



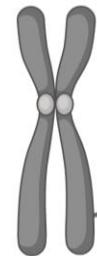
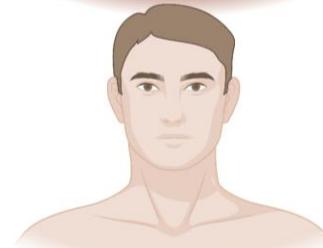
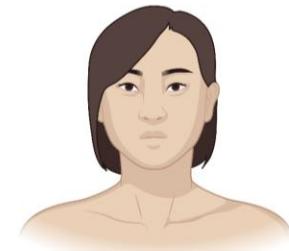
Deep learning for genomic discovery

Anshul Kundaje

Twitter:@anshulkundaje

Website: <http://anshul.kundaje.net>

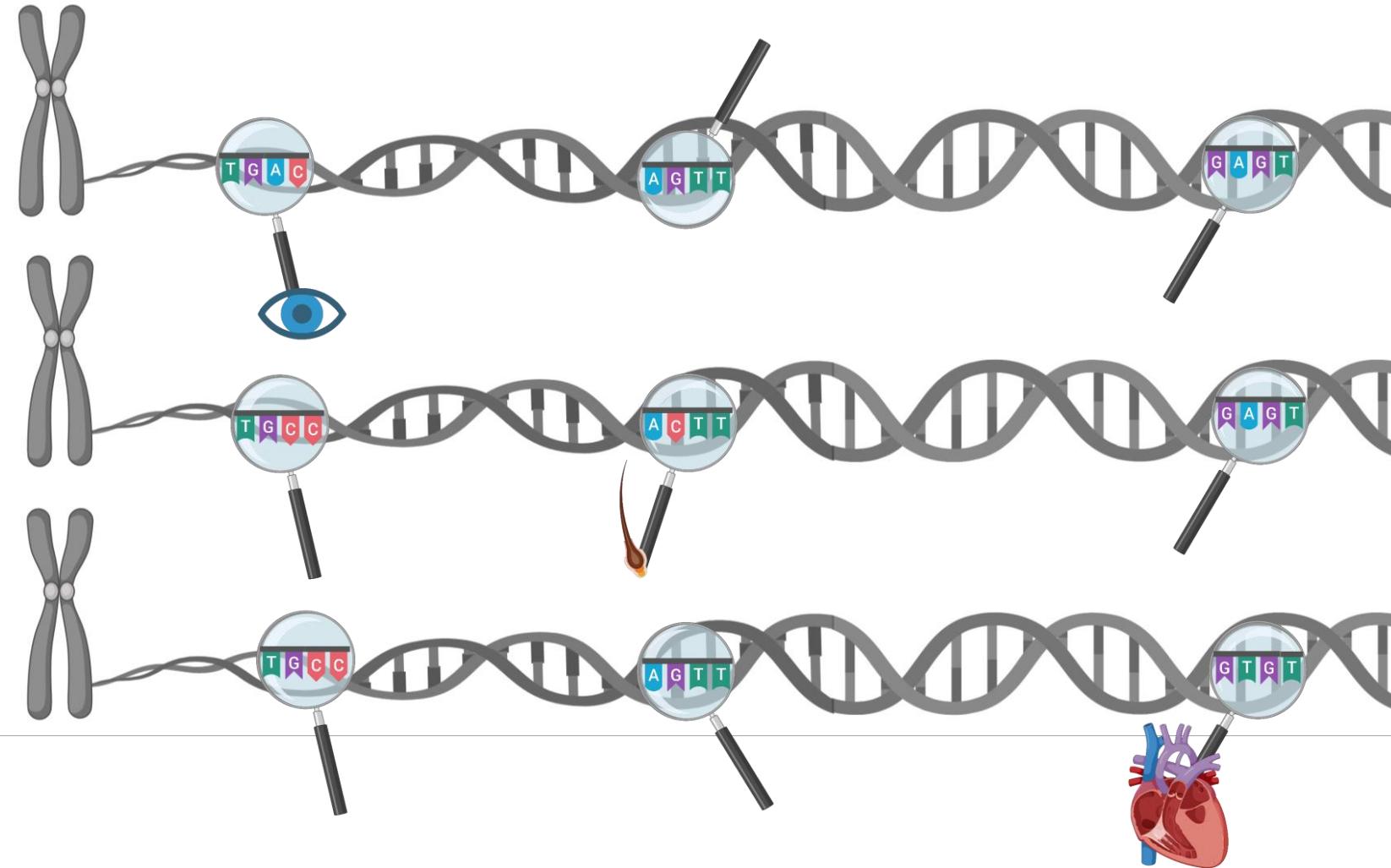
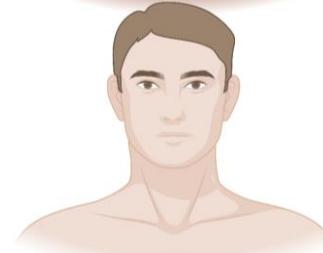
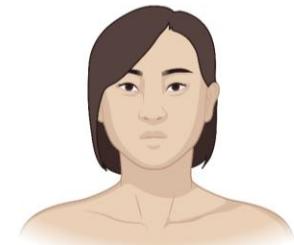
Genetic variants associated with traits and diseases



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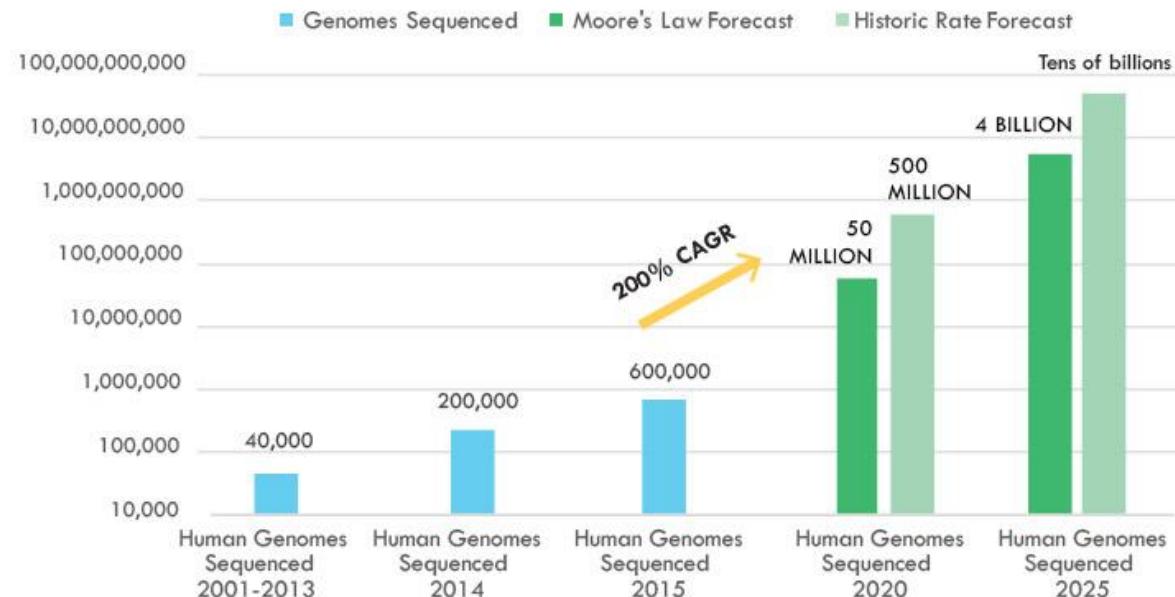


Genetic variants associated with traits and diseases

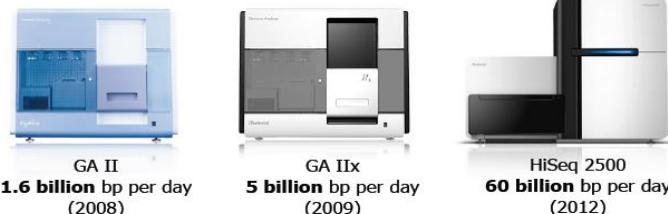


Population sequencing to identify disease-associated genetic variants

The Number of Human Genomes Sequenced (log scale)



Source: National Human Genome Research Institute (NHGRI), ARK Investment Management LLC



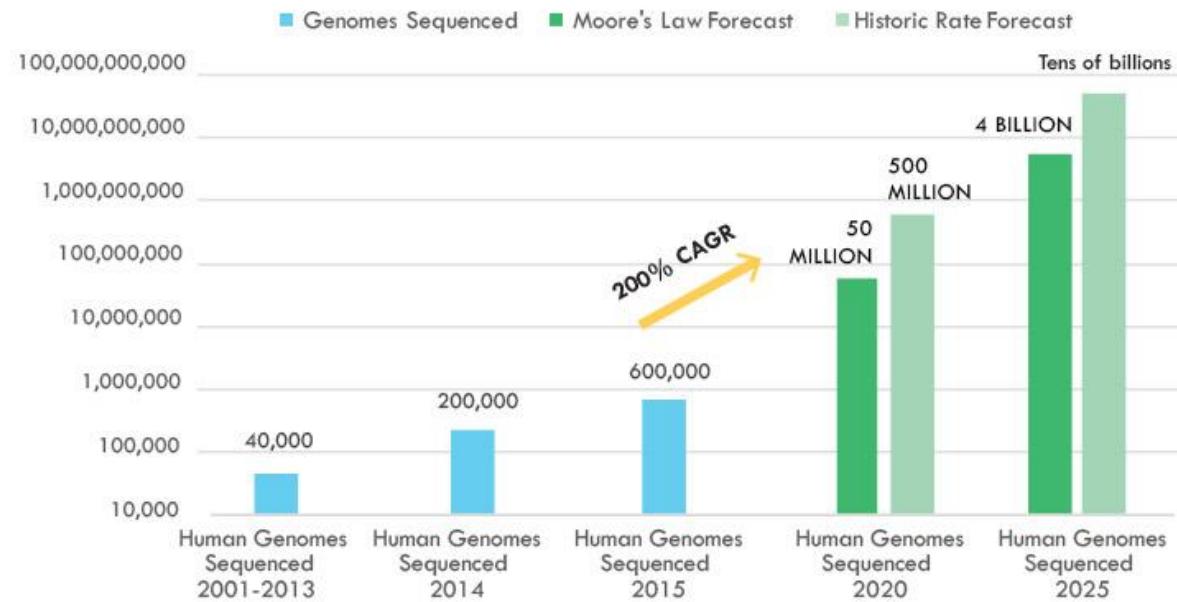
Images: www.illumina.com/systems
Numbers: www.politgenomics.com/high-generation-sequencing-informatics
Dates: Illumina press releases



Millions of common and rare genetic variants found in human population

Population sequencing to identify disease-associated genetic variants

The Number of Human Genomes Sequenced (log scale)



GA II
1.6 billion bp per day
(2008)



GA IIx
5 billion bp per day
(2009)

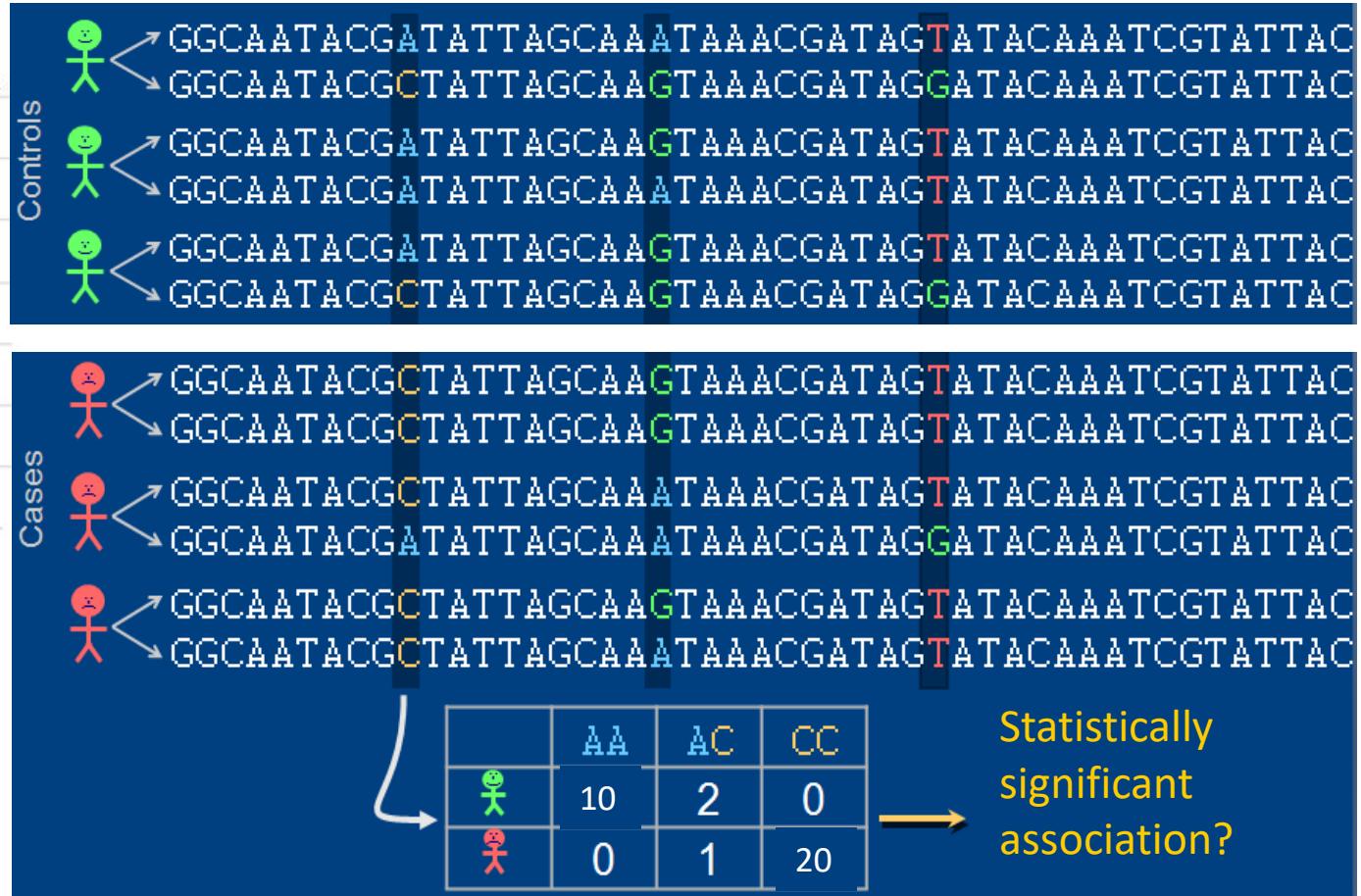


HiSeq 2500
60 billion bp per day
(2012)



Oxford Nanopore technology

Images: www.illumina.com/systems
Numbers: www.politigenomics.com/high-generation-sequencing-informatics
Dates: Illumina press releases



Millions of common and rare genetic variants found in human population

Genetic variants associated with Alzheimer's disease

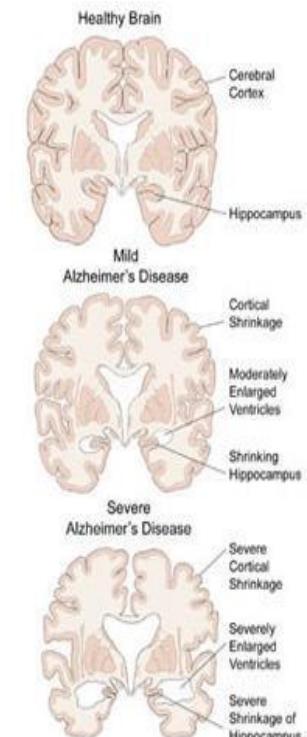
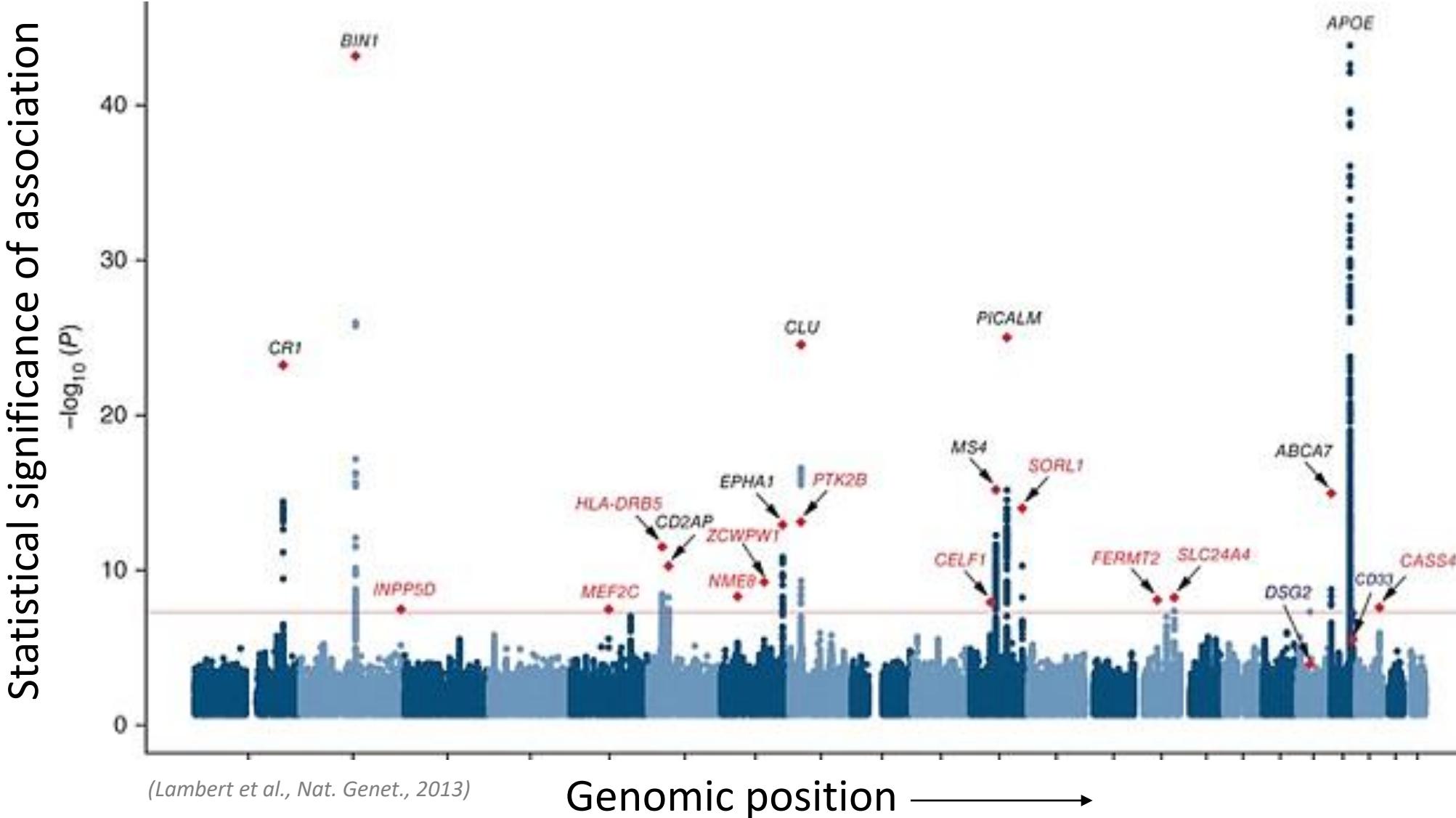


Illustration by Bob Morreale,
American Health Assistance
Foundation

TGCCAAGCAGCAAAGTTTGCTGCTTTATTTTAGCTCTTACTATATTCT
ACTTTACCATGAAAATATTGAGGAAGTTATTATATTCTATTTTATATAT
TATATATTATGTATTAAATATTACTATTACACATAATTATTTTATATATGA
AGTACCAATGACTCCTTTCCAGAGCAATAATGAAATTACAGTATGAAA
ATGGAAGAAATCAATAAAATTATACGTGACCTGTGGCGAAGTACCTATCGT
GACAAGGTGAGTACCATGGTGTATCACAAATGCTCTTCCAAAGCCCTCTCC
GCAGCTCTCCCCTATGACCTCTCATGCCAGCATTACCTCCCTGGACCC
CTTCTAACATGTCTTGAGATTCTAAGAATTCTTATCTTGGAACATCTT
GTAGCAAGAAAATGTAAGTTCTGTCAGAGCCTAACAGGACTTACATA
TTTGAUTGCAGTAGGCATTATATTAGCTGATGACATAATAGGTTCTGCATA
GTGTAGATAGGGATAAGCCAAATGCAATAAGAAAAACCATCCAGAGGAA
ACTCTTTTTTTCTTTCTTTCTTTCCAGATGGAGTCTCGCACTTC
TCTGTCACCCGGGCTGGAGCGCAGTGGTCAATCTGGCTCACTGCAACCT
CCACCTCCTGGGTCAGGTGATTCTCCCACCTCAGCCTCCGAGTAGTAGCT
GGAATTACAGGTGCGCGCTCCCACACCTGGCTAATTTTGATTCTTAGTA
GAGATGGGTTTACCATGTTGCCAGGCTGGTCTCAAACCTGCCCTCA
GGTGAUTGCCACCTGGCCTCCAGTGTGGTTACAGGCGTGAGCCA
CCGCGCCTGGCCTGGAGGAAACTCTAACAGGGAAACTAACAGGAGTTG
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CTTGAATCCTCCCAGCCAGAGAAAGAGTTCCACACCAGCCATTGTTCT
CTGGTAATGTCAGCCTCATCTGTTCTTAGGCTTACTGATATGTTGAA
ATGACAAAAGGCTACAGAGCATAGGTCCTCTAAATATTCTTCTGTGT
CAGATATTGAATACATAGAAATACGGTCTGATGCCATGAAAATGTATCAGCT
TCTGATAAAAGGCGGAATTATAACTACCGAGTGGTATGCTGAAGGGAGAC
ACAGCCTGGATATGCGAGGACGATGCAGTGTGGACAAAAGGCAGGTAT
CTCAAAAGCCTGGGAGCCAACTCACCCAAAGTAACGTAAAGAGAGAAACA
AACATCAGTGCAGTGGAAAGCACCCAAAGGCTACACCTGAATGGTGGGAAGC
TCTTGCTGCTATATAAAATGAATCAGGCTCAGCTACTATTATT

Decoding genome function

~ 3 billion nucleotides

TGCCAAGCAGCAAAGTTTGCTGCTTTATTTTAGCTCTTACTATATTCT
ACTTTACCATGAAAATATTGAGGAAGTTATTATATTCTATTTTATATAT
TATATATTATGTATTAAATATTACTATTACACATAATTATTTTATATATGA
AGTACCAATGACTCCTTTCCAGAGCAATAATGAAATTACAGTATGAAA
ATGGAAGAAATCAATAAAATTATACGTGACCTGTGGCGAAGTACCTATCGT
GACAAGGTGAGTACCATGGTGTATCACAAATGCTCTTCCAAAGCCCTCTCC
GCAGCTCTCCCCTATGACCTCTCATGCCAGCATTACCTCCCTGGACCC
CTTCTAACGATGTCTTGAGATTCTAAGAATTCTTATCTTGGAACATCTT
GTAGCAAGAAAATGTAAGTTCTGAGATTTCTAAGAATTCTTATCTTGGAACATCTT
TTTGAUTGCAGTAGGCATTATATTAGCTGATGACATAATAGGTTCTGTCTA
GTGTAGATAGGGATAAGCCAAAATGCAATAAGAAAAACATCCAGAGGAA
ACTCTTTTTTTCTTTCTTTCTTTCTTTCCAGATGGAGTCTCGCACTTC
TCTGTACCCGGGCTGGAGCGCAGTGGTGAATCTGGCTCACTGCAACCT
CCACCTCCTGGGTCAGGTGATTCTCCCACCTCAGCCTCCGAGTAGTAGCT
GGAATTACAGGTGCGCGCTCCCACACCTGGCTAATTCTTGTATTCTTAGTA
GAGATGGGTTTACCATGTTGCCAGGCTGGTCTCAAACCTGCCCTCA
GGTGAUTGCCACCTGGCCTCCCAGTGTGGTTACAGGCGTGAGCCA
CCGCGCCTGGCCTGGAGGAAACTCTAACAGGGAAACTAACAGGAAAGAGTTG
AGGCTGAGGAACTGGGCATCTGGTTGCTCTGCCAGACCACCAAGGCT
CTTGAATCCTCCCAGCCAGAGAAAGAGTTCCACACCAGCCATTGTTCT
CTGGTAATGTCAGCCTCATCTGTTCTTAGGCTTACTGATATGTTGAA
ATGACAAAAGGCTACAGAGCATAGGTCCTCTAAATATTCTTCTGTGT
CAGATATTGAATACATAGAAATACGGTCTGATGCCATGAAAATGTATCAGCT
TCTGATAAAAGGCGGAATTATAACTACCGAGTGGTATGCTGAAGGGAGAC
ACAGCCTGGATATGCGAGGACGATGCAGTGGTGGACAAAAGGCAGGTAT
CTCAAAAGCCTGGGAGCCAACTCACCCAAAGTAACGTGAAAGAGAGAAACA
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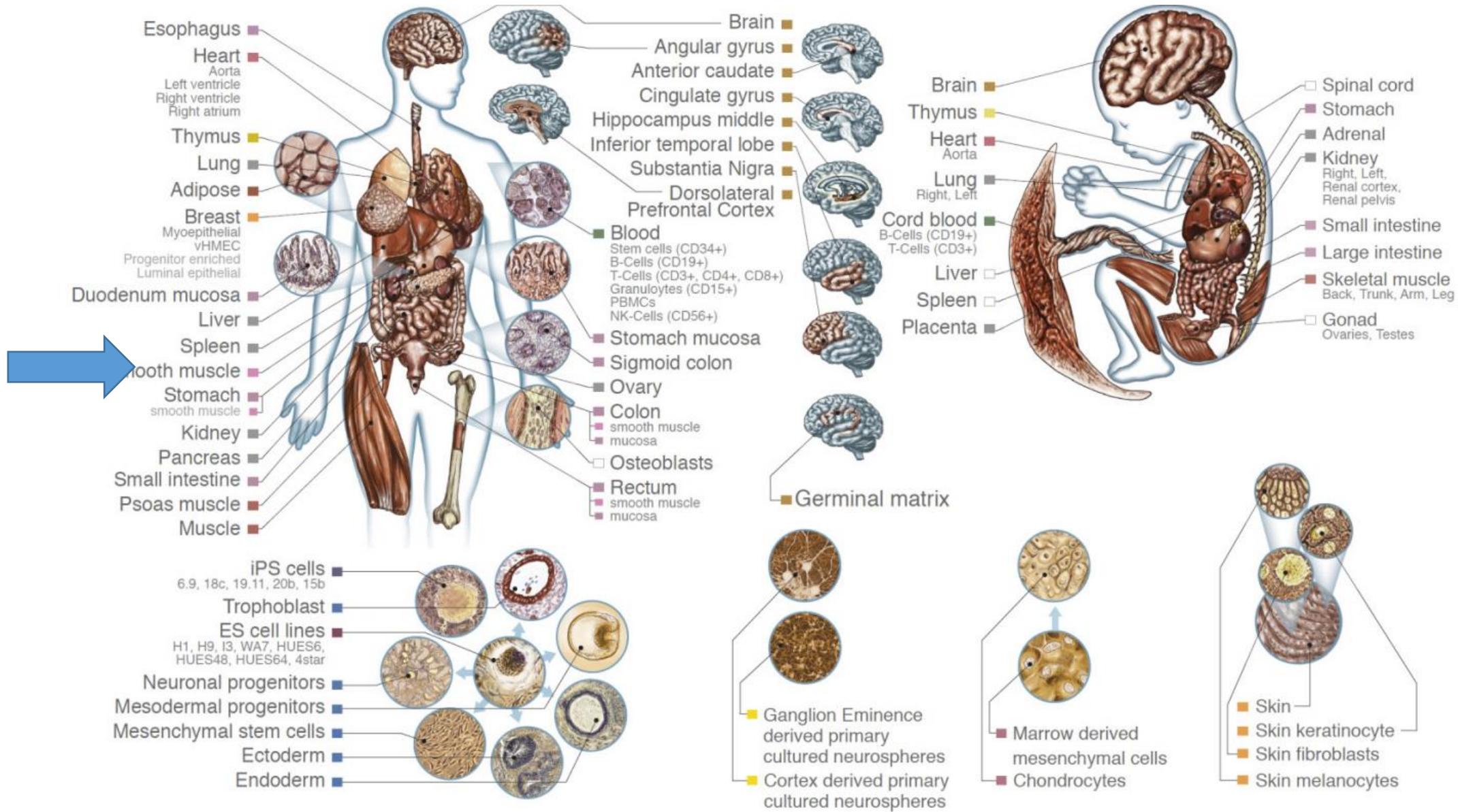
Decoding genome function

Function?

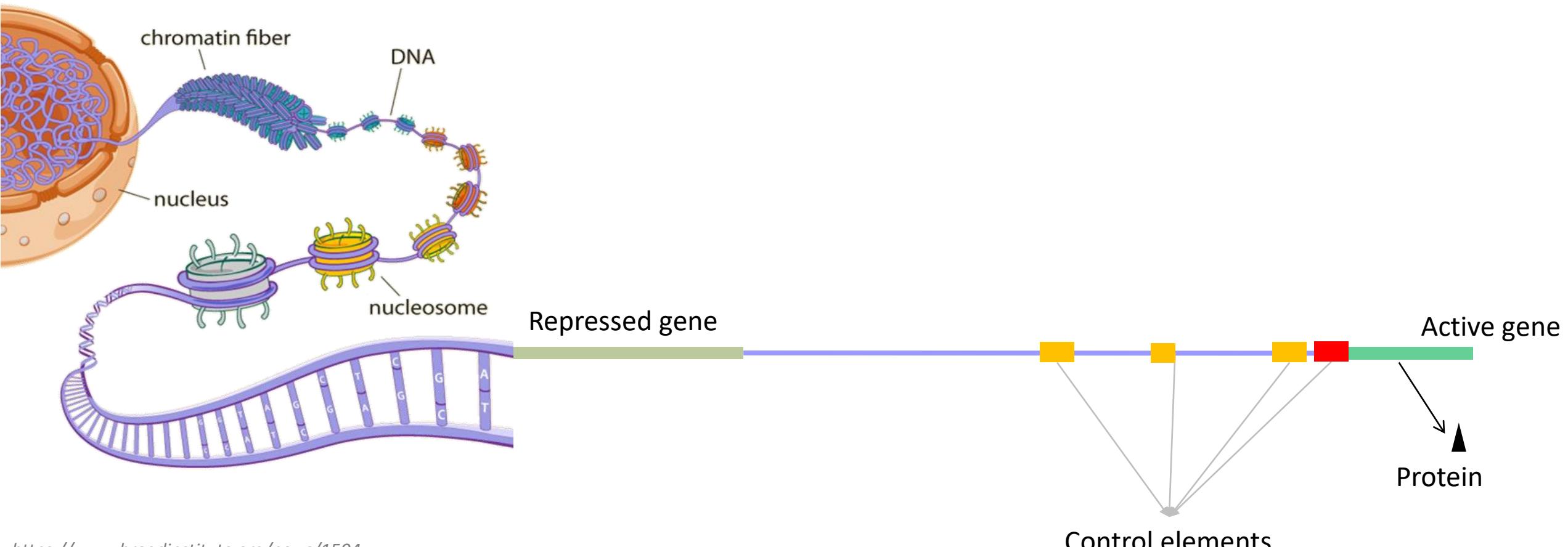
~ 3 billion nucleotides

One genome \leftrightarrow many cell types

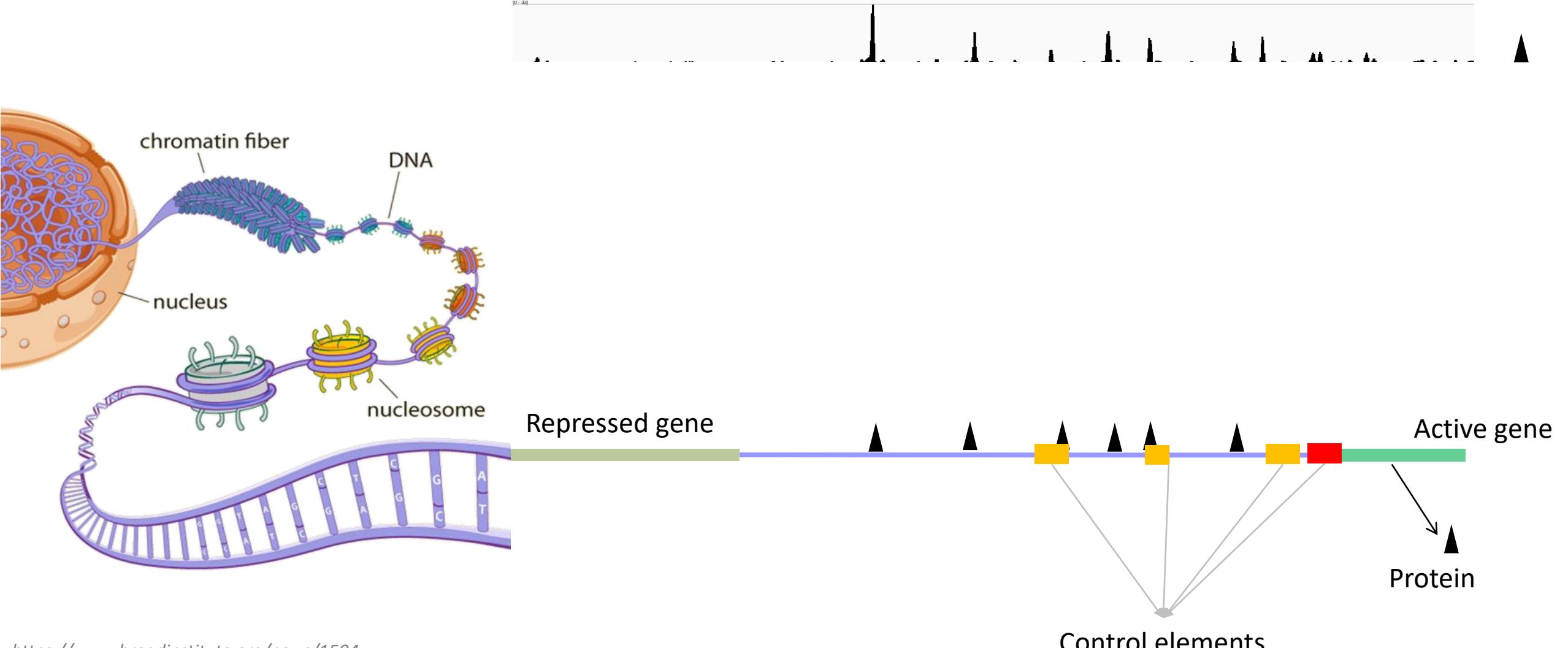
ACCAGTTACGACGG
TCAGGGTACTGATA
CCCCAAACCGTTGA
CCGCATTTACAGAC
GGGGTTGGGTTTT
GCCCCACACAGGTA
CGTTAGCTACTGGT
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ATTTGAAAAAAAAGT
TTGAGTTGGTTTT
TCACGGTAGAACGT
ACCTTACAAA.....



