Identify Disease-Causal Genes from GWAS Loci by 3D Genome Structure, Regulatory Landscapes & Deep Learning

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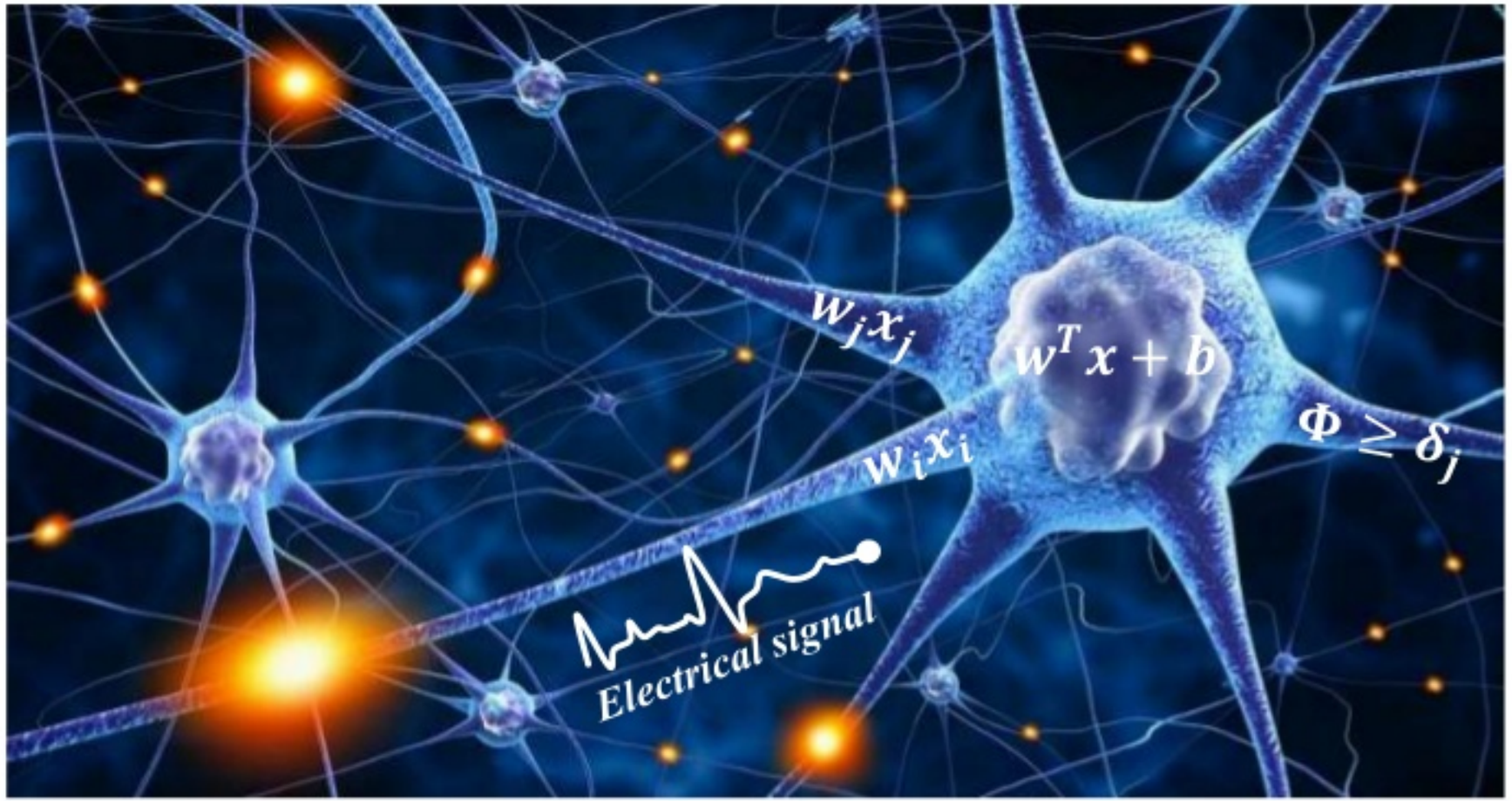
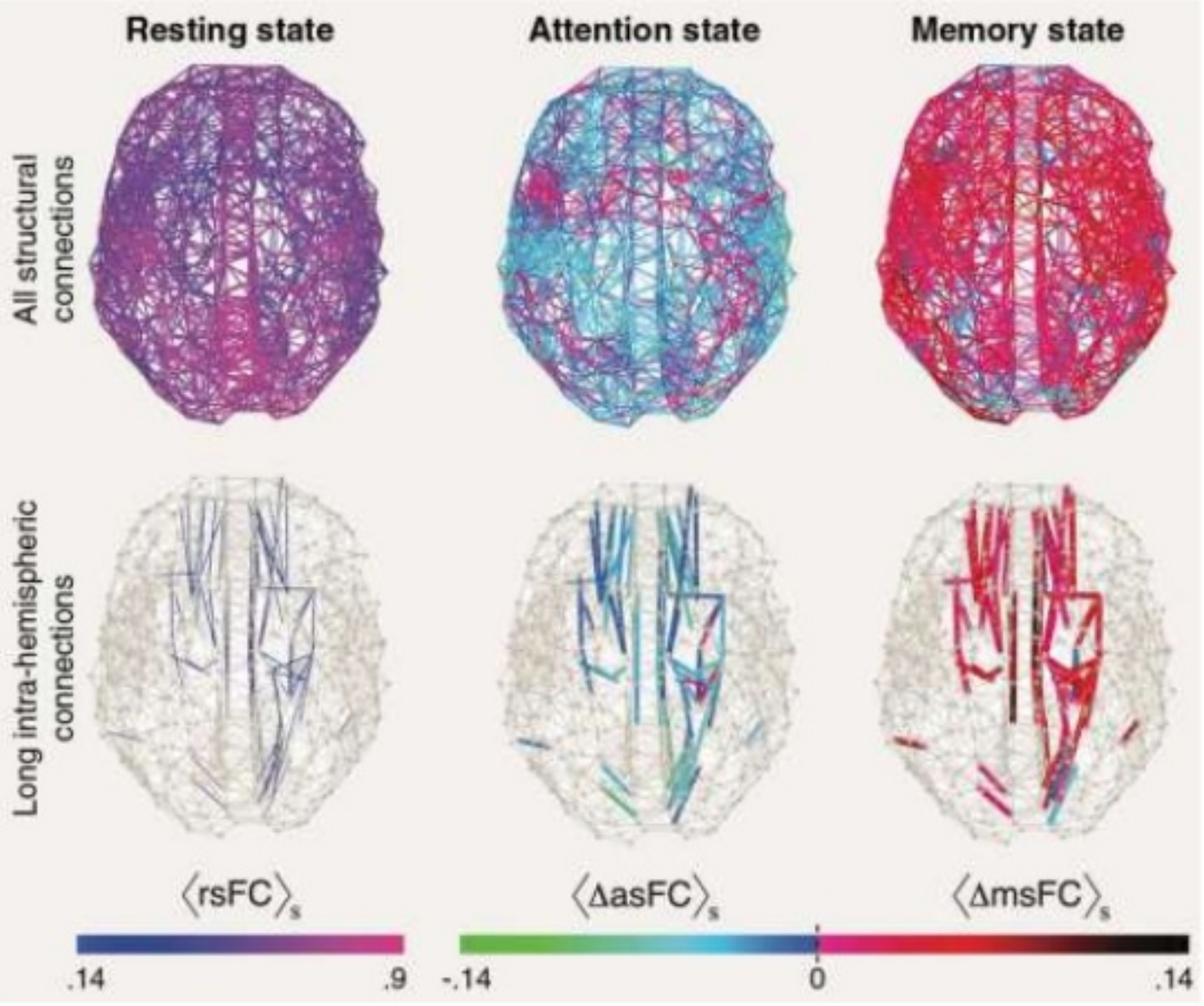
Deep Learning: The Inspiration

" the deepest concepts in mathematics are those which link one world of ideas with another"
---- Freeman Dyson



Deep Learning: The Natural Form



Science 2013 Nov

Deep-Learning: The Renaissance

The New York Times

Scientists See Promise in Deep-Learning Programs

by **JOHN MARKOFF** Nov. 23, 2012

In the 1960s, ….. believed that a workable artificial intelligence system was just 10 years away. In the 1980s, a wave of commercial start-ups collapsed, leading to what some people called the "**A.I. winter.**"

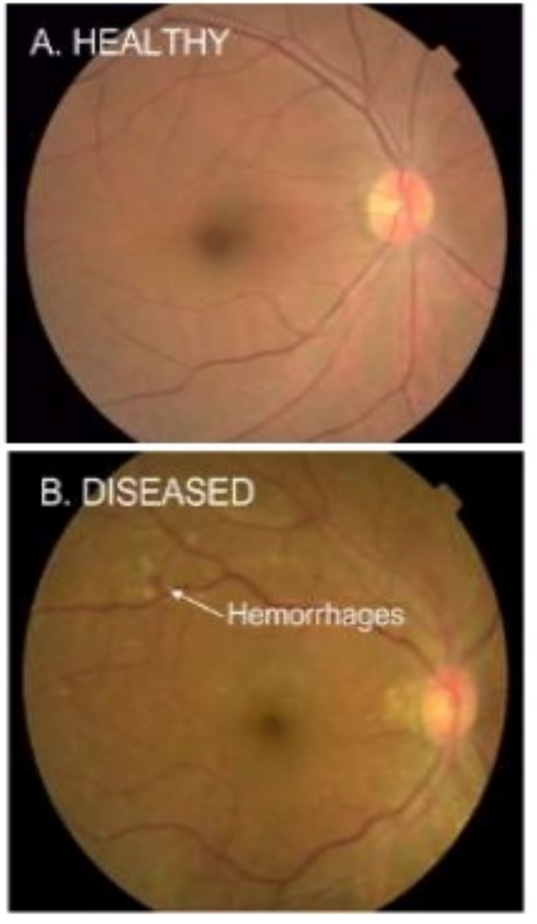
But recent achievements have impressed ….. In October, for example, a team of graduate students studying with the University of Toronto computer scientist Geoffrey E. Hinton won the top prize in a contest sponsored by Merck to design software to **help find molecules that might lead to new drugs**.

Deep Learning: Impact on Medicine

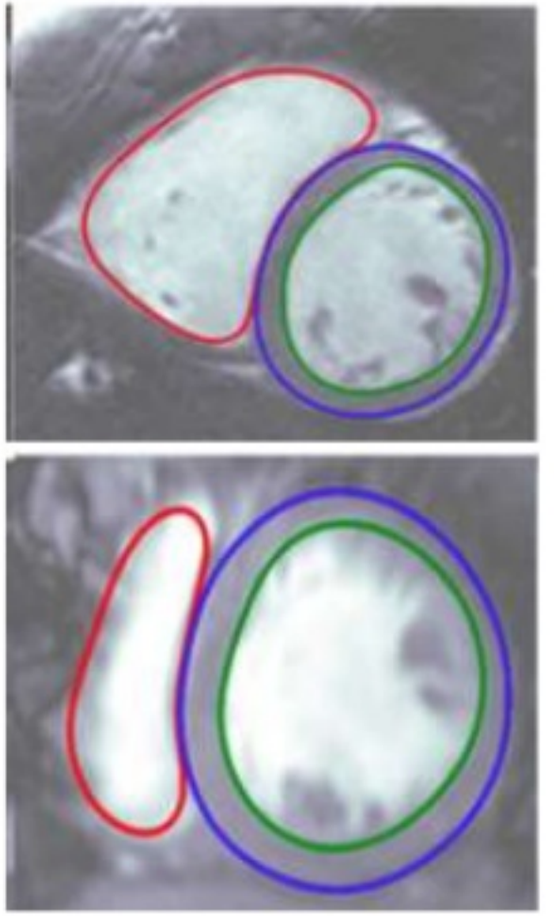
On par performance as 21 board-certified pathologists

Nature 2017 Feb

>90% specificity and sensitivity as board-certified ophthalmologists



Artery's Cardio DL wins FDA approval for clinical diagnosis (10-sec vs. 1hr)



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Deep Learning: The New Disruption

Can we leverage DL to identify genetic variants that are disease causal, so that we can treat diseases at its root level per individual patient ?

