Linking GWAS risk variants to disease genes by epigenomic mapping and prediction of functional enhancer-promoter interactions

Yuchun Guo, Gokul Ramaswami, Guanjue Xiang, Linhui Chen, Bryan Matthews, Jenna Weinstein, Brynn Akerberg, Yuting Liu, David Bumcrot

CAMP4 Therapeutics, Cambridge, MA, USA

Motivation

- ❑ Majority of GWAS loci are noncoding, strongly enriched in gene regulatory elements such as enhancers.
- ❑ Identifying the genes regulated by these enhancers promises to reveal disease mechanisms.
- ❑ However, it remains a major challenge to link functional enhancers to their target genes.

Approach

Enhancer-promoter interaction characterization (EPIC) is a machine learning model for predicting functional enhancer-promoter (E-P) pairs.

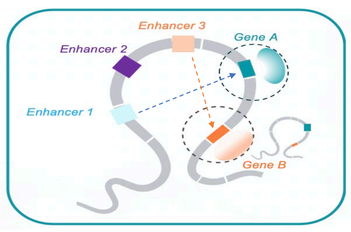
(Gasperini et al., 2019; Xie et al., 2019)

K562 enhancer epigenomic and chromatin interaction features

K562 CRISPR-based enhancer perturbation screening

EPIC: a machine learning model

Infer



Enhancer 1 – Gene A: Yes
Enhancer 2 – Gene A: No
Enhancer 3 – Gene B: Yes
…

Basic features

- HiChIP.AnchorSize: AnchorSize = 5kb, 10kb, 15kb, or 20kb (n=4)
- Assay.Position.WindowSize, where Assay=ATAC, H3K27ac, H3K4me1, H3K4me3, EP300, CTCF, or Input ChIP; Position = Enh or TSS; WindowSize = 300bp, 500bp, 1kb, 2kb, or 4kb (n=7*2*5=70)
- Genomic distance (n=1)

Feature engineering

APMI = $(ATAC.Enh.1kb * EP300.Enh.1kb * H3K4me1.Enh.4kb)^{1/3} * HiChIP.5kb$

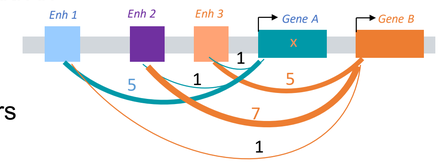
Based on APMI, we engineered a new set of features for quantifying the relative contribution of an enhancer ***e*** to a gene ***g*** from the gene perspective or enhancer perspective:

$$fracGene_{eg} = \frac{APMI_{eg}}{\sum_j APMI_{jg}}$$

where j indexes all the enhancers connected to gene ***g***.

$$fracEnh_{eg} = \frac{APMI_{eg}}{\sum_k APMI_{ek}}$$

where k indexes all the genes connected to enhancer ***e***.



	Enh1 - GeneA	Enh3 -GeneB
fracGene	$\frac{5}{1+1+5} = 0.71$	$\frac{5}{1+5+7} = 0.42$
fracEnh	$\frac{5}{1+5} = 0.83$	$\frac{5}{1+5} = 0.82$

In addition, we combined these features to form new features.

