Deep learning model for genetic variants and omics data

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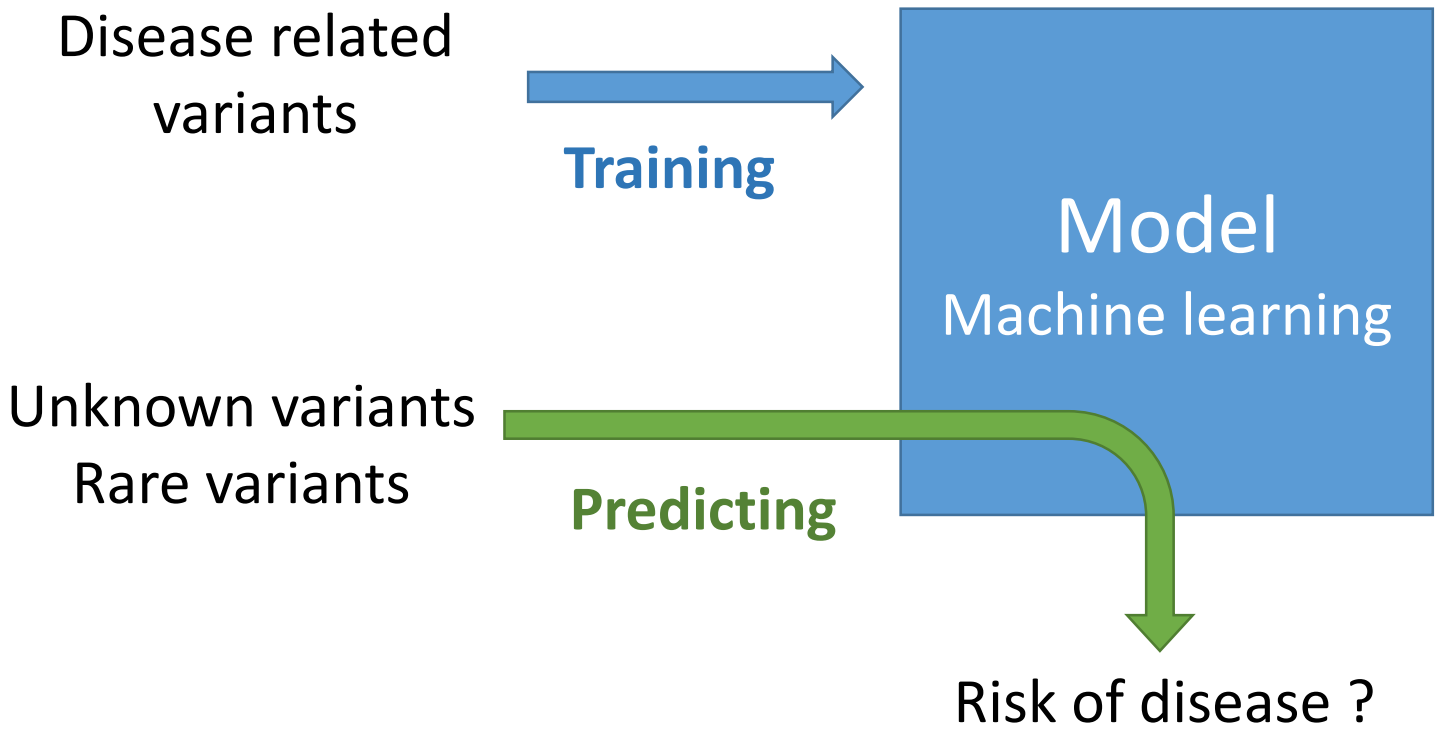
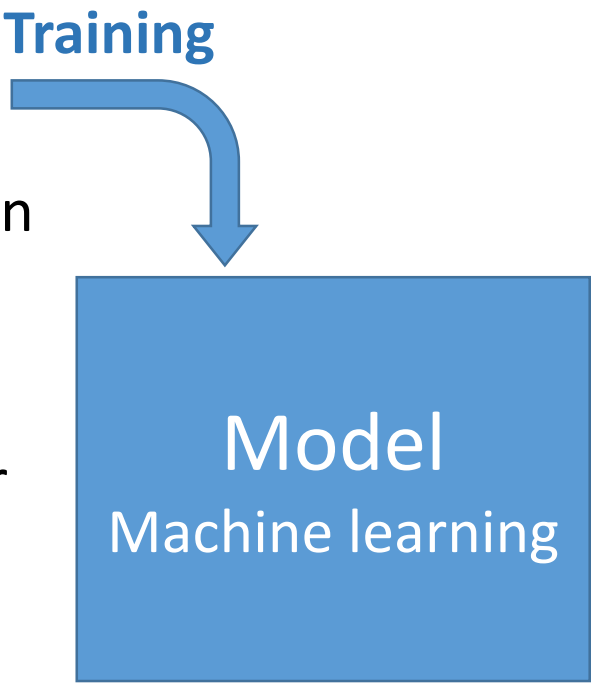
Goal: Disease = f(Variant)