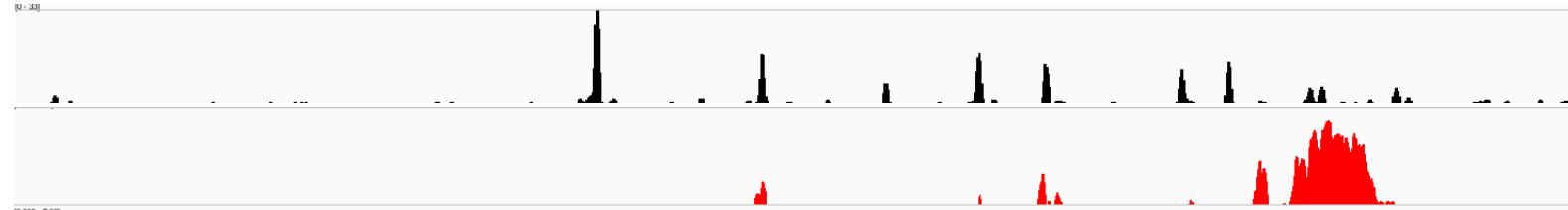
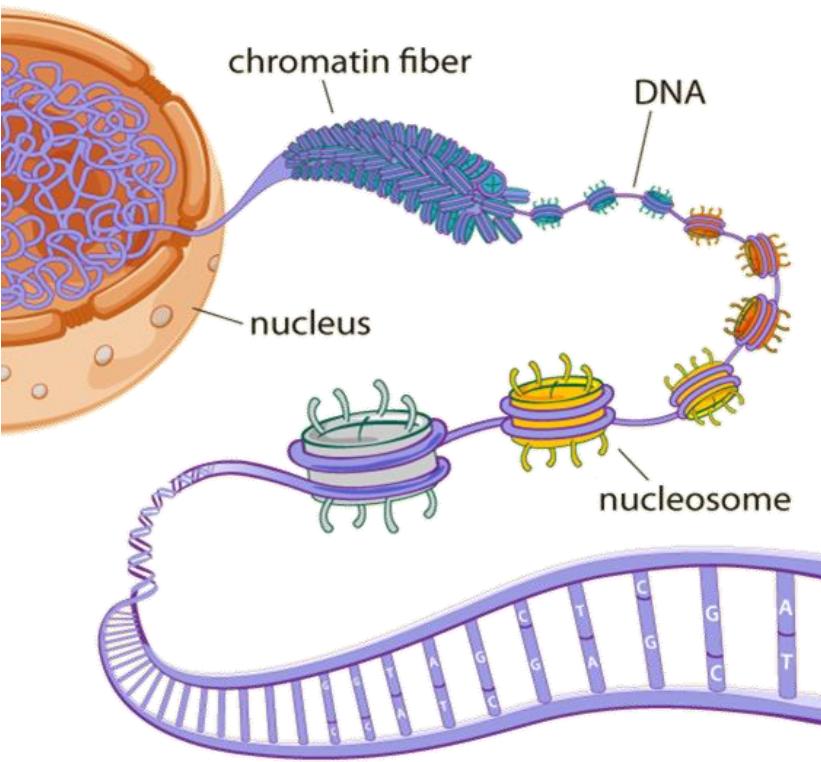
Molecular mapping of functional components of the genome



Molecular mapping of functional components of the genome



Molecular mapping of functional components of the genome



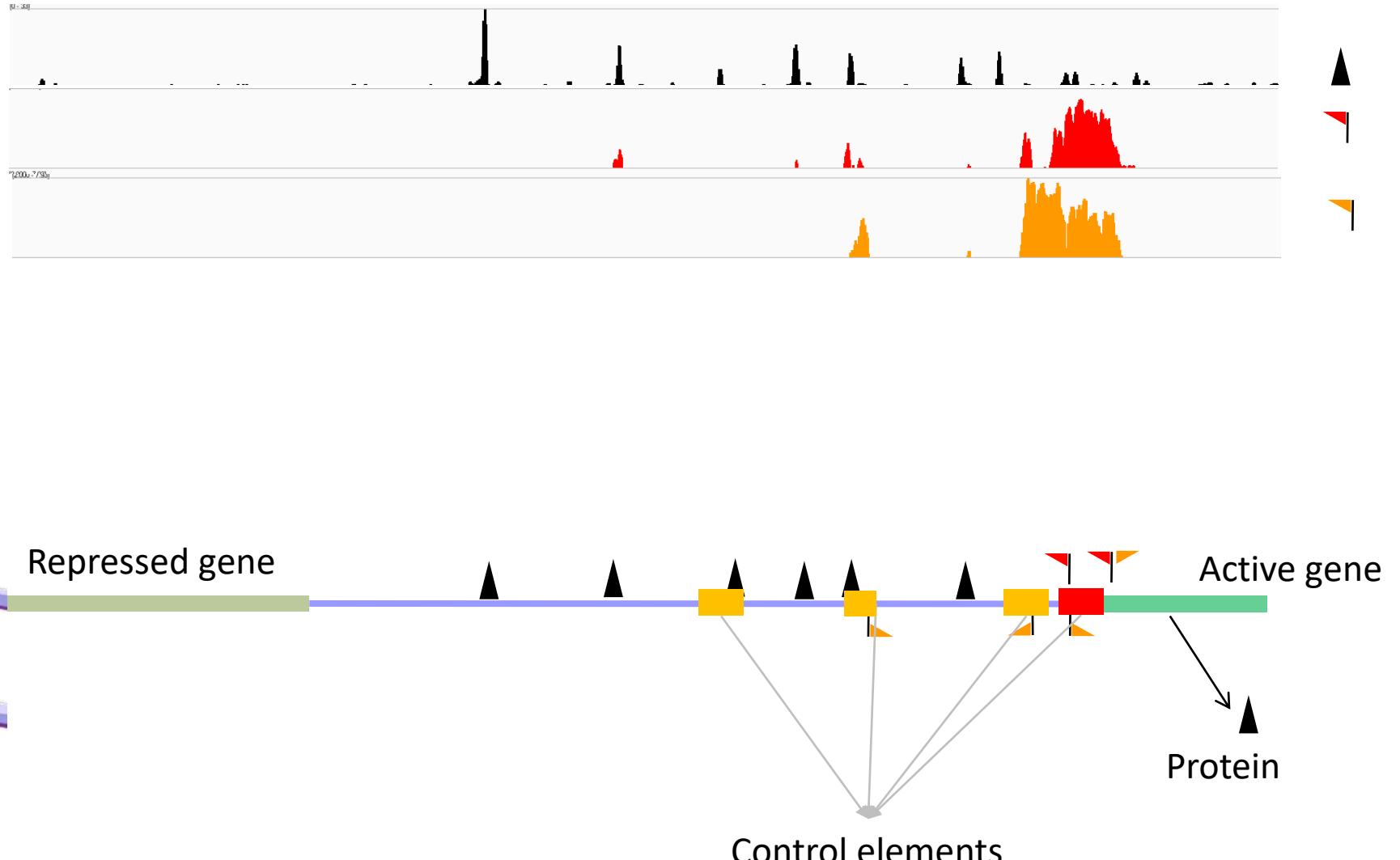
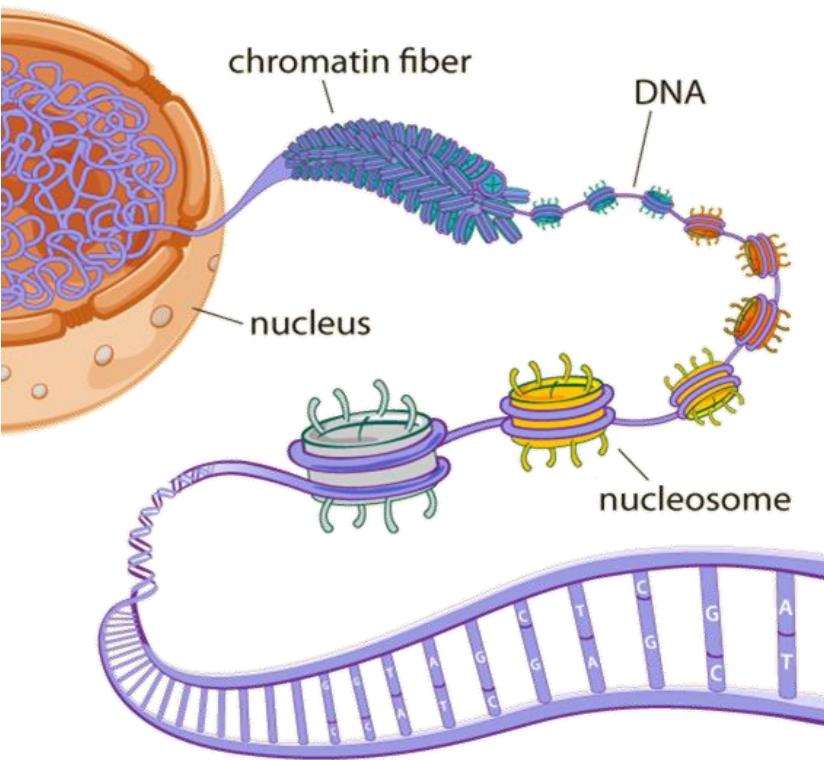
Repressed gene

Control elements

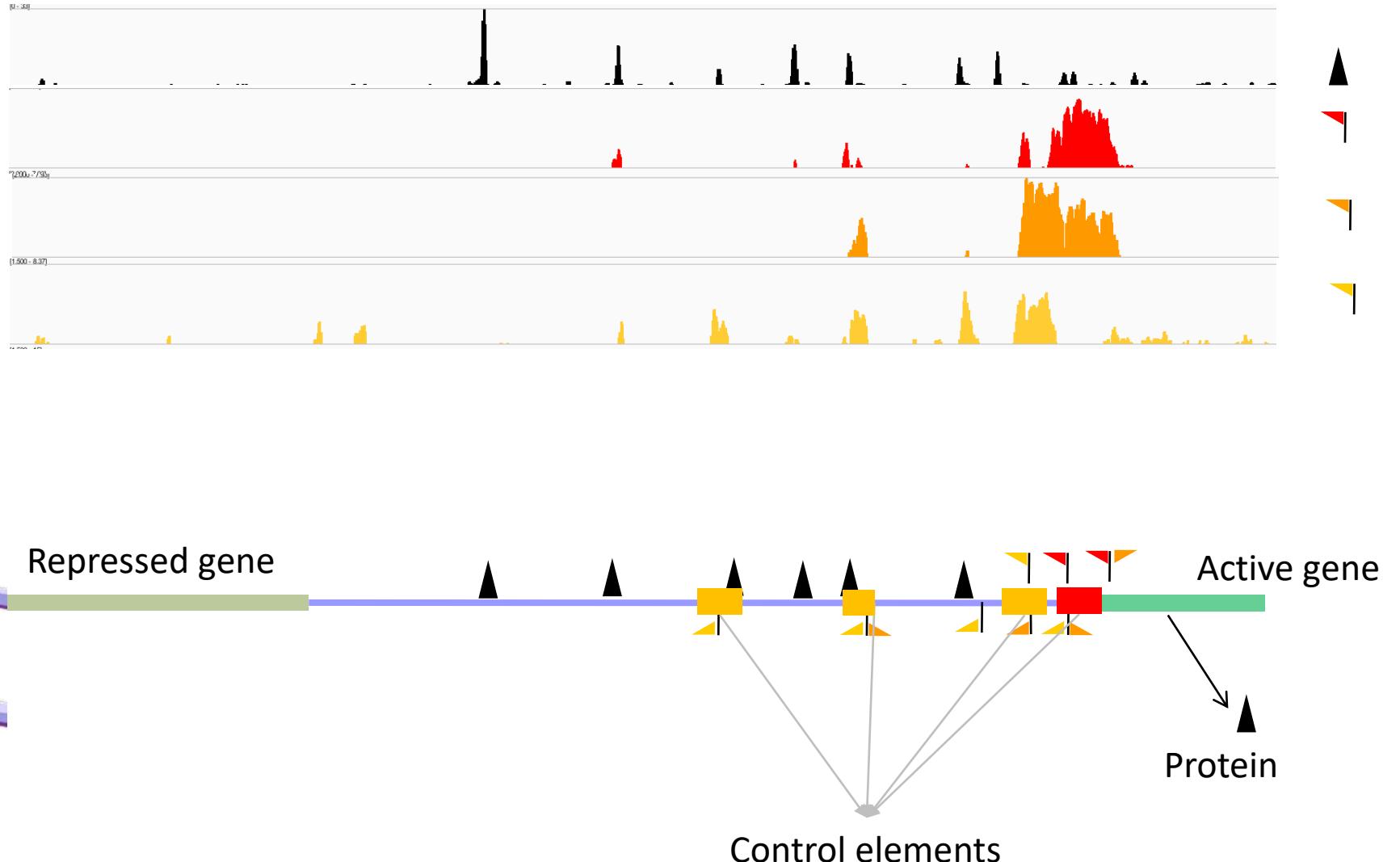
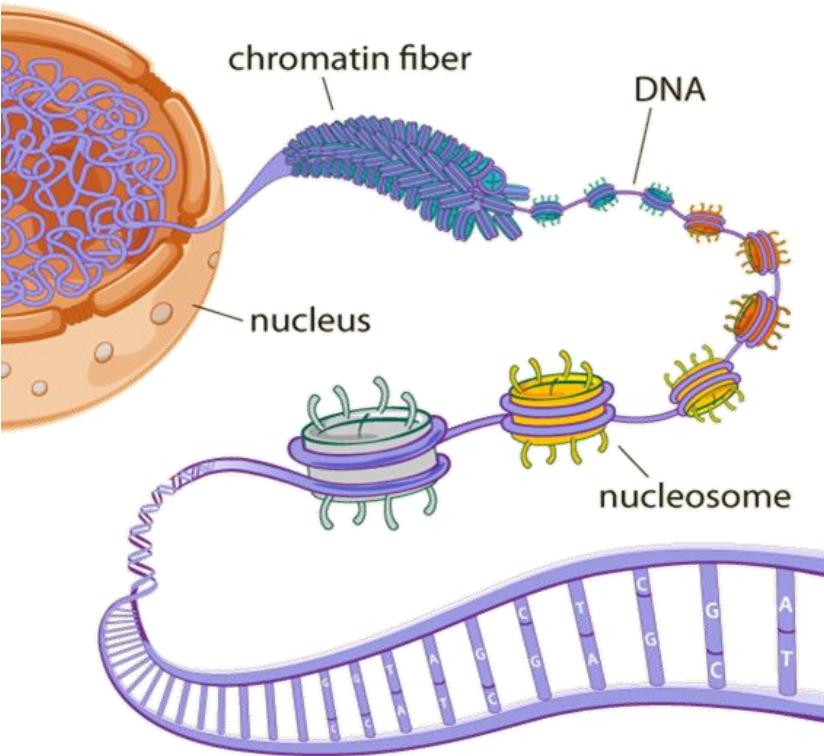
Active gene

Protein

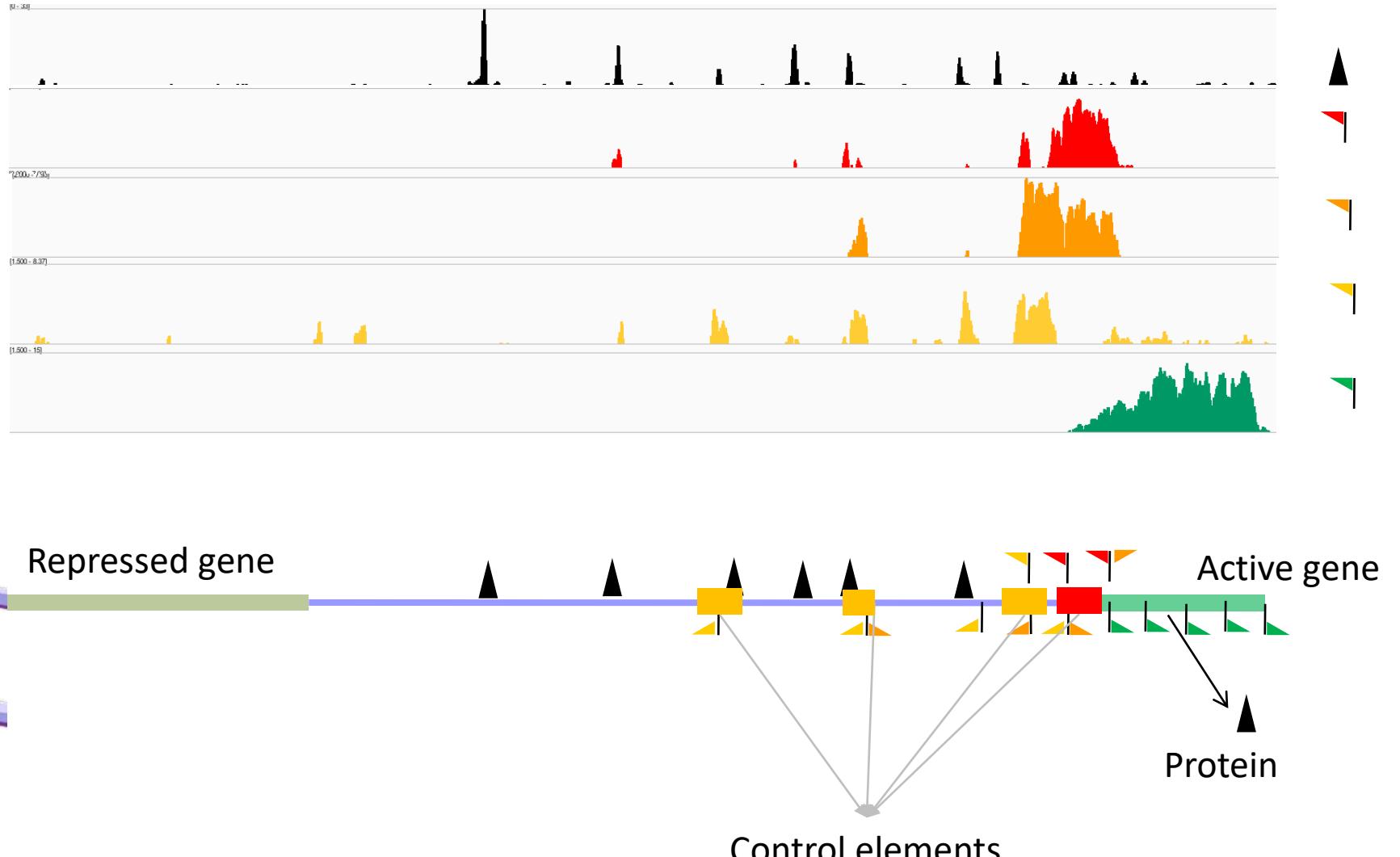
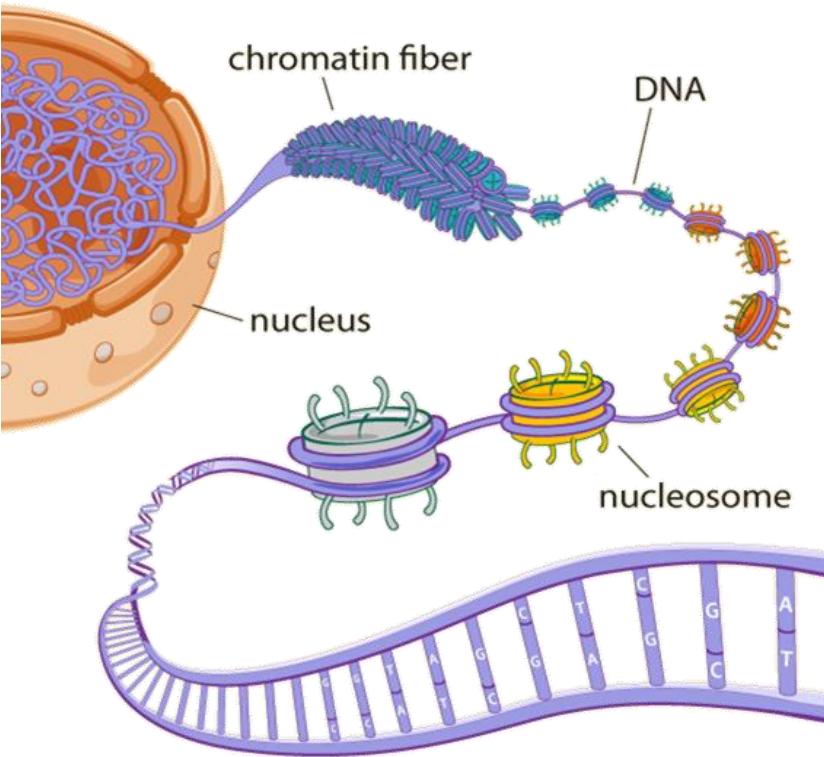
Molecular mapping of functional components of the genome



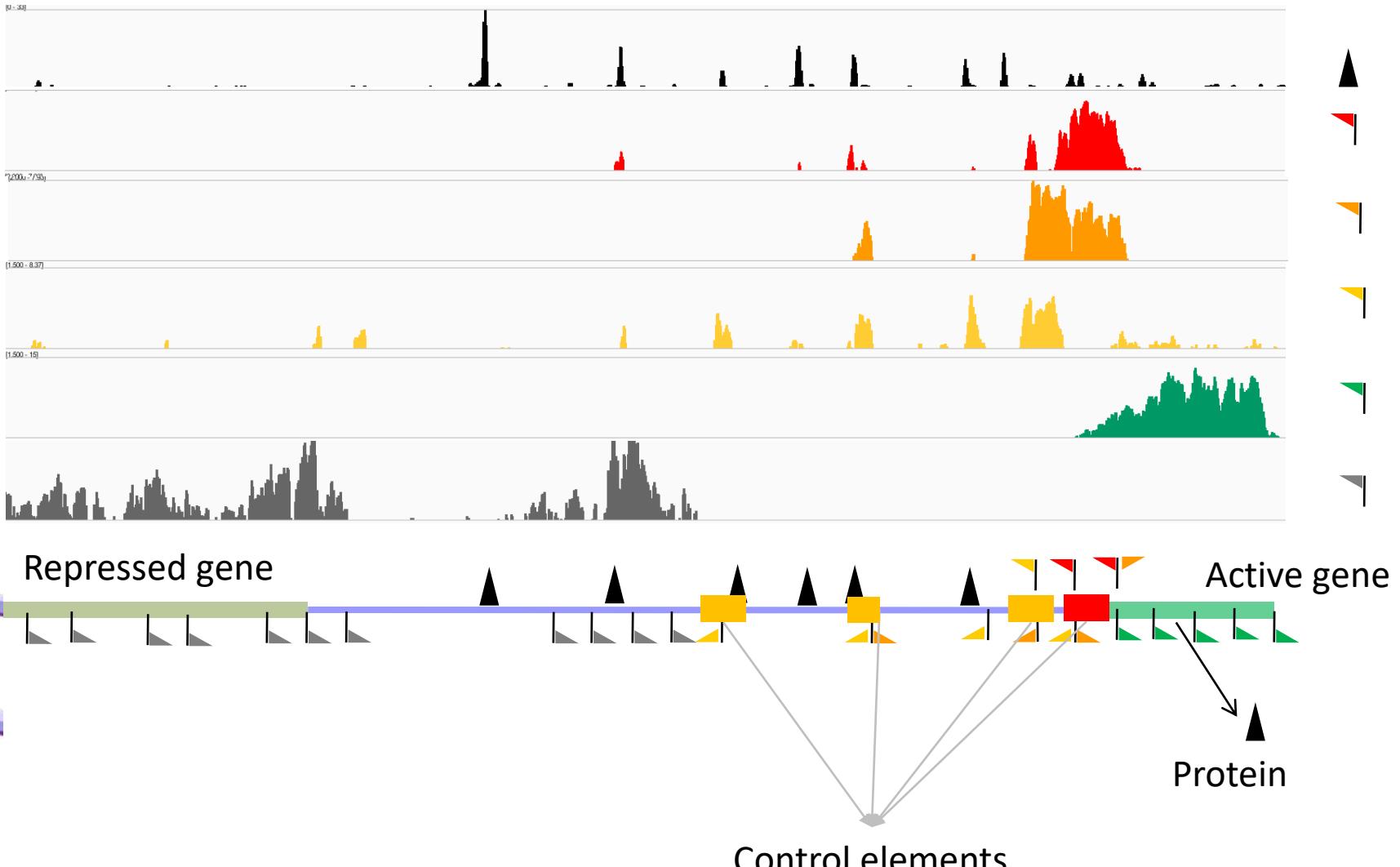
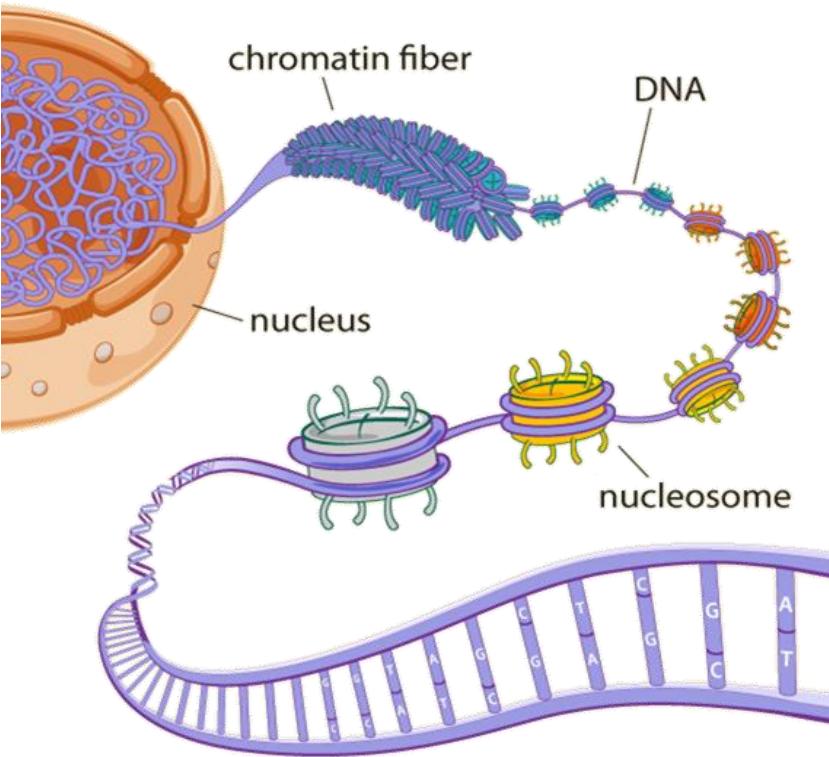
Molecular mapping of functional components of the genome