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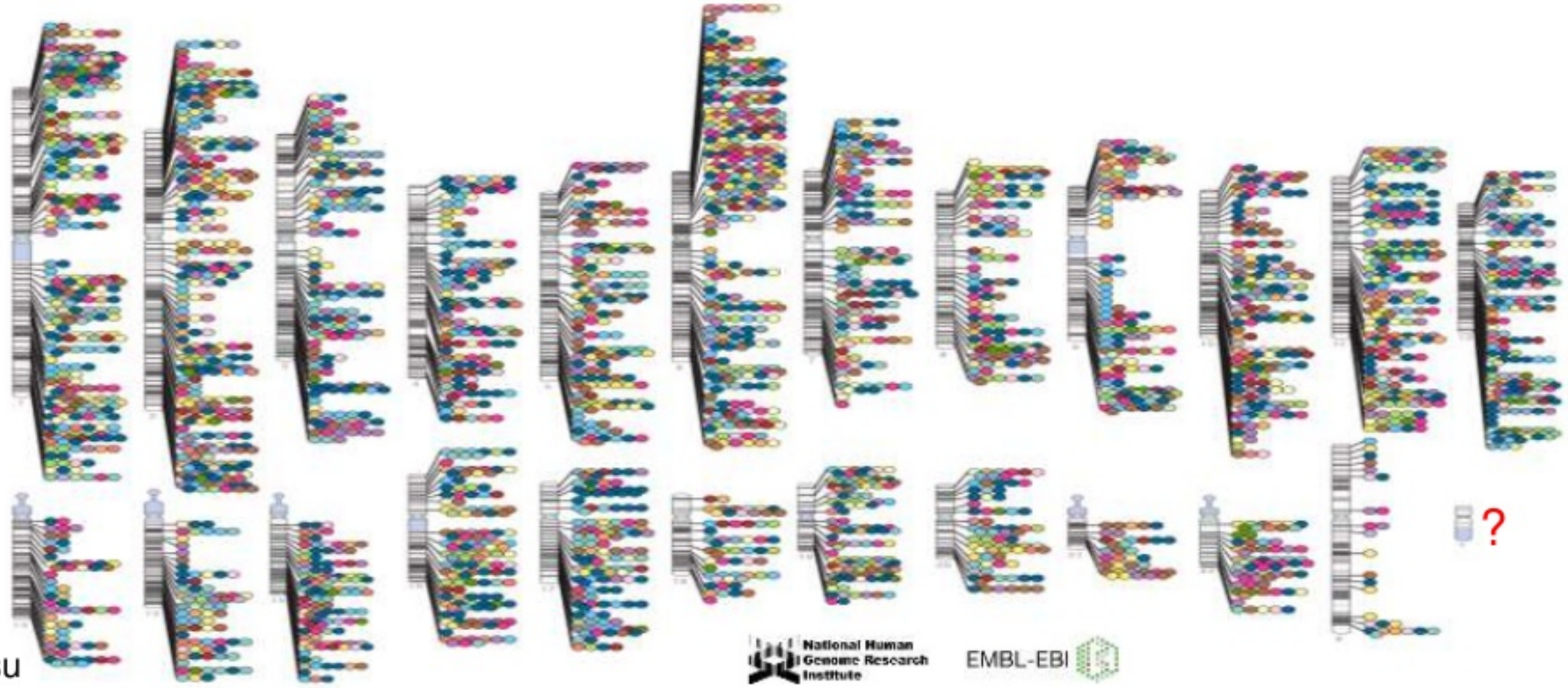
Genome-Wide Association Studies (GWAS) Catalog

- Identified ~13,000 genetic variants (single nucleotide mutations/ polymorphisms) to be associated with ~2,000 diseases/phenotypes



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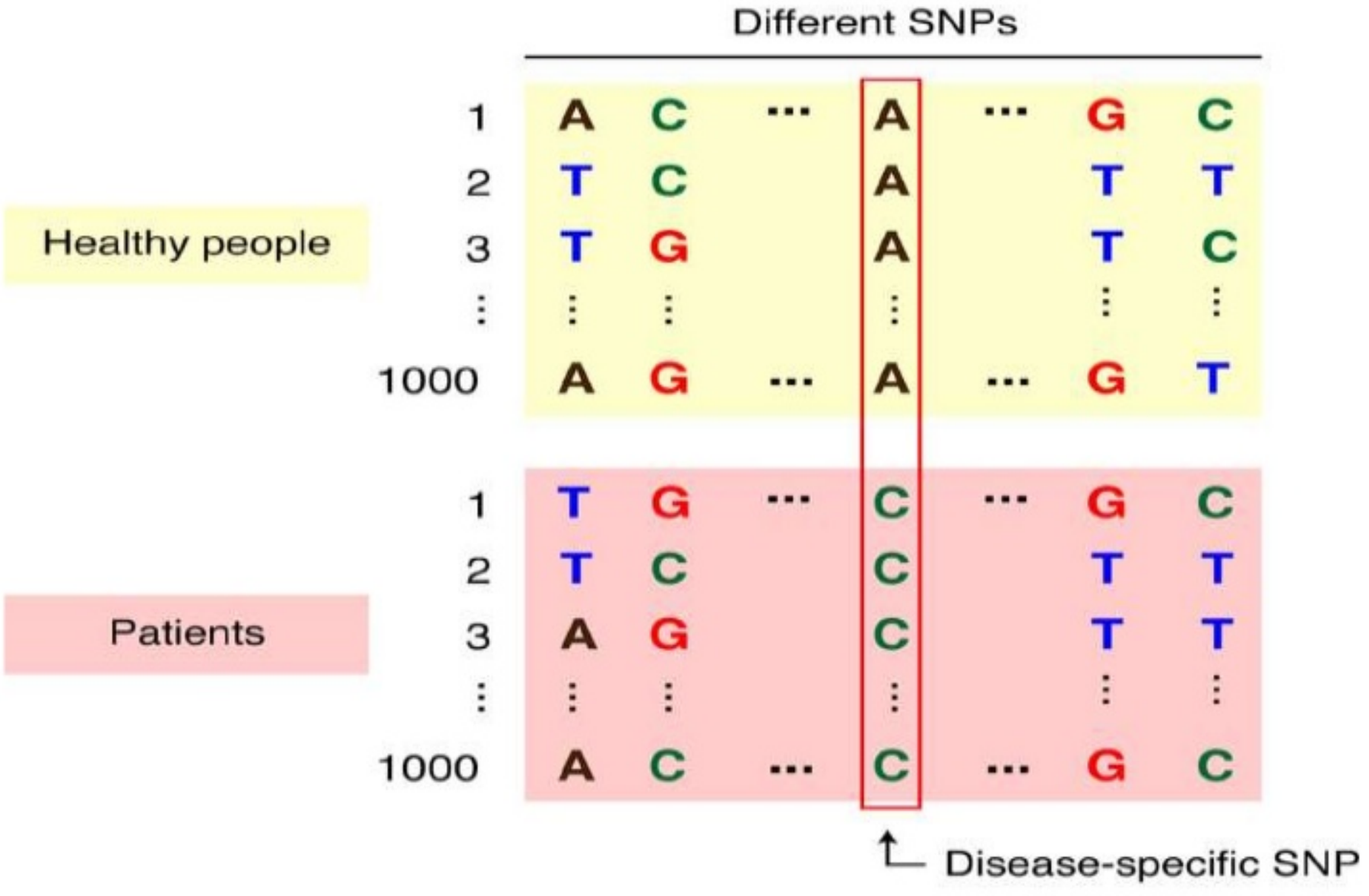
National Human Genome Research Institute

EMBL-EBI

Genome-Wide Association Scans



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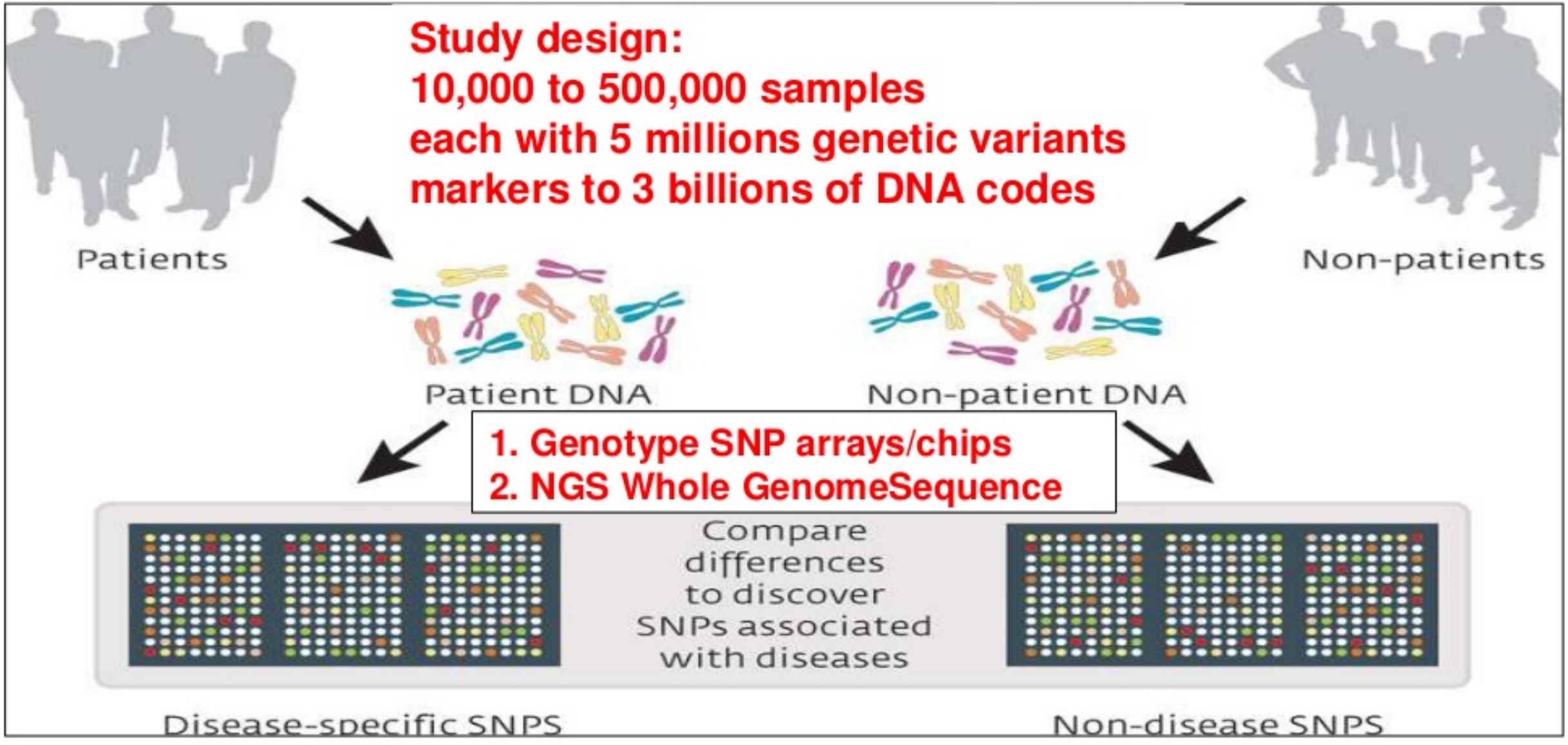
GWAS (Whole Genome Association) Scans



