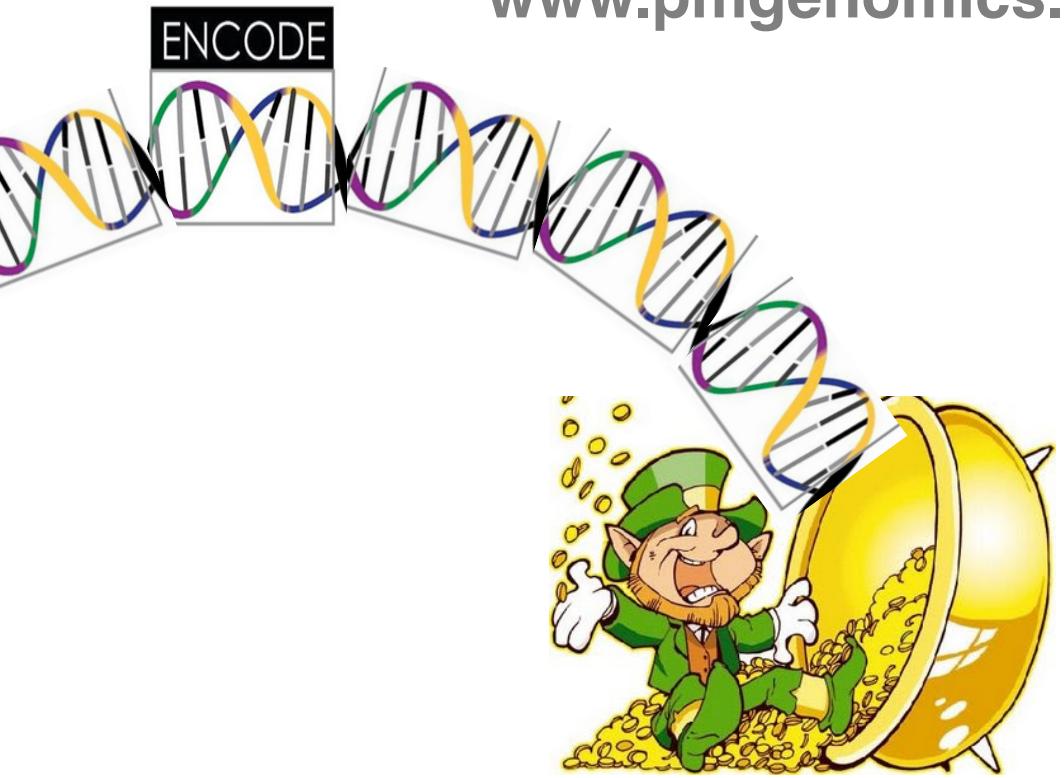
Cancer, Genetic Predispositions and Chromatin Architecture

www.pmgenomics.ca/lupienlab



Let's all be leprechauns

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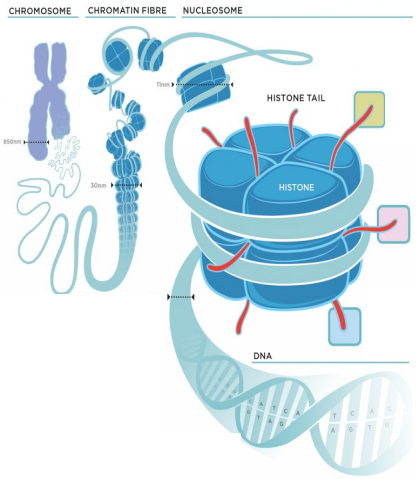
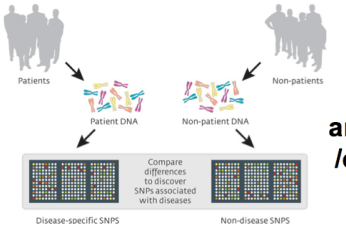
UNIVERSITY OF TORONTO

Three ways to exploit ENCODE data

1- Annotating the functional genome using epigenetics



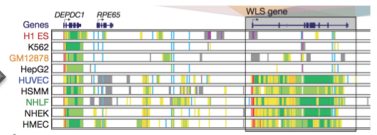
2- Finding the targets of genetic predispositions



GWAS

and /or

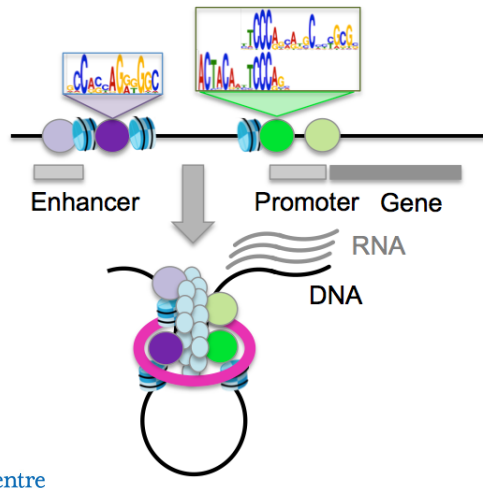
TCGA/ICGC



EPIGENOMES

Functional Interpretation of Genetic Alterations

3- Understanding the three-dimensional architecture of the genome



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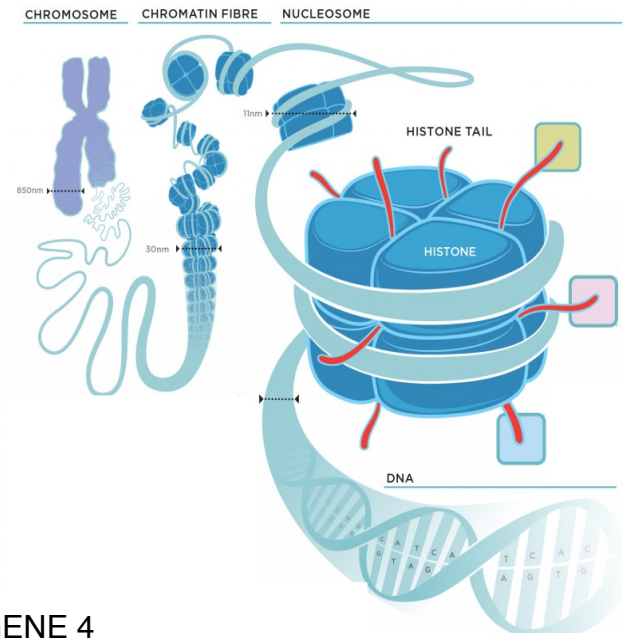
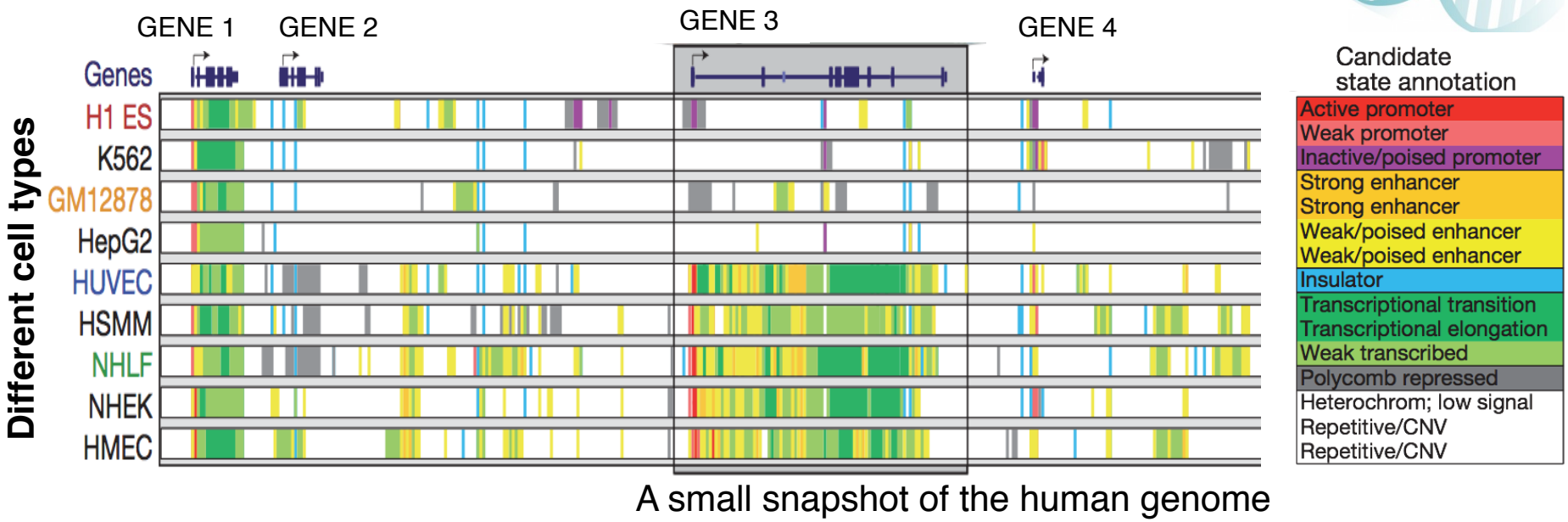
Epigenetic modifications annotate the functional elements across the genome

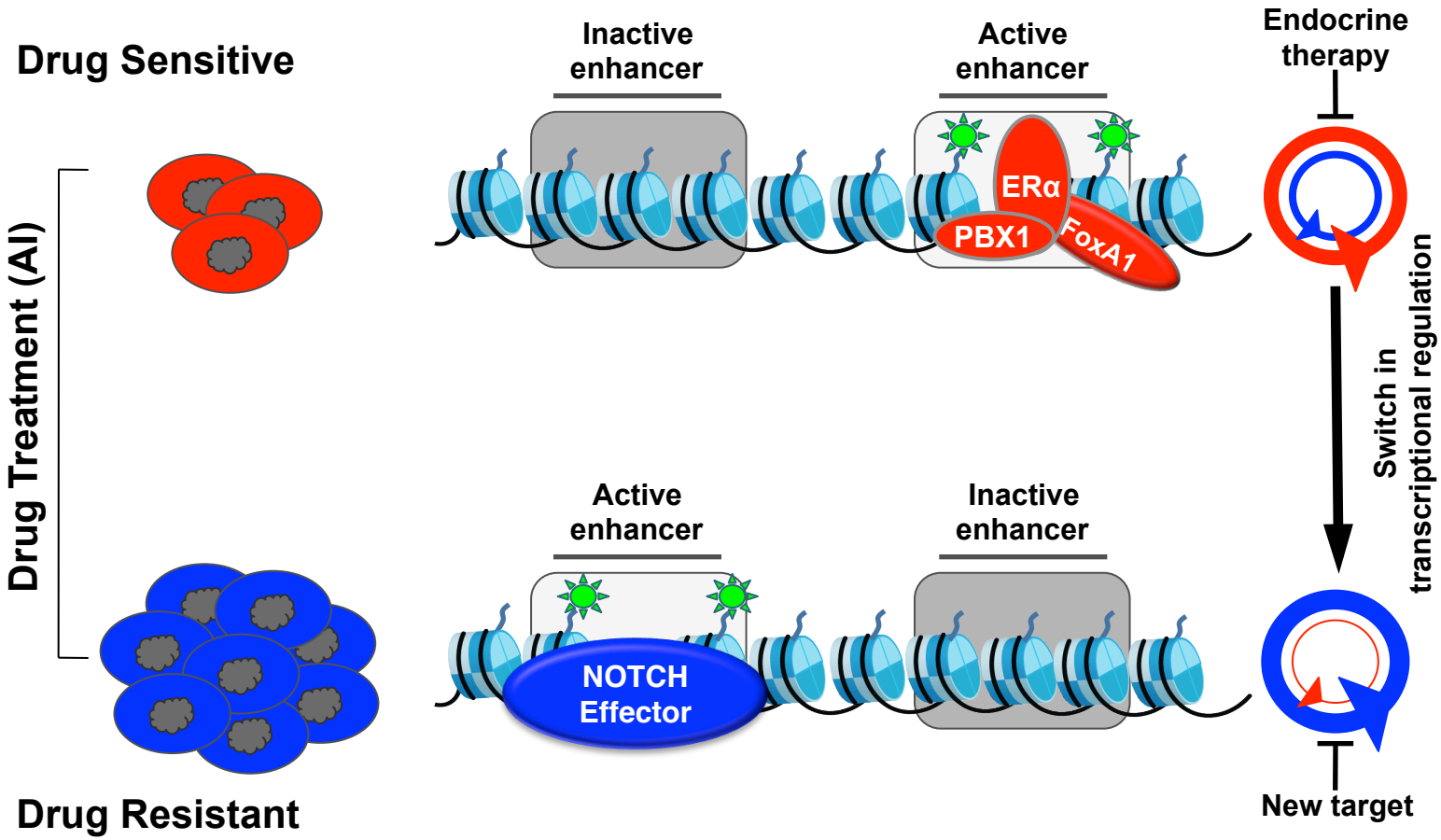




A small snapshot of the human genome

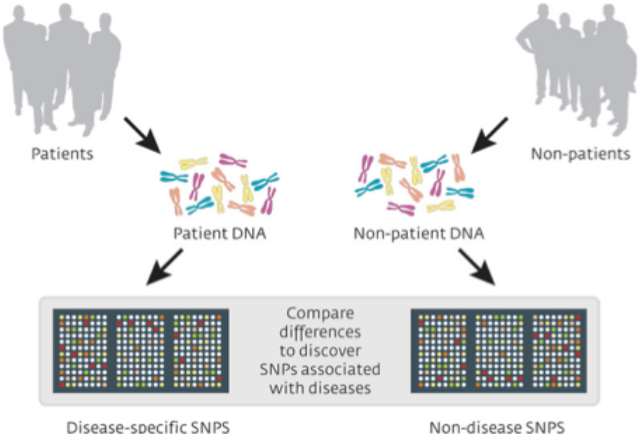
Heintzman et al (2007) Nat Genet. 39: 311-318
Lupien et al (2008) Cell. 132: 958-970
Heintzman et al (2009) Nature. 1-5
Ernst et al. (2011) Nature, 2011 pp. 1-9