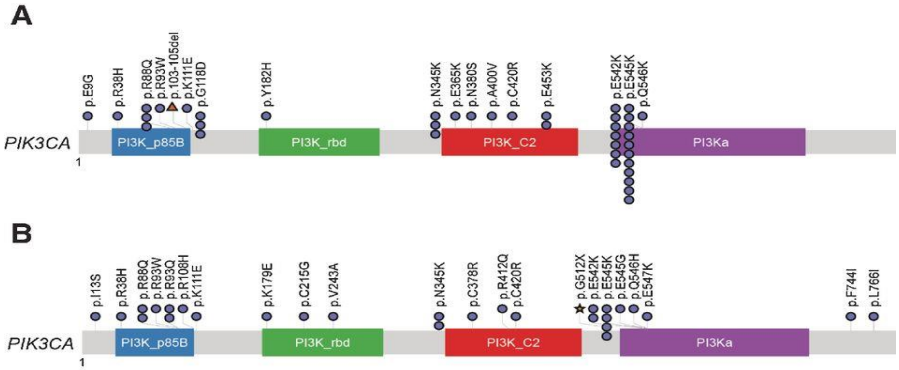
Machine learning for causal variants

1. What to train
    1. True variants
    2. False variants
    3. Feature extraction
2. How to train
    1. Model
    2. Hyper-parameter optimization
3. Validation
    1. Cross-validation
    2. Biologically



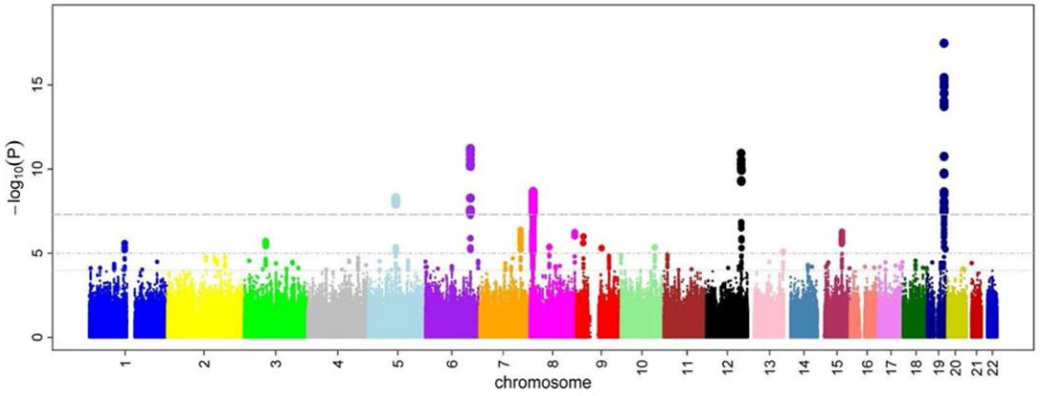
The true set: Disease related variants

Cancer recurrent mutation → cancer



LI, Xiangchun, et al. Distinct subtypes of gastric cancer defined by molecular characterization include novel mutational signatures with prognostic capability. *Cancer research*, 2016.

