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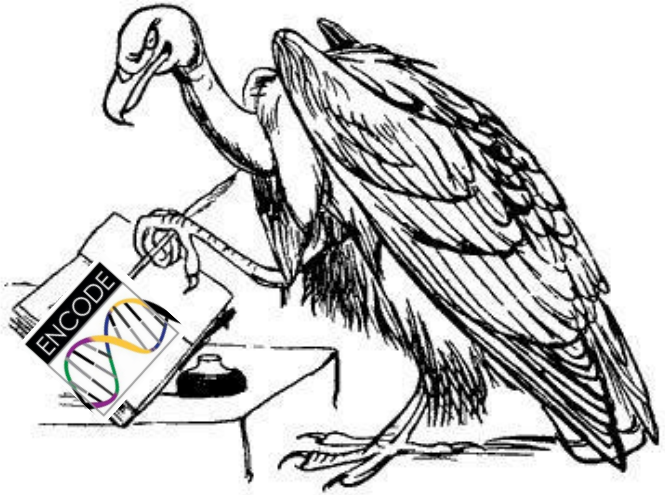
Regulatory Noncoding Variants in Breast Cancer

Mathieu Lupien, PhD

Senior scientist
Princess Margaret Cancer Centre

Assistant Professor
University of Toronto

Becoming an ENCODE user



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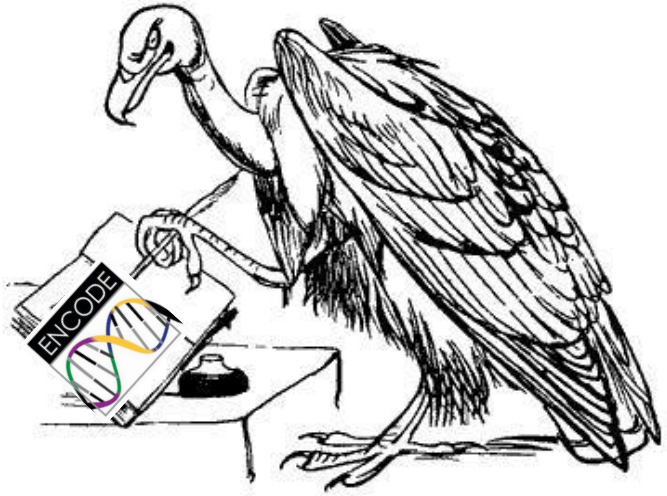

nature COMMUNICATIONS

ARTICLE

Received 28 Jul 2014 | Accepted 30 Dec 2014 | Published 3 Feb 2015

DOI: 10.1038/ncomms7186

ZNF143 provides sequence specificity to secure chromatin interactions at gene promoters

Swneke D. Bailey[1,2,*], Xiaoyang Zhang[3,*,†], Kinjal Desai[3], Malika Aid[4], Olivia Corradin[5], Richard Cowper-Sal·lari[1,†], Batool Akhtar-Zaidi[5,6,†], Peter C. Scacheri[5,6], Benjamin Haibe-Kains[1,2,4] & Mathieu Lupien[1,2,7]

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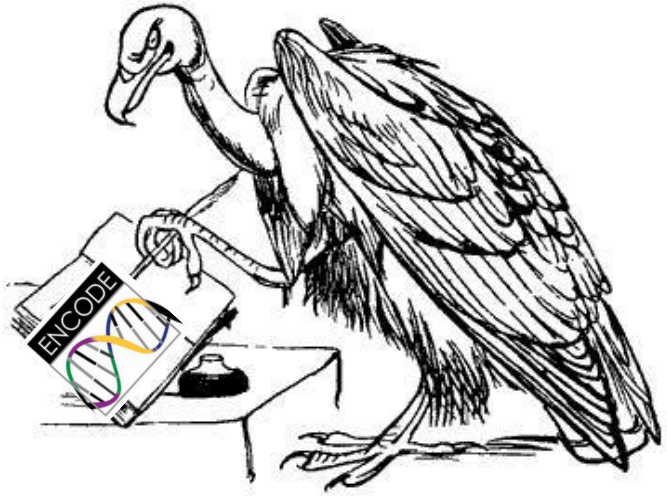

nature COMMUNICATIONS

Bioinformatics Advance Access published June 11, 2015

Bioinformatics, 2015, 1–3
doi: 10.1093/bioinformatics/btv321
Advance Access Publication Date: 20 May 2015
Applications Note

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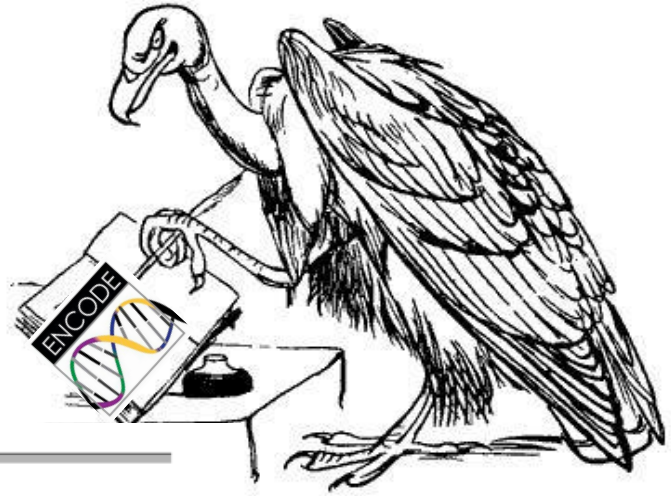
Gene expression

ABC: a tool to identify SNVs causing allele-specific transcription factor binding from ChIP-Seq experiments

Swneke D. Bailey[1,2], Carl Virtanen[1], Benjamin Haibe-Kains[1,2] and Mathieu Lupien[1,2,3,*]

Becoming an ENCODE user



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Combinatorial effects of multiple enhancer variants in linkage disequilibrium dictate levels of gene expression to confer susceptibility to common traits

Olivia Corradin,[1] Alina Saiakhova,[1] Batool Akhtar-Zaidi,[1] Lois Myeroff,[2] Joseph Willis,[2,3] Richard Cowper-Sal·lari,[4] Mathieu Lupien,[4] Sanford Markowitz,[1,2,5] and Peter C. Scacheri[1,2,6]

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nature COMMUNICATIONS

ARTICLE

Received 12 Mar 2014 | Accepted 14 Aug 2014 | Published 23 Sep 2014

DOI: 10.1038/ncomms5999

Evidence that breast cancer risk at the 2q35 locus is mediated through *IGFBP5* regulation

Maya Ghoussaini[1,*], Stacey L. Edwards[2,3,*] *et al.*[#]

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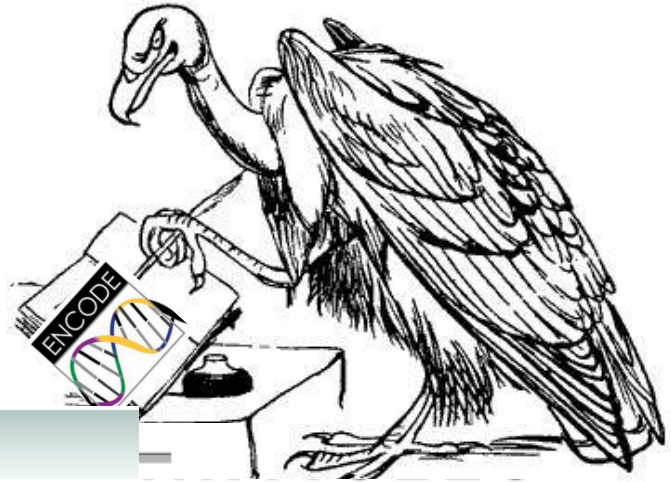

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Bioinformatics Advance Access published June 11, 2015

Bioinformatics, 2015, 1–3
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nature genetics

ARTICLE

Received 12

Breast cancer risk–associated SNPs modulate the affinity of chromatin for FOXA1 and alter gene expression

Richard Cowper-Sal·lari[1,2,7], Xiaoyang Zhang[1,2,7], Jason B Wright[1], Swneke D Bailey[3,4], Michael D Cole[1], Jerome Eeckhoute[5,6], Jason H Moore[1,2] & Mathieu Lupien[3,4]

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Bioinformatics, 2015, 1–3
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Science
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Epigenomic Enhancer Profiling Defines a Signature of Colon Cancer
Batool Akhtar-Zaidi *et al.*
Science **336**, 736 (2012);
DOI: 10.1126/science.1217277

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Becoming an ENCODE user

ng Defines a Signa[illegible]ancer

d SNPs modulate the affinity
d alter gene expression

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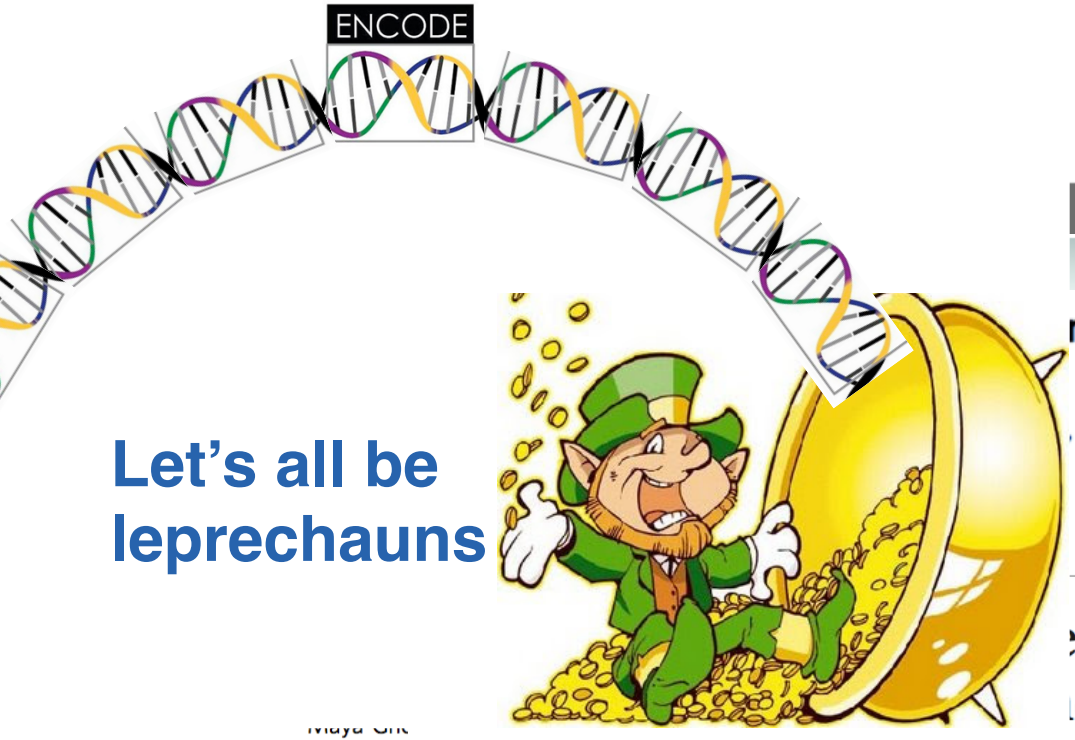
Becoming an ENCODE user