Epigenetic reprogramming underlies breast cancer resistance to standard-of-care



Magnani, et al. (2013). Proc. Natl. Acad. Sci. U.S.A. 110. pE1490-1499
Akthar-Zaidi et al (2012) Science. 11: 736-739

Functional interpretation of genetic predispositions using epigenetics



GWAS

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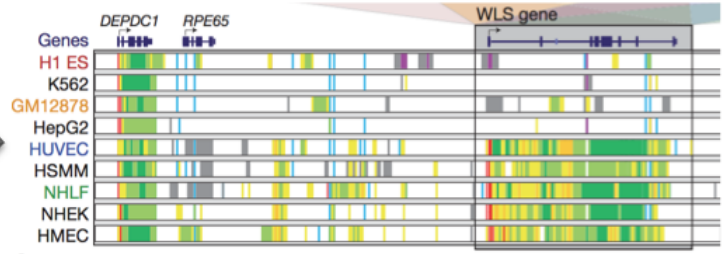
TCGA/ICGC

My contributions:

Akthar-Zaidi et al (2012) Science. 11: 736-739
Zhang et al (2012) Genome Research. 22: 1427-1436
Cowper Sal lari et al (2012) Nat Genet. 44: 1191-1198
Corradin et al (2014) Genome Research. 24: 1-13
Zhang et al (2014) Trends in Genetics. 30: 140-149
Ghoussaini et al. (2014). Nat Commun. 4: 4999
Chadar et al. (2014) MCB. 34: 3291-3304
Bailey et al (2015) Nat Commun. 2: 6186



EPIGENOMES

Functional Interpretation of Genetic Alterations

ENCODE

Ernst et al. (2010). Nature. 1-9
Schaub et al. (2012). Genome Res. 22:1748-1759
Maurano et al. (2012). Science. 337: 1190-1195
and many more…

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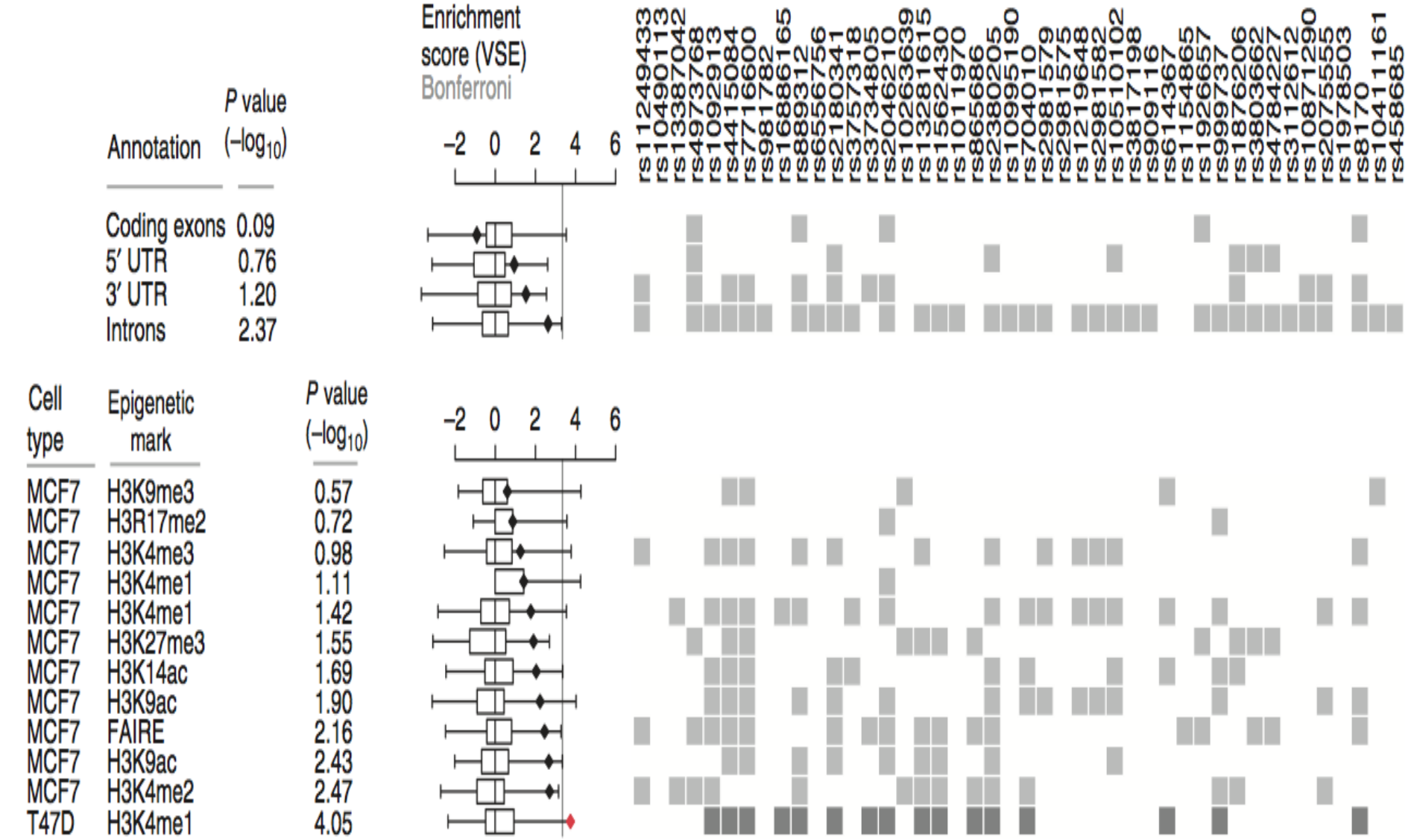
Variant Set Enrichment (VSE) approach – BCa GWAS risk-variants target enhancers



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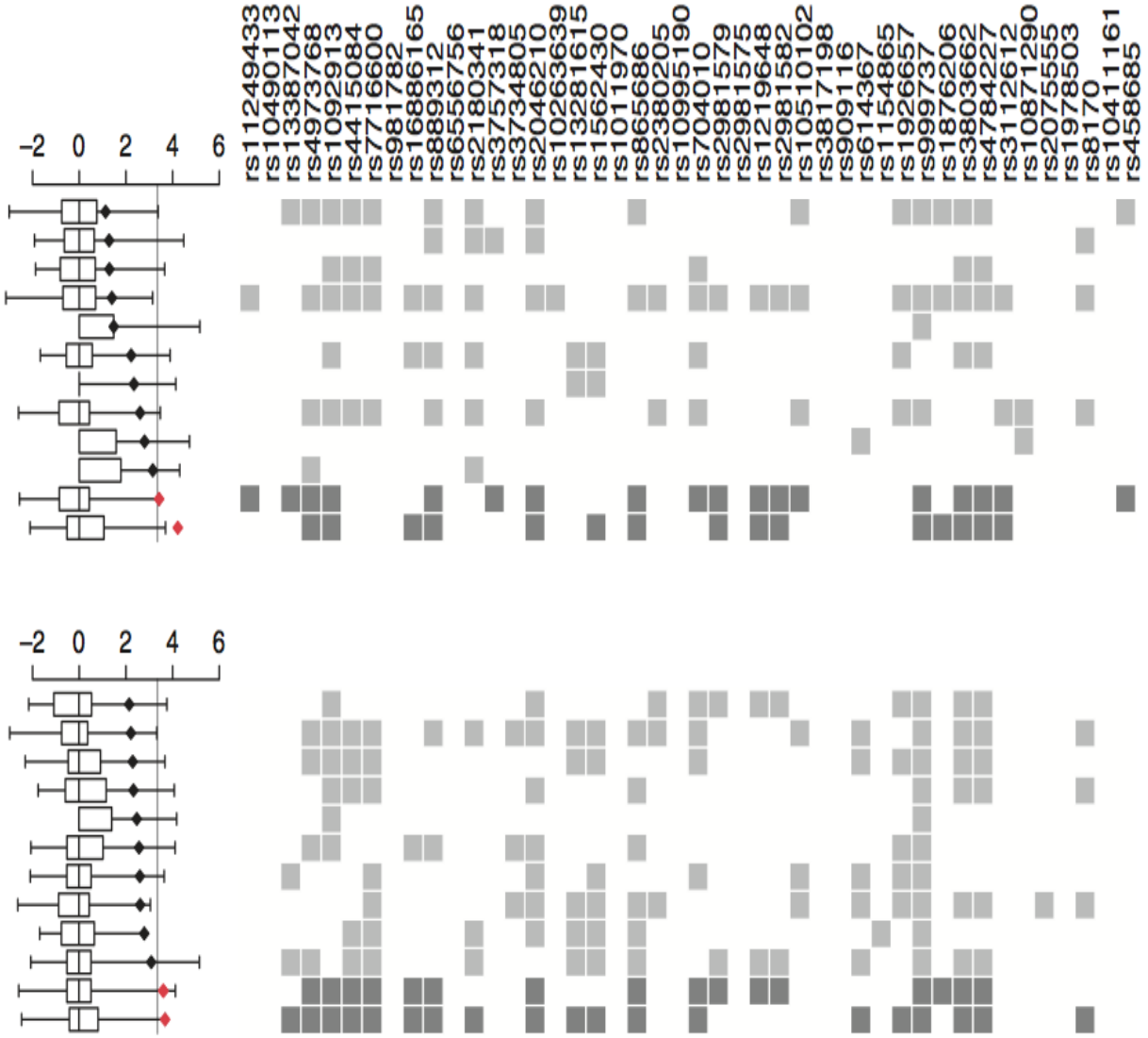
Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

BCa GWAS risk-variants target the ERa and FOXA1 transcription factors

Cell type	Binding site	*P* value ($-\log_{10}$)
MCF7	STAG1	0.89
MCF7	PolII	1.00
MCF7	FOXA1	1.01
MCF7	FOXA1	1.09
MCF7	ESR1	1.16
MCF7	ESR1	1.89
MCF7	c-Fos	2.02
MCF7	PolII	2.34
MCF7	TRIM24	2.59
T47D	ESR1	3.09
T47D	FOXA1	3.51
MCF7	FOXA1	4.92

Cell type	Binding site	Treatment	*P* value ($-\log_{10}$)
MCF7	SRC-3	E2 1 h	1.81
MCF7	RAD21	*CTCF*-KO	1.89
MCF7	ESR1	Full	1.98
MCF7	FOXA1	E2 45 min	2.02
MCF7	ESR1	E2 45 min	2.19
MCF7	RARA	AM580	2.31
MCF7	TRIM24	E2 6 h	2.35
MCF7	PBX1	Full	2.37
MCF7	ESR1	E2 45 min	2.60
ZR75	ESR1	E2 45 min	3.02
MCF7	FOXA1	E2 45 min	3.84
MCF7	ESR1	E2 45 min	3.97



Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

Assessing the role of genetic variants on transcription factor DNA binding affinity

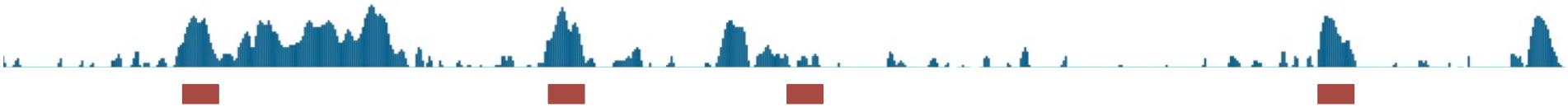
IntraGenomic Replicates (IGR) approach

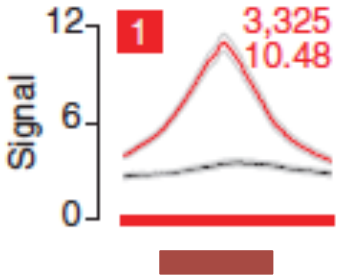
In sillico allele-specific DNA binding affinity predictor

GTGTTTGCTA[T/C]GATTAGTTC

TTGCTAT

ChIP-seq signal for your favorite TF





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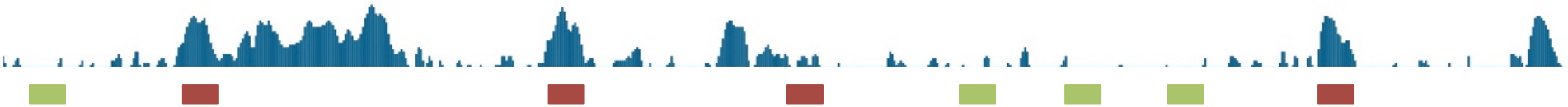

