

BayesReCon: Exploring the disease-specific regulome of Alzheimer's Disease using a Bayesian predictive model

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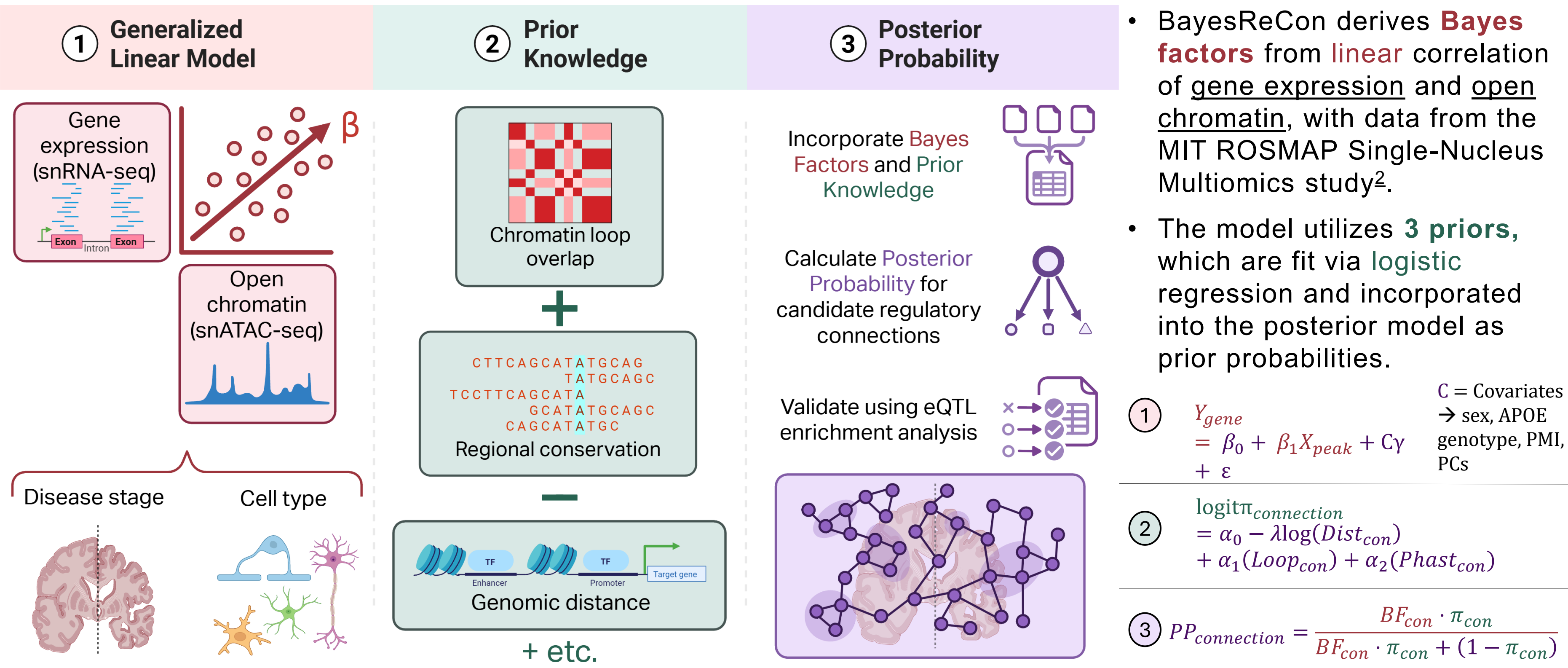
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BayesReCon is a Bayesian inference model designed to map cis-regulatory connections across diverse cell types and genomic landscapes. We used this model to examine the regulatory landscape across individuals with Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI) and No Cognitive Impairment (NCI), and identified novel cell-type-specific enhancer-gene interactions.

INTRODUCTION

- Gene expression dysregulation is a central driver of Alzheimer's Disease pathogenesis, resulting from the cumulative effects of expression-altering genetic variations.
- 90% of AD risk loci lie in noncoding regions of the genome, including promoters, enhancers and insulators¹.
- We use **BayesReCon** to identify cell-type-specific cis-regulatory connections to link GWAS risk loci to their target genes.

METHODS



FUTURE DIRECTIONS

1. Refine BayesReCon by implementing additional priors and optimizing prior coefficients. We aim to incorporate a co-accessibility prior examining enhancer-promoter interactions corroborated by ROSMAP snATAC-seq consensus peaks.
2. In vitro CRISPRi perturbation study. We plan to utilize CRISPR droplet sequencing (CROP-seq) to investigate candidate cis-regulatory connections prioritized using BayesReCon. ReNCell VM³, an immortalized human neural progenitor cell line, provides a robust system for this study, as the cells can be readily differentiated into networks of neurons and glia.