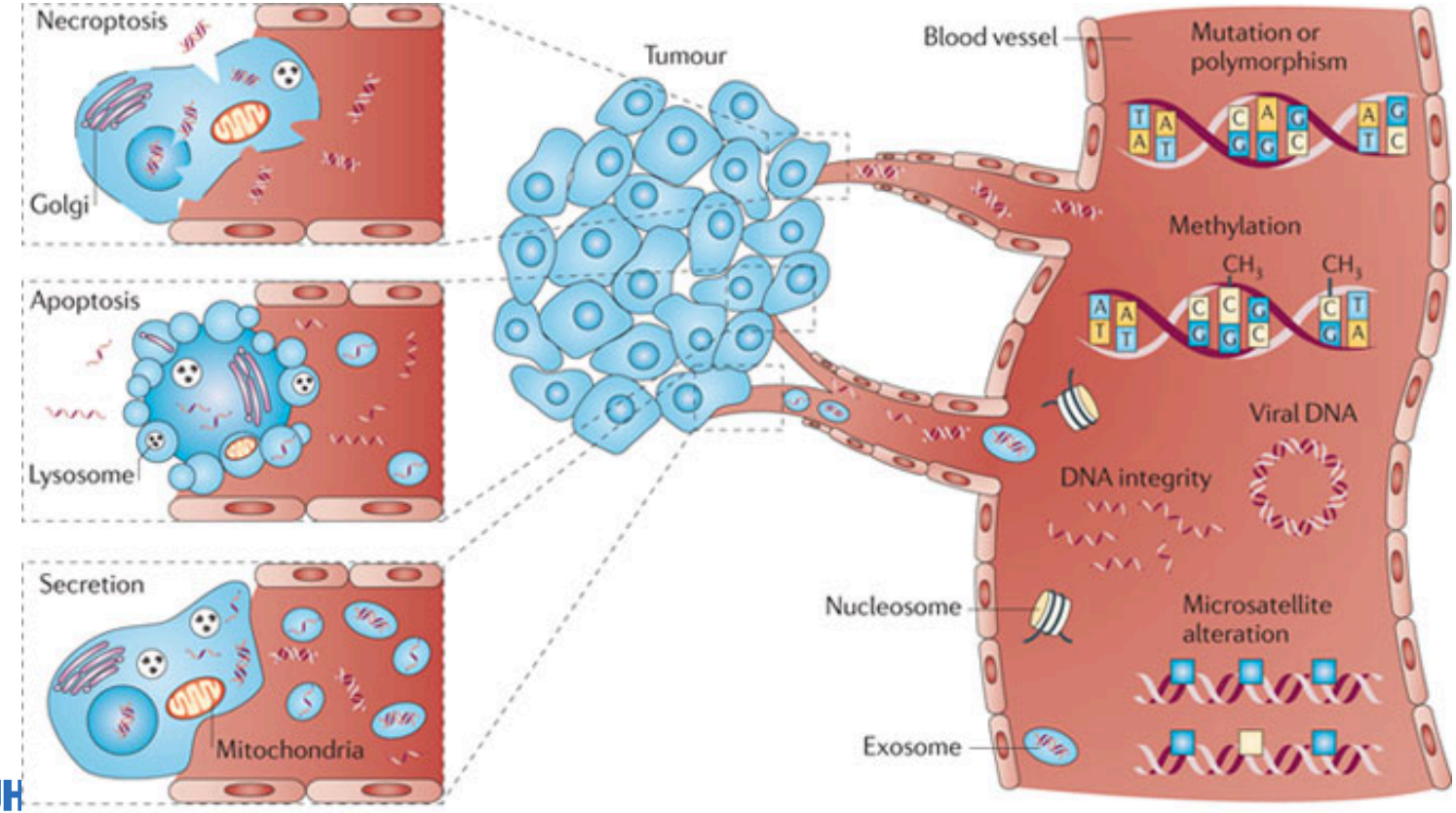
Let's all be leprechauns

ng Defines a Signa ancer

d SNPs modulate the affinity
d alter gene expression

Richard Cowper-Sal·lari[1,2,7], Xiaoyang Zhang[1,2,7], Jason B Wright[1], Swneke D Bailey[3,4], Michael D Cole[1], Jerome Eeckhoute[5,6], Jason H Moore[1,2] & Mathieu Lupien[3,4]

Profiling mutations informs the tumor biology and can serve to monitor disease development



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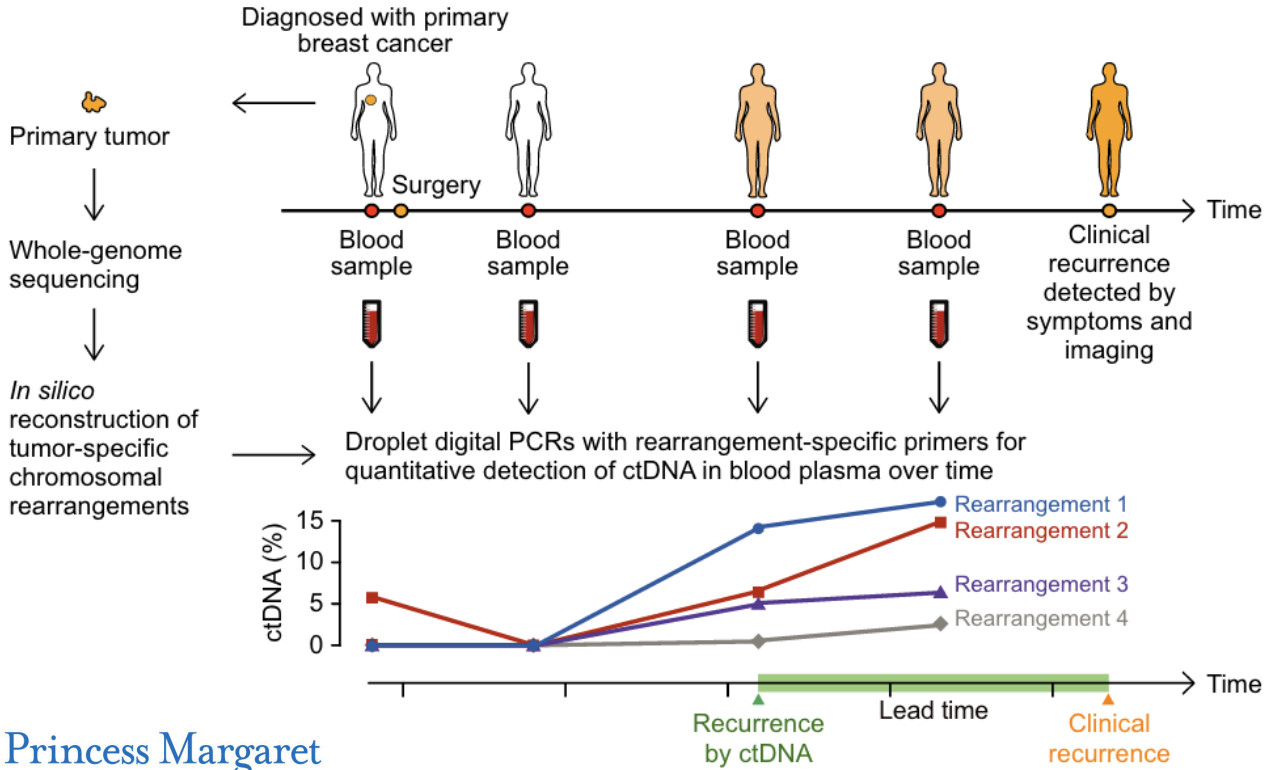
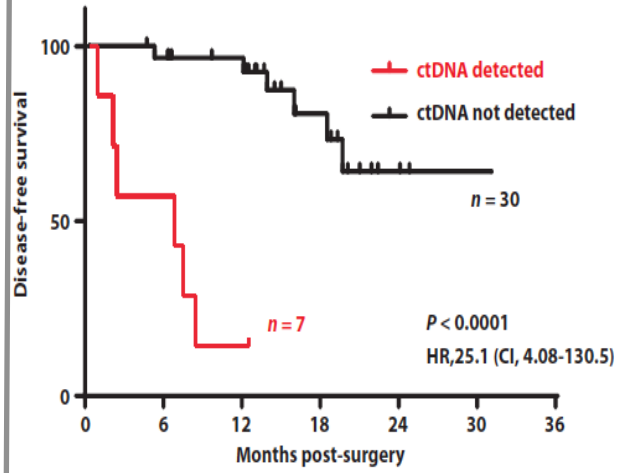
doi: 10.1038/nrc3066

Profiling mutations in blood biopsies can predict relapse in breast cancer





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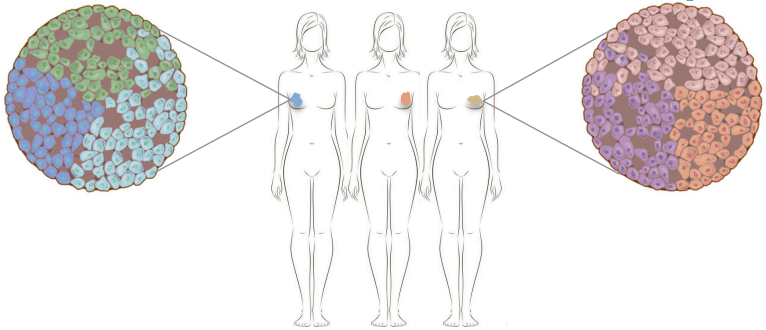
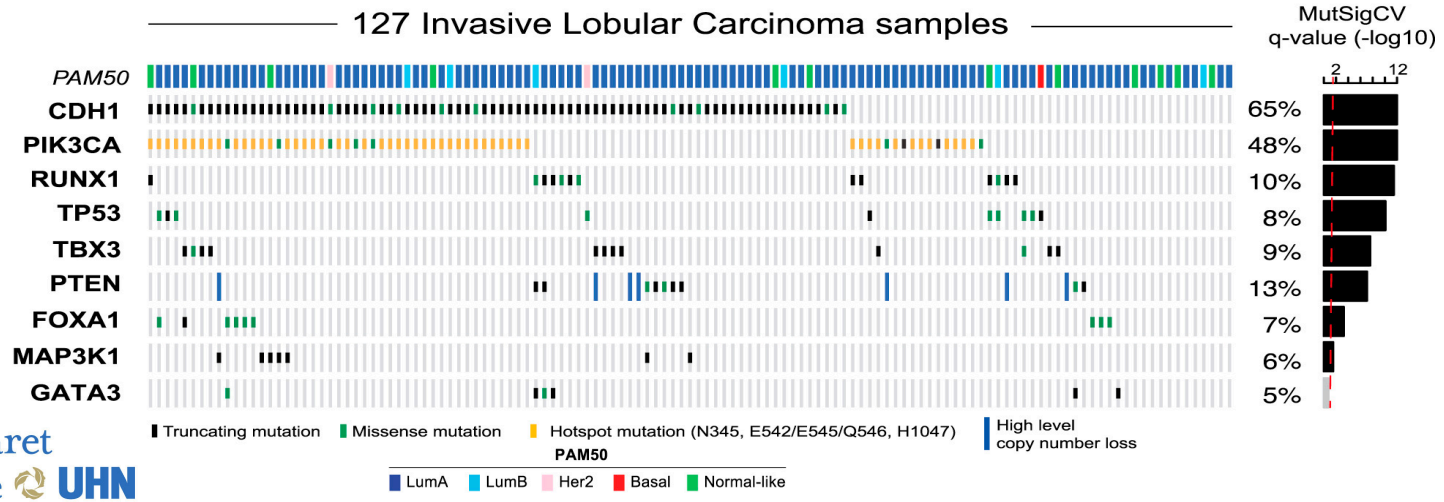
doi: 10.15252/emmm.201404913 and doi: 10.1126/scitranslmed.aab0021