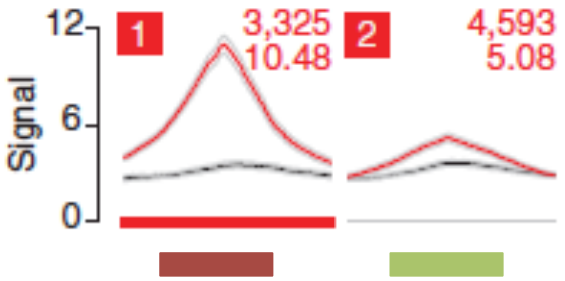

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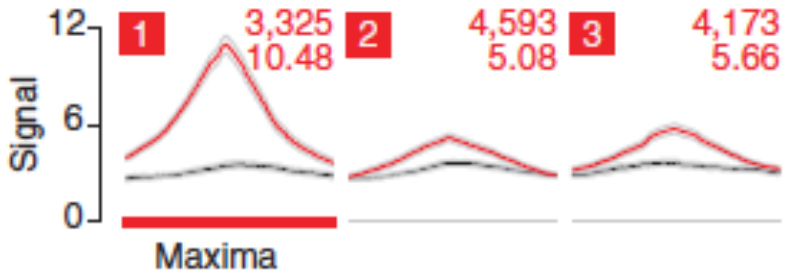
GCTA**T**GA



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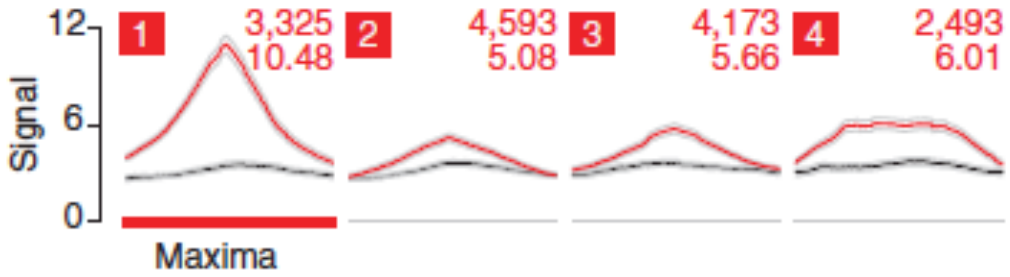

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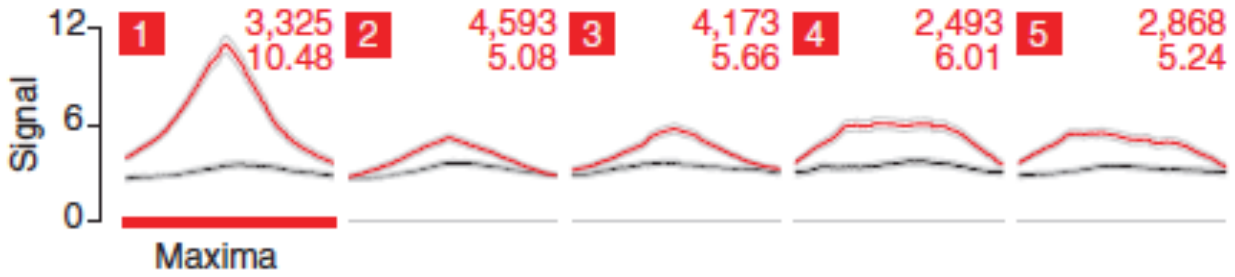
TA**T**GATT



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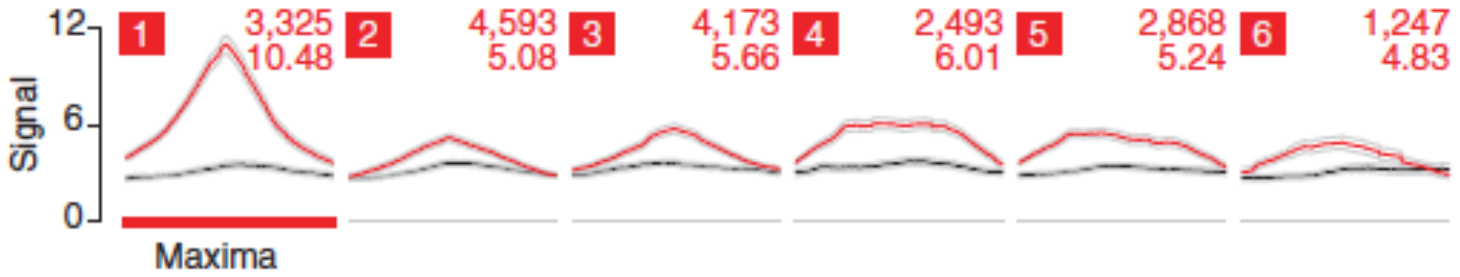

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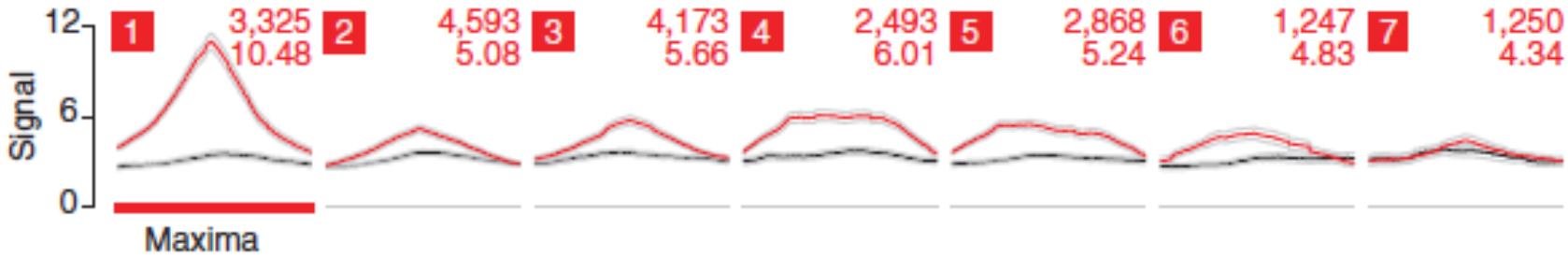

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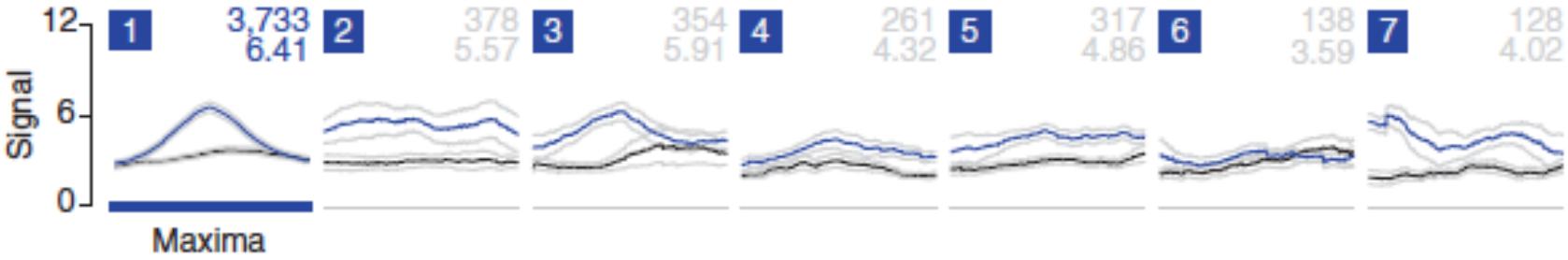

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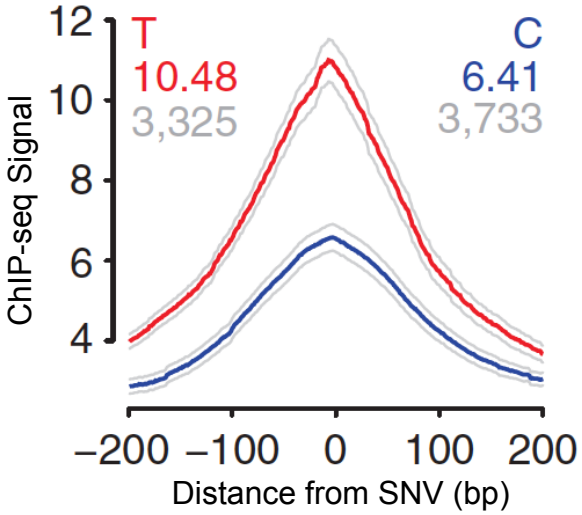
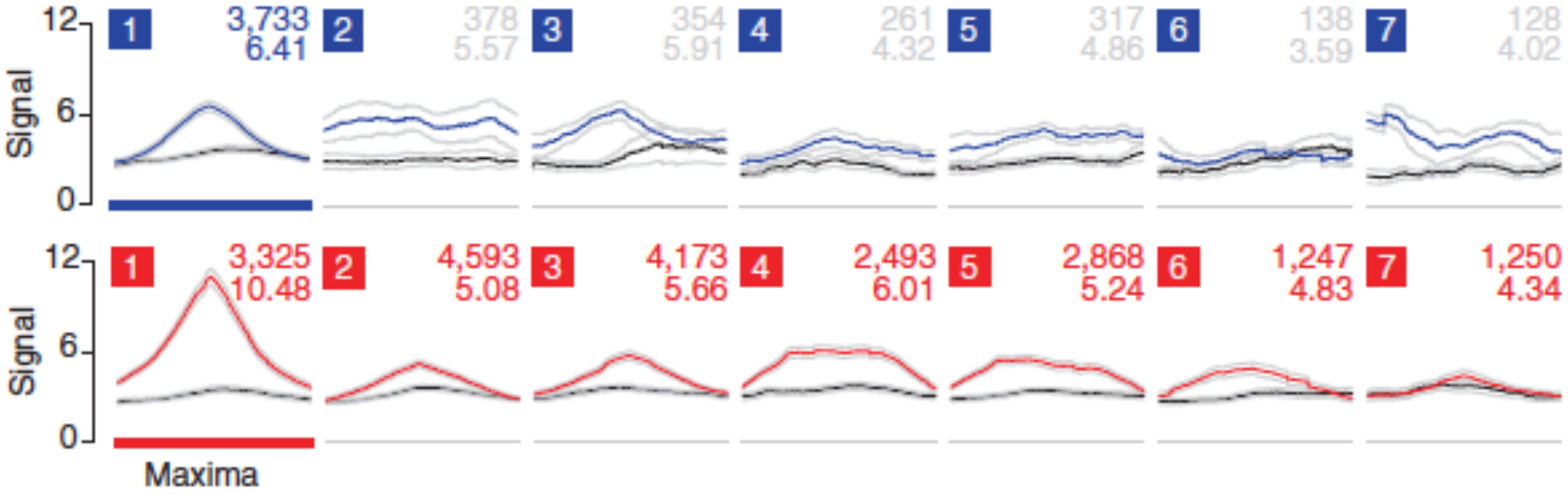
IGR predicts changes in binding affinity imposed by SNVs for any transcription factor





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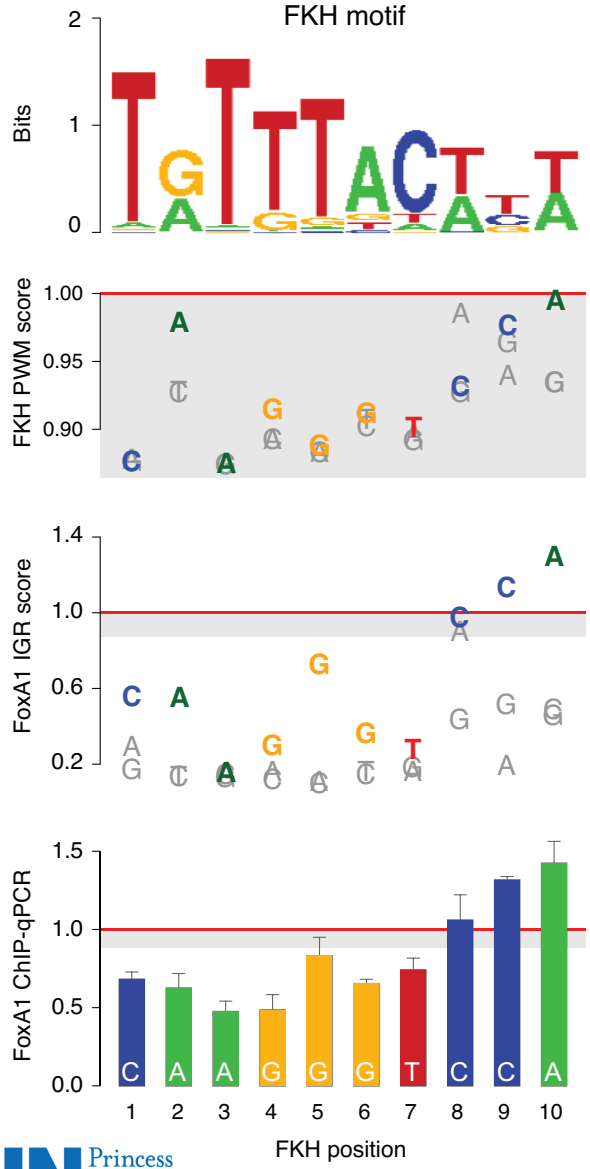
Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

