Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning (DeepBind)

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University of Virginia

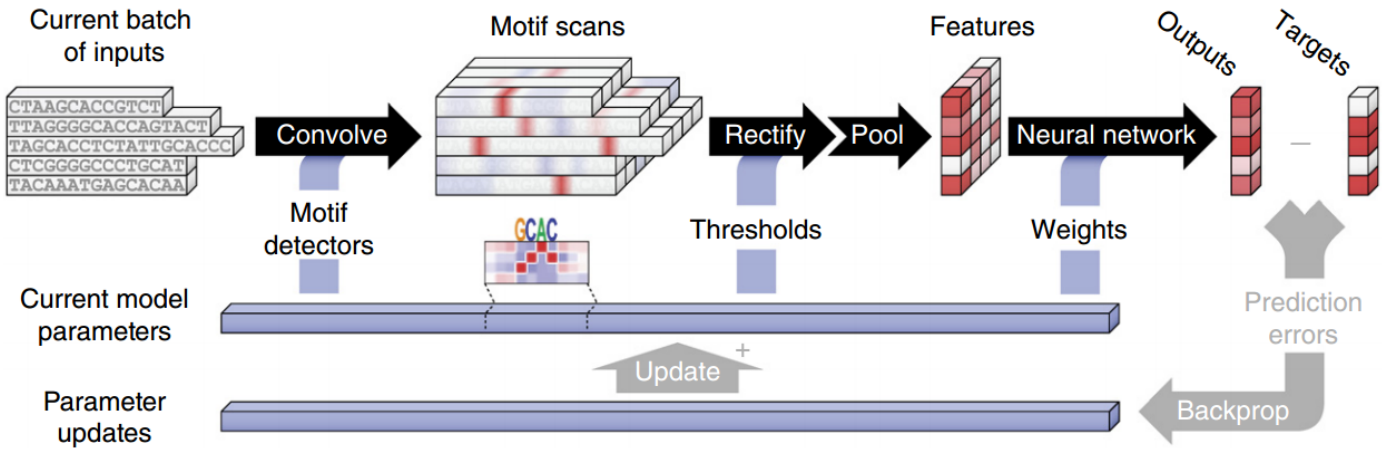
https://qdata.github.io/deep2Read/

Nature Biotech, 2015

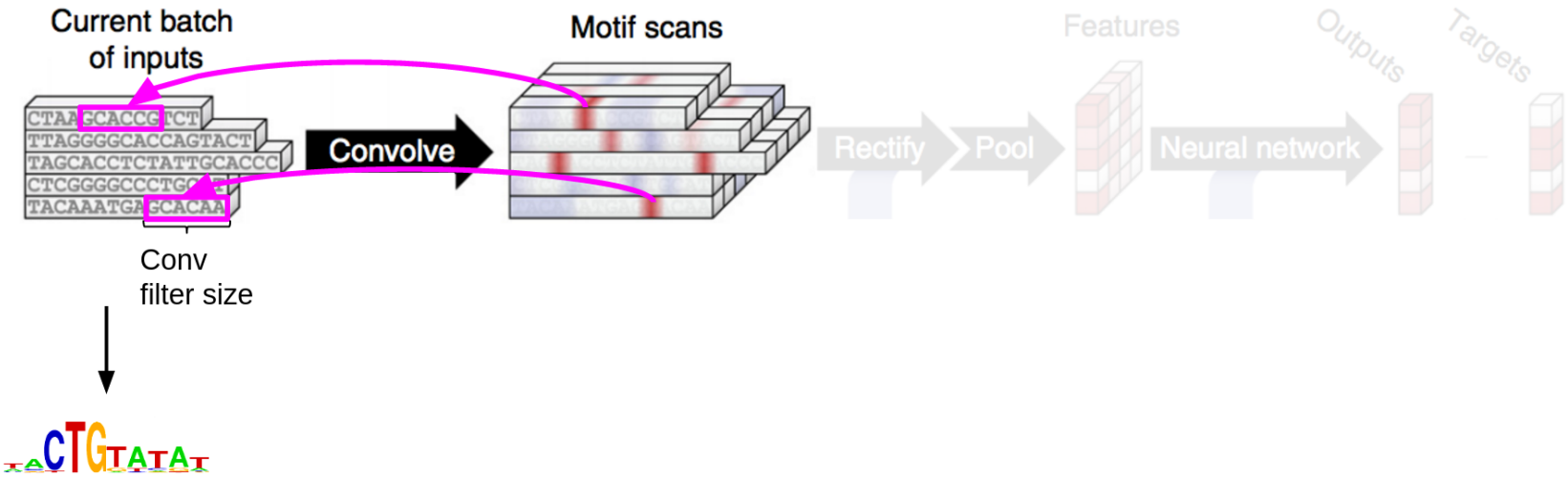
Overview