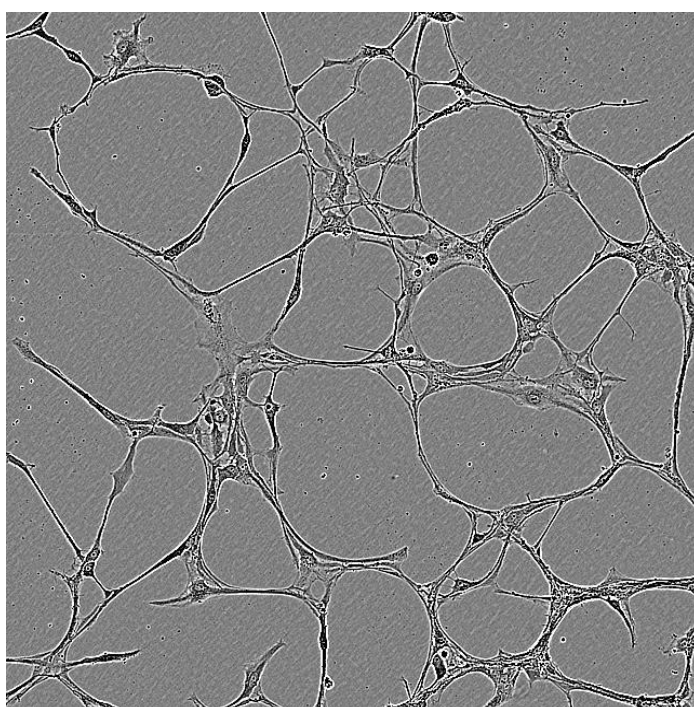


Figure 4: Differentiated ReNCell culture.