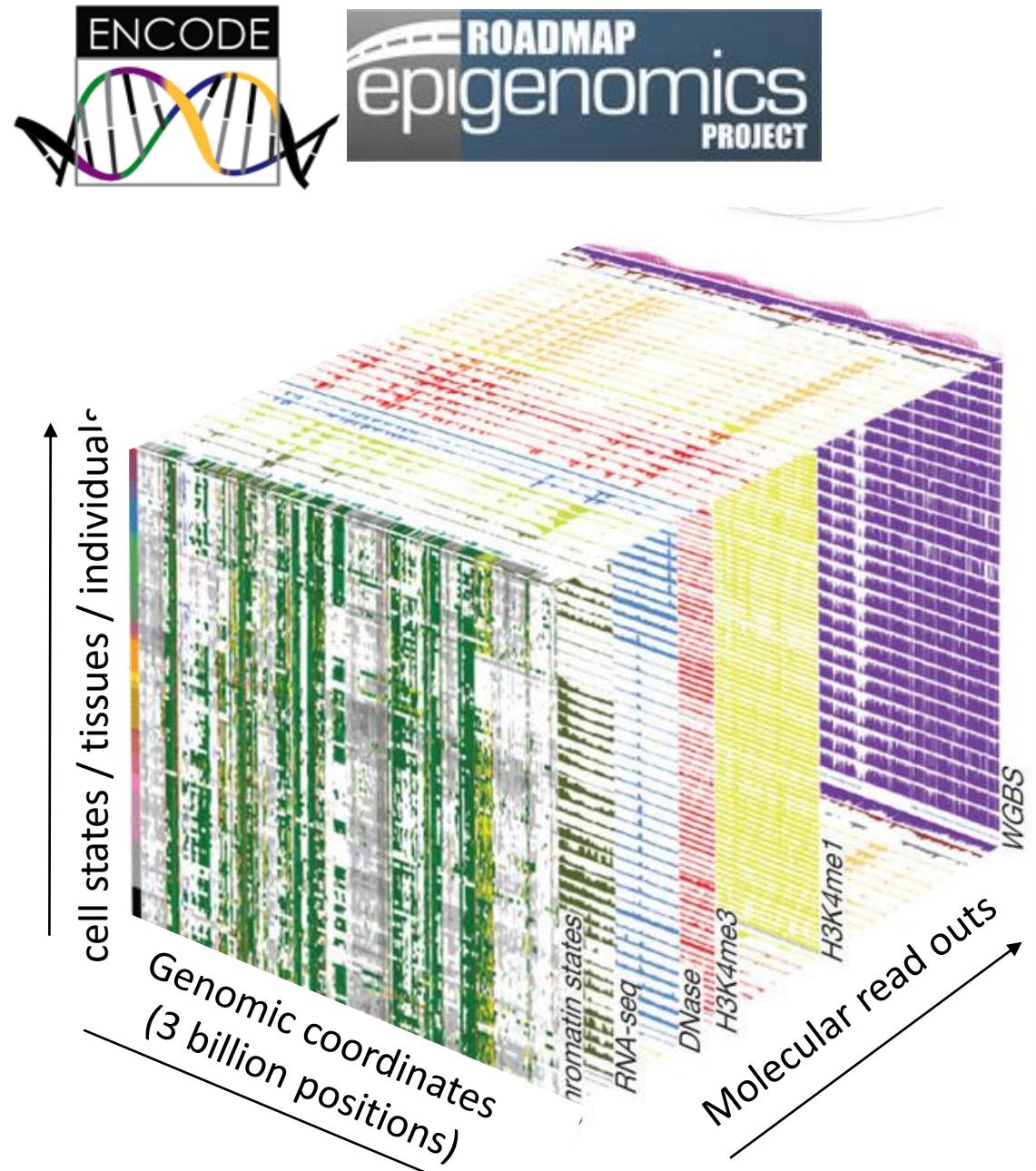


Molecular mapping of functional components of the genome

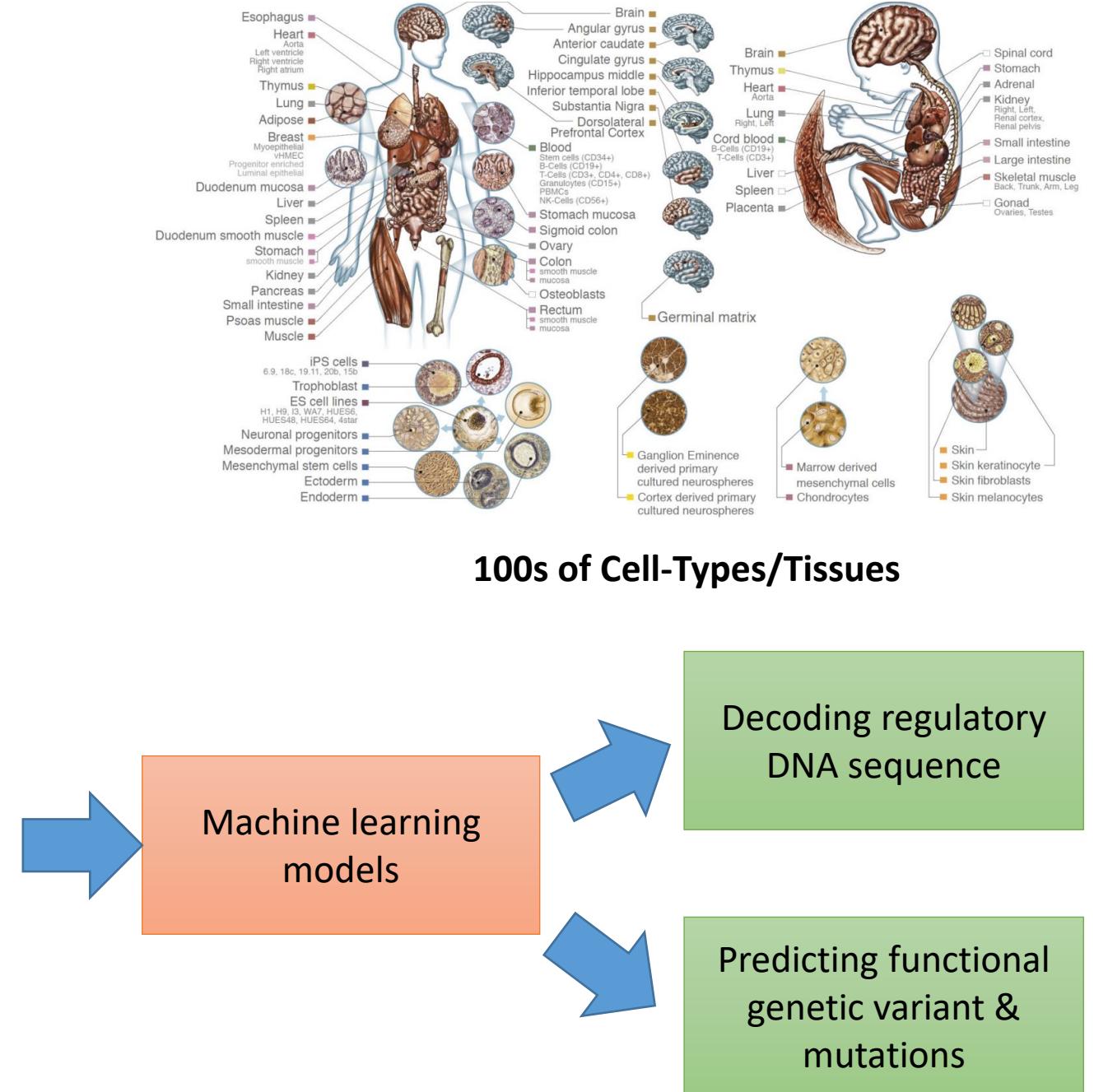


Molecular mapping of functional components of the genome





Dunham, Kundaje et al. 2012 Nature
Kundaje et al. 2015 Nature



>95% of disease variants are not disrupting protein coding gene regions

Benign

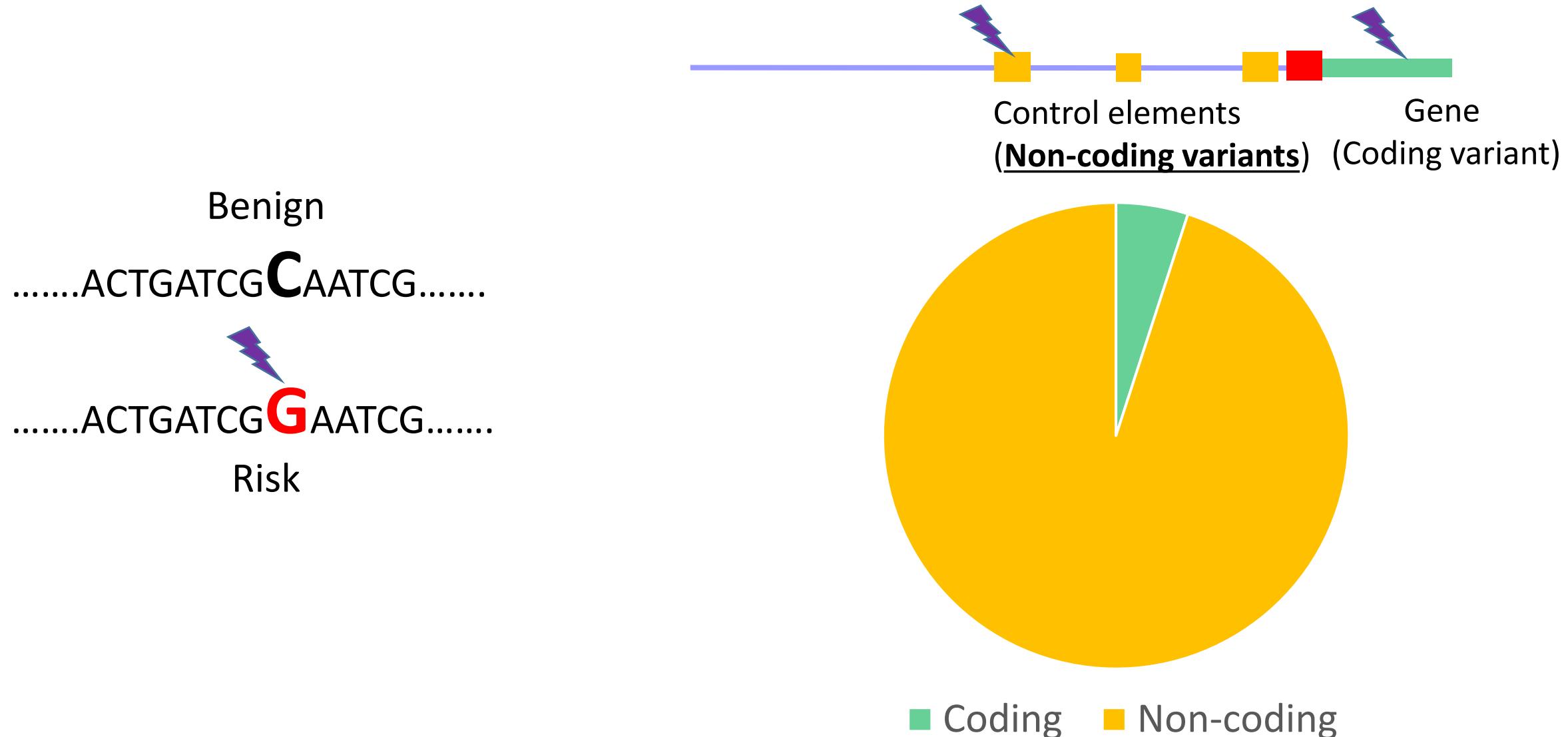
.....ACTGATCG**C**AATCG.....



.....ACTGATCG**G**AATCG.....

Risk

>95% of disease variants are not disrupting protein coding gene regions



Decoding syntax of regulatory DNA



Ziga Avsec



Avanti Shrikumar



Melanie Weilert

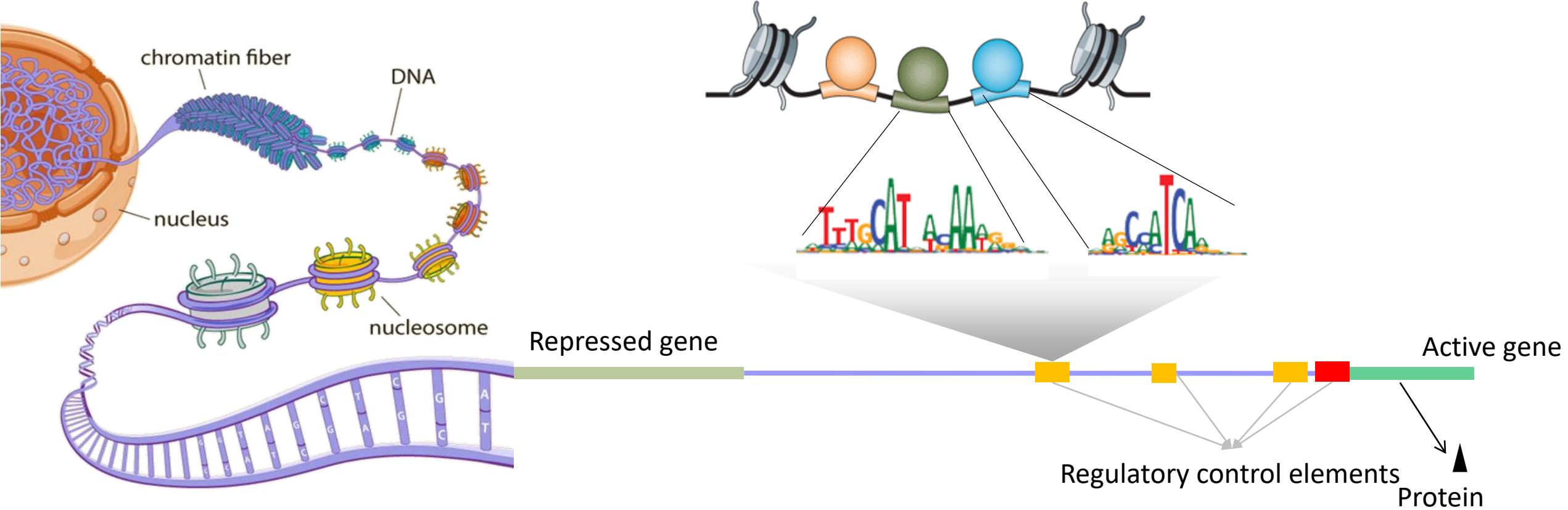


Amr Mohamed

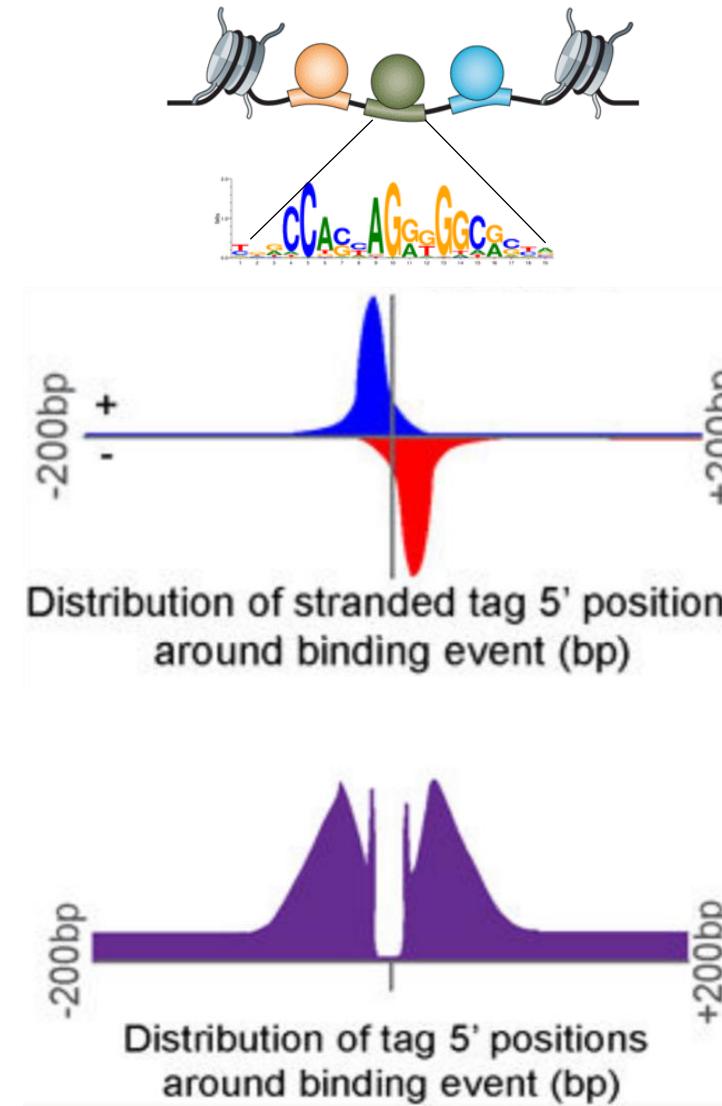


Julia Zeitlinger

Control elements encode syntax of DNA words recognized by regulatory protein complexes



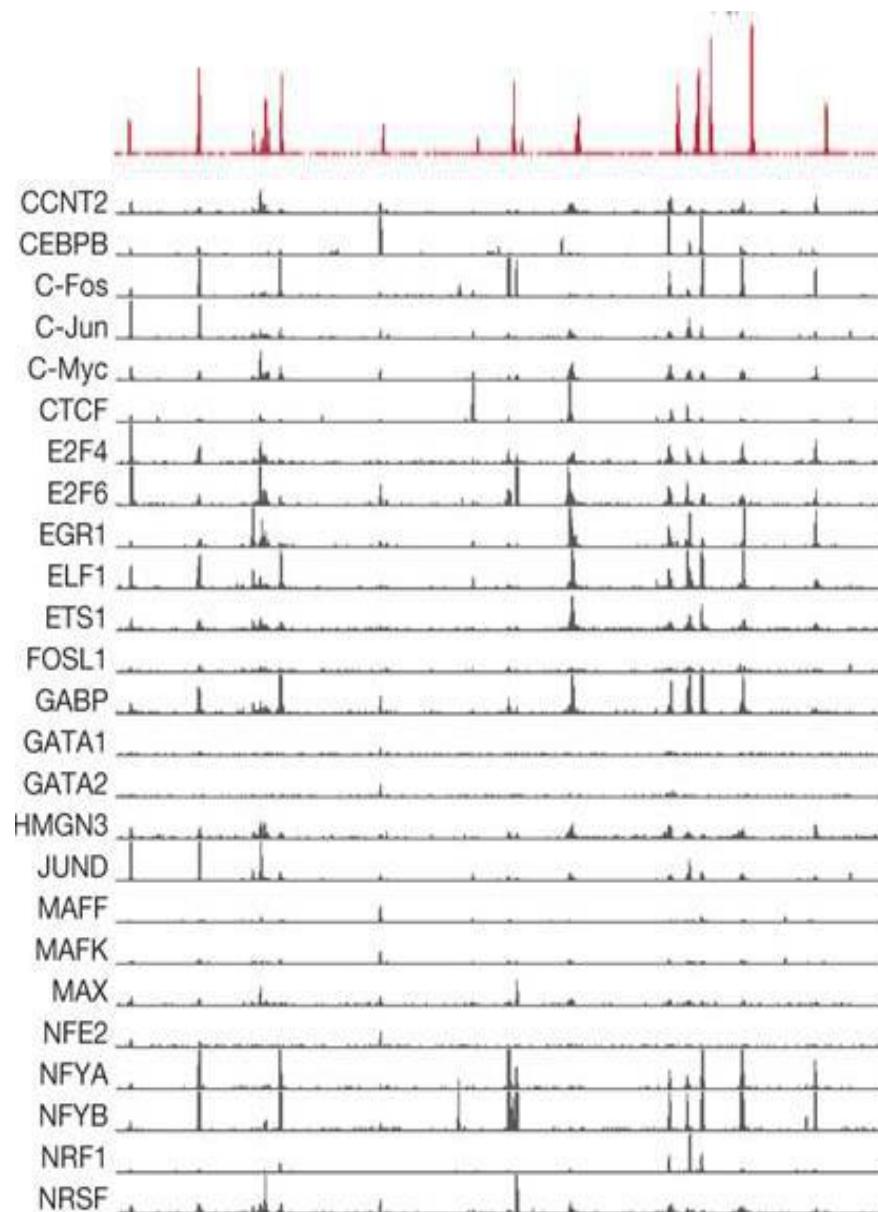
High-resolution ‘shapes’ of experimental profiles capture exquisite information about protein-DNA contacts



Protein-DNA binding expt.

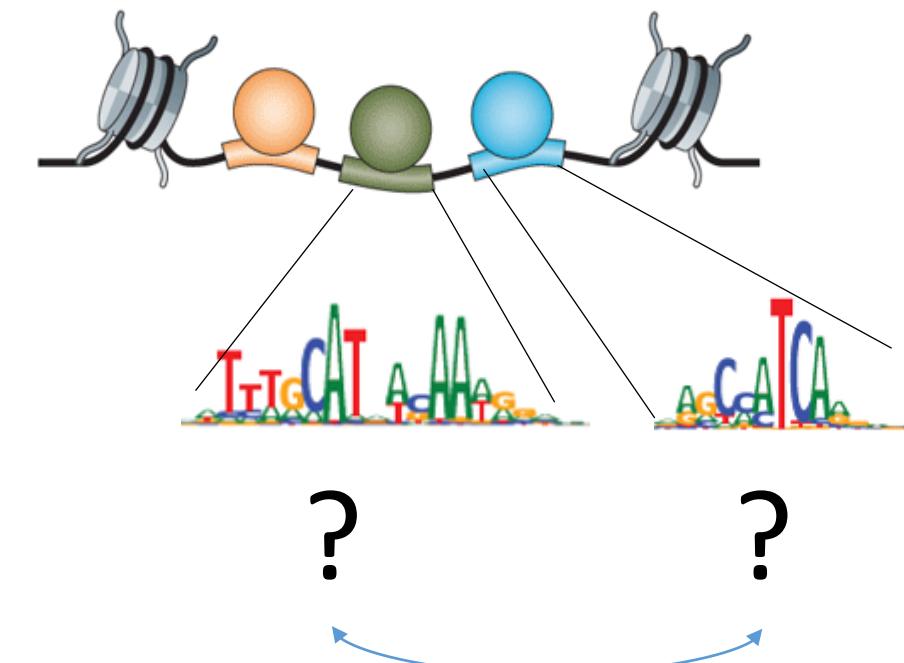
DNA accessibility experiments

Genome-wide maps of regulatory DNA (control elements)



DNA accessibility experiments

Protein-DNA
binding
experiments

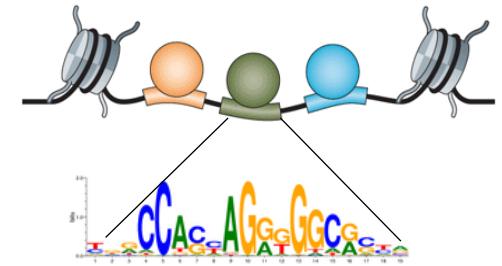
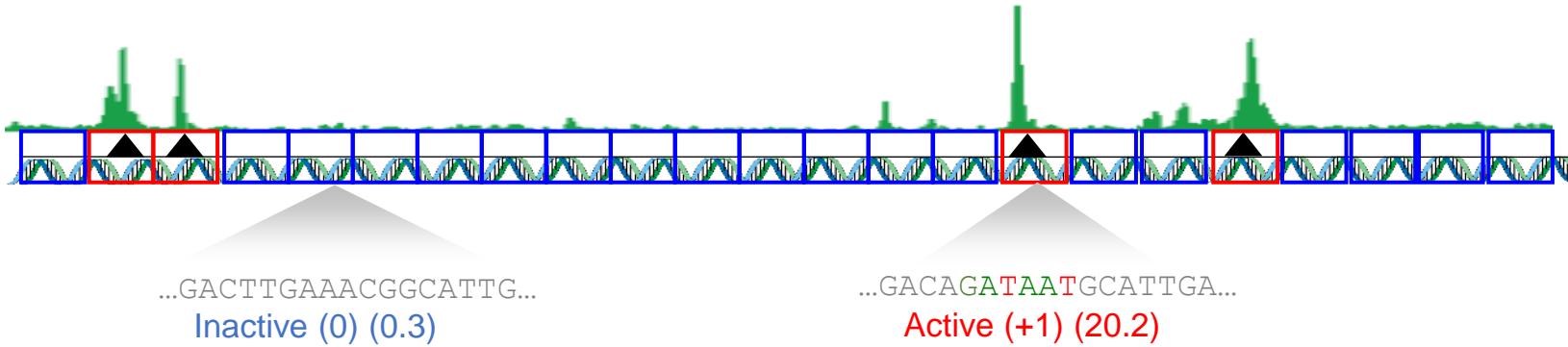


Adapted from Thurman et al 2012

Motif syntax: rules of
arrangement, preferred spacing,
orientation => cooperativity

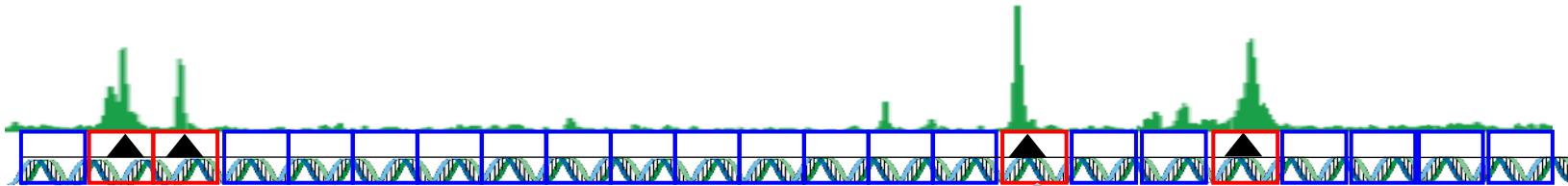
Predictive model of regulatory DNA

Transcription factor ChIP-seq data OR chromatin accessibility (DNase-seq / ATAC-seq data)



Predictive model of regulatory DNA

Transcription factor ChIP-seq data OR chromatin accessibility (DNase-seq / ATAC-seq data)



...GACTTGAAACGGCATTG...
Inactive (0) (0.3)

...GACAGA**T**AATGCATTGA...
Active (+1) (20.2)

...GACAGA**T**AA**T**GCATTGA...

...ACTGTCATGG**A**T**T**CT...

...**G**A**T**ATTCTACTGTAAAG...

DNA sequences (S_i)

...CAACCTTGAACGGCATTG...

...GACTTGAAACGGCATTG...

...CAGTATGCATACGTGAA...

Classification
or Regression
model
 $F(S_i)$

Arvey et al. 2012
Ghandi et al. 2014
Setty et al. 2015

Class = +1 (20.2)

Class = +1 (10.6)

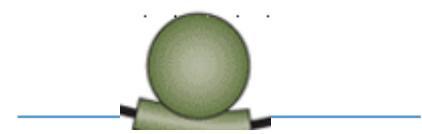
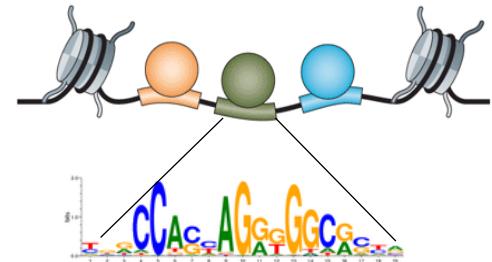
Class = +1 (15.8)

Measured
Labels (Y_i)

Class = 0 (0.3)

Class = 0 (1.2)

Class = 0 (3.5)

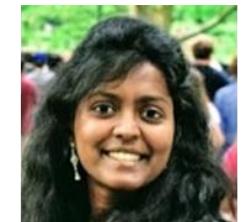


Unbound

Deep learning framework for decoding regulatory DNA



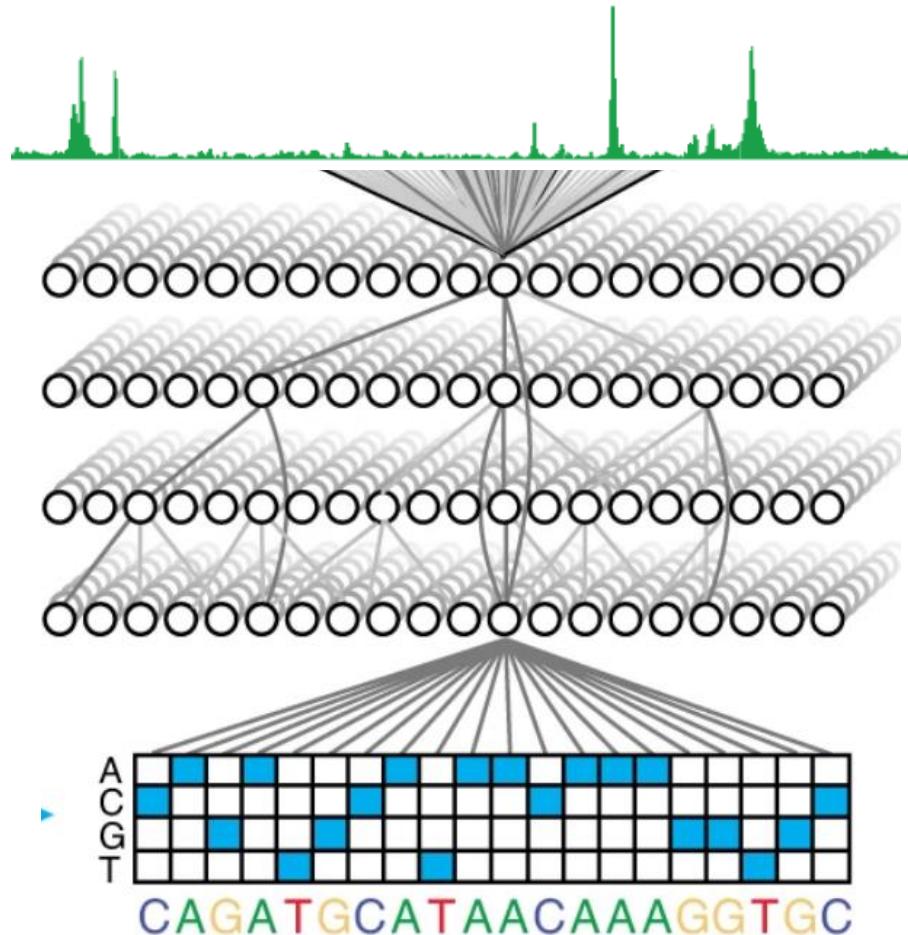
Ziga Avsec



Anusri Pampari



Anna Shcherbina



Avanti Shrikumar



Alex Tseng



Surag Nair



Jacob Schreiber

BPNet

(maps sequence to base-resolution profiles)

One model for every expt.

Avsec et al. 2021, *Nature Genetics*

Shrikumar et al. 2017, *ICML*

Tseng et al. 2020, *NeurIPS*

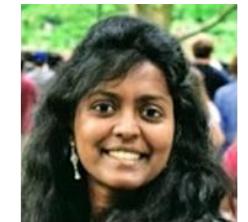
Nair et al. 2022, *Bioinformatics*

Schreiber et al. 2022, *Biorxiv*

Deep learning framework for decoding regulatory DNA



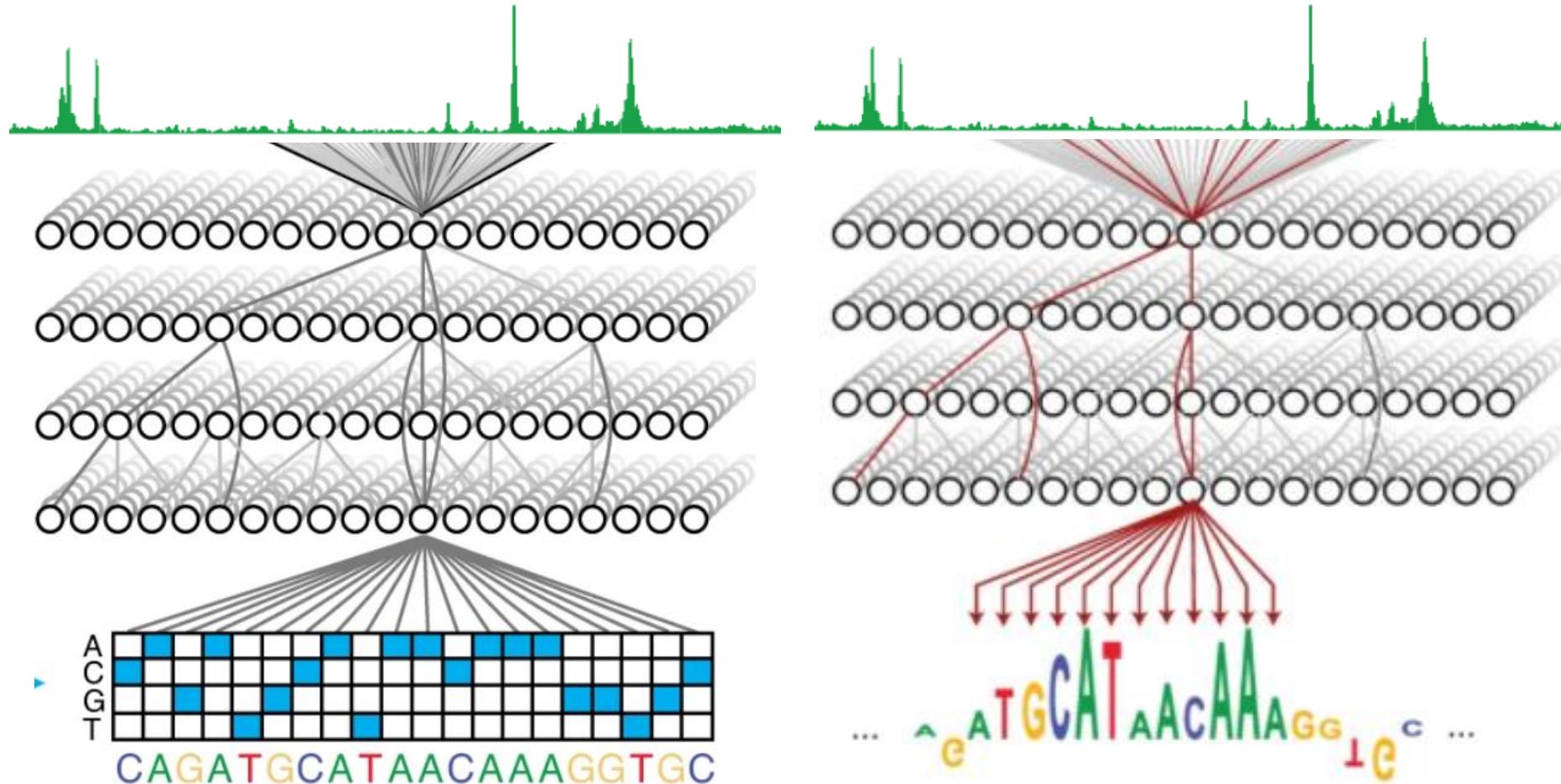
Ziga Avsec



Anusri Pampari



Anna Shcherbina



Avsec et al. 2021, *Nature Genetics*

Shrikumar et al. 2017, *ICML*

Tseng et al. 2020, *NeurIPS*

Nair et al. 2022, *Bioinformatics*

Schreiber et al. 2022, *Biorxiv*

BPNet
(maps sequence to base-resolution profiles)
One model for every expt.

