

Master Computer Science

Uncovering epigenetic drivers of cardiometabolic traits through histone and DNA methylation quantitative trait loci integration

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Abstract

Disease risk involves differences in genomic regulation, and despite many in-depth investigations, it remains unclear how causal relationships can be established due to the dynamic nature of genomic regulation and because they cannot be discerned as a cause or a consequence. Strengthened by conclusions from other fields, Mendelian randomization can aid in identifying the causal mechanisms underlying these diseases. MR analyses rely on establishing good genetic proxies for molecular profiles, called quantitative trait loci, which have been well established for gene expression and DNA methylation. Given the aetiology of complex disease likely lies in the interaction between molecular processes, it is crucial to look not only at how cellular changes cause disease, but also how they influence each other. Here, we take advantage of multiple databases (EWAS Atlas, EWAS Catalog, and GoDMC) to collate quantitative trait loci libraries from histone post-translational modifications and DNA methylation, and run a novel modular MR pipeline that uses the TwoSampleMR R package to perform the MR analyses. With this approach, we focused on 9 selected cardiometabolic traits and reported 36 interesting cases where we found directed associations between an exposure (i.e. SNP) and an outcome (i.e. trait; e.g. BMI) fitting into one of the seven designed scenarios encompassing all the envisaged ways in which associations can be observed between the histone post-translational modification quantitative trait loci and the trait.

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List of Abbreviations

AFR African
BMI Body mass index
bp Base pair(s)
CAD Coronary heart disease
${f caQTL}$ Chromatin accessibility quantitative trait locus
$\mathbf{ChIP}\operatorname{-seq}$ Chromatin immunoprecipitation followed by sequencing
CMD Cardiometabolic disease
${f CpG}$ Consecutive cytosine and guanine joined by a phosphodiester bond
CRP C-reactive protein
CVD Cardiovascular disease
DM Diabetes mellitus
DNA Deoxyribonucleic acid
\mathbf{DNAm} DNA methylation
\mathbf{eQTL} Expression quantitative trait locus
EUR European
EWAS Epigenome-wide association study
FG Fasting glucose
FI Fasting insulin
GWAS Genome-wide association study
HDL-C High-density cholesterol
$\mathbf{HOMA-IR}$ Homeostatic model assessment for insulin resistance
IV Instrumental variable
kbp Kilo base pair(s)

 \mathbf{LCL} Lymphoblastoid cell line

- ${\bf LD}\,$ Linkage disequilibrium
- ${\bf LDL-C}$ Low-density cholesterol
- \mathbf{mQTL} Methylation quantitative trait locus
- $\mathbf{M}\mathbf{R}$ Mendelian randomization
- NCP Nucleosome core particle
- \mathbf{PTM} Post-translational modification
- $\mathbf{QTL}\ \mathsf{Quantitative\ trait\ locus}$
- \mathbf{RCT} Randomized control trial
- ${\bf SMR}\,$ Summary-based Mendelian randomization
- ${\bf SNP}\,$ Single-nucleotide polymorphism
- ${\bf SUA}~$ Serum uric acid
- ${\bf T2D}\;\; {\sf Type}\; 2 \; {\sf diabetes}\;$
- ${\bf TC}~$ Total cholesterol
- ${\bf TF}~$ Transcription factor
- ${\bf TG}\ Triglyceride$
- \mathbf{YRI} Yoruban

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Chapter 1

Introduction

Understanding the molecular aetiologies of diseases is a vital stepping stone in the development of treatment and prevention measures. In epidemiology, observational studies are commonly used and able to provide insight into the plausible associations between disease exposures and outcomes. Unfortunately, observational studies' power is hindered by the effects of confounding and reverse causality, which in turn make the link between the aforementioned associations and causality unworkable [1]. Alternatively to observational studies, experimental studies can be used. Randomized controlled trials (RCTs) are part of the latter and are a very popular study design when aiming at inferring causality with the disadvantage of being expensive and time-consuming [1]. To circumvent this, Mendelian randomization (MR), an approach resilient to both reverse causation and confounding, has been rising in popularity in the past decade [2]. Applying MR to quantitative trait loci (QTLs) and genome-wide association studies (GWAS) data may help unveiling causality within the context of cardiometabolic disease and allow the uncovering of putative interactions between epigenetic mechanisms such as histone post-translational modifications (PTMs) and DNA methylation, as well as the identification of molecular processes that can potentially affect health outcomes. Being such a wide-ranging family of diseases, collating a large number of publicly available QTL libraries is essential. Furthermore, due to the nature of this approach (i.e. integrating data from different sources) and the relative newness of MR, there is also a need for developing a standardized pipeline.

1.1 Epigenetics

Epigenetics is the field that studies how some heritable changes in gene expression occur without any change to the underlying DNA sequence. Epigenetic mechanisms include molecular changes to DNA such as DNA methylation (DNAm) and histone PTMs that determine the accessibility of the underlying DNA sequence to the transcriptional machinery and also repel and recruit transcription factors (TFs) that can regulate gene expression. Common histone modifications include acetylation, methylation, and phosphorylation [3, 4].

Capturing and processing relevant biological information from epigenetics requires the integration of several research fields into one unique interdisciplinary scientific community. To that effect, linking data from genetics, transcriptomics, and phenotypes using the appropriate data sources may lead to new findings in the field [5] (see Figure 1.1).



Figure 1.1: Overview of epigenetics and how we can link results from several sources to make sense of raw biological data. eQTL: expression QTL; meQTL: methylation QTL; GWAS: genome-wide association study; EWAS: epigenome-wide association study; TWAS: transcriptome-wide association study. Adapted from Cazaly et al. [5].

1.1.1 DNA methylation

Of all known epigenetic marks, DNAm is the one considered to be the most stable and accessible, and has been shown to affect CG (or CpG) sites, i.e. regions of DNA where a cytosine nucleotide is immediately followed by a guanine nucleotide along the 5' \rightarrow 3' direction, as well as CHH and CHG sites, where H represents any nucleotide but guanine [3]. CpGs occur with high frequency in larger genomic regions called CpG islands. Henceforth in this project, we refer to CpG sites as CpGs. In mammals, DNA methylation involves the transfer of a methyl group (i.e. CH_3) onto the C5 position of a cytosine nucleotide, thus establishing a 5-methylcytosine, and is able to regulate gene expression through two mechanisms, namely, the recruitment of proteins involved in gene silencing, and the inhibition of the binding of transcription factors to DNA [6]. With regard to gene silencing, DNA becomes transcriptionally inactive due to the wrapping of chromatin around that site that is influenced by the structural conformation of histones leading to a compaction of the overall structure of the nucleosome which ultimately prevents access of the transcriptional machinery to chromosomal DNA [7]. Summarily, methylation of CpG islands allows the stabilization of the inactive state of chromatin (i.e. "heterochromatin"), thus silencing gene expression. Conversely, the demethylation of CpG sites allows gene expression to occur via switching to the active state of chromatin (i.e. "euchromatin") [8]. Although DNAm has generally been shown to be linked to gene expression silencing [9], in some instances it can effectively activate gene expression [10, 11].

1.1.2 The nucleosome

Structure

The basic repeating structural unit of eukariotic chromatin is called the "nucleosome". In order to fit the sheer amount of genetic information inside the nucleus of a given cell, there needs to be some kind of efficient mechanism for compaction and packaging of DNA. As it turns out, nucleosomes are very well suited for that task, and thus serve as the backbone for DNA packaging seen in chromatin. Each nucleosome carries 2 copies of each histone: H2A, H2B, H3, and H4. These 8 proteins are assembled into an octamer around which

a 145-147 base pairs (bp) DNA is wrapped around (\sim 1.65×). This assembly forms the so-called "nucleosome core" [12]. Nucleosome core particles (NCPs) are linked together by linker DNA of variable length (20-90 bp) [13]. In addition to the main four histone proteins, in many cases, each NCP is associated with a linker histone, H1, through the linker DNA [14]. The addition of H1 to the NCP adds another 20 bp, effectively wrapping two full turns of DNA around the histone octamer and establishing the structure that we call the "chromatosome" [15].

Histones



Figure 1.2: Complex between the nucleosome core particle H2A, H2B, H3, and H4) and a 146 bp long DNA fragment in *Xenopus Laevis*. Representations generated using PyMOL [16] (PDB id: **1AOI**).

Histone tails are subject to PTMs, which include methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation. These can impact gene expression by modifying chromatin conformation or through the recruitment of histone modifiers. Histone PTMs can affect the overall nucleosome structure by modifying the energy landscape of the nucleosome, as well as influencing the binding of histone chaperones and chromatin remodelers. The location and neighbourhood in which the PTM occurs within the nucleosome architecture determines its effect. For example, PTMs that occur in the vicinity of histone-DNA interfaces promote DNA unwrapping, thus increasing the chances for DNA-binding proteins (e.g. TFs) to access that region of DNA. On the other hand, it may also decrease the nucleosome conformational stability by negatively affecting crucial contacts near the dyad (the nucleosome dyad axis passes through a single base pair at the center of the

nucleosome structure) [17].

It is important to be aware that modification levels of PTMs on histones are susceptible to change. For example, lysine residues (K) can be mono-, di-, and trimethylated (Kme1, Kme2, and Kme3, respectively). In essence, the different combinations of histone PTMs are encapsulated into a hypothesis called the "histone code" which determines the structure of chromatin and its ability to be transcribed (e.g. H3K4me2 and hypomethylation of DNA are linked to active transcription) [18].

1.1.3 Experimental techniques

ChIP-seq

Chromatin immunoprecipitation followed by sequencing (ChIP-seq) is a well-known technology that can be used to map DNA-binding proteins and histone PTMs at very high resolution genome-wide (bp). Previously, chromatin immunoprecipitation followed by microarray (ChIP-chip) was more common to study the aforementioned interactions, but with the advent of ChIP-seq, ChIP-chip is now less popular due to lower resolution, higher noise, and smaller genome coverage [19]. ChIP-seq allows the identification of binding sequences of transcription factors (TFs), as well as the positions of histone PTMs [20].

A typical ChIP-seq analysis workflow includes: 1) sample preparation, sequencing, and mapping; 2) computational analysis [21, 22] (see Figure 1.3). Firstly, the DNA and associated proteins on chromatin are cross-linked *in vitro* or *in vivo*, and the subsequent chromatin-protein complexes are sheared via sonication or nuclease digestion. These DNA-protein fragments are then selectively immunoprecipitated using the appropriate antibody, and the resulting immunoprecipitated fragments are then unlinked, thus isolating the DNA which will be purified, sequenced, and mapped to the genome (i.e. read mapping). Here, genomic regions significantly enriched for ChIP reads are interpreted as peaks, representing plausible sites of interaction of proteins with DNA, and histone modification sites. Furthermore, ChIP-seq experiments can also be used in conjunction with different types of genomic assays (e.g. DNA methylation and chromatin conformation) [21].

The majority of ChIP-seq tools are designed to process sharp peaks located at specific genomic positions. But some histone PTMs are associated with rather large domains in the genome which leads to broadly distributed enrichment regions [19]. For example, enhancer markers such as H3K27ac and H3K4me1 produce sharp peaks, albeit sometimes leading to broadly enriched regions [23]. This peak characteristics variation consequently impacts the choice of computational tools to process the data resulting from ChIP [22].

(A) Sample preparation and sequencing



Figure 1.3: General ChIP-seq workflow. Adapted from Nakato and Sakata [22].

DNA methylation data

Changes in DNA methylation have been previously linked to cancer and several developmental diseases [24]. Fortunately, there is a multitude of experimental techniques that can be used to detect DNA methylation and allow the scientific community to thoroughly study it. DNA methylation of CG sites (i.e. CpGs) is commonly measured using Illumina Infinium BreadChip platforms [25]. The Illumina Infinium HumanMethylation27 BeadChip (27k) probes on 27k array target regions of the human genome to measure methylation levels at 27.5k CpGs in 14.5k genes. The Illumina Infinium HumanMethylation450 (450k) Bead-Chip array covers over 480k CpG sites and targets 96% of CpG islands in the human genome. The Infinium MethylationEPIC (EPIC) array has replaced the Infinium Methylation450 array, assaying almost double the number of sites assayed by the 450k array [25].

