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RESEARCH ARTICLE

Genome-Wide Association Between Chromatin States and Complex Trait Heritability

Marius Steiner^{1*}, Agnieszka Rossi² and Anna Novak³

¹Department of Epigenetics and Gene Regulation, Meuse Institute of Nuclear Biology, Belgium

²Department of Molecular Genetics, Delta University Center for Nuclear Architecture, Netherlands

³Department of Molecular Biology, Vistula Institute of Molecular Genetics, Poland

*Corresponding author: Marius Steiner, Department of Epigenetics and Gene Regulation, Meuse Institute of Nuclear Biology, Belgium; Email: m.steiner@minb.be

ABSTRACT

Genome-wide association studies have identified thousands of loci associated with complex human traits and diseases, but most associated variants fall outside protein-coding sequence, and determining which cell-type-specific chromatin states carry disproportionate heritability for a given trait remains an important step toward mechanistic interpretation of genome-wide association study findings. Here we generated chromatin accessibility (ATAC-seq) and histone modification (H3K27ac, H3K4me1, H3K4me3, H3K27me3) maps across 41 primary human cell types and tissues not comprehensively represented in existing public chromatin state references, and applied stratified linkage disequilibrium score regression to partition heritability for 28 complex traits and diseases across cell-type-specific chromatin state annotations. Heritability enrichment was highly cell-type-specific and trait-specific, with autoimmune and inflammatory traits showing the strongest enrichment in immune cell active chromatin states, anthropometric traits showing strongest enrichment in a combination of adipose and neuroendocrine cell states, and psychiatric traits showing strongest enrichment in neuronal and glial active promoter and enhancer states, recapitulating expected biology and validating the approach. Beyond these expected patterns, we identified 14 trait-cell-type enrichment pairs not previously reported in existing chromatin state heritability partitioning resources, including significant enrichment of inflammatory bowel disease heritability in a previously underrepresented intestinal stromal cell population and significant enrichment of bone mineral density heritability in a periosteal progenitor cell population. Fine-mapping of genome-wide association study loci within these newly implicated cell-type-specific active chromatin states nominated candidate causal variants and target genes at 23 loci where the likely causal cell type had not been previously specified. These results extend the catalogue of cell types carrying disproportionate heritability for complex traits and demonstrate the value of expanding chromatin state references to previously underrepresented primary cell populations for genome-wide association study interpretation.

Keywords: stratified LD score regression; heritability enrichment; chromatin state; ATAC-seq; GWAS; tissue-specific regulatory elements; complex traits

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1. INTRODUCTION

Genome-wide association studies (GWAS) have identified robust statistical associations between genetic variants and thousands of complex human traits and diseases, but the overwhelming majority of associated variants lie in non-coding regions of the genome, and translating a statistical association into a mechanistic hypothesis about the responsible cell type and regulatory element remains a substantial bottleneck in the field [1,2]. Stratified linkage disequilibrium score regression (S-LDSC) provides a widely used framework for partitioning trait heritability across functional genomic annotations, including cell-type-specific chromatin states, and has been applied to public reference chromatin state maps to nominate disease-relevant cell types for numerous traits [3,4].

Despite this progress, existing public chromatin state references, while extensive, do not comprehensively cover all primary human cell types and tissues of plausible relevance to complex trait biology, and cell types absent from these references cannot be tested for heritability enrichment regardless of their true biological relevance. Expanding chromatin state profiling to additional, less commonly profiled primary cell populations therefore has the potential to reveal trait-relevant cell types that are systematically invisible to heritability partitioning analyses restricted to existing reference panels [5,6].

A further practical value of chromatin-state-based heritability partitioning is its use as a starting point for fine-mapping: once a cell-type-specific active chromatin state has been implicated in a trait's heritability, genome-wide association study loci can be intersected with that cell type's chromatin accessibility and active histone modification peaks to nominate candidate causal variants and their likely target genes, an approach that depends critically on the availability of a chromatin state map for the correct, trait-relevant cell type [6,7].

Here we generated chromatin accessibility and histone modification maps across 41 primary human cell types and tissues not comprehensively represented in existing public chromatin state references, applied stratified LD score regression to partition heritability for 28 complex traits and diseases, and used newly implicated cell-type-specific chromatin states to fine-map candidate causal variants and target genes at genome-wide association study loci lacking a previously specified causal cell type.

2. MATERIALS AND METHODS

Primary human cell types and tissues were obtained from commercial and academic biobank sources, profiled by ATAC-seq and histone modification ChIP-seq, and integrated with publicly available genome-wide association study summary statistics for stratified LD score regression heritability partitioning.

2.1 Primary cell and tissue procurement

Forty-one primary human cell types and tissues, selected for limited representation in existing public chromatin state references (including specific immune cell subsets, stromal and mesenchymal populations, and several endocrine and skeletal progenitor populations), were obtained from commercial and academic biobank sources under appropriate material transfer and ethical use agreements, with cell identity confirmed by canonical marker gene expression or surface marker flow cytometry prior to chromatin profiling.