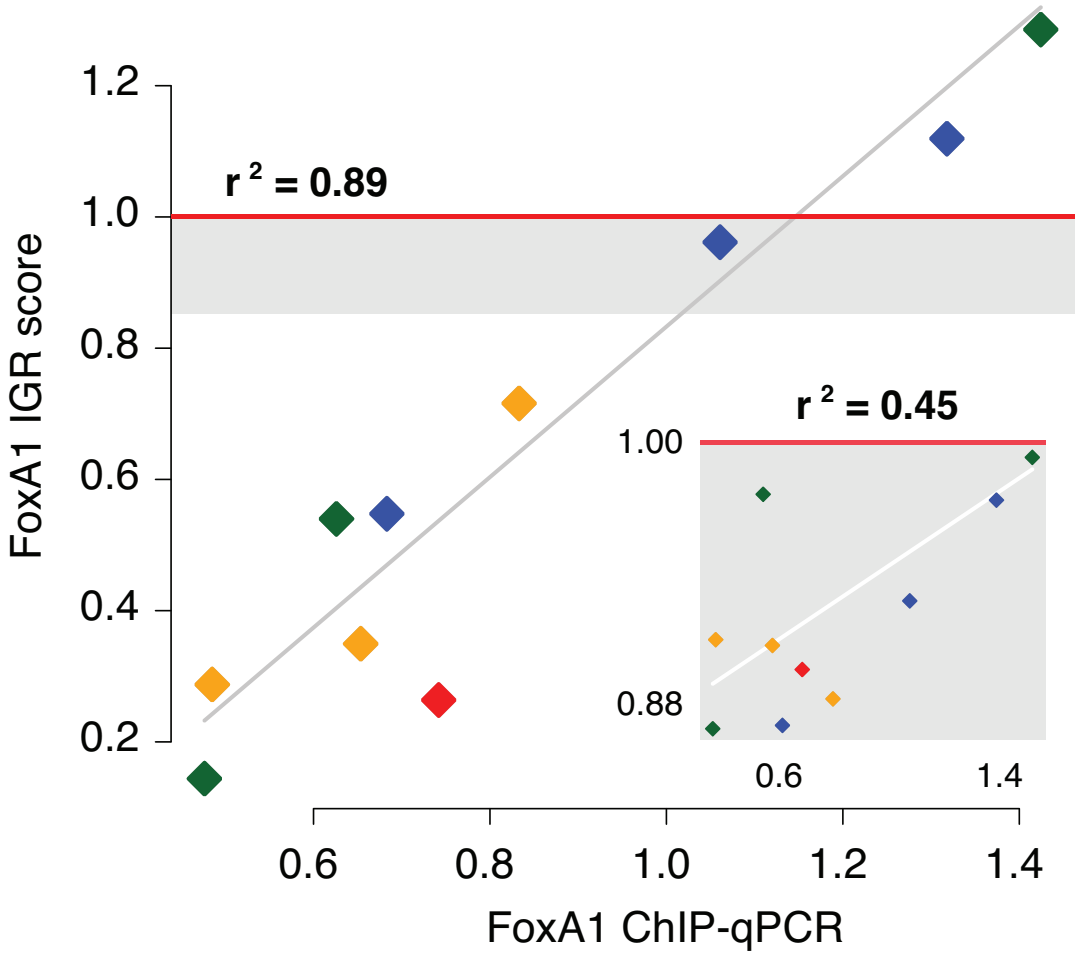
IntraGenomic Replicate (IGR) tool is a better predictor of DNA binding affinity than PWM

PWM

IGR

ChIP-qPCR





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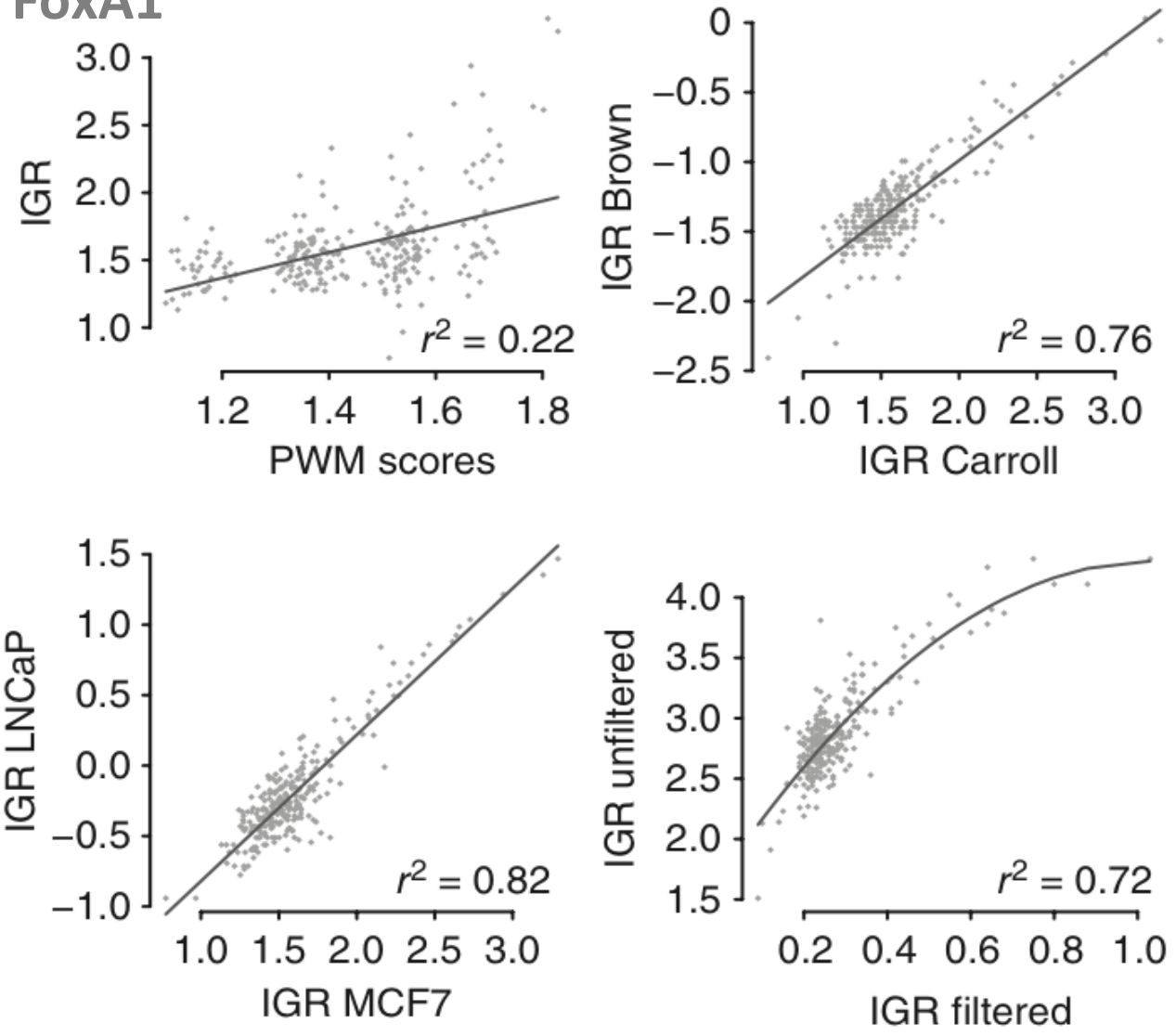
Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

IGR predictions are agnostic to cell-type or origin of ChIP-seq datasets

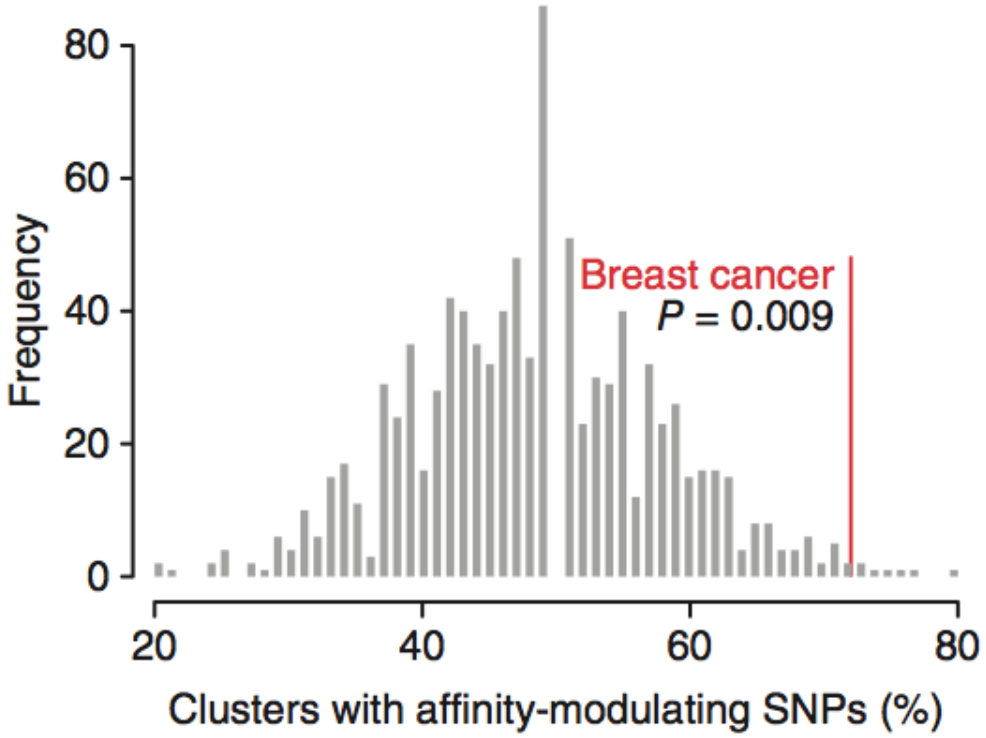
ChIP-seq: FoxA1



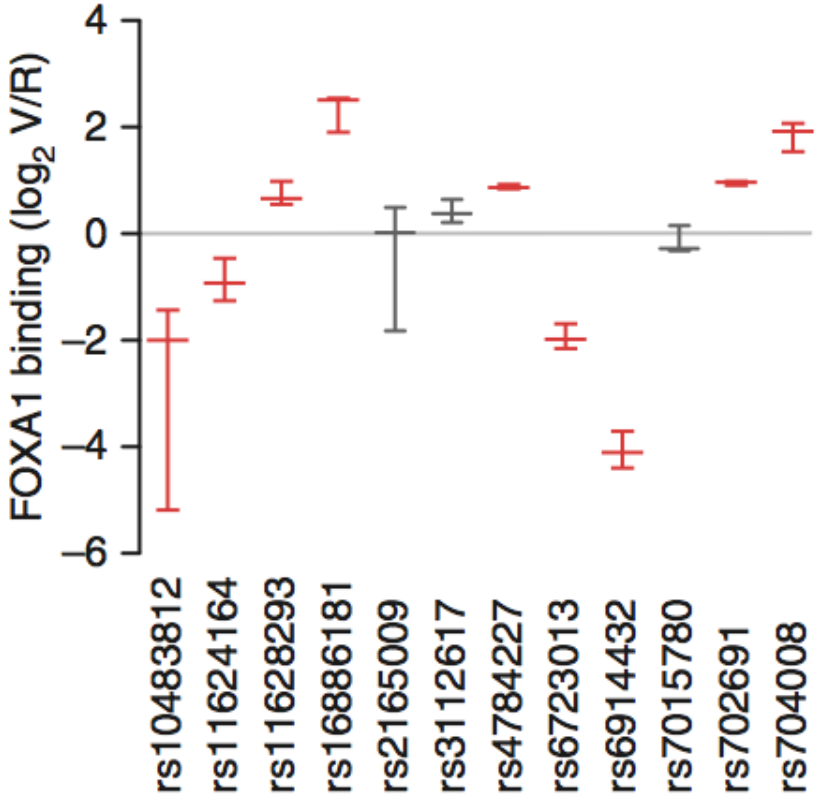
Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