1. Predict TFBSs in vivo using ChIP-Seq Data with 1-layer CNN
2. Extract TF-specific motifs using CNN kernel activations
3. Analyze SNPs with mutation maps by varying individual nucleotides

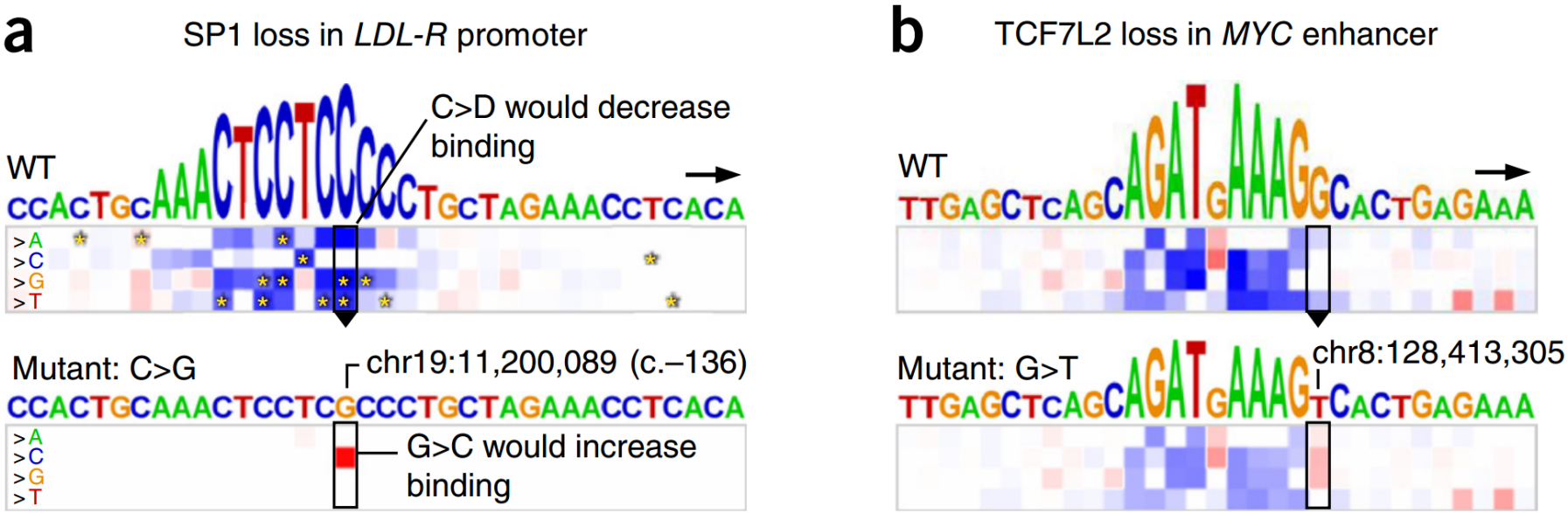
1. Predict TFBSs in vivo using ChIP-Seq Data with CNN