1.2 Cardiometabolic diseases

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) take the podium for the number one cause of death worldwide [26]. CVDs are part of cardiometabolic diseases (CMDs) which, by definition, include several disorders (abdominal adiposity, hypertension, dyslipidaemia, hyperinsulinaemia and glucose intolerance) that lead to CVDs and type 2 diabetes (T2D) [27]. According to the MeSH browser [28], CVDs (MeSH UID¹: D002318) include: cardiovascular abnormalities, cardiovascular infections, heart diseases, cardiovascular pregnancy complications, and vascular diseases.

Tackling with risk factors of T2D and CVD is a good start to deal with their prevention, but it requires a deeper understanding of the aetiology of CMDs nonetheless, hence the identification of the molecular mechanisms and risk factors associated with T2D and CVD (along with the aforementioned traits) being of vital importance [29]. The continued rise of CMD cases is largely due to the exposure to diverse environmental

¹Unique id

factors and lifestyle habits (e.g. low to non-existent physical activity, smoking, unhealthy diet, etc.) [30, 31]. And although most general practitioners (GPs) consider selective CMD prevention useful (82%), some GPs still do not see is as such [30]. Establishing the aetiology of CMDs will likely incentivize the remaining GPs to adopt a more preventive approach when it comes to CMDs. This includes the unraveling of molecular mechanisms, the identification of risk factors, as well as the association of CMDs with a plethora of different traits.

Some cardiometabolic traits include: body mass index (BMI), coronary heart disease (CAD), triglycerides (TGs), homeostatic model assessment for insulin resistance (HOMA-IR), C-reactive protein (CRP), waist circumference, fasting glucose (FG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), diabetes mellitus (DM), adiponectin, leptin, leptin receptor, serum uric acid (SUA), and aldosterone\renin ratio [32, 33]. Some of the aforementioned traits are implicitly linked (e.g. BMI and adiposity).

1.3 Instrumental variable analysis

In epidemiology and few other fields, instrumental variable (IV) analysis is of great interest and used to extract causal inferences in an observational setting (e.g. whenever experiments are not feasible or practical) by exploiting a natural experiment. By definition, an instrumental variable is a factor correlated with the exposure, though not associated with confounders, and for which there exists no pathway by which a given IV can have an influence on the outcome by any other means than through direct exposure (i.e. to a risk factor) [34].

Genetic variants (i.e. regions of the genome that differ between individuals) can be used as IVs. For a sizeable portion of these fragments of the genetic code, the functions of several genes and the pathways in which they are involved are known and extensively described in the literature. Since these genetic variants are fixed at conception, and hence are not affected by environmental factors (thus avoiding reverse causation), they are considered as being ideal candidates to be used as IVs [34].

1.4 Mendelian randomization

MR is an analytical method of great importance in the epidemiological field that uses genetic variants as IVs for modifiable risk factors that have an impact on population health [35]. As mentioned beforehand, using MR for inferring causality in given associations has the advantage of overcoming confounding and reverse causation which observational studies suffer from.

Since MR studies make use of IVs (i.e. genetic variants), they must fulfill 3 key assumptions [2, 35]:

- 1. **Relevance assumption**: The relevance assumption holds that the genotype is associated with the exposure.
- 2. **Independence assumption**: The independence assumption states that the genotype is independent of third-party factors affecting the outcome.

3. **Exclusion restriction assumption**: The exclusion restriction assumption states that the genotype is associated with the outcome solely through the exposure.

MR studies' power is determined by the sample size and the strength of the association between the chosen IV and the risk factor. Using so-called "weak" IVs may lead to low statistical power and bias. For single sample MR studies, the F statistic may be used to detect weak IVs [2]. Confounding may be caused by violations of the independence and exclusion restriction assumptions. Using so-called "negative control" populations, one could evaluate the plausibility of the assumptions [35].

To increase the statistical power, two-sample MR can be used, at the cost of two additional assumptions: both samples are assumed to represent the underlying population, and any overlap between the two samples can cause bias [35].

Chapter 2

Aims

This project aims at inquiring which molecular processes contribute to changes in cardiometabolic traits, and how these interact with each other. To that intent, the goals include:

- Understanding how molecular processes influence cardiometabolic traits
- Collating libraries of molecular QTLs
- Standardizing a summary-based MR workflow for application to different subsets of phenotypes
- Finding directed associations between epigenetic mechanisms associated with health outcomes

Chapter 3

Methods

In this chapter, we describe each step of the workflow depicted in Figure 3.1. Starting from data collection using QTLbase, followed by data preprocessing of the selected studies. Then we performed hQTL and methylation QTL (mQTL) data integration which involves 2 main steps: trait-associated CpG extraction (using EWAS Atlas and EWAS Catalog), and mQTL extraction (using GoDMC). Lastly, we performed summary-based Mendelian randomization (SMR) on the processed data and analysed the output.

The source code used in this project is hosted on GitHub at https://github.com/alxdrcirilo/ smr.git. Running the entire pipeline can be done via the main.R file located within the src directory. Note that the pipeline is modular and the aforementioned file can be edited to get the results from different parts of the analysis workflow, or for debugging purposes. Findings data available upon request.

3.1 Data collection

3.1.1 QTLbase

The first step in the workflow involved looking for publicly available hQTL data in different studies. Fortunately, the process of gathering the hQTL data required for this project was greatly simplified thanks to QTLbase [36], a flexible curated database that conveniently stores information regarding QTLs (21 different types; e.g. hQTL, eQTL, mQTL) across multiple tissues, phenotypes, and variants. At the moment of writing, the database was storing data for a total of 257 independent studies. Navigating through QTLbase is straightforward and, if need be, documentation is available as well with exhaustive descriptions on every piece of information provided by the database and how to extract, query, and filter through it.

3.1.2 hQTL data

Based on our aims, we looked thoroughly through QTLbase for adequate studies that were performed on lymphoblastoid cell lines (LCLs) and included data for hQTLs. We also took into account the maximum sample size and the year of publication; greater sample sizes and more recent studies were prioritized in our search. Following an in-depth search over all the studies listed on QTLbase, we selected 5 studies that included hQTL and caQTL data, both in LCLs, in African (AFR) and European (EUR) populations, and somewhat recent (\pm 5 years). We contacted the authors from all 5 articles, but could only proceed with the downstream analyses on 2 out of the 5. The aforementioned studies are listed in Table 3.1.

Article	xQTL	Tissue Cell type	Tissue State	Platform	Max Sample Size	Population	Year
1* [37]	hQTL caQTL	Lymphocyte	Normal	Illumina TrueSeq	75	African	2015
2^{*} [38]	hQTL	Lymphocyte	Lupus	Illumina NextSeq 500	358	European	2018
3 [39]	hQTL	Fibroblast Lymphocyte	Normal	Illumina HiSeq 2000	317	European	2019
4 [40]	caQTL	Lymphocyte	Normal	Illumina HiSeq 4000	500	African East Asian European	2019
5 [41]	caQTL	Lymphocyte	Normal	Illumina Genome Analyzer II	70	African	2012

Table 3.1: Overview of the articles selected for downstream analyses. Articles highlighted with an asterisk (*) contain data used in this project.

We collected histone peak and hQTL data from the supplementary data of Grubert et al. [37] and received additional information directly from one of the authors. For this study, we have data for 3 histone marks (i.e. H3K27ac, H3K4me1, and H3K4me3): the peak position (i.e. a range of bp within a chromosome), peak width, hQTL id, hQTL position, hQTL-peak effect size (β), hQTL-peak standard error (SE), hQTL effect allele (EA), hQTL alternative/other allele (OA), and effect/minor allele frequency (EAF/MAF). Summary descriptive statistics with regard to the histone peak width for all peaks in each of the 3 histone PTMs are listed in Table 3.2.

Table 3.2: Descriptive statistics of the histone peak width (in bp) in the source data for each histone PTM from Grubert et al. [37].

Histone	Histone peak width (bp)										
\mathbf{PTM}	Min	Max	Mean	Median							
H3K27ac	179	66690	3006	2038							
H3K4me1	213	106120	2927	1910							
H3K4me3	273	24992	2008	1462							

3.2 GWAS selection

In this project, we selected 9 cardiometabolic traits of interest from the literature. Using these traits, we identified large, recent, and relevant GWAS from the Integrative Epidemiology Unit GWAS (IEU GWAS) [42] (see Table 3.3). All of the 9 selected GWAS are less than 10 years old. Here, it is important to note that the sample size varies between the 9 studies (e.g. the sample sizes in the leptin and adiponectin GWAS studies are significantly smaller than in the BMI one). All studies include European populations, except for the adiponectin GWAS which includes a mixed population.

Trait	Sample size	Number of SNPs	Population	Year	GWAS id
Adiponectin	39883	2675209	Mixed	2012	ieu-a-1
BMI	681275	2336260	European	2018	ieu-b-40
\mathbf{FG}	133010	64432	European	2012	ieu-b-114
\mathbf{FI}	108557	64421	European	2012	ieu-b-116
HDL-C	403943	12321875	European	2020	ieu-b-109
LDL-C	440546	12321875	European	2020	ieu-b-110
Leptin	33987	2457011	European	2016	ebi-a-GCST003367
TC	115078	12321875	European	2020	$met-d-Total_C$
TG	441016	12321875	European	2020	ieu-b-111

Table 3.3: Overview of the 9 GWAS studies used to run the SMR analyses.

3.3 hQTL and mQTL integration

Having selected the traits of interest and gathered hQTL data, we now focused on integrating hQTL and mQTL data. To filter the hQTL data, we first looked at each hQTL peak and determined its span (i.e. the width of the hQTL peak). Using data from the databases EWAS Atlas [43] and EWAS Catalog [44], we looked for CpGs associated with a particular trait, for each hQTL peak, within the chromosomal location window defined by the aforementioned span. Solely peaks containing overlapping trait-associated CpG(s) were kept for further downstream analyses. For cases in which the hQTL peak contained more than one unique CpG, we only kept the CpG with the highest association with the trait (i.e. lowest p-value). This part of the workflow is highlighted in the blue box as depicted in Figure 3.1. It is important to note that this work is exploratory, thus we are not bound to look for CpGs within each peak. For example, if we wanted to be more stringent, we could for example have limited the search to half the span of the histone peak.

3.3.1 Trait-associated CpGs extraction

To extract trait-associated CpGs for each histone peak, we merge the data provided by EWAS Atlas and EWAS Catalog.

EWAS Atlas

EWAS Atlas¹ is a database that stores data on epigenome-wide association studies (EWAS). At the moment of writing, EWAS Atlas was holding a total of 616280 associations, 616 traits, 3379 cohorts, 192 tissues/cells, 1434 studies, and 907 publications. The database is part of the National Genomics Data Center from the China National Center for Bioinformation based in the Beijing Institute of Genomics, Chinese Academy of Sciences. It allows the user to straightforwardly browse through its catalog with convenient filters (e.g. trait, gene symbol, probe id). Although EWAS Atlas provides an API, we decided to download the full database and do any data preprocessing locally. The following files were downloaded and stored locally:

• EWAS_Atlas_associations.tsv² (n = 416331): contains data for trait-associated CpGs (e.g. for BMI).

¹Available at https://ngdc.cncb.ac.cn/ewas (last accessed 14-06-2021)

²Available at https://ngdc.cncb.ac.cn/ewas/downloads

- EWAS_Atlas_studies.tsv² (n = 1554): contains exhaustive information for every study included in the database.
- EPIC.hg19.manifest.tsv³ (n = 865918): basic hg19 annotation with suggested overall masking on the EPIC platform.
- HM450.hg19.manifest.tsv³ (n = 485577): basic hg19 annotation with suggested overall masking on the HM450 platform.