DeepLIFT, FastISM, Yuzu
(infers contribution of every base in each
control sequence thru lens of model)



Avanti Shrikumar



Alex Tseng

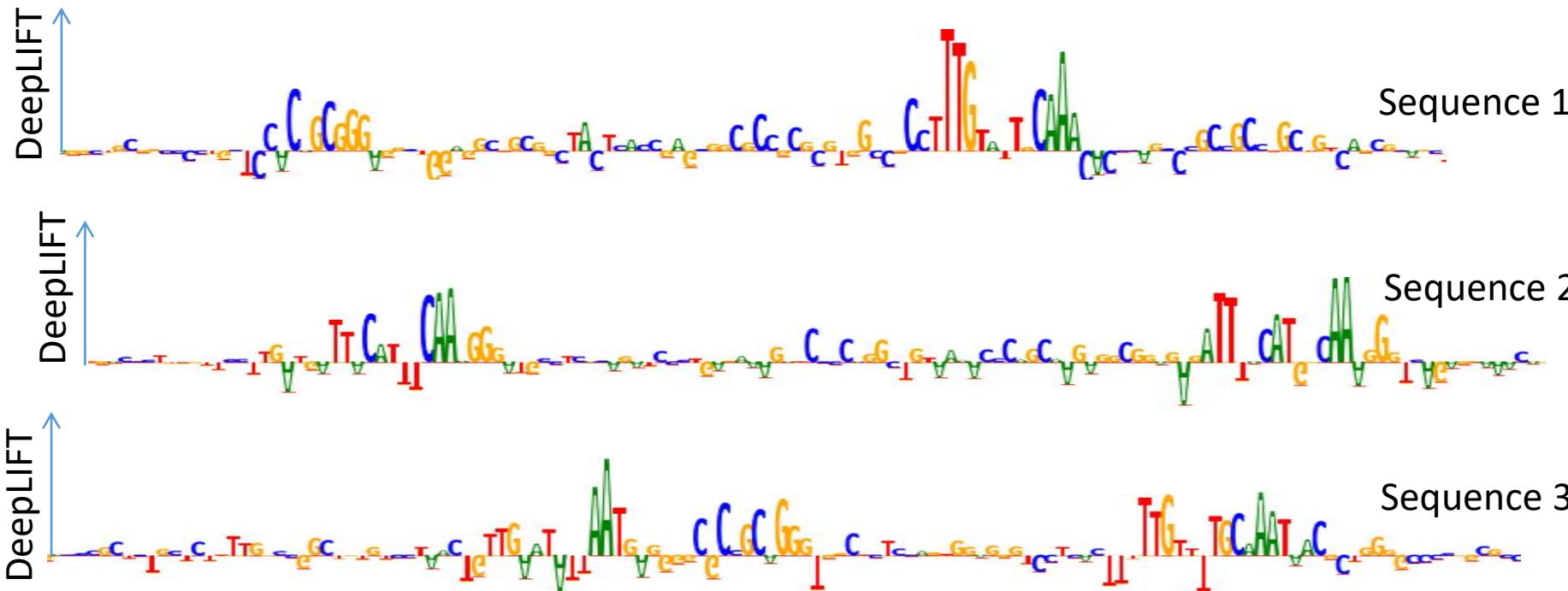


Surag Nair

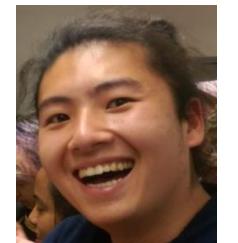


Jacob Schreiber

TF-MoDISCO: Consolidate predictive subsequences into non-redundant motif representations



Avanti Shrikumar

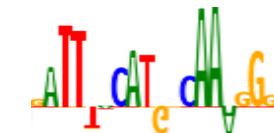
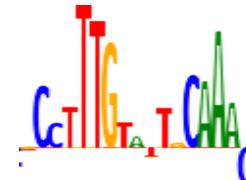
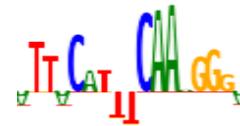


Alex Tseng

Shrikumar et al. 2018

Avsec et al. Nature Genetics 2021

TF-MoDISCO: Consolidate predictive subsequences into non-redundant motif representations



Avanti Shrikumar

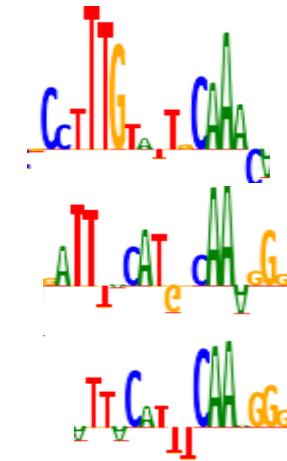
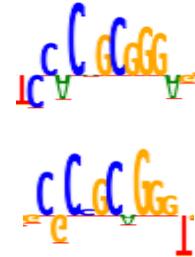


Alex Tseng

Shrikumar et al. 2018

Avsec et al. Nature Genetics 2021

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Avanti Shrikumar



Alex Tseng

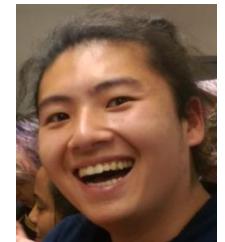
Shrikumar et al. 2018

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TF-MoDISCO: Consolidate predictive subsequences into non-redundant motif representations



Avanti Shrikumar

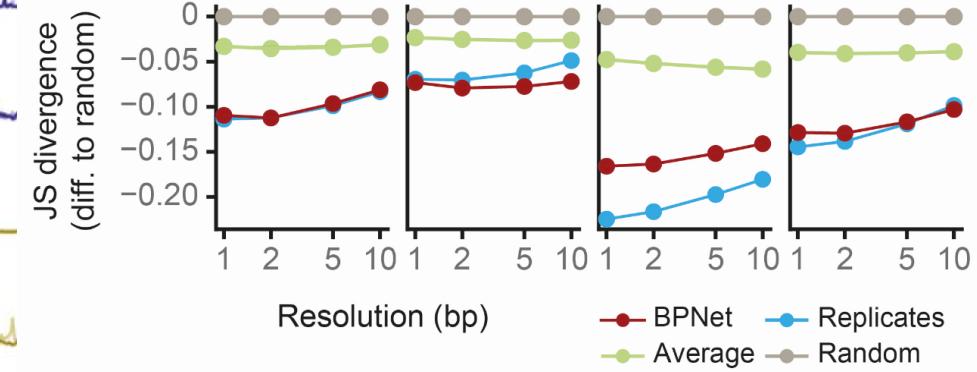
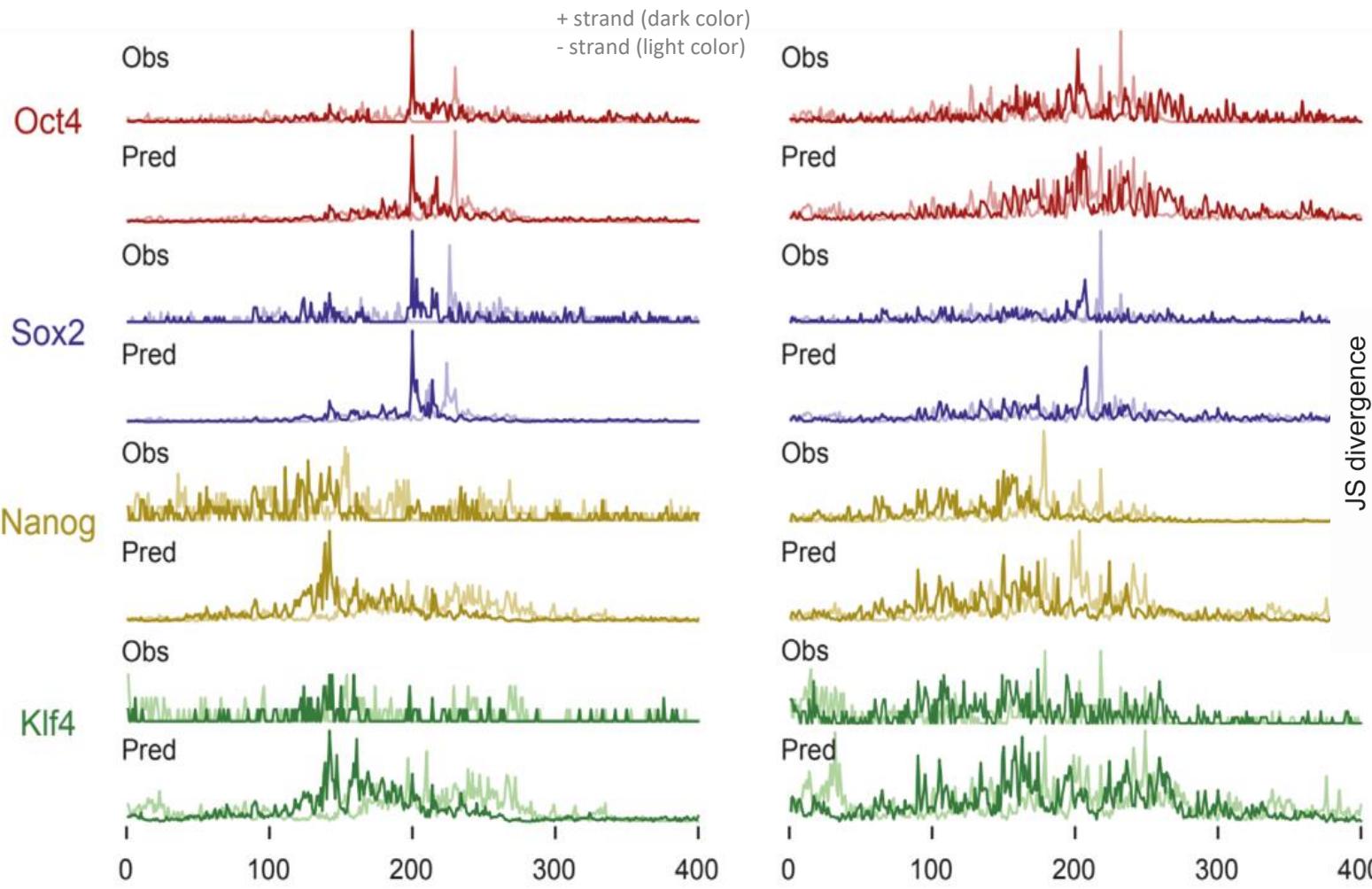


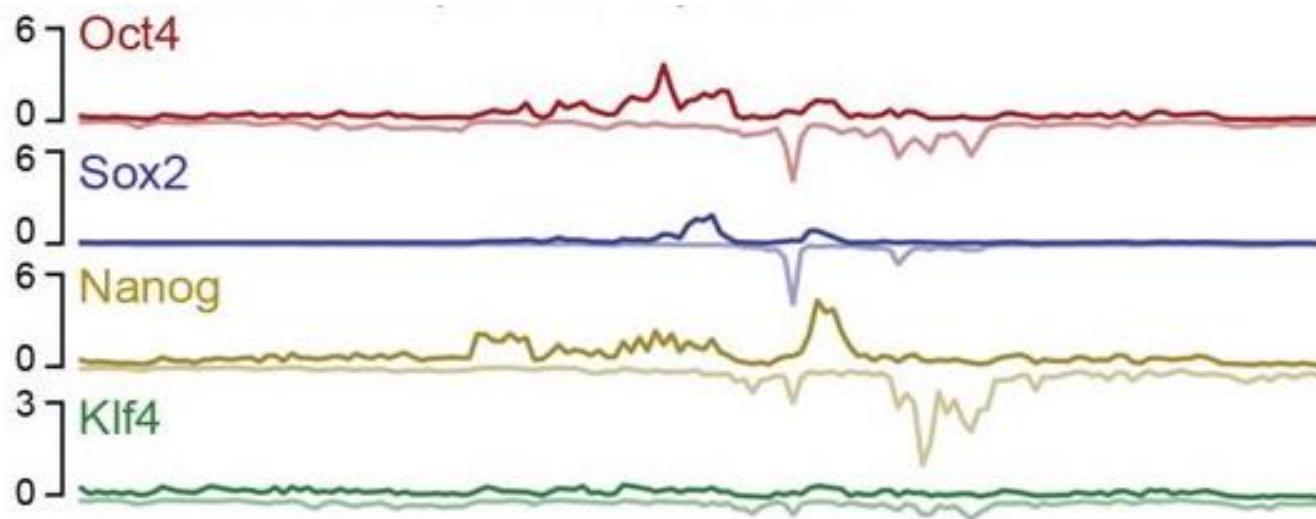
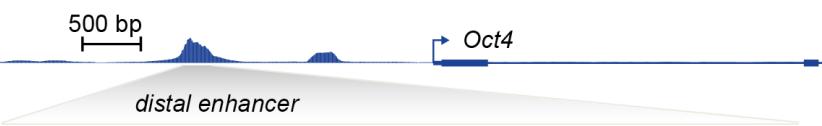
Alex Tseng

Shrikumar *et al.* 2018

Avsec *et al.* *Nature Genetics* 2021

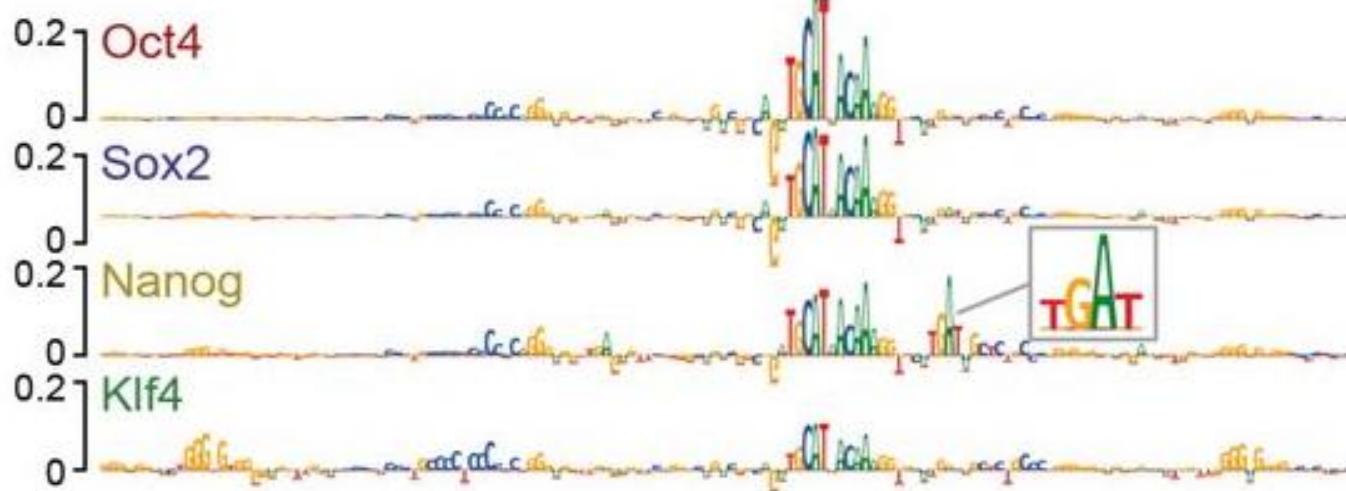
BPNet maps DNA sequence to base-resolution molecular profiles with accuracy on par with replicate expt. concordance





Profile contribution scores

DeepLIFT

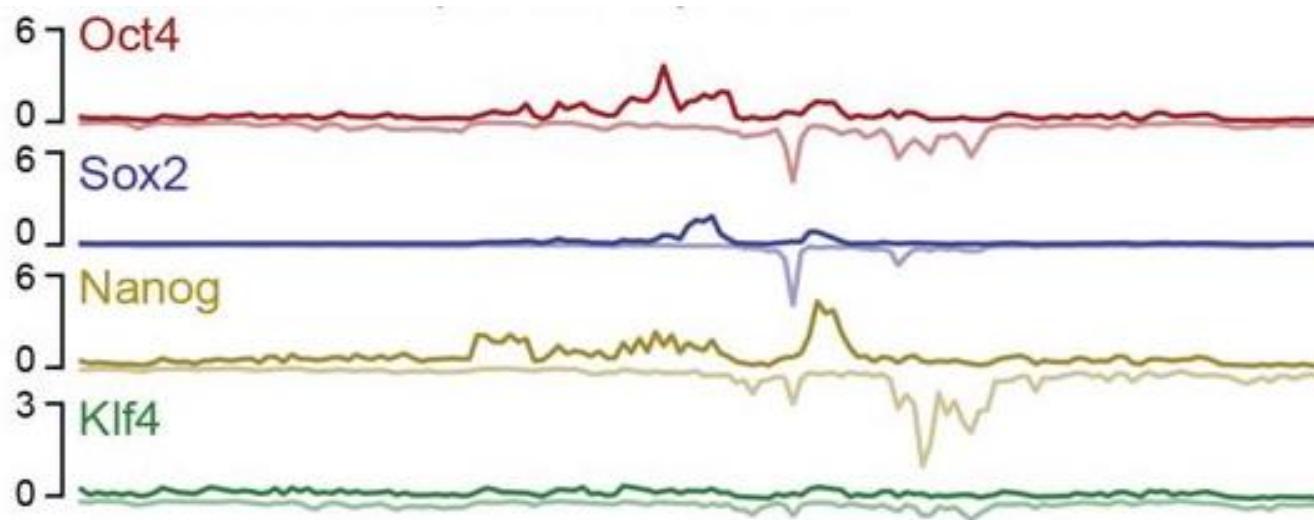
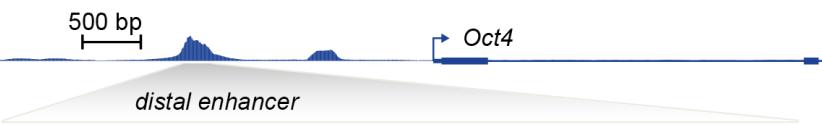


Avanti Shrikumar



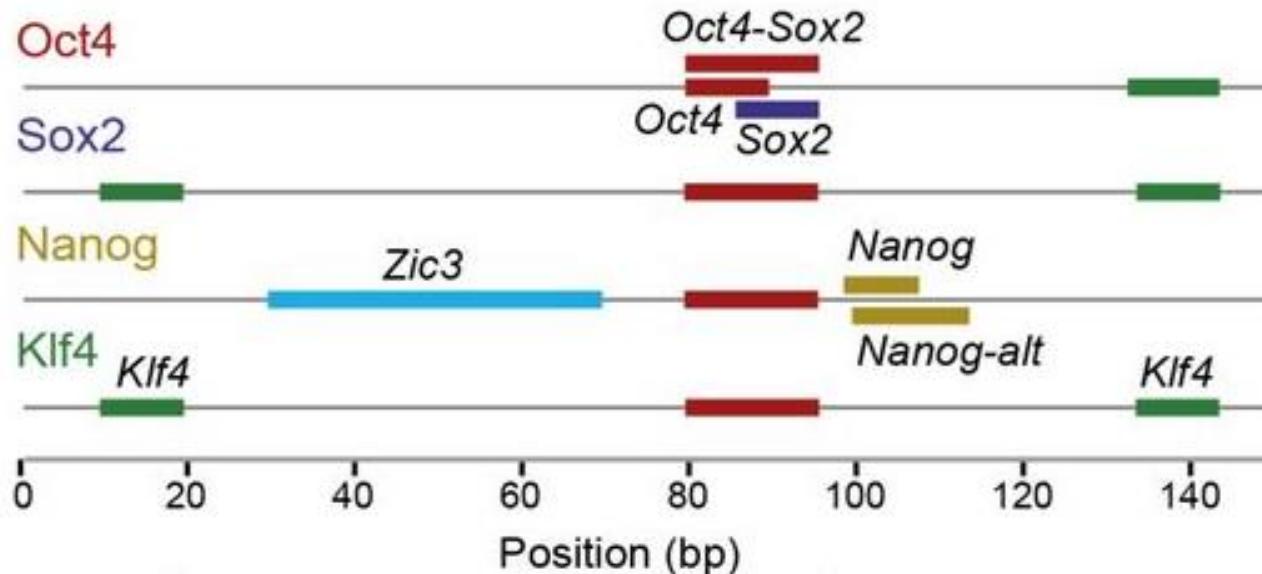
Alex Tseng

Shrikumar et al. 2017 ICML
 Shrikumar et al. 2019 ISMB
 Tseng et al. 2020 NeurIPS
 Greenside et al. 2018, ECCB



Profile contribution scores

DeepLIFT



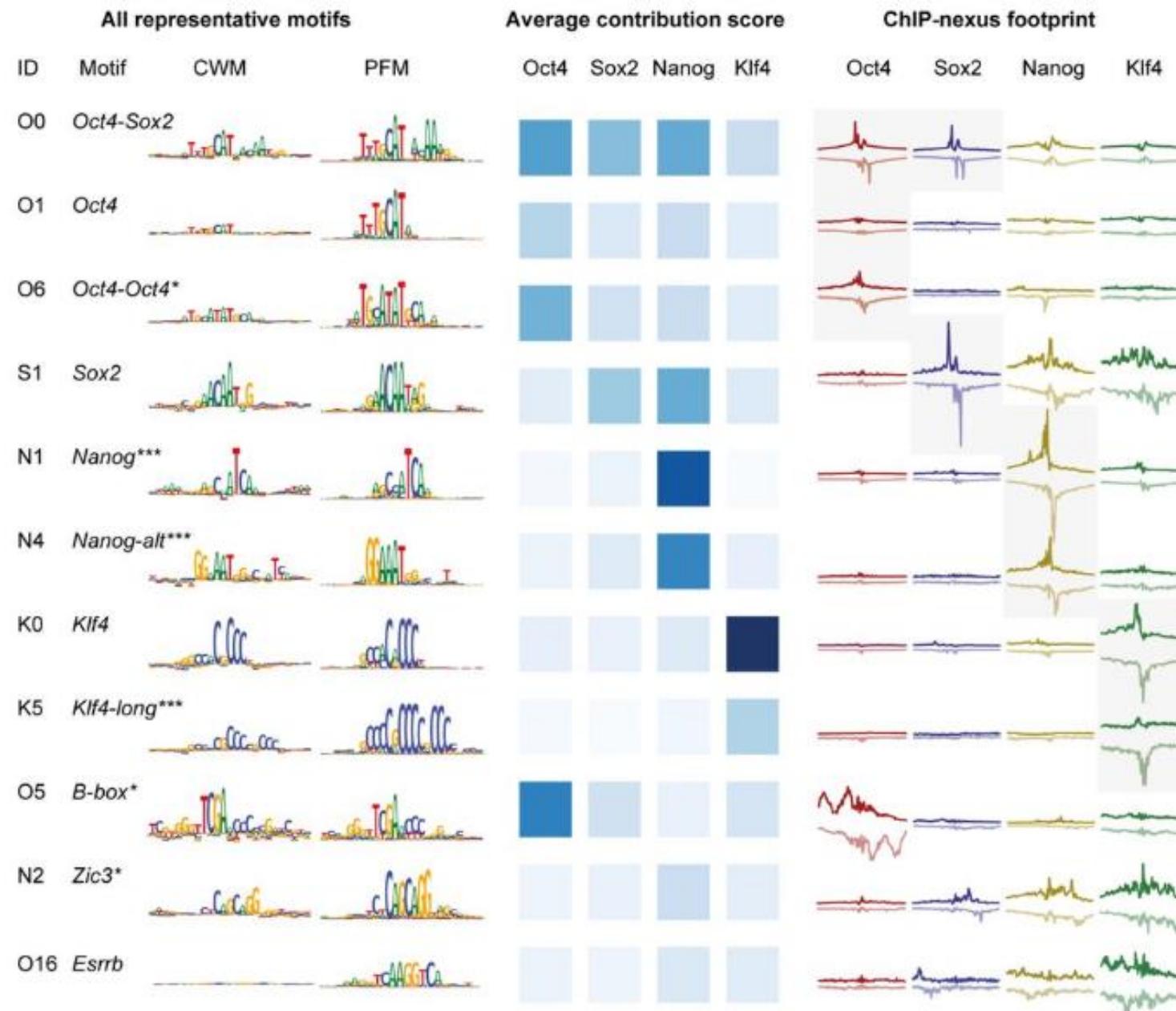
Avanti Shrikumar



Alex Tseng

Shrikumar et al. 2017 ICML
 Shrikumar et al. 2019 ISMB
 Tseng et al. 2020 NeurIPS
 Greenside et al. 2018, ECCB

Complex repertoire of motifs due to cooperative binding



50 motifs for 4 TFs!

Syntax discovery using *in-silico* perturbations

Use BPNet model as in-silico oracle to perform perturbation experiments



- 1) On synthetic sequences

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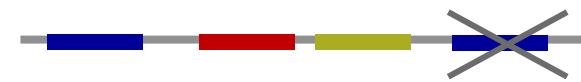
2) By mutating genomic sequences

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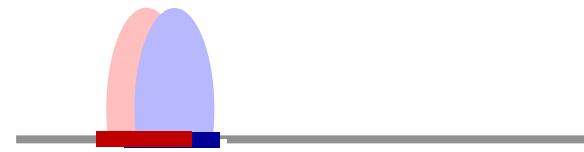
1) On synthetic sequences



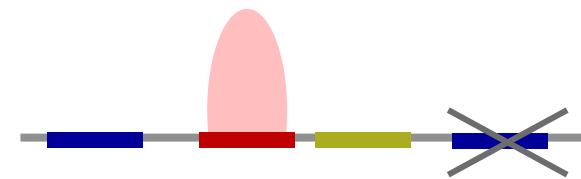
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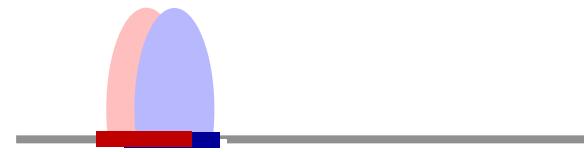
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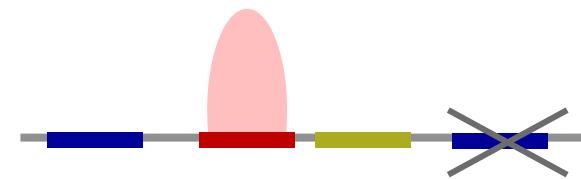
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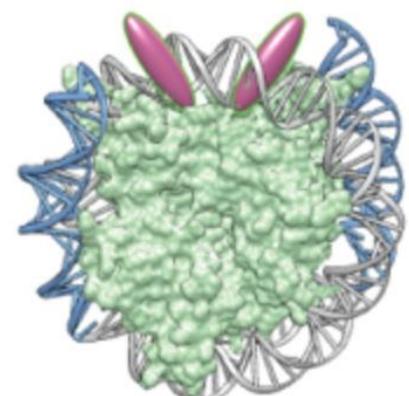
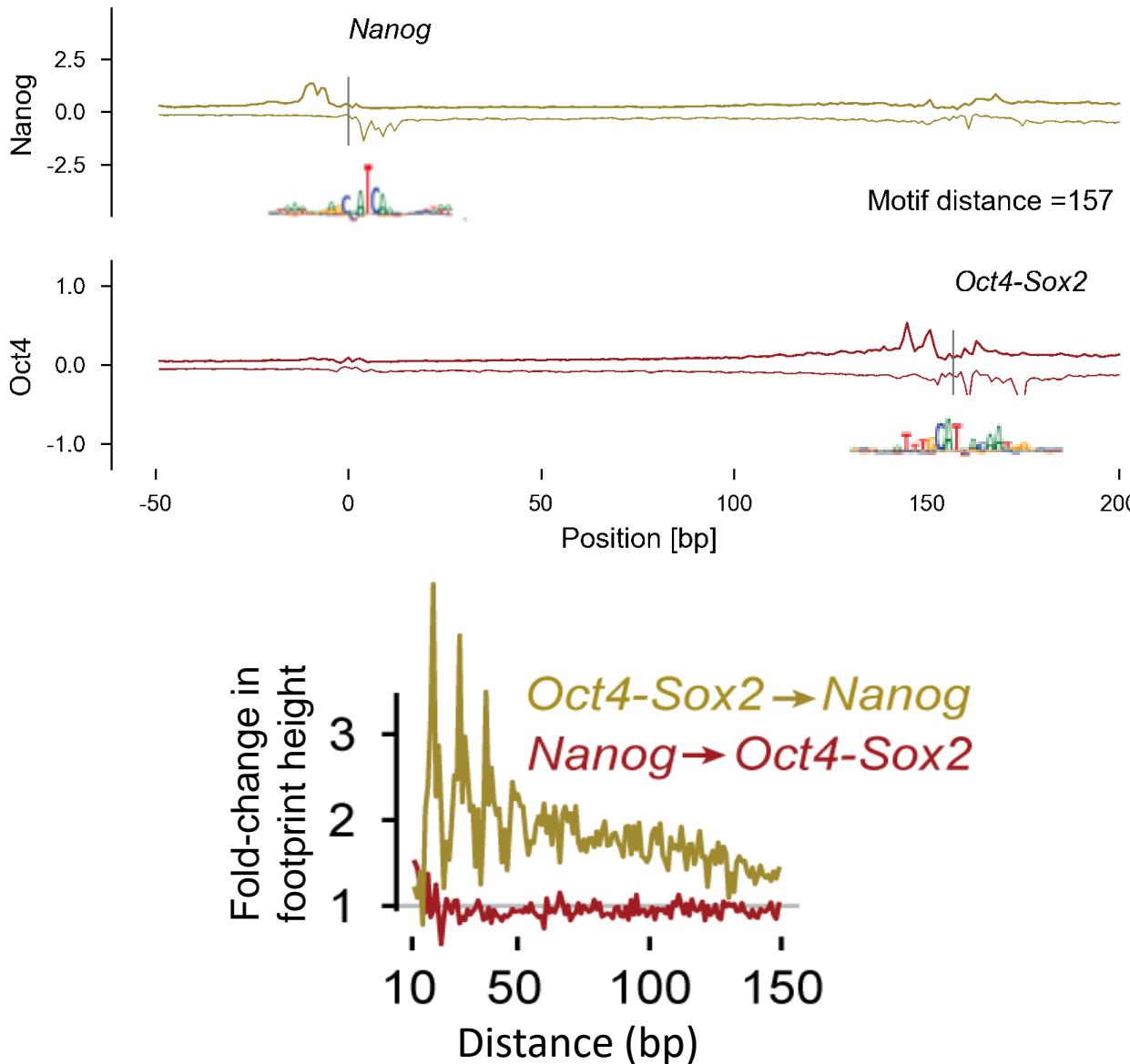
In silico biochemistry



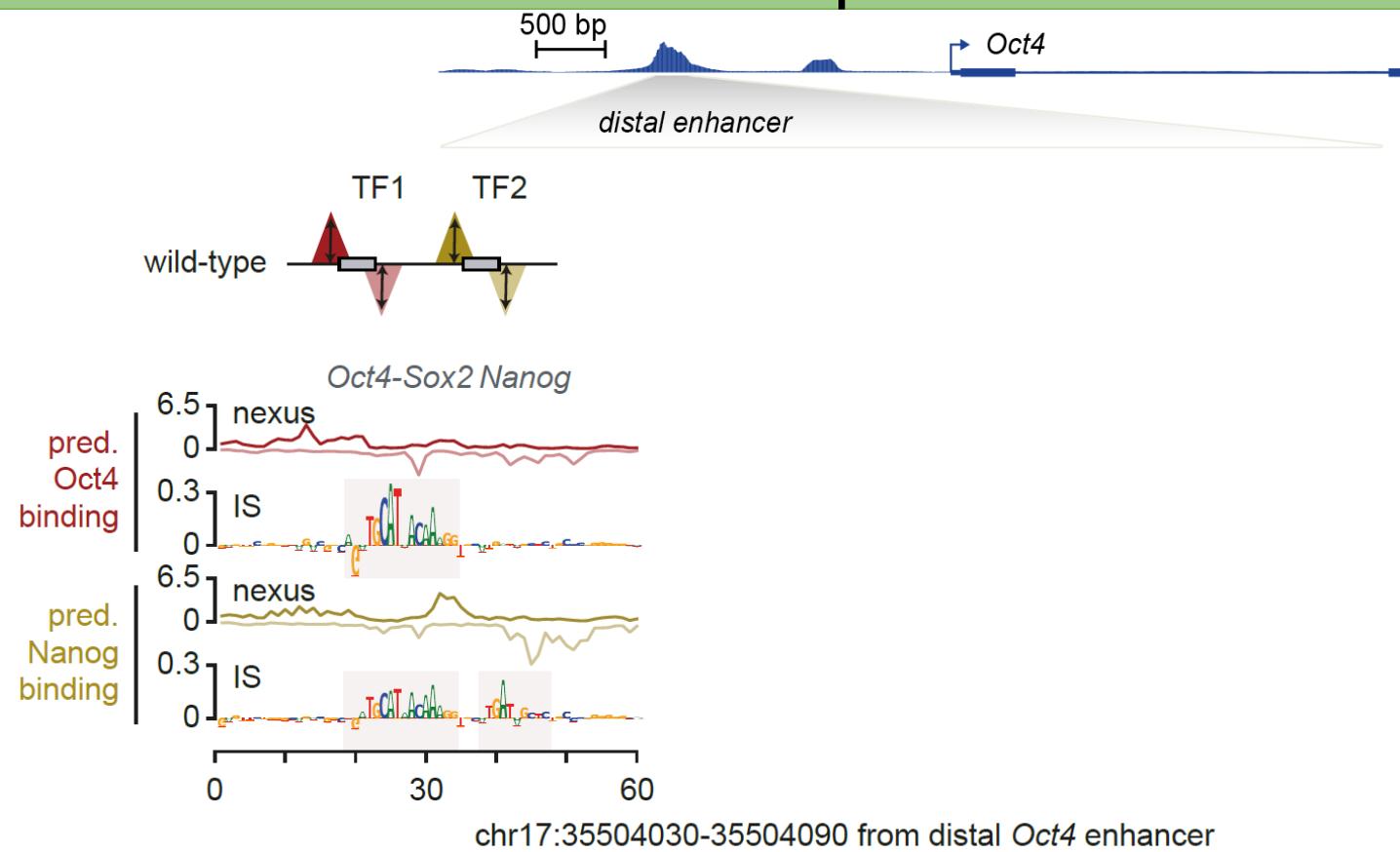
- 2) By mutating genomic sequences

In silico genetics

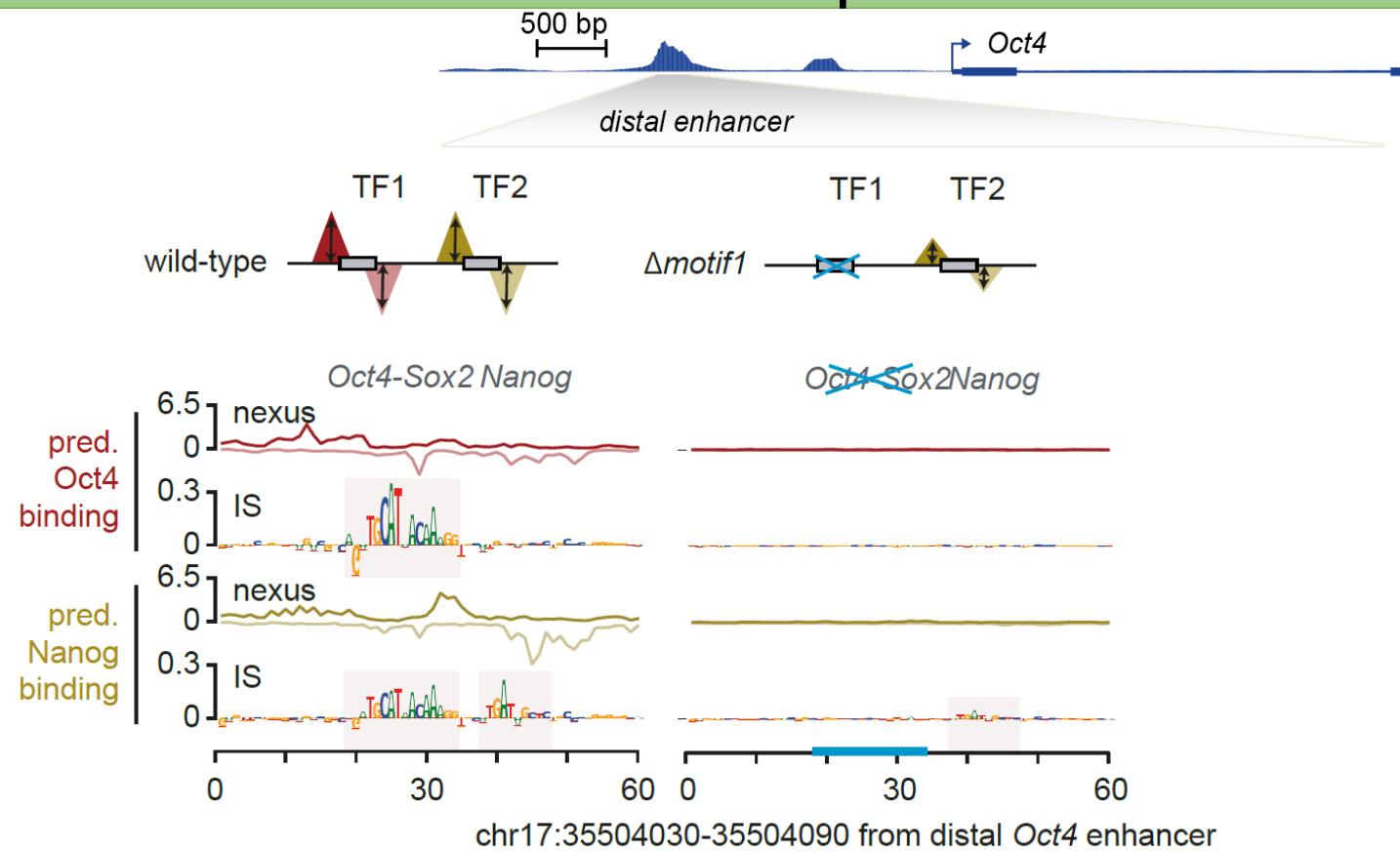
In-silico reporters: Designing synthetic sequences to query models to reveal syntax