2. Extract TF-specific motifs using CNN kernel activations



3. Analyze SNPs with mutation maps by varying individual nucleotides



Predicting effects of noncoding variants with deep learning based sequence model (DeepSEA)

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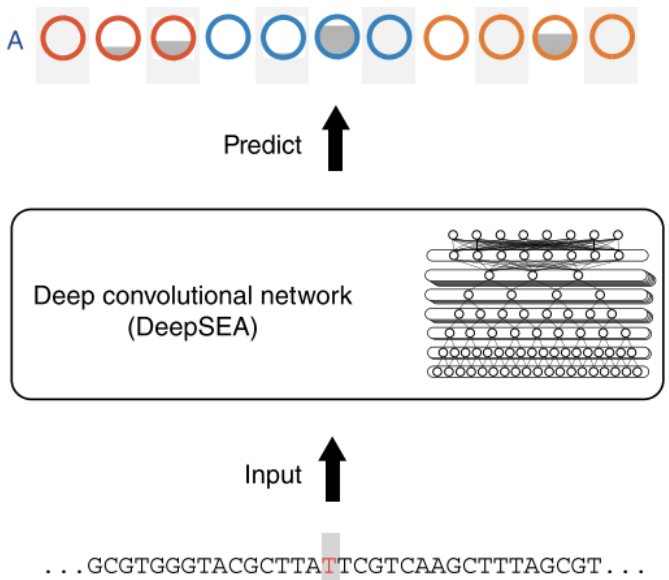
Nature Methods, 2015

Overview

1. Train and predict TFBS, HM, and DHS from raw sequence
2. Use chromatin predictions to predict variant effects of two separate allele input sequences