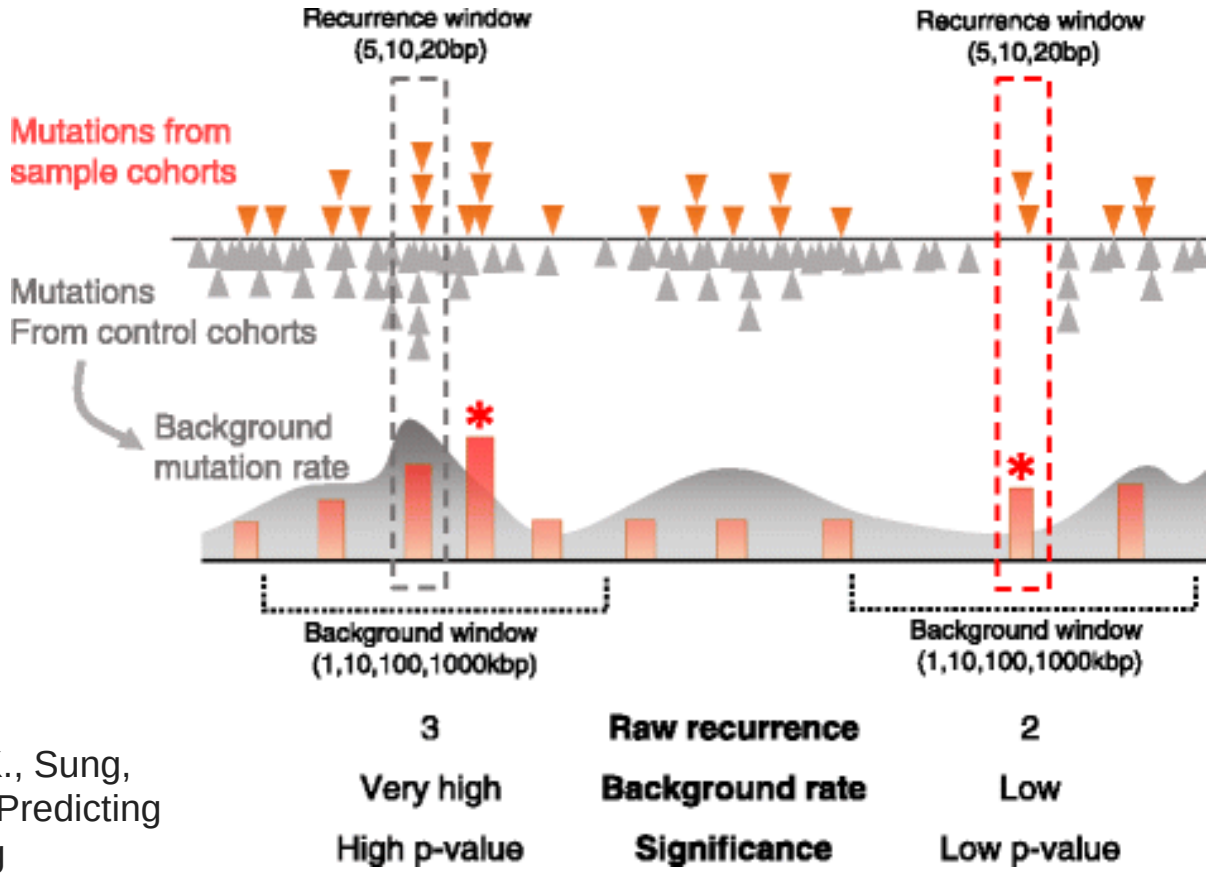
GWAS snps → common diseases



IKRAM, M. Kamran, et al. Four novel Loci (19q13, 6q24, 12q24, and 5q14) influence the microcirculation in vivo. *PLoS genetics*, 2010, 6.10: e1001184.

