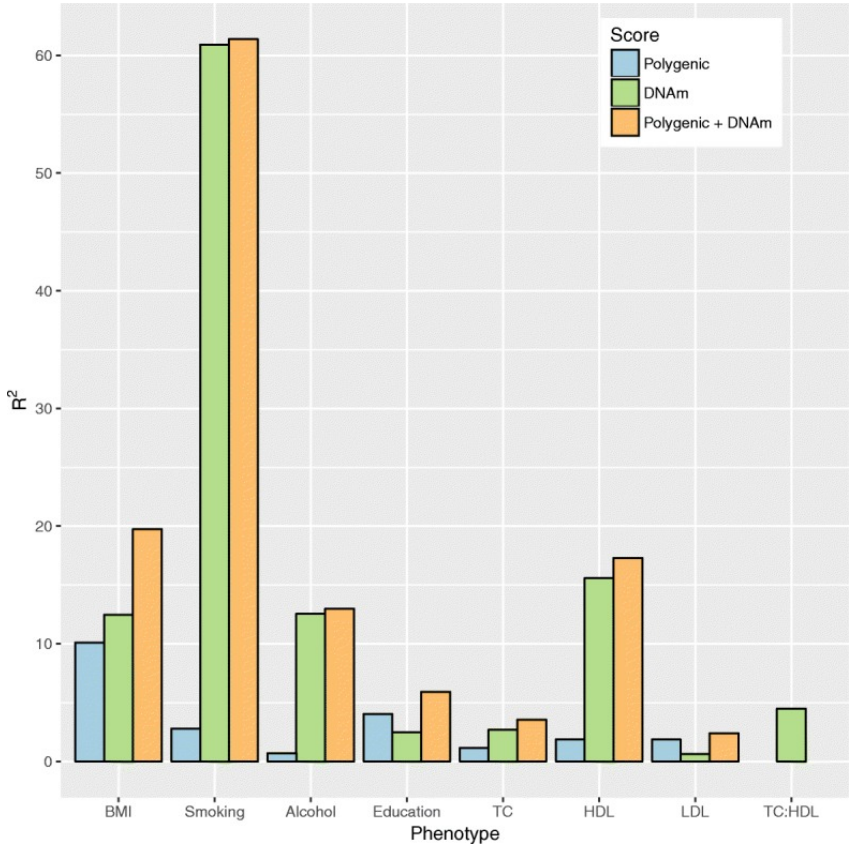




Meta-Analysis	tests, n	p-value threshold	SBP probes, n	DBP probes, n	total probes, n
Discovery	> 450,000	1E-7	25	9	31
Replication	31	0.0016	9	6	**13**
Overall	> 450,000	1E-7	102	56	126

EWAS of BP: Lessons Learned

- DNA methylation explains more of BP variance than genetic loci
  - DNAm score based on 13 replicated CpGs explained ~1.5% - 2% variance in BP
  - Genetic risk score based on known BP SNPs (N=261) explained between 0.003% and 0.1%
- Similar findings are observed for other traits