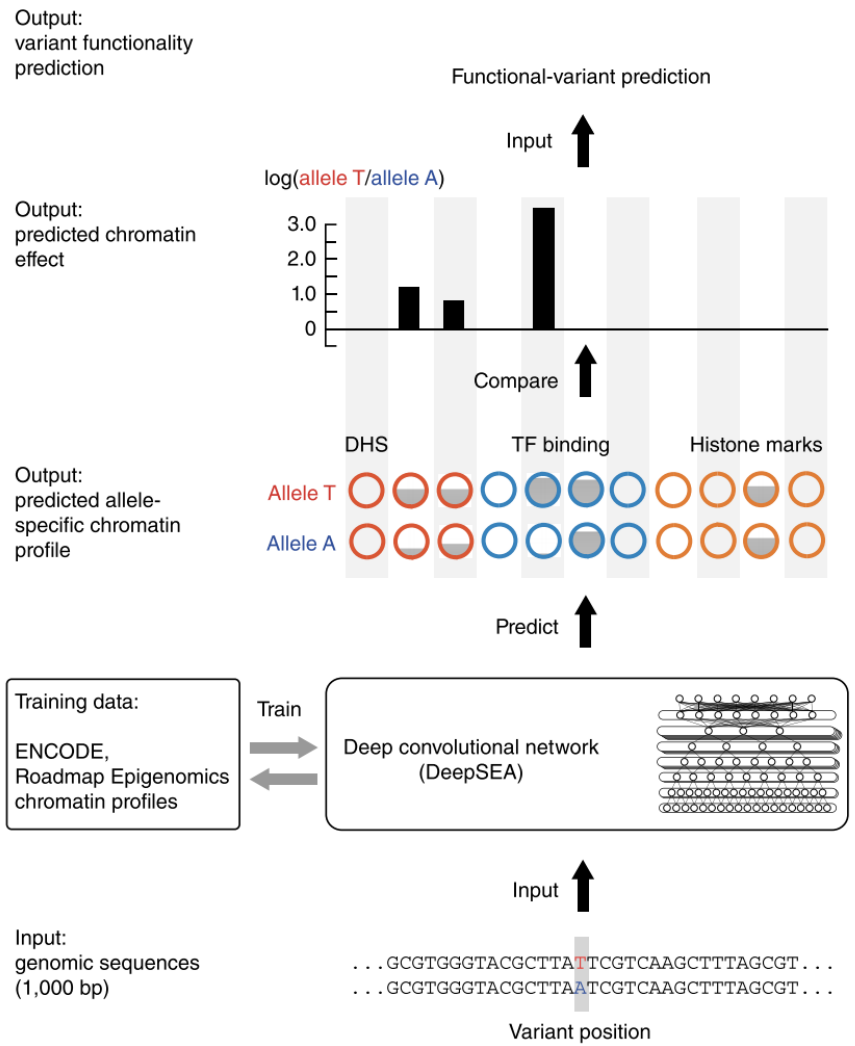
Task 1

- Input: 1000 length sequence
- Output: binary classification of: 690 TF binding profiles (160 different TFs), 125 DHS profiles and 104 histone mark profiles (total of 919 chromatin features).



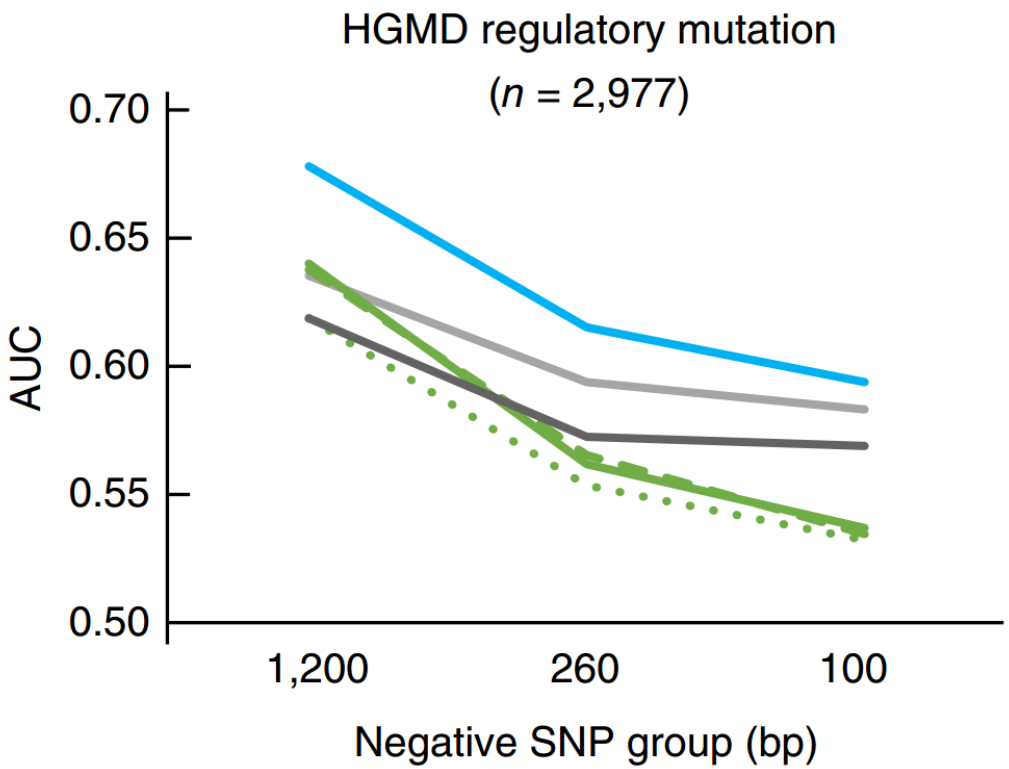
Task 2

- Input: Two 1000 length sequences (Allele A and Allele B)
- Output: Functional variant = yes/no



Results

- TFBS median AUC = 0.958
- DHS median AUC = 0.923
- HM median AUC = 0.856



Basset: learning the regulatory code of the accessible genome with deep convolutional neural networks