Recurrent mutations: Cause of cancer?

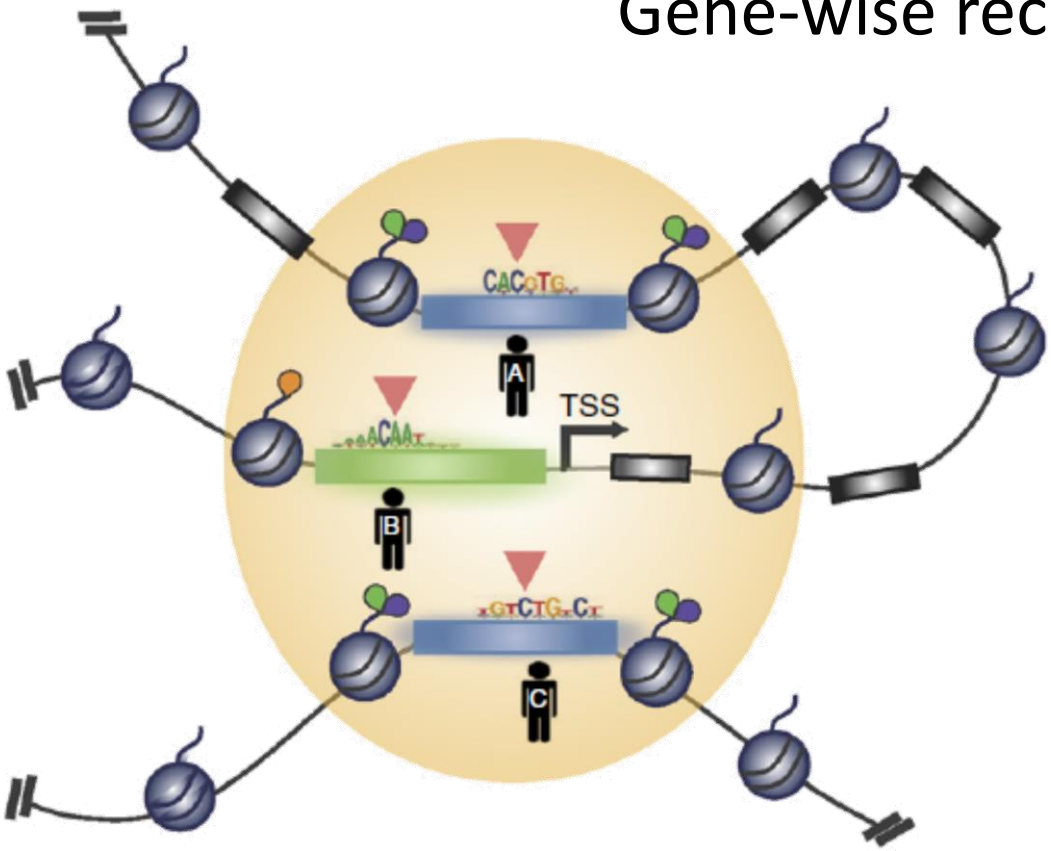
Site-specific recurrent mutations



Yang, W., Bang, H., Jang, K., Sung, M. K., & Choi, J. K. (2016). Predicting the recurrence of noncoding regulatory mutations in cancer. *BMC bioinformatics*, *17*(1), 492.

Recurrent mutations: Cause of cancer?