Inter-patient heterogeneity raises the need for a comprehensive set of mutations to profile





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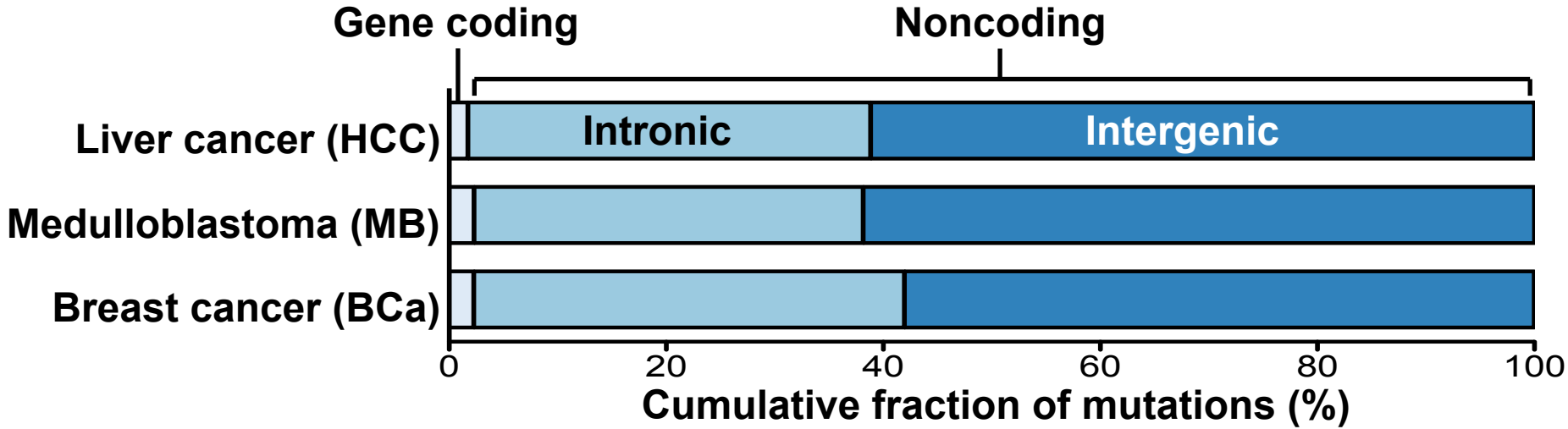
doi: 10.1016/j.cell.2015.09.033

Noncoding somatic mutations offer an opportunity to expand the list of driver mutations



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doi:10.1038/nature12477

The noncoding genome is a rich source of functional elements

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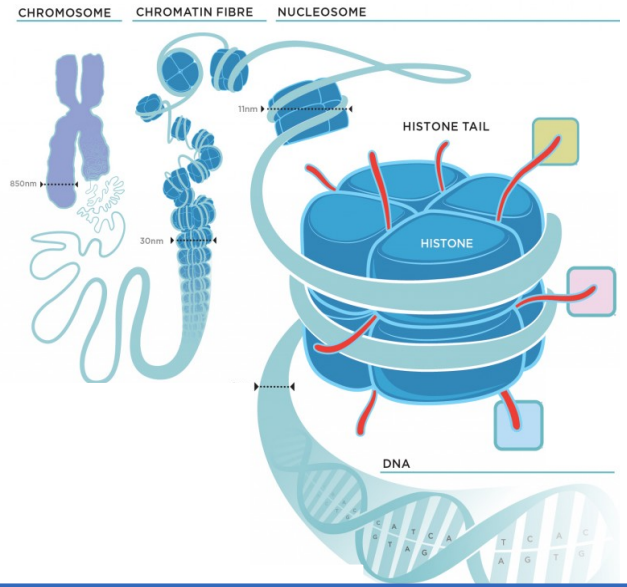
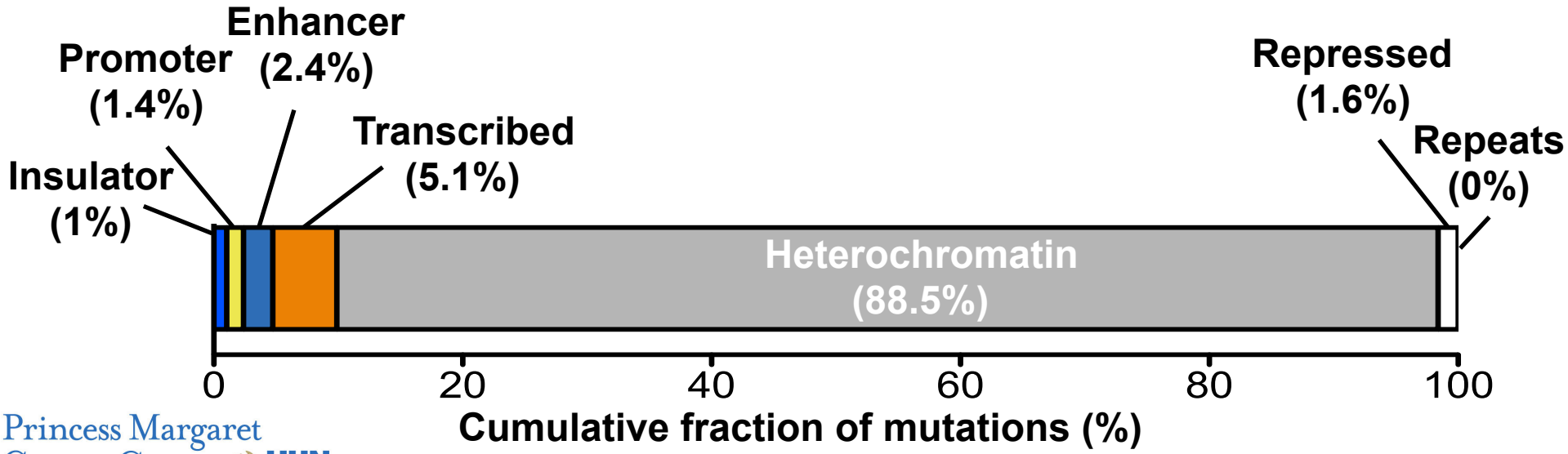
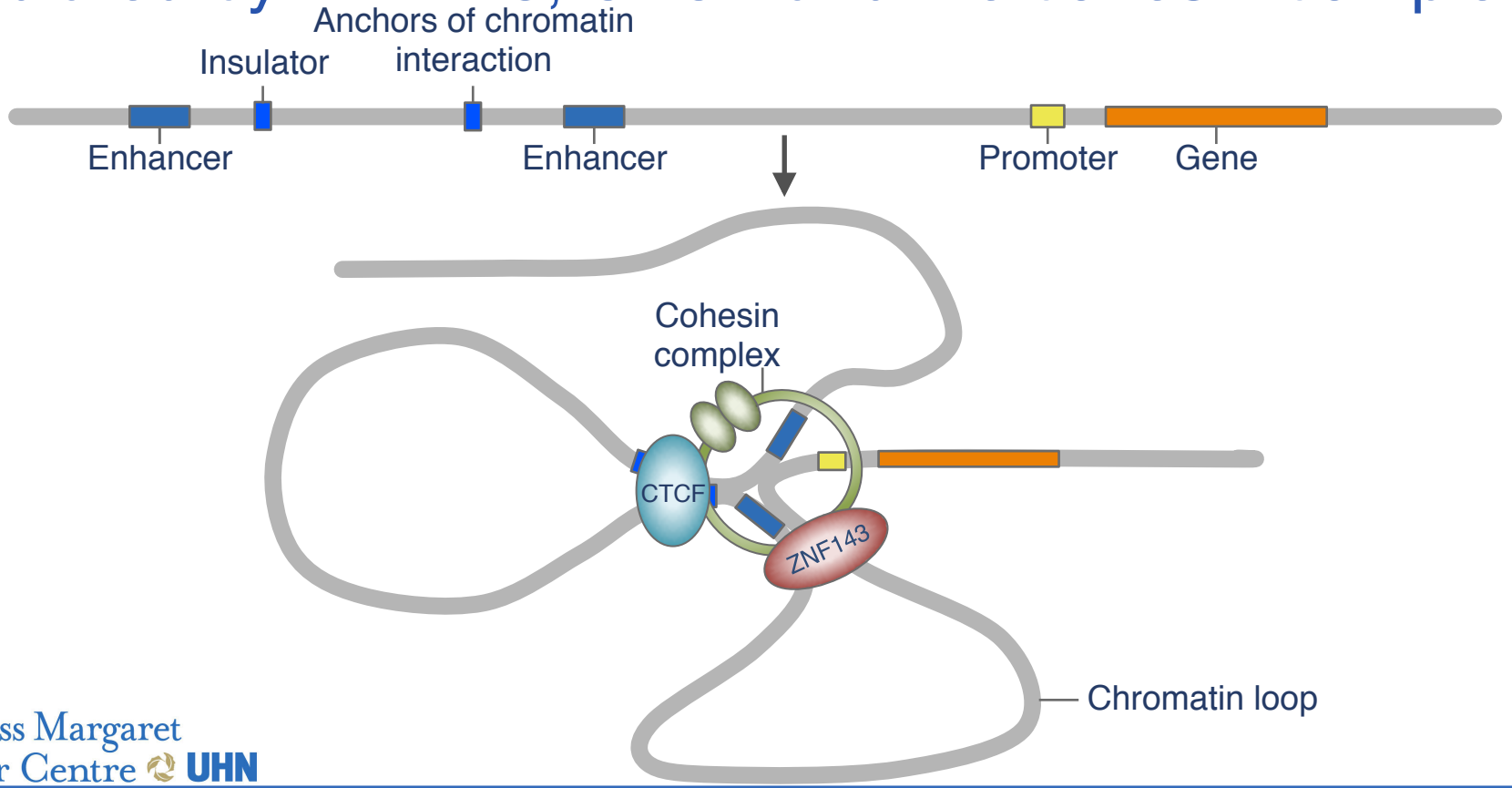