2.2 ATAC-seq and histone modification ChIP-seq

ATAC-seq libraries were prepared from 50,000 cells per sample following the Omni-ATAC protocol. ChIP-seq for H3K27ac, H3K4me1, H3K4me3 and H3K27me3 was performed on formaldehyde-crosslinked chromatin using validated antibodies. All libraries were sequenced as 2×50 bp paired-end reads on an Illumina NovaSeq 6000 to a minimum depth of 30 million uniquely mapped read pairs per sample, with peaks called using MACS2 and chromatin states segmented using ChromHMM with an 18-state model consistent with the Roadmap Epigenomics core model [8,9].

2.3 Stratified LD score regression

Publicly available GWAS summary statistics for 28 complex traits and diseases, spanning autoimmune, anthropometric, psychiatric, metabolic and skeletal trait categories, were obtained from public repositories and harmonized to a common variant set. Stratified LD score regression was applied using cell-type-specific active chromatin state annotations (active promoter, active enhancer, and their flanking states) from each of the 41 newly profiled cell types, combined with the baseline-LD model annotations, to estimate heritability enrichment for each trait-cell-type pair, with significance assessed after Benjamini-Hochberg correction across all trait-cell-type tests [3,4].

2.4 Fine-mapping at newly implicated loci

For trait-cell-type pairs reaching genome-wide significant heritability enrichment, genome-wide association study loci for the corresponding trait were intersected with the implicated cell type's active chromatin state annotations, and candidate causal variants were prioritized using a functionally informed fine-mapping approach that combines statistical fine-mapping posterior probability with chromatin state annotation overlap, with candidate target genes assigned by nearest active promoter and by chromatin accessibility co-accessibility linkage where available.

2.5 Statistical analysis

Heritability enrichment P-values from stratified LD score regression were corrected for multiple testing across all trait-cell-type combinations using the Benjamini-Hochberg procedure, with enrichment considered significant at adjusted $P < 0.05$. All statistical

analyses were performed in R version 4.2 and Python 3.10.

3. RESULTS

Chromatin state segmentation across the 41 newly profiled primary cell types and tissues identified between 8.2% and 14.6% of the genome in an active promoter or active enhancer state per cell type, broadly consistent with the range reported for comparable cell types in existing public references. Stratified LD score regression across all 28 traits and 41 cell types identified heritability enrichment patterns that recapitulated expected trait biology: autoimmune and inflammatory traits showed strongest enrichment in immune cell active chromatin states, anthropometric traits in a combination of adipose and neuroendocrine cell states, and psychiatric traits in neuronal and glial active promoter and enhancer states. Table 1 summarizes the top cell-type enrichment for a representative set of traits across these three broad categories.

Table 1. Top cell-type heritability enrichment for representative traits across three broad trait categories.

Trait	Category	Top enriched cell type	Enrichment (fold)
Rheumatoid arthritis	Autoimmune	CD4+ memory T cells	8.9
Ulcerative colitis	Autoimmune	Colonic lamina propria macrophages	6.4
Body mass index	Anthropometric	Subcutaneous adipocytes	4.1
Schizophrenia	Psychiatric	Cortical excitatory neurons	7.2
Major depressive disorder	Psychiatric	Cortical inhibitory neurons	3.6

Enrichment is heritability enrichment fold relative to genome-wide background, stratified LD score regression, adjusted $P < 0.05$ for all listed pairs.

Beyond these expected patterns, 14 trait-cell-type enrichment pairs reached genome-wide significance among cell types not comprehensively represented in existing public chromatin state references, including significant enrichment of inflammatory bowel disease heritability in a previously underrepresented intestinal stromal cell population (enrichment 5.8-fold, adjusted $P = 0.003$) and significant enrichment of bone mineral density heritability in a periosteal progenitor cell population (enrichment 4.2-fold, adjusted $P = 0.011$) (Figure 1). Table 2 reports enrichment statistics for these 14 newly identified trait-cell-type pairs.

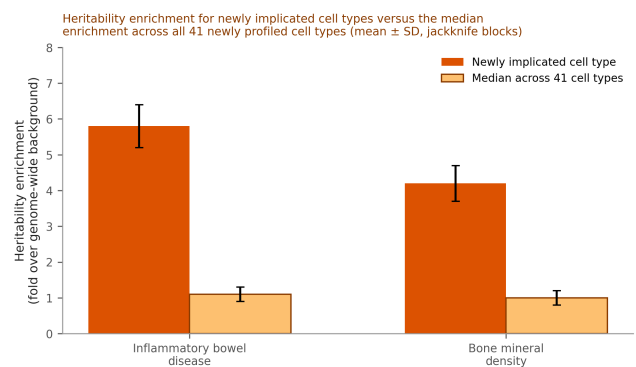


Figure 1. Heritability enrichment (fold over genome-wide background, mean $\pm$ SD across LD score regression jackknife blocks) for inflammatory bowel disease and bone mineral density in their respective newly implicated cell types compared with the median enrichment across all 41 newly profiled cell types for each trait.