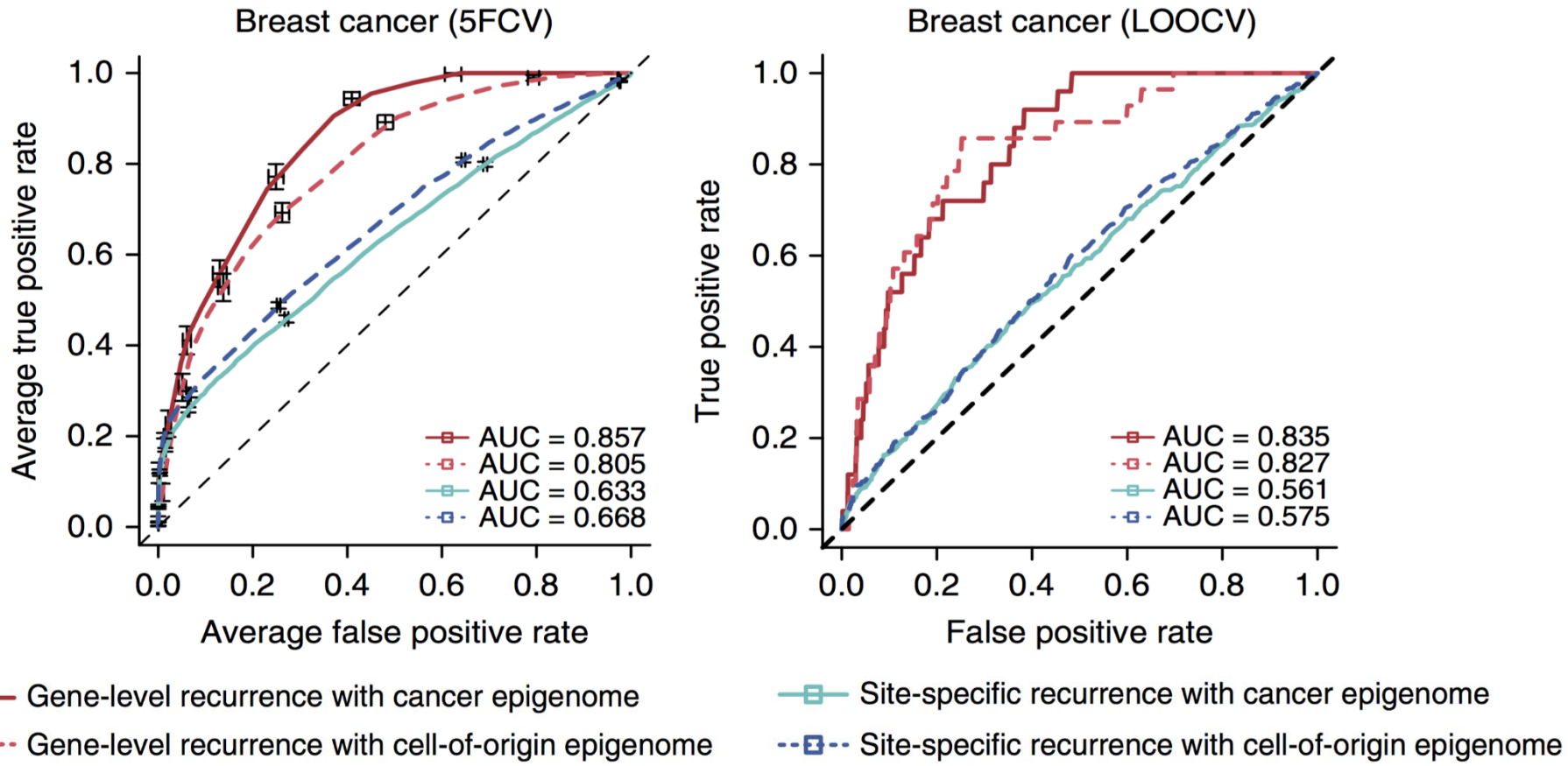
Gene-wise recurrent mutations



Kim, K., Jang, K., Yang, W., Choi, E. Y., Park, S. M., Bae, M., ... & Choi, J. K. (2016). Chromatin structure–based prediction of recurrent noncoding mutations in cancer. *Nature genetics*, *48*(11), 1321.