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Genome Research, 2016

Overview

1. Predict DHS signals from raw sequence using CNN
2. Extract motifs from filters - match filters to known TF motifs using TomTom
3. Predict the effect of SNP mutations on DHS signals

The Genetics of Transcription Factor DNA Binding Variation

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Cell, July 2016

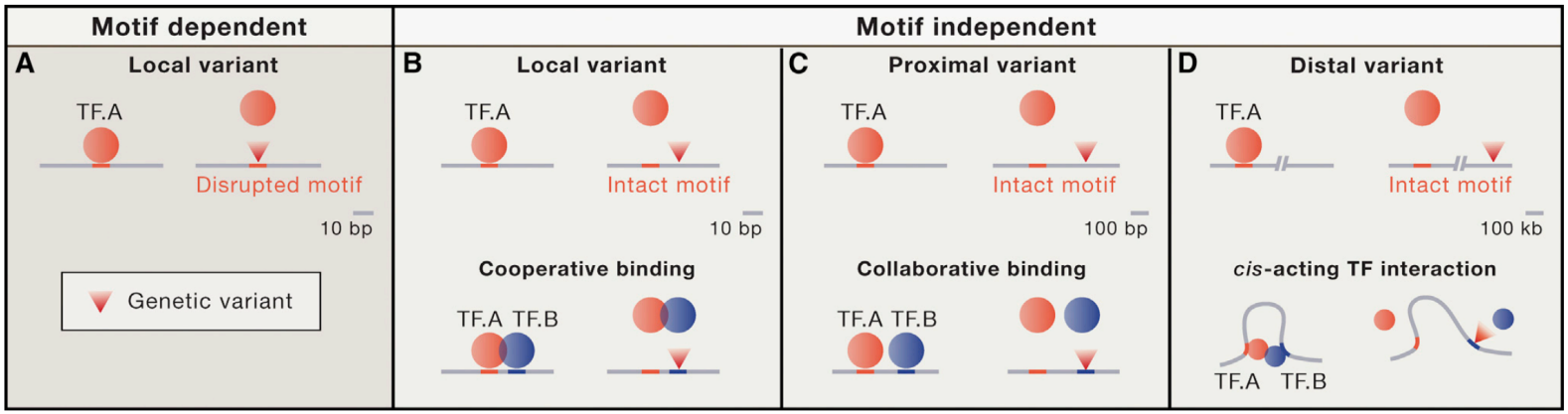
Identification of Causal Mutation and Affected Gene

- TF-DNA interactions are key drivers of phenotypic variation.
- However, the majority of TF binding changes are not driven by sequence variations in the TF motif of interest.
- It is wrong to assume we can match a GWAS SNP to the closest TFBS. Variants could be associated with genes $>$ 1Mbp away.