Firstly, we loaded EWAS_Atlas_associations.tsv into a dataframe (atlas_dat), and filtered through it, for each trait, using pre-defined terms (e.g. c("bmi", "body mass index")) in order to extract the trait-associated CpG (Probe.id) and its association p-value (P.value). Note that filtering using a given trait will naturally decrease the number of rows very considerably since only rows with CpGs associated with that trait will be kept.

Next, we merged the EPIC and HM450 data into one unique dataframe (merged), with each row containing data pertaining to one CpG: chromosome (CpG_chrm), starting position (CpG_beg, in bp), ending position (CpG_end, in bp), strand (probe_strand), and the CpG id (probeID).

The resulting dataframe (i.e. merged) was merged anew with the former (atlas_dat) by CpG (renamed on both dataframes as probeID), resulting in a new dataframe that includes all the required information for each trait-associated CpG, i.e. the chromosome in which it is located, the starting and ending positions (in bp), the association p-value, and the CpG id.

EWAS Catalog

EWAS Catalog⁴, as EWAS Atlas, is a database with the main purpose of providing the scientific community with access to a wide array of EWAS. It was developed and is currently maintained by the Intergrative Epidemiology Unit (IEU) at the University of Bristol, United Kingdom. As was the case with EWAS Atlas, we also downloaded the full database for EWAS Catalog. The following files were downloaded and stored locally:

- ewascatalog-results.txt (n = 1823781): contains exhaustive information for every study included in the database, including CpG id (CpG), chromosomal location (Location), chromosome (Chr), position (Pos, in bp), gene (Gene), association p-value (P), study id (StudyID), among others.
- ewascatalog-studies.txt (n = 1554): contains meta-data for all the studies recorded in the database (e.g. author(s), trait, study id).

As was the case with EWAS Atlas in section 3.3.1, we also first need to filter the data to only keep rows with information for the trait we're interested in (e.g. BMI). To that intent, we first load both the aforementioned files into memory, and we proceed to filter the meta-data (i.e. ewascatalog-studies.txt) using pre-defined terms (e.g. c("bmi", "body mass index")) to find one or more study ids that match our query. Furthermore, we also applied a tissue filter to solely include "whole blood" as we are working with LCLs. This step will generate a list of one ore more study ids that we can use to filter ewascatalog-results.txt by study id, hence exclusively keeping CpGs included in one or more studies associated with a given trait.

³Available at https://zwdzwd.github.io/InfiniumAnnotation

⁴Available at http://www.ewascatalog.org/ (last accessed 14-06-2021)

The resulting filtered dataframe will hold the required information for each trait-associated CpG, i.e. the chromosome, the position, the CpG id, and the association p-value.

3.3.2 mQTL data extraction

To incorporate mQTL data into our pipeline with hQTL data, we fetch the top mQTL for each CpG (if any) using the GoDMC database. Only fully integrated hQTL and mQTL peaks are saved. This part of the workflow is highlighted in the yellow box seen in Figure 3.1.

GoDMC

The Genetics of DNA Methylation Consortium (GoDMC⁵) is a database that focuses on consolidating data from multiple sources and prioritising the analysis of Illumina HM450 BeadChip and GWAS data. The database stores data from the mapping of cis and trans acting genetic influences on DNA methylation using 36 cohorts (n = 27750, for samples from European populations in whole blood). In total, approximately 420k DNA methylation sites were analysed using 10 million common variants. GoDMC provides a convenient browser that allows the user to search through it (e.g. querying the database with a given CpG or chromosomal location). The results from the query can be exported and saved locally for further analyses (e.g. SMR, requiring minimal data preprocessing). Furthermore, the GoDMC database also provides a RESTful API that allows the retrieval of more exhaustive information regarding SNPs and chromosome positions. In this project, we take advantage of the API to fully automate the process of extracting the relevant mQTLs.

Following section 3.3.1, we send queries to the GoDMC API using the trait-associated CpGs to retrieve cis-mQTLs. In the event that the database does not find any mQTL for a given CpG, then we discard the respective peak. Otherwise, we keep it and save the relevant variables to perform SMR. If we found multiple mQTLs for a given CpG, then we solely keep the one with the lowest p-value.

3.4 Data integration

For each trait (e.g. BMI), we extracted relevant CpGs (i.e. trait-associated) from the EWAS Atlas and EWAS Catalog databases. We then filtered the preprocessed data from Grubert et al. [37] based on the peaks that contained trait-associated CpGs within the peak width (i.e. a given range of bp within a chromosomal location). Peaks with no nearby CpGs were dropped, whilst for peaks with more than 1 CpG, we only kept the CpG with the lowest p-value (i.e. highest association).

3.5 Summary-based Mendelian randomization

Once we gathered and filtered the QTL data, we can proceed with running the SMR analyses. To that intent, we used well-documented TwoSampleMR R package [45, 46] to estimate the causal effect of an exposure (i.e. histone peak, e.g. H3K4ME3_1234) on an outcome (i.e. trait, e.g. BMI) solely using summary

⁵Available at http://mqtldb.godmc.org.uk/ (last accessed: 14-06-2021)

statistics from GWAS. This package provides the user with a complete set of tools to perform MR, including: data processing and harmonisation, statistical routines to estimate the causal effects, and a connection to large publicly available repositories of GWAS summary statistics required for the analyses (via the ieugwasr package⁶). This step of the workflow is highlighted by the blue box as seen in Figure 3.1.

3.5.1 Exposure data

TwoSampleMR requires a minimum set of variables to perform MR analyses: rsid (SNP), beta (effect size), se (standard error), and ea (effect/reference allele). In addition to these mandatory variables, we were also able to provide: oa (other/alternative allele), eaf (effect allele frequency), phenotype (e.g. H3K4ME3_1234), chr (chromosome), position (position in chromosome), and pval (p-value).

3.5.2 Running SMR

At this step, we integrated the hQTL (i.e. peak) and mQTL (i.e. CpG) with the GWAS data to perform SMR of:

- Each histone peaks effect (hQTL) on the trait
- Each CpGs effect (mQTL) on the trait

We saved the SMR effect size (β), standard error (SE), and p-values (pval) for each peak/CpG-trait combination. Only peaks where we could perform SMR for both the peak and the nearby CpG were kept. P-values were adjusted for multiple testing using the Bonferroni method.

3.6 Linkage disequilibrium

Investigating whether 2 alleles are in linkage disequilibrium (LD) is greatly facilitated by the LDlinkR R package which provides several functions that deal with different LD scenarios, including the LDpair function that allows the user to fetch some statistics (e.g. R^2) for a pair of SNPs within a given population (e.g. EUR). In this work, we feed the LDpair function with one pair of SNPs per row (i.e. 1 hQTL SNP and 1 mQTL SNP). To determine if a given pair of alleles is in LD, we check if the R^2 is above the threshold for the R^2 value (i.e. in LD: $R^2 > 0.3$). For every row in our results following SMR, we determine if each pair of alleles (i.e. hQTL SNP and mQTL SNP) are in LD within the EUR and YRI populations. We add these observations to our results, including R^2 values on both populations, naming the appropriate columns as 1d. (POP) and r2. (POP), where "POP" is the population. In essence, two SNPs are considered to be in LD when non-random association of alleles occurs at different loci within a given population.

⁶Available at https://github.com/MRCIEU/ieugwasr/ (last accessed: 14-06-2021)



Figure 3.1: Overview of the main workflow. Blue box: data preprocessing and CpG extraction; yellow box: extracting trait-associated cis-mQTLs (CpGs); red box: SMR.

Chapter 4

Results

In this chapter, we showcase the results from each step of the SMR analysis pipeline and establish the different designed scenarios in which our results can be encapsulated. We also give some in-depth examples for the biologically relevant scenarios.

4.1 Data preprocessing

Grubert et al. [37] identified cis-QTLs for H3K27ac (n = 14134), H3K4me1 (n = 22618), and H3K4me3 (n = 9570) from 75 unrelated Yoruba individuals (i.e. ethnic group originating from Western Africa). The raw data needed some data preprocessing before we could perform the SMR analyses. Namely, pruning the hQTL data to only contain peaks that have nearby CpG(s) (i.e. within each histone peak), and filtering the hQTLs via the integration of the source data with trait-associated CpGs (i.e. mQTLs). A density plot of the histone peak width for each of the 3 histone PTMs is shown in Figure 4.1. All 3 histone PTMs seem to have peaks' width averaging around 1.5-2 kbp.



Figure 4.1: Density plot of the width of the histone peak (in bp) from the source data for all 3 histone PTMs ($< P_{99}$). Data coloured by histone PTM (red: H3K27ac; green: H3K4me1; blue: H3K4me3).

4.1.1 hQTL filtering

For each of the 9 selected cardiometabolic traits, we filtered through the cis-hQTLs per histone PTM using trait-associated mQTL data (i.e. CpGs) integrated from EWAS Atlas and EWAS Catalog. An overview of the number of CpGs available for each of the 9 traits in each EWAS database is shown in Table 4.1. In most cases, EWAS Catalog held more CpGs for the selected traits. The number of CpGs used from the aforementioned databases, for each trait, is considerably lower (see Table 4.2).

Table 4.1: Number of trait-associated CpGs available from each EWAS database (i.e. EWAS Atlas and EWAS Catalog)

Detebase		Trait													
Database	Adiponectin	BMI	\mathbf{FG}	\mathbf{FI}	HDL-C	LDL-C	Leptin	TC	ΤG						
EWAS Atlas	3	2434	34	5	8	10	10	1	27						
EWAS Catalog	72	4787	10	22	3717	6795	0	2308	2394						

Table 4.2: Number of trait-associated CpGs used from each EWAS database (i.e. EWAS Atlas and EWAS Catalog).

Histone					Trait				
\mathbf{PTM}	Adiponectin	BMI	\mathbf{FG}	\mathbf{FI}	HDL-C	LDL-C	Leptin	TC	ΤG
H3K27ac	4	164	2	1	76	129	1	71	71
H3K4me1	3	159	1	1	82	97	1	57	66
H3K4me3	2	140	1	0	81	129	0	69	61
Total	9	463	4	2	239	355	2	197	198

In addition to the number of filtered cis-QTLs per GWAS, we also provide descriptive statistics for each GWAS with regard to the distance to the nearest trait-associated CpG in bp, as listed in Table 4.3 and

visualized in Figure 6.1. The density plot of the width of all histone peaks is shown in Figure 6.2.

Table 4.3: Descriptive statistics of the distance from each peak to the nearest trait-associated CpG for each trait. Includes the number of peaks in the data (Count), minimum (Minimum, bp), maximum (Maximum, bp), and median (Median, bp) distances from the histone peak to the nearest trait-associated CpG, and the 99% percentile (P_{99} , bp)).

Trait	Count	Minimum (bp)	Maximum (bp)	Median (bp)	Q (0.99 bp)
Adiponectin	9	70	1917	781	1852
BMI	463	4	26659	707	10291
\mathbf{FG}	4	509	3852	901	3770
$_{\rm FI}$	2	678	3852	2265	3820
HDL-C	239	1	28086	685	12577
LDL-C	355	0	52838	627	13007
Leptin	2	802	833	818	833
TC	197	0	26659	707	10291
TG	198	0	16897	677	6857

4.1.2 hQTL and mQTL integration

An overview of the number of trait-associated CpGs used as input for GoDMC API queries and the number of trait-associated mQTLs derived from those queries is shown in Table 4.4. Note that unique values (CpGs or mQTLs) from the output of GoDMC (e.g. n_m H3K27AC for BMI: 105 saved; 107 unique mQTLs from GoDMC) may be higher than the ones actually used due to the presence of NA values in some rows (which are dropped).

Table 4.4: The number of trait-associated CpGs that were used as input for GoDMC API queries are shown for each given trait under n_c . The number of trait-associated mQTLs that were found in GoDMC are shown for each given trait under n_m . Unique CpGs and mQTLs are highlighted with an asterisk (*) in the appropriate columns (i.e. n_c and n_m , respectively).