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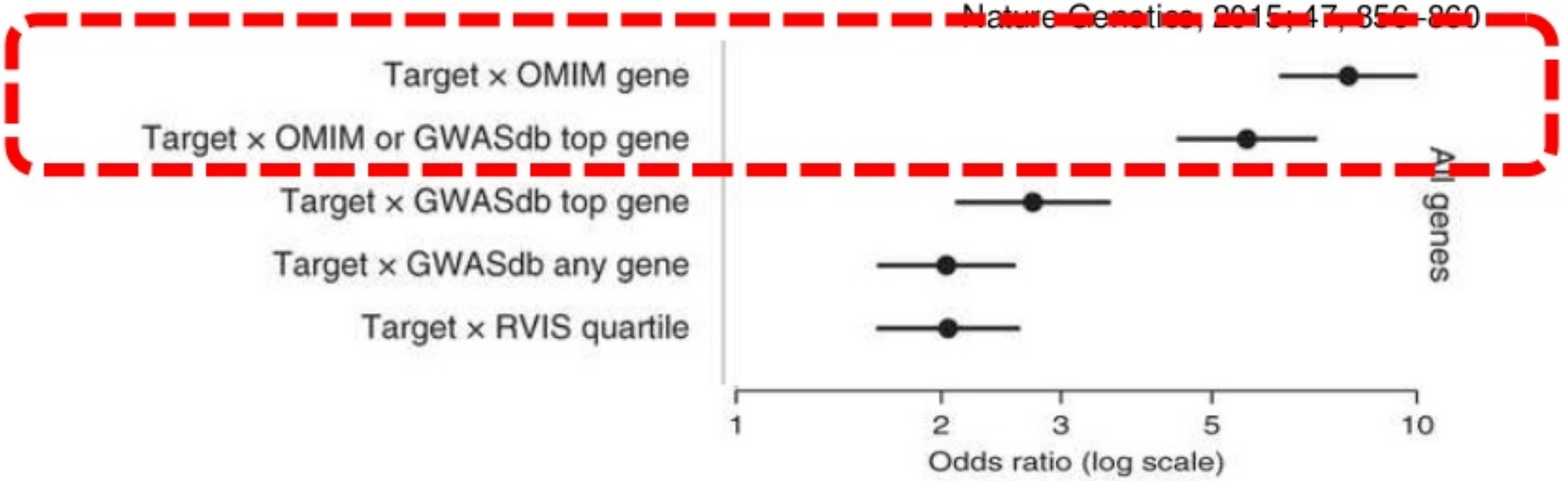
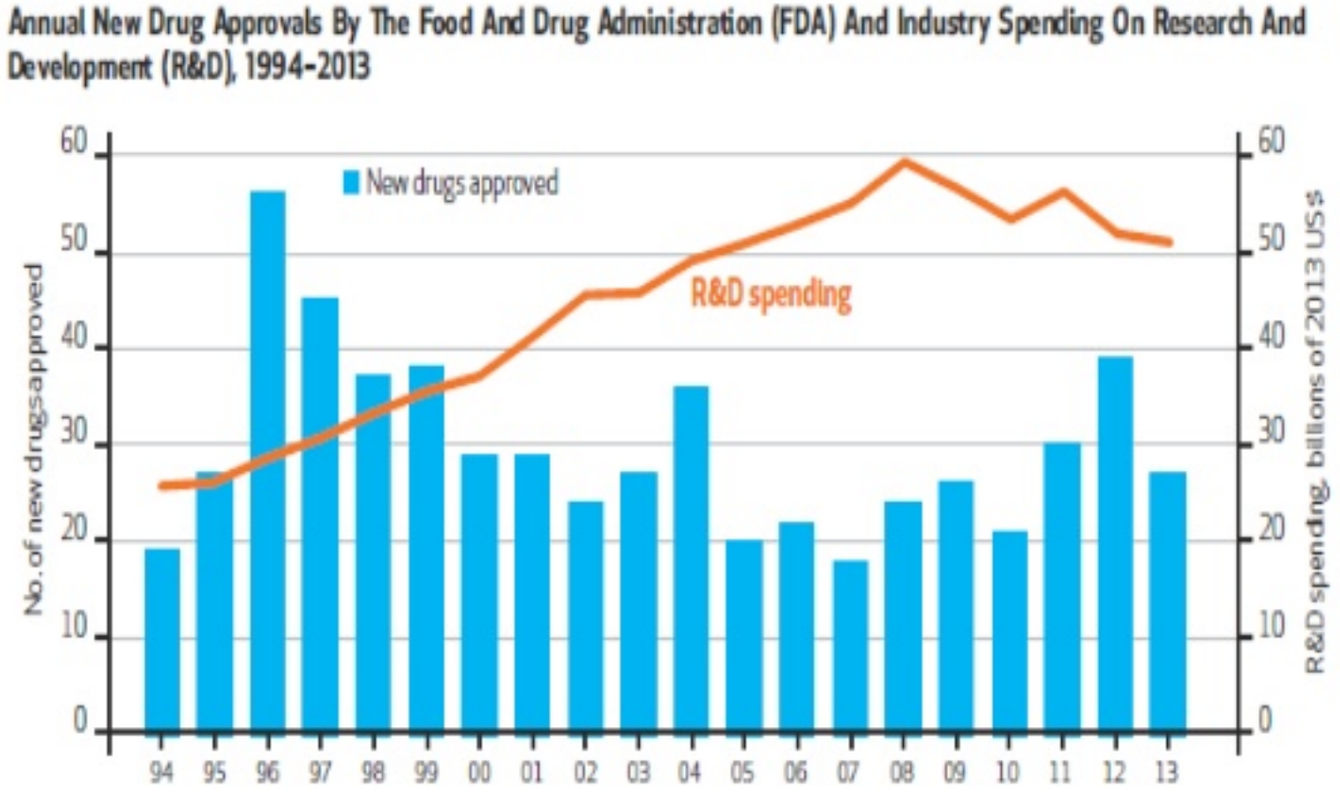
% Successfully Approved Drugs & Human Genetics

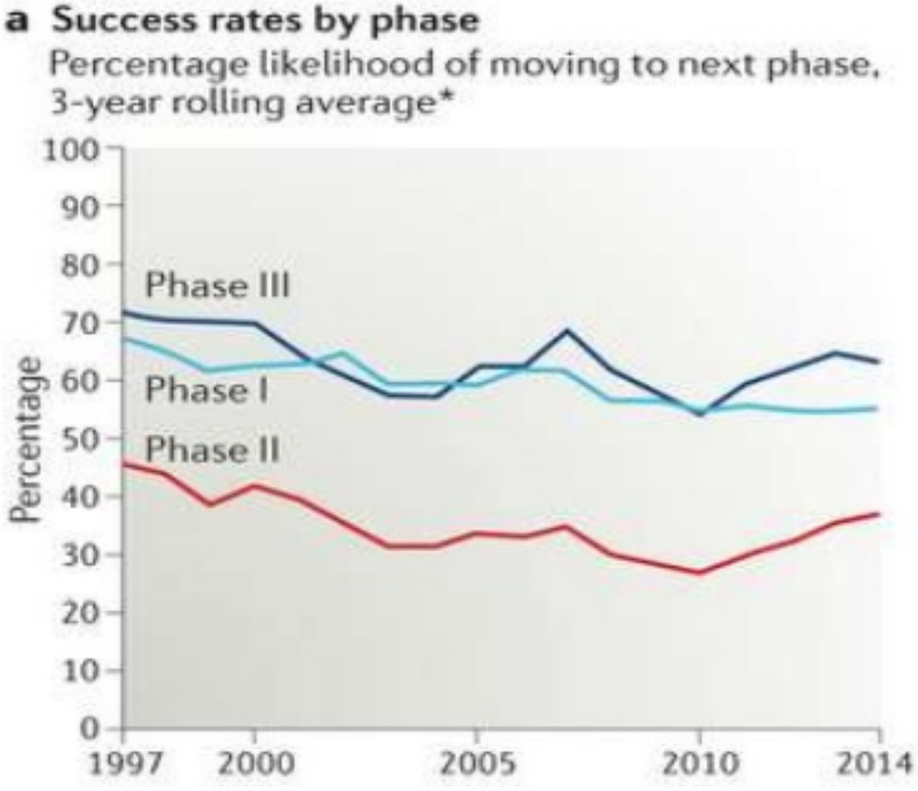
- The impact on medical care from GWAS could potentially be substantial



- FDA approved drugs with human genetic information are 5~10X more likely to be successful
- Failure targets at each drug development stage (pre-clinical, phase I, II, III) are more likely to be those targets without genetic validation

R&D Spending on New Drugs ≠ Drug Approvals





- New a better drug development pipeline
- Utilizing human genetic information/validation is the key

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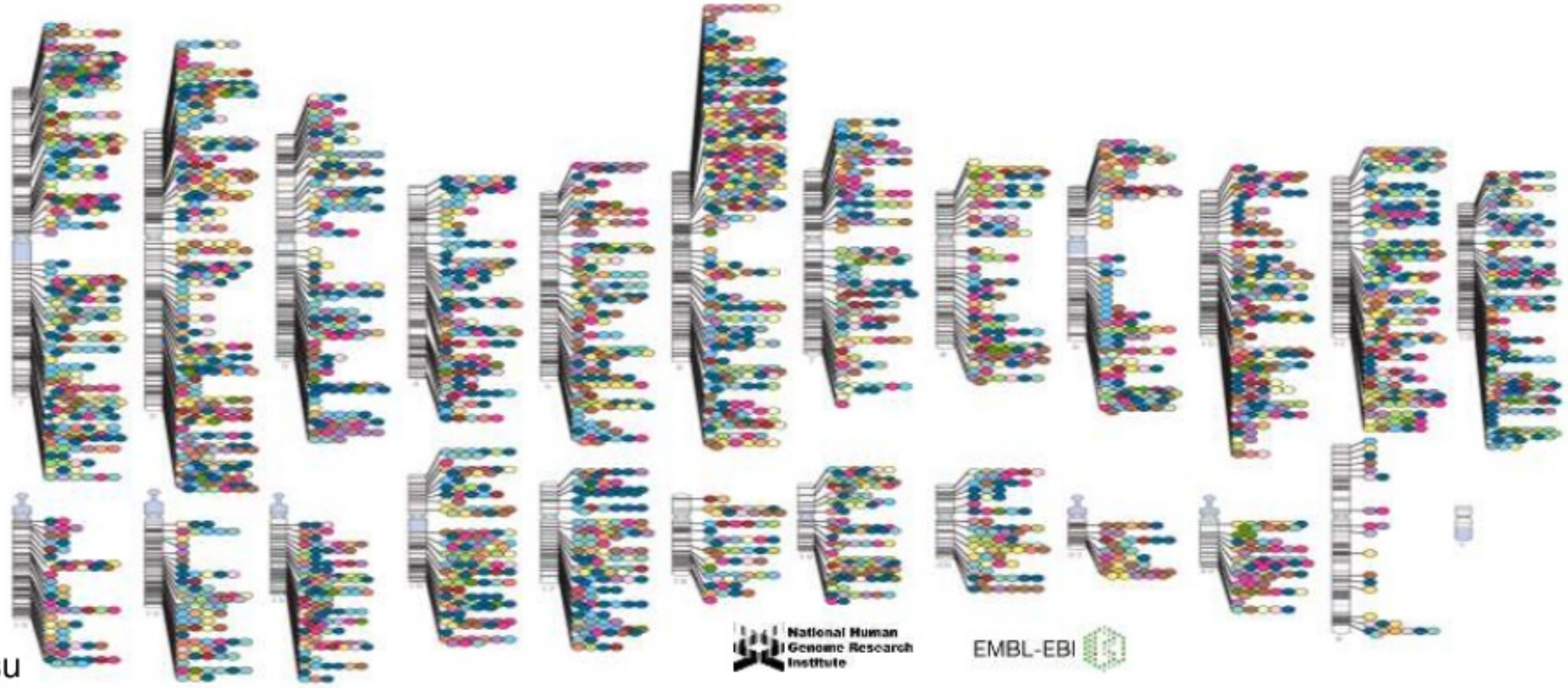