RESULTS

Examining BayesReCon Priors

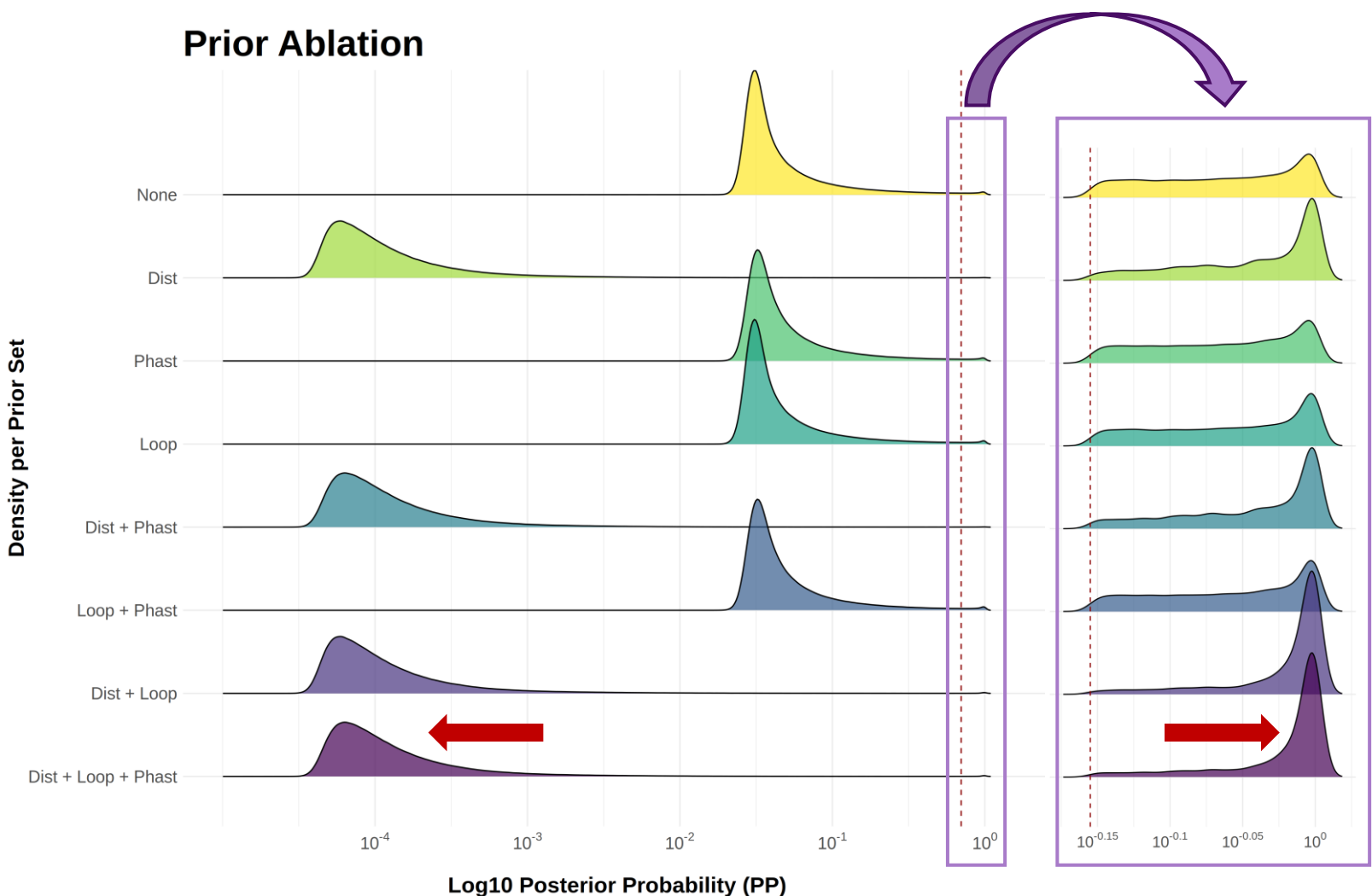


Figure 1: Density plot of prior ablation analysis for all genes in NCI excitatory neurons. The Distance prior alone minimizes the posterior probability of low-confidence connections. The Distance and Loop priors combined maximize the posterior probability of high-confidence connections. The red dotted line indicates a threshold of PP > 0.7.

eQTL Enrichment Analysis

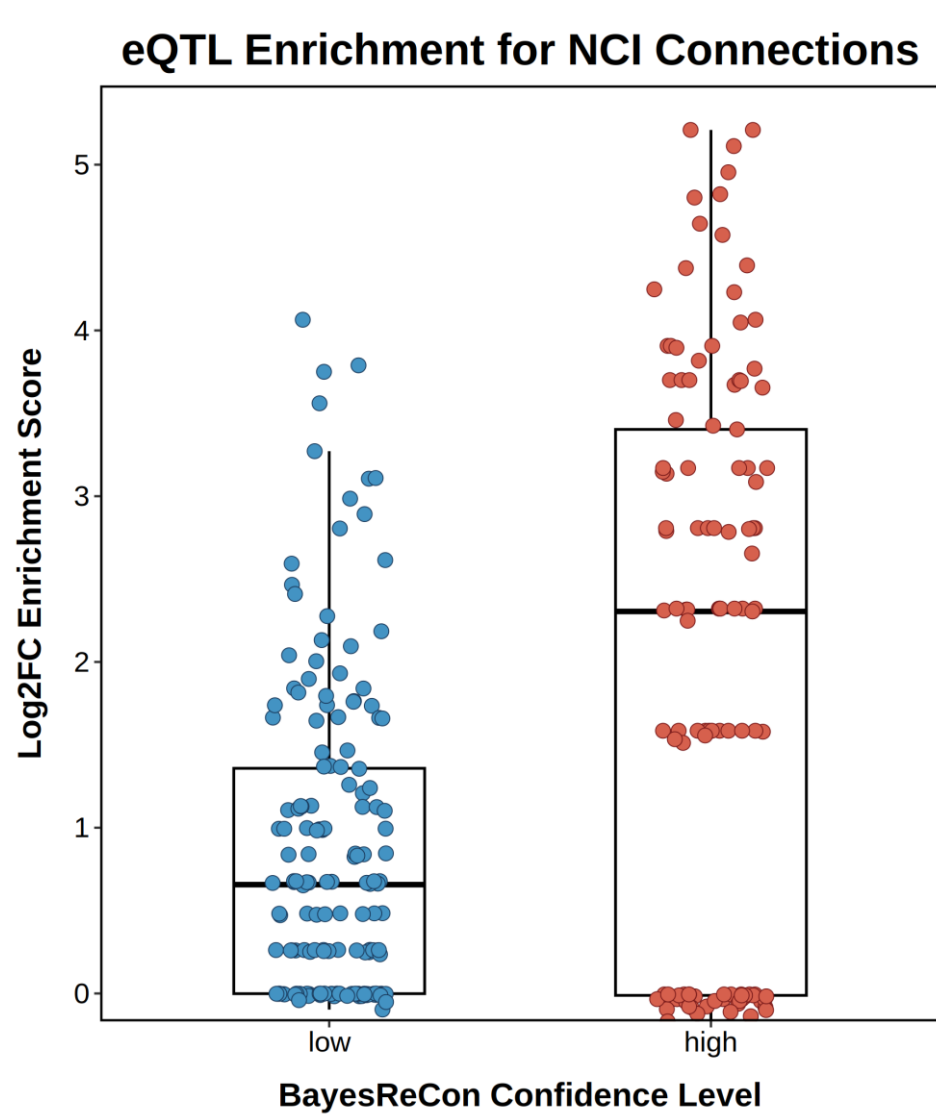


Figure 2: eQTL enrichment analysis of high- and low-confidence BayesReCon interactions in NCI samples. For the same set of eGenes, high-confidence predictions tend to show greater eQTL enrichment than low-confidence predictions.