Few mutations in breast cancer map to regulatory elements



Gene expression relies on chromatin interactions mediated by ZNF143, CTCF and the cohesin complex



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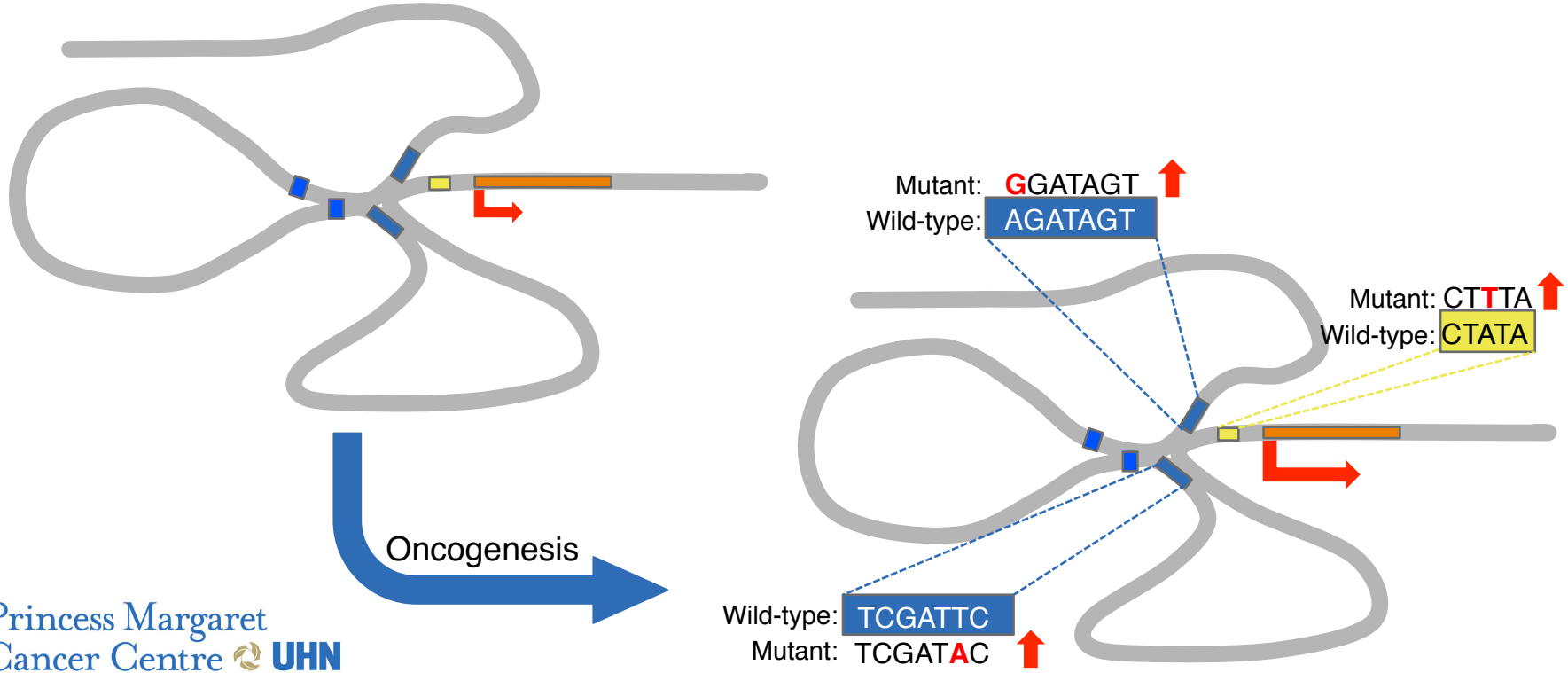
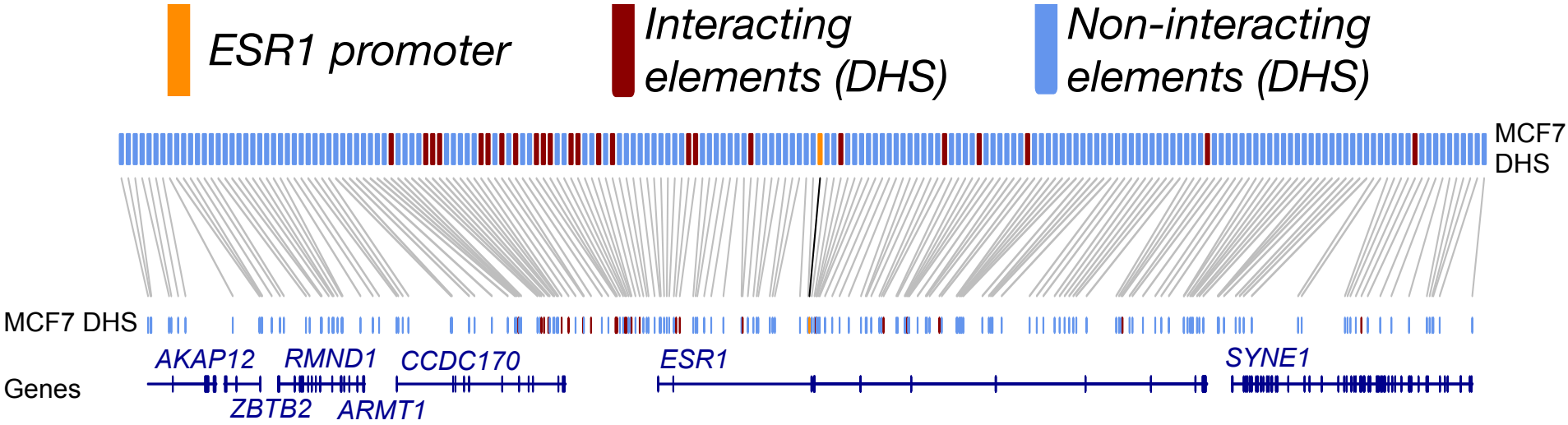
doi:10.1038/ncomms7186

Can driver noncoding mutations be found in the Sets of Regulatory Elements (SRE) of oncogenes or tumor suppressor genes?

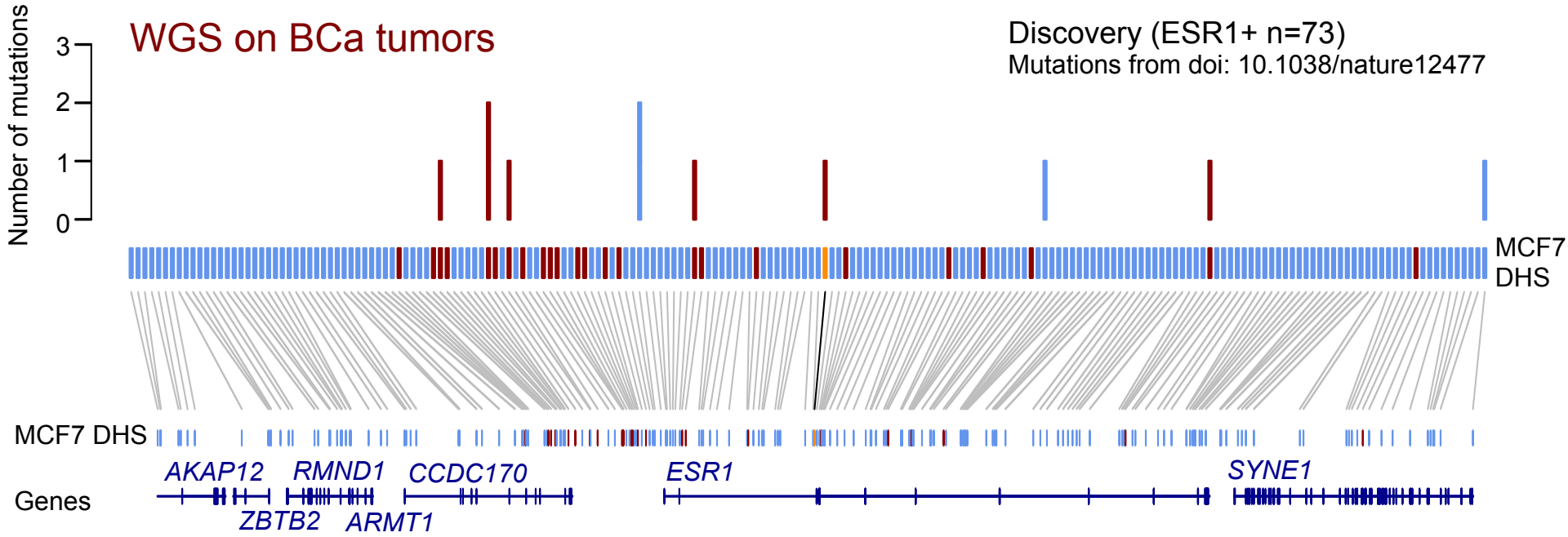


Case example: Delineating the SRE for the ESR1 gene



(C3D: ±500kb, r≥0.7)

Somatic mutations populate the SRE of the ESR1 gene



(C3D: ±500kb, r≥0.7)

