**Experience on Genome-wide identification of candidate enhancers:**

We have extensive experience in predicting high-confidence candidate enhancers for downstream functional analysis. Prior to inputting the data into our machine learning algorithms for candidate enhancer identification (described below), we process the datasets using tools developed in our lab, namely PeakSeq (69) and MUSIC (70), which have been applied by the ENCODE consortium and to ENCODE and Roadmap Epigenomics Consortium (RMEC) data.

As part of the ENCODE and modENCODE projects, Gerstein lab has developed methods that integrate ChIP-seq, chromatin, conservation, sequence and gene annotation data to identify gene-distal enhancers(73), which they have partially validated(74). In addition, the Gerstein lab has also developed a tool that utilizes the pattern within the histone marks to predict active regulatory regions in each tissue or cell line.

**Experience in Characterizing Variation in Enhancer Predictions:**

We have extensively analyzed patterns of variation in noncoding regions, along with their coding targets, creating the tool ncVAR for assessing genetic variation in TFBSs (75). In recent studies (62), we

have integrated and extended these methods to develop a prioritization pipeline called FunSeq (and

subsequently FunSeq2). FunSeq prioritizes variants with respect to their deleterious impact on many different types of noncoding functional elements, including TF binding sites, regulatory elements, and regions of open chromatin. It identifies the regions under strong selective pressure as estimated using the variant frequencies computed from the whole genome sequencing data in 1000 Genomes Project and uses these regions as sensitive and ultra-sensitive non-coding regions of the genome. For each noncoding mutation in a regulatory element, FunSeq analyzes the target of the affected regulatory element. Then it scores the impact of the variants and prioritizes them based on a number of factors like network connectivity and motif disruption. It identifies deleterious variants in many noncoding functional elements, including TF binding sites, enhancer elements, and regions of open chromatin corresponding to DNase I hypersensitive sites. We thus use FunSeq to annotate candidate enhancers.

We have also extensively characterized the regulatory elements in terms of their association with human diseases. On this front, we have developed LARVA that can identify recurrently damaging non-coding mutations and prioritize them with respect to their significance. To estimate significance, LARVA utilizes models that estimate background mutation frequencies in non-coding elements using as features the functional genomics datasets from ENCODE and RMEC projects. We have extensively used the whole genome sequencing datasets from 1000 Genomes Project, and polymorphism datasets from dbSNP and Exome Aggregation Consortium (ExAC) projects as reference backgrounds to filter out the non-causative mutations. We have integrated the tissue specific expression quantitative trait datasets (eQTL) from GTex Project to generate evidence for the causal variants.

**Experience on Linking Candidate Enhancers to Targets:**

We have previously developed computational pipelines for identification of targets of candidate regulatory elements, including methods that can successfully identify targets for gene-distal and gene-proximal regulatory

elements. Our methods utilize the correlation between the gene expression levels and the activity of the

regulatory element to identify significantly correlating activity. We also utilize sets of chromatin conformation datasets, generated from experiments including 4C, 5C, Hi-C, and ChIA-Pet. Furthermore, the Gerstein lab recently developed a method, named ENGINE, for utilizing these datasets in a machine learning framework for assigning targets to regulatory elements. ENGINE is a new version of the component of FunSeq that performs enhancer-target matching (<http://papers.gersteinlab.org/papers/funseq2>). In particular, the conformation datasets narrow down the possible targets of candidate enhancers to a subset of regions in which each candidate enhancer interacts. Specifically, ENGINE computes the correlation of the activity at the candidate enhancer region (using ENCODE and RMEC datasets) with the expression levels of the genes that each candidate enhancer region has contact with. Then, ENGINE uses the expression levels and several statistics about the shapes of the histone modification and transcription factor binding signals as additional features and builds a random forest based prediction model to score the candidate target genes. We have utilized the validated sets of enhancer-target gene linkages for training ENGINE. In our previous efforts, we have utilized ENCODE data to build a set of such linkages between candidate regulatory elements and their target genes.

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