IGR reveals that most BCa genetic risk-loci modulate FoxA1 binding to the DNA

IGR based allele-specific FoxA1 binding



Allele-specific ChIP-qPCR: FoxA1



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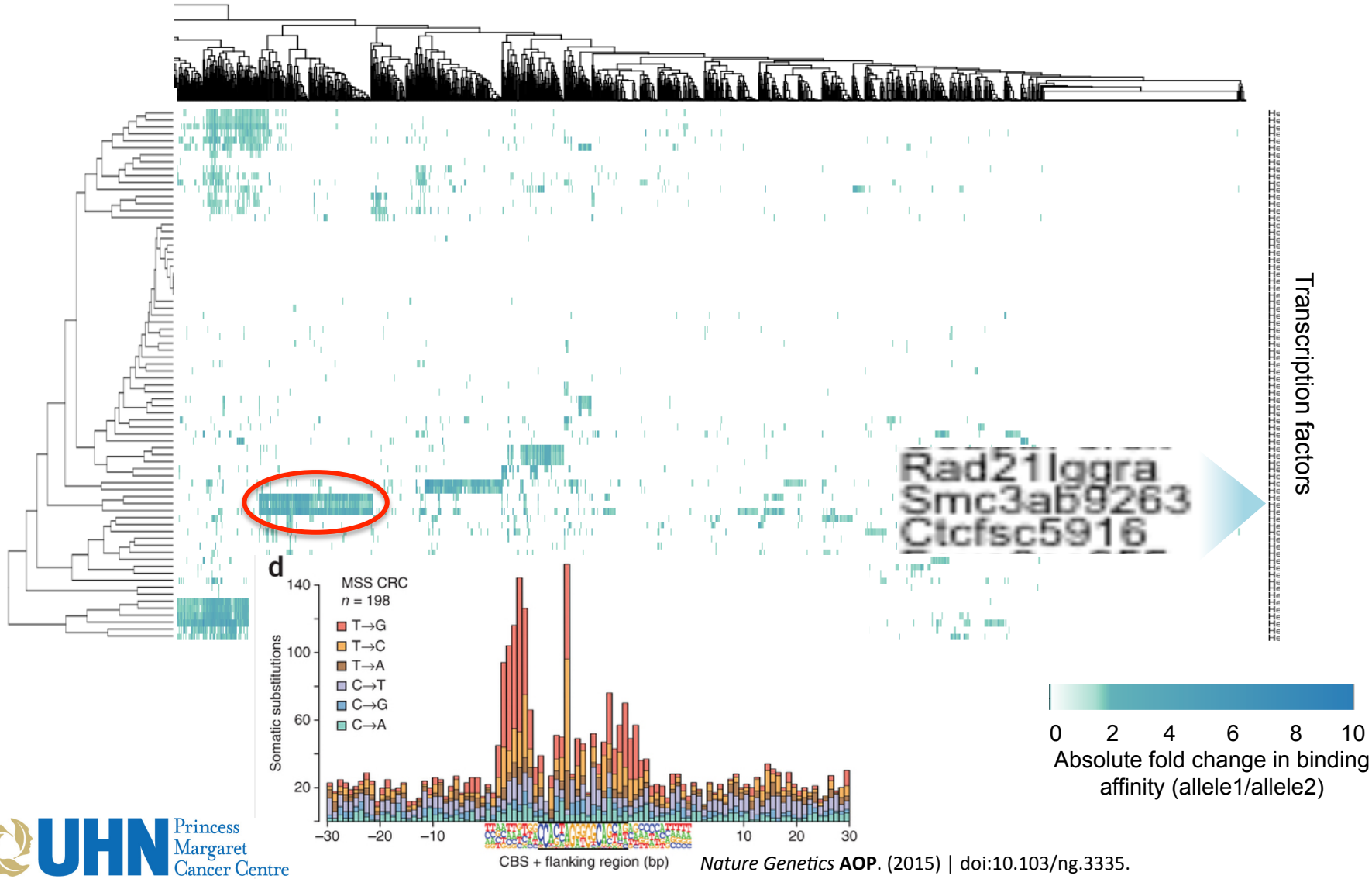
Cowper Sal-lari et al. (2012). Nature Genetics 44. p1191

Combining IGR with ENCODE: all genetic variants versus all transcription factors

IGR based analysis
>2000 Genetic alterations in DHS



Nature Genetics **AOP**. (2015) | doi:10.103/ng.3335.

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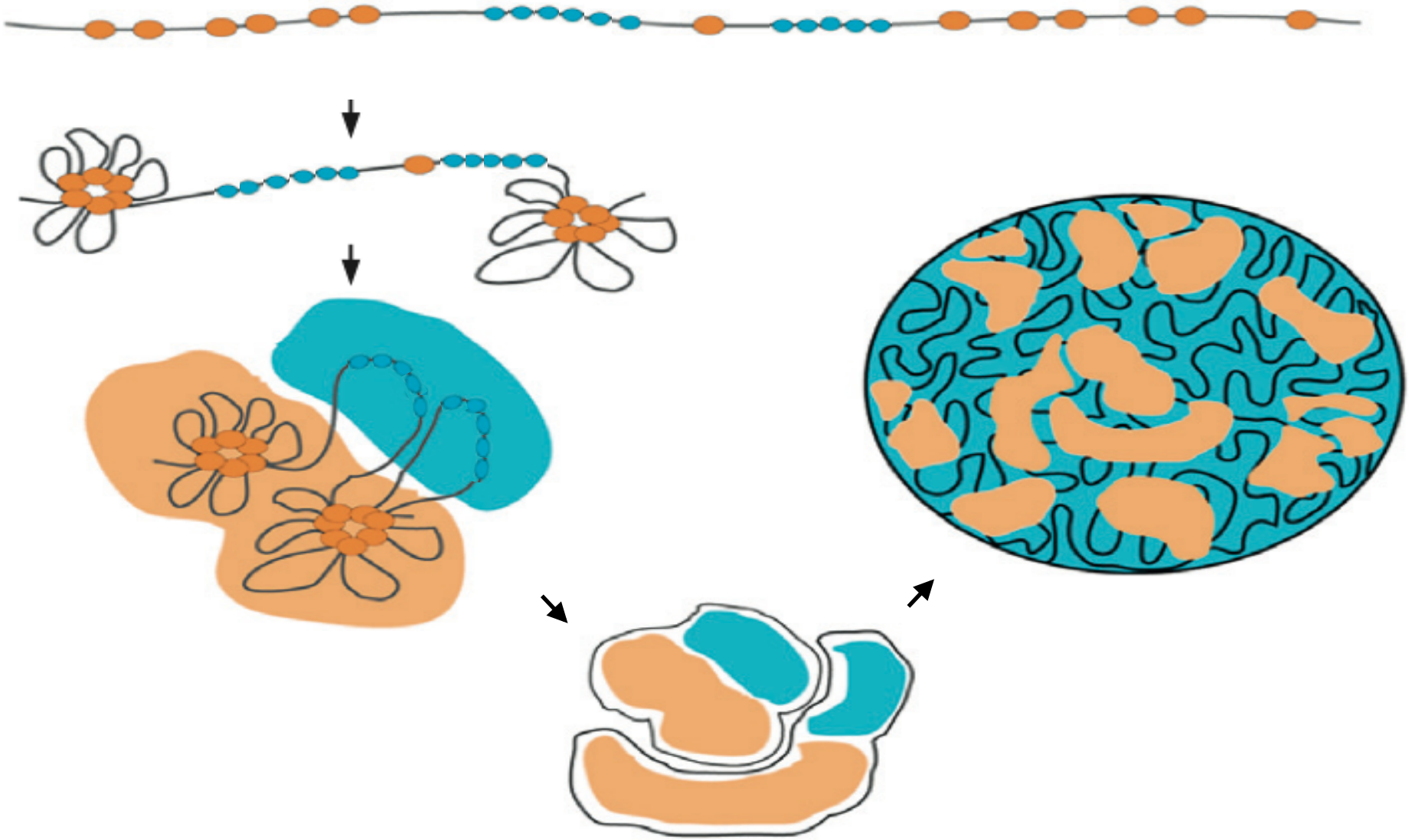
What are the target gene(s) of genetically or epigenetically altered regulatory elements?

Chromatin interactions define the social genome



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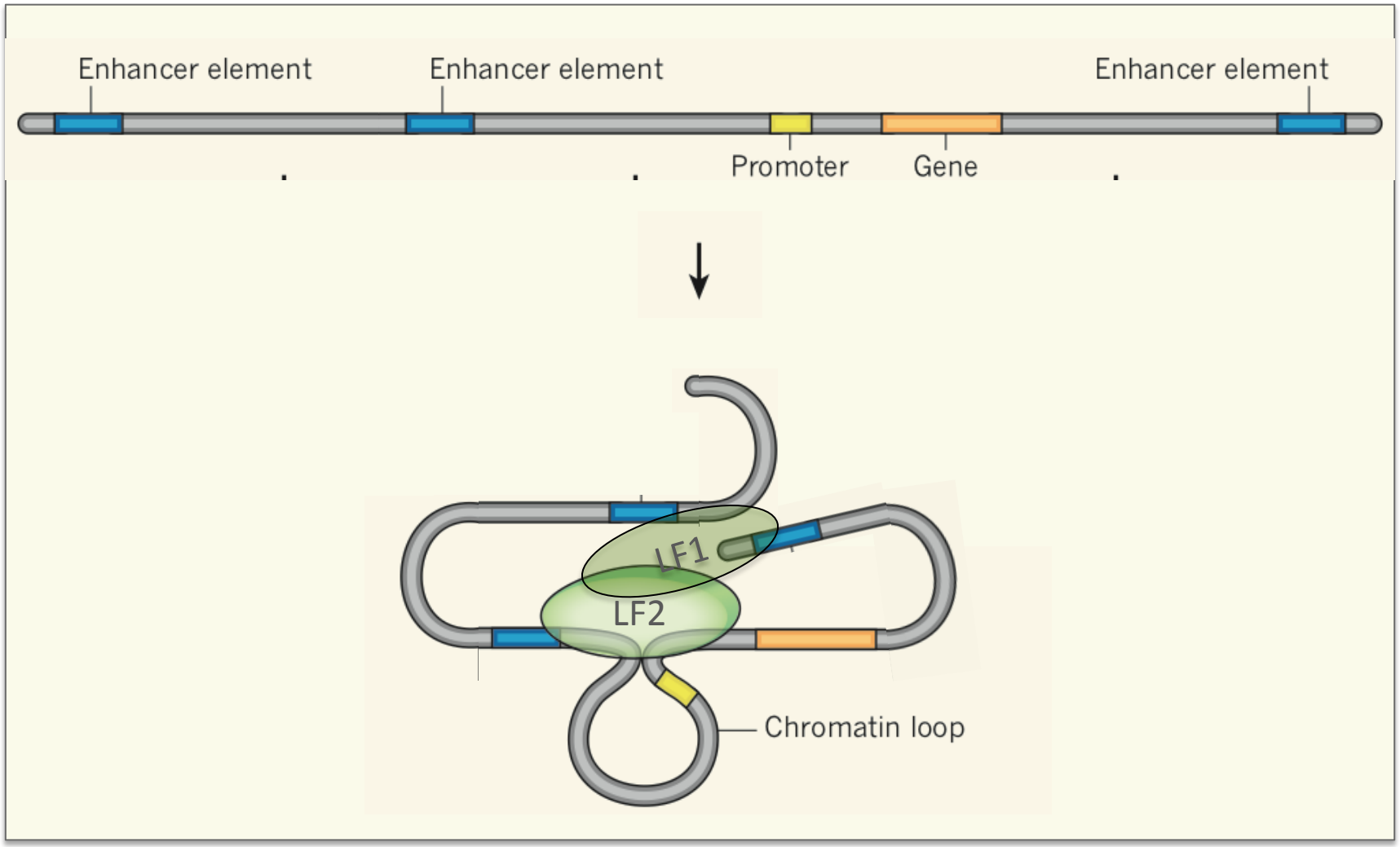
Sanyal, et al (2011) Current Opinion in Cell Biology. 23 p325-331