Histopo	Trait												
PTM	Adipo	nectin	BI	FG									
1 1 1/1	n _c	n _m	n_c	n _m	n _c	n _m							
H3K27ac	$4(4^*)$	$1(1^*)$	$164 (164^*)$	$105 (107^*)$	$2(2^*)$	$1(1^*)$							
H3K4me1	$3(3^*)$	0	$159 (159^*)$	$111 (113^*)$	$1 (1^*)$	$1 (1^*)$							
H3K4me3	$2(2^*)$	$1 (1^*)$	$140 (140^*)$	81 (83*)	$1 (1^*)$	0							

Histopo				Trait		
PTM	F	Ί	HD	L-C	LDL	-C
1 1 1/1	n _c	n_m	n _c	n_m	n_c	n _m
H3K27ac	$1(1^*)$	$1(1^*)$	76 (76*)	$30 (30^*)$	$129(129^*)$	$64~(65^*)$
H3K4me1	$1(1^*)$	$1(1^*)$	82 (82*)	$45~(47^*)$	$97 (97^*)$	$62~(64^*)$
H3K4me3	NA	NA	81 (81*)	$24 (24^*)$	$129 (129^*)$	$53 (54^*)$

Histone			,	Trait		
PTM	Lep	tin	Т	С	Т	G
1 1 1/1	n _c	n_{m}	n _c	n _m	n_c	n_{m}
H3K27ac	$1(1^*)$	$1(1^*)$	$71 (71^*)$	$32(32^*)$	71 (71*)	$33~(33^*)$
H3K4me1	$1 (1^*)$	$1(1^*)$	$57~(57^*)$	$34(34^*)$	$66~(66^*)$	$40~(41^*)$
H3K4me3	NA	NA	$69~(69^*)$	$25~(26^*)$	$61~(61^*)$	$26~(27^*)$

For the sake of clarity, an overview of the number of resulting cis-QTLs remaining after hQTL and mQTL data integration (to be used in the SMR analyses) is shown in Table 4.5.

Histone					Trait				
\mathbf{PTM}	Adiponectin	BMI	FG	\mathbf{FI}	HDL-C	LDL-C	Leptin	TC	TG
H3K27ac	1	105	1	1	30	64	1	32	33
H3K4me1	0	111	1	1	45	62	1	34	40
H3K4me3	1	81	0	0	24	53	0	25	26
Total	2	297	2	2	99	179	2	91	99

Table 4.5: Number of filtered cis-QTLs for each trait after hQTL and mQTL data integration.

4.2 SMR

An overview of the number of peaks at each step of the SMR analysis is shown in Table 4.6.

Table 4.6: Overview of the number of entries in the data at each crucial step of the SMR analyses for all 9 traits. G_d refers to the GWAS data retrieved from IEU GWAS, H_d refers to the data after performing harmonisation using the TwoSampleMR R package, and M_d refers to the resulting data after performing MR using the TwoSampleMR R package. The number of rows for the association between a given trait and hQTL peaks is shown as is (e.g. 3). The number of rows for the association between a given trait and mQTLs is highlighted with an asterisk (*). In M_d , only data containing SMR results of both the hQTL peak and its nearby mQTL are kept.

Histopo					Trait				
DTM	Ac	liponeo	etin		BMI			FG	
1 1 1/1	G _d	H_{d}	MR_{d}	G _d	H_{d}	MR_{d}	G _d	H_{d}	MR_{d}
H3K27ac	(1^*)	(1^*)	0	$56(70^*)$	$56(70^*)$	39	0	0	0
H3K4me1	0	0	0	$56(74^*)$	$56~(74^*)$	36	0	0	0
H3K4me3	0	0	0	47 (59*)	$47~(59^*)$	38	NA	NA	NA

Histone					Trait				
PTM		$_{\rm FI}$			HDL-C			LDL-C	
1 1 1/1	G _d	H_{d}	MR_d	G _d	H_{d}	MR_d	G _d	H_{d}	MR_d
H3K27ac	0	0	0	$21 (30^*)$	$21 (30^*)$	20	$47~(63^*)$	$47~(63^*)$	44
H3K4me1	0	0	0	$33~(44^*)$	$33~(44^*)$	32	$50 (59^*)$	$50~(59^*)$	46
H3K4me3	NA	NA	NA	$18(22^*)$	$18 (22^*)$	16	$42~(53^*)$	$42~(53^*)$	38

Histopo					Trait				
PTM		Leptin			TC			TG	
1 1 1/1	G_{d}	H_{d}	MR_{d}	G_{d}	H_{d}	MR_d	G _d	H_{d}	MR_d
H3K27ac	(1^*)	(1^*)	0	$27 (32^*)$	$27 (32^*)$	26	$24 (33^*)$	$24(33^*)$	23
H3K4me1	$1(1^*)$	$1(1^*)$	1	$30(34^*)$	$30(34^*)$	30	$28 (39^*)$	$28 (39^*)$	27
H3K4me3	NA	NA	NA	$23~(25^*)$	$23~(25^*)$	21	$19(26^*)$	$19(26^*)$	19

For significant results (histone peak and/or CpG), we considered:

 Using eQTLGen [47] to assess if the h/mQTL was also associated with the expression of a relevant gene (i.e. cis-eQTL)

- Using the LDpair function from the LDlinkR R package [48] to assess if there was a strong correlation between the hQTL and the mQTL (see section 3.6)
- If there was an overlapping histone peak in Pelikan et al. [38] which we could use for replication purposes

4.3 Scenarios

After gathering the results from the summary-based Mendelian randomization (SMR) analyses for all the nine selected cardiometabolic traits, we designed a series of possible scenarios in which each pair of hQTL peak and its closest mQTL could fit in. In total, there are seven different scenarios taken into account, albeit only four of these will be up for interpretation (herein named "cases"). Here, the p-values give us information regarding the evidence of directed association (i.e. between the peak and the trait, and between the CpG and the trait), and the R^2 (ranging between 0 and 1) gives us the strength of correlation (i.e. whether a set of SNPs are in LD or not). If p-values are greater than 0.05, then we assume there is no directed association, and if R^2 is greater than 0.3, we assume the pair of SNPs to be in LD (i.e. MR would should not be able to distinguish between them). Scenarios A, B, and F are not followed up. For scenario A, we found no evidence of directed association for both the peak and CpG with the selected trait, thus we don't investigate further. For scenario B, we only found evidence of directed association for the peak and the trait, but not for the CpG and the trait. Here, R^2 is greater than 0.3, thus the SNPs are in LD. Since it is hard to understand how MR was able to distinguish between the hQTL and the mQTL even though they are in LD, we do not follow up scenario B. Scenario F is similar to scenario B, except that here the directed association is found between the CpG and the trait, and not between the peak and the trait. We did not follow up scenario F for the same reasons than scenario B. The aforementioned scenarios and their properties are listed in Table 4.7. In total, 456 peaks resulted from the SMR analyses and were included in 1 of the 7 scenarios (see Figure 4.2).

Scenario	Peak MR p-value	CpG MR p-value	$\frac{R^2}{(\mathrm{EUR})^1}$	Interpretation
А	> 0.05	> 0.05	NA	Not followed up
В	<= 0.05	> 0.05	>0.3	Not followed up
\mathbf{C}	<= 0.05	> 0.05	< 0.3	Case 1
D	<= 0.05	<= 0.05	>0.3	Case 2
Е	<= 0.05	<= 0.05	< 0.3	Case 3
F	> 0.05	<= 0.05	>0.3	Not followed up
G	> 0.05	<= 0.05	< 0.3	Case 4

Table 4.7: Overview of the possible scenarios for the interpretation of the MR analyses.

¹ European population



Figure 4.2: Barplot of the histone peaks included in the 7 possible scenarios.

From all seven possible scenarios, only four (i.e. scenarios C, D, E, and G) allow further analysis and interpretation. The aforementioned scenarios will henceforth be referred to as "cases". For each case, we have the following interpretation:

- Case 1: Evidence that the two analyses are different and that histone PTM is the driving mechanism.
- Case 2: Not possible to distinguish between the histone PTM and methylation mechanisms, both are candidates for the driving mechanism.
- Case 3: Evidence that the two analyses are different, although both appear to influence the trait.
- Case 4: Evidence that the two analyses are different and that methylation is the driving mechanism.

In total, there are 36 (hQTL peak, mQTL) pairs that fit into one of the 4 aforementioned cases, as tabulated in Table 4.8. These "top pairs" come from four of the original GWAS studies, namely, ieu-b-109 (HDL-C), ieu-b-110 (LDL-C), ieu-b-111 (TG), and ieu-b-40 (BMI). In total, there are 15 pairs that fit in case 1, 7 in case 2, 4 in case 3, and 10 in case 4. And with regard to the histone mark, 12 pairs are in H3K27ac, 13 in H3K4me1, and 11 in H3K4me3.

#	Trait	Chr^1	${ m hQTL}$	mQTL SNP	Histone PTM	$LD^{2'}$ (EUB) ³	$LD^{2'}$ (VBI) ⁴	R^2 (EUR) ³	R^2 (VRI) ⁴	Case
1	BMI	11	rs11020992	rs61895493	H3K27AC	F	F	0.0864	0.0668	1
2	BMI	11	rs6483382	rs61895493	H3K4ME3	F	F	0.0864	0.0656	1
3	BMI	22	rs2413048	rs136274	H3K4ME1	F	F	0.0148	0.0039	1
4	HDL-C	9	rs10984990	rs77354872	H3K27AC	F	F	0.0133	0.0226	1
5	HDL-C	9	rs3753025	rs68023192	H3K27AC	F	\mathbf{F}	0.0062	0.0133	1
6	HDL-C	9	rs3753025	rs68023192	H3K4ME3	F	\mathbf{F}	0.0062	0.0133	1
7	HDL-C	11	rs17726787	rs113097600	H3K4ME3	Т	Т	0.1347	0.5694	1
8	HDL-C	22	rs13057194	rs5753625	H3K4ME3	Т	Т	0.1683	0.1186	1
9	ΤG	11	rs3751033	rs11222341	H3K4ME3	Т	\mathbf{F}	0.1102	0.0153	1
10	TG	17	rs72625946	rs2940227	H3K4ME1	F	F	0.0015	0.009	1
11	ΤG	19	rs11671664	rs4802262	H3K27AC	F	\mathbf{F}	0.0315	0.0089	1
12	ΤG	19	rs892149	rs721885	H3K27AC	F	Т	0.0341	0.1333	1
13	ΤG	19	rs892149	rs721885	H3K4ME1	F	Т	0.0341	0.1333	1
14	ΤG	19	rs11671664	rs4802262	H3K4ME3	F	\mathbf{F}	0.0315	0.0089	1
15	ΤG	19	rs892149	rs721885	H3K4ME3	F	Т	0.0341	0.1333	1
16	BMI	6	rs56874662	rs9379875	H3K27AC	Т	F	0.3489	0.0033	2
17	BMI	16	rs1868157	rs4783556	H3K27AC	Т	Т	0.8665	0.2895	2
18	BMI	16	rs1868157	rs4783556	H3K4ME1	Т	Т	0.8665	0.2895	2
19	BMI	16	rs1868157	rs4783556	H3K4ME3	Т	Т	0.8665	0.2895	2
20	BMI	22	rs12158556	rs5756763	H3K4ME1	Т	Т	0.7709	0.326	2
21	HDL-C	3	rs6798146	rs62274121	H3K4ME1	Т	\mathbf{F}	0.3084	0.0305	2
22	HDL-C	4	rs2595103	rs12642151	H3K4ME1	Т	Т	0.9731	0.8582	2
23	BMI	8	rs6997893	rs4733037	H3K4ME3	F	F	0.0244	0.0035	3
24	HDL-C	3	rs782445	rs113761591	H3K4ME1	\mathbf{F}	\mathbf{F}	0.0524	NA	3
25	HDL-C	6	rs2855807	rs2256747	H3K4ME1	\mathbf{F}	\mathbf{F}	0.051	0.0034	3
26	HDL-C	11	rs7101772	rs7117404	H3K27AC	F	\mathbf{F}	0.052	NA	3
27	BMI	2	rs6720165	rs10930199	H3K4ME1	Т	\mathbf{F}	0.2441	0.0501	4
28	BMI	12	rs1990714	rs72649521	H3K27AC	\mathbf{F}	\mathbf{F}	0.0011	NA	4
29	BMI	12	rs11066714	rs72649521	H3K4ME1	\mathbf{F}	\mathbf{F}	0.0011	NA	4
30	HDL-C	16	rs223869	rs28401442	H3K4ME3	Т	\mathbf{F}	0.1119	0.0023	4
31	LDL-C	9	rs10760118	rs10818492	H3K27AC	\mathbf{F}	Т	0.0441	0.1074	4
32	LDL-C	9	rs1930778	rs10818492	H3K4ME1	\mathbf{F}	Т	0.0439	0.1074	4
33	LDL-C	19	rs11667718	rs1029709	H3K27AC	Т	\mathbf{F}	0.1024	0.0067	4
34	LDL-C	19	rs77664054	rs142448599	H3K27AC	\mathbf{F}	\mathbf{F}	0.0041	NA	4
35	LDL-C	19	rs77664054	rs142448599	H3K4ME1	\mathbf{F}	\mathbf{F}	0.0041	NA	4
36	LDL-C	19	rs11667718	rs1029709	H3K4ME3	Т	\mathbf{F}	0.1024	0.0067	4

Table 4.8: Overview of the 36 (hQTL, mQTL) pairs that fit into 1 of the 4 cases.

