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# Comprehensive Identification of Pleiotropic Associations for Chronic Lymphocytic Leukemia

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# Comprehensive Identification of Pleiotropic Associations for Chronic Lymphocytic Leukemia

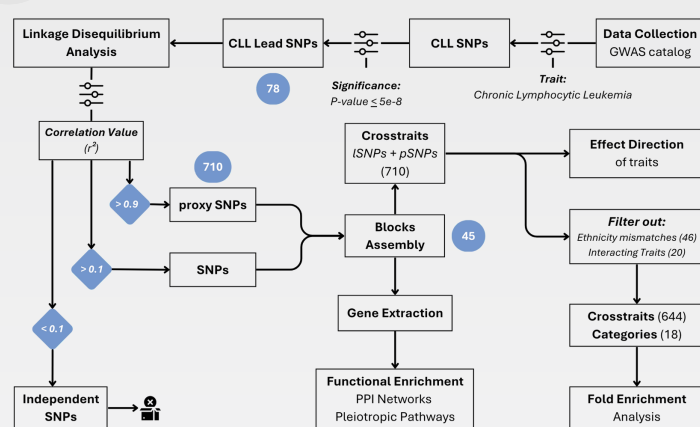
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## 1 Introduction

**Chronic Lymphocytic Leukemia (CLL)** is the most frequent type of leukemia in the western hemisphere [1]. Despite being an indolent B-cell disorder, it presents a wide array of possible clinical outcomes and can evolve aggressively [1]. Previous Genome-Wide Association Studies (GWAS) identified several genetic variants inherited at birth and predisposing to the development of CLL in later years [2]. Here we catalogue single nucleotide polymorphisms (SNPs) associated with CLL, which we map and extend by linkage disequilibrium across multiple genomic regions, and explore their pleiotropic potential, i.e. their involvement in other phenotypic traits and diseases.

## 2 Study Design



**Fig1. Overview of Leptin SNP and Cross-Trait Association Workflow**

### Data Sources and Tools



**GWAS Catalog** (NHGRI-EBI, GRCh38; last update: March 11, 2024) used for SNP-trait associations [3]



**R statistical software** (4.3.2) used in data handling and analysis [4]



**LDproxy** (NIH/LDlink): Identify correlated SNPs in given populations (proxySNPs) [5]

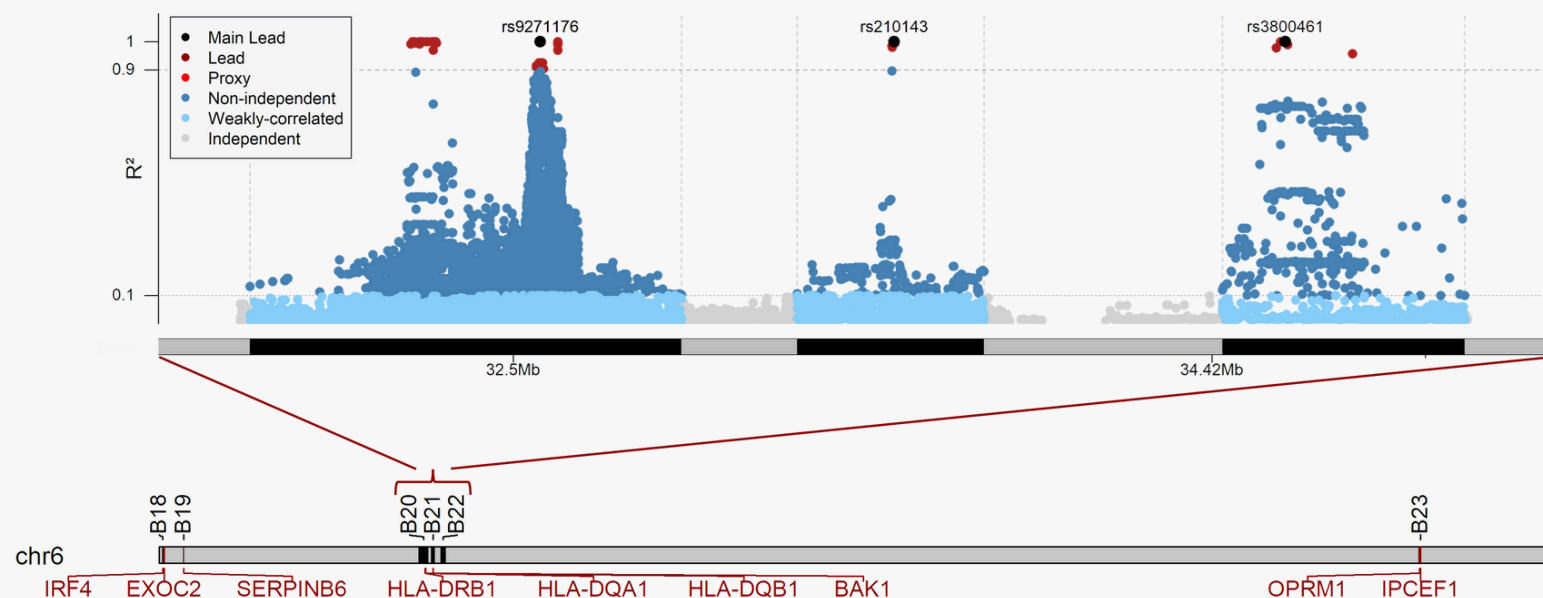
## 3 Results

### Lead and Proxy SNPs Identification

- 78 ISNPs associated with CLL at genome-wide significance ( $p < 5e-8$ )
- 710 pSNPs in strong Linkage Disequilibrium (LD) ( $r^2 > 0.9$ ) with ISNPs (ISNPs = lead SNPs; pSNPs = proxy SNPs)

