3D Genome Provides a Lens to Understand Biological Mechanisms Underlying Psychiatric Disorder

Hyejung Won

UNC Department of Genetics &
Neuroscience Center
@hyejung_won

10/26/2019

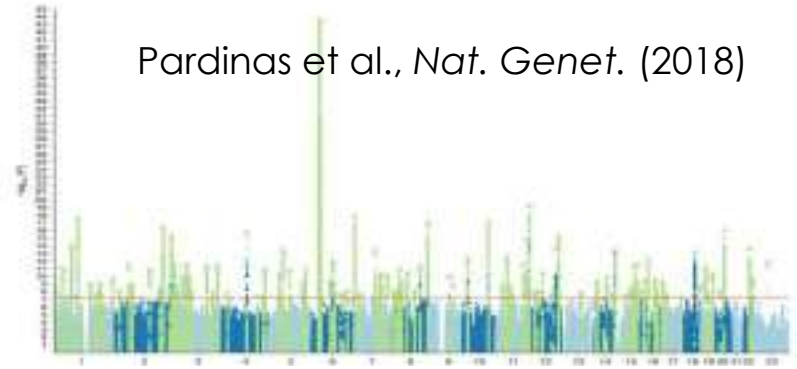
Psychiatric Genetics : Two classes of variation

Common variation	Rare variation
Common in population	Rare in population
Small effect size	Large effect size
Explains a large proportion of variation	Explains a small proportion of variation (except neurodevelopmental disorders)
GWAS	Exome sequencing

Psychiatric Genetics: Common variation

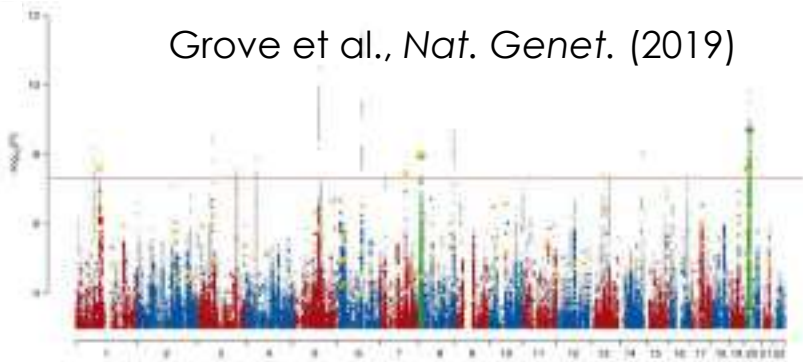
Schizophrenia

Pardinas et al., *Nat. Genet.* (2018)



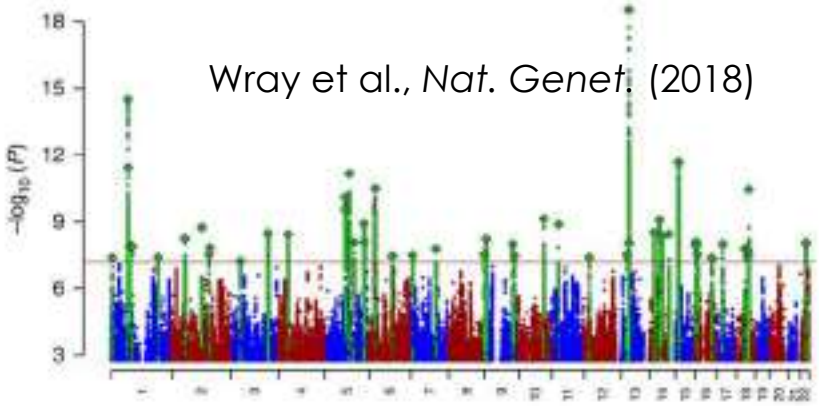
Autism

Grove et al., *Nat. Genet.* (2019)



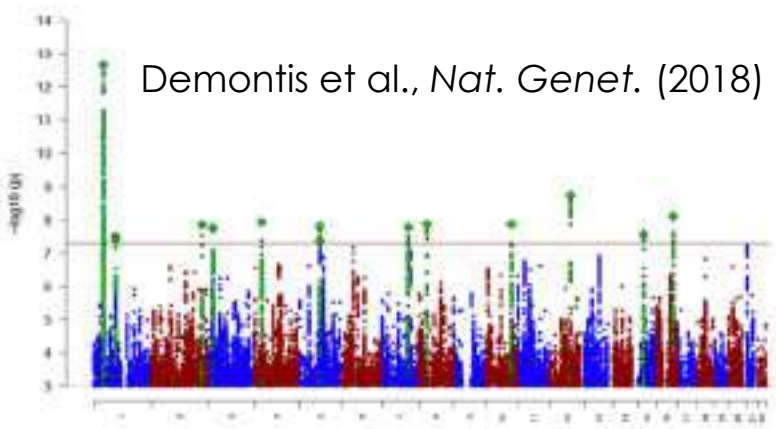
Depression

Wray et al., *Nat. Genet.* (2018)



ADHD

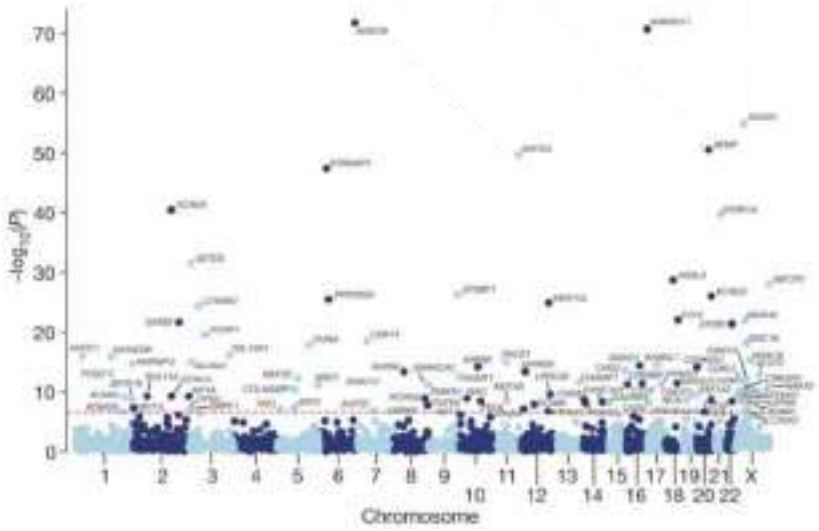
Demontis et al., *Nat. Genet.* (2018)



GWAS has been super successful,
identifying many genomic regions associated with psychiatric disorders.

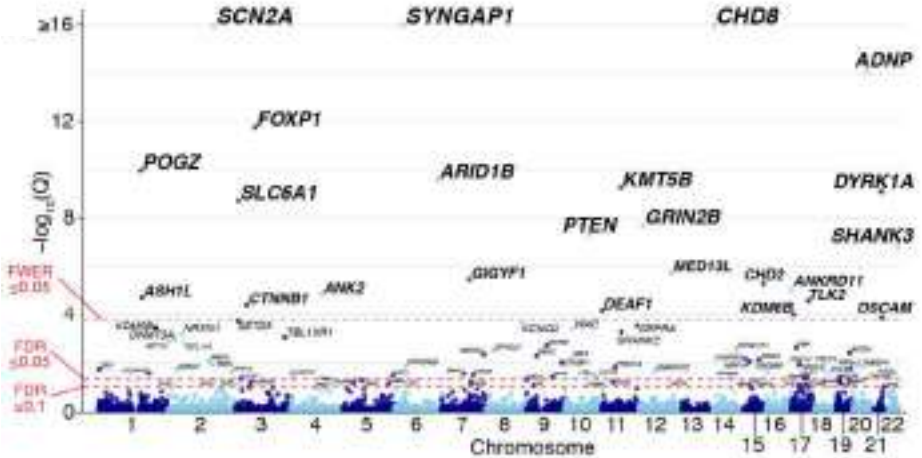
Psychiatric Genetics: Rare variation

299 DD risk genes



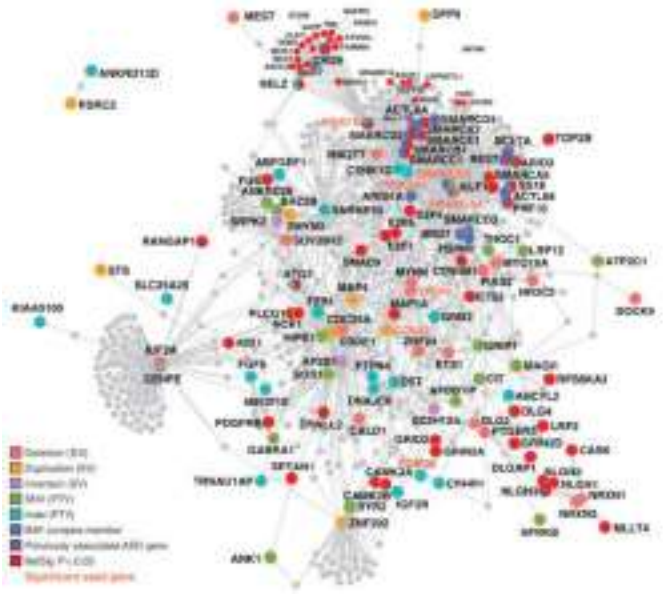
Kaplanis et al., *bioRxiv* (2019)
Deciphering Developmental Disorders Study, *Nature* (2017)