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Genome-Wide Association Studies (GWAS) Catalog

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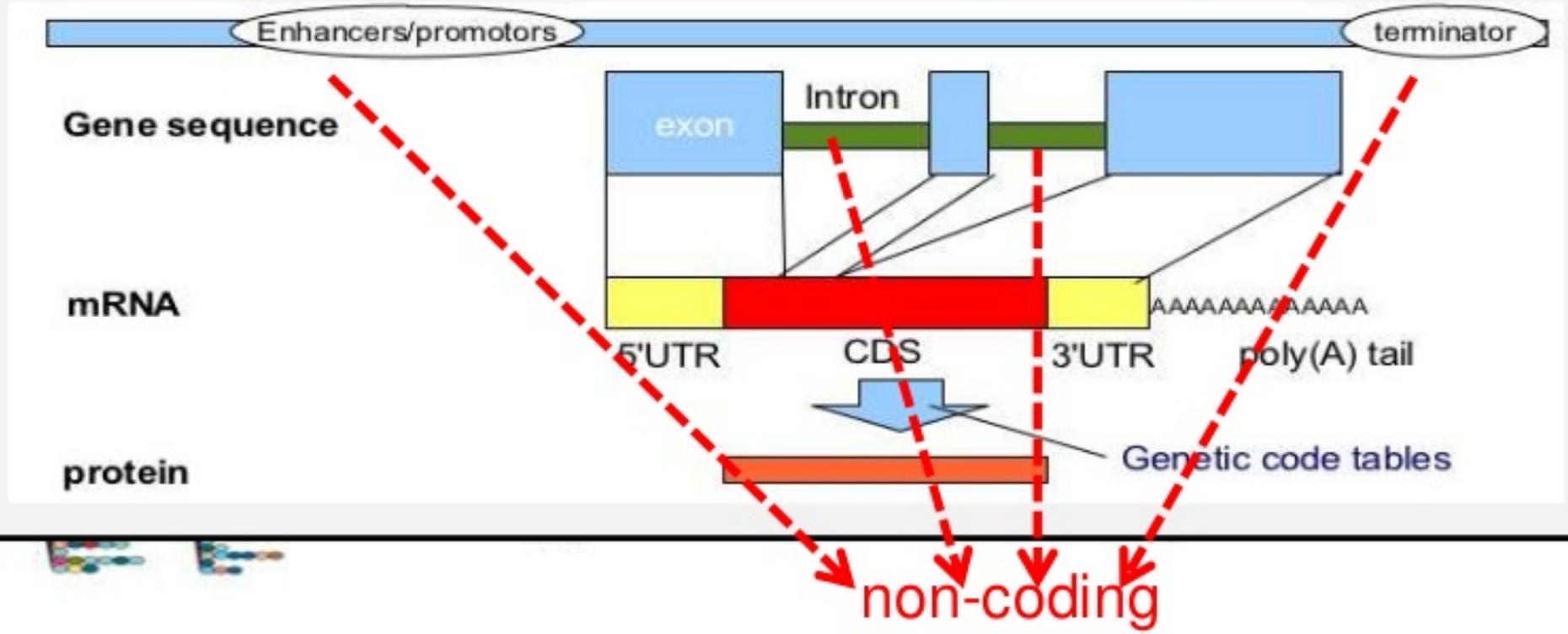
- **91% of** disease-associated **genetic variants are located in non-protein-coding regions; used to call "junk DNA"**
- **Unknown function, difficult to translate findings into clinical use**



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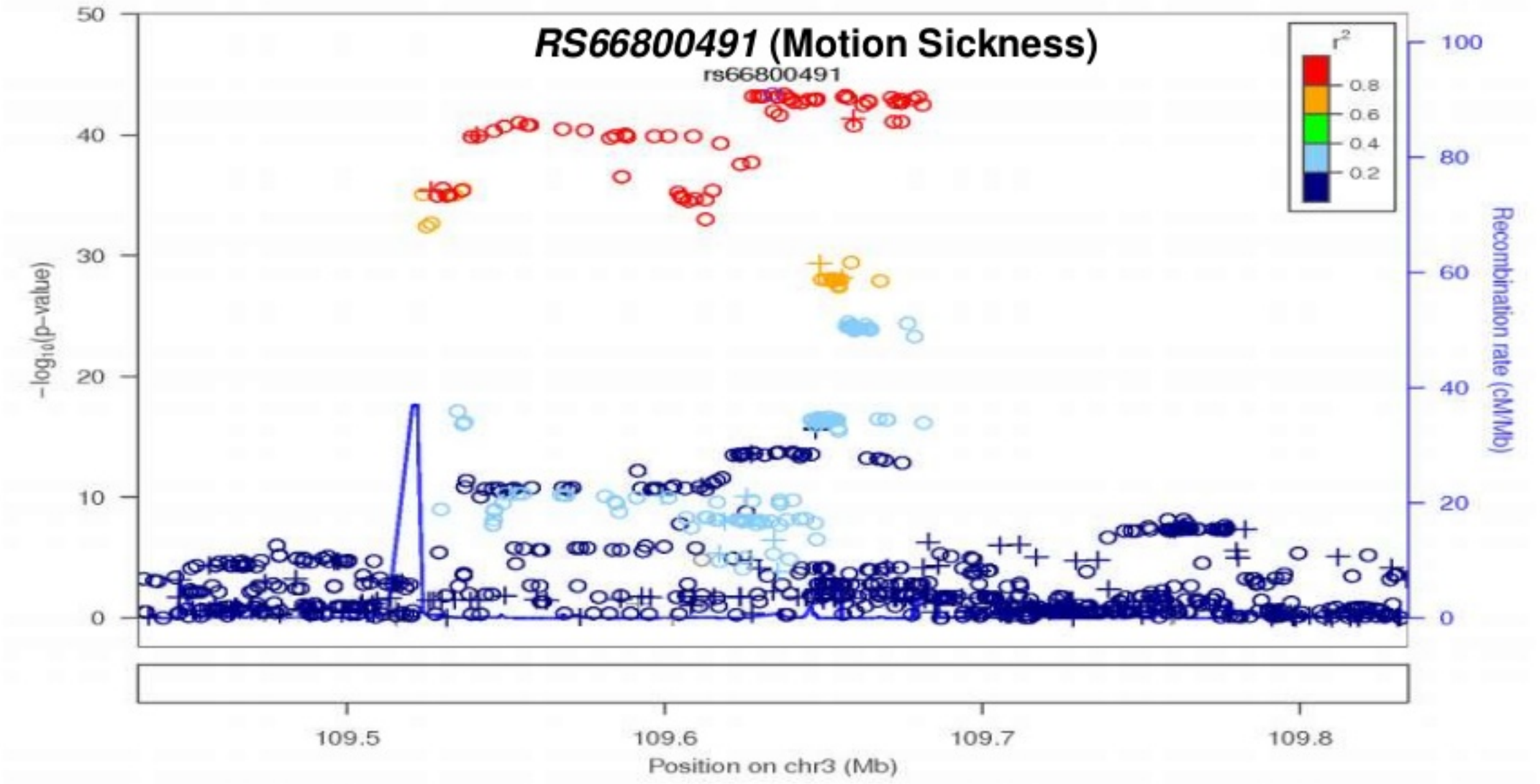
Associated Variants Located in Gene Desert



Genetic Coordination: 1D Physical Location on Linear DNA Sequences

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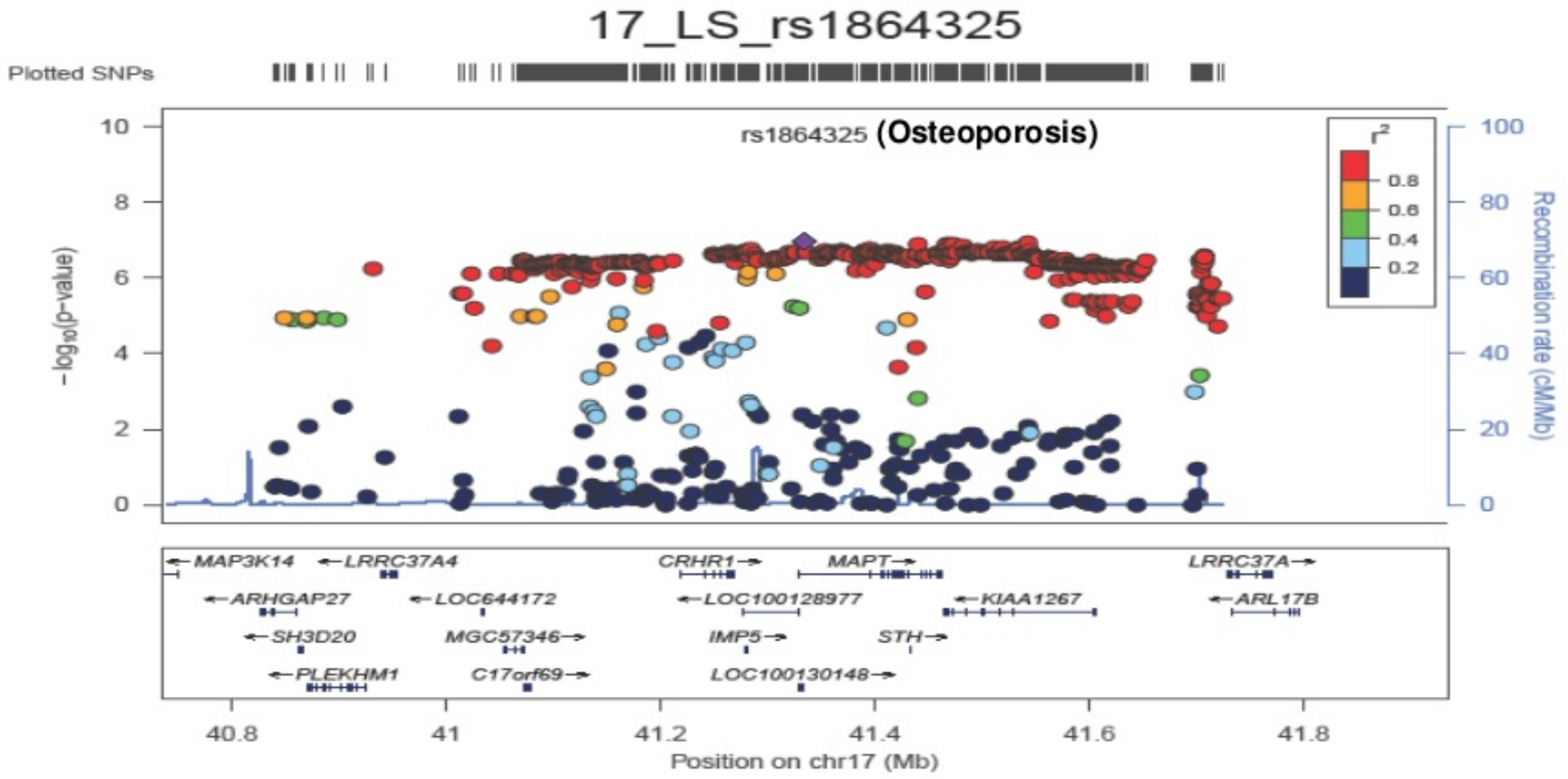
Too Many Genes: Which Gene(s)?