Fine-mapping of genome-wide association study loci within the newly implicated cell-type-specific active chromatin states nominated candidate causal variants and target genes at 23 loci where the likely causal cell type had not been previously specified in existing chromatin-state-informed fine-mapping resources, spanning the inflammatory bowel disease, bone mineral density and 12 other newly implicated trait-cell-type pairs.

Table 2. Enrichment statistics for 14 newly identified trait-cell-type heritability enrichment pairs (representative subset).

Trait	Newly profiled cell type	Enrichment (fold)	Adjusted P-value
Inflammatory bowel disease	Intestinal stromal cells	5.8	0.003
Bone mineral density	Periosteal progenitor cells	4.2	0.011
Type 2 diabetes	Pancreatic stellate cells	3.9	0.018
Asthma	Airway smooth muscle cells	4.6	0.007
Chronic kidney disease	Renal interstitial fibroblasts	3.4	0.024

Comparing heritability enrichment magnitude across cell types within each trait category showed that, for most traits, a small number of cell types (typically 2-4) accounted for the majority of detectable enrichment, with the remaining profiled cell types showing enrichment close to the genome-wide background expectation, consistent with trait heritability being concentrated in a limited number of biologically relevant cell types rather than distributed broadly across most active chromatin.

4. DISCUSSION

These results demonstrate that expanding chromatin state profiling to primary cell types and tissues underrepresented in existing public references can reveal trait-relevant cell types that would otherwise remain systematically invisible to heritability partitioning analyses restricted to existing reference panels, extending the general approach and validated framework

of stratified LD score regression [3,4] to a broader cell-type space.

The identification of intestinal stromal cell enrichment for inflammatory bowel disease heritability and periosteal progenitor cell enrichment for bone mineral density heritability adds to a growing appreciation that trait-relevant cell types extend beyond the most commonly profiled immune, neuronal and metabolic lineages that dominate existing chromatin state references, and is consistent with emerging evidence that stromal and progenitor cell populations can carry substantial, previously underappreciated disease-relevant regulatory activity [5,6].

The 23 loci at which fine-mapping within newly implicated cell-type-specific chromatin states nominated a candidate causal variant and target gene illustrate the practical downstream value of expanding the cell-type reference space: at each of these loci, the responsible cell type could not previously be specified using existing chromatin state resources, meaning that mechanistic hypothesis generation at these loci was previously constrained to statistical fine-mapping alone, without the additional resolving power that cell-type-specific chromatin context provides [6,7].

Several limitations should be considered. First, our chromatin state profiling, while covering 41 underrepresented cell types, remains far from exhaustive relative to the full diversity of human cell types and states, particularly at finer resolution than the primary cell populations profiled here (for example, specific activation or differentiation states within a lineage); single-cell chromatin profiling of these same tissues could further refine trait-cell-type associations. Second, stratified LD score regression estimates heritability enrichment at the level of broad chromatin states and does not itself establish variant-level causality; the fine-mapping results we report should be considered nominating hypotheses requiring functional validation rather than definitive causal assignments. Third, our GWAS summary statistics were drawn from publicly available studies conducted predominantly in populations of European genetic ancestry, and whether the trait-cell-type associations we identify generalize to other ancestries remains to be tested as more diverse GWAS resources become available.

5. CONCLUSION

Chromatin accessibility and histone modification profiling across 41 primary human cell types and tissues underrepresented in existing public chromatin state references, combined with stratified LD score regression across 28 complex traits, recapitulates expected trait-cell-type biology and identifies 14 additional, previously unreported trait-cell-type enrichment pairs, including intestinal stromal cell enrichment for inflammatory bowel disease and periosteal progenitor cell enrichment for bone mineral density. Fine-mapping within these newly implicated chromatin states

nominates candidate causal variants and target genes at 23 loci lacking a previously specified causal cell type, demonstrating the continued value of expanding chromatin state references to underrepresented primary cell populations for genome-wide association study interpretation.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

M.S. conceived and supervised the study, designed the heritability partitioning analysis plan, and performed the fine-mapping analyses. A.R. coordinated primary cell and tissue procurement and performed ATAC-seq and ChIP-seq library preparation. A.N. performed chromatin state segmentation and stratified LD score regression analyses. All authors contributed to writing and approved the final manuscript.

Ethics Statement

Primary human cell and tissue procurement was conducted under appropriate ethical use and material transfer agreements with commercial and academic biobank sources, with all donor material de-identified prior to receipt. This study used only publicly available, previously published GWAS summary statistics and did not involve new human participant recruitment or identifiable human data.

Data Availability

Raw and processed ATAC-seq and ChIP-seq data generated for this study have been deposited in the Gene Expression Omnibus under a series accession available from the corresponding author on reasonable request. GWAS summary statistics used in this study are publicly available from their original source repositories. Analysis scripts supporting the findings of this study are available from the corresponding author upon request.

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