184 ASD risk genes



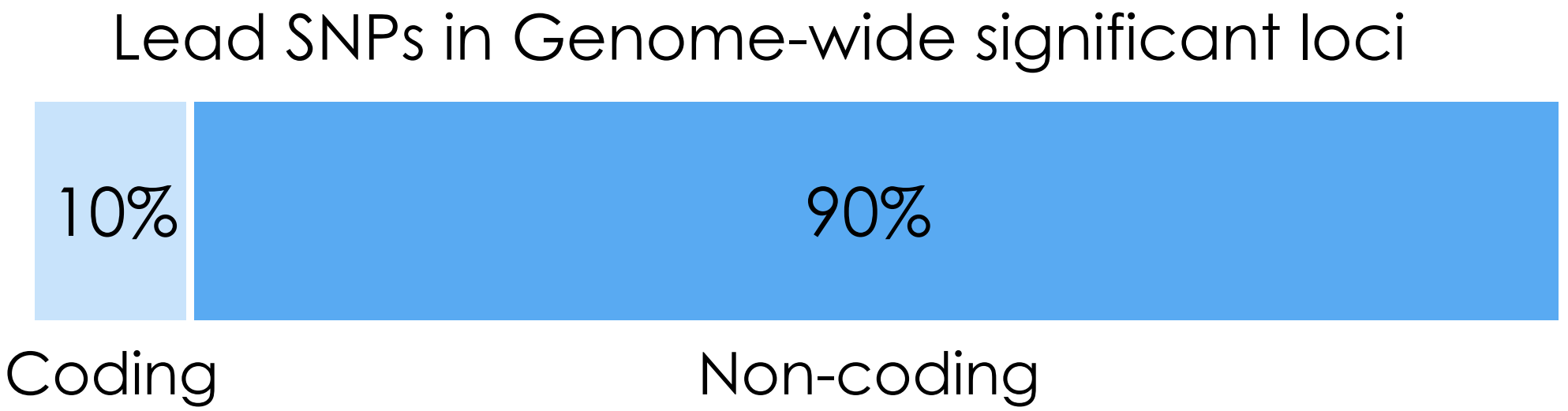
Satterstrom et al., *bioRxiv* (2019)

69 ASD risk genes



Ruzzo et al., *Cell* (2019)

Challenge: non-coding variation

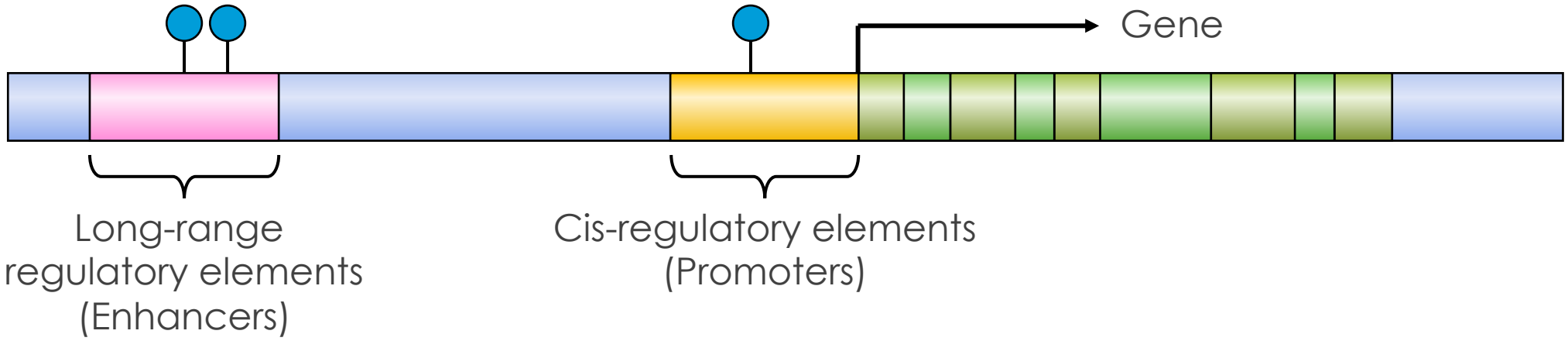


Most GWAS SNPs reside in **non-coding genomic regions** with poorly understood functionality.

Whole genome sequencing can identify non-coding rare variation in ASD.

Watanabe et al., *Nat. Genet.* (2019); Brandler et al., *Science* (2018)

Solving the mystery of non-coding genome



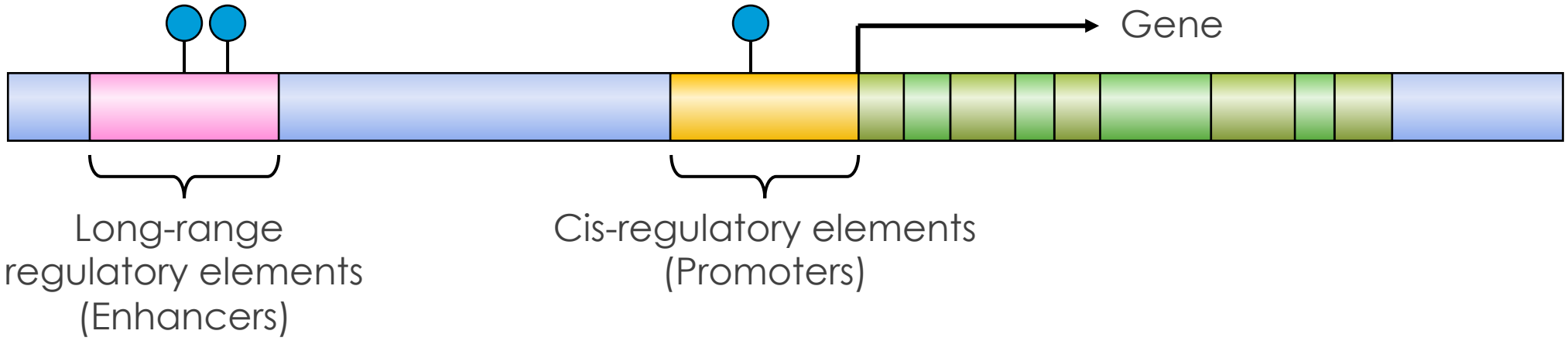
Common variants associated with psychiatric disorders are enriched in regulatory elements.

Rare de novo ASD risk variants are enriched in promoters and TFBS.

→ A **map of gene regulation** is critical to deciphering the biological impact of these variants.