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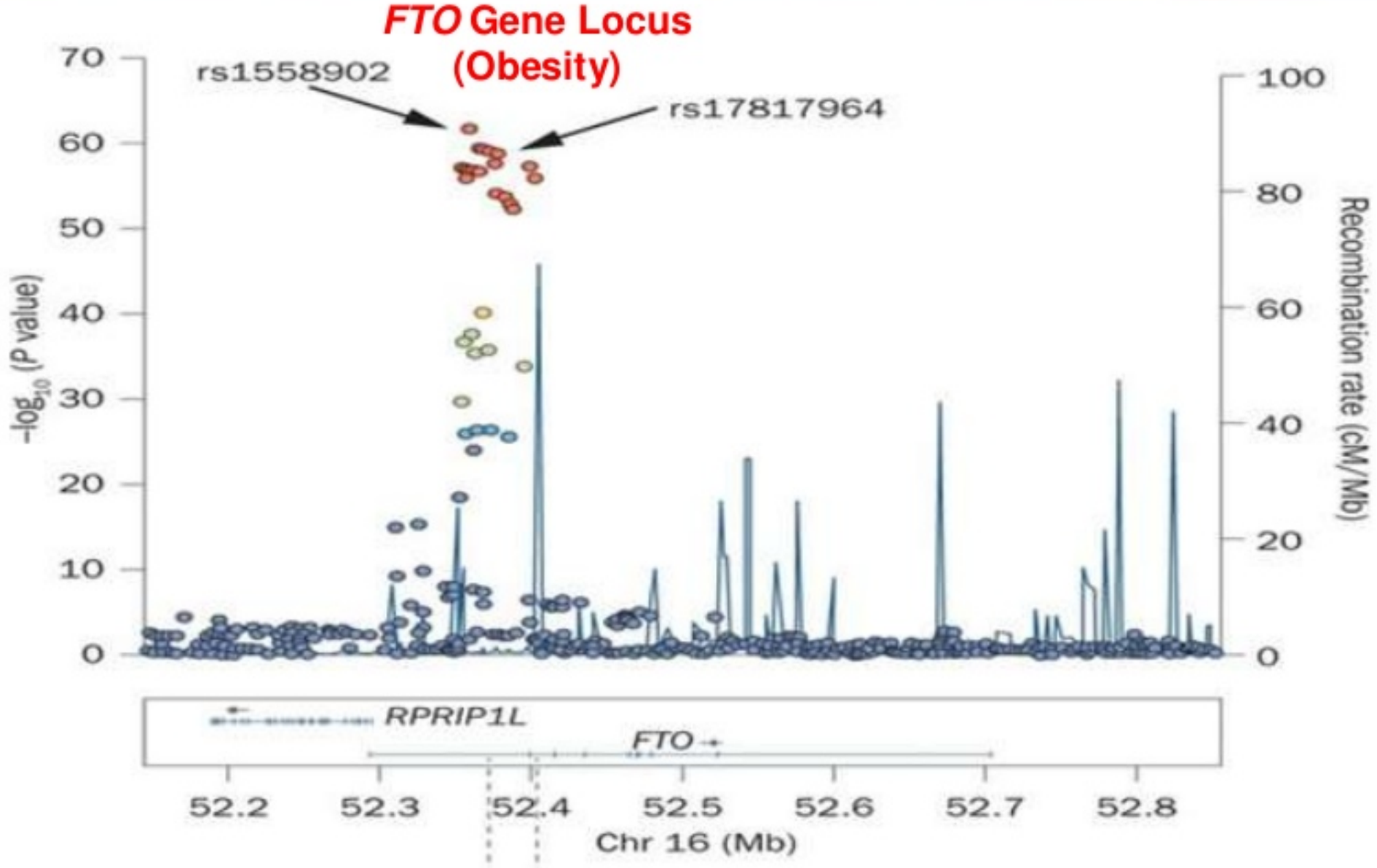
Associated Variants Located in Introns: Looks Promising?



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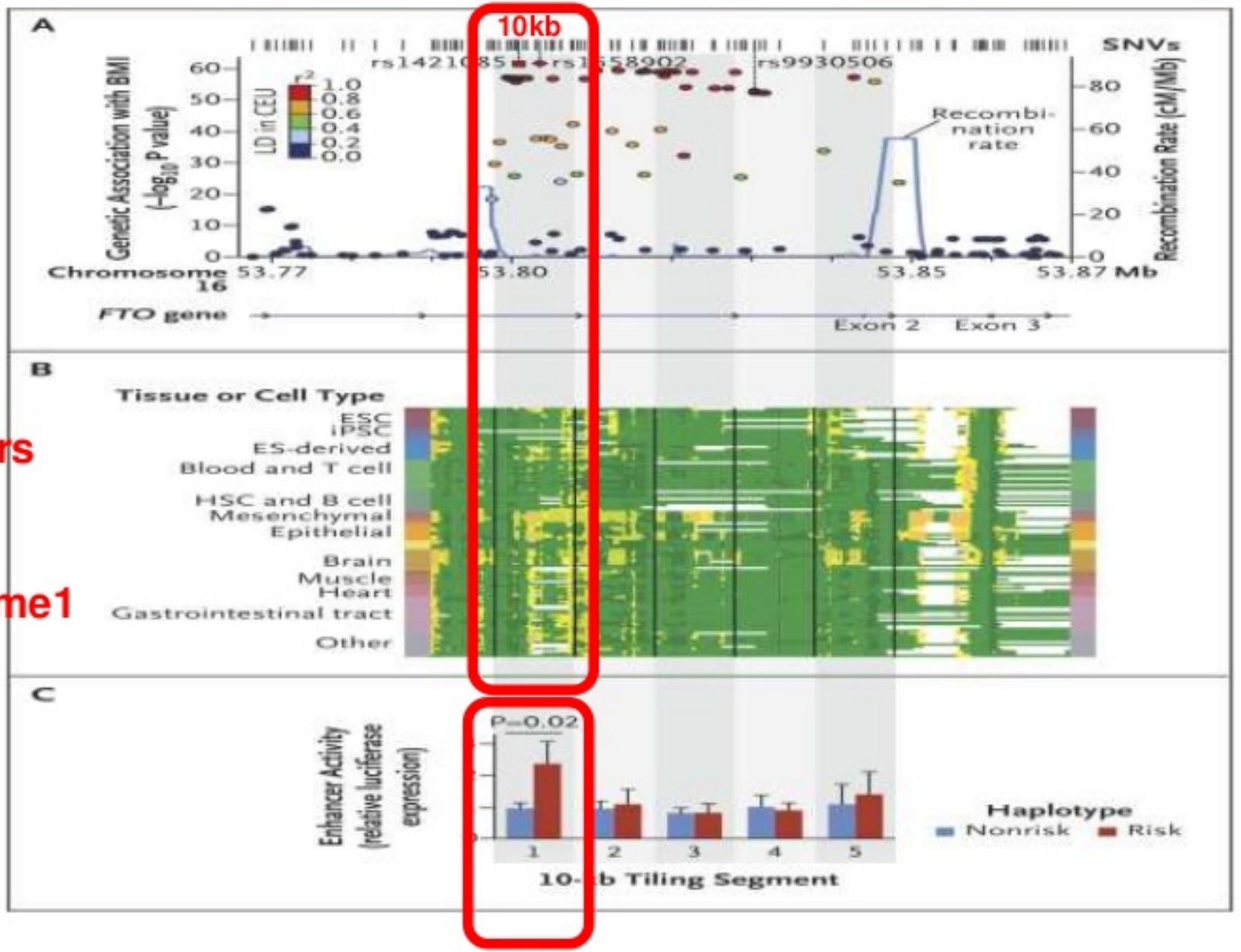
Functional Genomics Approaches

Tissue-Specific Active Enhancers predicted by Histone Marks H3K27ac, H3K4me1 P300

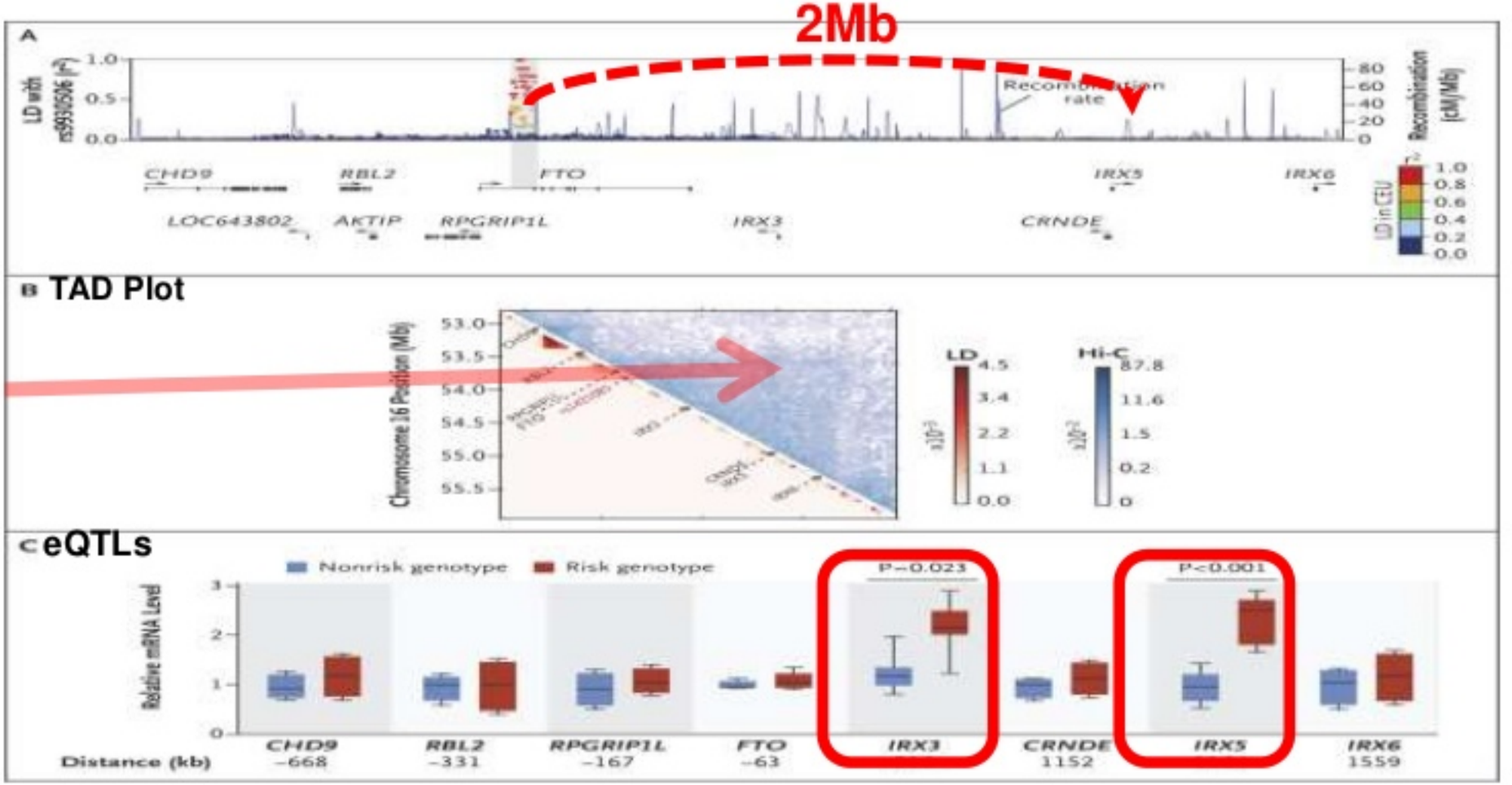


NEJM, 2016

3D Genome Interaction Structure with *IRX5* Gene

- Tissue-Specific Chromatin Confirmation Capture (3C Tech)
- eQTLs (associations between variants and gene expression)
- Allele-specific expression