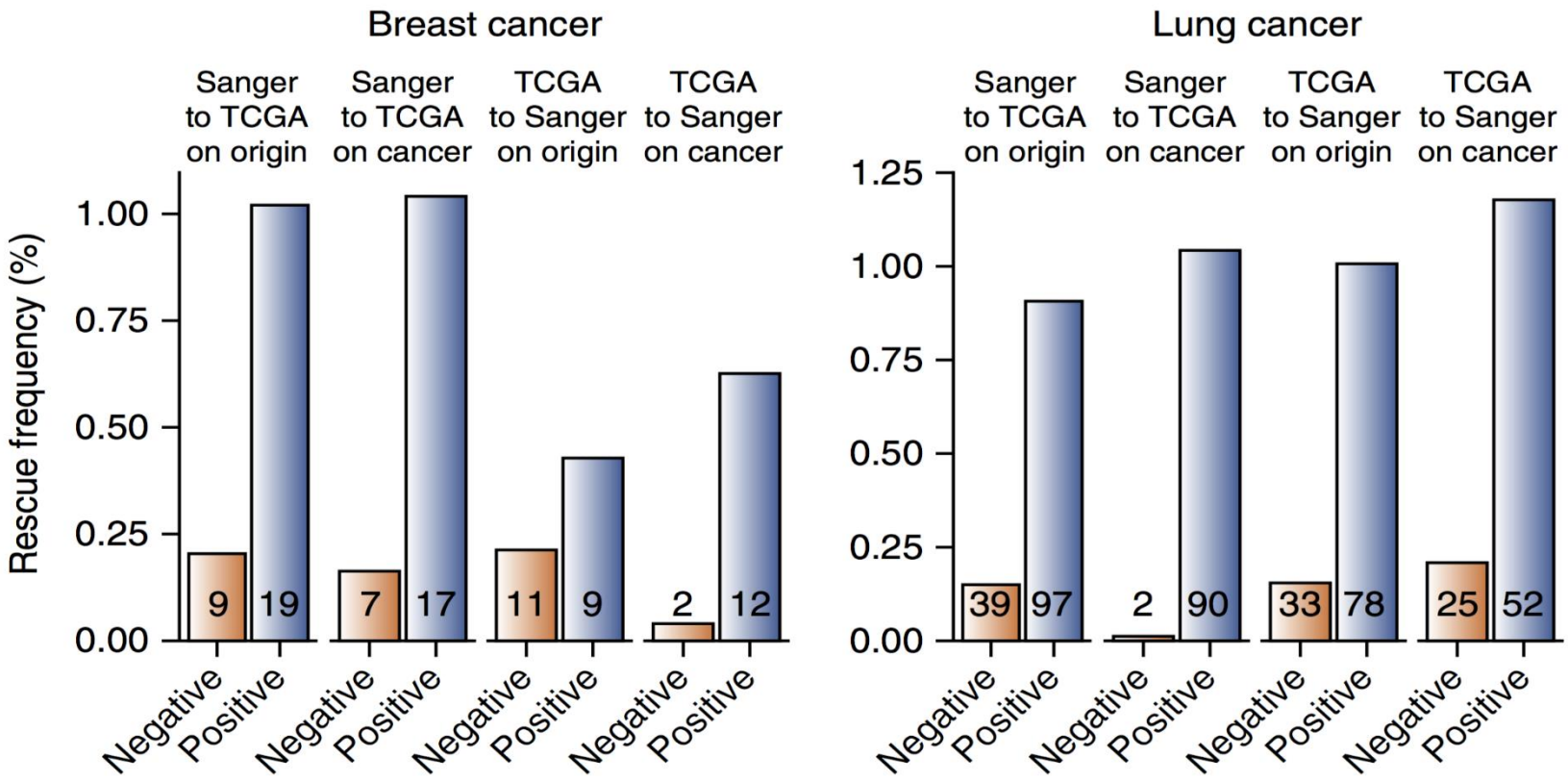
Recurrent mutations may be causal

Performance of model