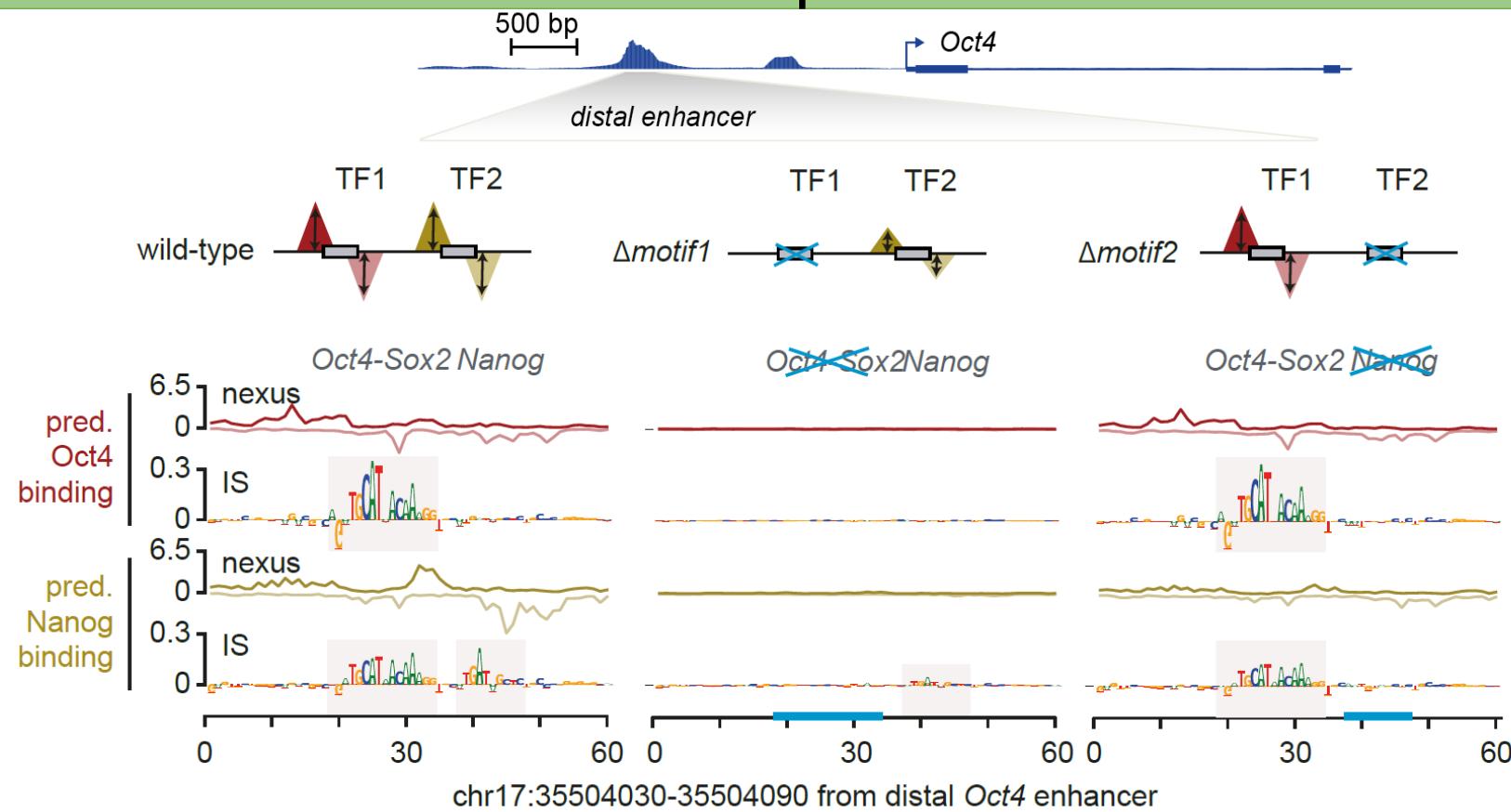
in-silico genome editing: Deciphering syntax by perturbing genomic sequences



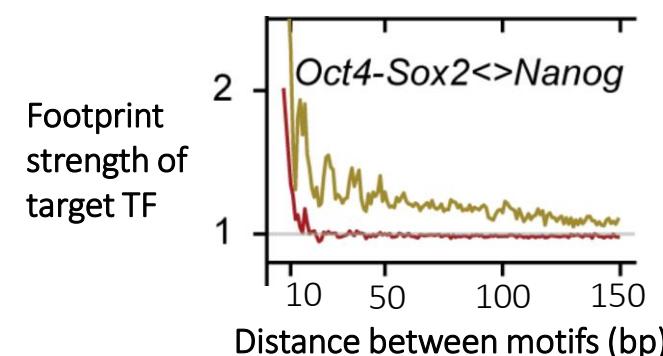
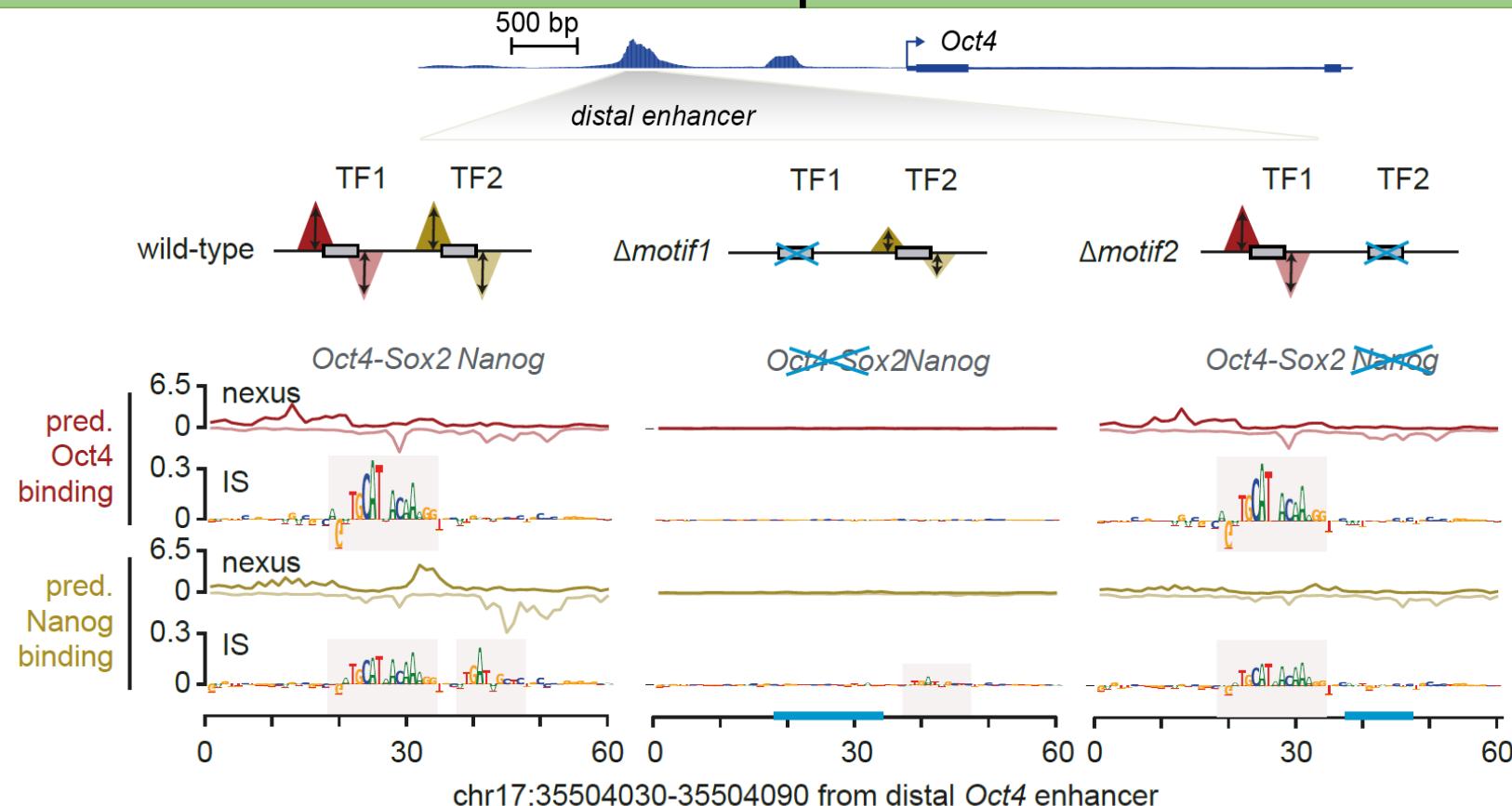
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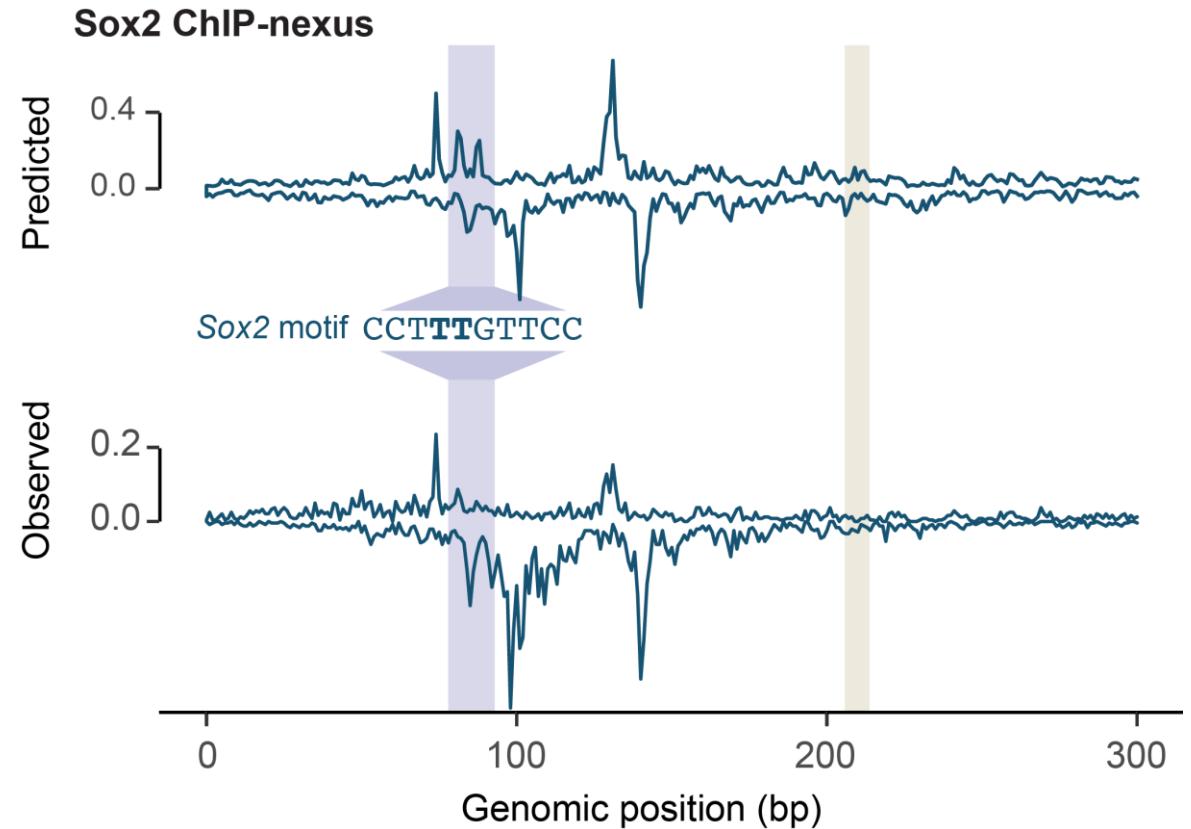
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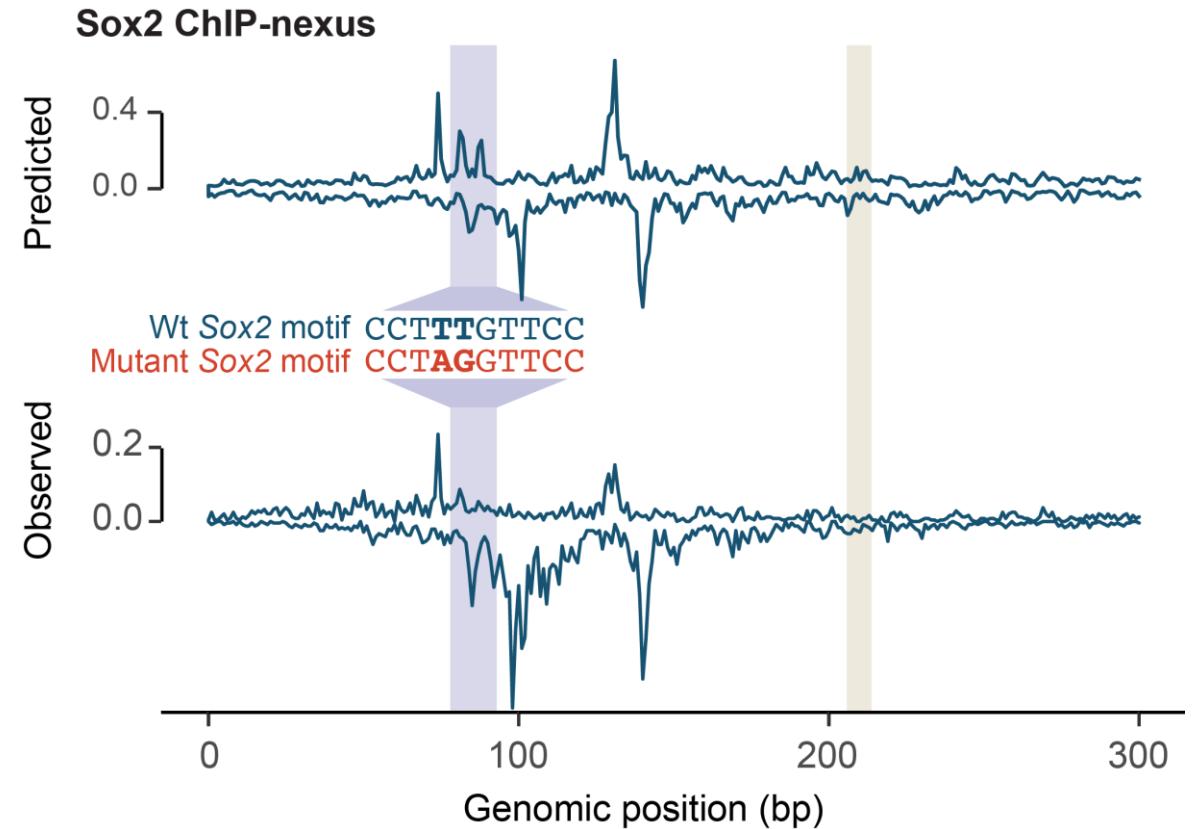


Designing CRISPR experiments to validate motif syntax



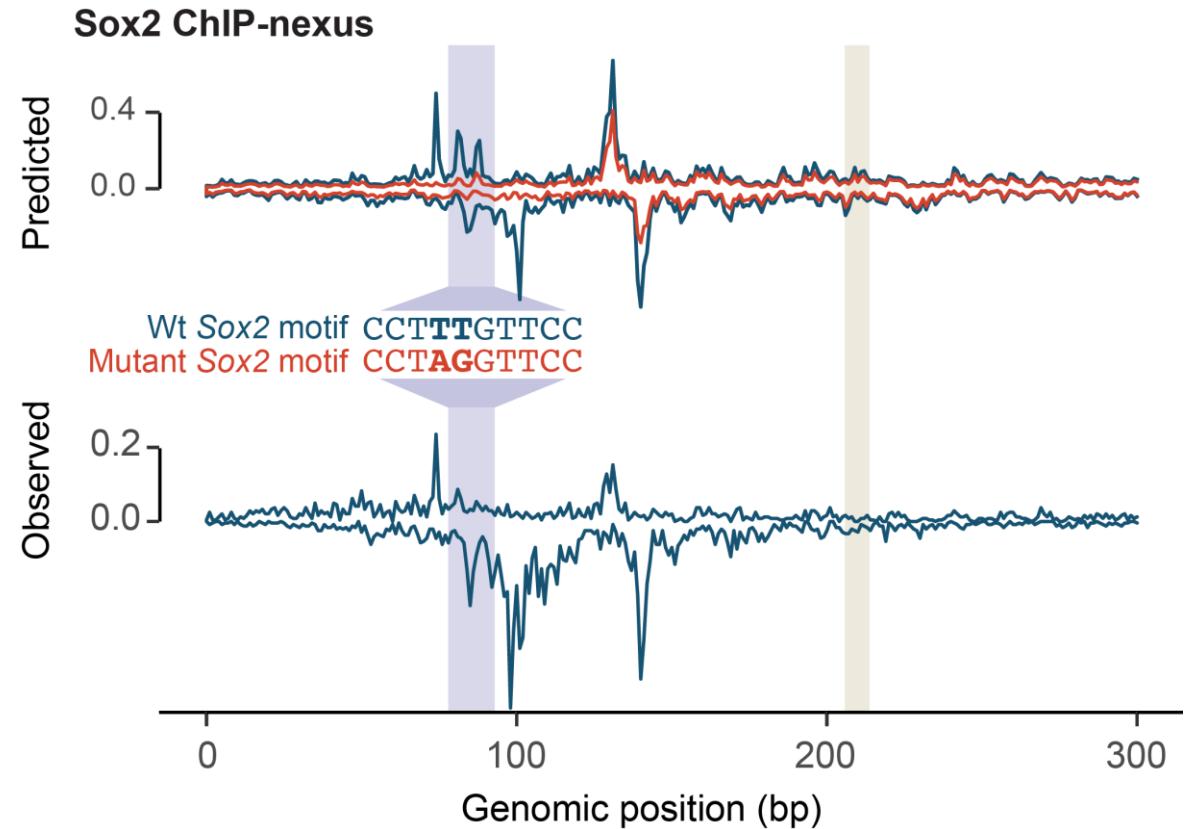
Julia Zeitlinger, Sabrina Krueger, Melanie Weilert

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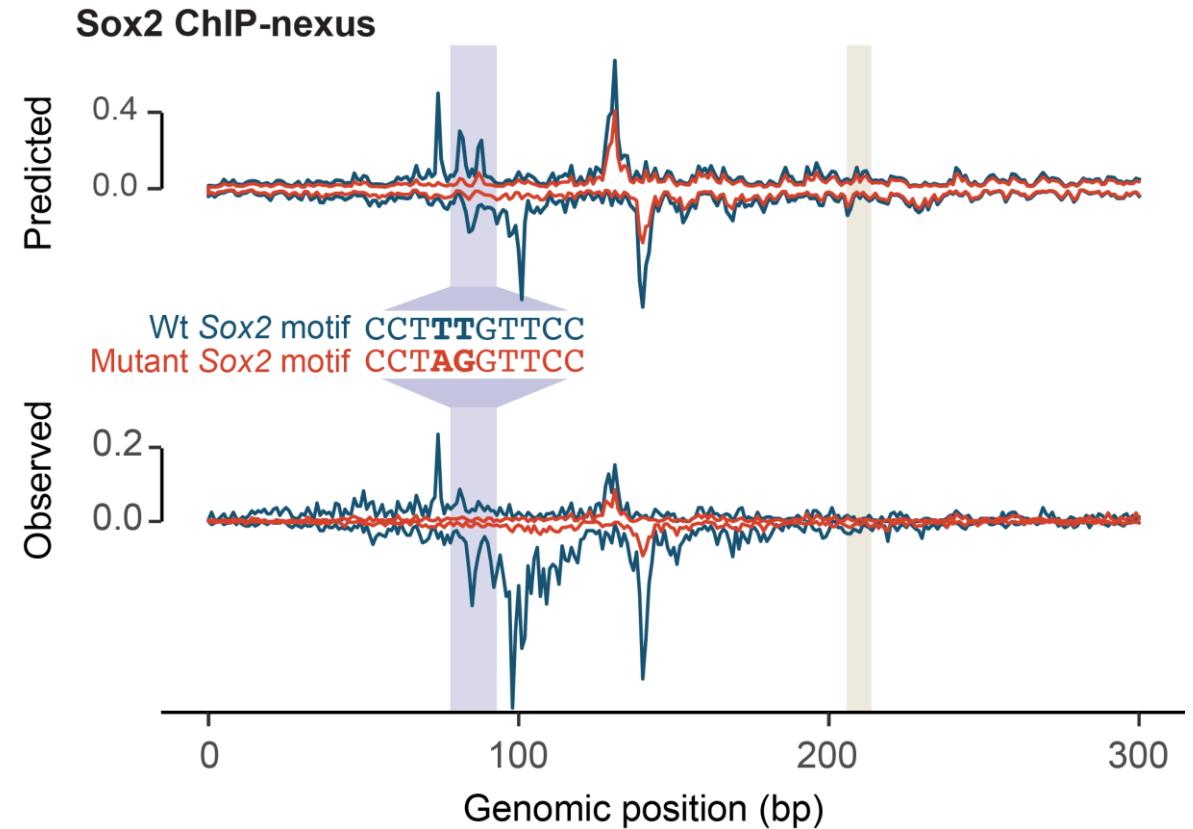
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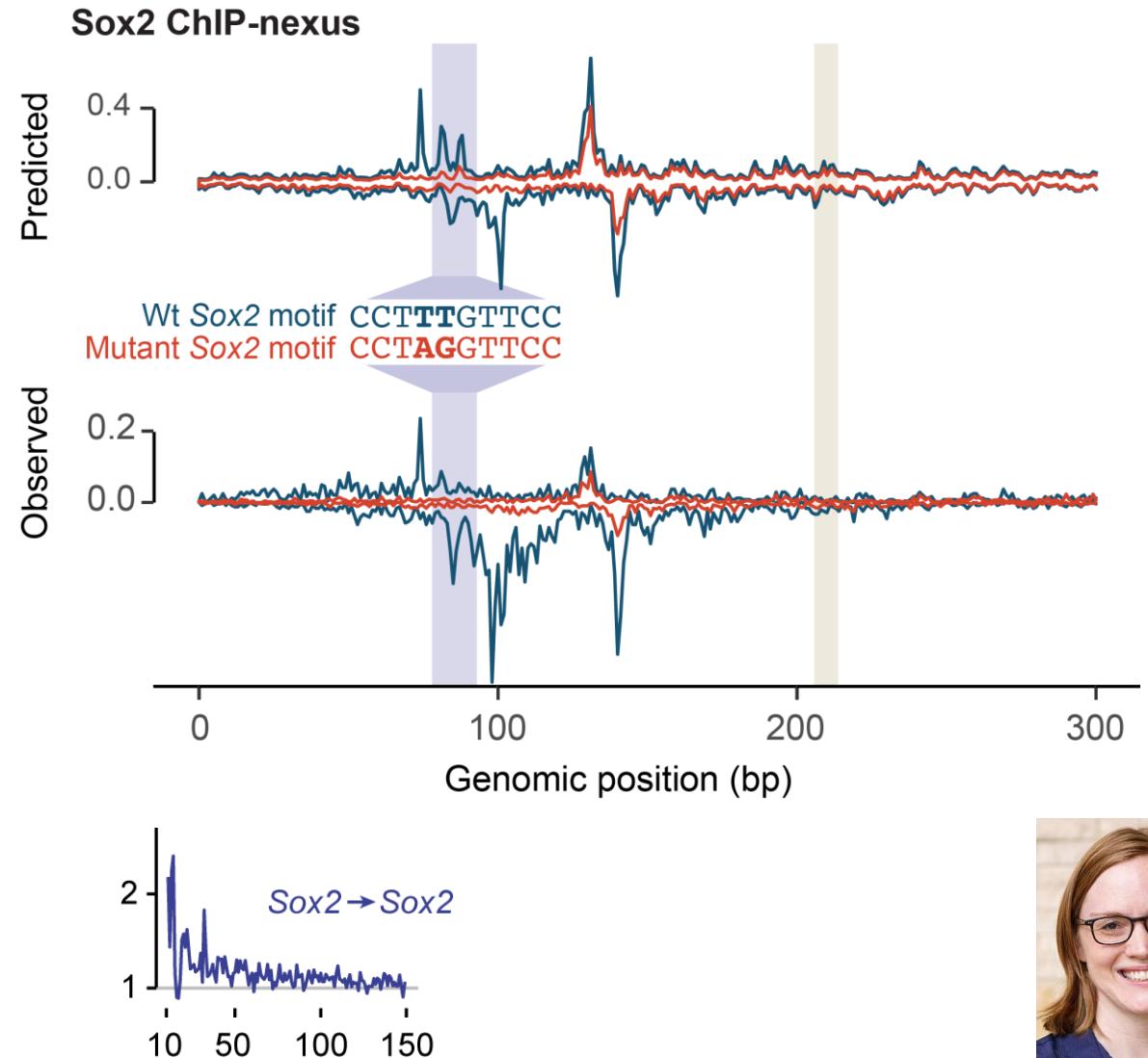
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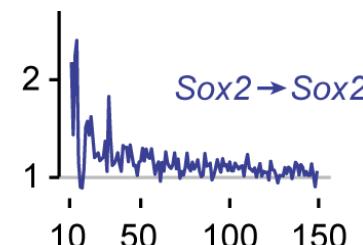
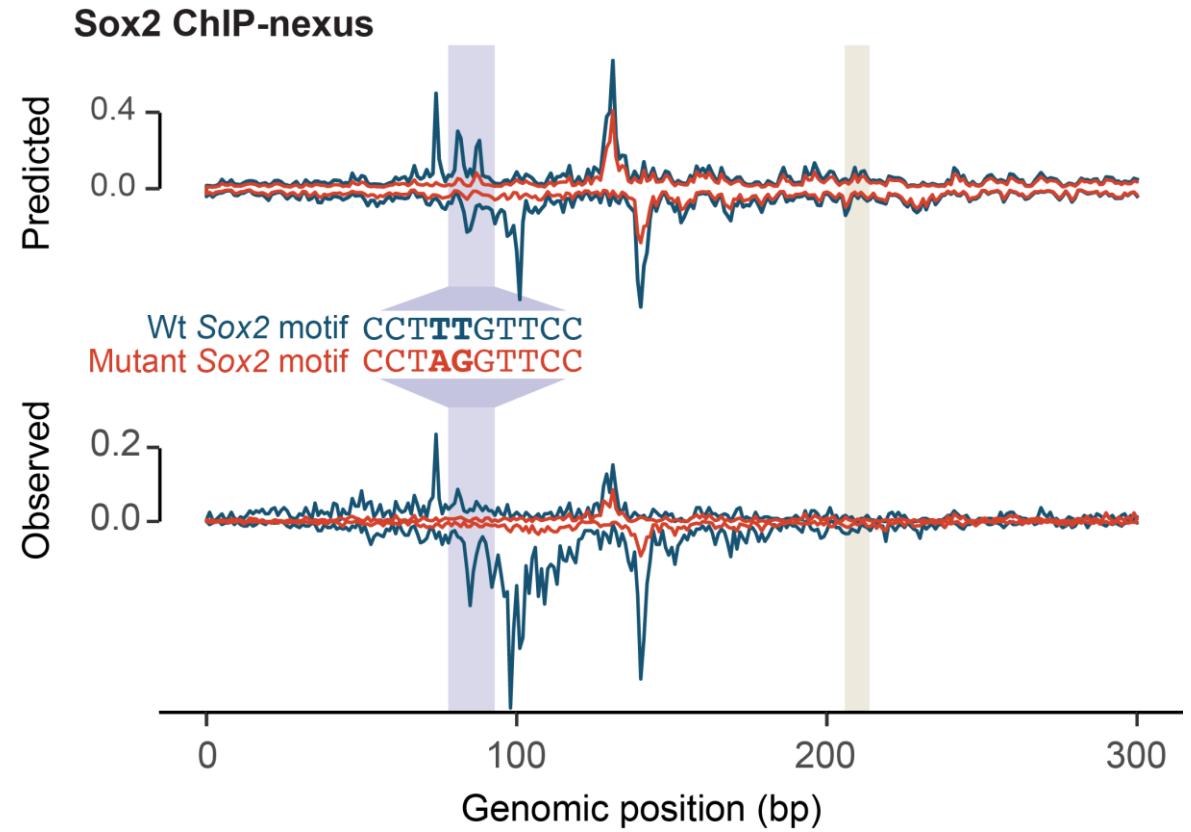
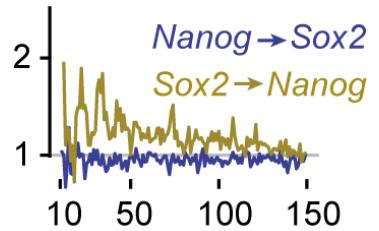
Julia Zeitlinger, Sabrina Krueger, Melanie Weilert

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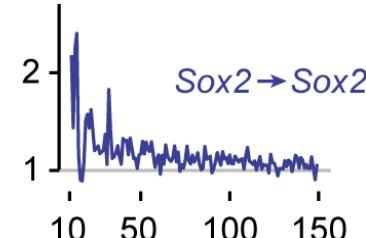
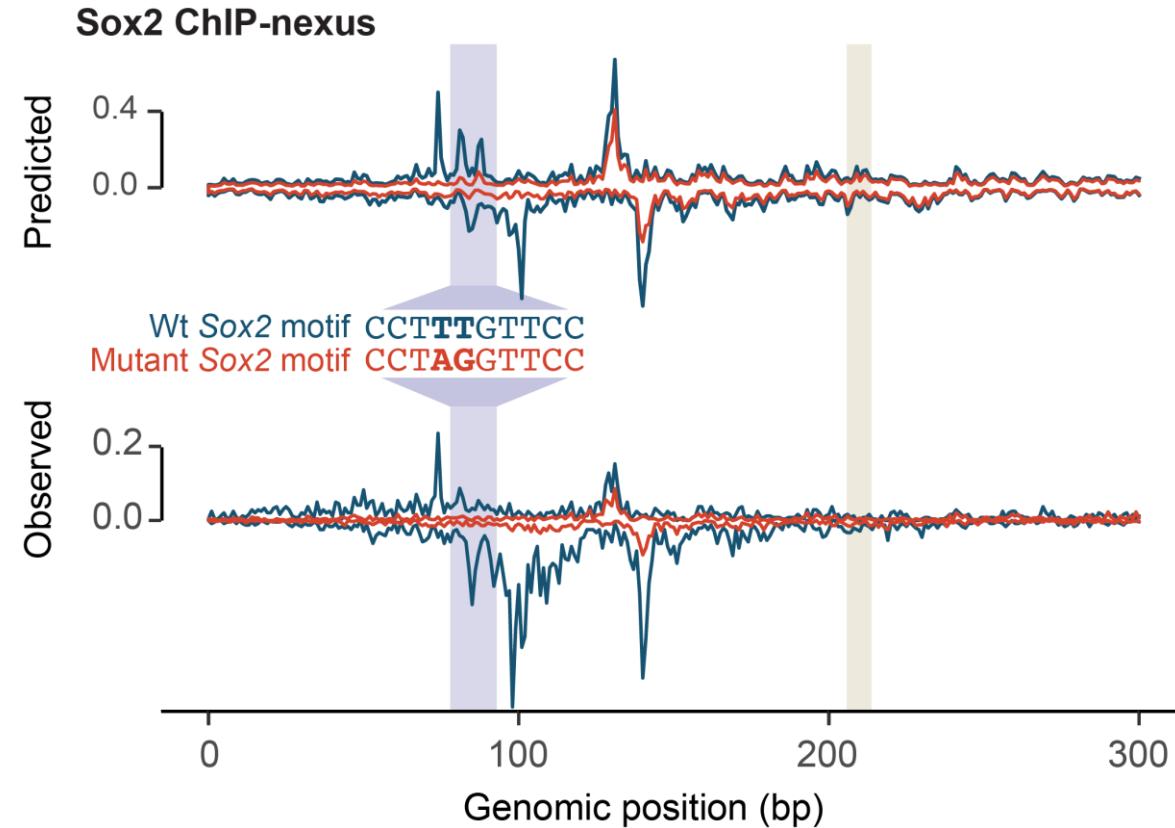
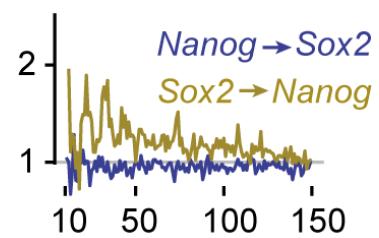
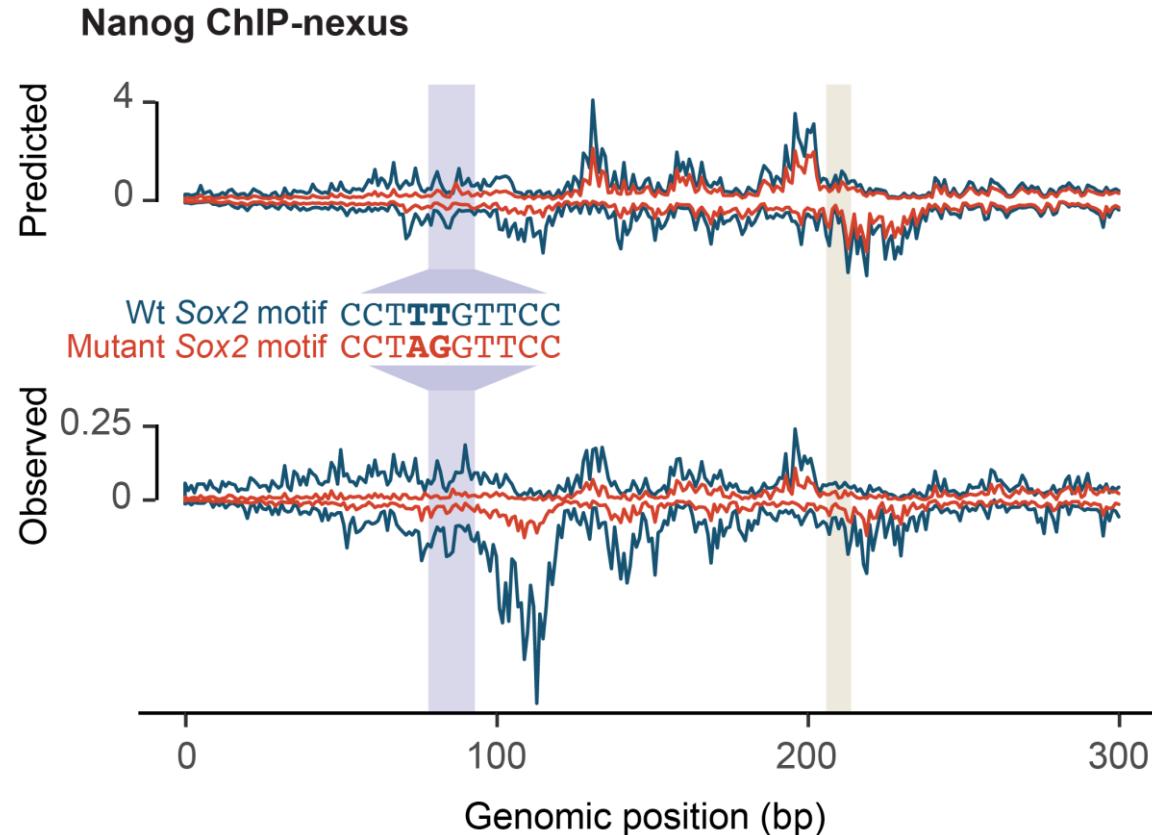
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Designing CRISPR experiments to validate motif syntax