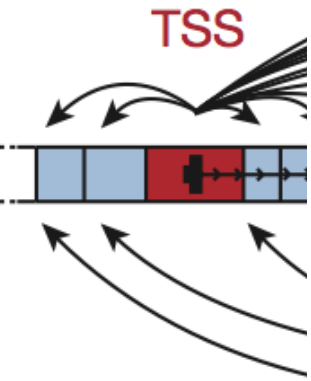
The social genome needs matchmakers

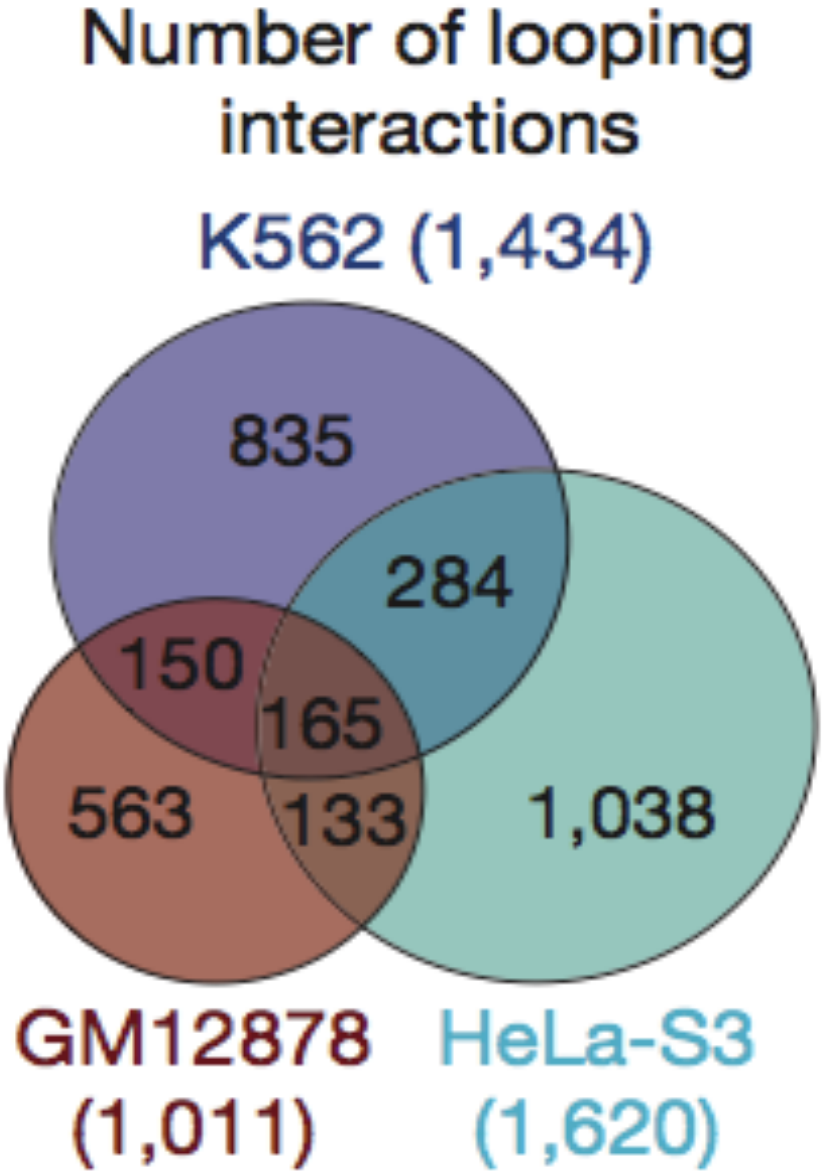
okcupid

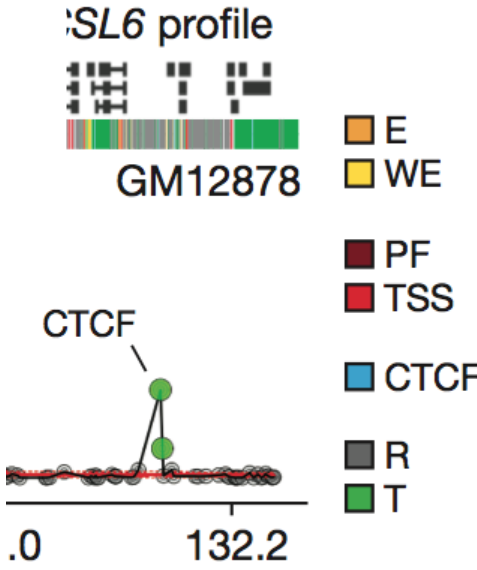
Chromatin interactions bring regulatory elements to their target gene(s)



Detecting chromatin interactions through Chromatin Conformation Capture (3C) assays







Sanyal, et al (2013) Na

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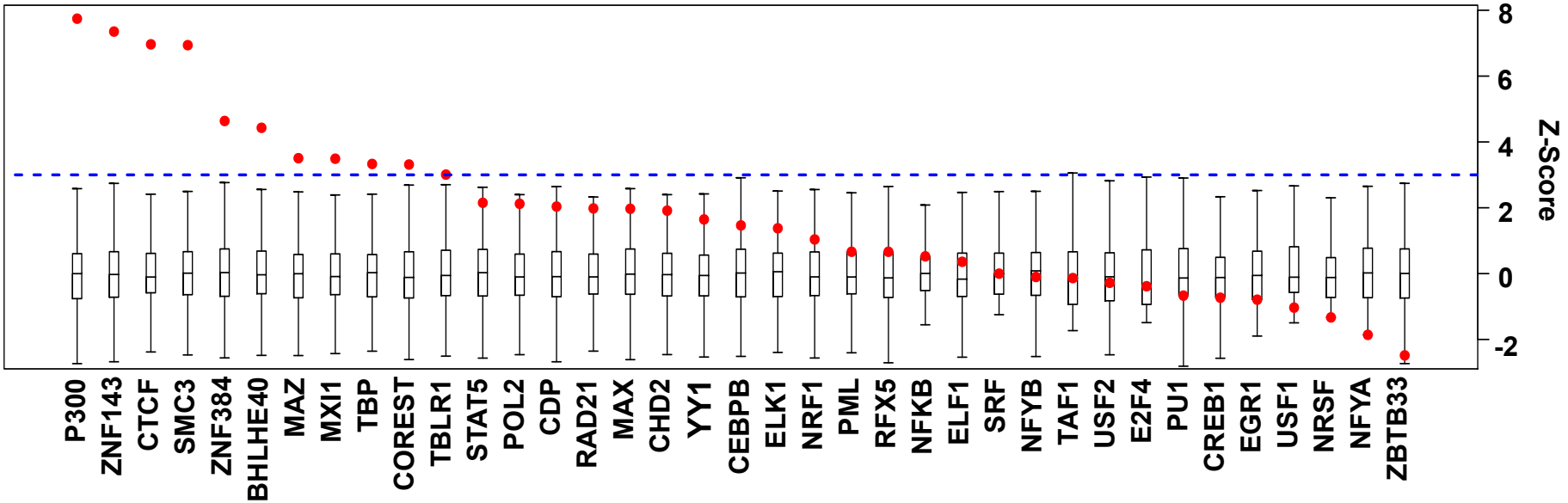
ZNF143 and a few more transcription factors preferentially binds chromatin loop anchors

GM12878 cells



Enrichment of transcription factor binding sites at 5C anchors

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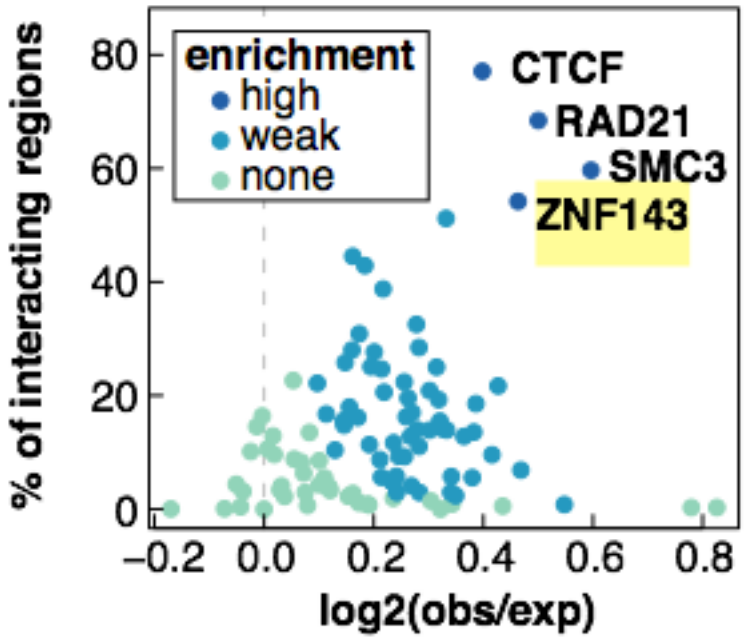
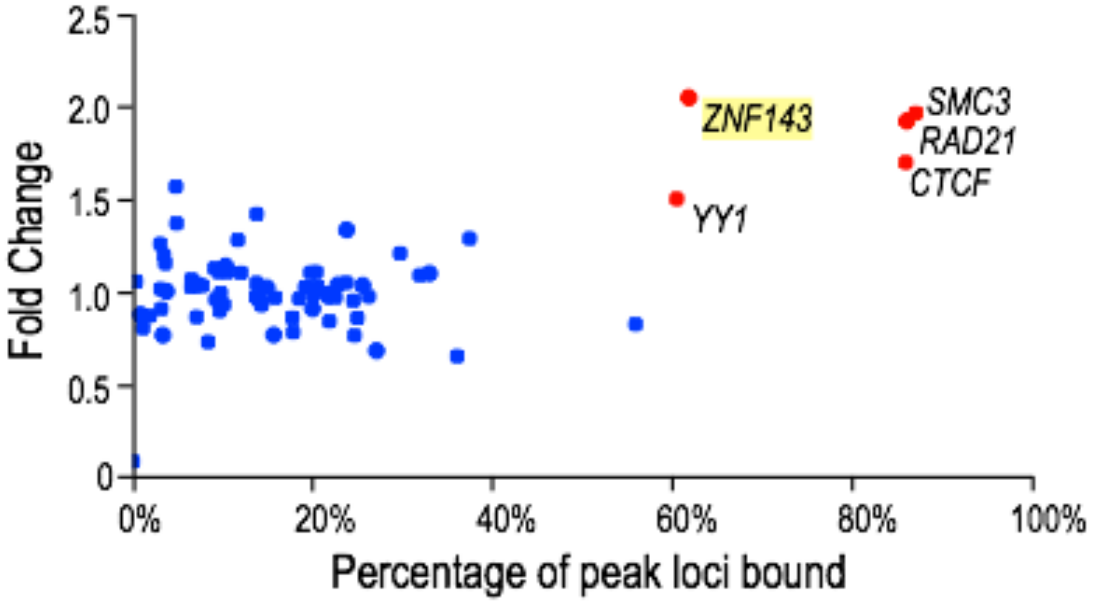
Bailey et al 2015. Nat Commun. 2: 6186

ZNF143 enrichment at chromatin loop anchors “validated” by others

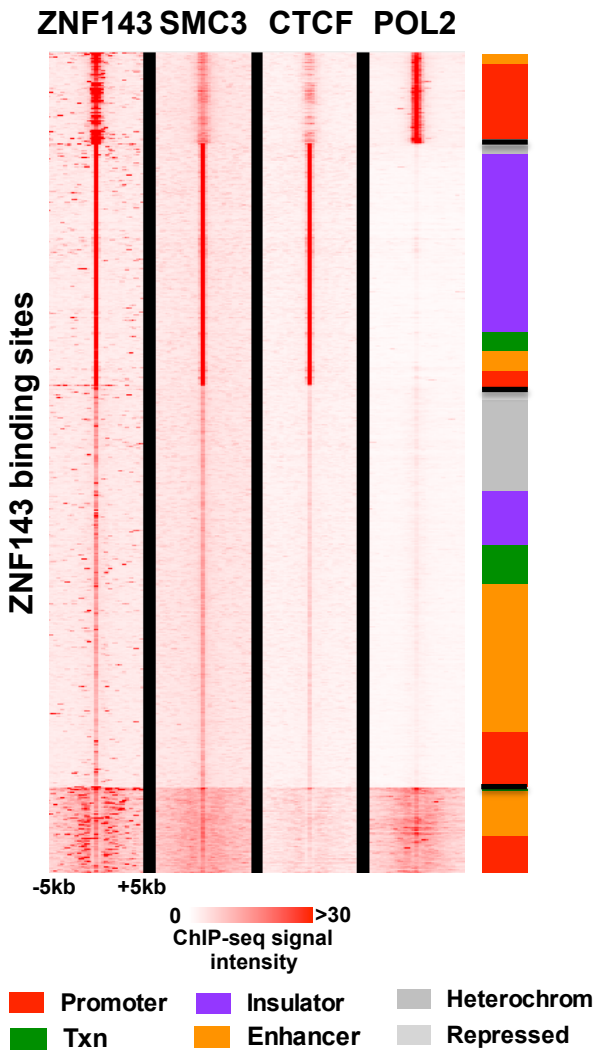


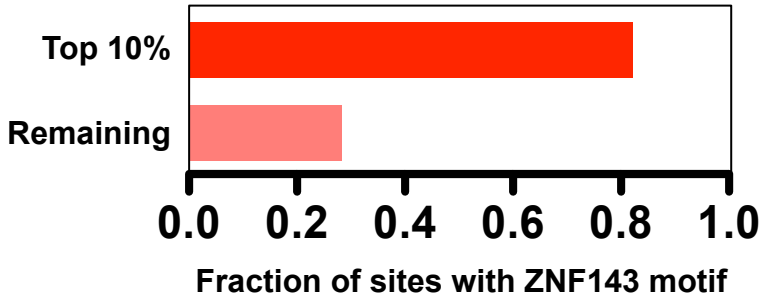
Heidari et al. Genome Research. Sept 2014