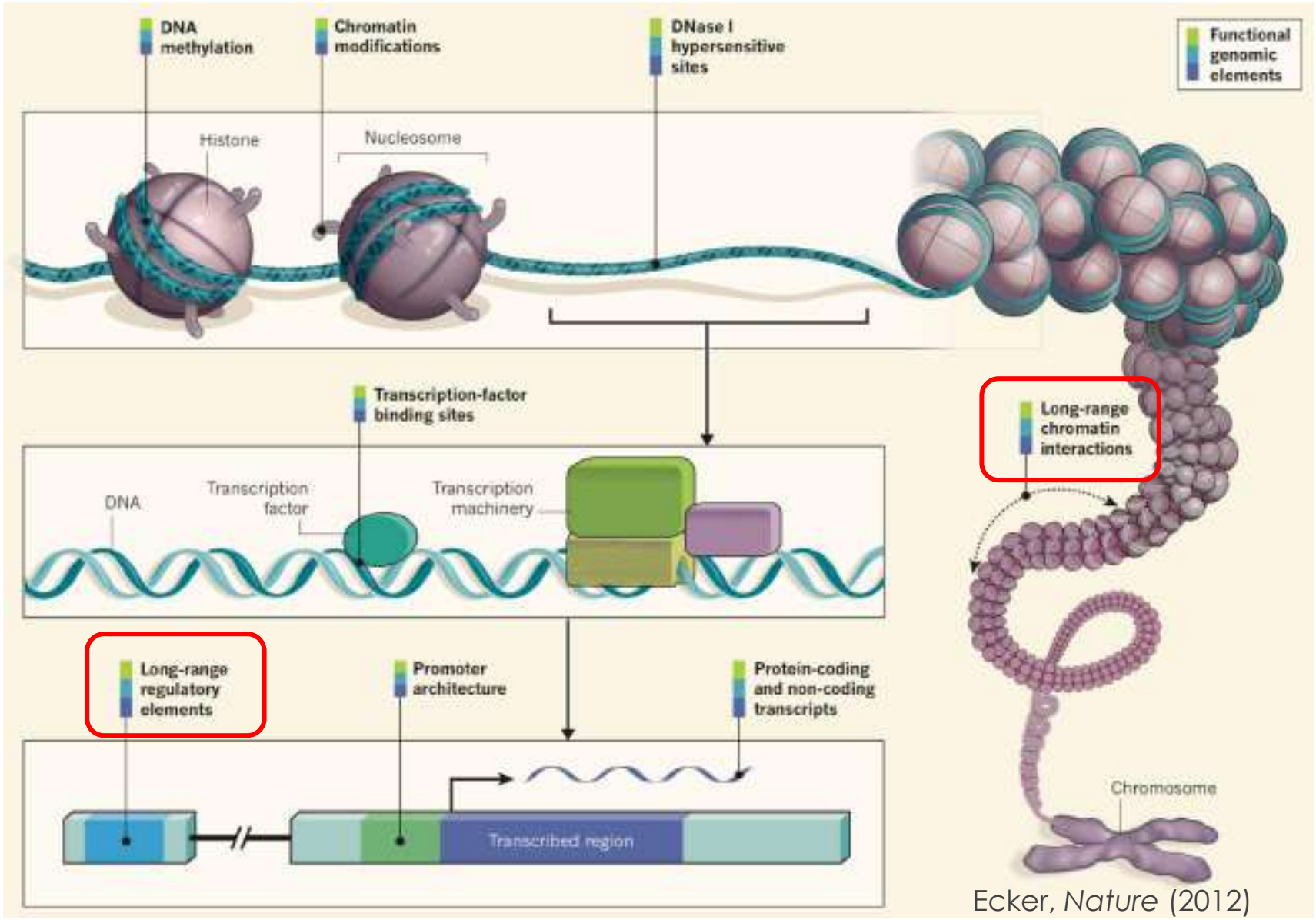
Finucane et al., *Nat. Genet.* (2015); An et al., *Science* (2018); Zhou et al., *Nat. Genet.* (2019)

Solving the mystery of non-coding genome

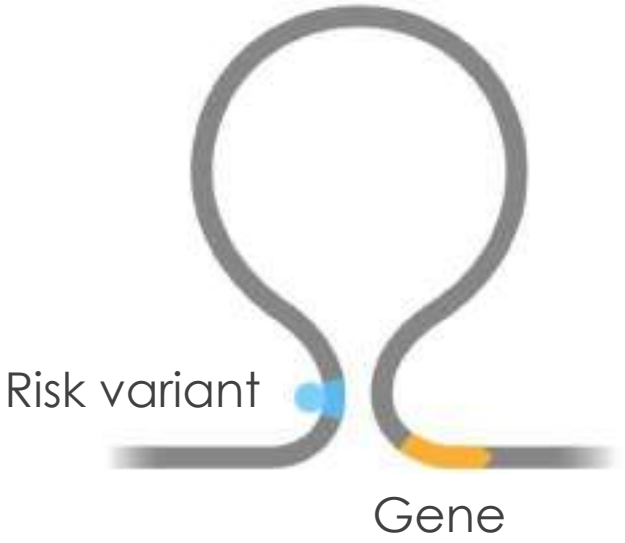


The first critical step to understand the biological impact of non-coding variation is to identify their **target genes**.

Solving the mystery of non-coding genome

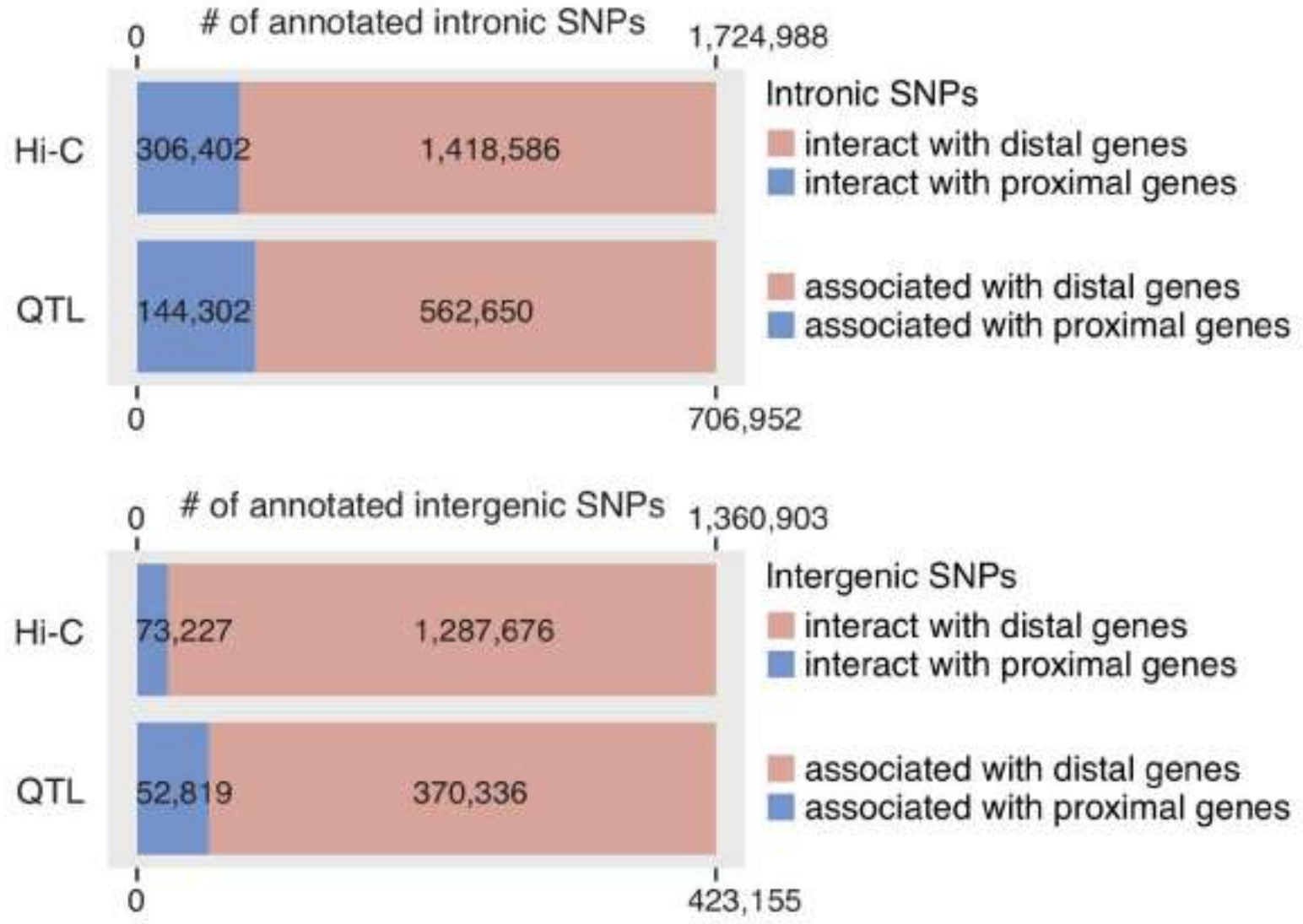


Ecker, *Nature* (2012)



Hypothesis: non-coding risk variants may affect distal target genes via chromatin interactions

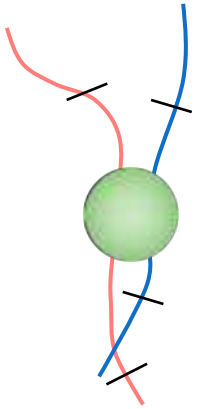
Non-coding SNPs often regulate non-nearest genes



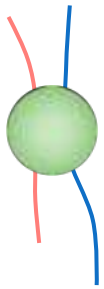
Sey et al., *bioRxiv* (2019)