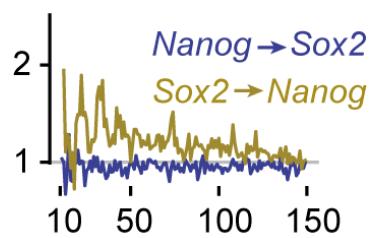
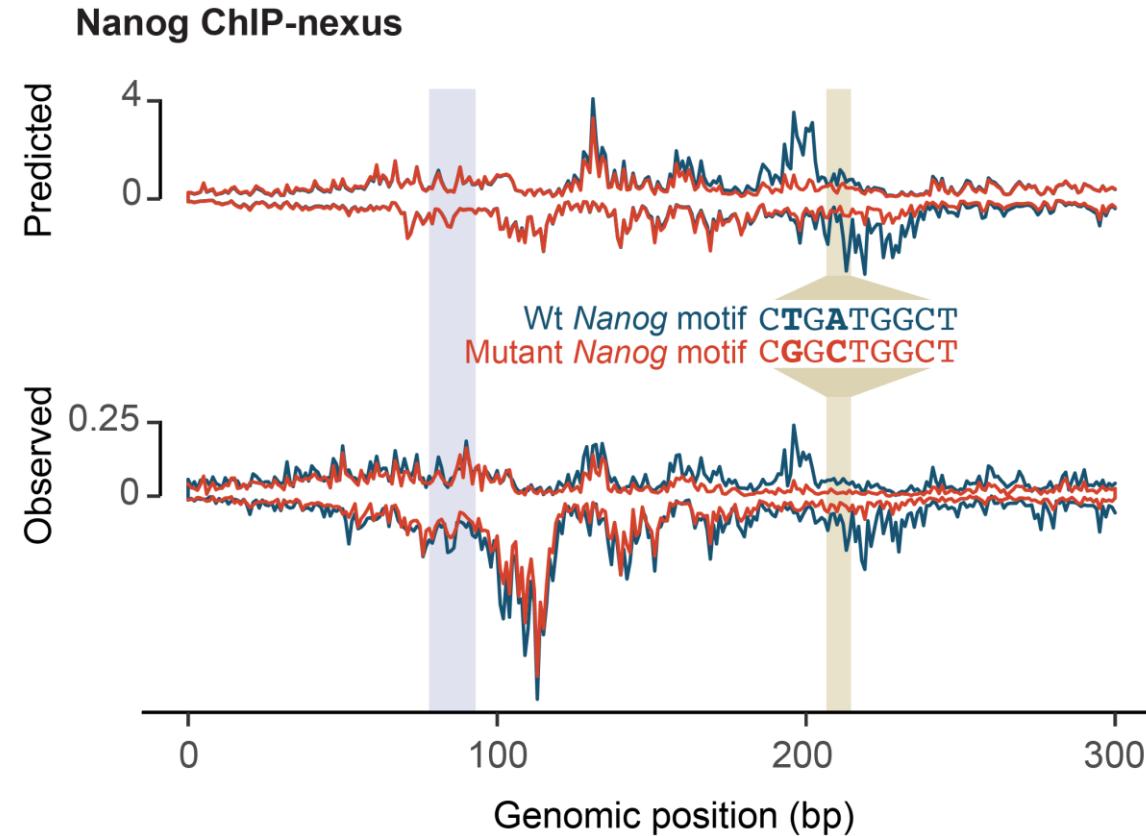
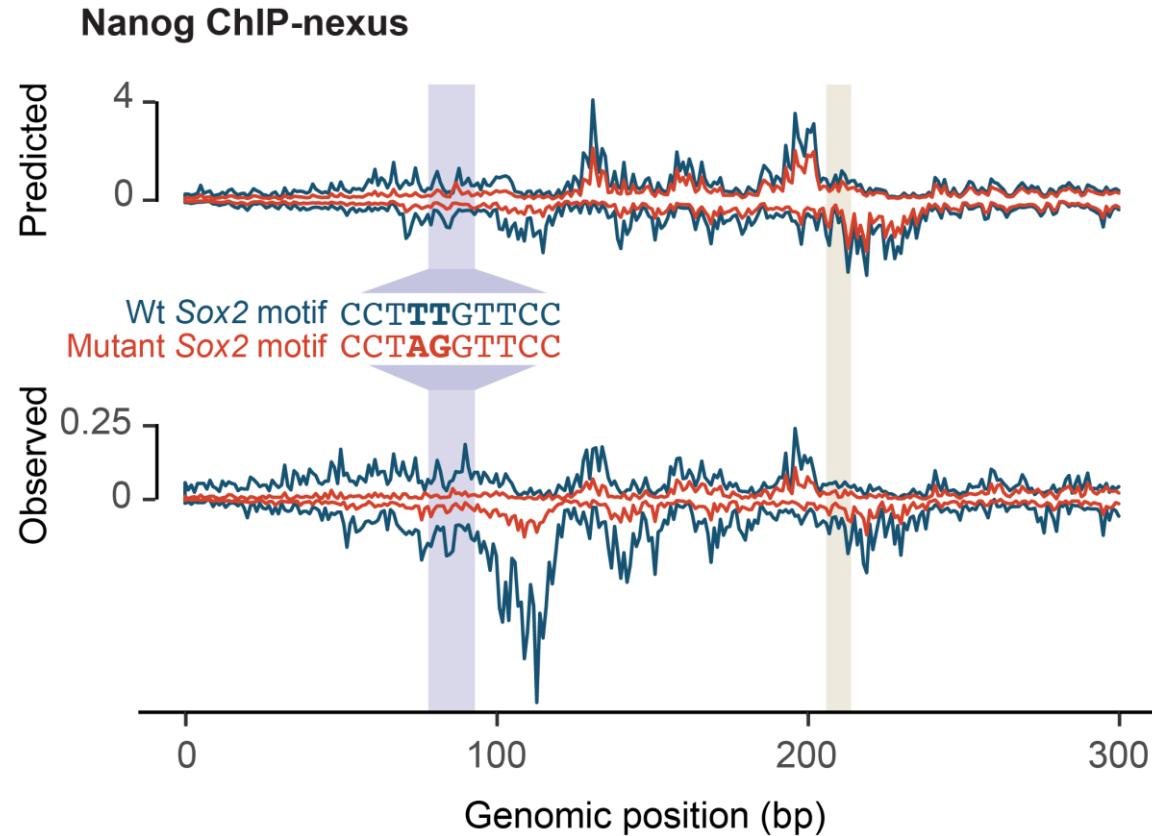
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Designing CRISPR experiments to validate motif syntax



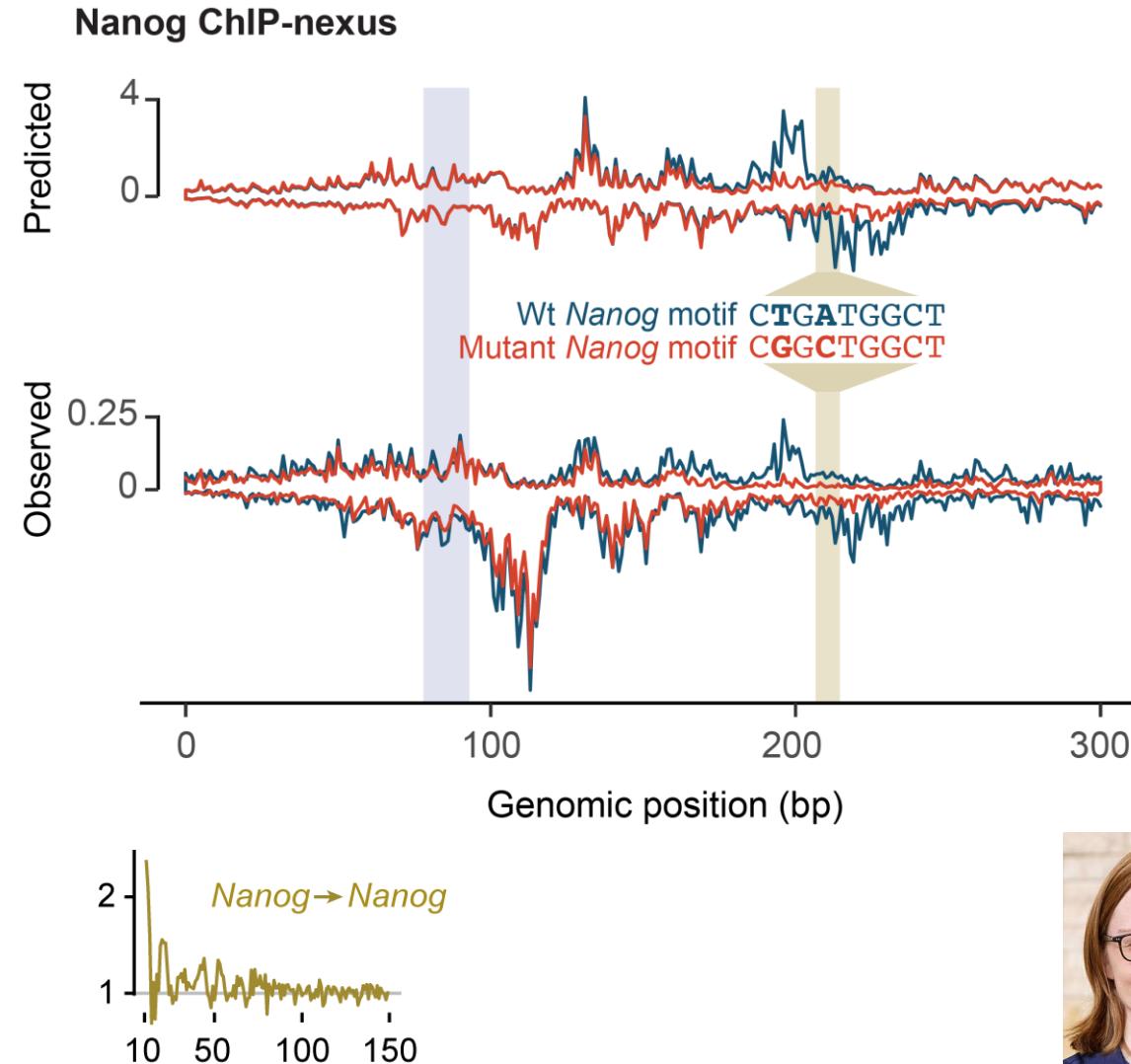
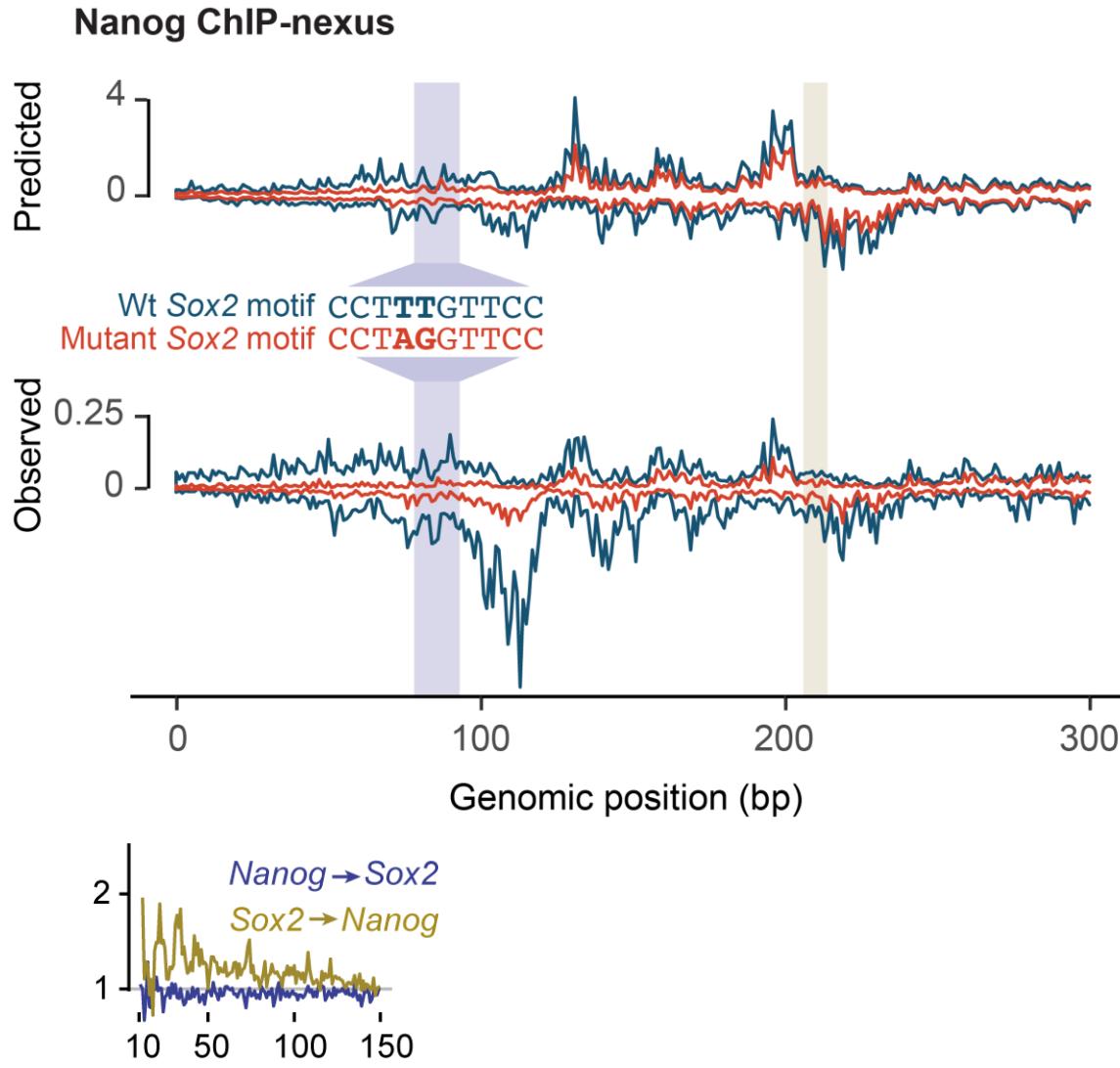
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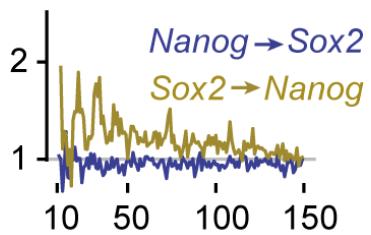
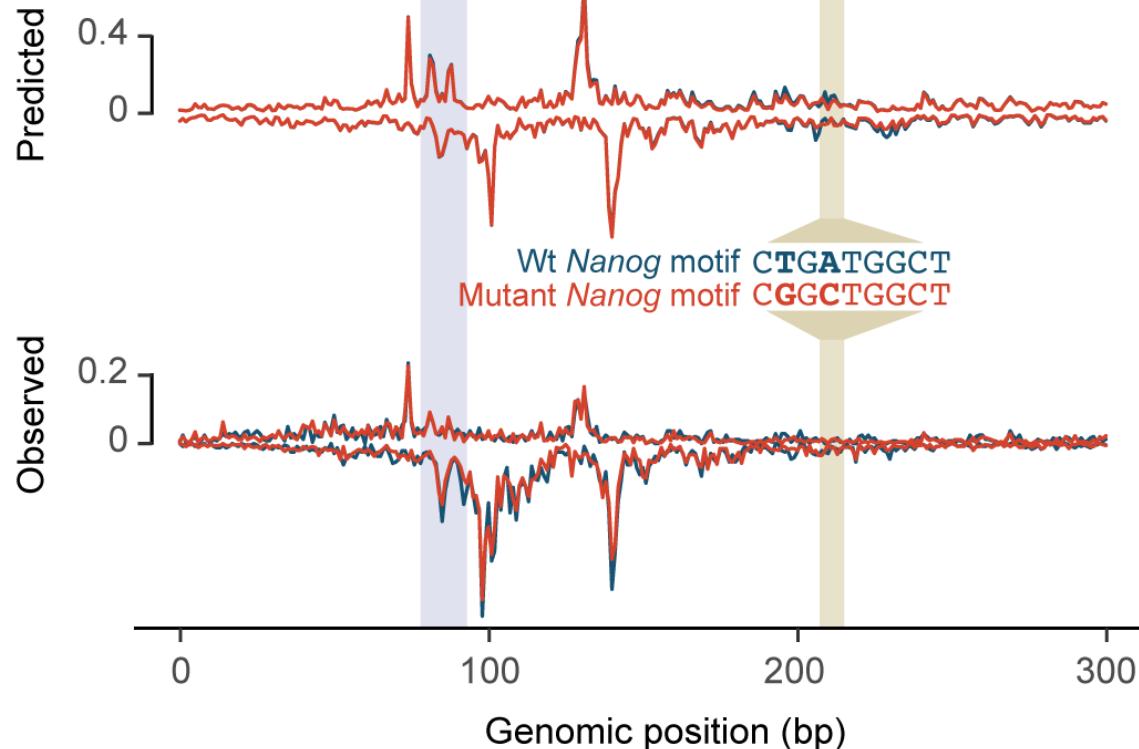
Designing CRISPR experiments to validate motif syntax



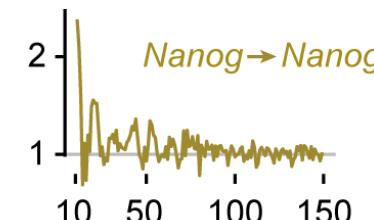
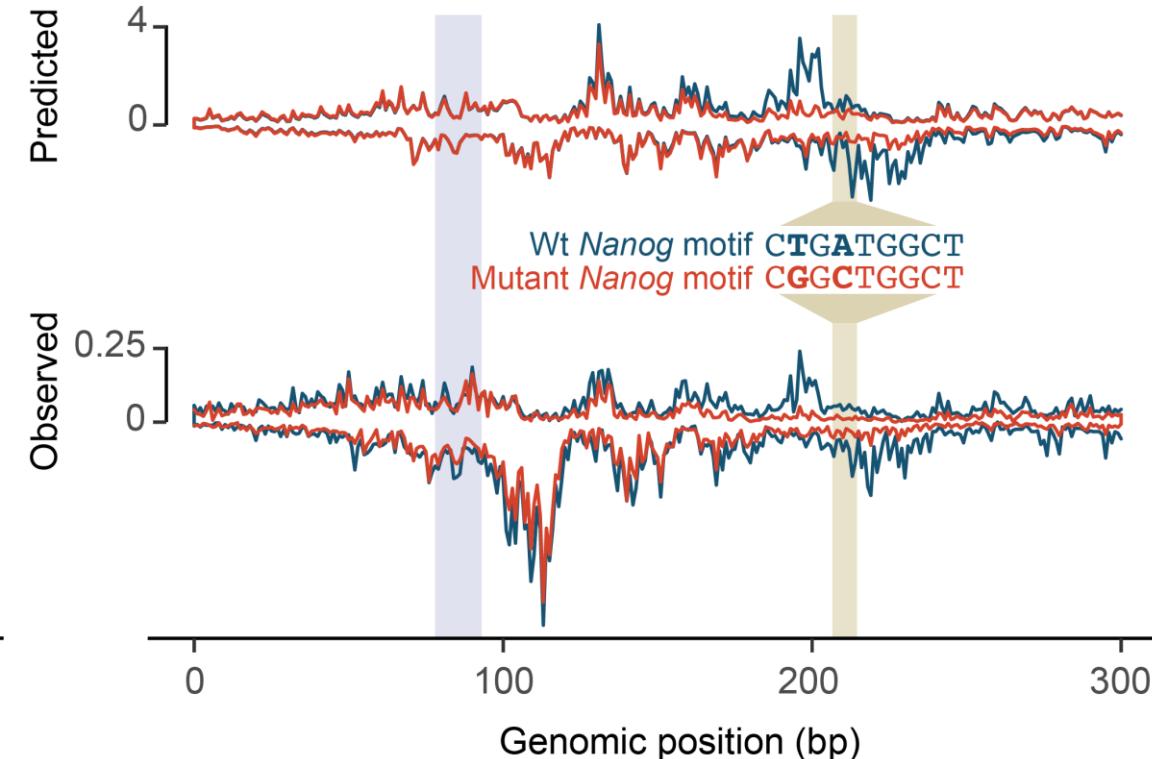
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Designing CRISPR experiments to validate motif syntax

Sox2 ChIP-nexus



Nanog ChIP-nexus



Julia Zeitlinger, Sabrina Krueger, Melanie Weilert

Deciphering genetic variants



Soumya Kundu



Laksshman Sundaram



Ryan Corces



Howard Chang



Tom Montine



Mo Ameen



Tom
Quertermous



Will Greenleaf

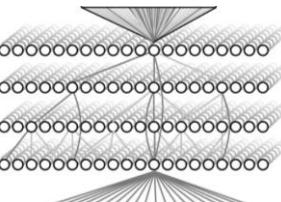


Sergiu Pasca

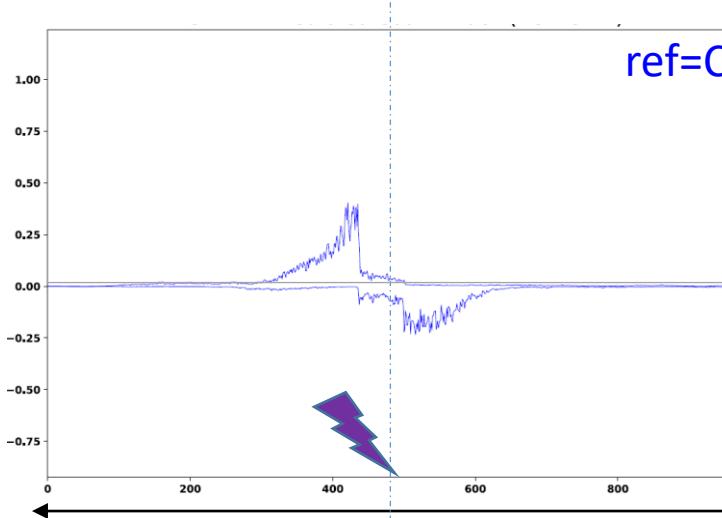
In-silico mutagenesis: Predict effect of genetic variant on molecular activity

Predicted molecular profile of protein-DNA binding

PredictedSignal

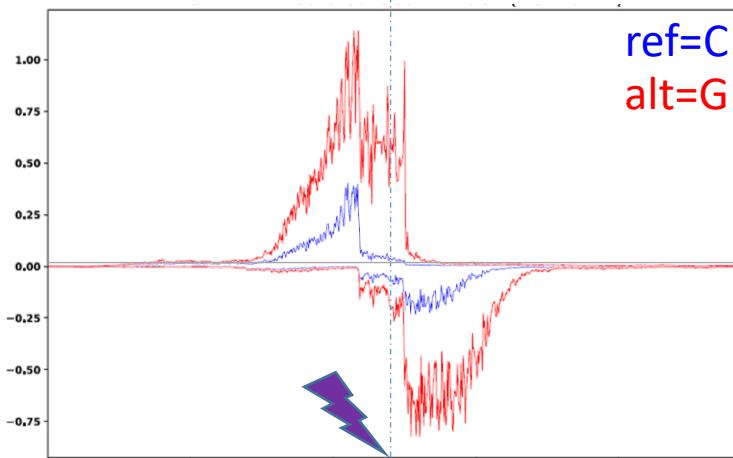
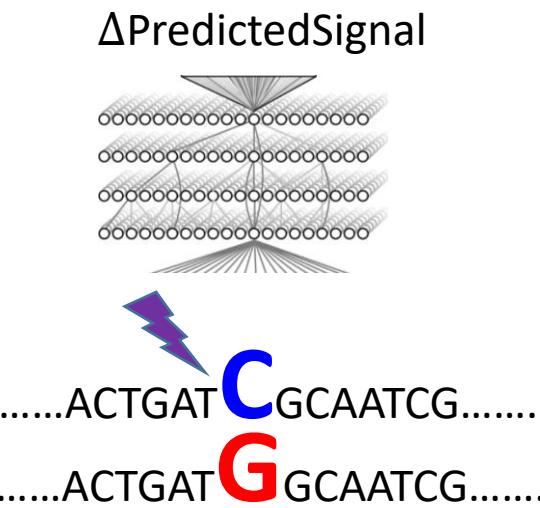


.....ACTGAT**C**GCAATCG.....



In-silico mutagenesis: Predict effect of genetic variant on molecular activity

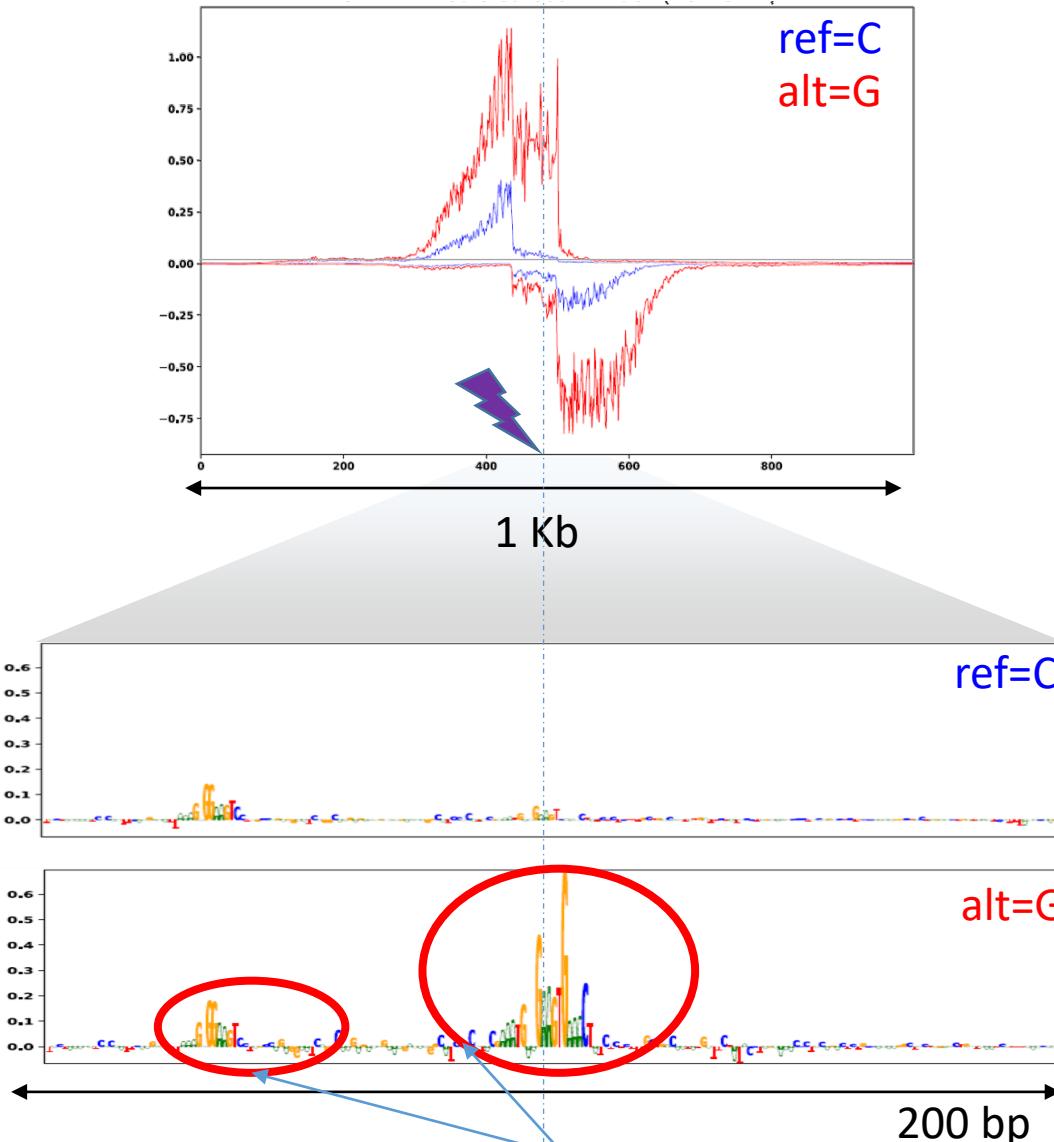
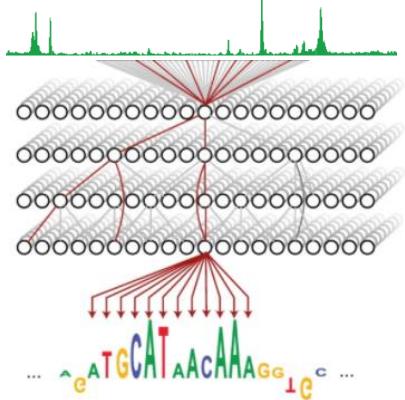
Predicted molecular profile of protein-DNA binding



1 Kb

Interpret disrupted predictive sequence syntax

Predicted molecular profile of protein-DNA binding



Sequence binding motifs of SPI1 DNA binding protein

Genetic variants associated with Alzheimer's disease

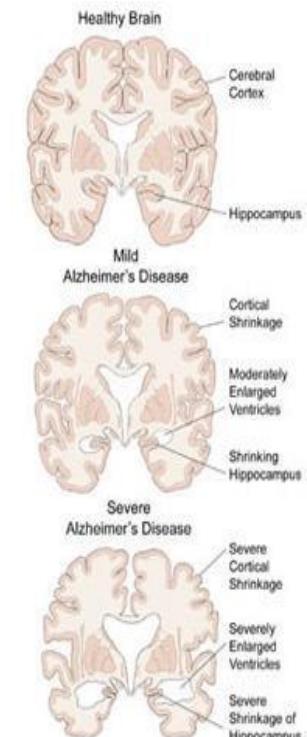
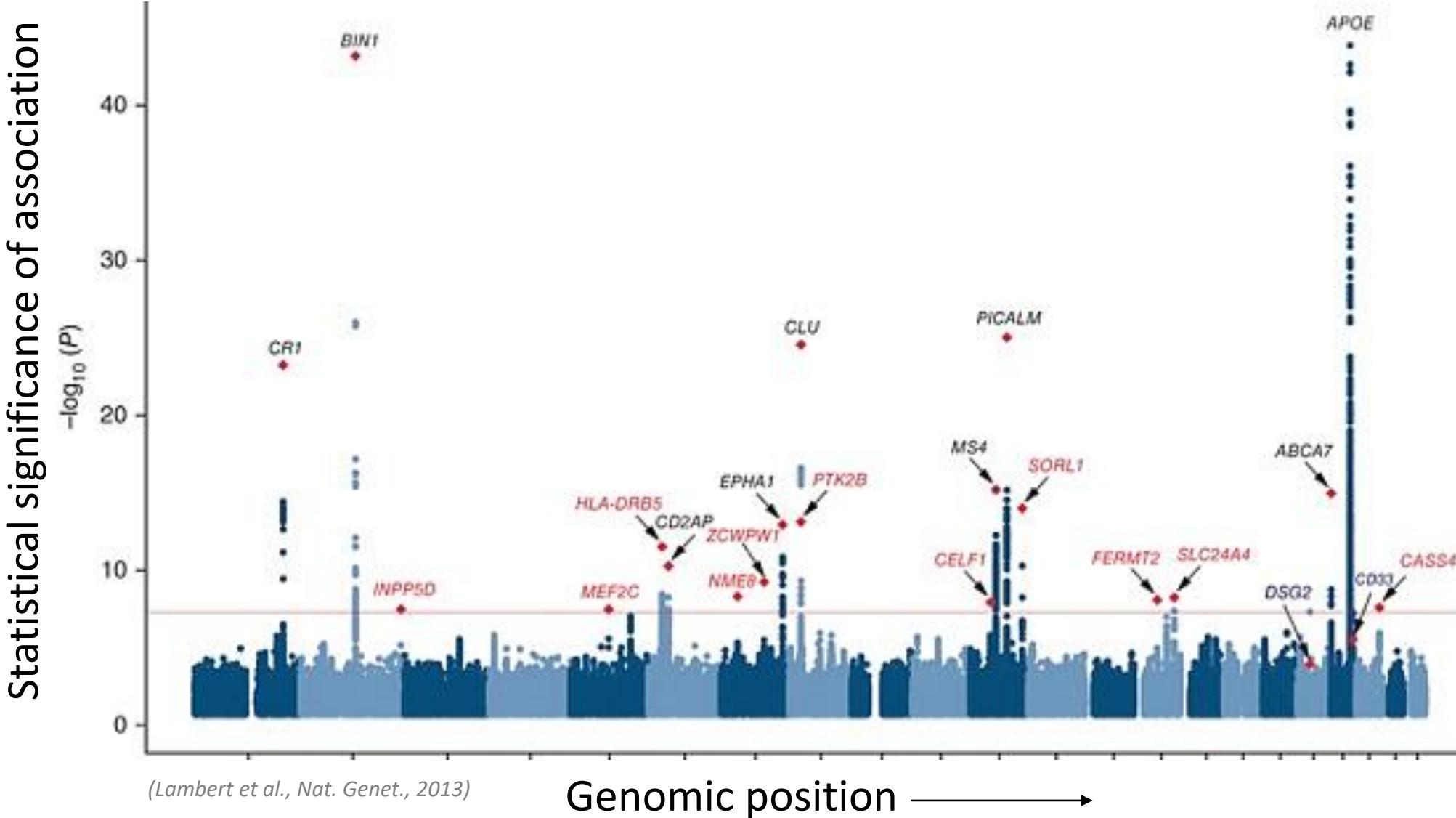