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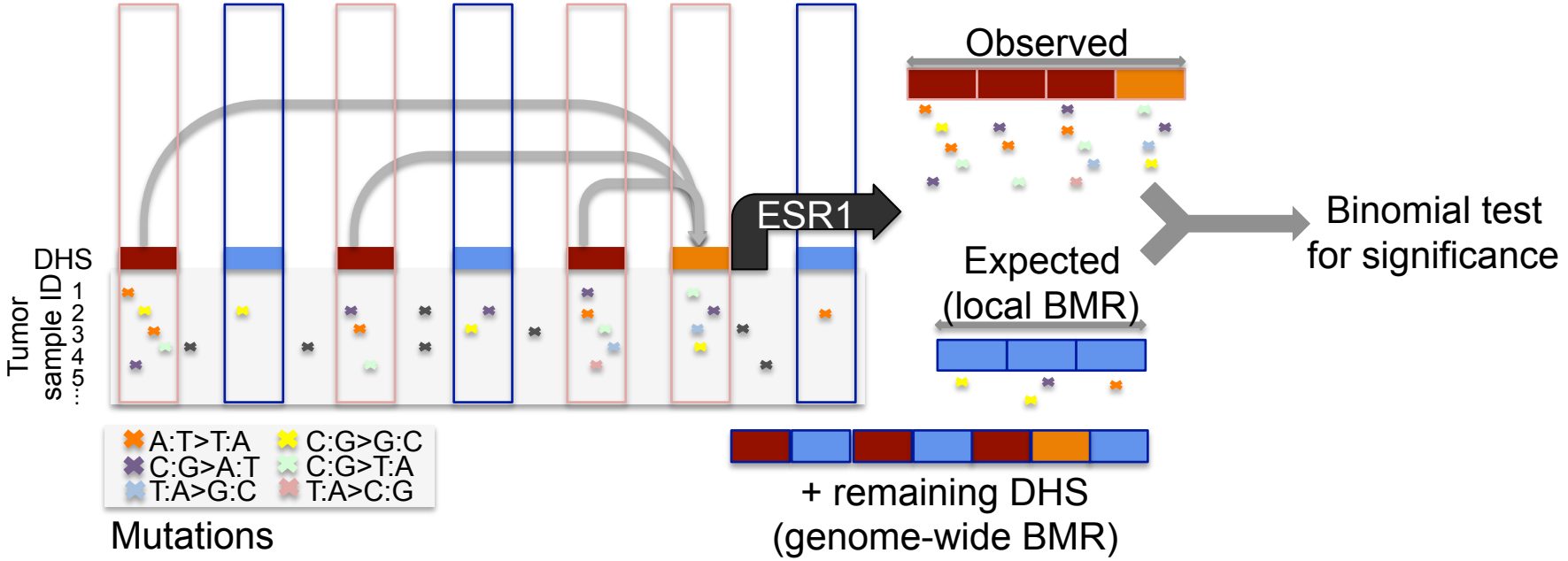
ESR1 promoter

Interacting elements (DHS)

Non-interacting elements (DHS)

MuSE tool offers a method to calculate the statistical enrichment of mutations in SREs

MuSE: Mutational Significance in sets of regulatory Elements



The ESR1 gene is significantly mutated in its SRE in breast cancer

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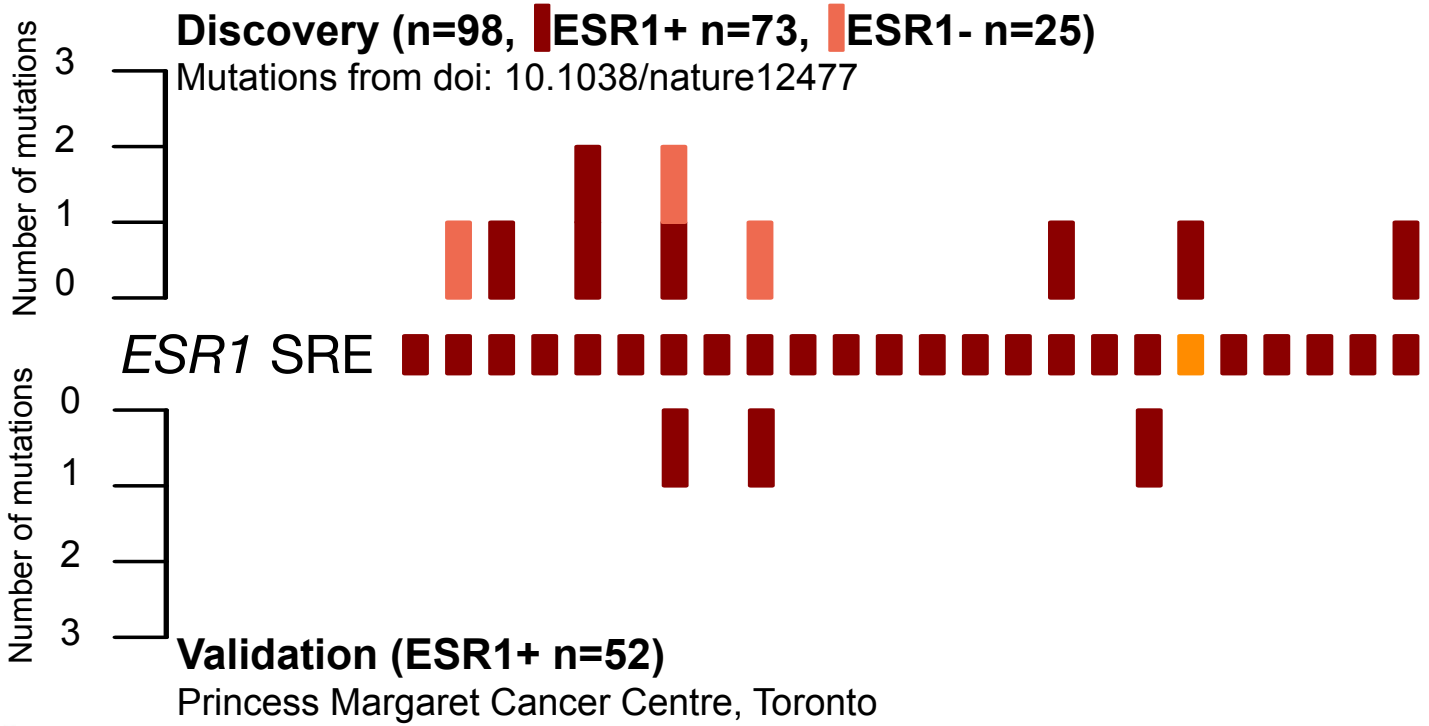
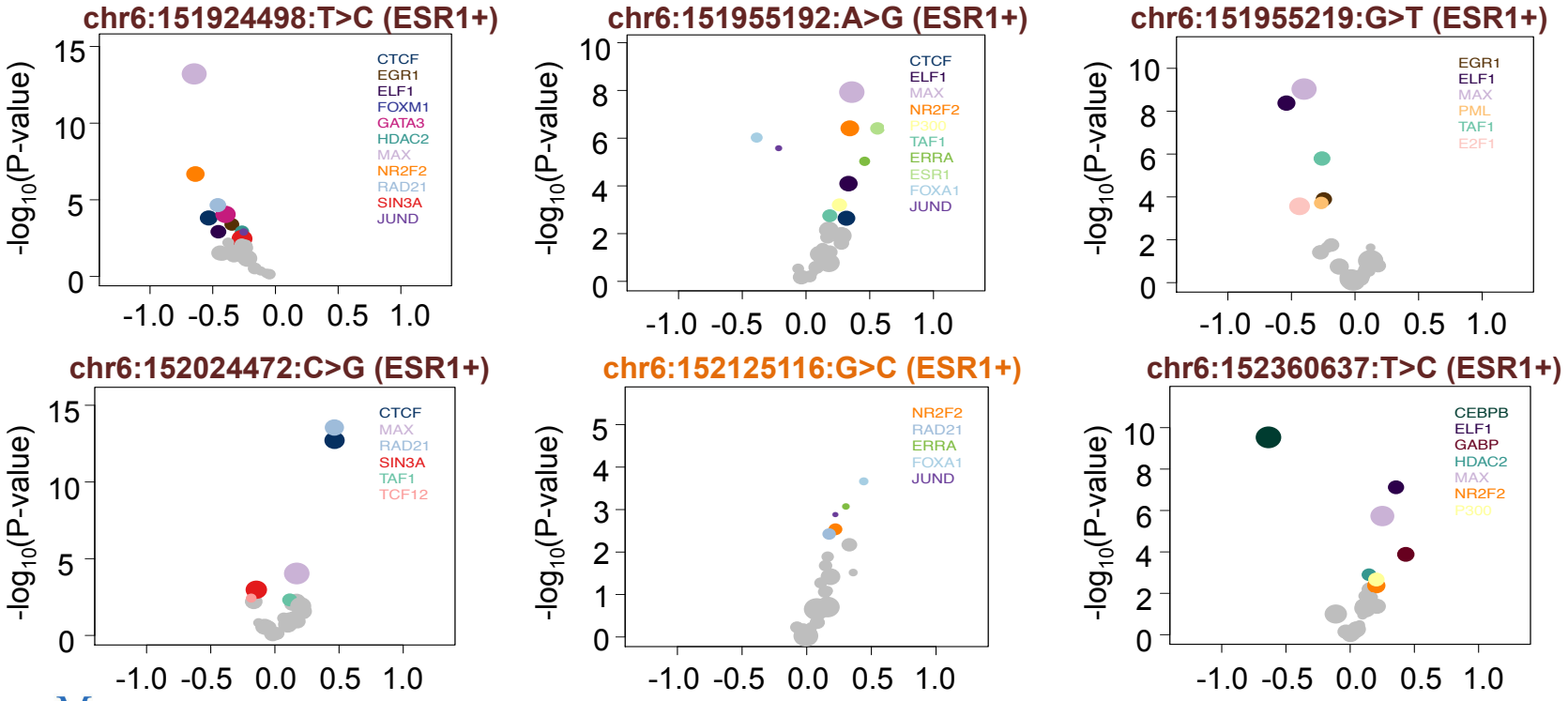
Discovery (ESR1+ n=73, ±500kb, r≥0.9, $p=7.02 \times 10^{-5}$,FDR=0.045)
Mutations from doi: 10.1038/nature12477

Mutations in the SRE of ESR1 are identified in an independent cohort of samples



Are noncoding mutations in the set of regulatory elements of the ESR1 gene functional?