Hi-C: Genome-wide Chromosome Conformation Capture

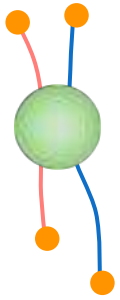
Crosslink



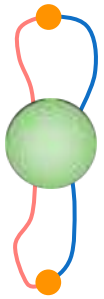
Restriction enzyme digest



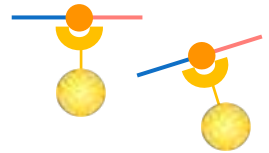
Biotinylation



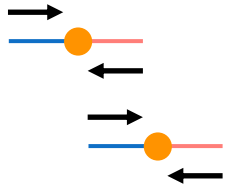
Ligation



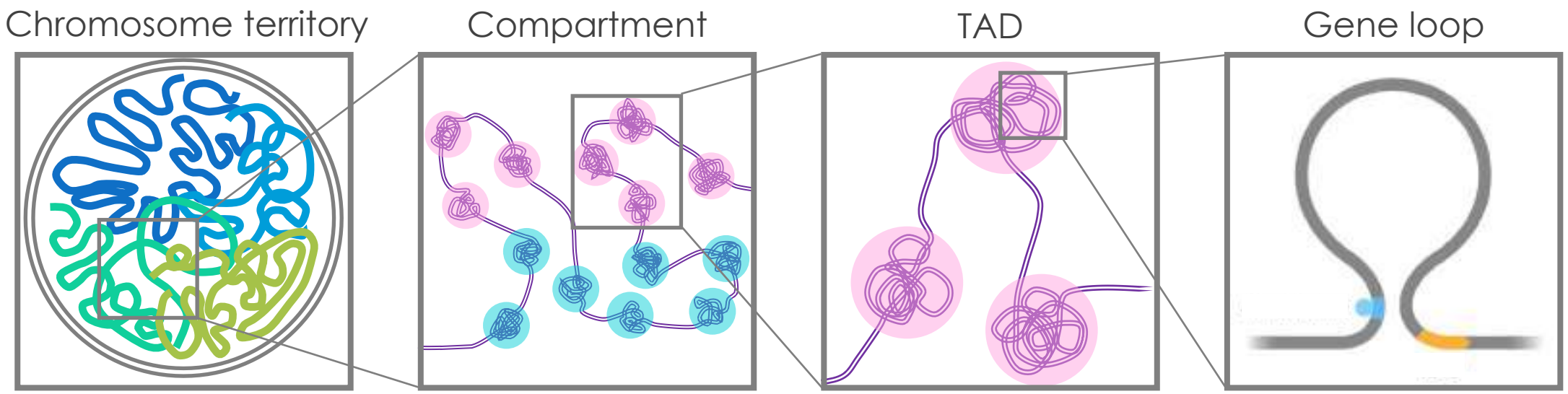
Biotin pull down



Sequencing

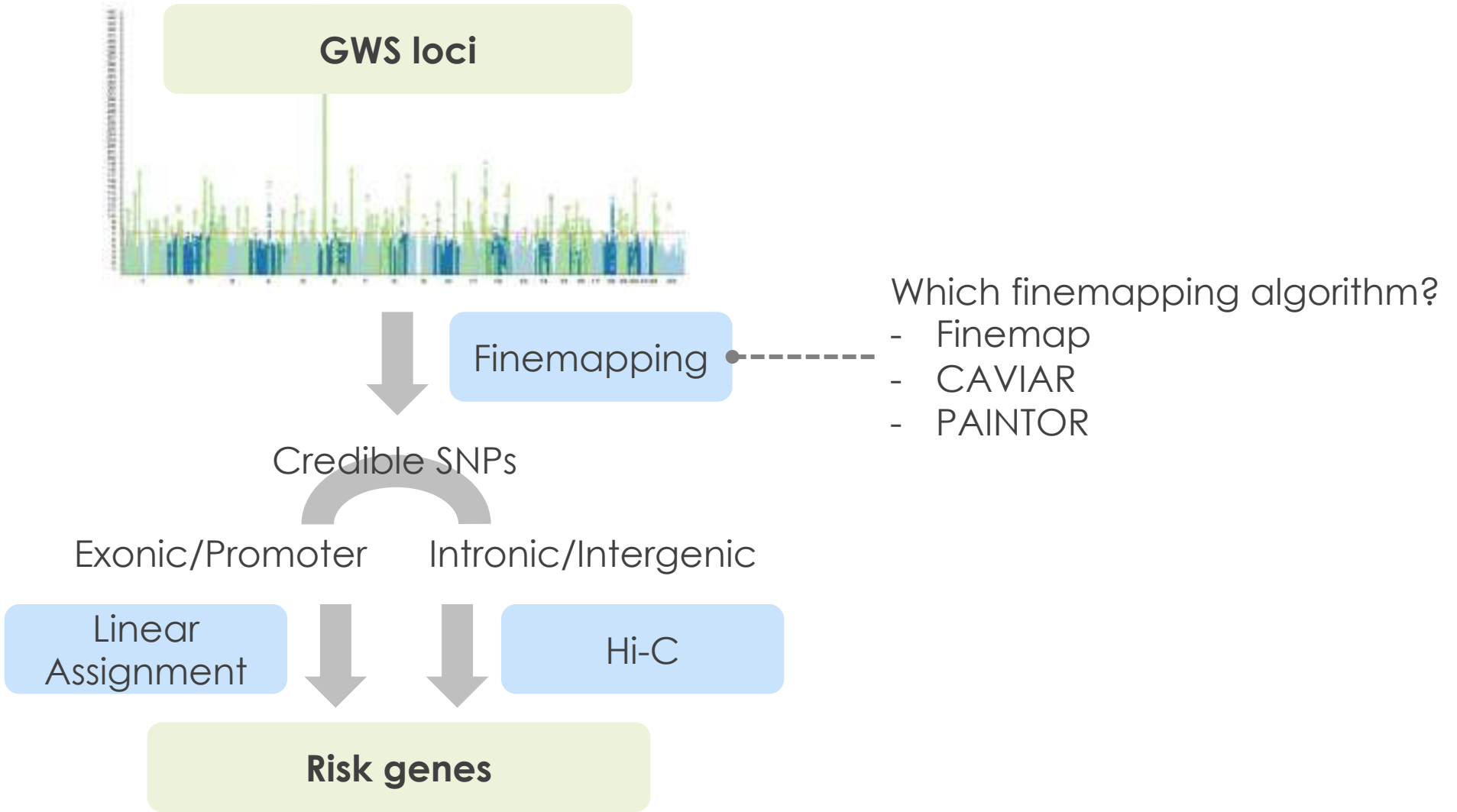


Hi-C identified functional organization principles of the genome



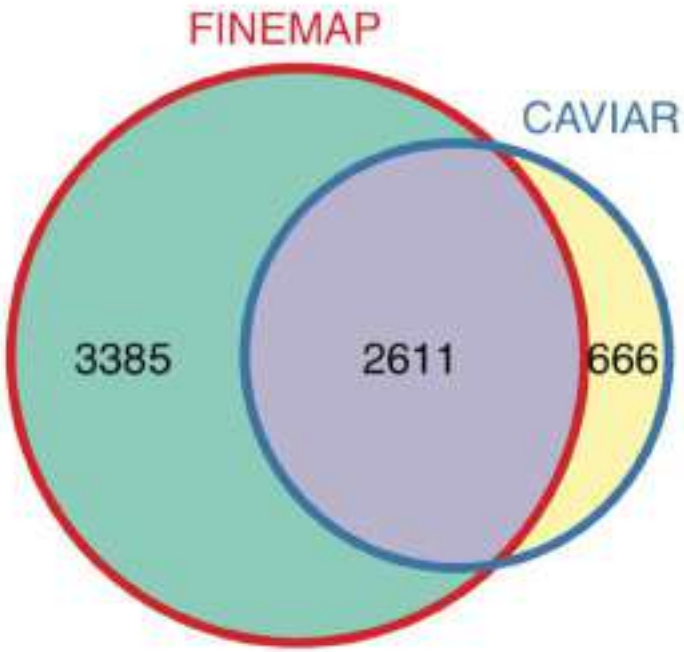
Hypothesis: non-coding risk variants may affect distal target genes via chromatin interactions.

