Systematic tissue and cell type-specific functional annotation highlights immune-related DNA elements for late-onset Alzheimer's disease

Qiongshi Lu[1,#], Ryan L Powles[2,#], Sarah Abdallah[3], Derek Ou[3], Qian Wang[2], Yiming Hu[1], Yisi Lu[4], Wei Liu[1], Shubhabrata Mukherjee[5], Paul K Crane[5], Hongyu Zhao[1,2]

[1]Department of Biostatistics, Yale School of Public Health; [2]Program of Computational Biology and Bioinformatics, Yale University; [3]Yale University School of Medicine; [4]Department of Immunobiology, Yale University; [5]Division of General Internal Medicine, Department of Medicine, University of Washington; [#]Equal Contribution

Identify tissue-specific functional genome

As complex disease research rapidly advances, evidence has emerged that disease-associated variants are enriched in regulatory DNA elements. Therefore, functional annotation of the non-coding genome is critical for understanding the genetic basis of human complex diseases. Here, we present **GenoSkyline-Plus**, an extension of our previous work through integration of an expanded set of epigenomic and transcriptomic annotations to produce high-resolution, single tissue annotations [1, 2] (**Fig 1**; also see poster #1702).

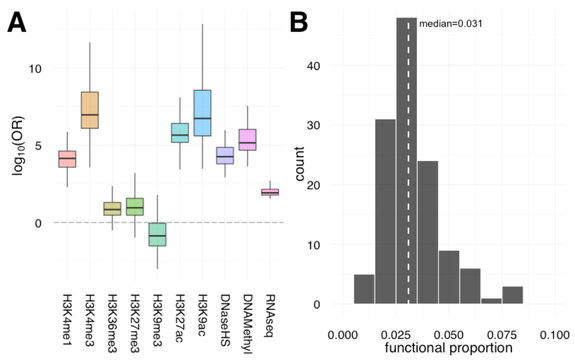


Figure 1. Basic characteristics of GenoSkyline-Plus annotation. (A) Odds ratio of predicting functionality. Each box represents the odds ratio for the same data type across 127 GenoSkyline-Plus tracks. **(B)** Histogram of predicted functional proportion across 127 annotation tracks. Dashed line marks the median functional proportion.

Stratify heritability by tissue and cell type for human complex traits

To demonstrate the ability of GenoSkyline-Plus to systematically provide novel insights into complex disease etiology, we jointly analyzed summary statistics from 45 GWAS (N_{total}~3.8M) and identified biologically relevant tissues for a broad spectrum of complex traits (**Fig 2**).

Additionally, we performed an in-depth case study of late-onset Alzheimer's disease (LOAD). Our analyses suggest a strong connection between LOAD heritability and genetic variants contained in regions of the genome functional in monocytes (**Fig 3**). Furthermore, we show that the localization of SNPs to monocyte functional regions suggests shared inheritance with Parkinson's disease (PD; **Fig 4**).