Mutations are predicted by the IGR tool to alter binding of transcription factors to the chromatin



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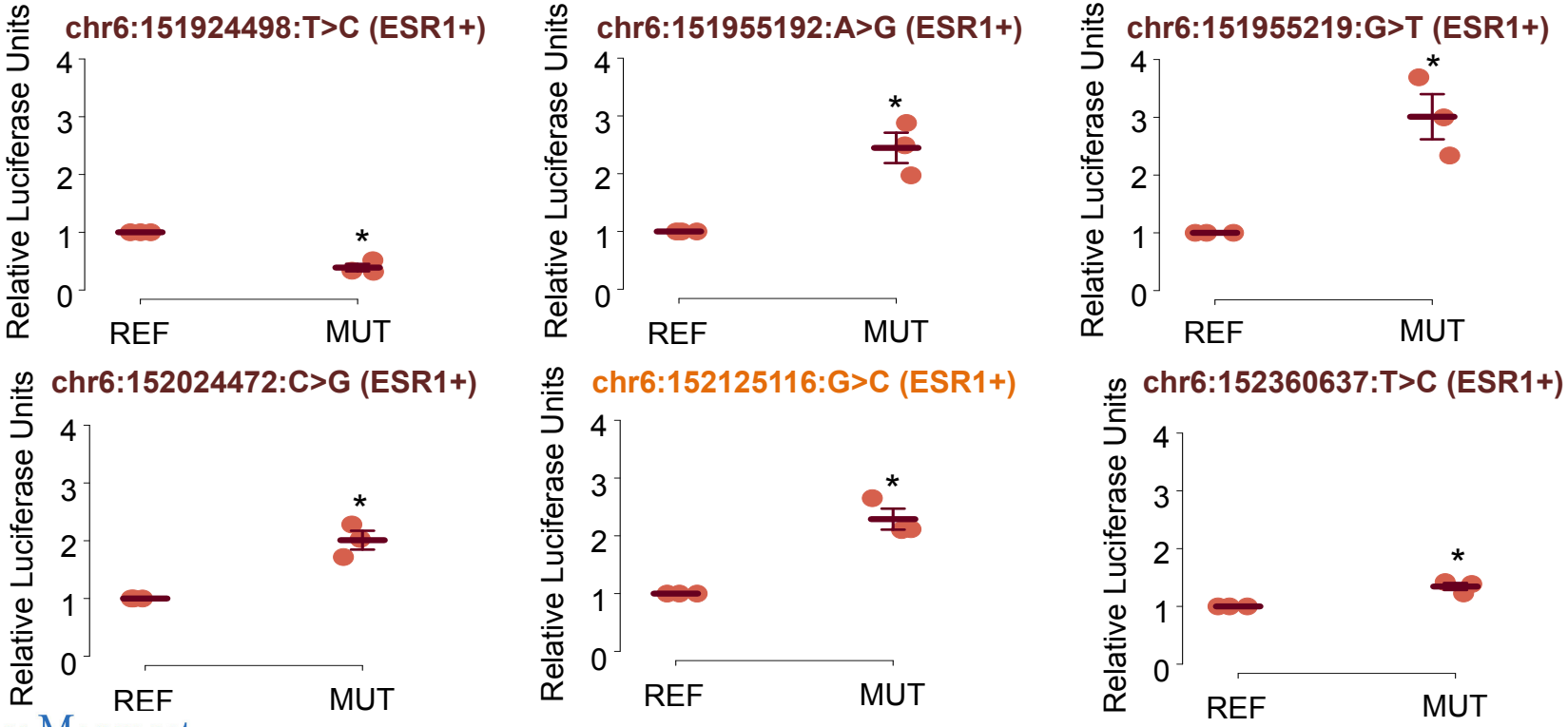
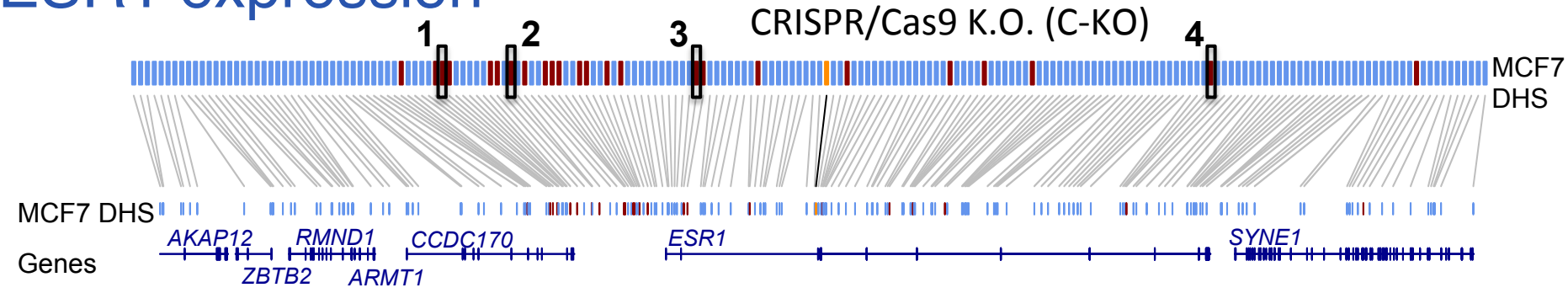
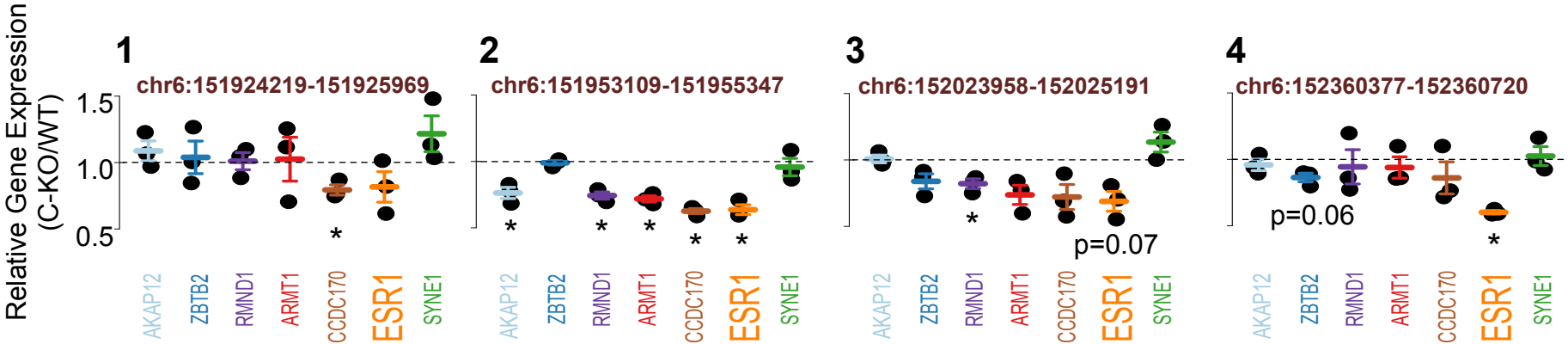
Most mutations increase the transactivation potential of regulatory elements based on luciferase reporter assays



CRISPR/Cas9 deletion of mutated enhancers reduces ESR1 expression





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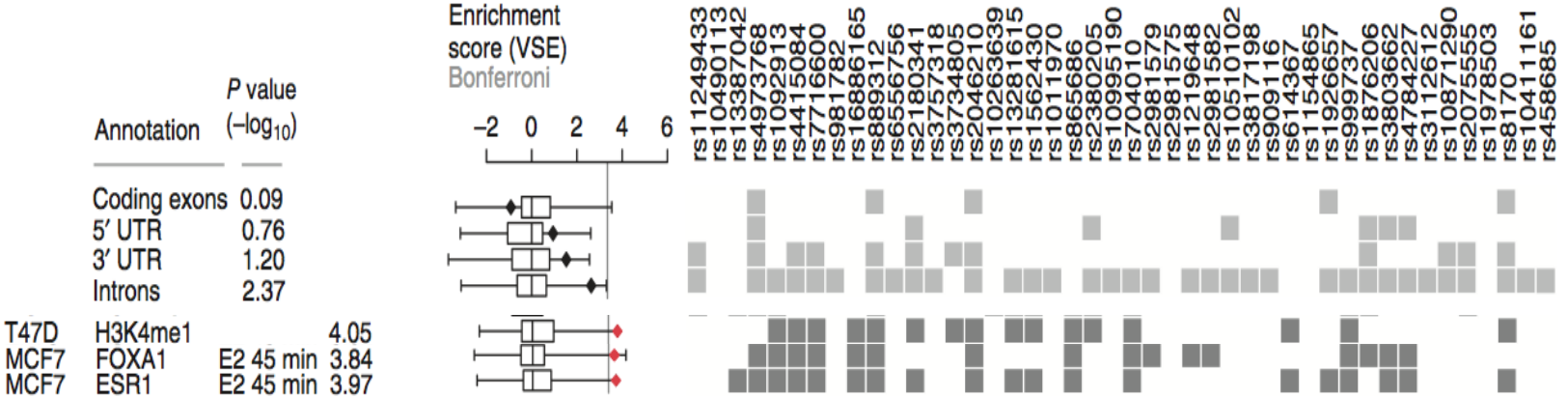
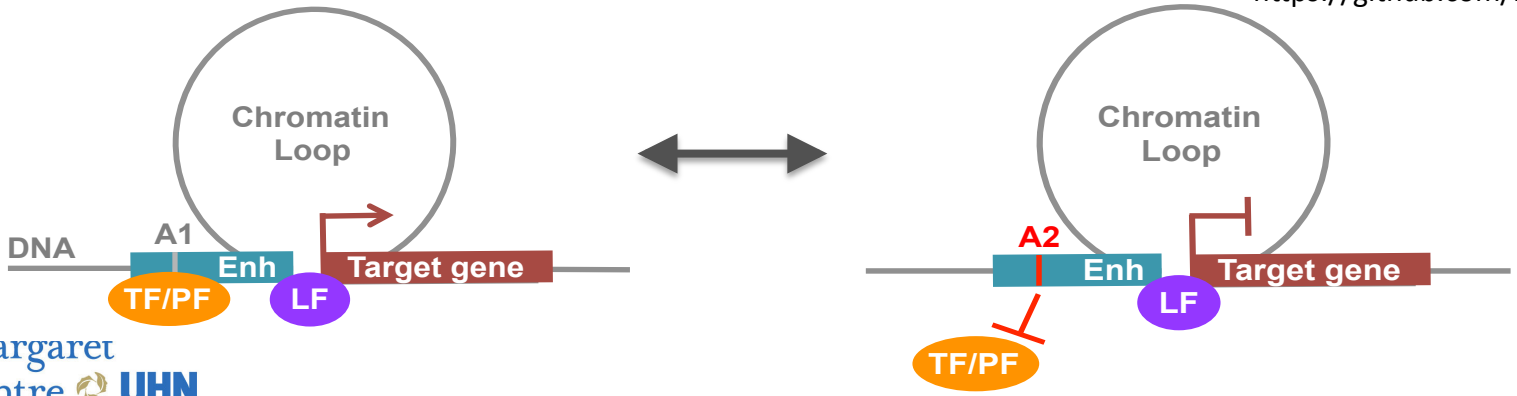
Are breast cancer inherited risk-variants converging on the same regulatory elements?