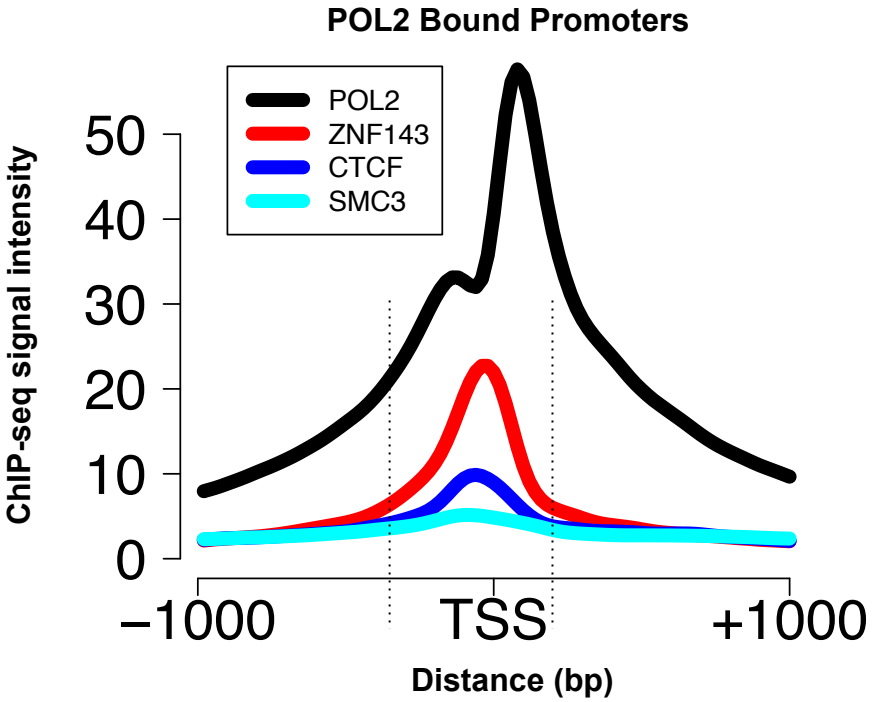


Rao et al. Cell. December 2014

ZNF143 preferentially binds promoters next to RNA Pol II





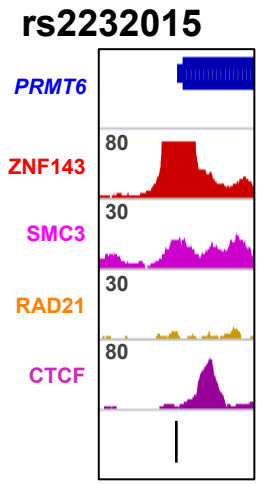


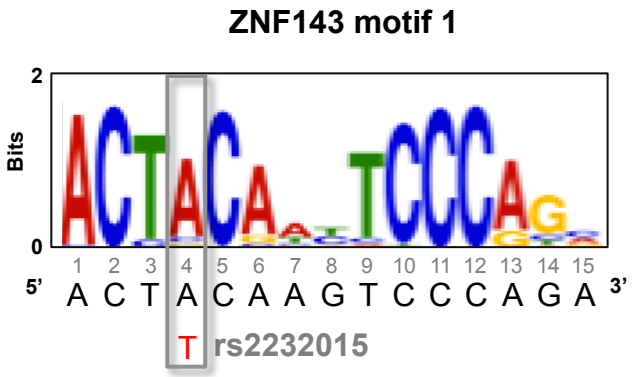
GM12878 cells

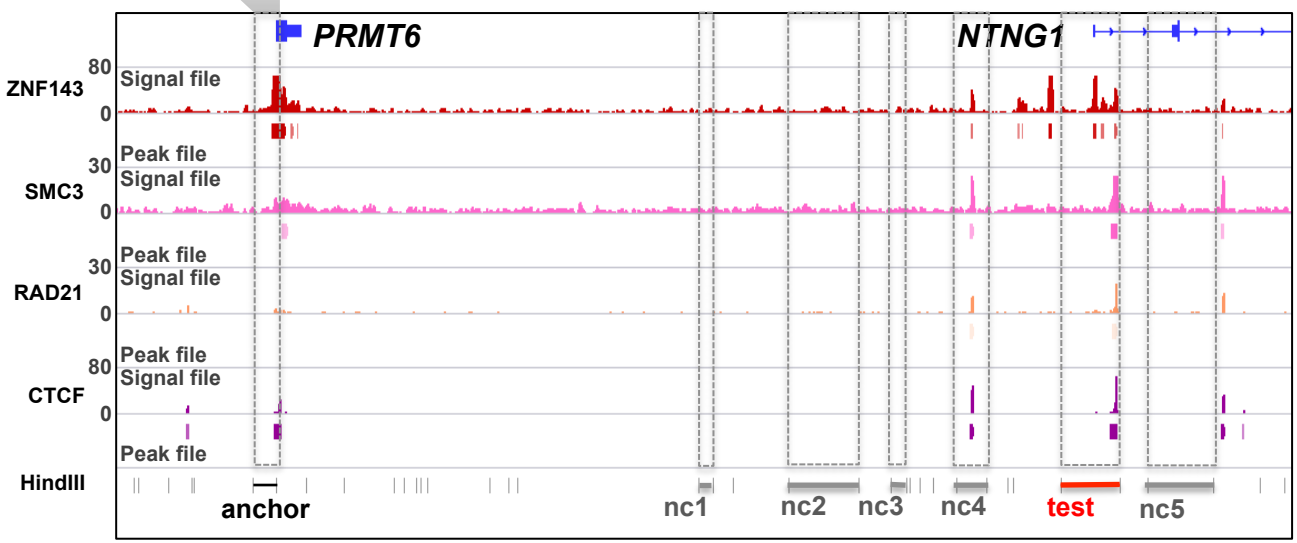
UHN Princess Margaret Cancer Centre

Bailey et al 2015. Nat Commun. 2: 6186

Disrupting ZNF143 binding to the chromatin antagonizes chromatin loop formation







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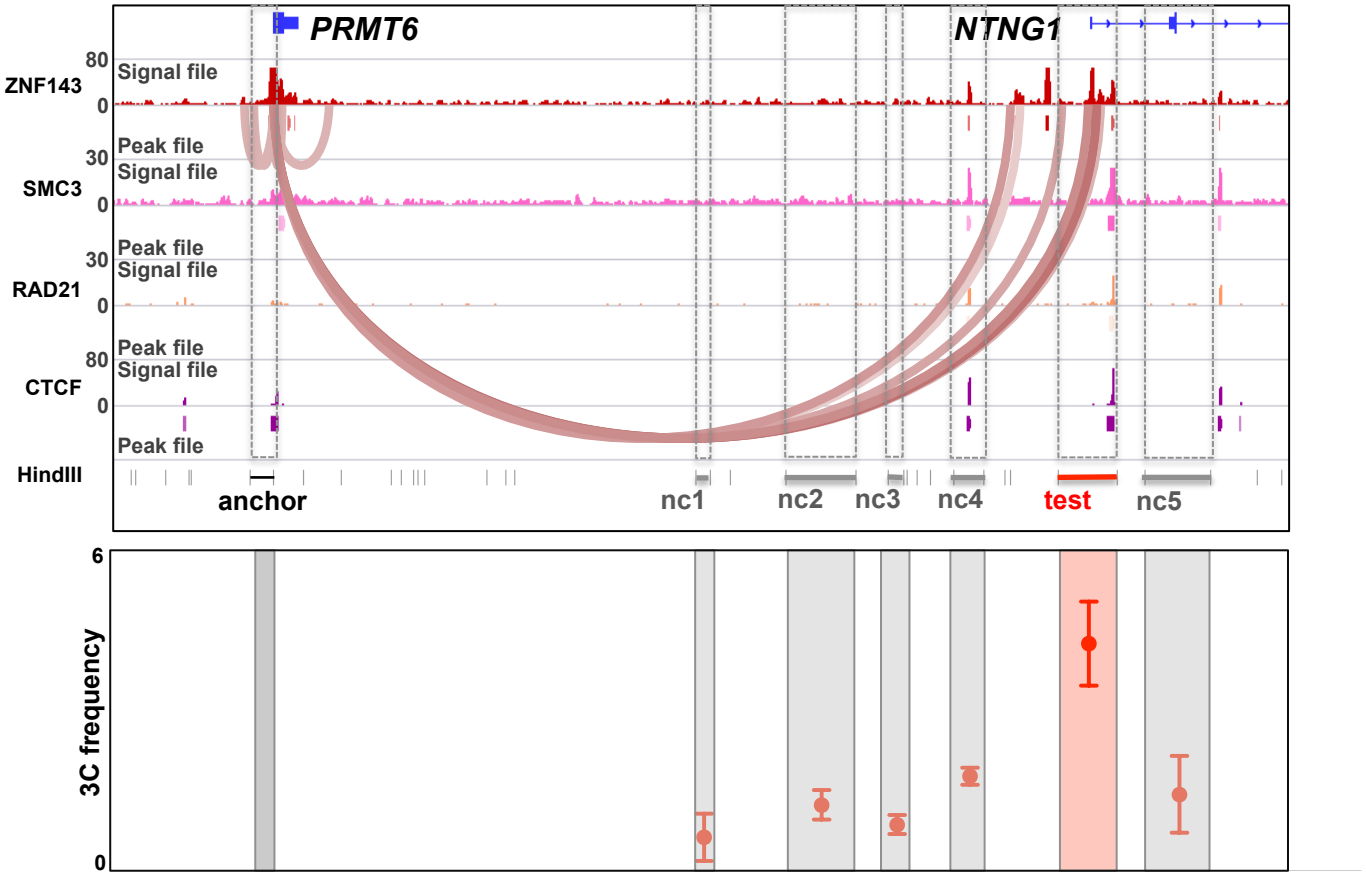
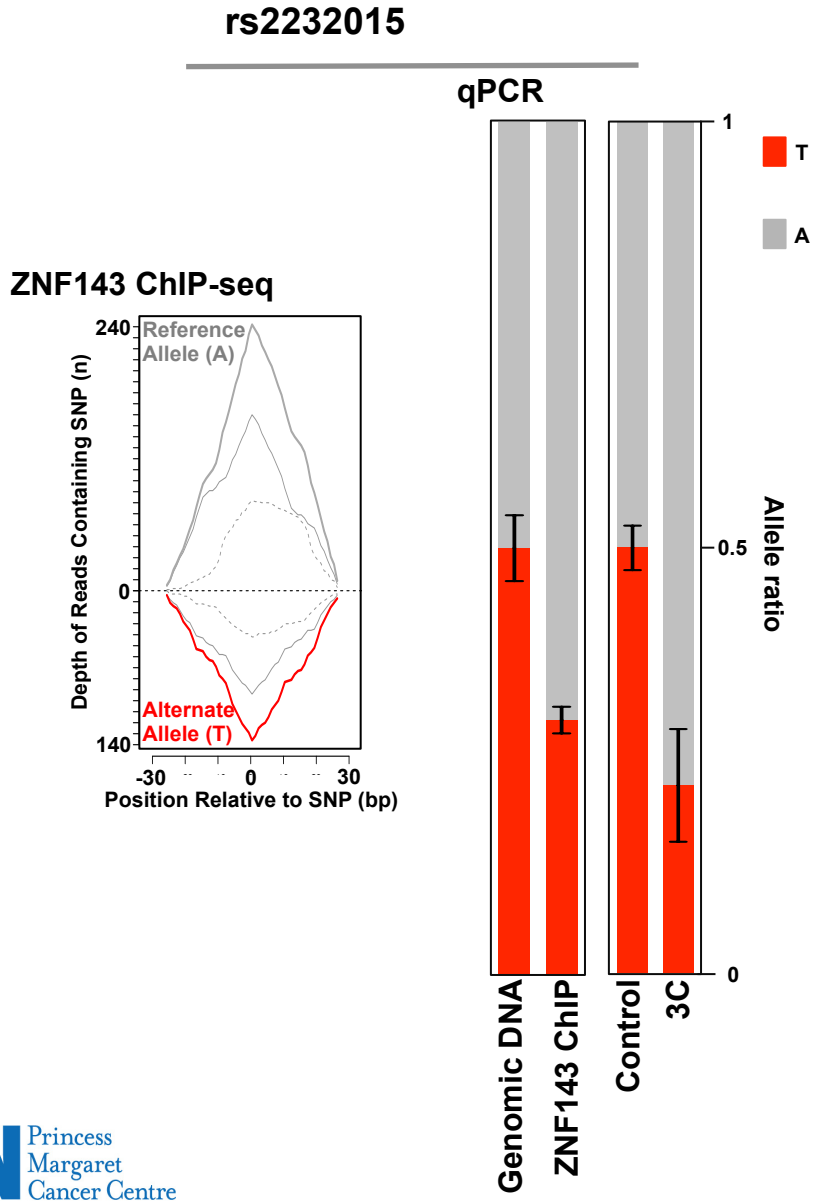
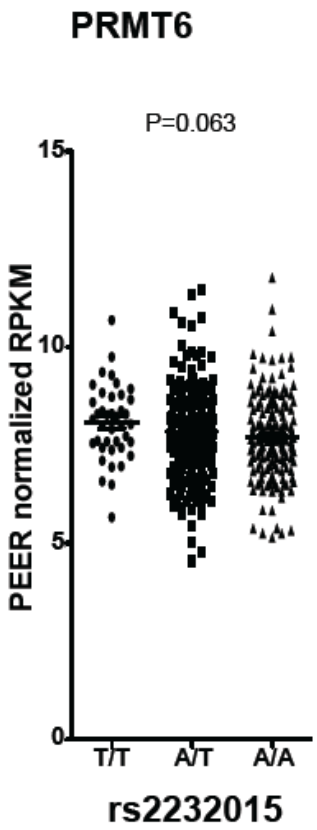
Disrupting ZNF143 binding to the chromatin antagonizes chromatin loop formation