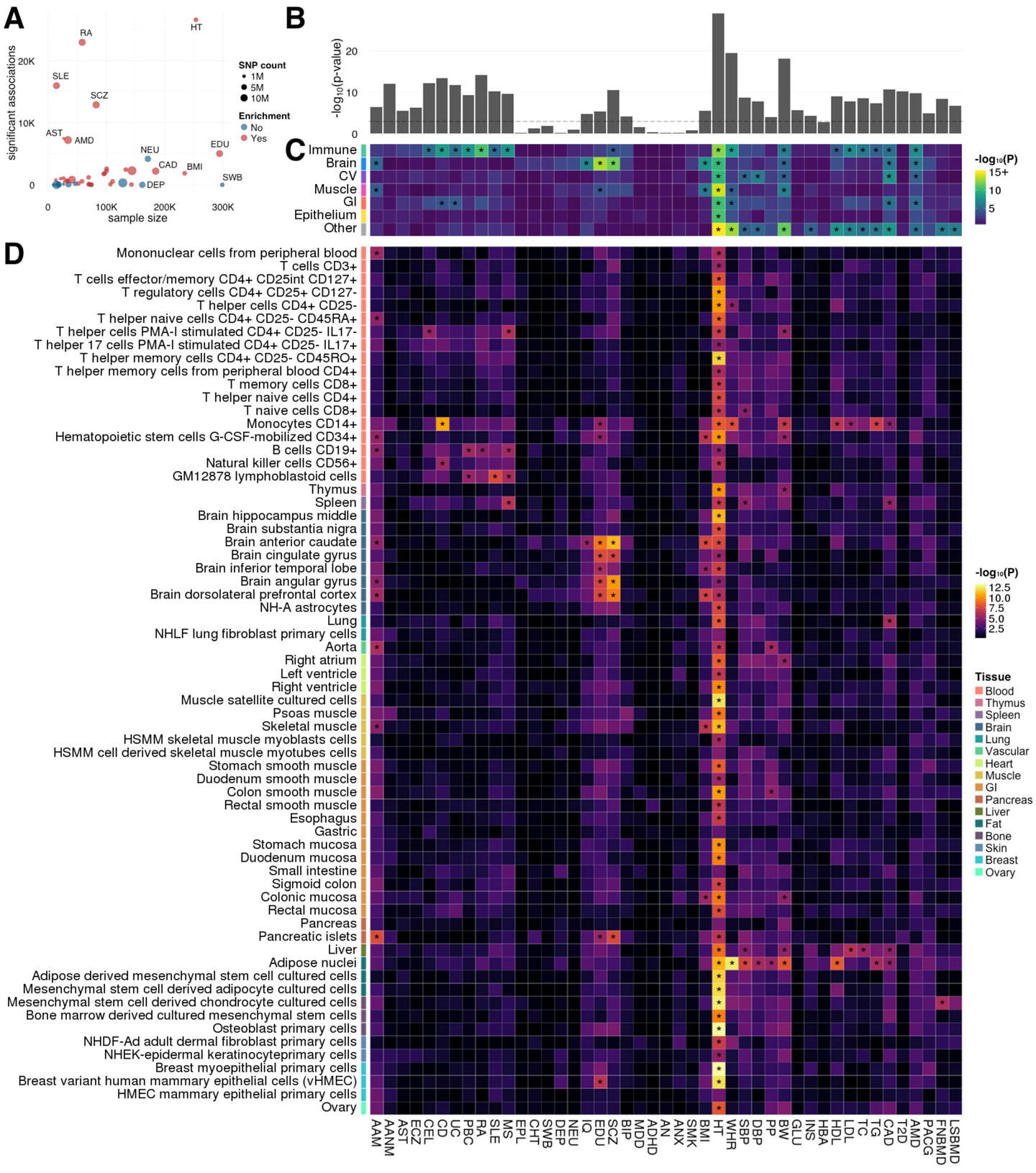


Figure 2. Enrichment analysis for 45 human complex traits. (A) Relationship between GWAS sample size, total count of significant associations, and signal enrichment in the functional genome. **(B)** Enrichment in the general functional genome predicted by GenoCanyon annotation. **(C)** Enrichment across 7 broadly defined tissue tacks. **(D)** Enrichment in 66 GenoSkyline-Plus tissue and cell tracks. Enrichment was estimated using LDSC [3].

Figure 3. Enrichment results for LOAD and PD. (A) Enrichment in 7 broadly defined tissue tracks. **(B)** Enrichment analysis using 66 GenoSkyline-Plus tissue and cell tracks. **(C)** Percentage of variants covered by each annotated category and percentage of heritability explained by variants in that category.

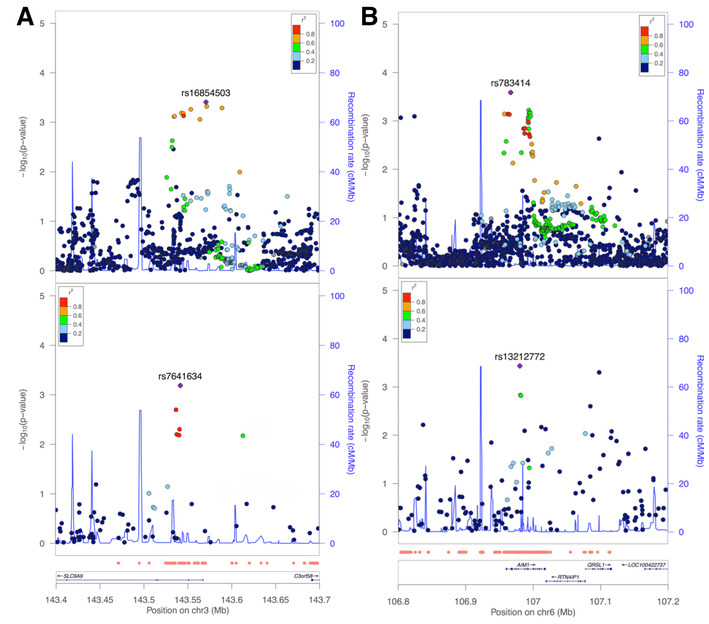


Figure 4. Identify pleiotropic effect between LOAD and PD. (A-B) Association peaks in candidate pleiotropic loci *SLC9A9* and *AIM1*. The upper and the lower panels represent associations for LOAD and PD, respectively. Monocyte-specific functional regions are highlighted by red dots above the gene annotations.

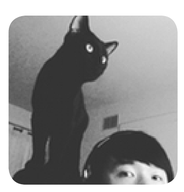
Summary

With the help of GenoSkyline-Plus annotations, we identified strong enrichment for LOAD and PD heritability in functional DNA elements related to innate immunity. In addition, our analysis clearly indicated that monocyte functional elements in particular appear to be highly relevant in explaining LOAD and PD heritability. Finally, we identified enrichment for shared genetic components between AD and PD in the monocyte functional genome, which hints at a shared neuroinflammation pathway between these two neurodegenerative diseases.

References

[1] Lu et al. (2016). Systematic tissue-specific functional annotation of the human genome highlights immune-related DNA elements for late-onset Alzheimer's disease. *bioRxiv*: 078865.
[2] Lu et al. (2016). Integrative tissue-specific functional annotations in the human genome provide novel insights on many complex traits and improve signal prioritization in genome wide association studies. *PLOS Genetics*, 12(4): e1005947.
[3] Finucane et al. (2015). Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nature Genetics,* 47(11), 1228-1235.

About me



@QiongshiLu

Qiongshi Lu is a PhD candidate in Biostatistics at Yale University. His research focuses on integrative functional annotations of the human genome and their applications in human genetics.