$$fracGmE_{eg} = fracGene_{eg} * fracEnh_{eg}$$

$$fracGpE_{eg} = fracGene_{eg} + fracEnh_{eg}$$

$$apmiGene_{eg} = fracGene_{eg} * APMI_{eg}$$

$$apmiEnh_{eg} = fracEnh_{eg} * APMI_{eg}$$

$$apmiGmE_{eg} = fracGmE_{eg} * APMI_{eg}$$

$$apmiGpE_{eg} = fracGpE_{eg} * APMI_{eg}$$

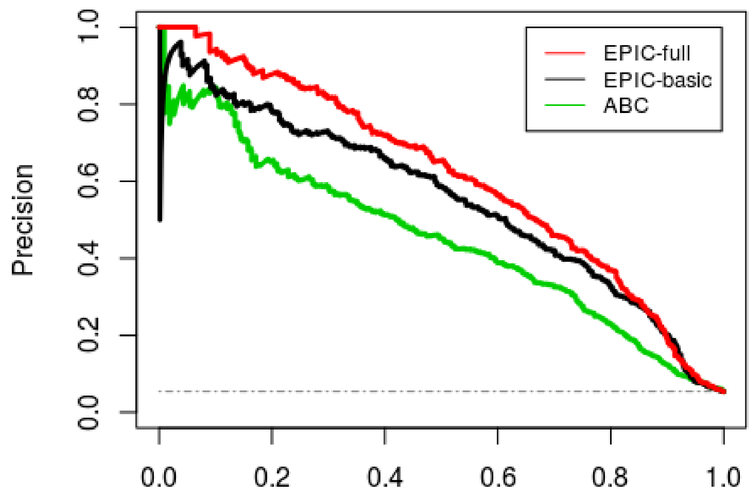
Machine learning model

- Random forest classification model trained on K562 data
- Five-fold cross-validation
- Genetic algorithm for feature selection

Results

EPIC outperforms ABC model in predicting enhancer-promoter pairs (holdout test data)

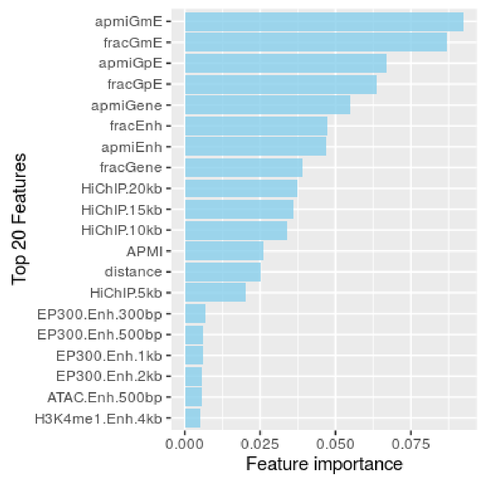
ABC = $(ATAC.Enh.500bp * H3K27ac.Enh.500bp)^{1/2} * HiC.5kb$ (Fulco et al., 2019)



Model	AUPR	AUROC
EPIC-full	**0.613**	**0.918**
EPIC-basic	0.551	0.912
ABC	0.451	0.885

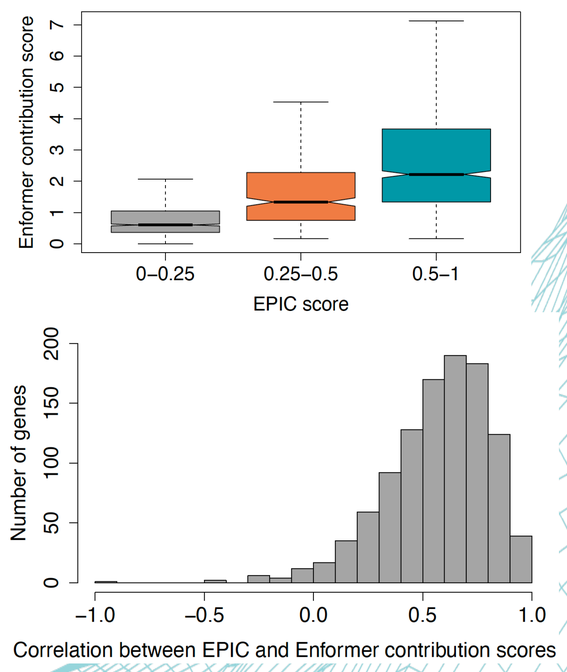
- The area under receiver operating characteristic (AUROC) curve of EPIC-full is significantly higher than that of ABC (p = 1.6e-10) (DeLong, et al., 1988).
- The AUROC of EPIC-full is significantly higher than that of EPIC-basic (p = 0.01), demonstrating the value of feature engineering.