³⁶ | LDL-C 19 rs11
¹ Chromosome
² Linkage disequilibrium
³ European population
⁴ Yoruba population

4.4 In-depth case analysis

4.4.1 Case 1

In case 1, we uncovered evidence for a directional association between histone PTMs and the trait, but insufficient evidence to suggest that nearby methylation was associated with the same trait. Here, the SNPs instrumenting these two molecular traits are not in LD for the European population. This may represent a scenario where histone PTM, and not DNA methylation, is affecting the trait. To verify this, we consider the following hypotheses:

- 1. The hQTL is an eQTL of a relevant gene but the mQTL is not.
- 2. SMR of a EUR hQTL peak within the width of the YRI one.

In total, there are 15 hQTL peaks matching this case: 3 for BMI, 5 for HDL-C, and 7 for TG.

hQTL: H3K4ME3_4407

The hQTL peak H3K4ME3_4407 spans 3989 bp on chromosome 19, with the centre of the peak 531 bp away from its hQTL SNP (rsid: rs11671664, $\beta = 0.90$, p < 0.001). The TG-associated CpG cg14661225 [49] is 1358 bp away, and methylation at this CpG is also highly associated ($\beta = 0.27$, p < 0.001) with the nearby mQTL SNP rs4802262. This mQTL is not in LD with the hQTL in the European population ($R^2 = 0.0315$), and so we can expect SMR analyses investigating the histone peak and methylation's effect on triglycerides to be distinct. SMR provided evidence of this histone PTM being directionally associated with triglycerides (Bonferroni p = 0.029), but did not provide sufficient evidence to suggest nearby DNA methylation at cg14661225 affected triglyceride levels (Bonferroni p = 0.999). There was no overlapping histone peak in the second hQTL mapping study for us to replicate this result with. The aforementioned hQTL is also a known cis-eQTL for 4 genes, including SYMPK, which contains SNPs implicated in triglyceride measurement GWAS (as well as LDL-C and HDL-C measurement, body mass index, and body fat percentage). The mQTL was not an eQTL for any of these for genes, but was for SNRPD2 which has not been found to be associated with triglyceride levels. This could potentially indicate a pathway through which histone trimethylation in this region could influence triglycerides. An overview of the genomic features found for this example of case 1 is shown in Figure 4.3.



Figure 4.3: Overview of genomic features for case 1: CpG position, mQTL position, histone peak range, hQTL position, relevant nearby gene, mQTL-CpG associations, and eQTL-gene associations. Figure rendered using the Gviz R package [50].

4.4.2 Case 2

We found evidence for a directional association between histone PTMs and the trait, and between nearby methylation and that trait. The SNPs instrumenting these two molecular traits are in LD, thus SMR cannot distinguish between them. This may represent a scenario where histone modification and methylation are both affecting the trait. In total, there are 7 hQTL peaks matching this case: 5 for BMI, and 2 for HDL-C.

hQTL: H3K4ME3_3286

The hQTL peak H3K4ME3_3286 spans 3115 bp on chromosome 16, with the centre of the peak 278 bp away from its hQTL (rsid: rs1868157, $\beta = -0.90$, p < 0.001). The BMI-associated CpG cg26899718 [51] is 1421 bp away, and methylation at this CpG is highly associated ($\beta = 0.18$, p < 0.001) with the nearby mQTL SNP (rsid: rs4783556). SMR provided evidence of this histone PTM being directionally associated with BMI (Bonferroni p = 0.004) and this evidence was also present when looking at the effect of methylation at cg26899718 (Bonferroni p < 0.001). Since the mQTL and hQTL are highly correlated ($R^2 = 0.87$), this exemplifies a situation where SMR fails to distinguish between the two epigenetic mechanisms. Here, a study focused on only one level of the epigenome may conclude that a causal link has been identified, but when including data on both histone modifications and methylation, we observe that no such conclusion can be reached. As expected, both the hQTL and mQTL were eQTLs of many of the same genes (13 overlapping genes out of the 18 unique genes using eQTLGen).

4.4.3 Case 3

In the scope of case 3, as seen in case 2, we found evidence for a directional association between histone PTMs and the traits, as well as between nearby methylation and that same trait. The difference between this case and the previous one lies in the fact that, in this scenario, the SNPs intrumenting the two molecular traits are not in LD, and SMR should be able to distinguish between them. In total, there are 4 hQTL peaks matching this case: 1 for BMI, and 3 for HDL-C.

hQTL: H3K27AC_1183

The hQTL peak H3K27AC_1183 spans 2711 bp on chromosome 11, with the centre of the peak 1433 bp away from its hQTL (rsid: rs7101772, $\beta = 0.69$, p < 0.001). The HDL-associated CpG cg09580214 is 589 bp away, and methylation at this CpG is highly associated ($\beta = 0.50$, p < 0.001) with the nearby mQTL SNP rs7117404. SMR provided evidence of this histone PTM being directionally associated with HDL-C levels (Bonferroni p < 0.001), and this was also observed with methylation at rs7117404 (Bonferroni p < 0.001). Here, since the mQTL and hQTL are not correlated in the European population ($R^2 = 0.0052$), in principle, SMR is able to distinguish between the two epigenetic mechanisms. The hQTL mentioned beforehand is a known cis-eQTL for 12 genes, including MTCH2, which is highly expressed in white adipose tissue and adipocytes, and thought to play a regulatory role in adipocyte differentiation [52, 53]. With regard to the mQTL, eQTLGen found that it is a known cis-eQTL for 10 genes, 7 of which overlap with the ones found for the hQTL. It is possible that the hQTL and mQTL both affect HDL-C levels through different mechanisms. An overview of the genomic features found for this example of case 1 is shown in Figure 4.4.



Figure 4.4: Overview of genomic features for case 1: CpG position, mQTL position, histone peak range, hQTL position, relevant nearby gene, mQTL-CpG associations, and eQTL-gene associations. Figure rendered using the Gviz R package [50].

4.4.4 Case 4

With regard to the final case, conversely to case 1, we found evidence for a directional association between DNA methylation and the trait, but insufficient evidence to suggest that the histone PTM was associated with the same trait. Again, here the SNPs instrumenting these two molecular traits are not in LD for the European population. It may be a case in which DNA methylation is the driving mechanism affecting the trait, and not histone PTM. In total, there are 10 hQTL peaks matching this case: 3 for BMI, 1 for HDL-C, and 6 for LDL-C.

hQTL: H3K27AC_1988

The hQTL peak H3K27AC_1988 spans 1492 bp on chromosome 12, with the centre of the peak 108 bp away from its hQTL SNP (rsid: rs1990714; $\beta = 0.64$, p < 0.001). The BMI-associated CpG cg24727480 [54] is 36 bp away, and methylation at this CpG is highly associated ($\beta = -0.22$, p < 0.001) with the nearby mQTL SNP rs72649521. This mQTL is not in LD with the hQTL in the European population ($R^2 = 0.0011$), hence we expect SMR analyses investigating the hQTL peak and methylation's effect on BMI to be distinct. Here, SMR provided evidence of the nearby DNA methylation at cg24727480 being directionally associated with BMI (Bonferroni p < 0.001), but not the histone PTM (Bonferroni p = 0.999). This hQTL is a known cis-eQTL for 1 gene, KCTD10, which overlaps with one of the 6 genes found for the mQTL. According to GeneCards [55], KCTD10 contains SNPs implicated in alcohol consumption and HDL-C measurement GWAS which possibly have an impact on BMI. Noteworthily, the mQTL is a known cis-eQTL for ACACB, which

studies have linked its variants to obesity and diabetes [56], adipose gene expression regulation [57], and BMI [58]. An overview of the genomic features found for this example of case 1 is shown in Figure 4.3.



Figure 4.5: Overview of genomic features for case 1: CpG position, mQTL position, histone peak range, hQTL position, relevant nearby gene, mQTL-CpG associations, and eQTL-gene associations. Figure rendered using the Gviz R package [50].

Chapter 5

Discussion

With this project, we set the aim of understanding how molecular processes could influence cardiometabolic traits. To that effect, we looked at the interactions between 2 epigenetic mechanisms (i.e. histone PTMs and DNA methylation) using QTL data that we processed via a novel modular SMR analysis pipeline. Using this approach, based on the raw data from Grubert et al. [37], we reduced the data to 36 hits that fit into 1 of the 4 cases included in our 7 designed scenarios. From the results we found that most of the hits (15) were cases in which the histone PTM was the driving mechanism, closely followed (10) by cases in which the DNA methylation was the driving mechanism.

Initially, we set out to run our SMR-based analysis pipeline on the data included in 5 different studies (see Table 3.1). Unfortunately, we were only able to proceed with 2 of them since the remaining ones were either missing required data or crucial data processing steps were omitted, rendering replication of some parts of the studies unviable. Thus, in this chapter, we focus on discussing the results from the SMR-based analysis pipeline applied to the data from Grubert et al. [37] according to the workflow shown in Figure 3.1.

Although QTLbase provides a straightforward way of finding relevant articles, there is a noticeable lack of standardization when it comes to reporting results from QTL mapping studies to perform bidirectional MR. Ideally, the scientific community could formulate a set of conventions for reporting epigenetic assays (including QTL data), as pointed out by Carter et al. [59]. This would significantly decrease the amount of data preprocessing required for performing SMR analyses, as well as increase the reproducibility of said studies.

The first step of our approach required the integration of hQTL and mQTL data. To that effect, we collected the supplementary data from Grubert et al. [37] along with additional files kindly provided by the authors. The data in Grubert et al. [37] included all the required variables to perform SMR for 3 histone PTMs (H3K27ac, H3K4me1, and H3K4me3) and our pipeline successfully performed the SMR analysis. Although in the case of Pelikan et al. [38], we were missing data on the effect allele frequency (EAF) which we extracted from the Ensembl Rest API using reference SNP cluster ids (rsids) as input. Data from Pelikan et al. [38] was used for replication purposes from the results of SMR on Grubert et al. [37]. Unfortunately, the most interesting peaks (see Table 4.7) did not overlap between the two articles. This may be derived from the fact that they used different populations (i.e. EUR vs YRI).