Intensity of 3D Physical Interaction by Hi-C seq



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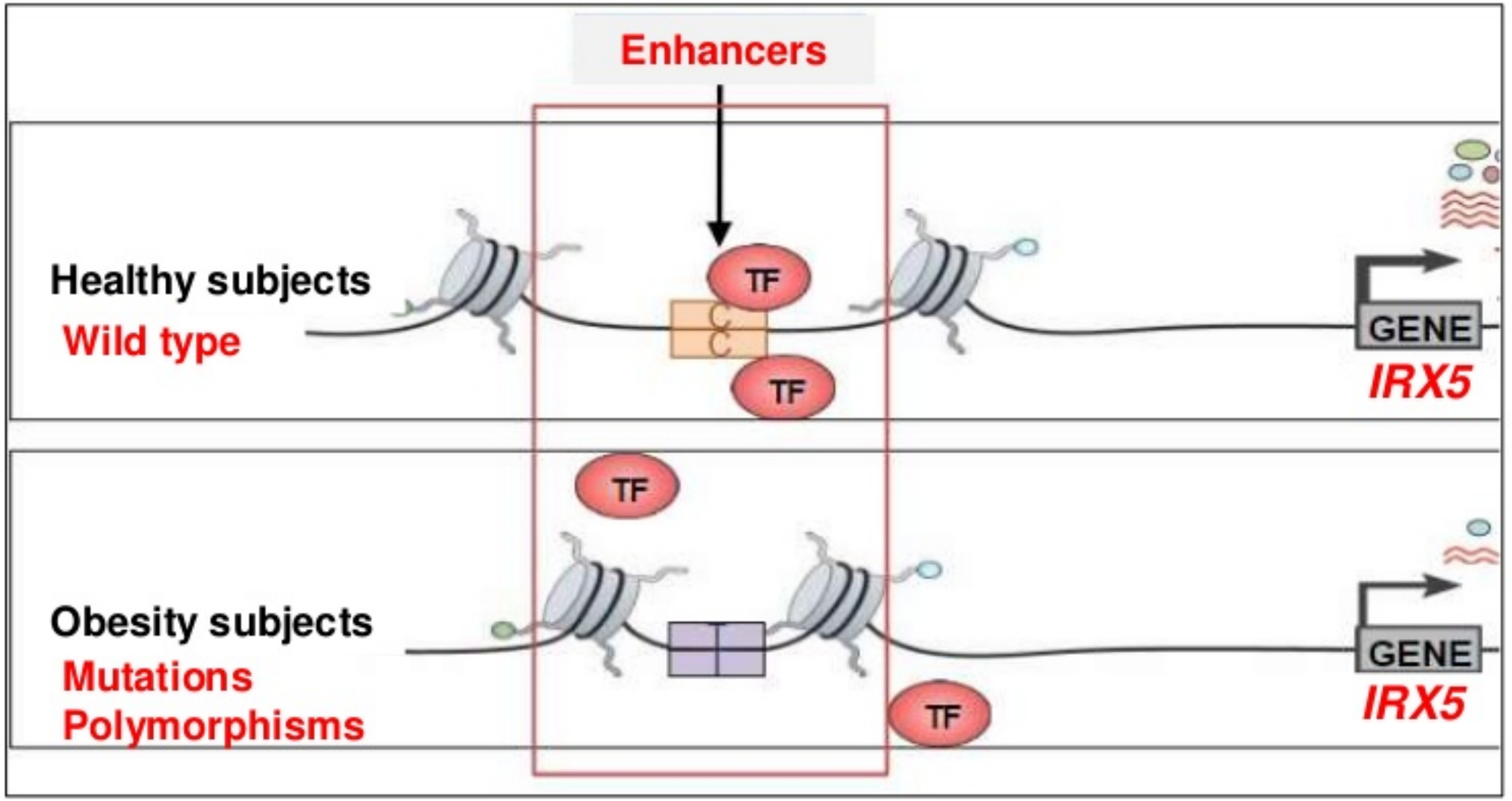
NEJM, 2016

FTO Genetic Variants and *IRX5* Gene Regulation

- Obesity associated genetic variants disrupt TF binding and then reduce *IRX5* gene expression



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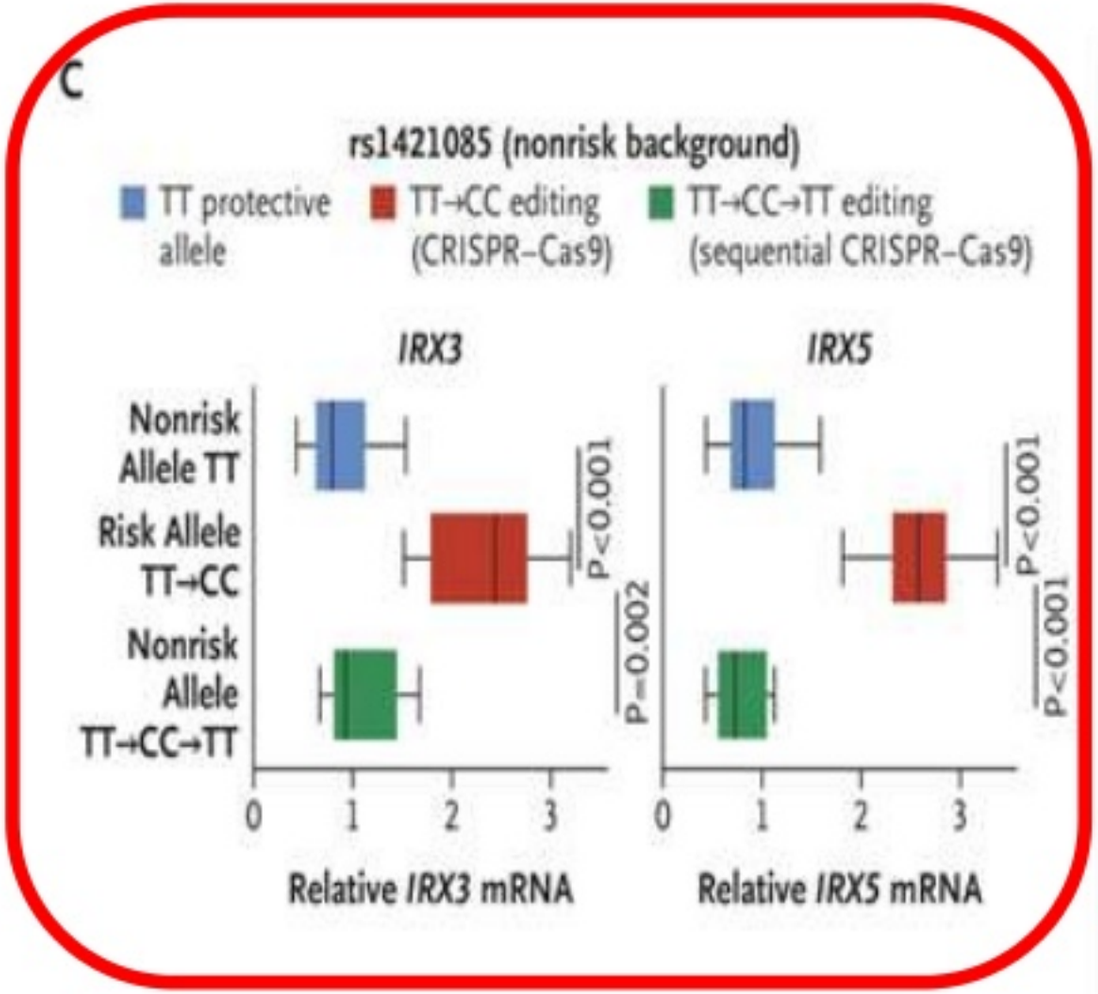
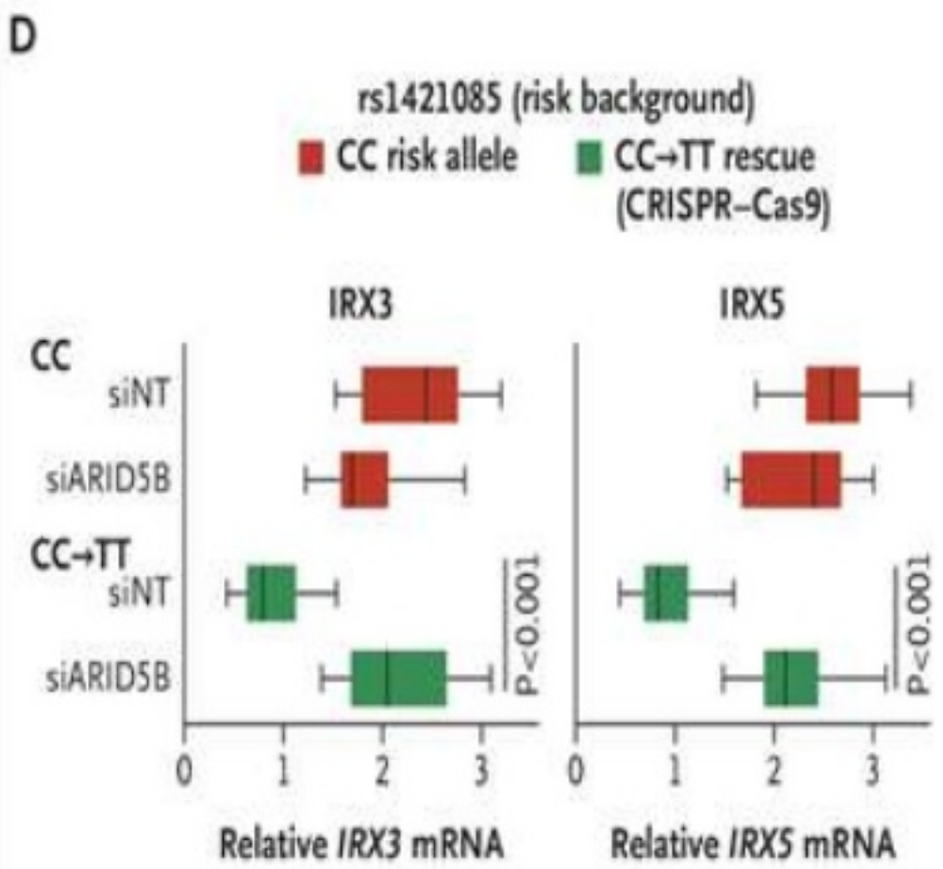
Gene-Editing: Functional Validation

- **Gene Editing by CRISPR/Cas9 in Human adipocytes from subjects carried "risk allele" and subjects carried "protective allele"**
- **The Risk Allele C: Gain-of-function**