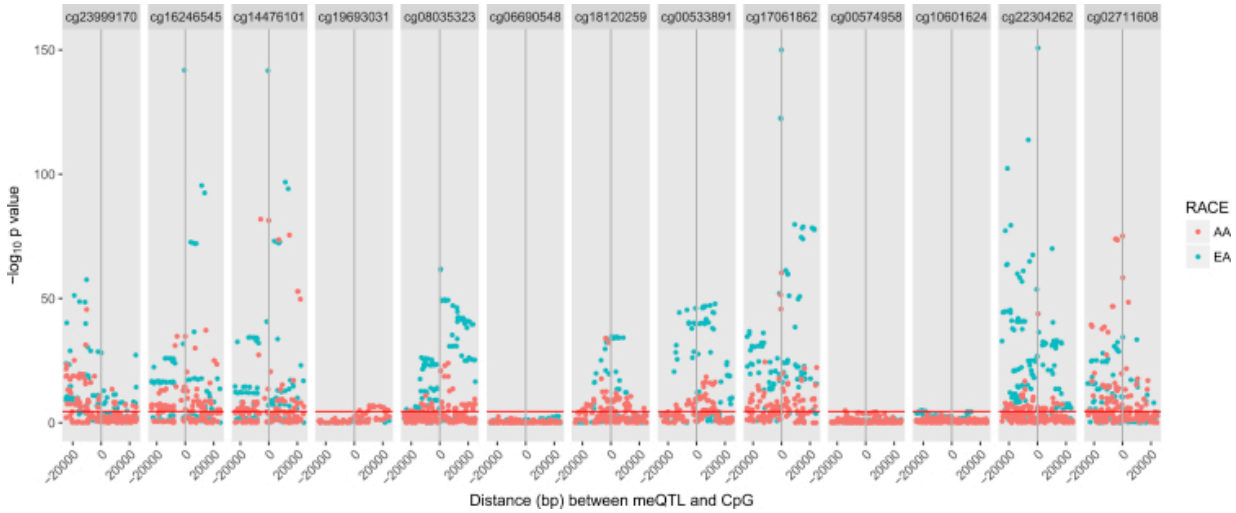


McCartney at al. 2018; PMID: 30257690

EWAS of BP: Lessons Learned

- Many identified BP-associated CpGs are heritable
  - replicated probes average h^2 = 30-60%; epigenome-wide average h^2 = 12%
- meQTLs could be identified in 10 of the 13 BP-associated CpGs
  - 9 of 13 CpGs showed substantial evidence for meQTLs in EA and AA ancestries, with evidence for weak meQTLs at one additional CpG site in each ancestry
  - Seven of the 10 meQTLs showed nominal association with BP

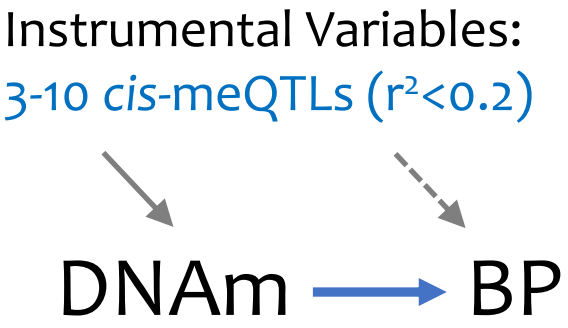
meQTL mapping in in 4,036 EAs and 2,595 AAs and confirmed in an independent dataset (ARIES)



P-value of association of SNPs with DNAm relative to the CpG location (±25 kb)

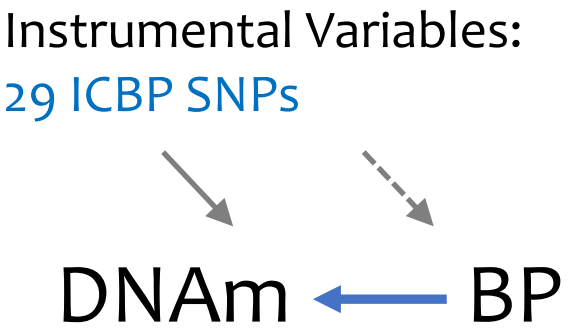
EWAS of BP: Lessons Learned

- DNAm influences BP but also BP influences DNAm levels
  - Evidence through bidirectional Mendelian randomization
  - Instrumental variables:
    - meQTL
    - BP-associated SNPs