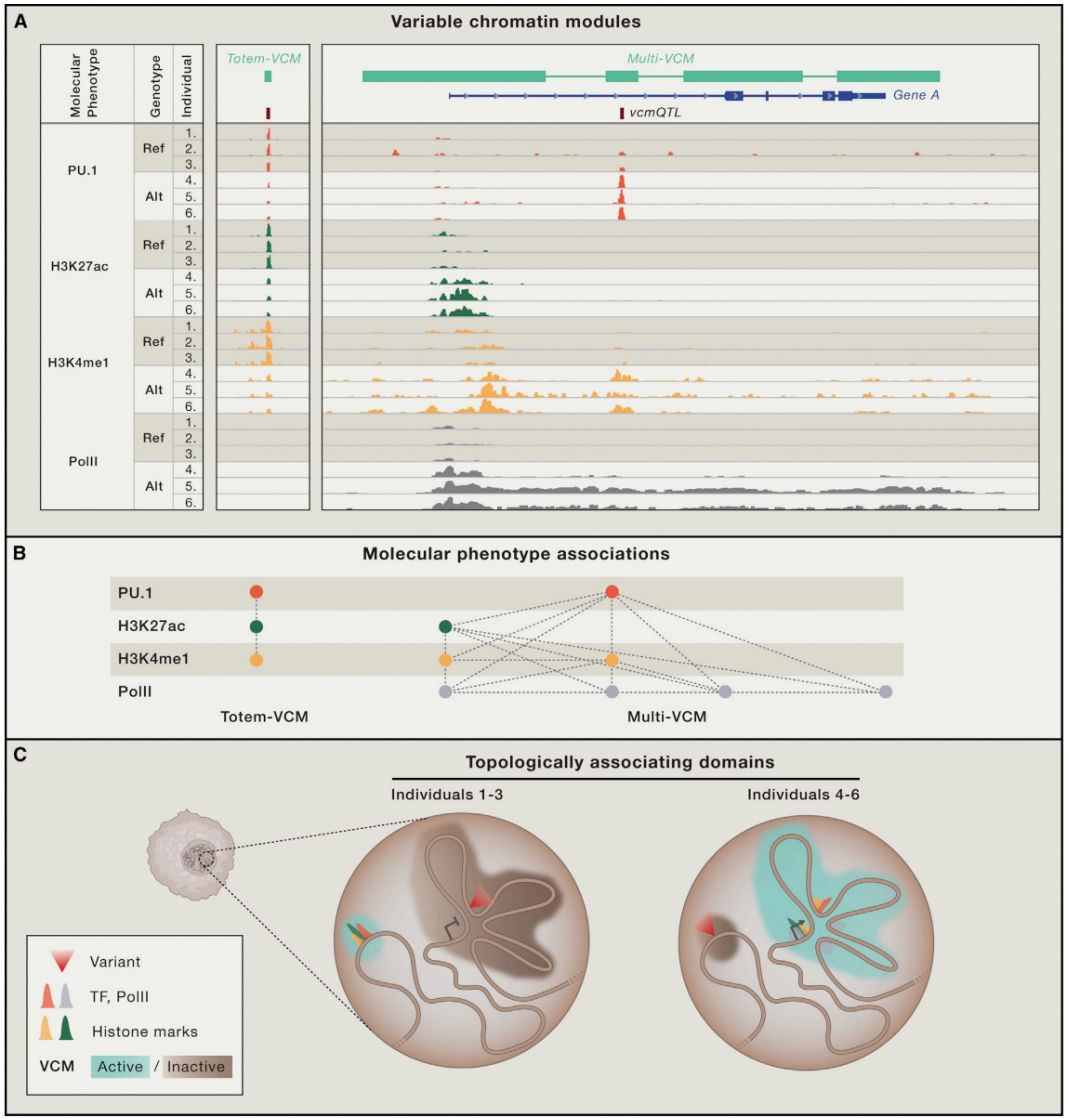
Problem: Incomplete TF Motif Catalog

- Over 1/3 of human TFs are devoid of consensus motifs
- Co-binding has largely been underrepresented in predictive models.
- A variant located either proximally ($<$200 bp) or distally to the focal motif affects the binding of the respective TF

Co-binding


Motif dependent
Motif independent
A
Local variant
TF.A
Disrupted motif
10 bp
Genetic variant
B
Local variant
TF.A
Intact motif
10 bp
Cooperative binding
TF.A TF.B
C
Proximal variant
TF.A
Intact motif
100 bp
Collaborative binding
TF.A TF.B
D
Distal variant
TF.A
Intact motif
100 kb
cis-acting TF interaction
TF.A TF.B

Co-binding


A
Variable chromatin modules
Molecular Phenotype
Genotype
Individual
Totem-VCM
Multi-VCM
Gene A
vcmQTL
PU.1
H3K27ac
H3K4me1
PolII
Ref
Alt
B
Molecular phenotype associations
PU.1
H3K27ac
H3K4me1
PolII
Totem-VCM
Multi-VCM
C
Topologically associating domains
Individuals 1-3
Individuals 4-6
Variant
TF, PolII
Histone marks
VCM
Active / Inactive