

A novel epigenetic tools for monitoring metabolic health

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Introduction: Adipocyte death caused by local inflammation is one feature in the early biological development of metabolic unhealth and diabetes. When cells become necrotic or apoptotic, cell DNA is released into the bloodstream, which is known as cell-free DNA (cfDNA). DNA methylation is cell type-specific and each cell type has its unique DNA methylation pattern. Detecting cell-type-specific DNA methylation levels reflect the presence of certain cell type in each sample.

Hypothesis

By identifying adipocyte/liver-specific cfDNA methylation in plasma, we could infer the adipocyte/liver death and metabolic unhealth.

Methods

1. Identifying the differential methylation at CpG loci specific to adipocyte and liver using 323 whole-genome bisulfite sequencing samples consisted of 28 types of tissues.
2. Validating the specificity of adipocyte marker by the targeted amplicon sequencing.
3. Designing the methylation-specific PCR assay to detect liver and adipose signal.
4. Testing and optimizing the PCR testing assay by digital droplet PCR.
5. Examining the analytic validation of this PCR testing assay using 42 plasma samples from CSIRO EpiScope cohort.

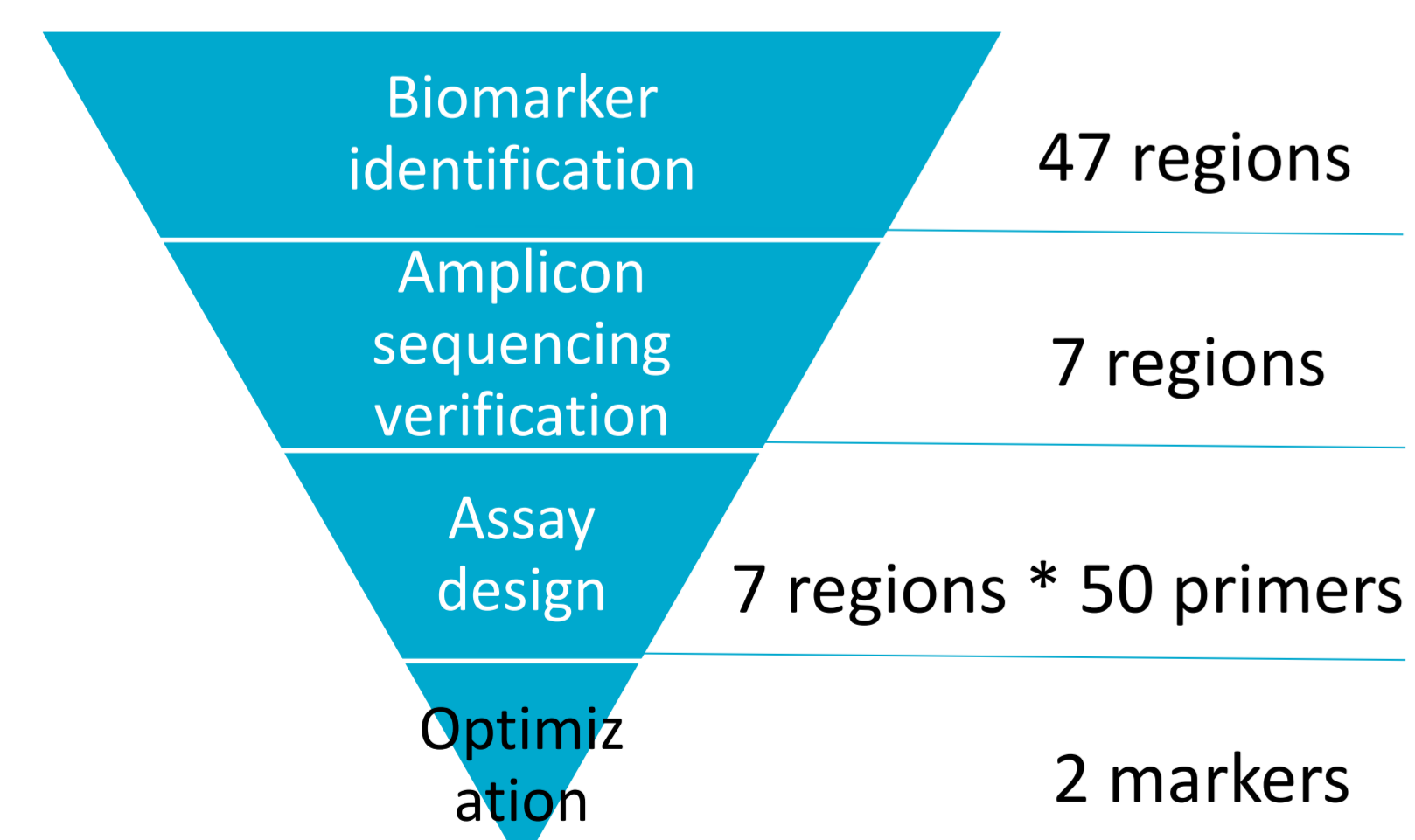


Figure 1: workflow of this study.