Noncoding inherited risk-variants for breast cancer preferentially map to enhancers



https://github.com/mlupien/VSE



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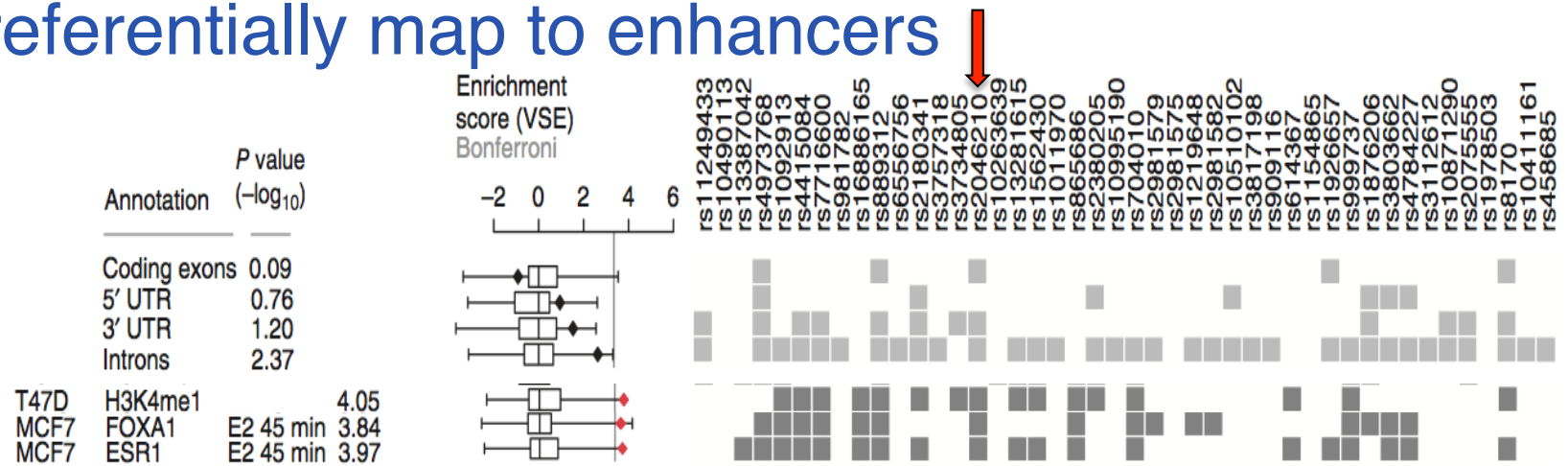
doi: 10.1038/ng.2416 and doi: 10.1016/j.tig.2014.02.006

Noncoding inherited risk-variants for breast cancer preferentially map to enhancers



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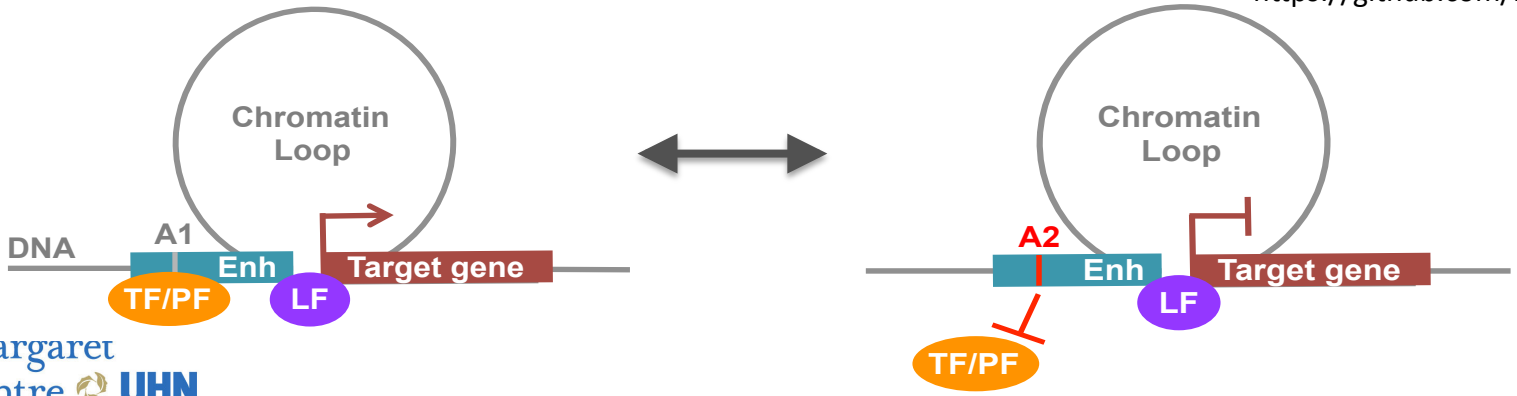

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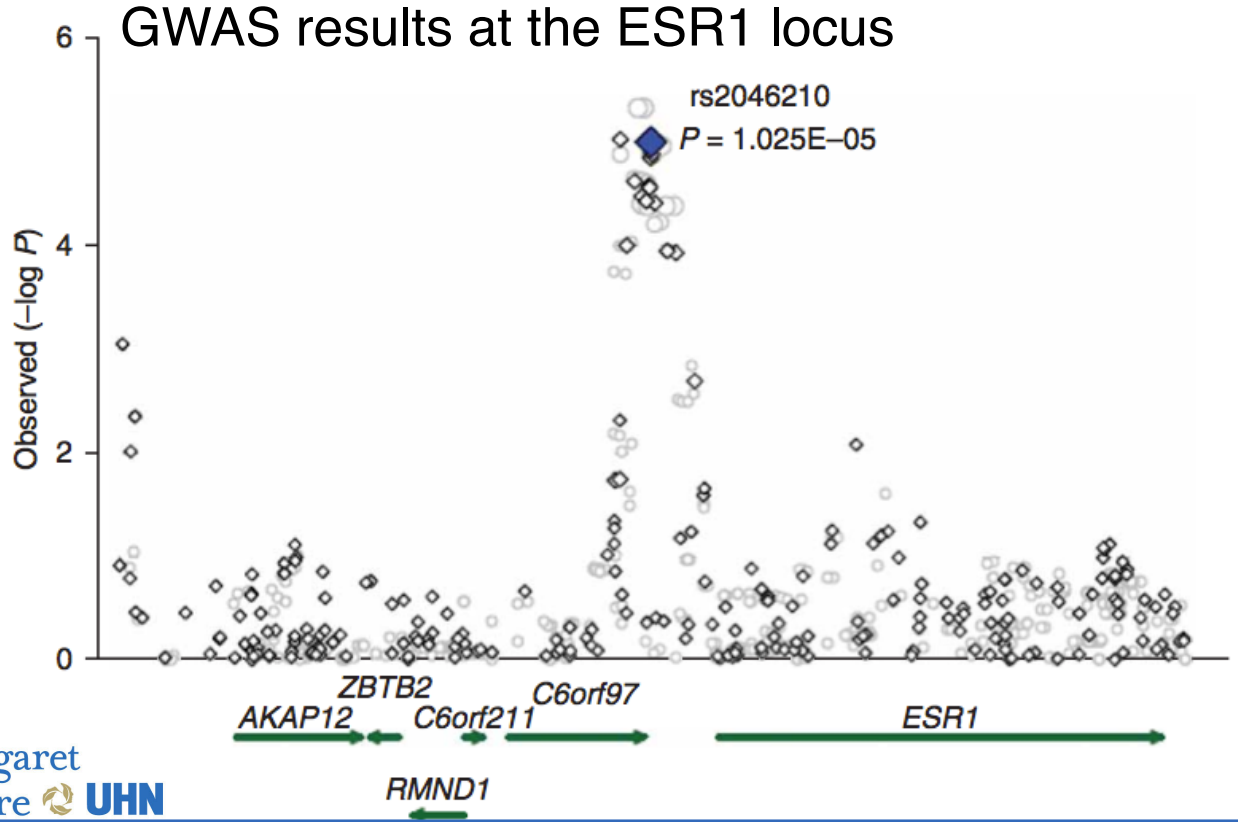
doi: 10.1038/ng.2416 and doi: 10.1016/j.tig.2014.02.006

The rs2046210 breast cancer risk-locus maps to enhancers and lies in the ESR1 gene locus



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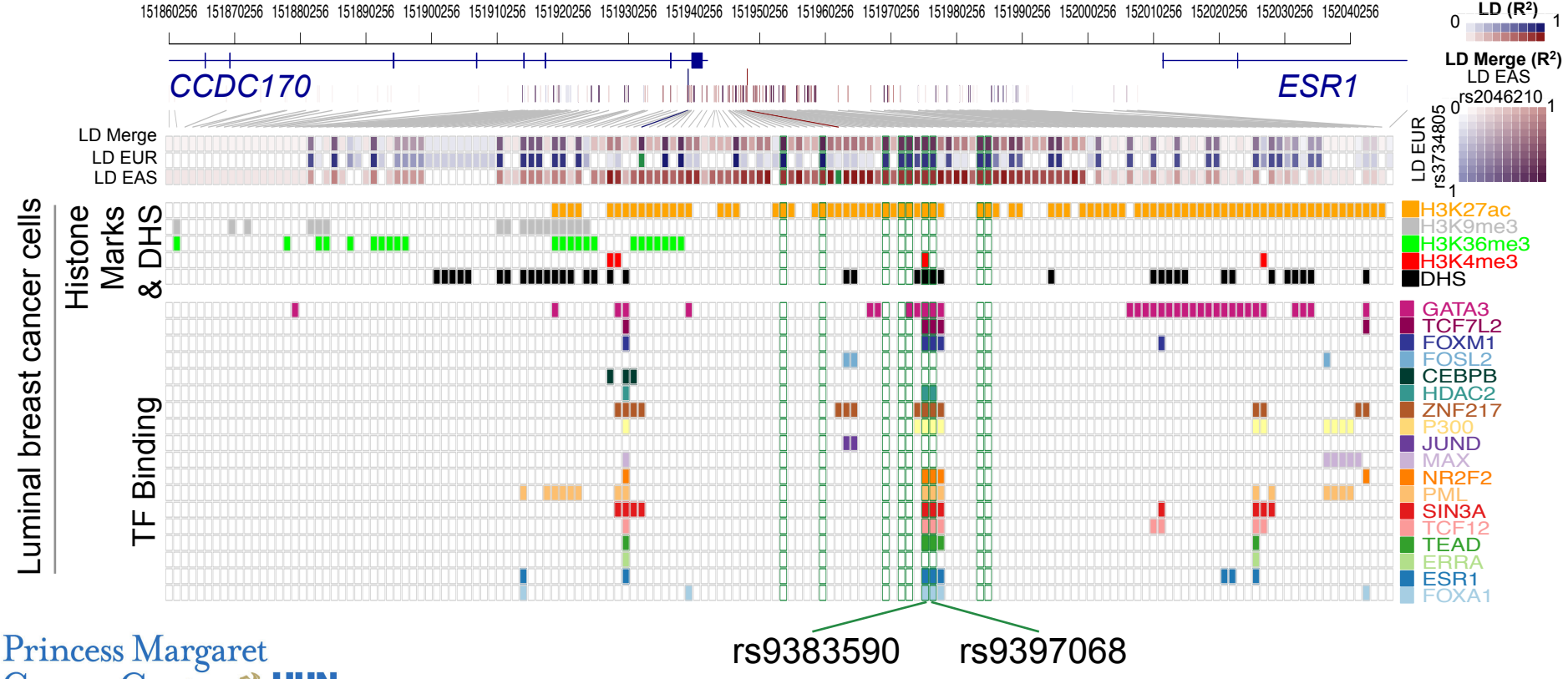
Zheng, W., et al (2009) Nat Genet. 41. 324-328