Predicting Cis-regulatory Connections with BayesReCon

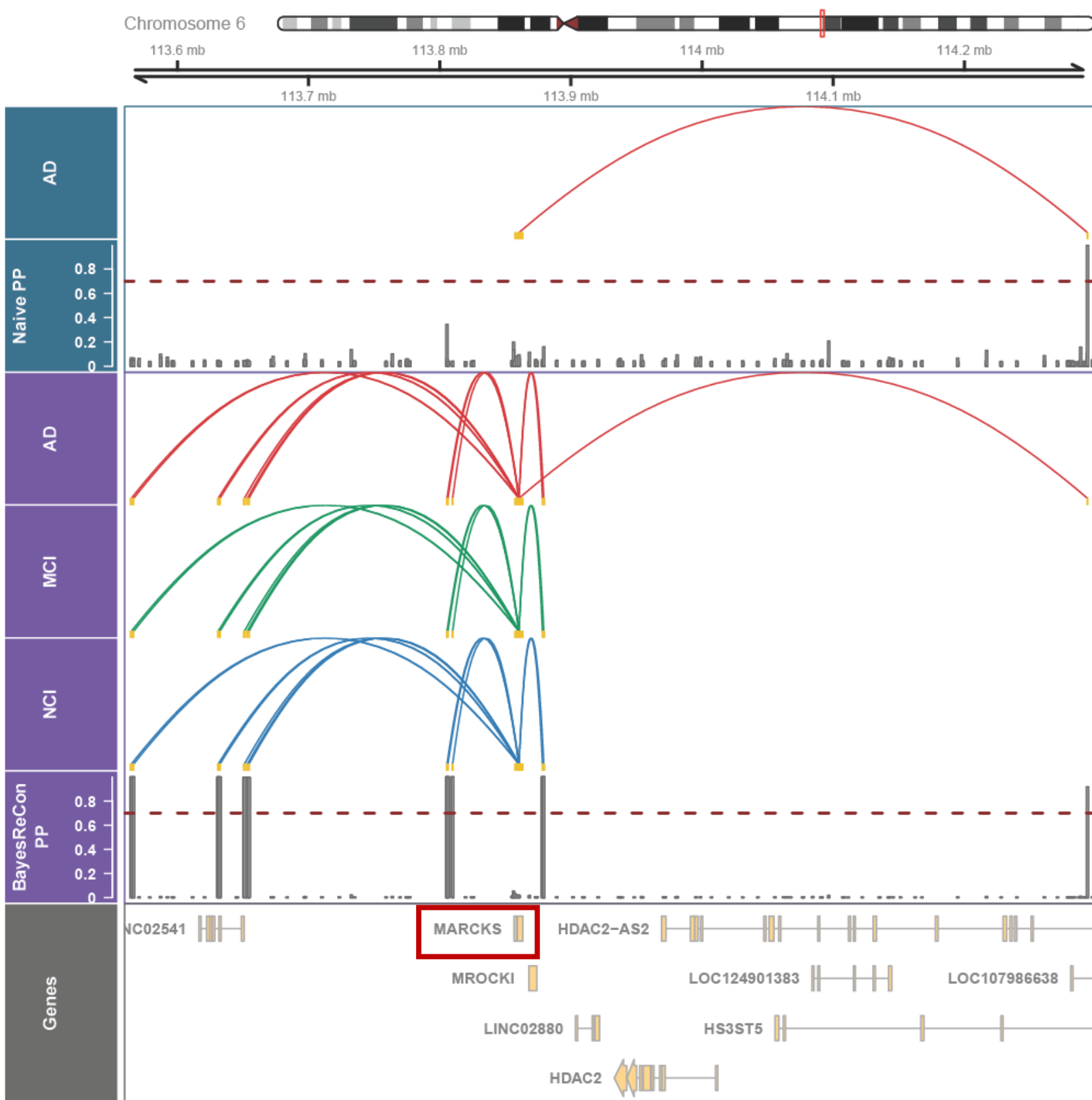


Figure 3: Predicted cis-regulatory interactions for the MARCKS gene in microglia. BayesReCon predicts new interactions that the naive model alone is underpowered to detect. The novel connections identified by BayesReCon are common among all disease stages, while the single AD-specific interaction prevails in both models.

REFERENCES

1. Watanabe K, Stringer S, Frei O, Umičević Mirkov M, de Leeuw C, Polderman TJC, van der Sluis S, Andreassen OA, Neale BM, Posthuma D. A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet.* 2019 Sep;51(9):1339-1348.
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