Engineered features rank highest in feature importance



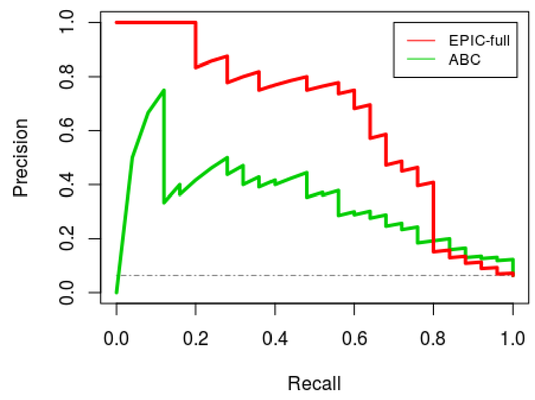
E-P interaction scores are concordant between EPIC and Enformer

- Enformer is a deep learning model that predicts gene expression and chromatin states from DNA sequence (Avsec, et al., 2021).
- Enformer contribution scores for hepatocyte enhancers are consistent with EPIC scores on an overall and gene-by-gene basis.



EPIC outperforms ABC model in linking GWAS loci to causal genes in a new cell type

- We generated epigenomic data in human primary hepatocytes and discovered about 30,000 E-P interactions using EPIC.
- Evaluate prediction of causal genes for liver-related GWAS loci using a curated set of "gold standard" locus-gene pairs (Mountjoy, et al., 2021)
  - ➢ Positive: GWAS locus-gene pairs in the gold standard set
  - ➢ Negative: GWAS loci connecting to other genes within 500kb



EPIC
- AUPRC=0.643
- AUROC=0.879
- 80% precision at 50% sensitivity

ABC model
- AUPRC=0.337
- AUROC=0.877
- 40% precision at 50% sensitivity

Linking liver-related GWAS loci to putative target genes

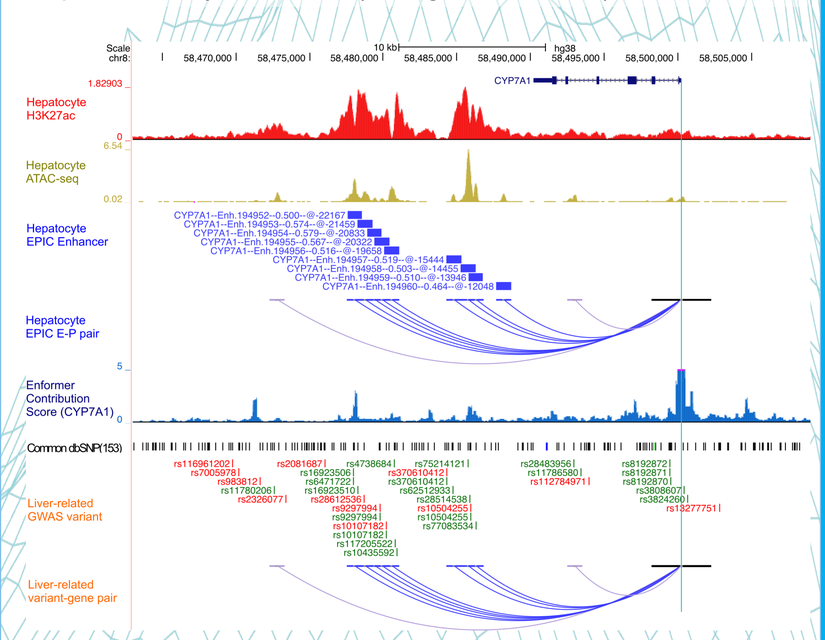
661 lead variants

1408 fine-mapped variants

997 EPIC E-P pairs

481 genes

Enhancers for CYP7A1 overlap with fine mapped variants across 15 lead SNPs representing associations from 32 GWAS studies of cholesterol (total, LDL, HDL), triglyceride levels, cholelithiasis, and cholestasis. CYP7A1 is a well characterized enzyme regulator of bile acid and cholesterol homeostasis and these enhancers have been experimentally validated (Wang, et al., 2018).



Conclusions

- ❑ EPIC enables accurate cell-type-specific prediction of functional E-P interactions using epigenomic data.
- ❑ EPIC outperforms an established method in predicting E-P interactions and in linking GWAS loci to causal genes in a new cell type.
- ❑ Applying EPIC to diverse human cell types may help discover disease-causing genes and enable development of novel therapeutics that target enhancers of disease-related genes.