The rs9383590 and rs9397068 are putative causal SNPs of the rs2046210 risk-locus



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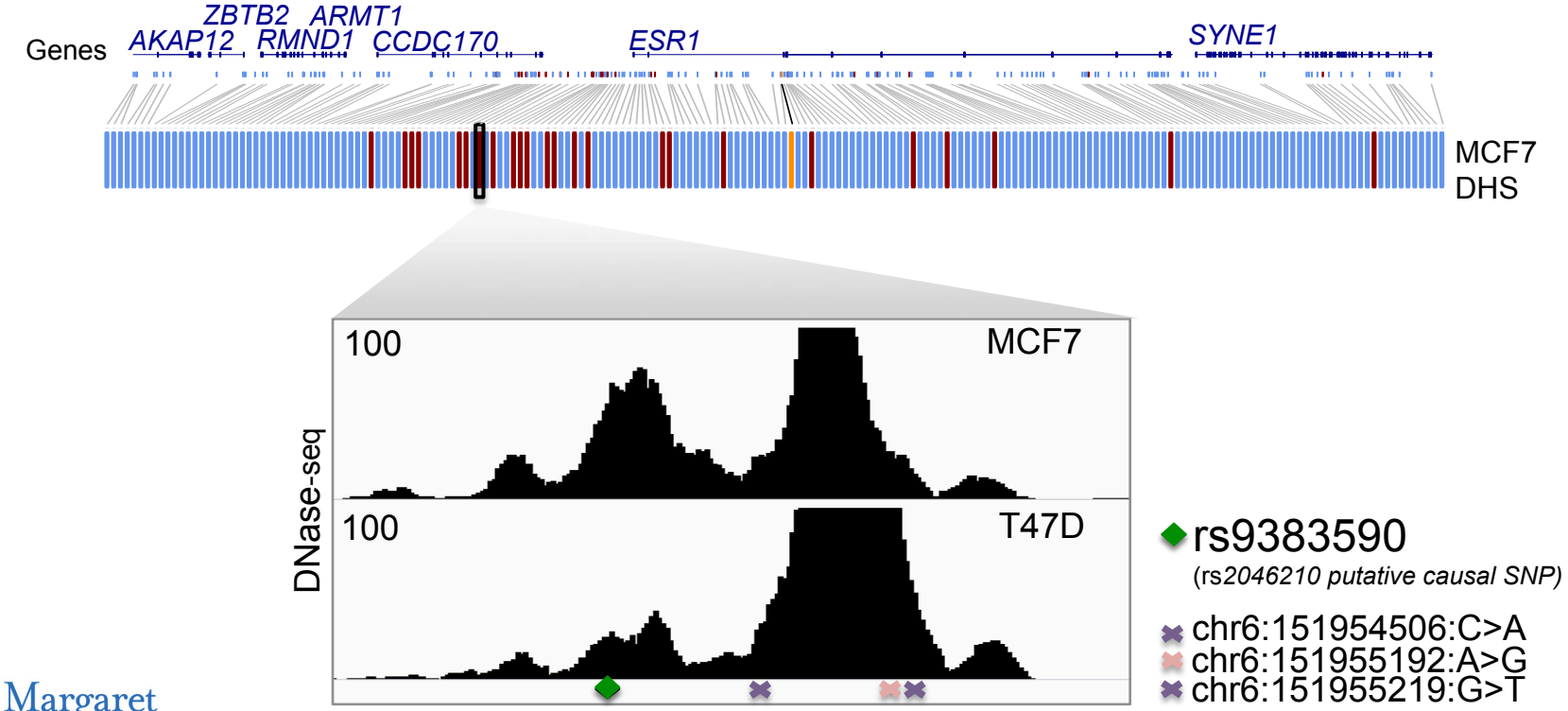
Somatic mutations and genetic variants converge on one ESR1 regulatory element



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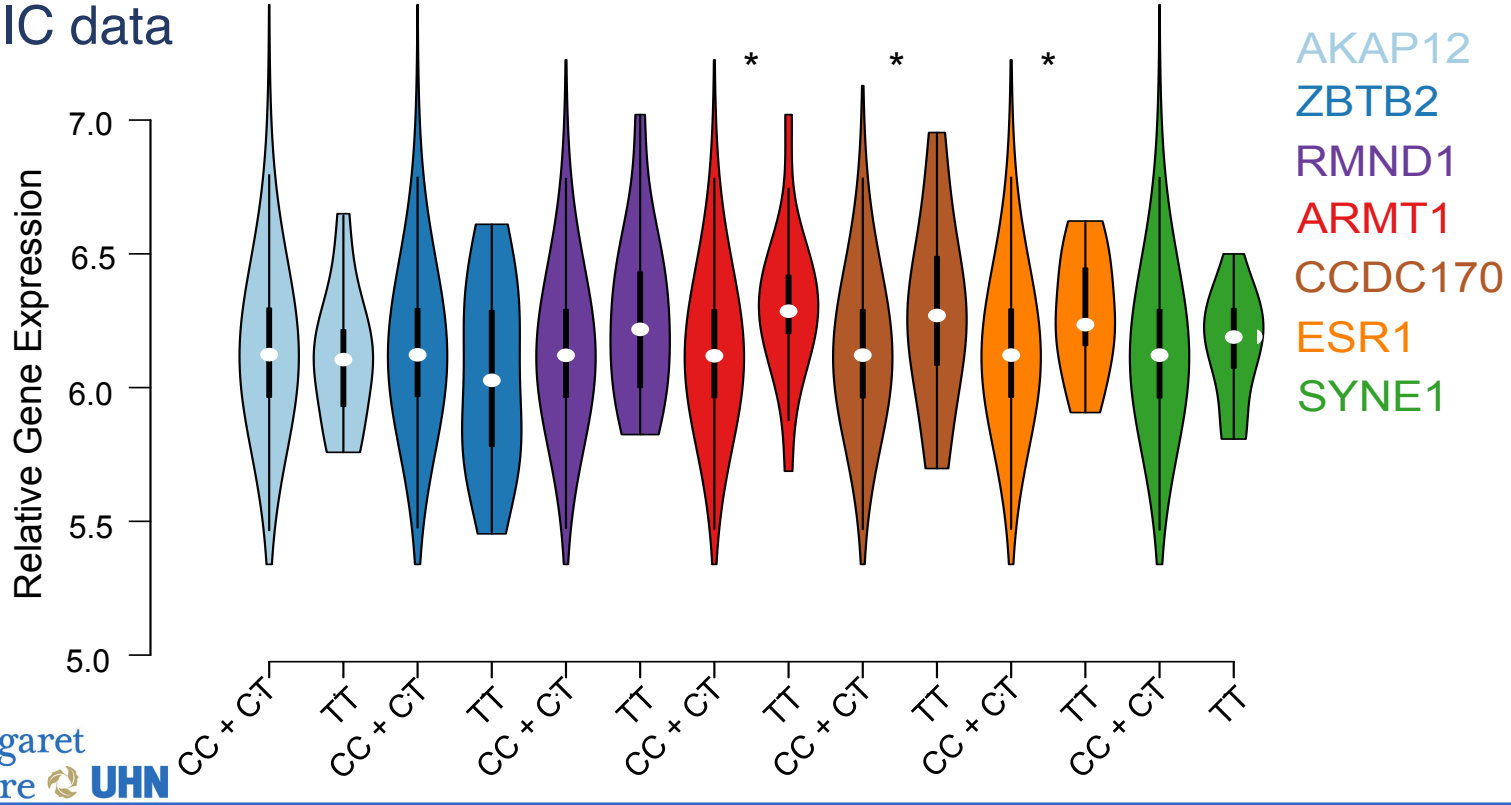
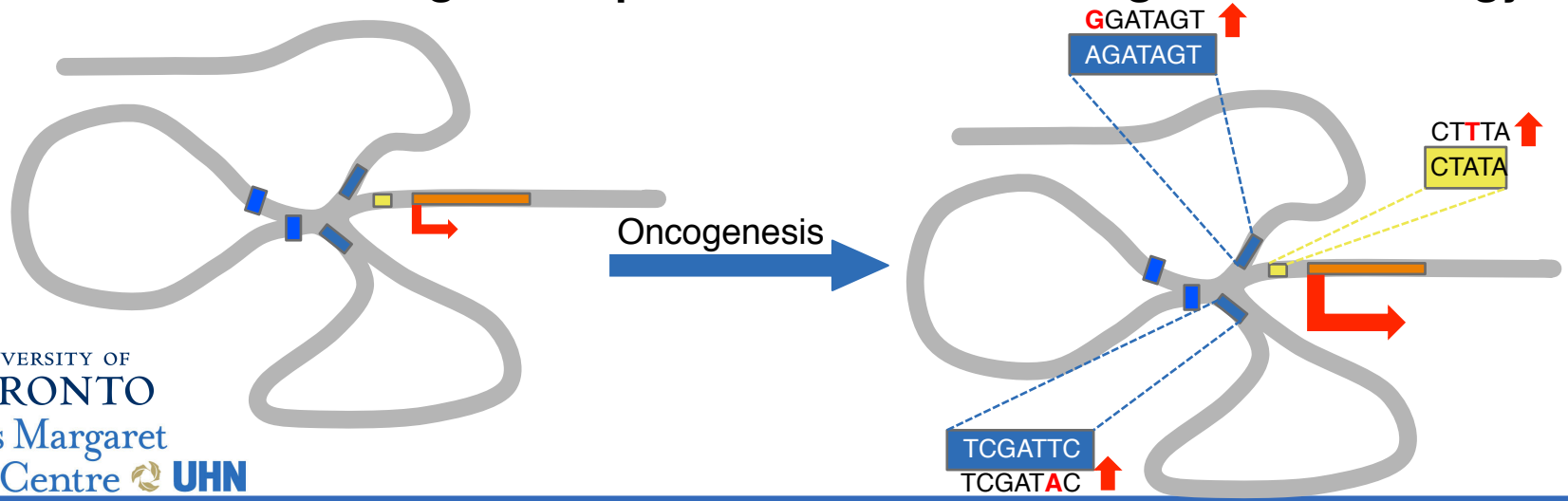
The rs9383590 SNP is an expression Quantitative Trait Loci (eQTL) for the ESR1 gene

METABRIC data



Summary

1. Gain-of-function noncoding mutations enrich within the Set of Regulatory Elements (SRE) of the ESR1 gene in breast cancer.
2. Somatic mutations and genetic variants converge on the SRE of the ESR1 gene.
3. Our method can serve to prioritize noncoding mutations to include in panels for disease monitoring and improve our understanding of tumor biology.



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Thank you!

www.pmgenomics.ca/lupienlab

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Trevor J. Pugh
Jennifer Sylvester
Kelsie Thu
S.Y. Cindy Wang

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Richard C. Sallari (MIT)
Nicholas A. Sinnott-Armstrong (Stanford U.)

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Ontario Institute for Cancer Research

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