Forward Causality

cg08035323

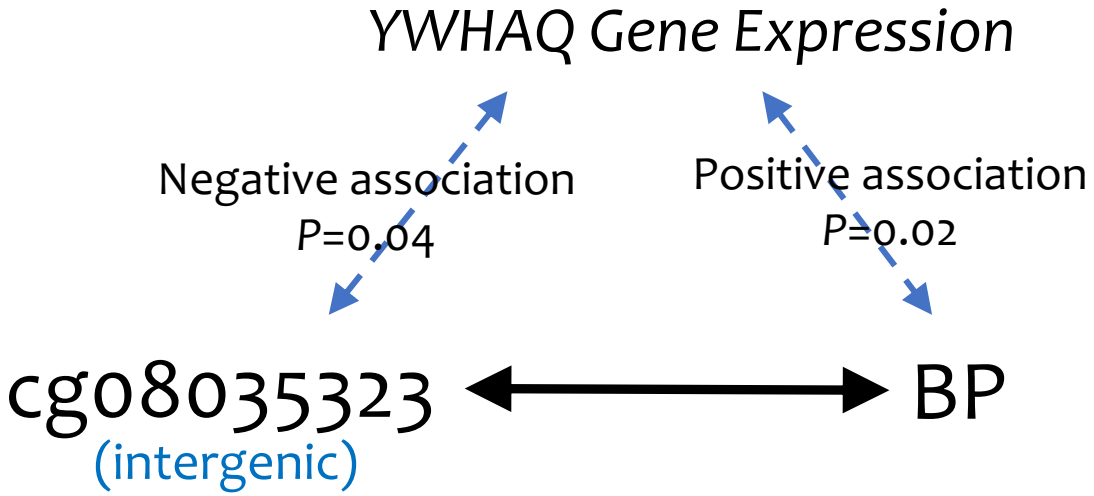


Reverse Causality

cg00533891
cg00574958
cg02711608
cg22304262

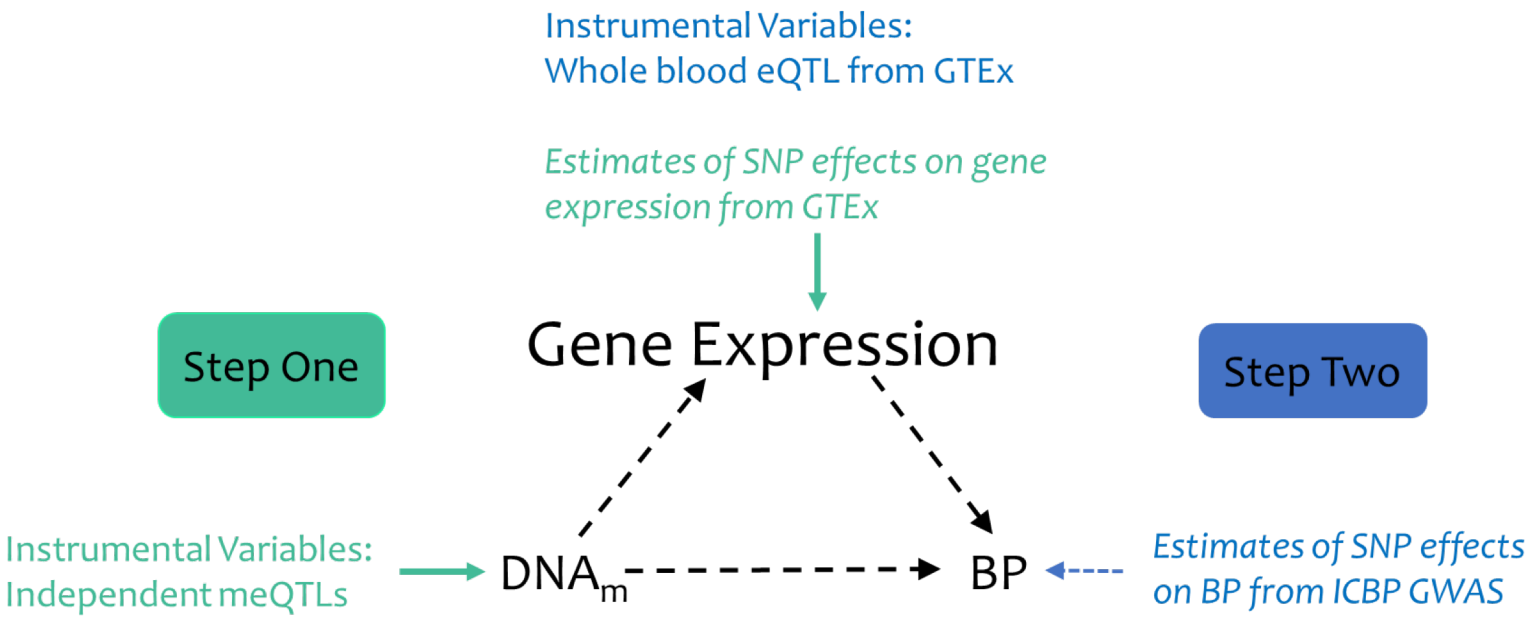
EWAS of BP: Lessons Learned

- Integration of other omics (gene expression) improves interpretability of EWAS findings