In this project, we designed an experiment in which our results were categorized into 7 different scenarios (4 of which are of interest; "cases") by tuning different variables (MR p-values and R²). Our analysis amounted to 36 interesting peaks out of the few thousands peaks in the source data (n = 46322): 15 peaks in case 1 (3 for BMI, 5 for HDL-C, and 7 for TG), 7 peaks in case 2 (5 for BMI and 2 for HDL-C), 4 peaks in case 3 (1 for BMI and 3 for HDL-C), and 10 peaks in case 4 (3 for BMI, 1 for HDL-C, and 6 for LDL-C). Almost half of the peaks falling into one of the 4 cases were included in case 1. Some peaks have NA values in the R² (YRI) column because of population-specific alleles. Population-specific SNPs are non-randomly distributed throughout the genome and significantly associated with recombination hotspots [60]. Another observation we made is the fact that out of the 9 traits we studied, only 4 (BMI, HDL-C, LDL-C, and TG) survived the SMR and subsequent analyses. It is important to highlight that some traits hold more studies than others (e.g. BMI has been much more studied than leptin levels).

Noteworthily, scenarios B and F had practically no results. In this case, mQTLs and hQTLs are in high LD but results from the SMR analysis are different: SMR is able to distinguish the exposures, and it presumably shouldn't be able to in these two scenarios. For scenarios C and G, SMR is able to distinguish between the mQTLs and hQTLs (not in LD), and it seems like we have more results for case 1 (i.e. scenario B) than case 4 (i.e. scenario F). It would be interesting to follow up this lead and see if, for example, histone PTMs have more influence than DNA methylation when looking at cardiometabolic traits.

The default R^2 threshold to determine if a pair of alleles are in LD set by the LDpair function of the LDlinkR R package is set to 0.1. But in our analysis, we were slightly more flexible (i.e. $R^2 = 0.3$) since we aimed at a more exploratory analysis. It is plausible that decreasing the threshold for this variable would lead to more significant results (e.g. $R^2 < 0.1$) at the cost of less flexibility. On the other hand, increasing it (e.g. $R^2 > 0.3$) could possibly give more hits, some of which could potentially be biologically relevant. Alternatively, one could also try out different widths for each histone peak where we look for trait-associated CpGs. Lastly, the experiment could be rearranged to include more in-depth scenarios that incorporate multiple p-value cut-offs and effect size estimates.

Due to the fact that we ran the SMR analyses per h/mQTL-trait association (i.e. we only look at 1 instrument/SNP at a time), one limitation worth mentioning is that we were not able to check if there were pleiotropic effects (i.e. SNPs affecting 2 or more traits through through independent pathways). Furthermore, because a genetic variant (i.e. 1 SNP) proxying for an exposure (e.g. H3K27ac_1234) may only explain a small part of the variance observed for a given trait (e.g. BMI), MR does require a large sample size, which is not always the case.

With respect to the aims of this project, we successfully collated libraries of molecular QTLs (hQTL and mQTL) and standardized a SMR workflow that can be applied to different subsets of phenotypes. In the future, it would be beneficial to the growing field to focus on gathering larger amounts of data from multiple sources (including different types of QTLs, e.g. caQTLs), performing MR on these larger sets of data, and creating database with standardized data formats that can be used as input for the TwoSampleMR R package.

Bibliography

- Michael V. Holmes, Mika Ala-Korpela, and George Davey Smith. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. *Nature Reviews Cardiology*, 14(10):577–590, 2017. doi: 10.1038/nrcardio.2017.78.
- [2] A. G. C. Boef, O. M. Dekkers, and S. Le Cessie. Mendelian randomization studies: a review of the approaches used and the quality of reporting. *International Journal of Epidemiology*, 44(2):496–511, 2015. doi: 10.1093/ije/dyv071.
- [3] Vardhman K. Rakyan, Thomas A. Down, David J. Balding, and Stephan Beck. Epigenome-wide association studies for common human diseases. *Nature Reviews Genetics*, 12(8):529–541, 2011. doi: 10.1038/nrg3000.
- [4] Eveline M. Ibeagha-Awemu and Xin Zhao. Epigenetic marks: regulators of livestock phenotypes and conceivable sources of missing variation in livestock improvement programs. *Frontiers in Genetics*, 6, 2015. doi: 10.3389/fgene.2015.00302.
- [5] Emma Cazaly, Joseph Saad, Wenyu Wang, Caroline Heckman, Miina Ollikainen, et al. Making sense of the epigenome using data integration approaches. *Frontiers in Pharmacology*, 10, 2019. doi: 10.3389/ fphar.2019.00126.
- [6] Lisa D Moore, Thuc Le, and Guoping Fan. Dna methylation and its basic function. Neuropsychopharmacology, 38(1):23–38, 2012. doi: 10.1038/npp.2012.112.
- [7] Robert Santer. Cellular mechanisms of aging. Brocklehursts Textbook of Geriatric Medicine and Gerontology, page 42–50, 2010. doi: 10.1016/b978-1-4160-6231-8.10008-x.
- [8] Zahava Siegfried and Howard Cedar. Dna methylation: A molecular lock. *Current Biology*, 7(5), 1997. doi: 10.1016/s0960-9822(06)00144-8.
- [9] Peter A. Jones. The dna methylation paradox. *Trends in Genetics*, 15(1):34–37, 1999. doi: 10.1016/s0168-9525(98)01636-9.
- [10] Scott M. Langevin and Karl T. Kelsey. The fate is not always written in the genes: Epigenomics in epidemiologic studies. *Environmental and Molecular Mutagenesis*, 54(7):533–541, 2013. doi: 10.1002/ em.21762.
- [11] C. Jake Harris, Marion Scheibe, Somsakul Pop Wongpalee, Wanlu Liu, Evan M. Cornett, et al. A dna methylation reader complex that enhances gene transcription. *Science*, 362(6419):1182–1186, 2018. ISSN 0036-8075. doi: 10.1126/science.aar7854.

- [12] Karolin Luger, Armin W. Mäder, Robin K. Richmond, David F. Sargent, and Timothy J. Richmond. Crystal structure of the nucleosome core particle at 2.8a. *Nature*, 389(6648):251–260, 1997. doi: 10.1038/38444.
- [13] Heather J. Szerlong and Jeffrey C. Hansen. Nucleosome distribution and linker dna: connecting nuclear function to dynamic chromatin structure. *Biochemistry and Cell Biology*, 89(1):24–34, 2011. doi: 10. 1139/o10-139.
- [14] J. Widom. Role of dna sequence in nucleosome stability and dynamics. *Quarterly Reviews of Biophysics*, 34(3):269–324, 2001. doi: 10.1017/s0033583501003699.
- [15] Robert T. Simpson. Structure of the chromatosome, a chromatin particle containing 160 base pairs of dna and all the histones. *Biochemistry*, 17(25):5524–5531, 1978. doi: 10.1021/bi00618a030.
- [16] LLC Schrödinger and Warren DeLano. Pymol. URL http://www.pymol.org/pymol.
- [17] Gregory D. Bowman and Michael G. Poirier. Post-translational modifications of histones that influence nucleosome dynamics. *Chemical Reviews*, 115(6):2274–2295, 2014. doi: 10.1021/cr500350x.
- [18] Isabelle Vaillant and Jerzy Paszkowski. Role of histone and dna methylation in gene regulation. Current Opinion in Plant Biology, 10(5):528–533, 2007. doi: 10.1016/j.pbi.2007.06.008.
- [19] Peter J. Park. Chip-seq: advantages and challenges of a maturing technology. Nature Reviews Genetics, 10(10):669–680, 2009. doi: 10.1038/nrg2641.
- [20] Matteo Pellegrini and Roberto Ferrari. Epigenetic analysis: Chip-chip and chip-seq. Next Generation Microarray Bioinformatics Methods in Molecular Biology, page 377–387, 2011. doi: 10.1007/ 978-1-61779-400-1_25.
- [21] Ryuichiro Nakato and Katsuhiko Shirahige. Recent advances in chip-seq analysis: from quality management to whole-genome annotation. *Briefings in Bioinformatics*, 2016. doi: 10.1093/bib/bbw023.
- [22] Ryuichiro Nakato and Toyonori Sakata. Methods for chip-seq analysis: A practical workflow and advanced applications. *Methods*, 187:44–53, 2021. doi: 10.1016/j.ymeth.2020.03.005.
- [23] C. Lin, A. S. Garrett, B. De Kumar, E. R. Smith, M. Gogol, et al. Dynamic transcriptional events in embryonic stem cells mediated by the super elongation complex (sec). *Genes & Development*, 25(14): 1486–1498, 2011. doi: 10.1101/gad.2059211.
- [24] Suhasni Gopalakrishnan, Beth O. Van Emburgh, and Keith D. Robertson. Dna methylation in development and human disease. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 647 (1-2):30–38, 2008. doi: 10.1016/j.mrfmmm.2008.08.006.
- [25] Kathleen Cheung, Marjolein J. Burgers, David A. Young, Simon Cockell, and Louise N. Reynard. Correlation of infinium humanmethylation450k and methylationepic beadchip arrays in cartilage. *Epigenetics*, 15(6-7):594–603, 2019. doi: 10.1080/15592294.2019.1700003.
- [26] Cardiovascular diseases (CVDs). https://www.who.int/en/news-room/fact-sheets/detail/ cardiovascular-diseases-(cvds), May 2017. Accessed: 28-10-2020.
- [27] Miles Fisher. Cardiometabolic disease: the new challenge? Practical Diabetes International, 23(3):95–97, 2006. doi: 10.1002/pdi.909.
- [28] Mesh browser. https://meshb.nlm.nih.gov/record/ui?ui=D002318. Accessed: 28-10-2020.

- [29] Kim V.e. Braun, Eliana Portilla, Rajiv Chowdhury, Jana Nano, Jenna Troup, et al. The role of epigenetic modifications in cardiometabolic diseases. *Epigenetics of Aging and Longevity*, page 347–364, 2018. doi: 10.1016/b978-0-12-811060-7.00017-6.
- [30] Anne-Karien M De Waard, Monika Hollander, Joke C Korevaar, Mark M J Nielen, Axel C Carlsson, et al. Selective prevention of cardiometabolic diseases: activities and attitudes of general practitioners across europe. *European Journal of Public Health*, 29(1):88–93, 2018. doi: 10.1093/eurpub/cky112.
- [31] Sarah Costantino, Shafeeq A. Mohammed, Samuele Ambrosini, and Francesco Paneni. Epigenetic processing in cardiometabolic disease. *Atherosclerosis*, 281:150–158, 2019. doi: 10.1016/j.atherosclerosis.2018.09.029.
- [32] Jennifer E. Ho, Elizabeth L. Mccabe, Thomas J. Wang, Martin G. Larson, Daniel Levy, et al. Cardiometabolic traits and systolic mechanics in the community. *Circulation: Heart Failure*, 10(5), May 2017. doi: 10.1161/ circheartfailure.116.003536.
- [33] K. L. Mohlke, M. Boehnke, and G. R. Abecasis. Metabolic and cardiovascular traits: an abundance of recently identified common genetic variants. *Human Molecular Genetics*, 17(R2), October 2008. doi: 10.1093/hmg/ ddn275.
- [34] Stephen Burgess, Dylan S Small, and Simon G Thompson. A review of instrumental variable estimators for mendelian randomization. *Statistical Methods in Medical Research*, 26(5):2333–2355, 2015. doi: 10.1177/0962280215597579.
- [35] Neil M Davies, Michael V Holmes, and George Davey Smith. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *Bmj*, 2018. doi: 10.1136/bmj.k601.
- [36] Zhanye Zheng, Dandan Huang, Jianhua Wang, Ke Zhao, Yao Zhou, et al. QTLbase: an integrative resource for quantitative trait loci across multiple human molecular phenotypes. *Nucleic Acids Research*, 48(D1):D983–D991, 10 2019. ISSN 0305-1048. doi: 10.1093/nar/gkz888.
- [37] Fabian Grubert, Judith B. Zaugg, Maya Kasowski, Oana Ursu, Damek V. Spacek, et al. Genetic control of chromatin states in humans involves local and distal chromosomal interactions. *Cell*, 162(5):1051–1065, 2015. doi: 10.1016/j.cell.2015.07.048.
- [38] Richard C. Pelikan, Jennifer A. Kelly, Yao Fu, Caleb A. Lareau, Kandice L. Tessneer, et al. Enhancer histone-qtls are enriched on autoimmune risk haplotypes and influence gene expression within chromatin networks. *Nature Communications*, 9(1), 2018. doi: 10.1038/s41467-018-05328-9.
- [39] O. Delaneau, M. Zazhytska, C. Borel, G. Giannuzzi, G. Rey, et al. Chromatin three-dimensional interactions mediate genetic effects on gene expression. *Science*, 364(6439), 2019. doi: 10.1126/science.aat8266.
- [40] Ashley Tehranchi, Brian Hie, Michael Dacre, Irene Kaplow, Kade Pettie, et al. Fine-mapping cis-regulatory variants in diverse human populations. *eLife*, 8, 2019. doi: 10.7554/elife.39595.
- [41] Jacob F. Degner, Athma A. Pai, Roger Pique-Regi, Jean-Baptiste Veyrieras, Daniel J. Gaffney, et al. Dnase i sensitivity qtls are a major determinant of human expression variation. *Nature*, 482(7385):390–394, 2012. doi: 10.1038/nature10808.
- [42] Ben Elsworth, Matthew Lyon, Tessa Alexander, Yi Liu, Peter Matthews, et al. The mrc ieu opengwas data infrastructure. 2020. doi: 10.1101/2020.08.10.244293.
- [43] Mengwei Li, Dong Zou, Zhaohua Li, Ran Gao, Jian Sang, et al. Ewas atlas: a curated knowledgebase of epigenomewide association studies. *Nucleic Acids Research*, 47(D1), 2018. doi: 10.1093/nar/gky1027.
- [44] Thomas Battram, Paul Yousefi, Gemma Crawford, Claire Prince, Mahsa Sheikhali Babei, et al. The ewas catalog: a database of epigenome-wide association studies. 2021. doi: 10.31219/osf.io/837wn.