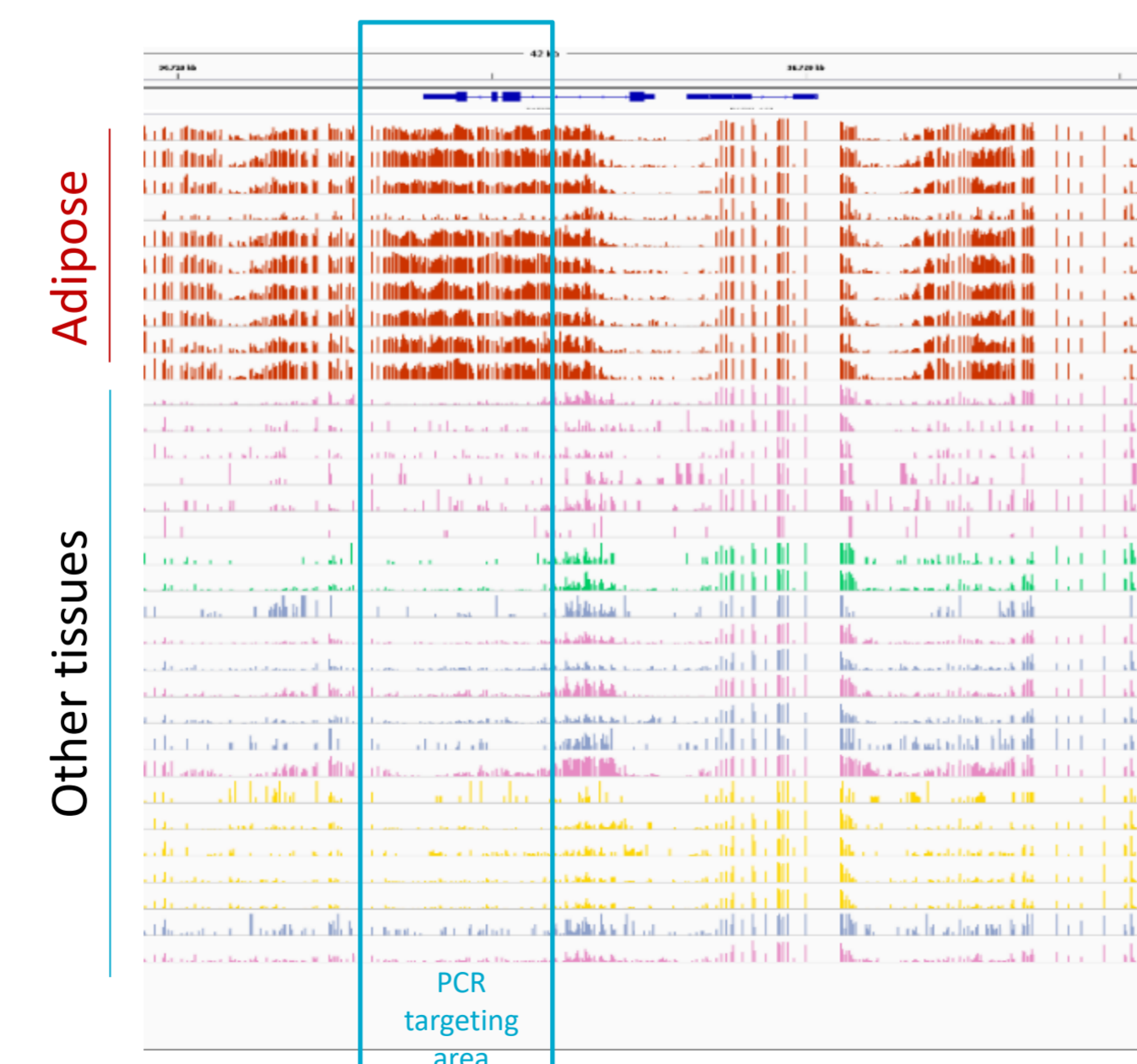


Figure 2: IGV showing the PCR targeting area in genome. Adipose has a methylated CpGs while the other tissues have hypomethylated CpGs.