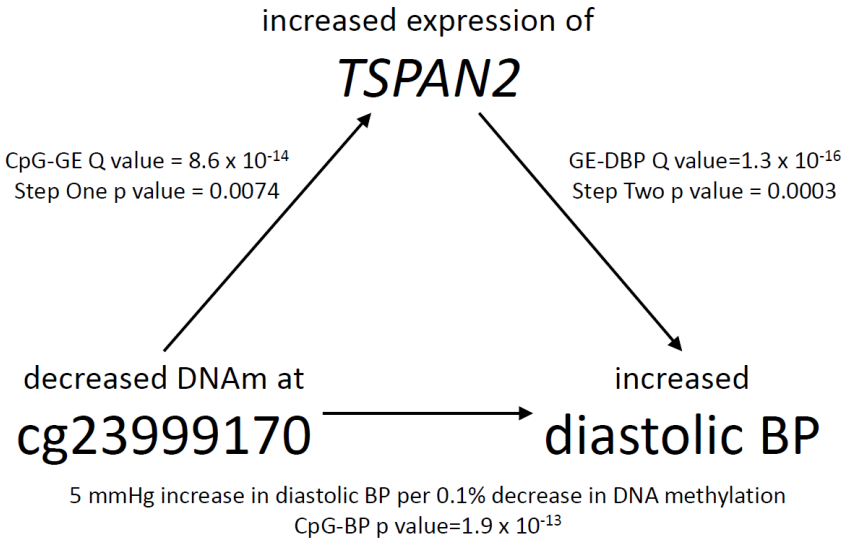


Blood DNAm, blood gene expression, and BP measured in the same sample

Assessing Functional Causality: Two-Step Mendelian Randomization

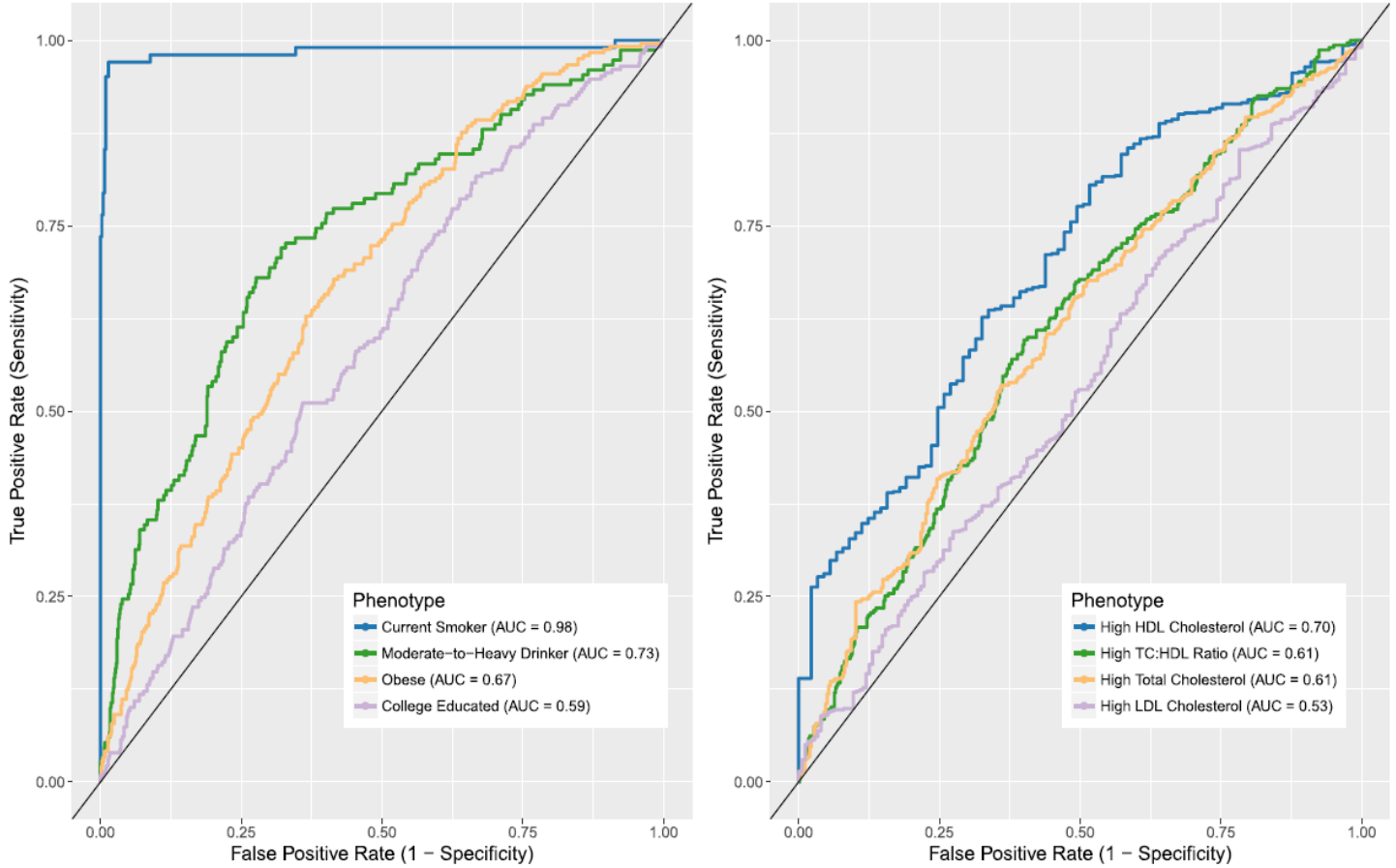


Causal mediation by gene transcripts associated with DNAm & BP



Application of DNAm to (Risk) Prediction

- How well does DNAm predict cardiometabolic traits?
  - DNAm scores generated in the GS cohort (N=5087) and validated in LBC1936 cohort (N=895)