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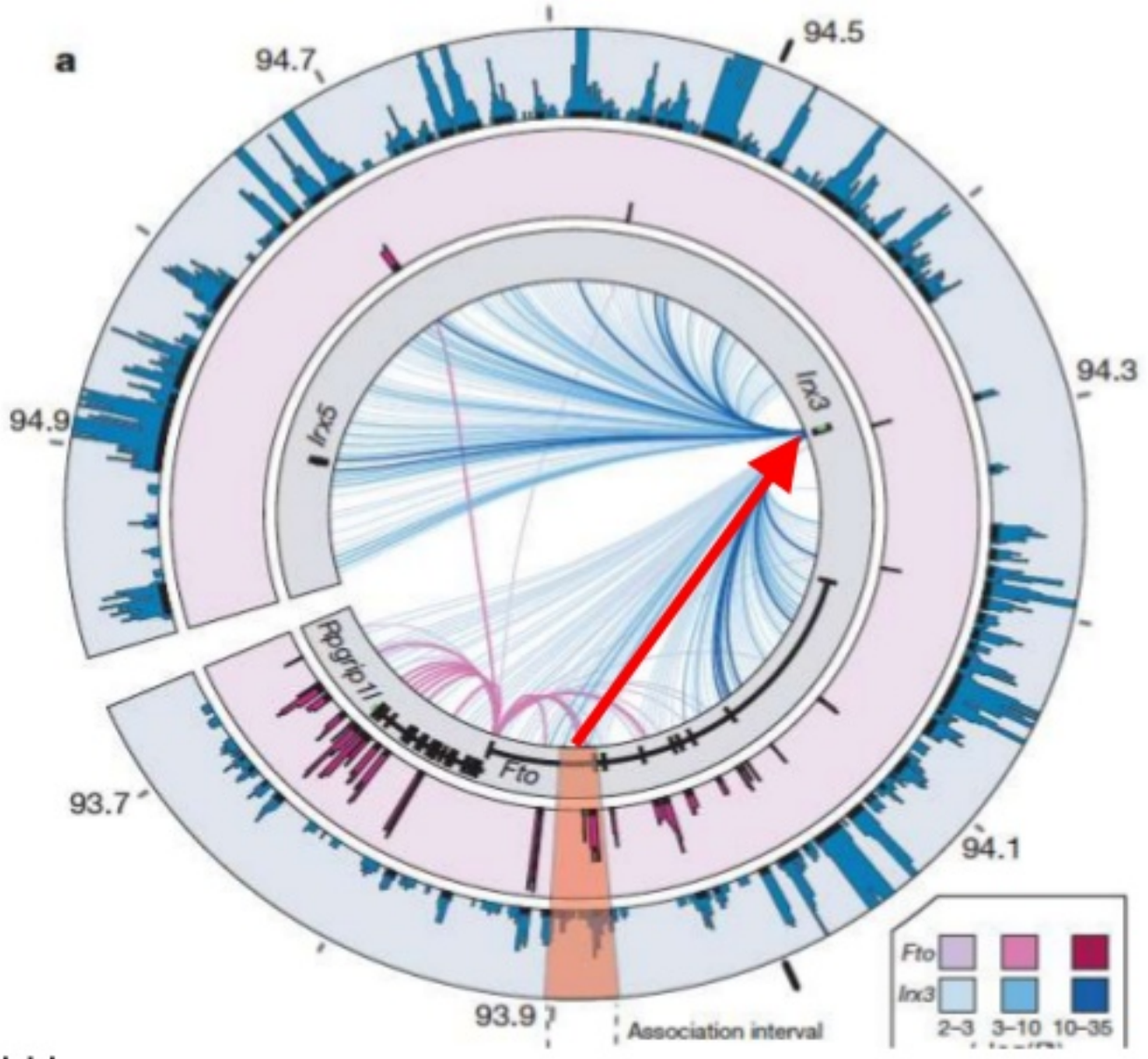
NEJM, 2016

FTO Variants Link to *Irx3* Gene in Brain



- The obesity associated variants physically interacts with promoter of *Irx3* gene, but not *Fto*, not *Irx5* in mouse brain by 4C-seq
- 4C-seq: Regional Chromatin Confirmation Capture (3C Tech)

Nature, 2014

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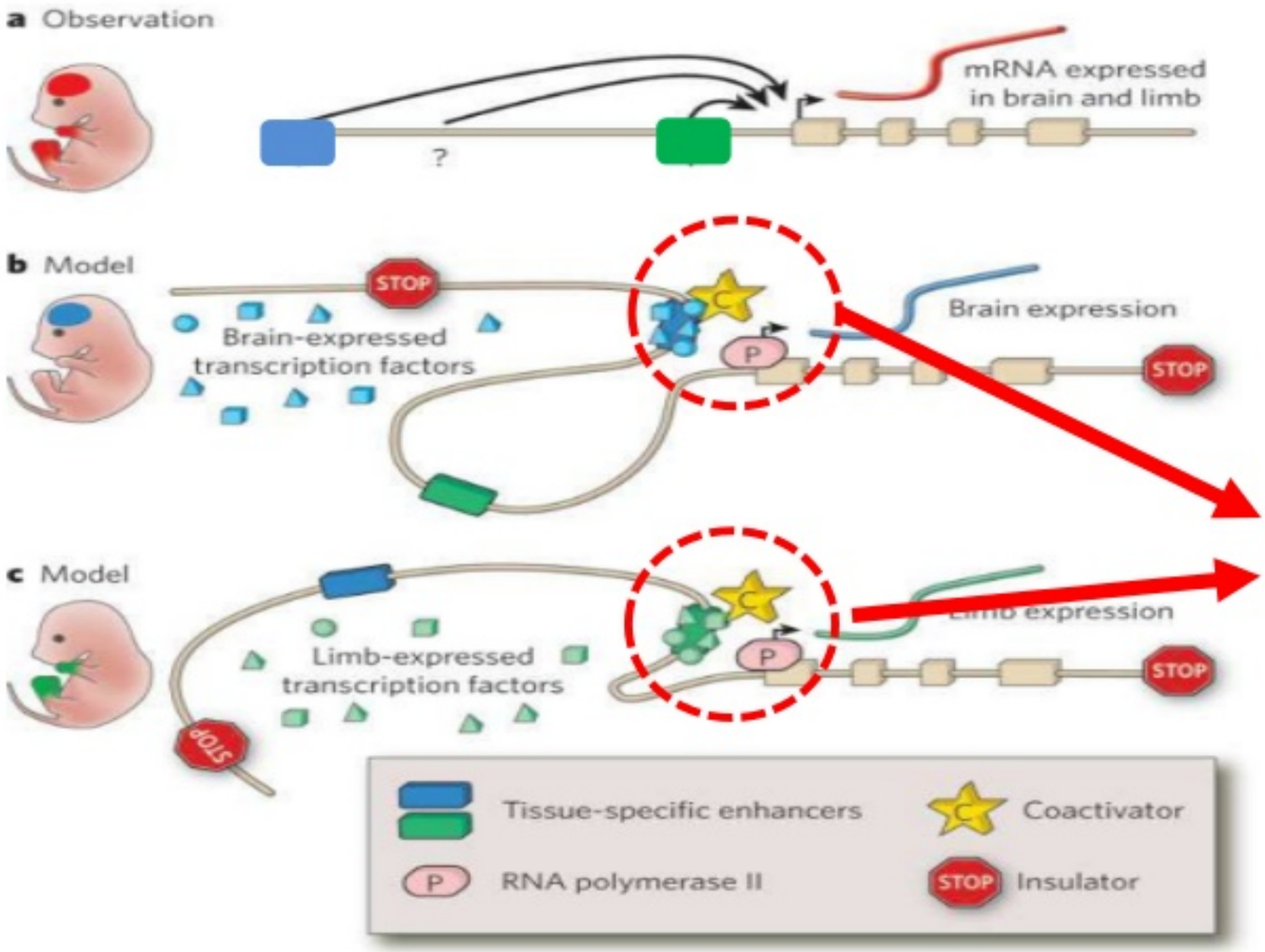
Gene Regulatory Models



Gene regulatory elements in physical proximity (3D space) with the gene promoters via looping mechanisms

Tissue (Cell)-Specific DNA Loops: Enhancer-Promoter Interactions

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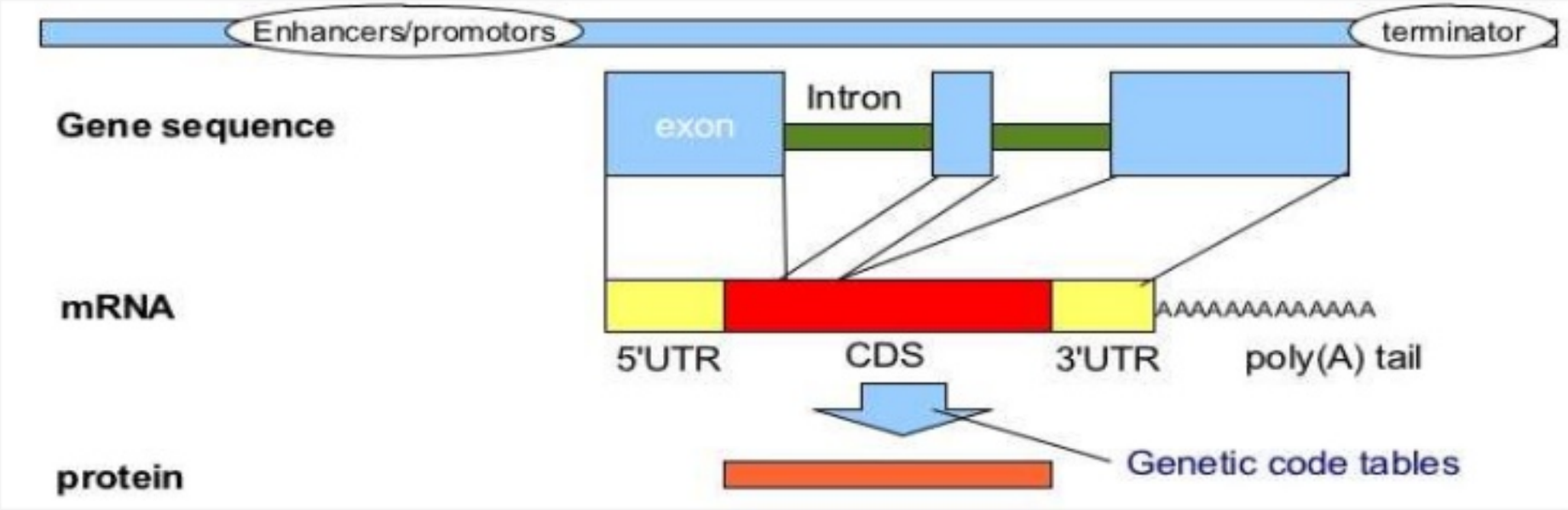
Nature, 2009, 461, 199-205

Genome-Widely Identify/Predict Targeted Genes?