Bailey et al 2015. Nat Commun. 2: 6186

Disrupting ZNF143 binding to the chromatin antagonizes chromatin loop formation





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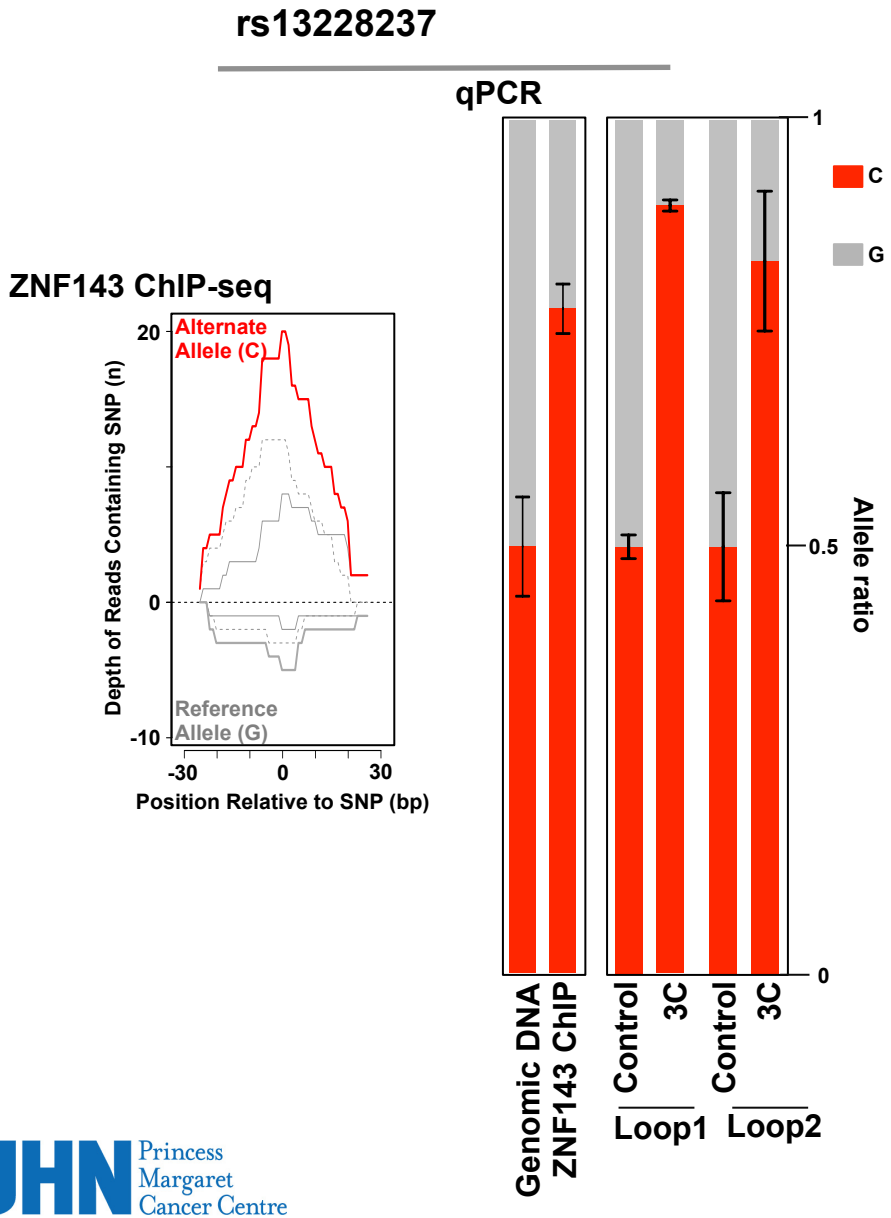
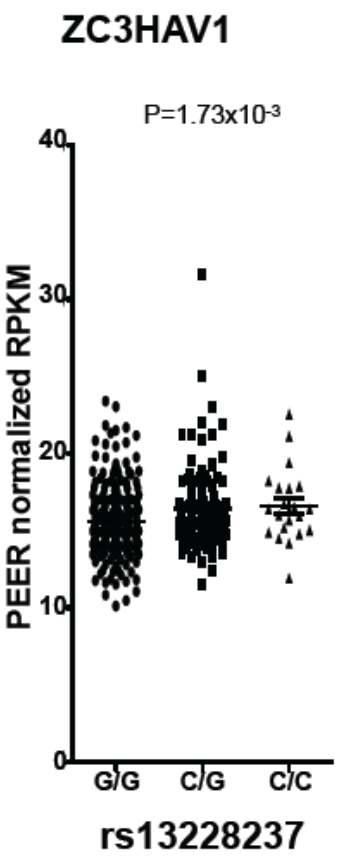
Disrupting ZNF143 binding to the chromatin antagonizes chromatin loop formation





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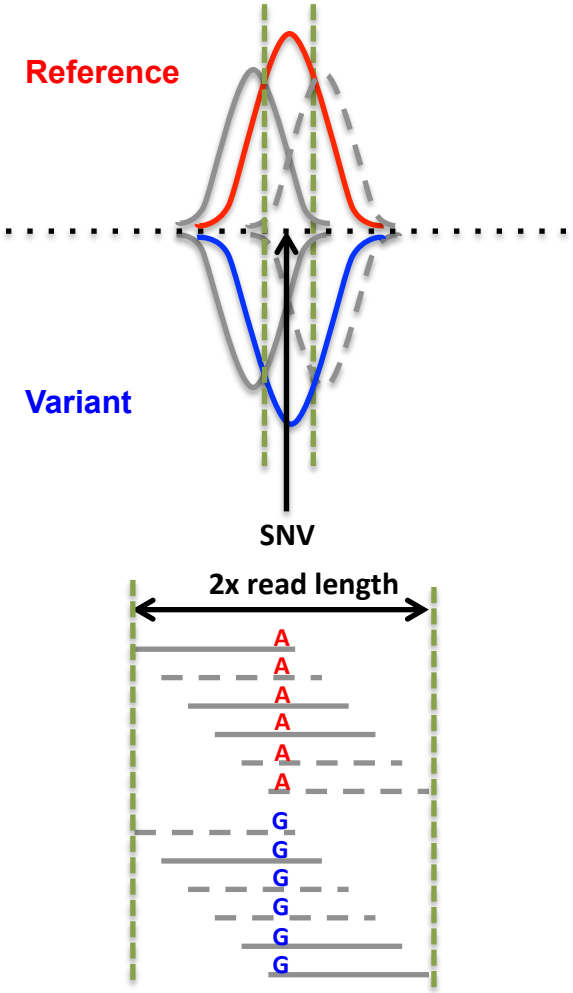
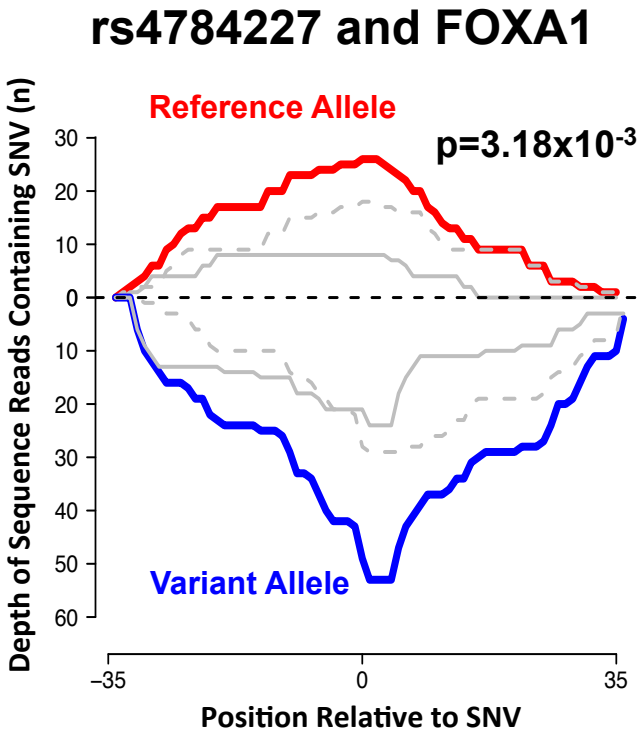
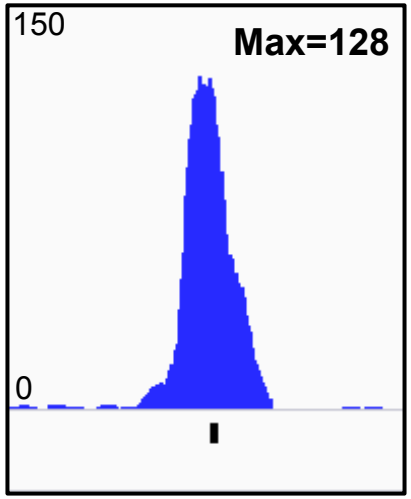
Allele-specific Binding from ChIP-seq (ABC)

https://github.com/mlupien/ABC







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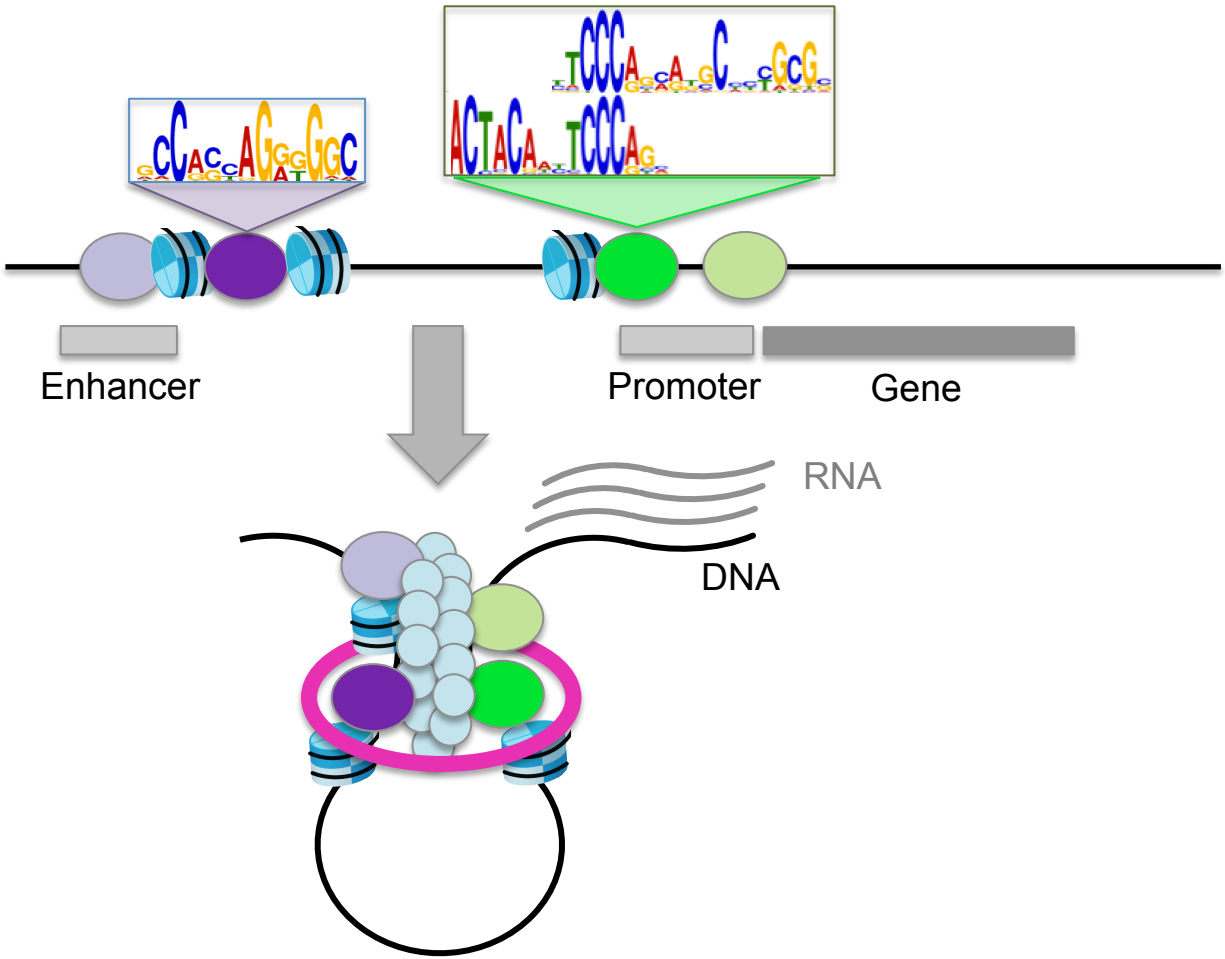
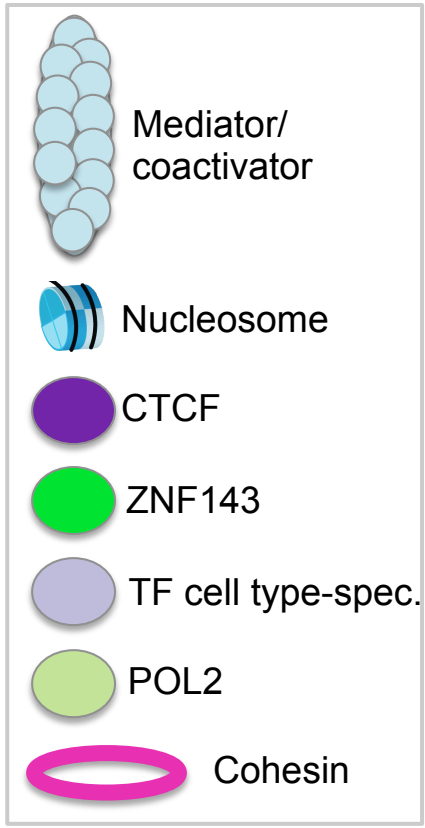
Bailey et al 2015. Bioinformatics. btv321

ZNF143 secures chromatin interactions at promoters





Thank you!

www.pmgenomics.ca/lupienlab

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