  - Near perfect discriminatory power for current smokers
  - Moderate discrimination of obesity, heavy drinking, and high HDL
  - Poor discrimination of high(college) education and high LDL



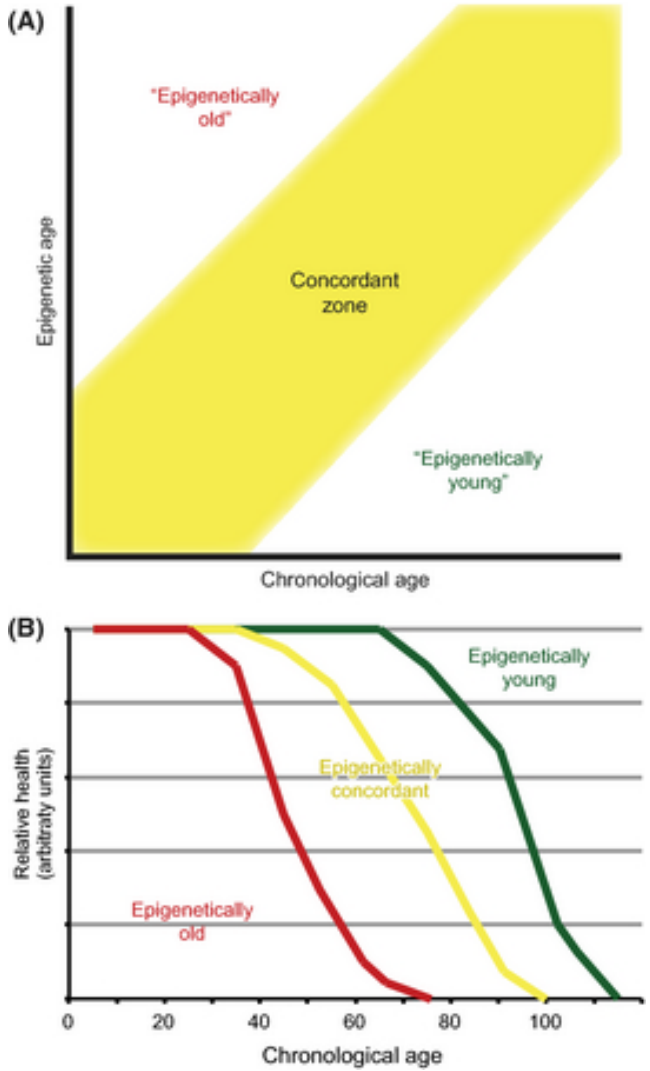
ROC analysis for DNAm predictors of smoking, alcohol, education, BMI, and lipid traits in in the LBC1936 cohort

McCartney at al. 2018; PMID: 30257690

Association of DNAm risk scores, polygenic risk scores, and phenotypes with mortality