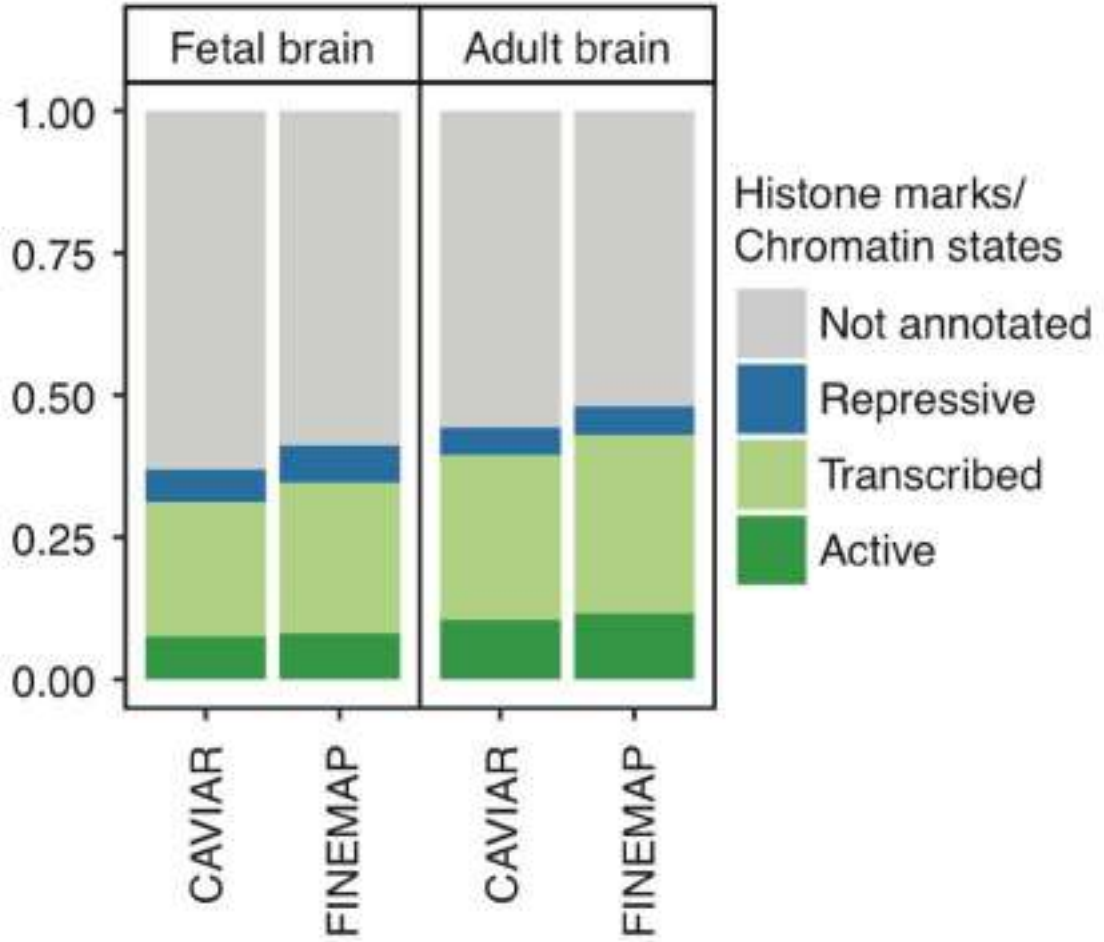
Chromatin interactions help predict SNP functionality



Mah & Won, *Schizophrenia Research* (2019)

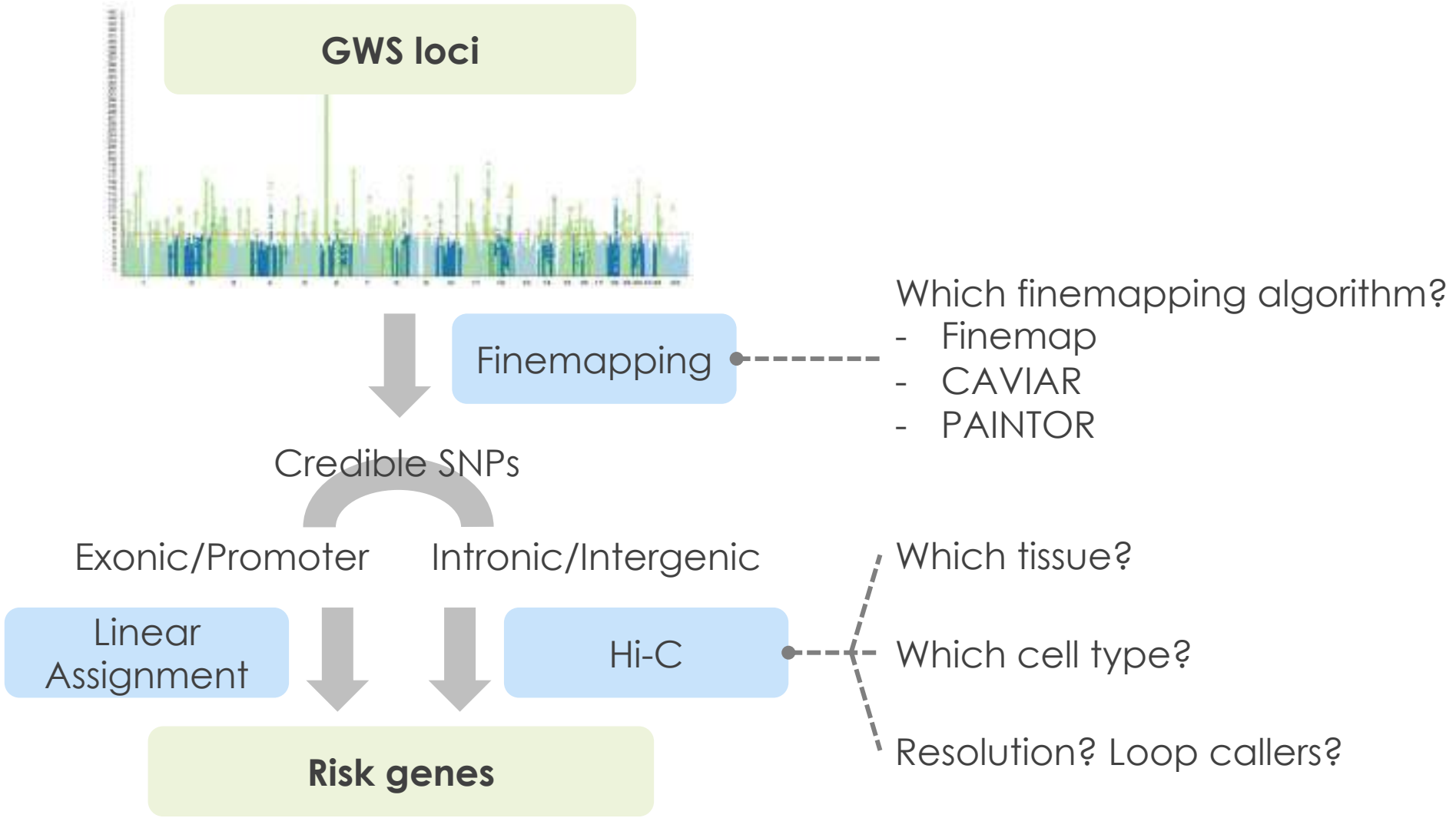
Finemapping algorithm matters





Mah & Won, *Schizophrenia Research* (2019)

Chromatin interactions help predict SNP functionality



Mah & Won, *Schizophrenia Research* (2019)

Hi-C data matters

Development

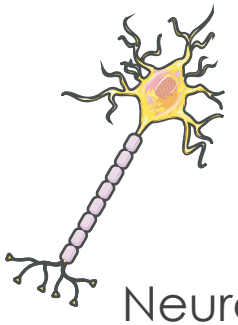
Fetal brain

Adult brain

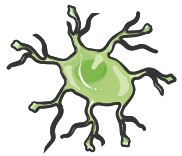
Won et al., *Nature* (2016)

Wang et al., *Science* (2018);
Jung et al., *Nat. Genet.* (2019)