- [45] G. Hemani, J. Zheng, B. Elsworth, K. Wade, D. Baird, et al. The mr-base platform supports systematic causal inference across the human phenome. *eLife*, 7:e34408, 2018. doi: 10.7554/eLife.34408. URL https://elifesciences.org/articles/34408.
- [46] G. Hemani, K. Tilling, and G. Davey Smith. Orienting the causal relationship between imprecisely measured traits using gwas summary data. *PLoS Genetics*, 13(11):e1007081, 2017. doi: 10.1371/journal.pgen.1007081. URL https://doi.org/10.1371/journal.pgen.1007081.
- [47] Urmo Võsa, Annique Claringbould, et al. Unraveling the polygenic architecture of complex traits using blood eqtl metaanalysis. *bioRxiv*, 2018. doi: 10.1101/447367. URL https://www.biorxiv.org/content/early/2018/ 10/19/447367.
- [48] Timothy A. Myers, Stephen J. Chanock, and Mitchell J. Machiela. Ldlinkr: An r package for rapidly calculating linkage disequilibrium statistics in diverse populations. *Frontiers in Genetics*, 11(157), 2020. doi: 10.3389/fgene. 2020.00157.
- [49] H. Toinét Cronjé, Hannah R. Elliott, Cornelie Nienaber-Rousseau, and Marlien Pieters. Replication and expansion of epigenome-wide association literature in a black south african population. *Clinical Epigenetics*, 12(1), 2020. doi: 10.1186/s13148-019-0805-z.
- [50] Florian Hahne and Robert Ivanek. Visualizing genomic data using gviz and bioconductor. Methods in Molecular Biology Statistical Genomics, page 335–351, 2016. doi: 10.1007/978-1-4939-3578-9_16.
- [51] L E Wilson, S Harlid, Z Xu, D P Sandler, and J A Taylor. An epigenome-wide study of body mass index and dna methylation in blood using participants from the sister study cohort. *International Journal of Obesity*, 41(1): 194–199, 2016. doi: 10.1038/ijo.2016.184.
- [52] Agné Kulyté, Mikael Rydén, Niklas Mejhert, Elisabeth Dungner, Eva Sjölin, et al. Mtch2 in human white adipose tissue and obesity. The Journal of Clinical Endocrinology & Metabolism, 96(10), 2011. doi: 10.1210/jc.2010-3050.
- [53] F. Bernhard, K. Landgraf, N. Klöting, A. Berthold, P. Büttner, et al. Functional relevance of genes implicated by obesity genome-wide association study signals for human adipocyte biology. *Diabetologia*, 56(2):311–322, 2012. doi: 10.1007/s00125-012-2773-0.
- [54] Y M Geurts, P-A Dugué, J E Joo, E Makalic, C-H Jung, et al. Novel associations between blood dna methylation and body mass index in middle-aged and older adults. *International Journal of Obesity*, 42(4):887–896, 2017. doi: 10.1038/ijo.2017.269.
- [55] Gil Stelzer, Naomi Rosen, Inbar Plaschkes, Shahar Zimmerman, Michal Twik, et al. The genecards suite: From gene data mining to disease genome sequence analyses. *Current Protocols in Bioinformatics*, 54(1), 2016. doi: 10.1002/cpbi.5.
- [56] J.a. Riancho, L. Vázquez, M.a. García-Pérez, J. Sainz, J.m. Olmos, et al. Association of acacb polymorphisms with obesity and diabetes. *Molecular Genetics and Metabolism*, 104(4):670–676, 2011. doi: 10.1016/j.ymgme. 2011.08.013.
- [57] Lijun Ma, Ashis K. Mondal, Mariana Murea, Neeraj K. Sharma, Anke Tönjes, et al. The effect of acacb cis-variants on gene expression and metabolic traits. *PLoS ONE*, 6(8), 2011. doi: 10.1371/journal.pone.0023860.
- [58] Lijun Ma, Mariana Murea, James A. Snipes, Alejandra Marinelarena, Jacqueline Krüger, et al. An acacb variant implicated in diabetic nephropathy associates with body mass index and gene expression in obese subjects. *PLoS* ONE, 8(2), 2013. doi: 10.1371/journal.pone.0056193.
- [59] Ava C Carter, Howard Y Chang, George Church, Ashley Dombkowski, Joseph R Ecker, et al. Challenges and recommendations for epigenomics in precision health. *Nature Biotechnology*, 35(12):1128–1132, 2017. doi: 10.1038/nbt.4030.

[60] Ananyo Choudhury, Scott Hazelhurst, Ayton Meintjes, Ovokeraye Achinike-Oduaran, Shaun Aron, et al. Population-specific common snps reflect demographic histories and highlight regions of genomic plasticity with functional relevance. BMC Genomics, 15(1):437, 2014. doi: 10.1186/1471-2164-15-437.

Chapter 6

Appendix



Distance from histone peak to nearest trait-associated CpG (bp)

Figure 6.1: Density plot of the distance from the histone peak to the nearest trait-associated CpG (in bp) for each GWAS after hQTL filtering. Refer to Table 3.3 for GWAS id to trait conversion, and vice-versa.



Figure 6.2: Density plot of the width of the histone peak (in bp) after hQTL filtering for each trait. Refer to Table 3.3 for GWAS id to trait conversion, and vice-versa.

#	file	cpg.db	cpg.dist	cpg.id	exposure	h.be	h.chr	h.ea	h.eaf	h.oa	h.outcome.be	h.outcome.ea	h.outcome.eaf	h.outcome.oa	h.outcome.pval	h.outcome.se
1	BMI	ctlg	261	cg20096208	H3K27AC_1796	-0.695125539	11	A	0.4908	C	0.0065	A	0.3181	C	0.0004	0.0018
0	BMI	ctlg	876	cg20096208	H3K4ME3_1192	-1.048771959	11	⊢	0.489	υ	0.0065	Γ	0.3184	U	0.000430002	0.0018
ю	BMI	ctlg+atlas	2336	cg08548559	H3K4ME1_12573	0.862913118	22	U	0.2808	۲	0.0073	U	0.4826	A	2.30001E-05	0.0017
4	HDL-C	ctlg	1078	cg22695151	H3K27AC_13576	0.821964309	6	F	0.3287	υ	0.00770107	F	0.299955	υ	0.000219999	0.00208223
ß	HDL-C	ctlg	324	cg13654468	H3K27AC_13503	-0.996677472	6	υ	0.1518	U	0.0180903	υ	0.080413	U	2.99999E-07	0.0035308
9	HDL-C	ctlg	679	cg13654468	H3K4ME3_9161	-0.838750291	6	υ	0.1518	U	0.0180903	υ	0.080413	U	2.99999E-07	0.0035308
7	HDL-C	ctlg	895	cg13308137	H3K4ME3_773	-1.279016348	11	U	0.07209	۷	-0.0217877	U	0.854505	A	6.70039E-16	0.00269802
œ	HDL-C	ctlg	1251	cg27178145	H3K4ME3_5458	-0.64857992	22	⊢	0.3313	υ	0.00765756	F	0.588185	U	8.50002E-05	0.00194902
6	TG	ctlg	884	cg14779329	H3K4ME3_621	-0.58613526	11	υ	0.4054	۷	-0.00700987	U	0.53246	A	0.000449997	0.00199801
10	ТG	ctlg	1954	cg15731920	H3K4ME1_8418	-1.238202091	17	υ	0.1532	⊢	-0.0139488	υ	0.926414	μ	0.00032	0.00387594
11	TG	ctlg	975	cg14661225	H3K27AC_6342	1.094482416	19	U	0.1552	۷	-0.0120662	U	0.89995	A	0.000269998	0.00331118
12	ТG	ctlg	154	cg25232942	H3K27AC_6409	0.76863682	19	υ	0.2504	۲	-0.0183955	υ	0.944046	A	2E-05	0.00431504
13	ТG	ctlg	224	cg25232942	H3K4ME1_10259	0.984583574	19	υ	0.2504	۲	-0.0183955	υ	0.944046	A	2E-05	0.00431504
14	ТG	ctlg	1358	cg14661225	H3K4ME3_4407	0.901097834	19	U	0.1552	۲	-0.0120662	U	0.89995	A	0.000269998	0.00331118
15	TG	ctlg	160	cg25232942	H3K4ME3_4457	0.834920651	19	υ	0.2504	٩	-0.0183955	υ	0.944046	A	2E-05	0.00431504
16	BMI	ctlg	137	cg04020984	H3K27AC_11600	0.719527464	9	υ	0.06969	۷	-0.0104	U	0.8855	A	2.1E-05	0.0025
17	BMI	atlas	1639	cg26899718	H3K27AC_4794	-0.941712308	16	U	0.3656	υ	0.0076	U	0.4116	υ	1.7E-05	0.0018
18	BMI	atlas	2813	cg26899718	H3K4ME1_7821	-0.752077439	16	U	0.3656	υ	0.0076	U	0.4116	U	1.7E-05	0.0018
19	BMI	atlas	1421	cg26899718	H3K4ME3_3286	-0.901568505	16	U	0.3656	υ	0.0076	U	0.4116	U	1.7E-05	0.0018
20	BMI	atlas	291	cg06594770	H3K4ME1_12708	-0.91878869	22	U	0.3964	٩	0.0062	U	0.5325	A	0.0004	0.0017
21	HDL-C	ctlg	1638	cg00673344	H3K4ME1_14296	-0.666496098	с	٩	0.379	υ	-0.0149669	A	0.627108	U	4.00037E-14	0.00197987
22	HDL-C	ctlg	1331	cg24925400	H3K4ME1_15370	0.552875069	4	٩	0.2734	U	0.00794391	A	0.748791	U	0.000309999	0.00220286
23	BMI	ctlg+atlas	4782	cg15681255	H3K4ME3_8944	-0.540682882	8	٩	0.2845	U	-0.0101	A	0.7254	U	1.7E-07	0.0019
24	HDL-C	ctlg	2967	cg22077997	H3K4ME1_13939	0.713955946	ъ	٩	0.2877	⊢	0.0077558	A	0.228304	μ	0.000649995	0.00227371
25	HDL-C	ctlg	1565	cg26799196	H3K4ME1_18764	-1.043903786	9	υ	0.3415	⊢	0.0100658	U	0.382995	T	2.69998E-07	0.00195692
26	HDL-C	ctlg	589	cg09580214	H3K27AC_1183	0.687511925	11	٩	0.3175	U	-0.0398467	A	0.713946	U	5.50047E-80	0.00210397
27	BMI	ctlg	39	cg16421616	H3K4ME1_11697	0.887451809	0	⊢	0.276	٩	-0.0047	μ	0.2839	A	0.0140001	0.0019
28	BMI	ctlg+atlas	36	cg24727480	H3K27AC_1988	0.642381877	12	⊢	0.113	U	-0.0072	μ	0.98872	U	0.37	0.008
29	BMI	ctlg+atlas	927	cg24727480	H3K4ME1_3185	0.625021608	12	υ	0.1064	⊢	-0.0073	υ	0.9893	μ	0.36	0.008
30	HDL-C	ctlg	189	cg27017172	H3K4ME3_3252	-0.727864021	16	υ	0.1164	٩	-0.0030703	υ	0.928482	A	0.4	0.00366138
31	LDL-C	ctlg	783	cg13501527	H3K27AC_13579	-0.619530078	6	υ	0.3071	⊢	-0.00130351	υ	0.352876	μ	0.55	0.00218112
32	LDL-C	ctlg	753	cg13501527	H3K4ME1_21800	-0.962485752	6	٩	0.3071	υ	-0.00130299	A	0.352913	U	0.55	0.00218114
33	LDL-C	ctlg	428	cg03153658	H3K27AC_6482	-0.636376144	19	υ	0.2885	⊢	0.00183269	U	0.621069	Τ	0.39	0.00213481
34	LDL-C	ctlg	505	cg06705122	H3K27AC_6390	-1.024287176	19	٩	0.04353	U	0.000700856	A	0.988895	U	0.94	0.00992821
35	LDL-C	ctlg	511	cg06705122	H3K4ME1_10232	-1.29928694	19	٩	0.04353	U	0.000700856	A	0.988895	U	0.94	0.00992821
36	LDL-C	ctlg	647	cg03153658	H3K4ME3_4528	-0.660178901	19	υ	0.2885	⊢	0.00183269	U	0.621069	Τ	0.39	0.00213481