Trait	Predictor	HR	95% CI	P
Alcohol	Phenotypic	0.93	0.82 – 1.07	0.362
	Epigenetic	**1.24**	**1.08 – 1.43**	**0.003**
	Genetic	1.05	0.92 – 1.21	0.479
Smoking	Phenotypic (Current smoker)	1.91	0.98 – 3.70	0.057
	Epigenetic	**1.29**	**1.05 – 1.57**	**0.013**
	Genetic	0.98	0.86 – 1.13	0.801
Education	Phenotypic	0.9	0.78 – 1.05	0.178
	Epigenetic	**0.81**	**0.71 – 0.93**	**0.004**
	Genetic	0.96	0.84 – 1.11	0.59
BMI	Phenotypic	1.14	0.99 – 1.32	0.077
	Epigenetic	1.01	0.87 – 1.17	0.903
	Genetic	1.1	0.95 – 1.28	0.184
Total cholesterol	Phenotypic	0.86	0.74 - 1.00	0.047
	Epigenetic	0.98	0.83 - 1.14	0.774
	Genetic	*1.14*	*1.00 - 1.31*	*0.064*
HDL cholesterol	Phenotypic	0.92	0.77 - 1.09	0.324
	Epigenetic	0.92	0.78 - 1.08	0.314
	Genetic	1.08	0.94 - 1.25	0.274
LDL cholesterol	Phenotypic	0.9	0.78 - 1.05	0.176
	Epigenetic	1.01	0.86 - 1.19	0.926
	Genetic	1.1	0.95 - 1.28	0.181
Waist-to-hip ratio	**Epigenetic**	**1.24**	**1.08 - 1.42**	**0.002**
	Genetic	0.93	0.82 - 1.07	0.315
% body fat	Epigenetic	1.08	0.93 - 1.23	0.328
	Genetic	**1.18**	**1.03 - 1.36**	**0.016**