Cell type

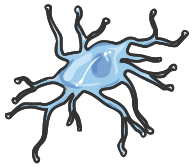


Neuron



Astrocyte

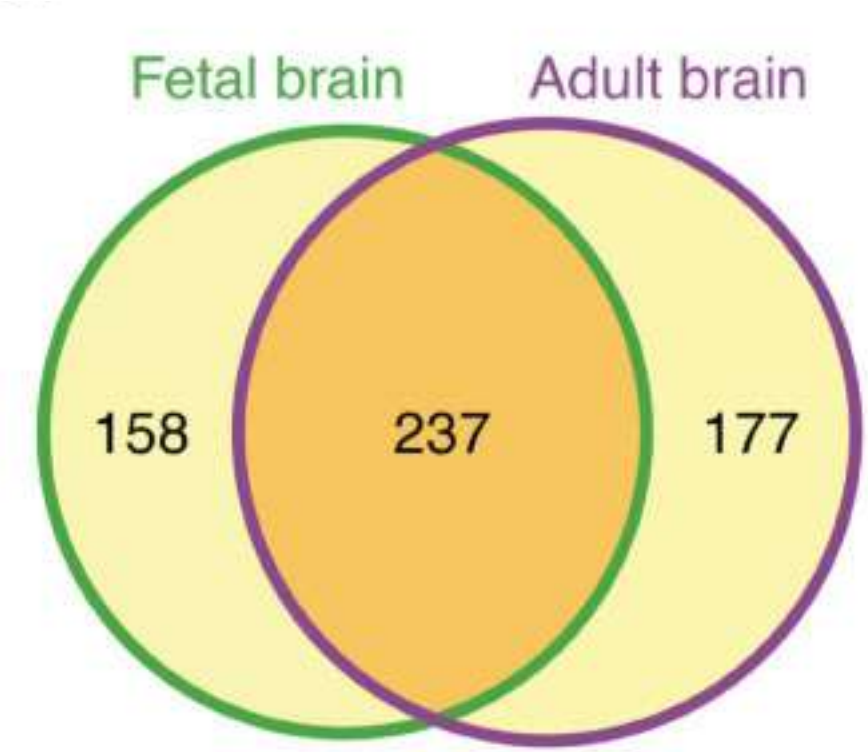
Oligodendrocyte

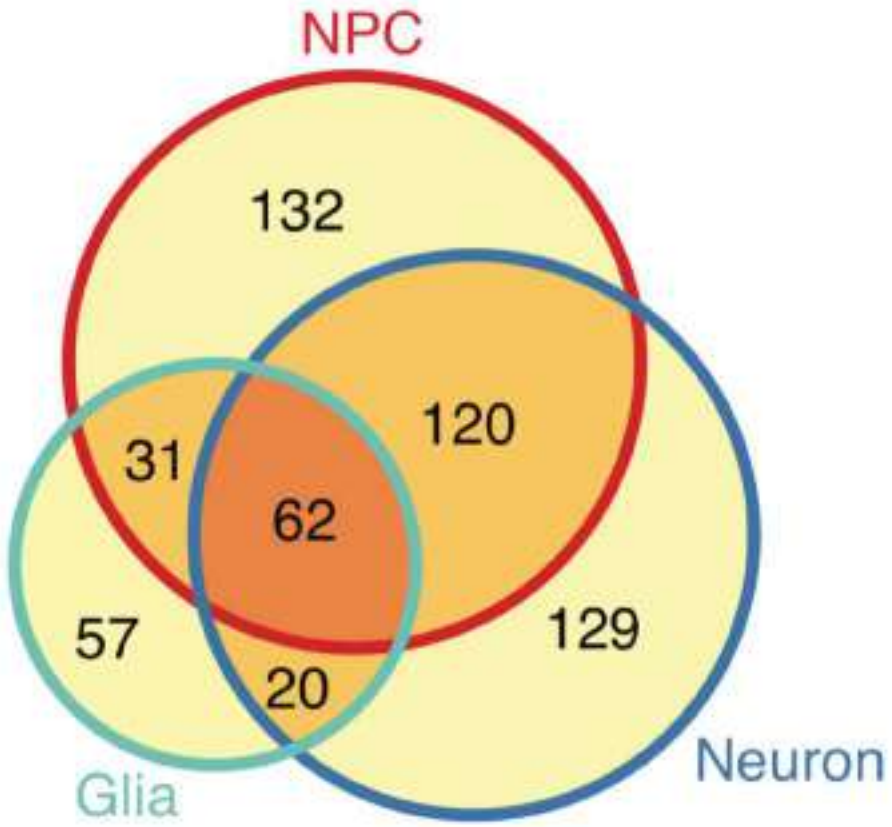


Microglia

Rajarajan et al., *Science* (2018);
Song et al., *Nat. Genet.* (2019);
Nott et al., *bioRxiv* (2019)

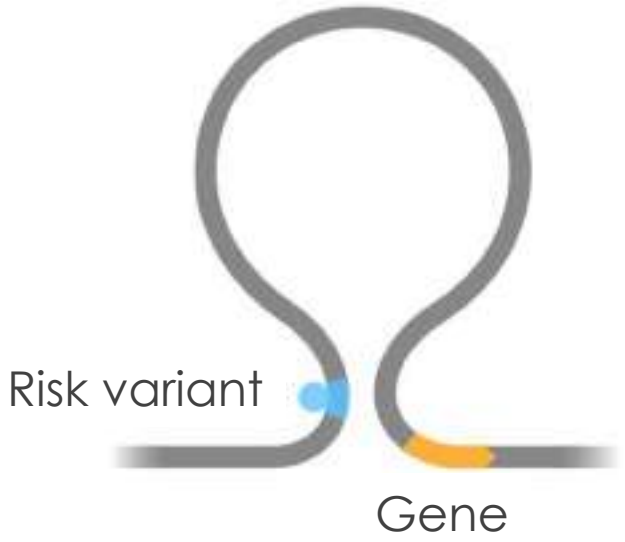
Hi-C data matters





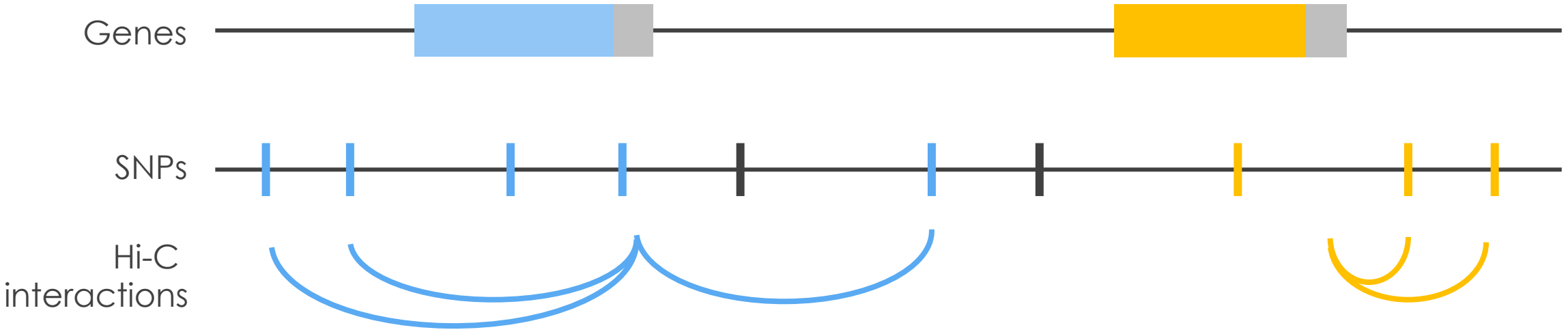
Mah & Won, *Schizophrenia Research* (2019)

Disclaimer: Limitations of Hi-C



1. Resolution: Hi-C cannot capture proximal interactions within 10kb.
2. Other regulatory mechanisms:
   - Some risk variants may disrupt global chromatin structure (e.g. TADs or compartments).
   - Hi-C cannot capture other gene regulatory mechanisms such as splicing.
3. Directionality: Hi-C does not predict whether the risk variant will upregulate or downregulate the target gene.

Hi-C coupled MAGMA (aka **H-MAGMA**)