- Identified ~13,000 genetic variants (single nucleotide mutations/ polymorphisms) to be associated with ~2,000 diseases/phenotypes

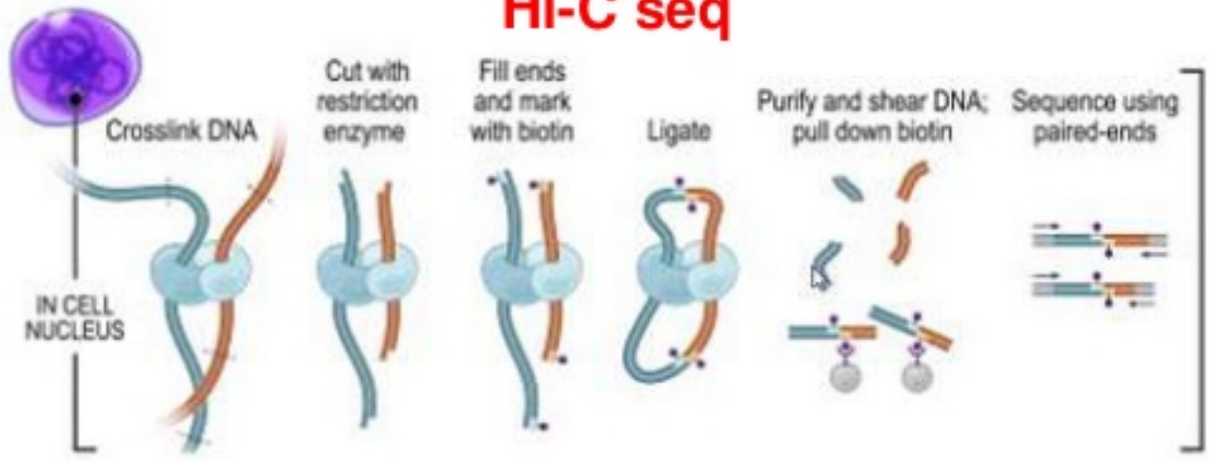
- **91% of disease-associated genetic variants are located in non-protein-coding regions; used to call "junk DNA"**
- **Unknown function, difficult to translate findings into clinical use**
- **May involve in tissue/cell type-specific gene regulation**



Chromosome Conformation Capture To Identify DNA Loops

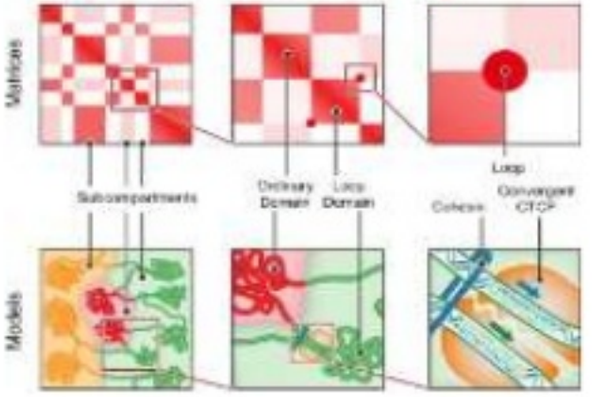
- **3C, 4C, 5C, HiC, capture-HiC, etc to estimate 3D interaction among genome**

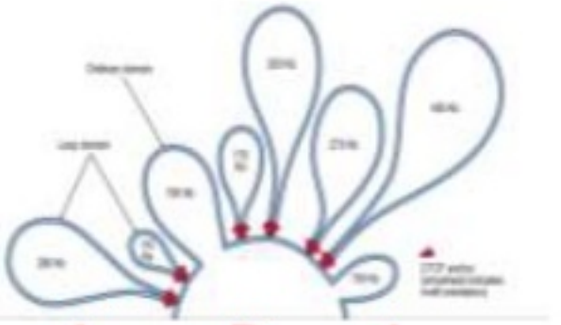
Hi-C seq



Science. 2009.; 326(5950): 289–293
Nat Rev Genet. 2010;11(6):439-46.
Cell. 2014;159(7):1665-80
Nature Genetics 2016; 48, 488–496

Contact Map





Loop Domains

Enhancer-Promoter
Enhancer-Enhancer
Promoter-Promoter
Physical Interactions
False-Pos (seq error, miss-matched cutting,…)

Prediction

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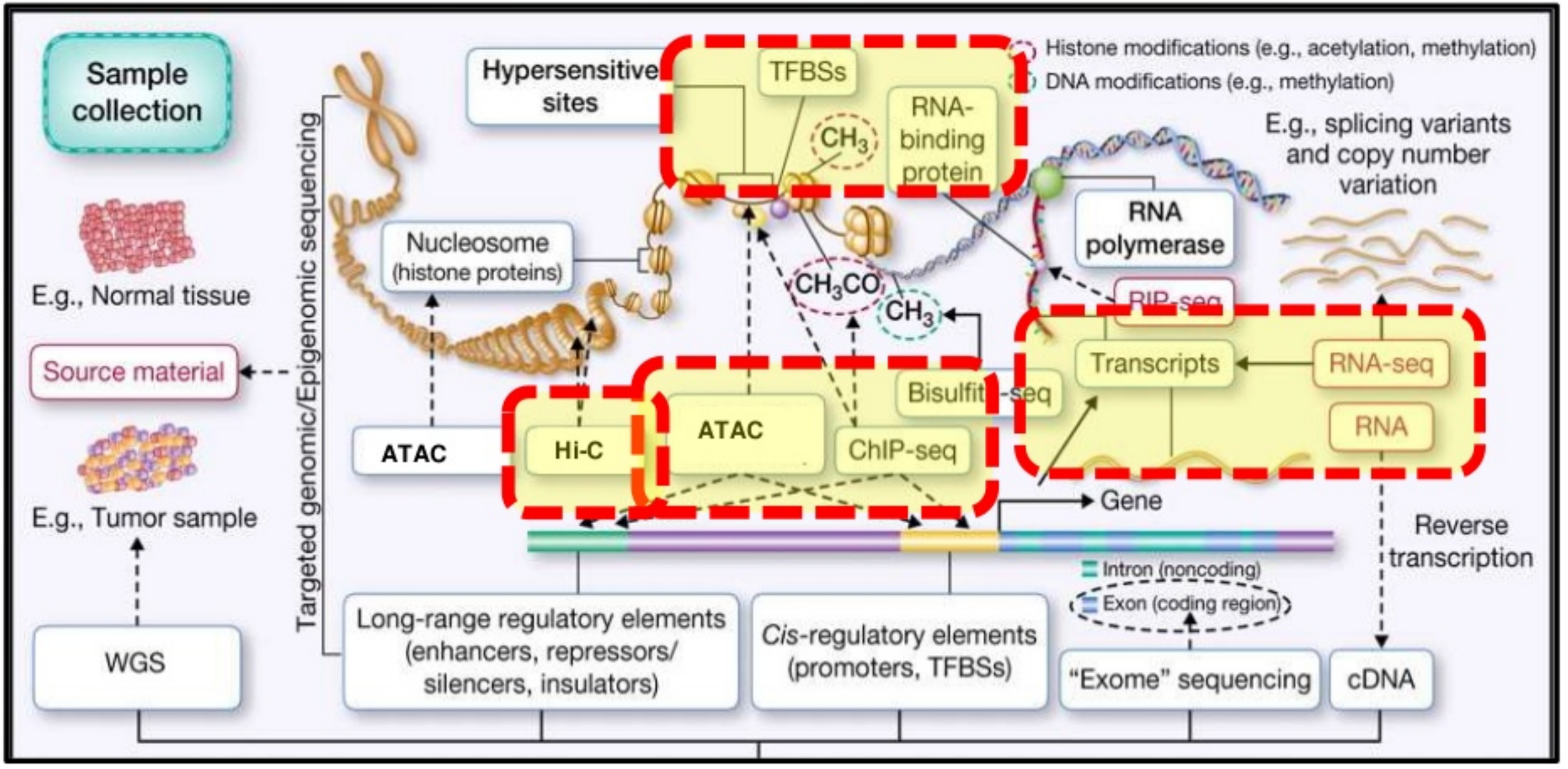
Building Tissue-Specific Gene Regulatory Circuits



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Building Gene Regulatory Circuits On Human Heart

- Omics experiments on normal human primary cardiac fibroblasts and myocytes from atrium and ventricle; HMSC; skeletal muscle cells
- Publicly available (low resolution): Left ventricle, right ventricle and aorta tissues

Experiments	Functions	Notes
ATAC-seq	Active cis-regulatory region	Active TF binding
Hi-C	Chromatin confirmation capture	1.5 to 2 kb resoultion (DpnII, 2 Billions Reads, 2Tb)
ChIP-seq	H3K4me3: Aactive promoter	Predicted chromatin states by HMM
	H3K27ac: Active enhancer/promoter	
	CTCF: Insulator	
	Cohesin: Insulator-RAD21	
	Cohesin: Insulator-SMC3	
	H3K27me3: Polycomb repressed/bivalent promoter/enhancer	
	H3K9me3: Heterochromatin	
	H3K36me3: Transcribed region	
RNA-seq	mRNA (active and)	Isoforms; coexpression with TF
	microRNA and small RNA	Enhancer RNA

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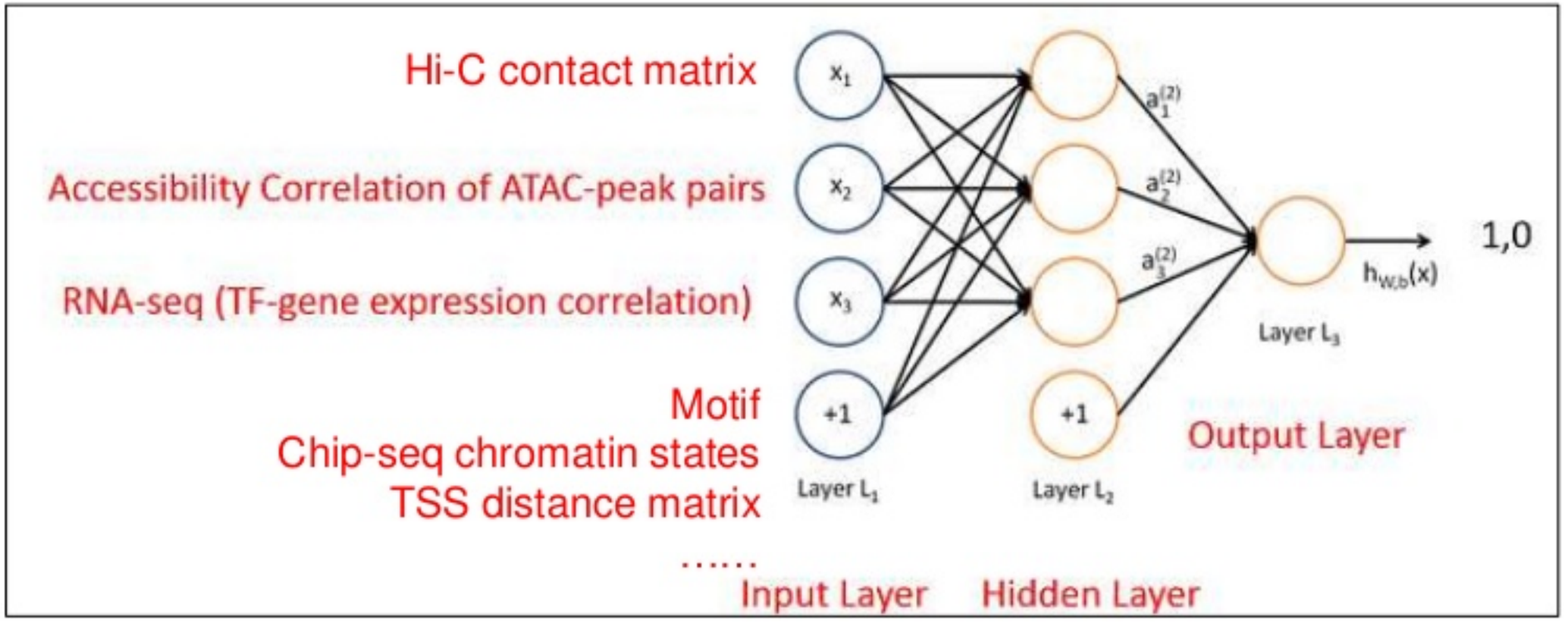
Model Gene Regulation with Deep Neural Network (DNN)

- **DNN implemented in the TensorFlow to predict enhancer-promoter gene pairs**



- **Training sets** (VISTA: enhancer elements are in 100kb of genes):
  1,564 Enhancer-promoter gene pairs (the positive set) functionally validated to have regulatory relationships in mouse models
  1,207 EP pairs without regulatory relationships (the negative set)

Acknowledgements

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The Jackson Laboratory
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