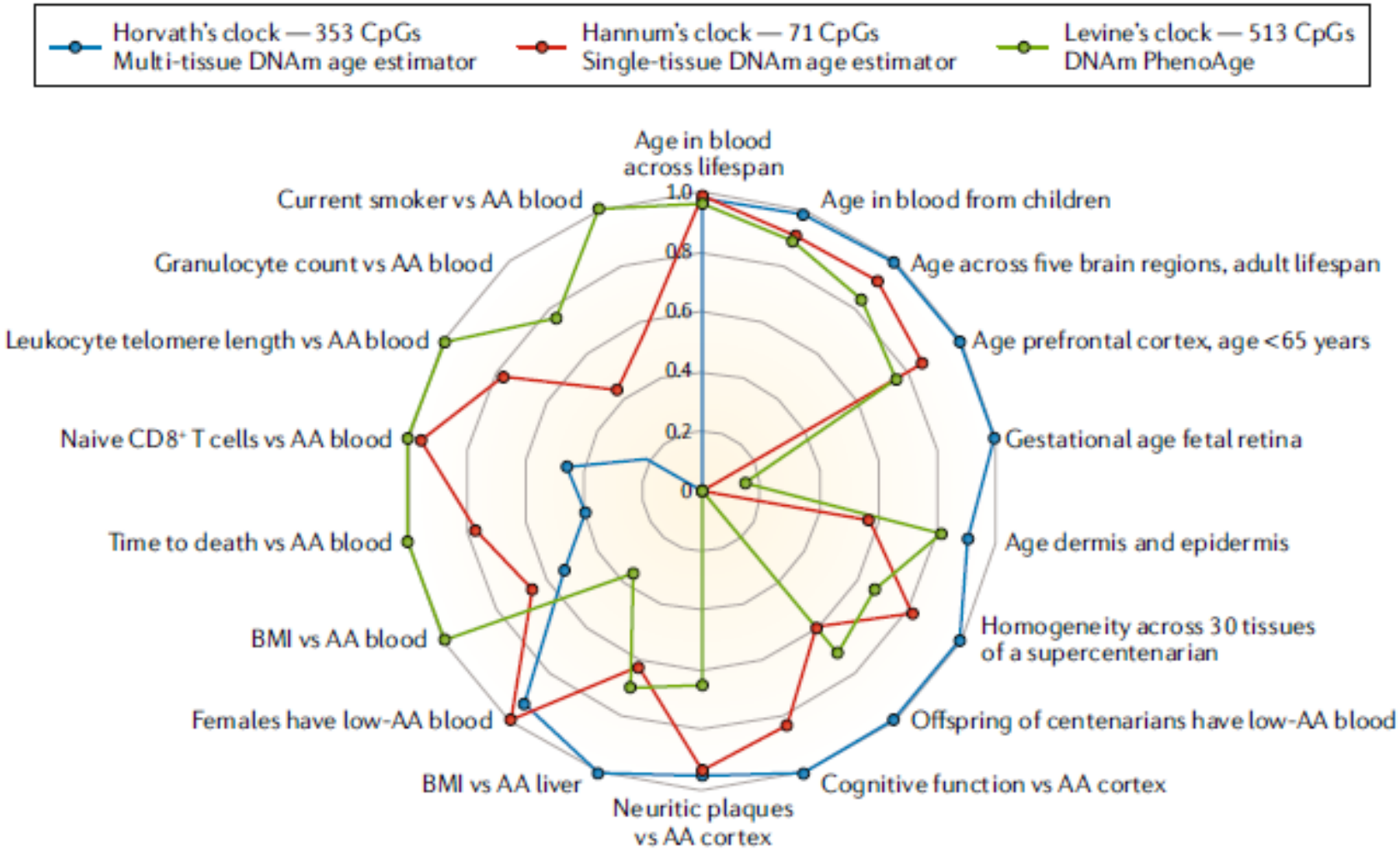
Application of DNAm to Age Prediction



- DNAm-based age estimators
  - Age has a strong impact on genome-wide DNAm levels
  - DNAm age estimators are based on sets of CpGs selected to best estimate chronological age
- **Age acceleration:** Deviation of the DNA methylation-predicted age from the chronological age – Index of an individual's rate of aging
- Discrepancies between a person's DNA methylation age and chronological age may be detrimental to health
  - Association between blood DNA methylation-derived measures of accelerated aging and all-cause mortality (*Marioni et al. 2015*)

Aging Cell, 2015, 14:924

Application of DNAm to Age Prediction



Horvath and Raj, 2018. PMID: 29643443

Conclusions

- EWAS identifies new genomic regions influencing complex traits not previously implicated by GWAS but care must be taken in the interpretation of epigenetic associations
- DNAm scores explain a substantial proportion of phenotypic variance and are able to predict health and lifestyle factors with some success
- Data suggest a potential application of DNAm signatures as proxies for self-(un)reported phenotypes, such as smoking
- DNAm age biomarkers of aging for identifying anti-aging interventions?
  - DNAm is dynamic and tissue-specific. The predictive abilities of DNAm may depend on the characteristics of the population/ tissue in which the score was derived

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Thank you!

DNA Methylation Analysis Identifies Loci for Blood Pressure Regulation

Melissa A. Richard,[1,52,*] Tianxiao Huan,[2,3,52] Symen Ligthart,[4,52] Rahul Gondalia,[5] Min A. Jhun,[6] Jennifer A. Brody,[7] Marguerite R. Irvin,[8] Riccardo Marioni,[9,10,11] Jincheng Shen,[12] Pei-Chien Tsai,[13] May E. Montasser,[14] Yucheng Jia,[15] Catriona Syme,[16] Elias L. Salfati,[17] Eric Boerwinkle,[18,19] Weihua Guan,[20] Thomas H. Mosley, Jr.,[21] Jan Bressler,[18] Alanna C. Morrison,[18] Chunyu Liu,[2,3,22] Michael M. Mendelson,[2,3,23] André G. Uitterlinden,[24] Joyce B. van Meurs,[24] BIOS Consortium, Oscar H. Franco,[4] Guosheng Zhang,[25,26,27] Yun Li,[25,28] James D. Stewart,[5,29] Joshua C. Bis,[7] Bruce M. Psaty,[30] Yii-Der Ida Chen,[15] Sharon L.R. Kardia,[6] Wei Zhao,[6] Stephen T. Turner,[31] Devin Absher,[32] Stella Aslibekyan,[8] John M. Starr,[9,33] Allan F. McRae,[11,34] Lifang Hou,[35] Allan C. Just,[36] Joel D. Schwartz,[37] Pantel S. Vokonas,[38] Cristina Menni,[13] Tim D. Spector,[13] Alan Shuldiner,[14,39] Coleen M. Damcott,[14] Jerome I. Rotter,[15] Walter Palmas,[40] Yongmei Liu,[41] Tomáš Paus,[42,43,44] Steve Horvath,[45] Jeffrey R. O'Connell,[14] Xiuqing Guo,[15] Zdenka Pausova,[16,46] Themistocles L. Assimes,[17] Nona Sotoodehnia,[47] Jennifer A. Smith,[6] Donna K. Arnett,[48] Ian J. Deary,[9,49] Andrea A. Baccarelli,[37] Jordana T. Bell,[13] Eric Whitsel,[5,50] Abbas Dehghan,[4,51] Daniel Levy,[2,3,53] and Myriam Fornage[1,18,53,*]

- CHARGE Epigenetics Working Group