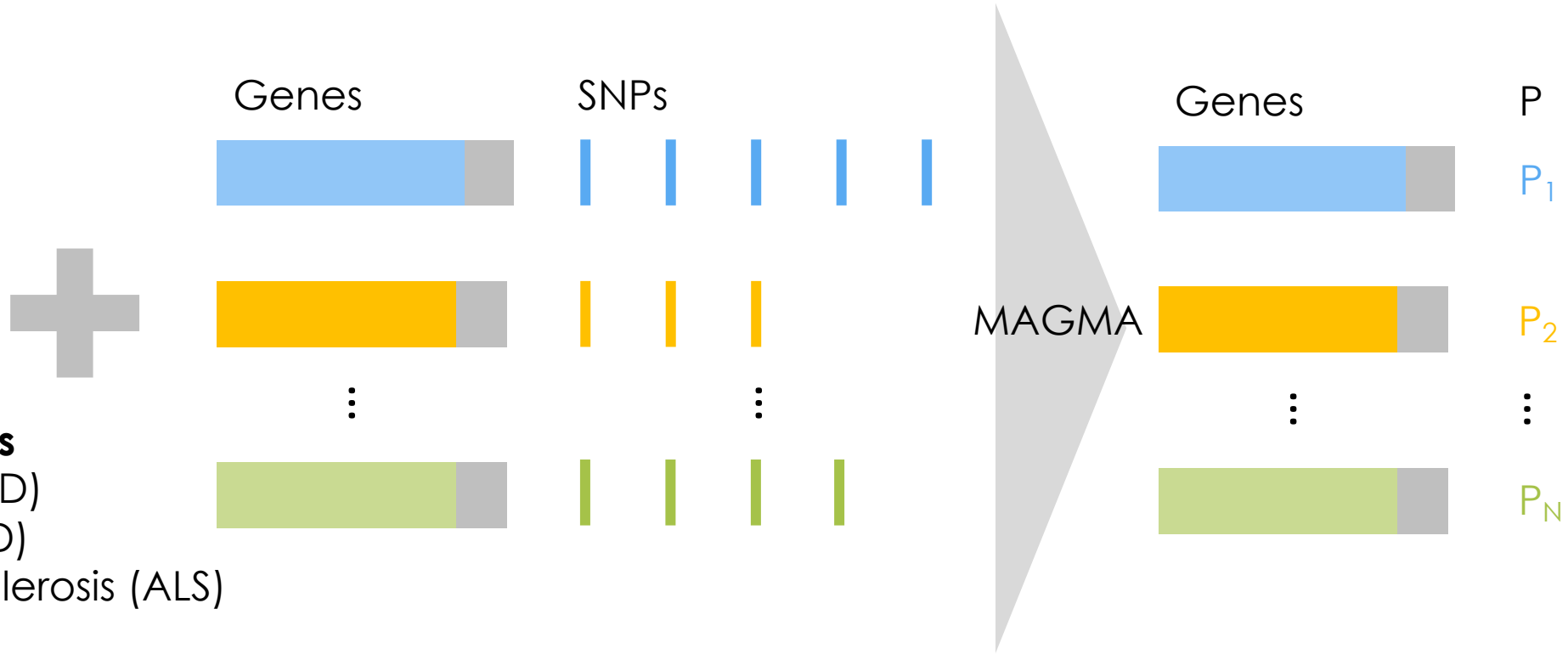


Sey et al., *bioRxiv* (2019)

Hi-C coupled MAGMA (aka **H-MAGMA**)

Psychiatric Disorders
ADHD
Autism (ASD)
Schizophrenia (SCZ)
Bipolar (BD)
Depression (MDD)

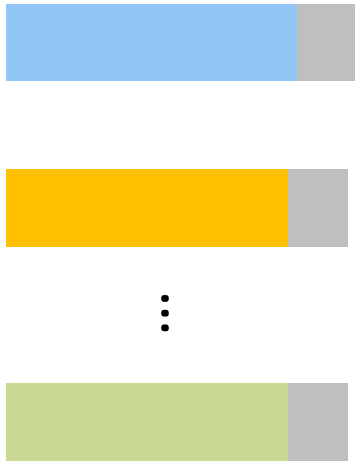
Degenerative Disorders
Alzheimer's Disease (AD)
Parkinson's Disease (PD)
Amyotrophic lateral sclerosis (ALS)
Multiple sclerosis (MS)



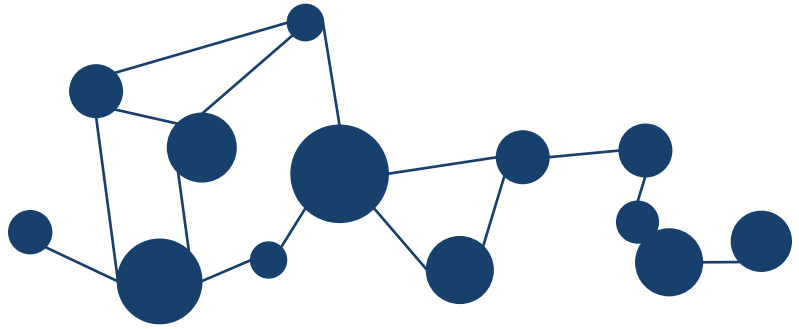
Sey et al., *bioRxiv* (2019)

Moving beyond GWAS: Biological characterization

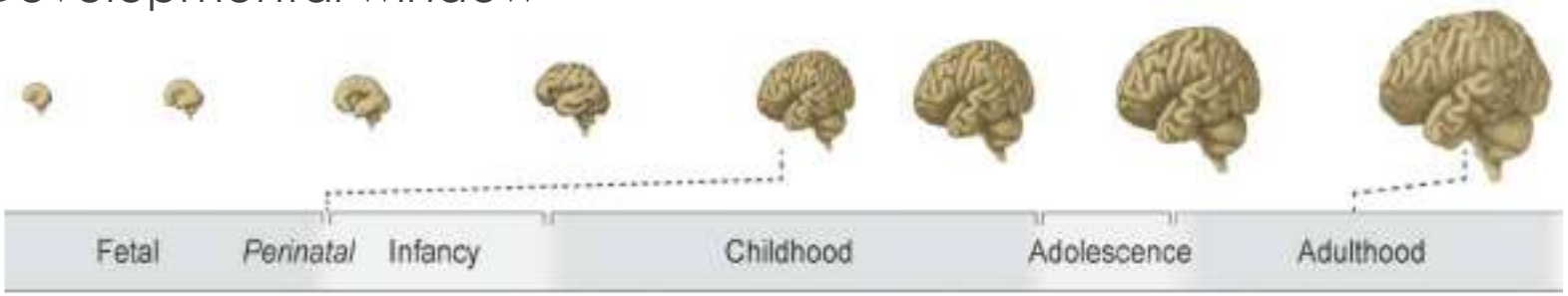
Genes



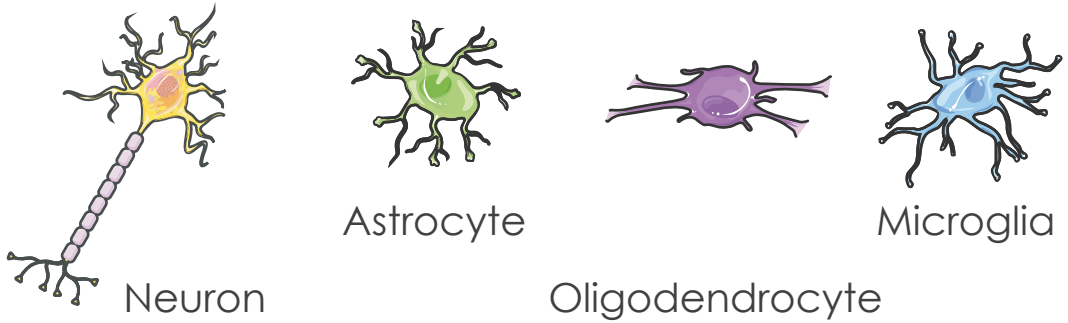
Biological processes



Developmental window



Central cell types



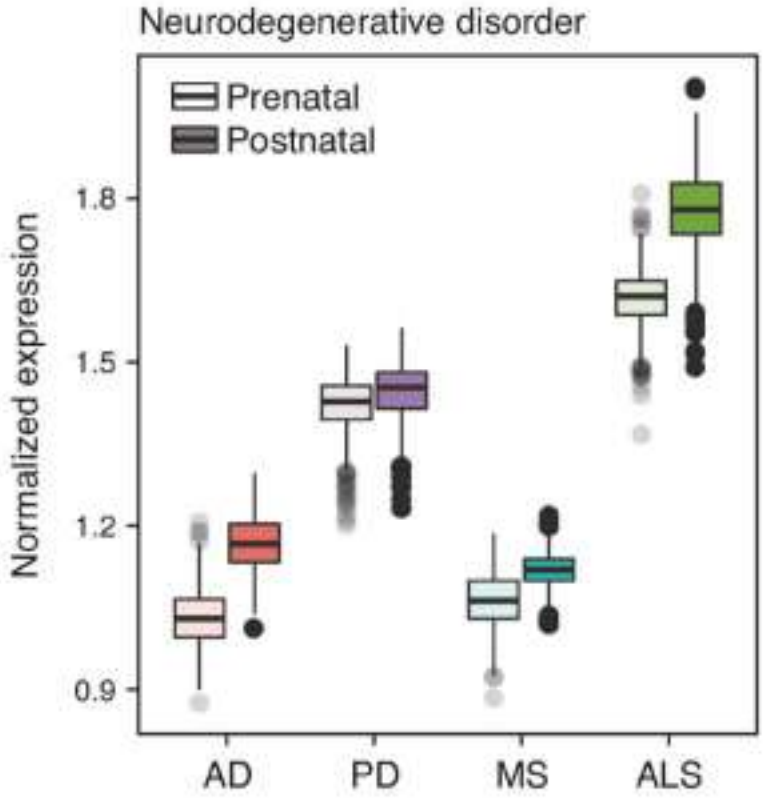
Sey et al., *bioRxiv* (2019)