		Cases (N = 42)
Gender	Male	9
	Female	33
Obesity	Lean	12
	Obese	22
	Diabetes	8
MHO category	Lean	12
	MHO	7
	MAO	21

Table 1: The clinical characteristics of CSIRO EpiScope cohort. MHO, metabolic healthy obesity; MAO, metabolic abnormal obesity

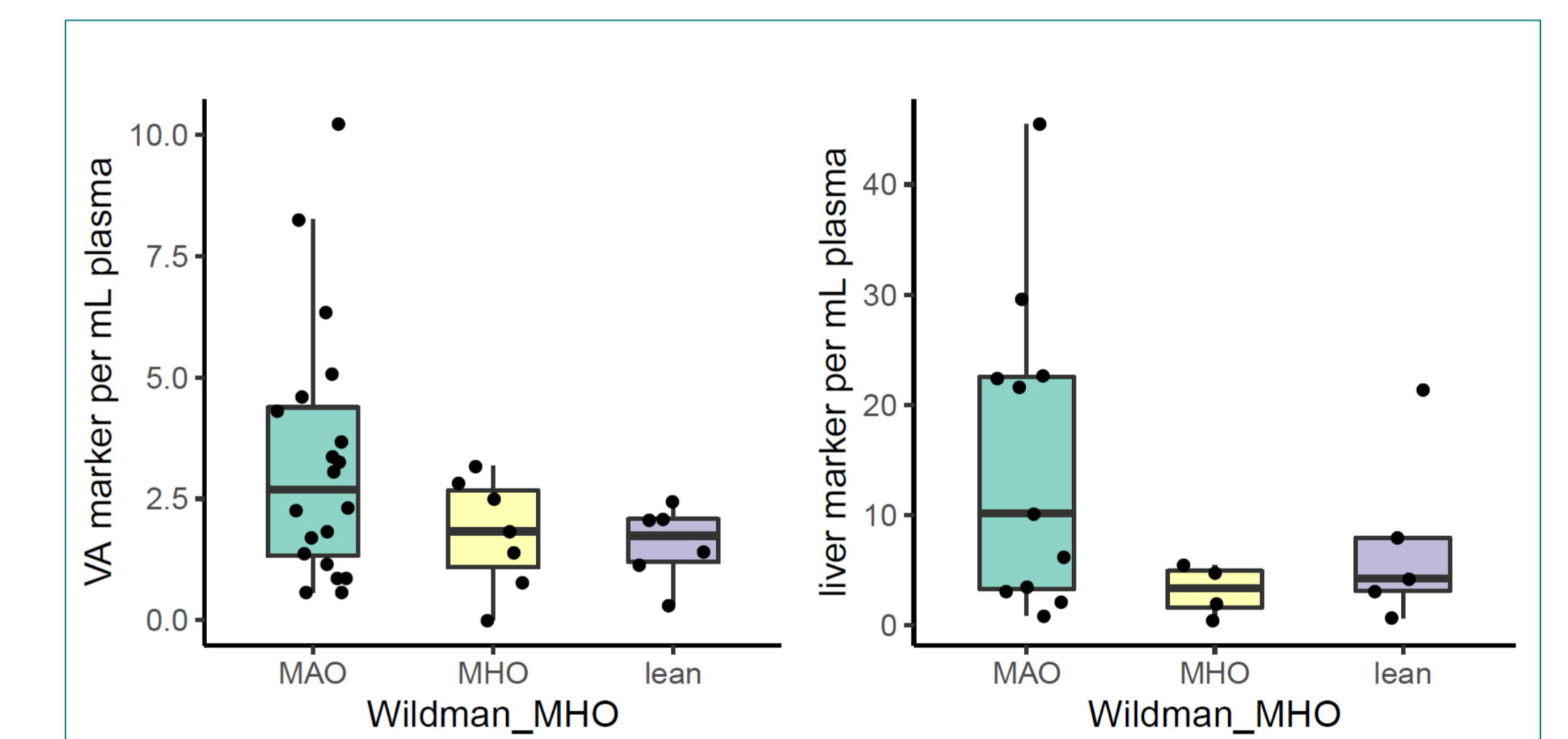


Figure 3: MAO has a higher concentration of Adipose and liver cfDNA than MHO and lean people.

Results and Discussion

1. Successfully identified adipose and liver hypermethylated regions.
2. Designed a 4-plex assay with 2 adipose and one liver locus to detect cfDNA in response to metabolic health.
3. Validated the analytical utility of this detection assay in 42 plasma samples.
4. MAO has a higher concentration of Adipose and liver cfDNA than MHO and lean people.

Impact and Future Direction

- This assay enables the delivery of precision medicine in obesity management by stratification of metabolic unhealth.
- This assay is potentially a companion diagnostic for the metabolic diseases treatment.