BDR SEMINAR via Zoom

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Tuesday, May 31, 2022

9:30-10:30

Zoom meeting URL will be announced on the event day by e-mail.

※This seminar is only for BDR members.

Expanding massively parallel reporter assay to identify human variants that impact regulatory elements

Summary

Genome wide studies have identified a number of non-coding loci associated with human traits. However, pinpointing causal variant(s) from a haplotype block with high linkage disequilibrium remains difficult. To address this challenge, we applied Massively Parallel Reporter Assay (MPRA), which characterizes non-coding elements at scale and measures allelic differences of their activity.

First, we performed MPRA to test ~18,000 variants associated with autoimmune diseases. By examining variants that showed allele specific activity and chromatin accessibility in T cells, we identified putatively causal variants that enriched for statistically fine-mapped variants. To validate this prioritizing method, we deleted an orthologous sequence of rs72928038 in mice, resulting in reduced expression of genes for T cell stemness and higher propensity to differentiate effector T cells upon acute viral infection.

Second, to characterize repressive elements, for which standard MPRA is not optimized, we also engineered MPRAduo that detects the interaction of two non-coding elements in a vector. We comprehensively characterized human RE1 silencers under combinations with different enhancers, identifying ~1,500 variants that impact RE1 silencer. Furthermore, we found principles of REST binding motif for functional silencer, cofactor binding profile, and grammar for non-canonical REST binding motifs.

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