Illustration by Bob Morreale,
American Health Assistance
Foundation

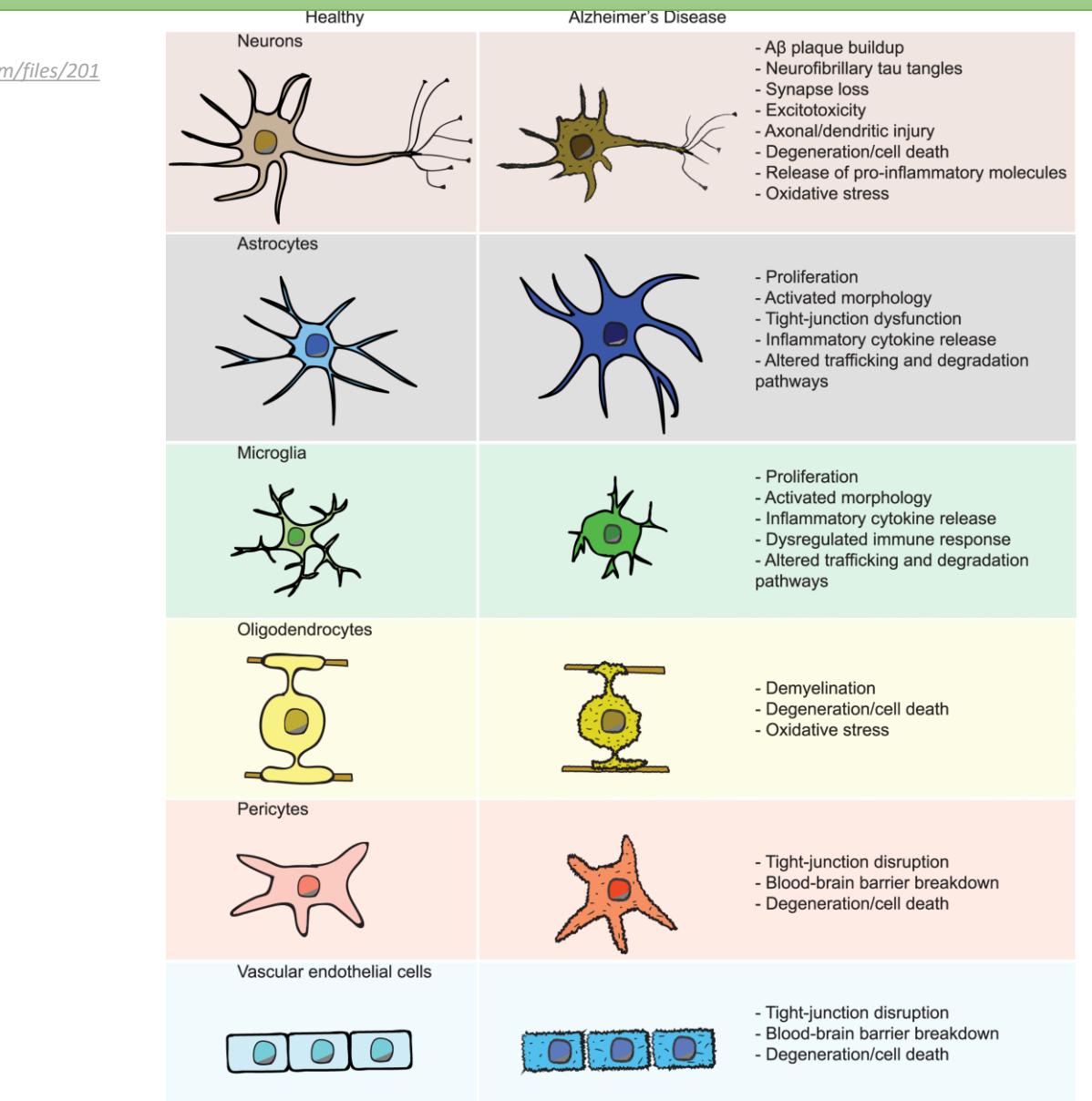
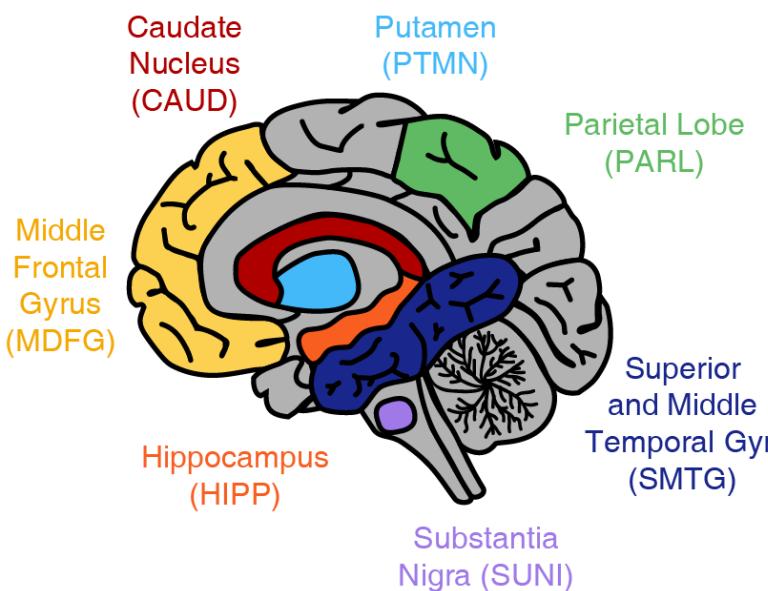
Problem: Which variant in the disease-associated locus is causal & what does it do?



The brain is a complex tissue with many different cell types

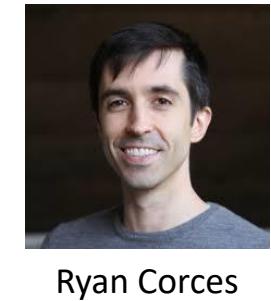
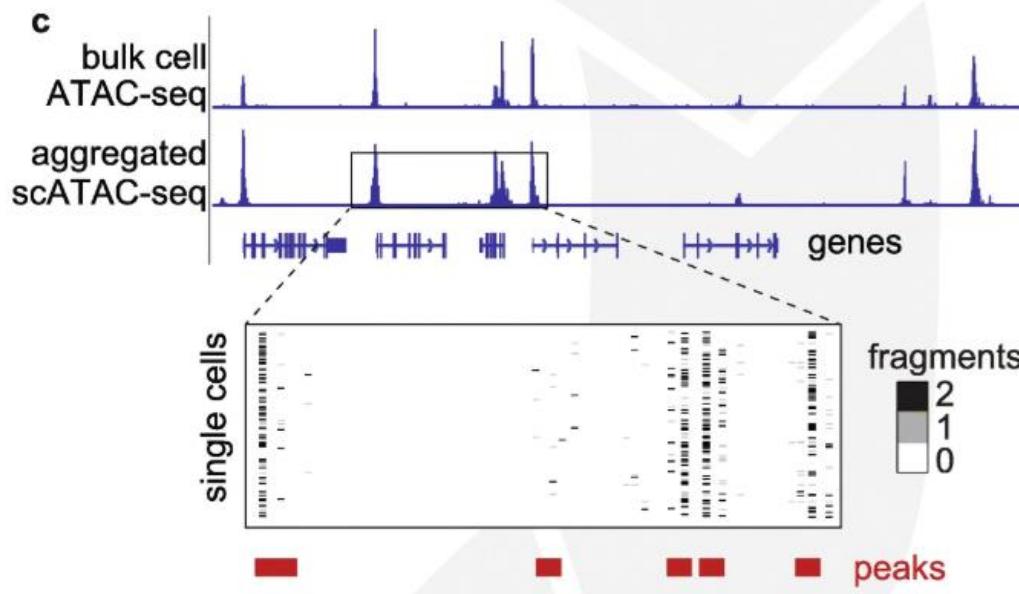


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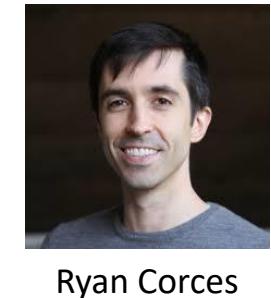
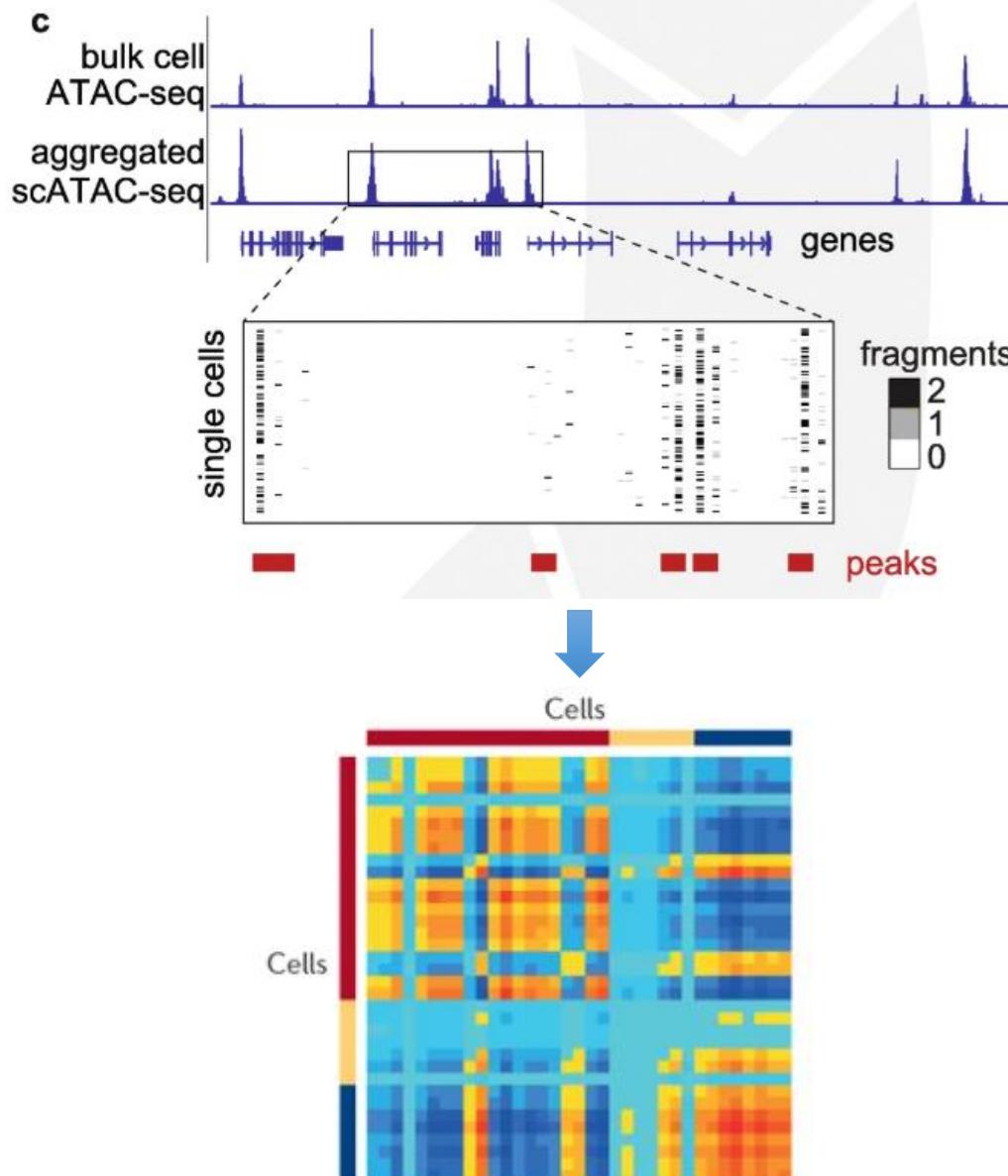


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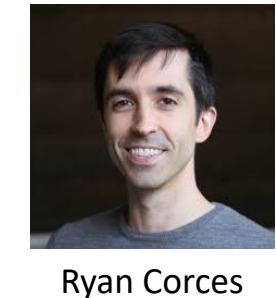
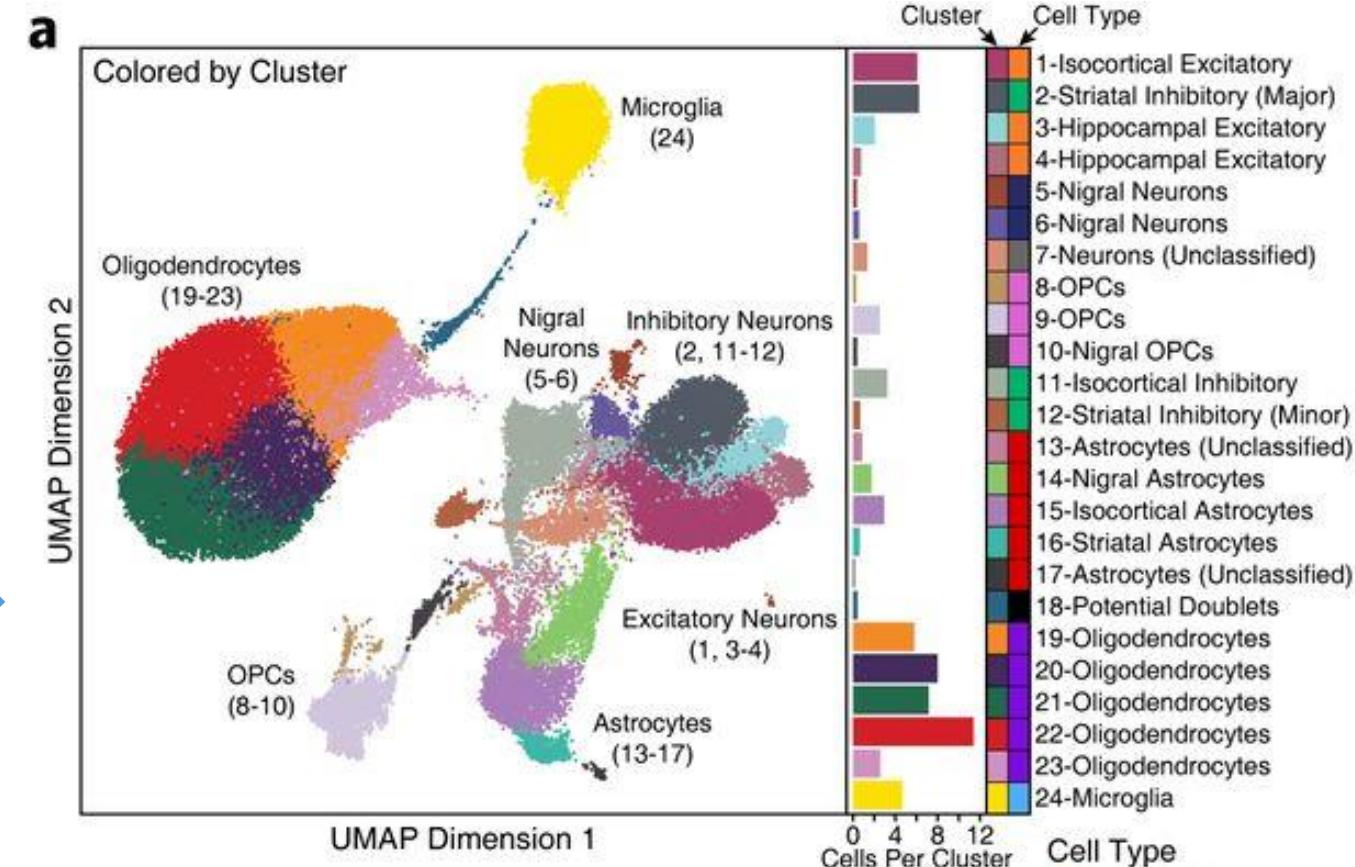
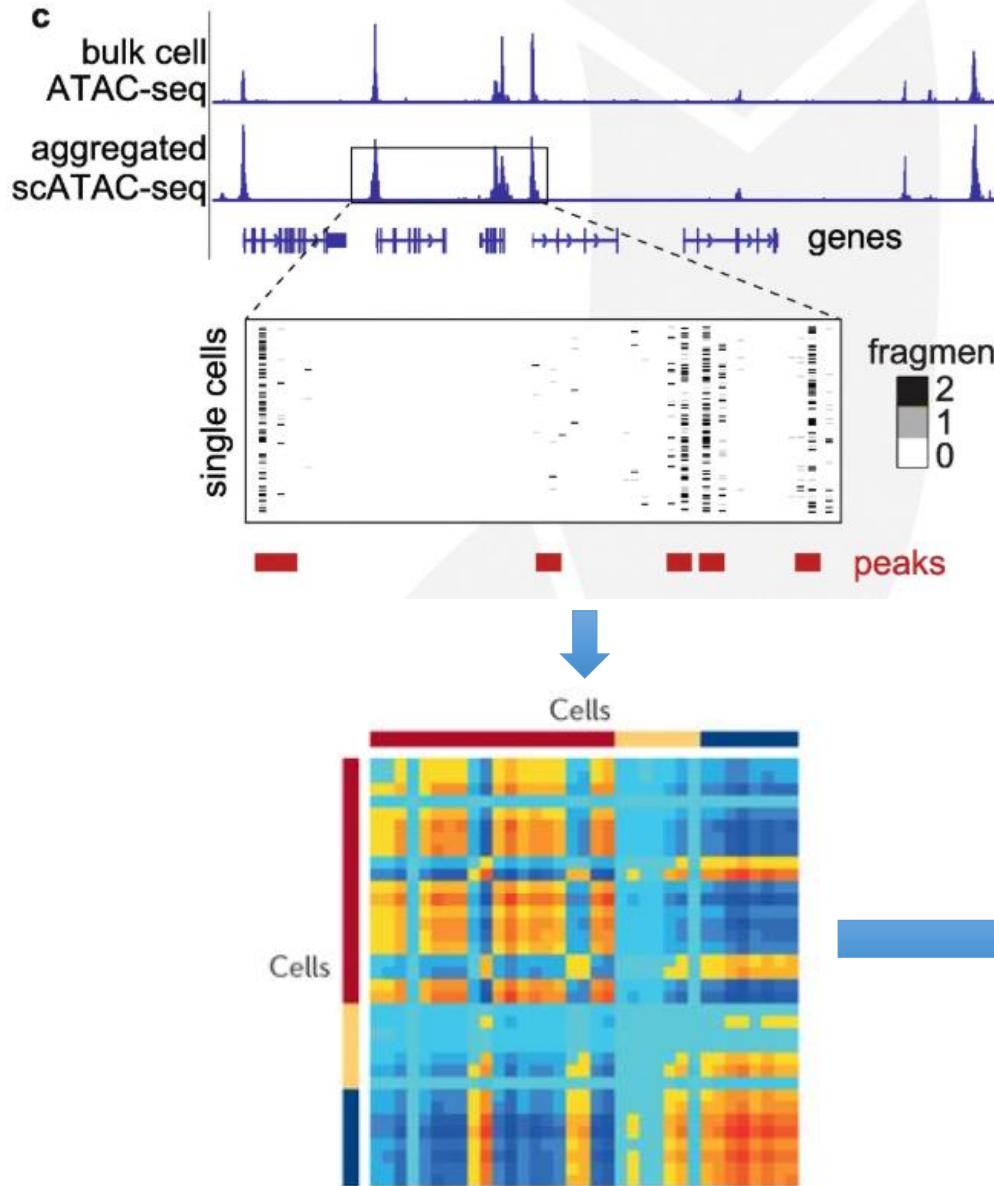
Computationally deciphering cell types in the brain



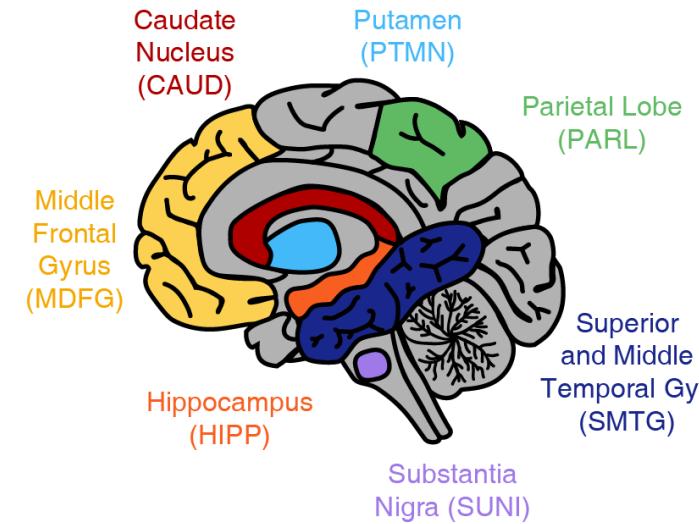
Computationally deciphering cell types in the brain



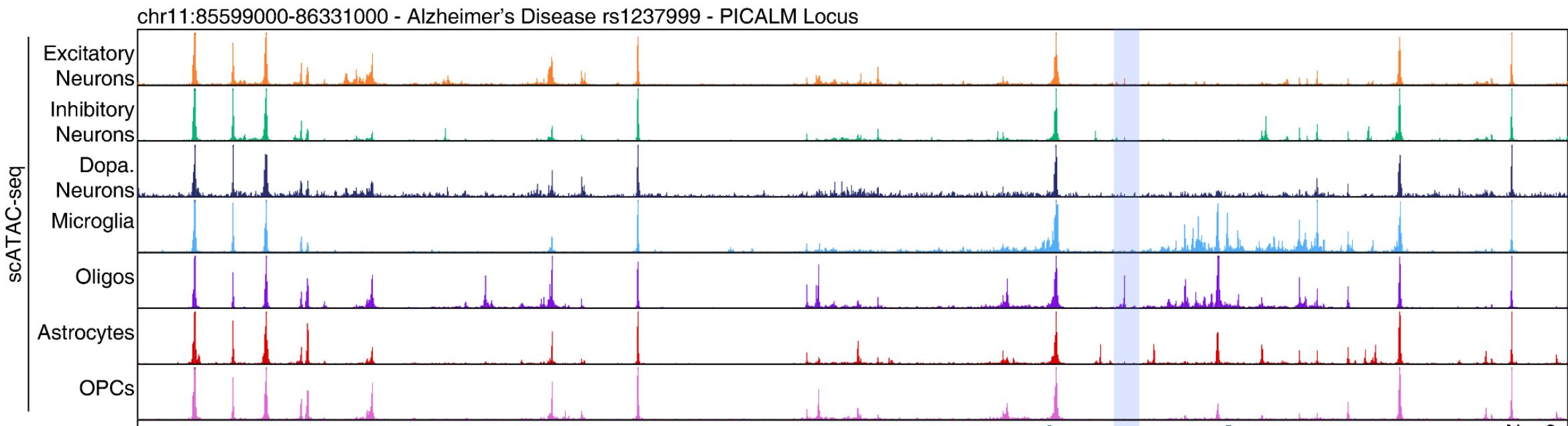
Computationally deciphering cell types in the brain



Molecular profiling of cell types in the brain

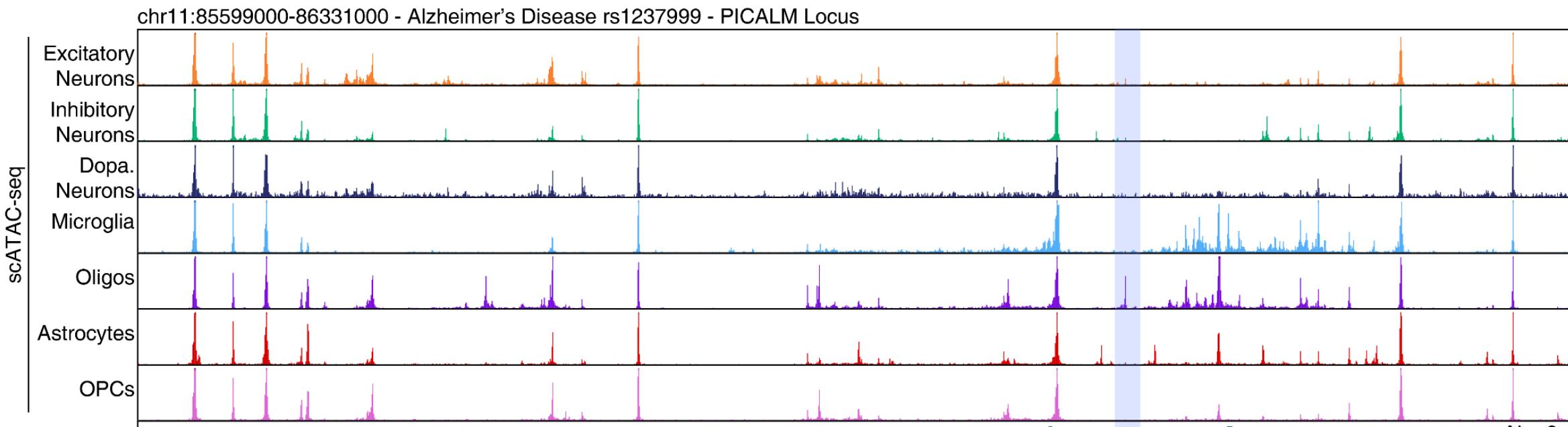
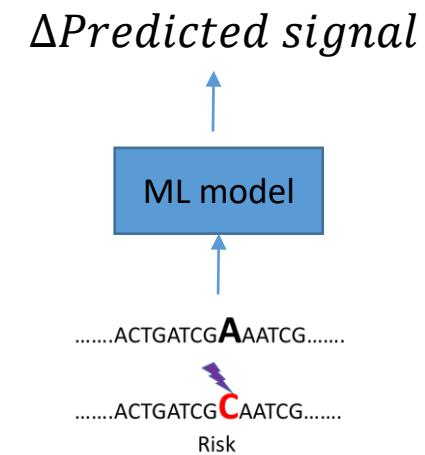
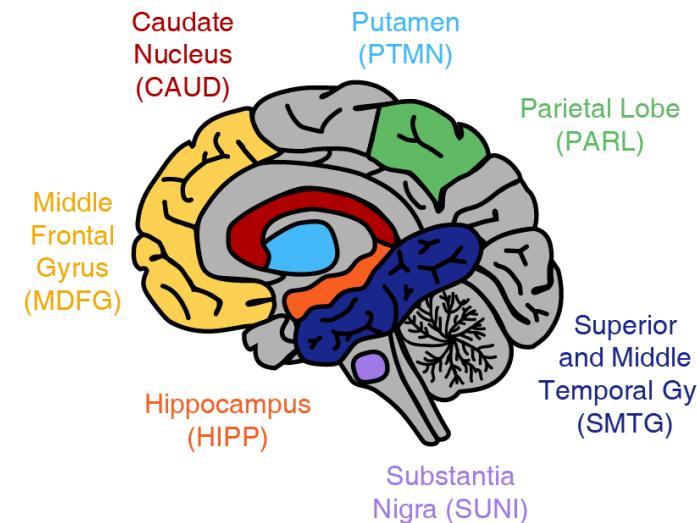


Corces et al. 2020, *Nature Genetics*



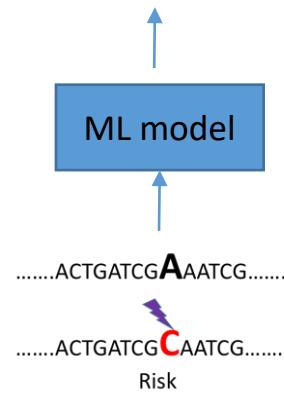
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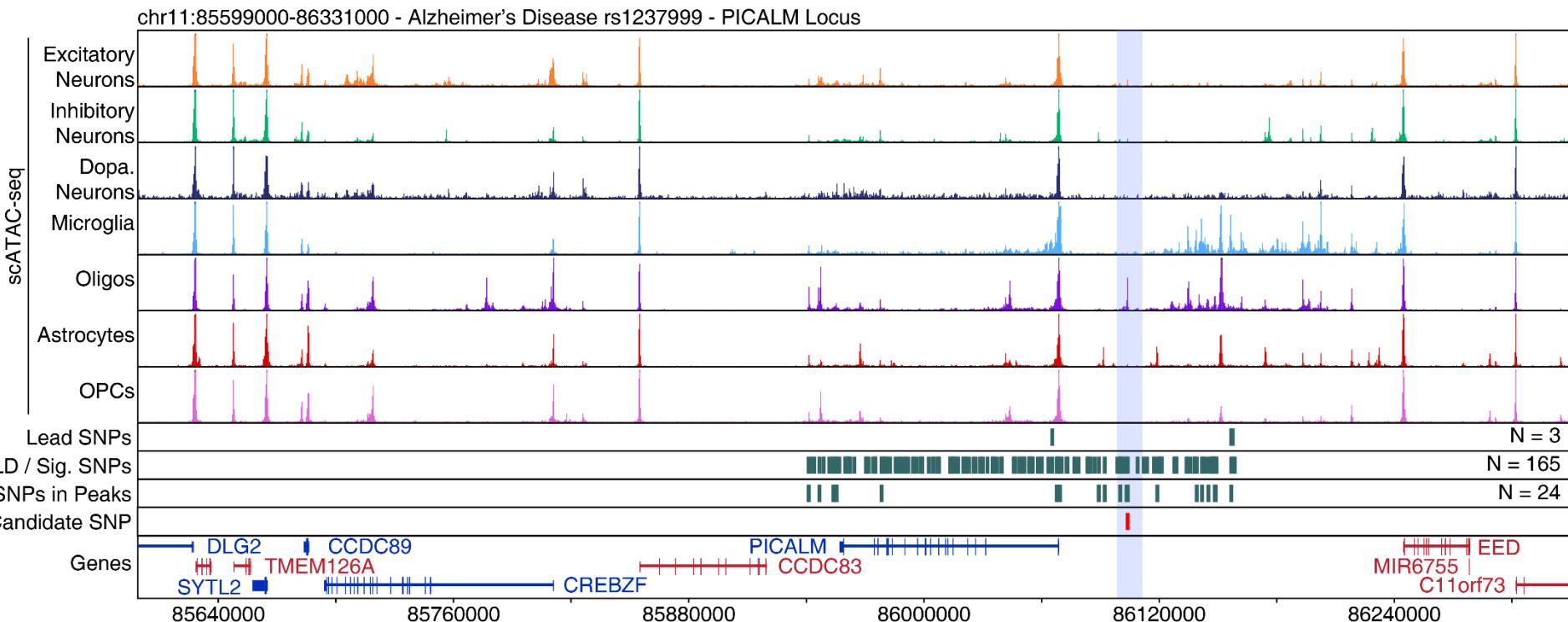


