The 162nd RIKEN BRC SEMINAR

November 28, Monday, 2022, 16:00-17:00

(by Zoom, English seminar)

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"Identifying human regulatory variants using massively parallel reporter assays"

Abstract

Genome wide studies have identified a number of non-coding loci associated with human traits. However, pinpointing causal variant(s) is difficult mainly due to their high linkage disequilibrium. To address this challenge, we applied Massively Parallel Reporter Assays (MPRA), which characterize non-coding elements at scale and measures allelic differences of their activities.

First, we characterized ~18,000 variants associated with autoimmune diseases using MPRA in human T cells. By examining variants that showed allele specific activity and chromatin accessibility in T cells, we identified 60 putatively causal variants that enriched for statistically fine-mapped variants. We validated this prioritizing method by making a mouse model which has a deletion of the sequence homologous to a human variant at Bach2 locus: the mouse showed differential expression of T cell stemness genes and higher propensity to differentiate effector T cells upon acute viral infection.

Second, we engineered MPRAduo, which examines *cis*-interactions of two non-coding elements. Our pilot experiment showed that MPRAduo can characterize repressive elements under multiple combinations with an activating element. Then, we comprehensively characterized human REST binding sites (RE1 silencers) using MPRAduo, identifying ~1,500 variants that impact silencer activity. Furthermore, we revealed principles of REST binding motif, cofactor binding profiles, and the grammar of non-canonical REST binding motifs for a functional silencer.

Chaired by Toshihiko Shiroishi

The Zoom connection address will be sent to those who apply.

For applications and inquiries, please contact;

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