### Genomic Block Distribution

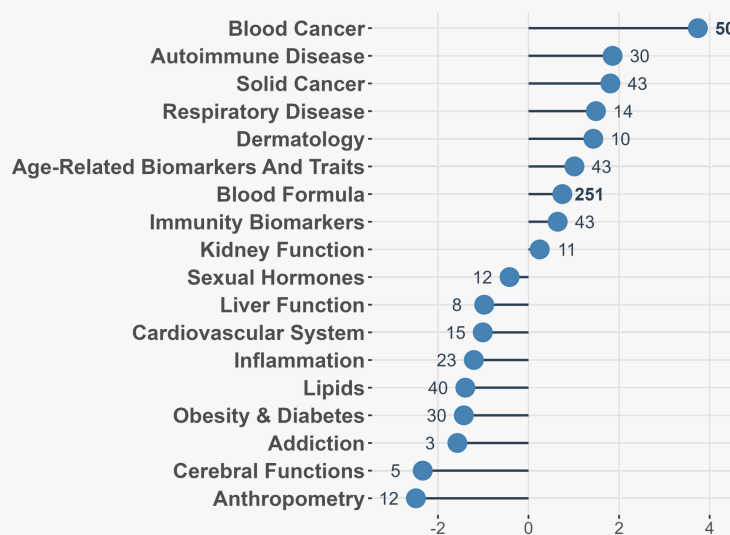
All variants clustered into 45 LD genetic blocks



**Fig2. Zoom on HLA Region: Genomic Block Structure and SNP Mapping**  
 Example selected due to the well-established role of HLA in CLL pathogenesis [6]

### Cross-Trait Filtering and Enrichment Analysis

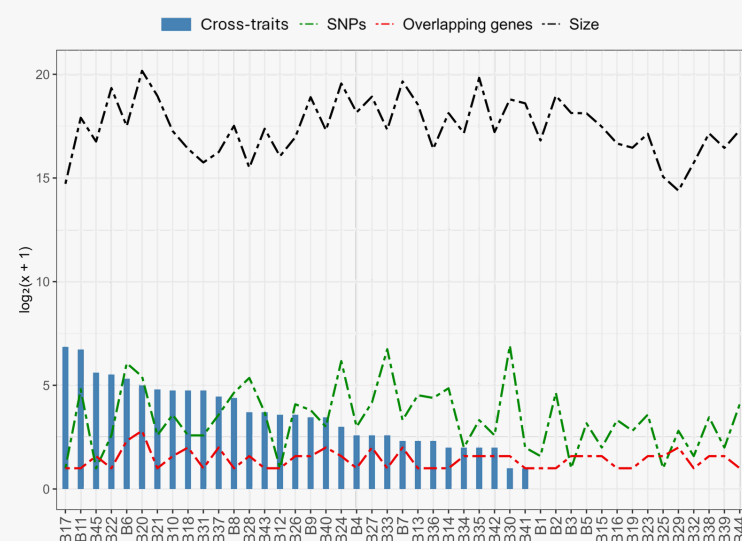
- 643 cross-traits**, grouped into **18 categories** (filters applied: ethnicity mismatches, cohort size -  $N > 1000$ , interaction studies)
- Trait-category fold-enrichment analysis followed the equation:
 
$$e = \frac{f_{\text{trait}}(\text{SNPs})}{f_{\text{trait}}(\text{GWAS})}$$
  - e: Fold enrichment
  - f: frequency
- Blood cancer** category largely over-represents traits related to **B-cell lymphoma** (including diffuse large B-cell lymphomas - DLBCL)



**Fig3. Enrichment of Categories Among Leptin-Associated SNPs**

### Pleiotropy Distribution Across Genomic Blocks

- Per-block distribution of l/pSNPs, cross-traits and overlapping genes
- Number of cross-traits does not follow a linear relationship with SNP count and/or block size



**Fig4. Distribution of Pleiotropy Among the Leptin Genomic Blocks**

- Some genes are highly pleiotropic while other only govern a function at a time.
- Approximately 2/3 of the blocks display pleiotropic potential

## 5 Conclusions

### Deeper Understanding of CLL Genetics Through Pleiotropic Mapping and Cross-Trait Associations

By revisiting the accumulated knowledge from **GWAS** and reconstructing the **pleiotropic associations** surrounding the **genetic architecture of CLL**, we confirmed findings **previously reported in observational studies** and genetically validated those described at a **physiological level**. Additionally, we identified **novel associations**—particularly with other **hematologic malignancies** and more **aggressive lymphomas**—broadening current insight into the **development and evolution of CLL**.

## 6 Next Steps

### Perspectives

The pipeline will be applied to investigate pleiotropy in *de novo* and secondary DLBCL, identify shared genetic susceptibility, and characterize functional pleiotropy and the underlying molecular pathways. Future directions include:

- GWAS** on **CLL**, **de novo** and **secondary DLBCL** in the UK-Biobank
- Estimation of **genetic overlap** between these disorders, with particular attention to the transformation of **CLL** into **Richter syndrome**
- Identification of overlap of **pleiotropic variants** and **genotype-phenotype associations** between the disorders
- Identification of **gene networks** and **biological functions** through **protein-protein interaction (PPI) network expansion**
- Causal inference via **Mendelian Randomization** and exploration of **gene-environment** interactions through **phenome-wide association studies** (pheWAS)

## 7 References

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