Predicting and interpreting causal AD variants

Δ Predicted signal



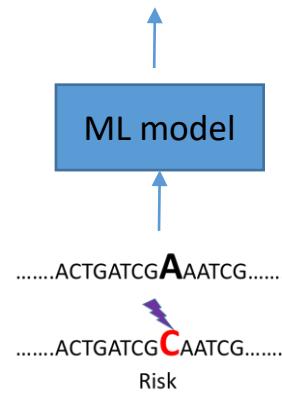
Anna Shcherbina



Soumya Kundu

Predicting and interpreting causal AD variants

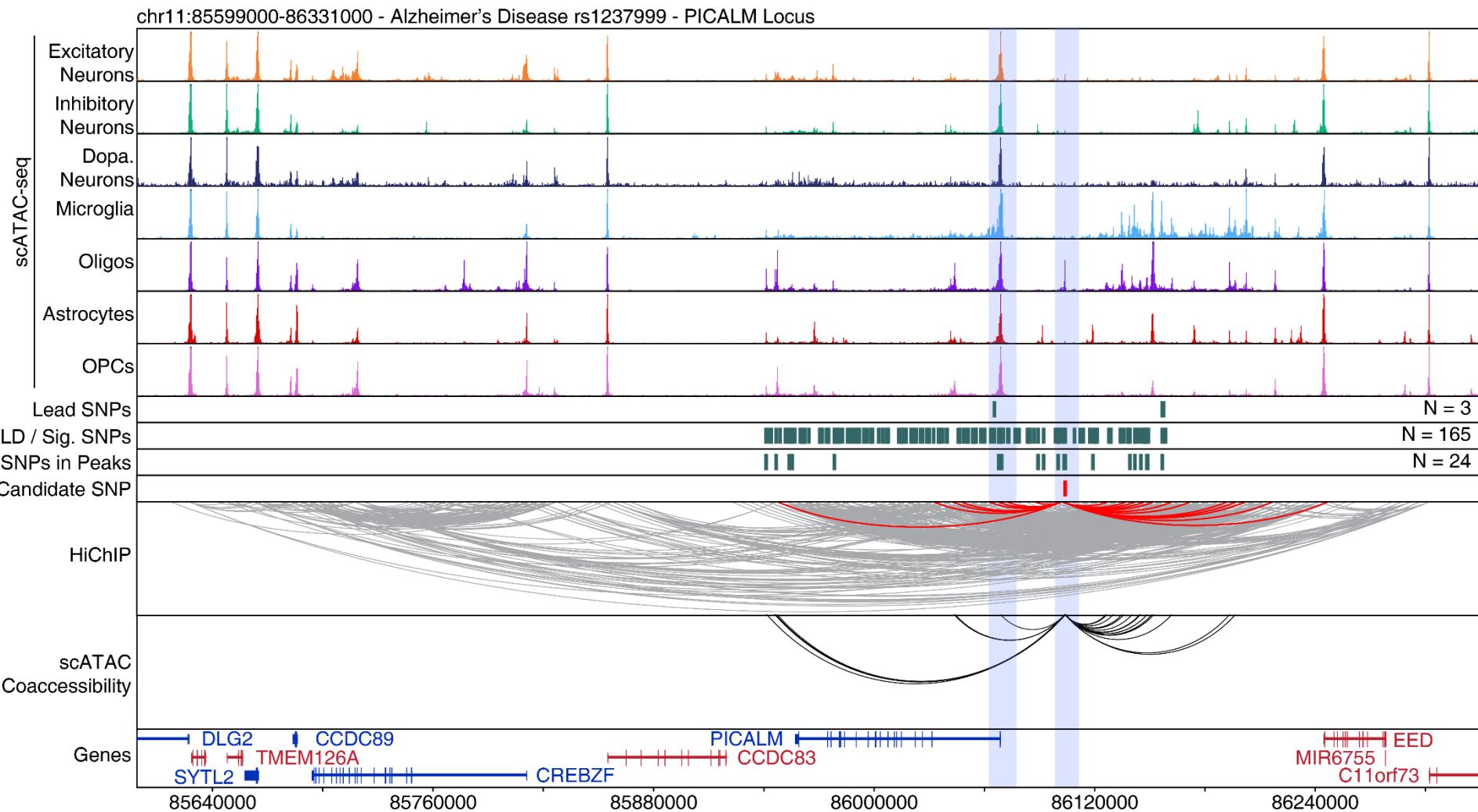
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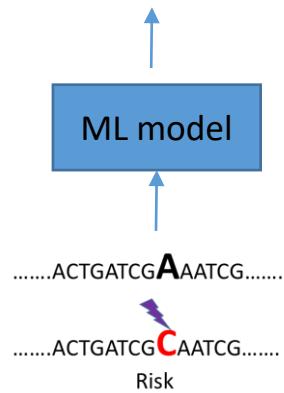


Soumya Kundu



Predicting and interpreting causal AD variants

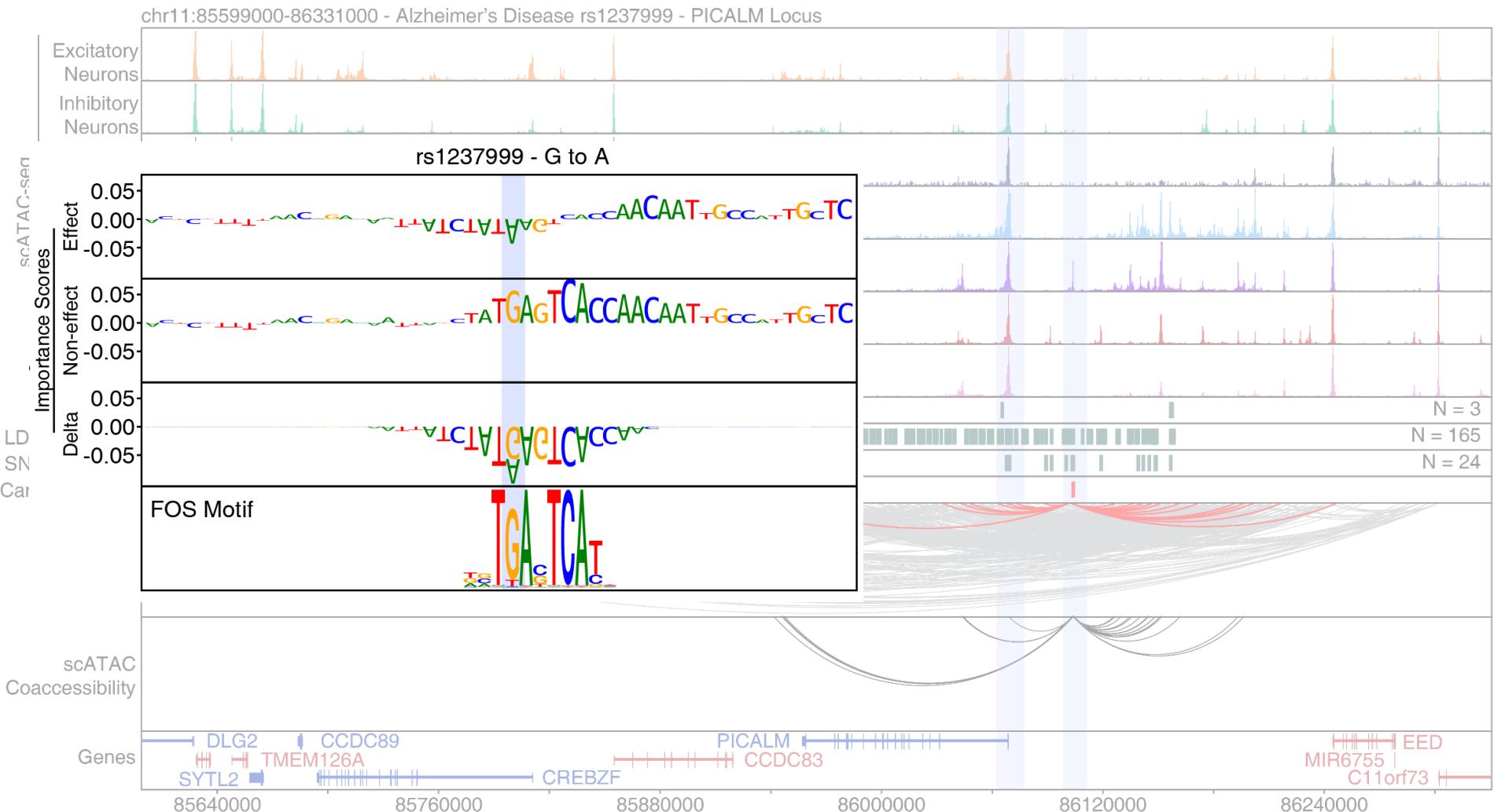
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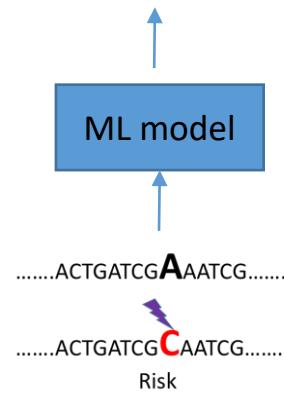


Soumya Kundu



Predicting and interpreting causal AD variants

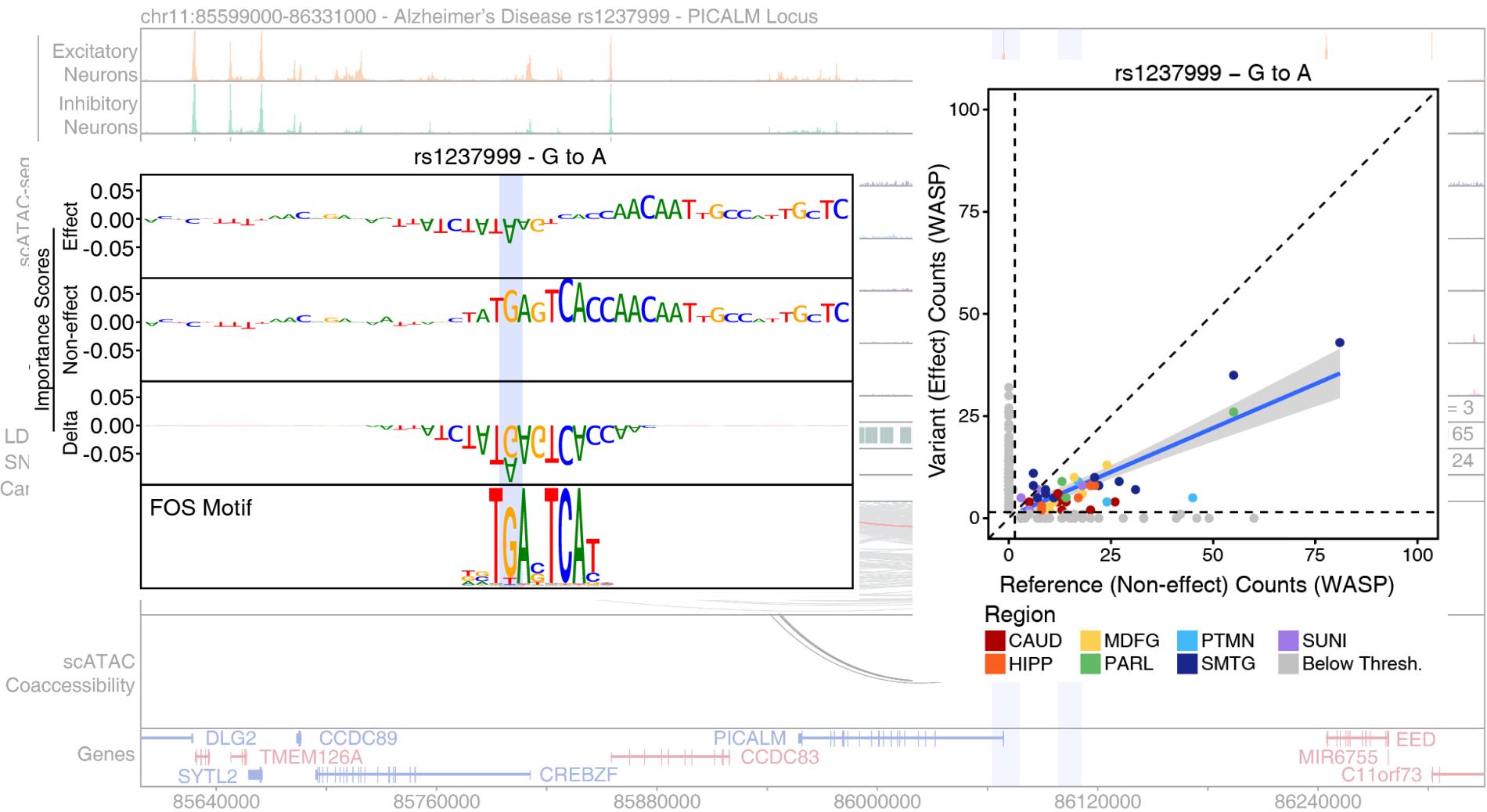
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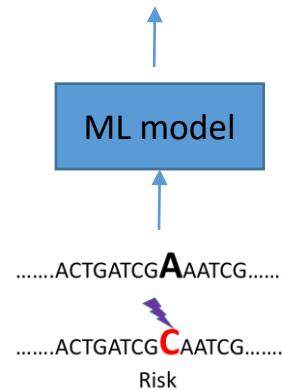


Soumya Kundu



Predicting and interpreting causal AD variants

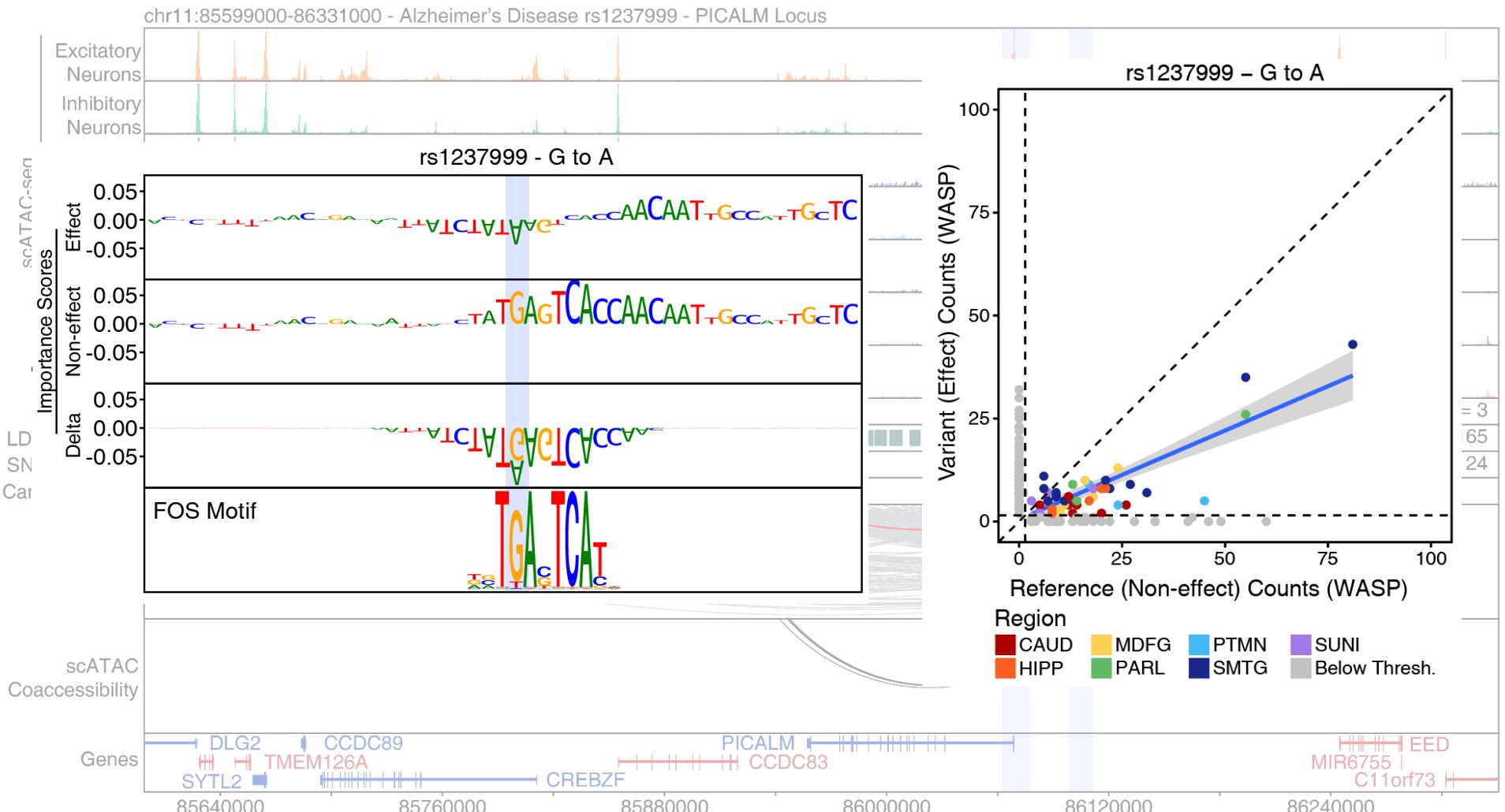
Δ Predicted signal



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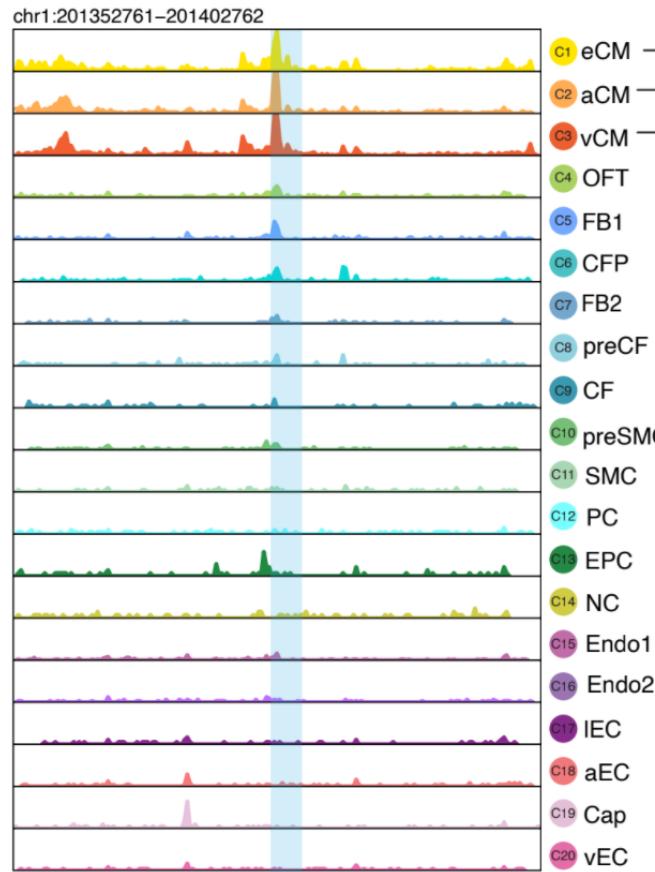
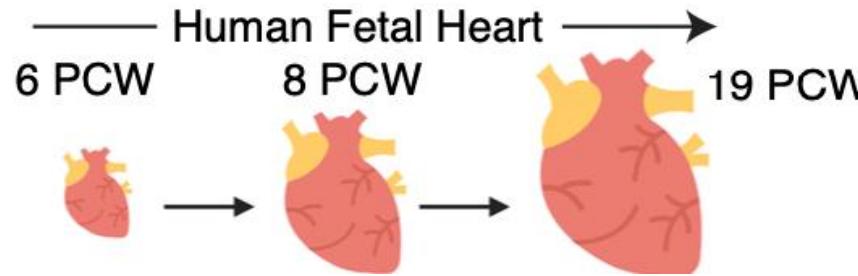


Soumya Kundu



Genetic variant rs1237999 disrupts a sequence motif of the FOS protein in a control element of the PICALM gene in oligodendrocyte cells in the brain

Predicting *de-novo* non-coding mutations in congenital heart disease

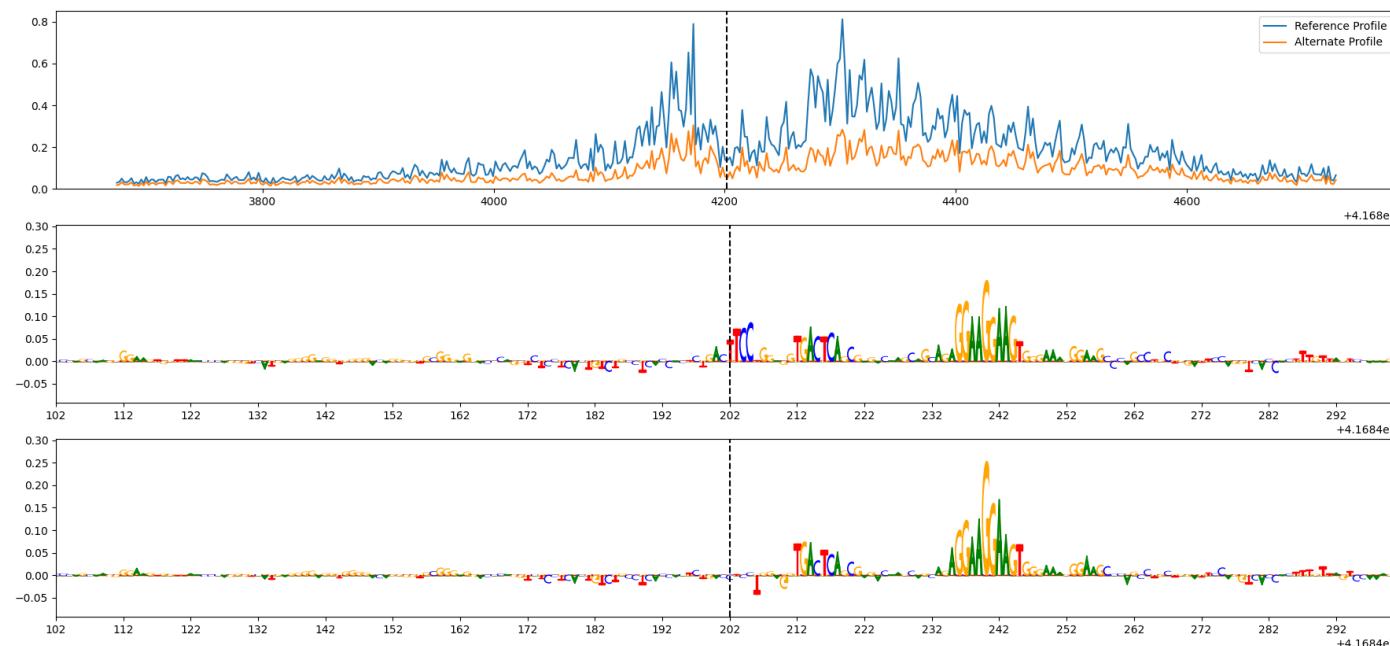
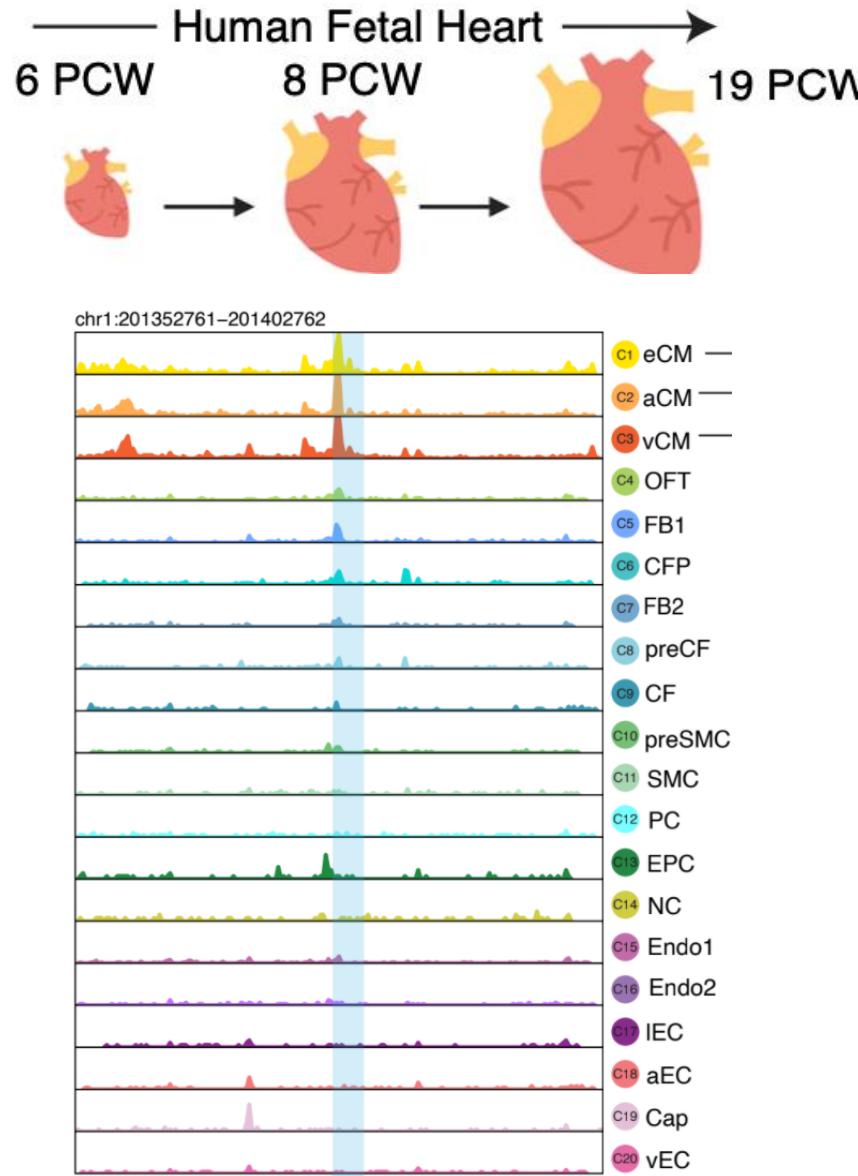


Laksshman
Sundaram



Mo Ameen

Predicting *de-novo* non-coding mutations in congenital heart disease



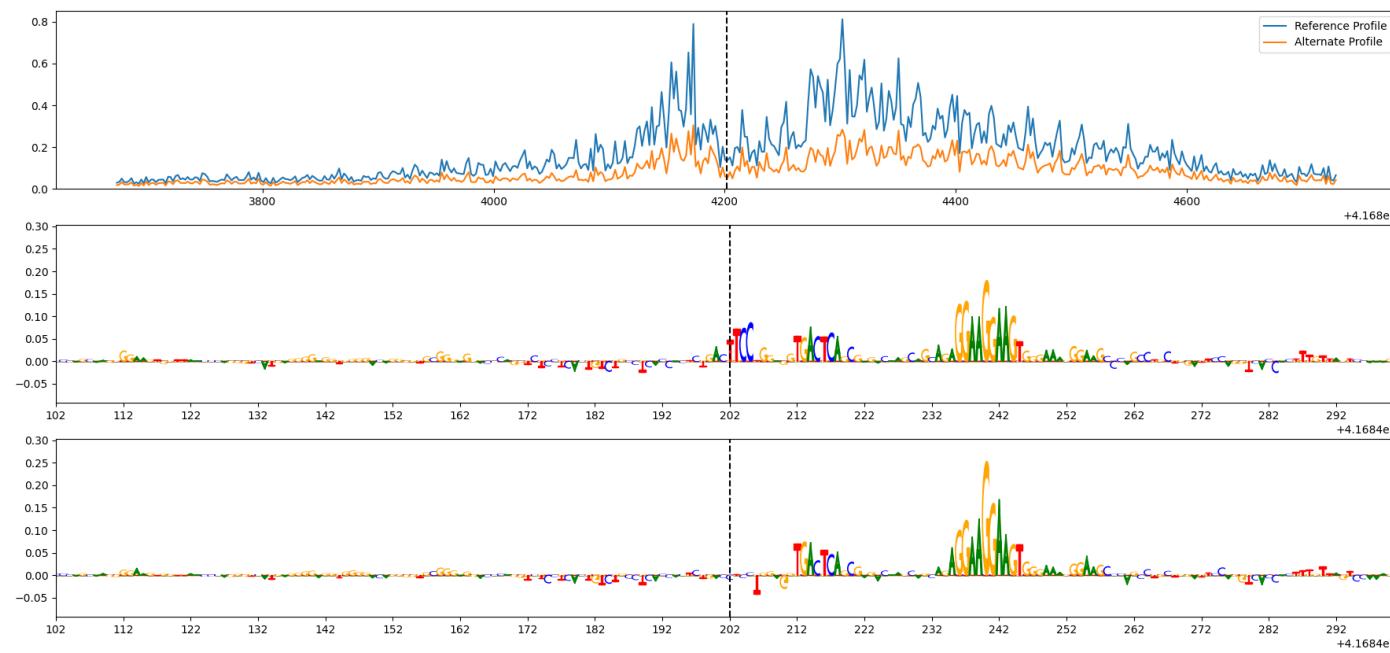
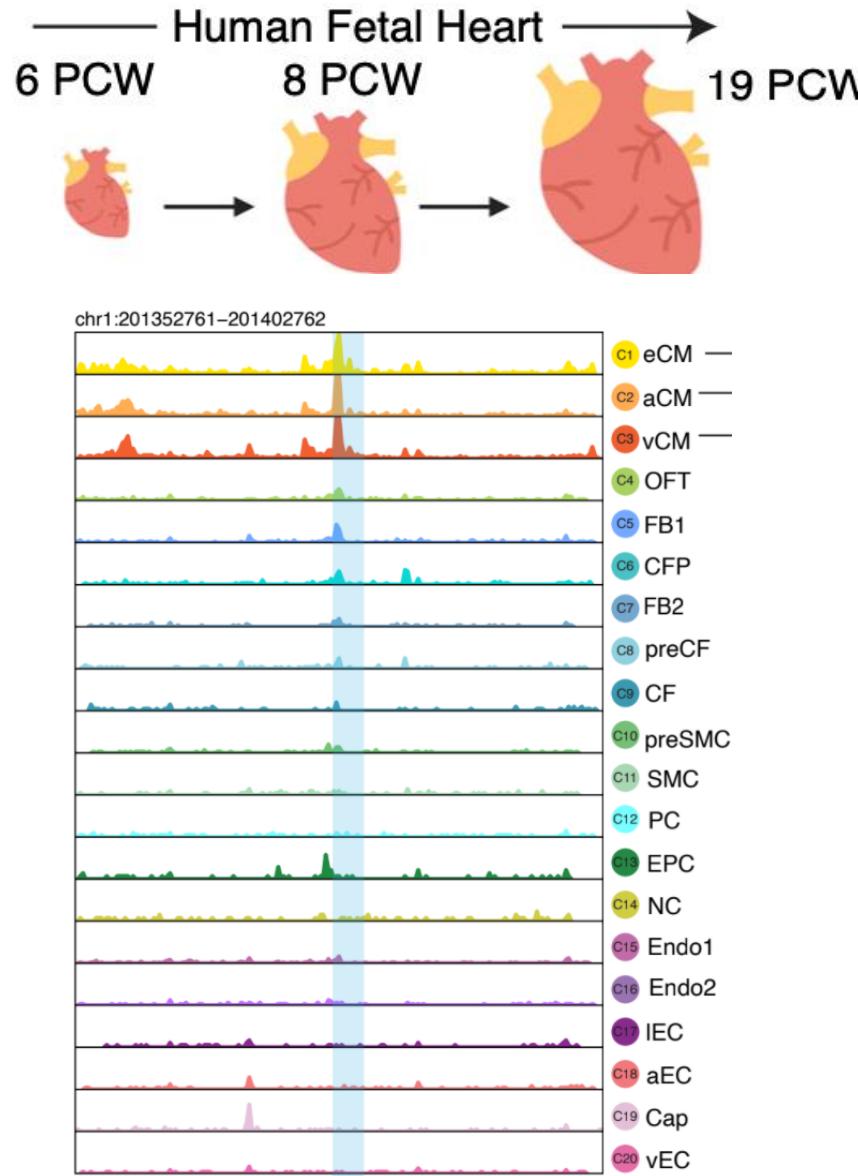
Laksshman
Sundaram



Mo Ameen

Prediction: Mutation disrupts ETV motif in control element active in arterial endothelial cells

Predicting *de-novo* non-coding mutations in congenital heart disease

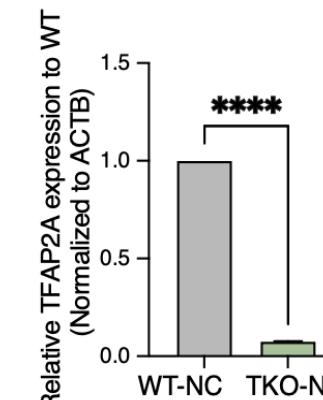
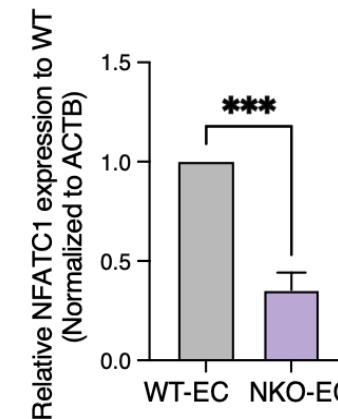
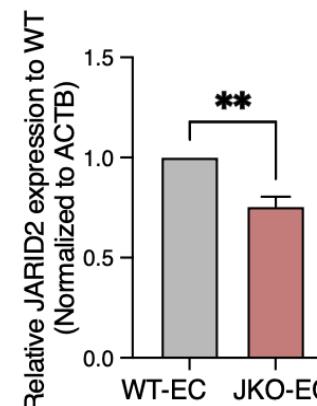


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Prediction: Mutation disrupts ETV motif in control element active in arterial endothelial cells



Summary

- Large-scale molecular profiling datasets => decipher genome function
- Neural networks can map DNA sequence to molecular profiles with unprecedented accuracy
- Models can be interpreted to decipher functional DNA letters, words and syntax
- Models can be used to decipher disease-associated mutations
- Predictions are validated by genome editing experiments
- Predictions can provide clues for therapeutic interventions

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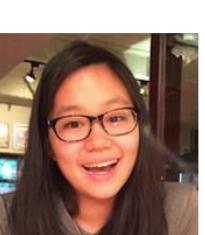
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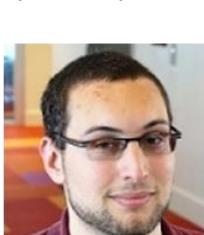
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