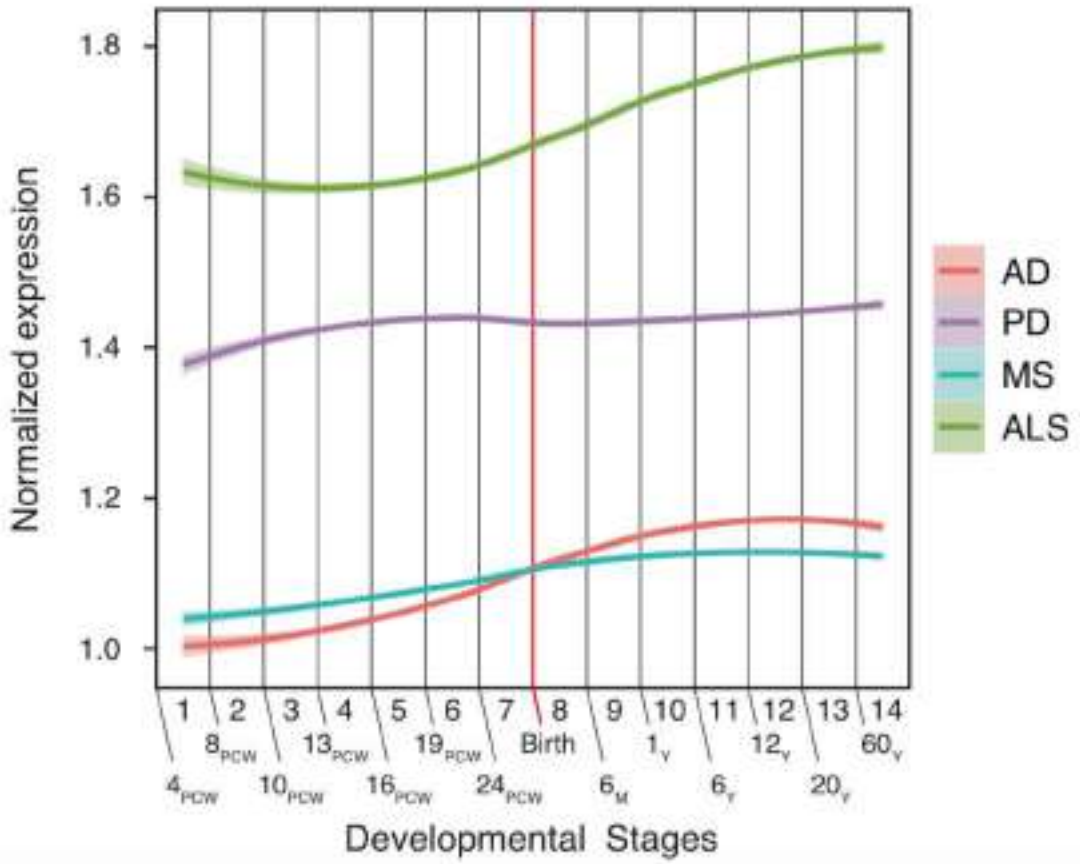
Biological processes enriched for brain diseases

Pathways shared in all brain diseases	Transcriptional regulation, RNA splicing, Neuronal differentiation, Neuronal apoptosis, Synapse, Glutamatergic transmission
Pathways represented in psychiatric disorders	GABAergic transmission, Dopamine, Acetylcholine, Monoamine, Serotonin
Pathways represented in degenerative disorders	Glial differentiation and migration, Myelination, Inflammation and immune response, Aging, Tau, Amyloid beta

Sey et al., *bioRxiv* (2019)

Developmental expression trajectories of brain disease risk genes



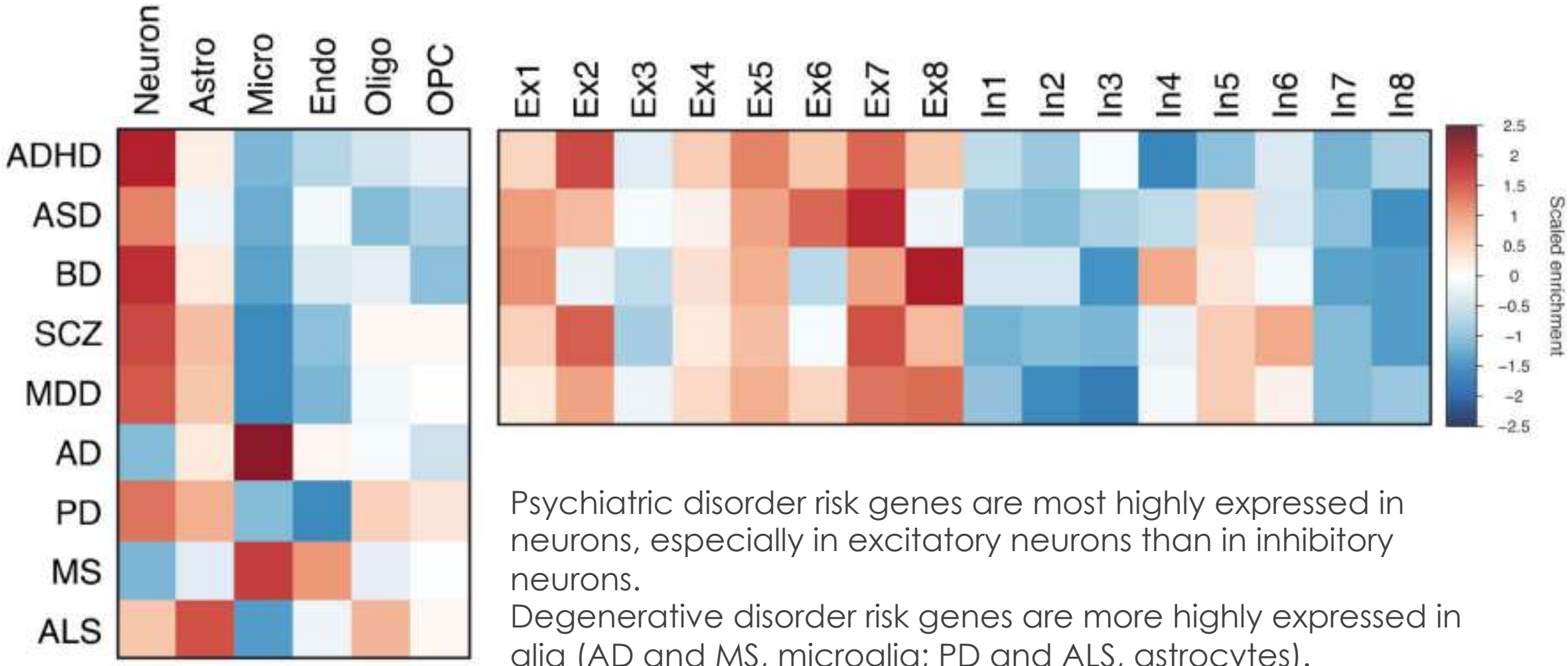


Psychiatric disorder risk genes are highly expressed during mid-gestation.

Degenerative disorder risk genes gradually increase their expression across a lifespan.

Sey et al., *bioRxiv* (2019)

Cellular etiology of brain diseases

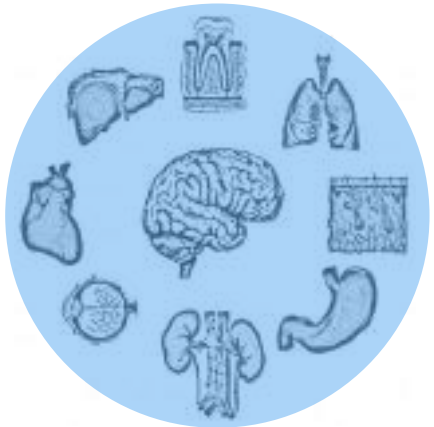


Psychiatric disorder risk genes are most highly expressed in neurons, especially in excitatory neurons than in inhibitory neurons.
Degenerative disorder risk genes are more highly expressed in glia (AD and MS, microglia; PD and ALS, astrocytes).

Sey et al., *bioRxiv* (2019)

Summary

Genome is folded in **3D** space, which is critical to understanding the gene regulation, and linking risk variants to their target genes.



Gene regulatory landscape is highly tissue- and cell-type specific.

Moving the search space from SNPs to genes allows us to identify **cellulo-spatio-temporal dynamics** of brain disorder risk genes.

Acknowledgement

Collaborators & Friends: Dan Geschwind, Schahram Akbarian, Kristen Brennand, Jason Stein
Harper Fauni, Xander Arguello

Funding: NIMH New Innovator Award, NIMH R00, SFARI/SPARK,
NARSAD Young Investigator Award