Table 6.1: Top results from the SMR analysis.

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21	0.3179	۷	-0.00984897	U	0.327699	A	1.40001E-06	0.0020412	chr3:156817128:SNP	4.303E-45	0.000131544855933	1.39941336098982E-06
22	0.2529	υ	-0.00802252	A	0.250814	U	0.000280001	0.00220561	chr4:111592425:SNP	1.03E-29	0.025895536507009	0.000275484430926
23	0.3495	υ	0.0095	Τ	0.3376	U	2.30001E-07	0.0018	chr8:27093495:SNP	0	2.64134997790244E-05	1.3075989989616E-07
24	0.2033	υ	-0.0160751	Т	0.200254	U	1.59993E-11	0.00238637	chr3:127305355:SNP	0	1.52812359212266E-09	1.62566339587517E-11
25	0.14	F	-0.0274445	U	0.143996	Τ	4.10015E-24	0.00270966	chr6:31311950:SNP	0	3.88586035215497E-22	4.13389399165422E-24
26	0.1423	۷	-0.0264899	9	0.140832	A	4.00037E-22	0.00273906	chr11:47127153:SNP	0	3.75814221011028E-20	3.99802362777689E-22
27	0.4337	υ	-0.0073	⊢	0.4371	U	2.39999E-05	0.0017	chr2:151501903:SNP	1.841E-23	0.00354286705023	1.75389457932183E-05
28	0.0755	υ	0.0175	Τ	0.0663	U	3.50002E-08	0.0032	chr12:109905564:SNP	0	9.15505350753275E-06	4.53220470669938E-08
29	0.0755	υ	0.0175	Т	0.0663	U	3.50002E-08	0.0032	chr12:109905564:SNP	0	9.15505350753275E-06	4.53220470669938E-08
30	0.151	υ	0.0098072	A	0.146336	U	0.000230001	0.00266506	chr16:57376581:SNP	0	0.021931115764206	0.000233309742172
31	0.084	۷	0.0152638	IJ	0.086609	A	4E-05	0.00371354	chr9:123730554:SNP	2.382E-27	0.006796211346149	3.95128566636552E-05
32	0.084	۷	0.0152638	U	0.086609	A	4E-05	0.00371354	chr9:123730554:SNP	2.382E-27	0.006796211346149	3.95128566636552E-05
33	0.2814	υ	0.0100912	Т	0.273305	U	1.40001E-05	0.00232155	chr19:57046007:SNP	0	0.002376504420018	1.38168861628944E-05
34	0.1701	υ	0.0141354	A	0.17677	U	2E-07	0.00271783	chr19:49373036:SNP	4.85E-208	3.4095969323227E-05	1.98232379786178E-07
35	0.1701	υ	0.0141354	A	0.17677	U	2E-07	0.00271783	chr19:49373036:SNP	4.85E-208	3.40959693232227E-05	1.98232379786178E-07
36	0.2814	υ	0.0100912	F	0.273305	U	1.40001E-05	0.00232155	chr19:57046007:SNP	0	0.002376504420018	1.38168861628944E-05

-	•		1	1	1		1	1	1	1	1	1	1	1	1	2	5	2	2	2	7	2	ε	ε	ю	ε	4	4	4	4	4	4	4	4	4	4
scn.(ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	⊢	⊢	F	F	F	⊢	F	⊢	F	⊢
scn.F	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
scn.E	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	⊢	⊢	⊢	⊢	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
scn.D	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	F	F	F	⊢	F	F	⊢	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
scn.C	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	⊢	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
scn.B	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
scn.A	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш	ш
r2.YRI	0.0668	0.0656	0.0039	0.0226	0.0133	0.0133	0.5694	0.1186	0.0153	0.009	0.0089	0.1333	0.1333	0.0089	0.1333	0.0033	0.2895	0.2895	0.2895	0.326	0.0305	0.8582	0.0035	NA	0.0034	NA	0.0501	NA	NA	0.0023	0.1074	0.1074	0.0067	NA	NA	0.0067
r2.EUR	0.0864	0.0864	0.0148	0.0133	0.0062	0.0062	0.1347	0.1683	0.1102	0.0015	0.0315	0.0341	0.0341	0.0315	0.0341	0.3489	0.8665	0.8665	0.8665	0.7709	0.3084	0.9731	0.0244	0.0524	0.051	0.052	0.2441	0.0011	0.0011	0.1119	0.0441	0.0439	0.1024	0.0041	0.0041	0.1024
mark	H3K27AC	H3K4ME3	H3K4ME1	H3K27AC	H3K27AC	H3K4ME3	H3K4ME3	H3K4ME3	H3K4ME3	H3K4ME1	H3K27AC	H3K27AC	H3K4ME1	H3K4ME3	H3K4ME3	H3K27AC	H3K27AC	H3K4ME1	H3K4ME3	H3K4ME1	H3K4ME1	H3K4ME1	H3K4ME3	H3K4ME1	H3K4ME1	H3K27AC	H3K4ME1	H3K27AC	H3K4ME1	H3K4ME3	H3K27AC	H3K4ME1	H3K27AC	H3K27AC	H3K4ME1	H3K4ME3
m.snp.pos	94725824	94725824	31195391	123827352	107504423	107504423	46713062	31854846	130705653	36246433	46149886	50196451	50196451	46149886	50196451	26444732	68400952	68400952	68400952	38079239	156817128	111592425	27093495	127305355	31311950	47127153	151501903	109905564	109905564	57376581	123730554	123730554	57046007	49373036	49373036	57046007
m.snp	rs61895493	rs61895493	rs136274	rs77354872	rs68023192	rs68023192	rs113097600	rs5753625	rs11222341	rs2940227	rs4802262	rs721885	rs721885	rs4802262	rs721885	rs9379875	rs4783556	rs4783556	rs4783556	rs5756763	rs62274121	rs12642151	rs4733037	rs113761591	rs2256747	rs7117404	rs10930199	rs72649521	rs72649521	rs28401442	rs10818492	rs10818492	rs1029709	rs142448599	rs142448599	rs1029709
m.se	0.0120071	0.0120071	0.0103785	0.0153268	0.0158365	0.0158365	0.0167895	0.0092714	0.009615	0.0109789	0.0101144	0.0097197	0.0097197	0.0101144	0.0097197	0.0131949	0.0085443	0.0085443	0.0085443	0.0084602	0.0090692	0.0099206	0.008916	0.011044	0.0149618	0.0128939	0.0086253	0.0164561	0.0164561	0.0121642	0.0156445	0.0156445	0.0093498	0.0112578	0.0112578	0.0093498
#		0	ŝ	4	2	9	7	8	6	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36

SMR results

- 1. exposure: Histone peak (e.g. H3K4ME3_1234)
- 2. cpg.db: Source database from which the nearby CpG was retrieved
- 3. cpg.dist: Distance from the nearby CpG to the histone peak
- 4. cpg.id: CpG id (e.g. cg cg00029284)
- 5. h.be: Effect size of the histone peak
- 6. h.chr: Chromosome on which the histone peak is located
- 7. h.ea: Effect allele of the histone peak
- 8. h.eaf: Effect allele frequency of the histone peak
- 9. h.oa: Other allele of the histone peak
- 10. h.peak: Centre position of the histone peak within a chromosome (in bp)
- 11. h.pos: Histone peak position (in bp)
- 12. h.pval: Histone peak p-value
- 13. h.se: Histone peak standard error
- 14. h.snp: Histone peak SNP
- 15. h.snp.pos: Position of the histone peak SNP
- 16. h.width: Histone peak width
- 17. m.be: Effect size of the mQTL
- 18. m.chr: Chromosome on which the mQTL is located
- 19. m.ea: Effect allele of the mQTL
- 20. m.eaf: Effect allele frequency of the mQTL
- 21. m.oa: Other allele of the mQTL
- 22. m.pos: Position of the mQTL within a chromosome (bp)
- 23. m.pval: mQTL p-value
- 24. m.se: mQTL standard error
- 25. m.snp: mQTL SNP
- 26. m.snp.pos: Position of the mQTL SNP
- 27. mark: Histone PTM (or mark)
- 28. h.pval.mr: P-value for the peak-trait association after MR
- 29. h.pval.adj.mr: Adjusted p-value (Bonferroni) for the peak-trait association after MR
- 30. h.outcome.be: Effect size of the outcome for the histone peak
- 31. h.outcome.se: Standard error of the outcome for the histone peak
- 32. h.outcome.pval: P-value of the outcome for the histone peak
- 33. h.outcome.ea: Effect allele of the outcome for the histone peak
- 34. h.outcome.oa: Other allele of the outcome for the histone peak
- 35. h.outcome.eaf: Effect allele frequency of the outcome for the histone peak

- 36. m.pval.mr: P-value for the mQTL-trait association after MR
- 37. m.pval.adj.mr: Adjusted p-value (Bonferroni) for the mQTL-trait association after MR
- 38. m.outcome.be: Effect size of the outcome for the mQTL
- 39. m.outcome.se: Standard error of the outcome for the mQTL
- 40. m.outcome.pval: P-value of the outcome for the mQTL
- 41. m.outcome.ea: Effect allele of the outcome for the mQTL
- 42. m.outcome.oa: Other allele of the outcome for the mQTL
- 43. m.outcome.eaf: Effect allele frequency of the outcome for the mQTL