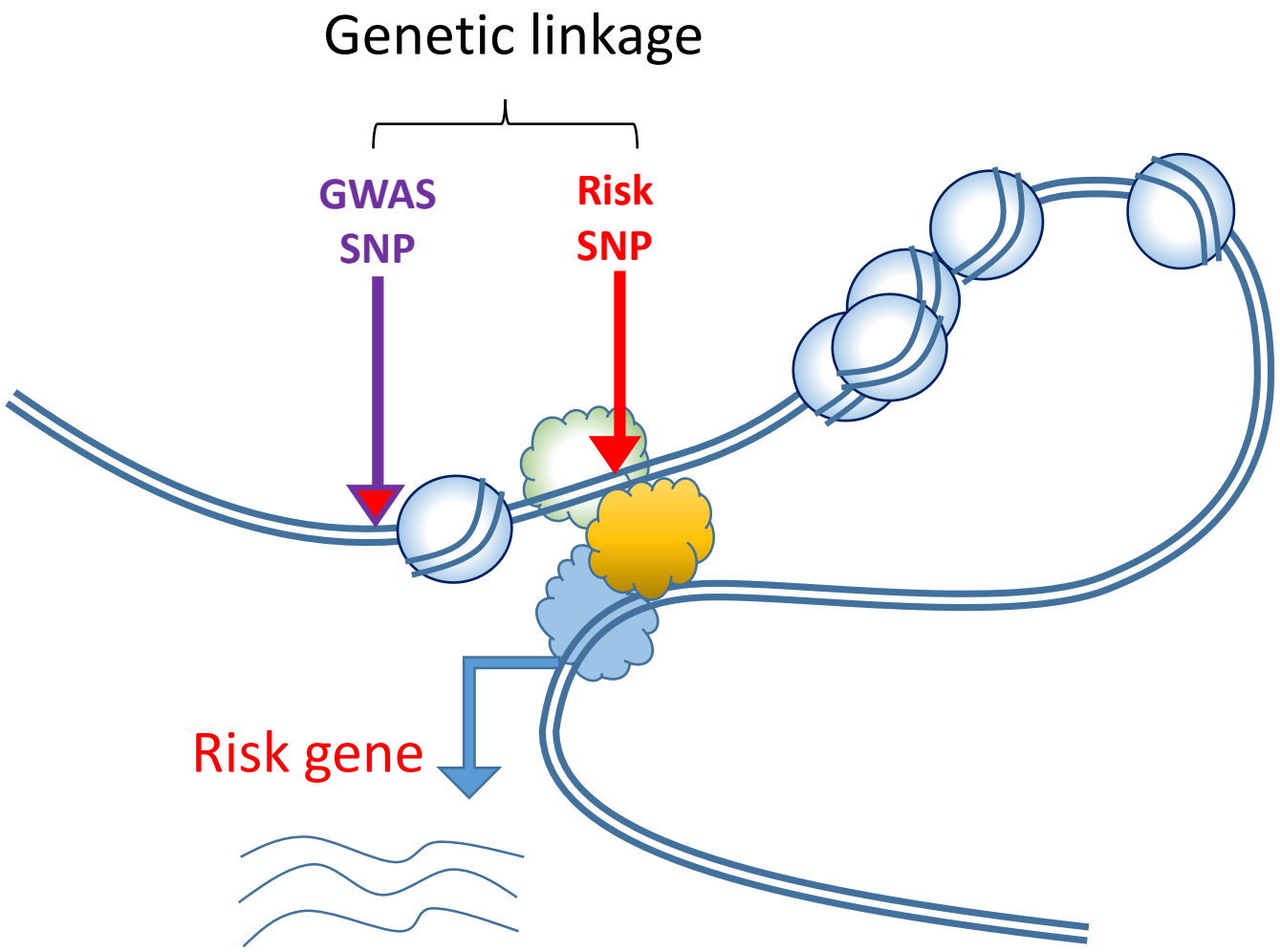


Verification in new data

Prediction of model

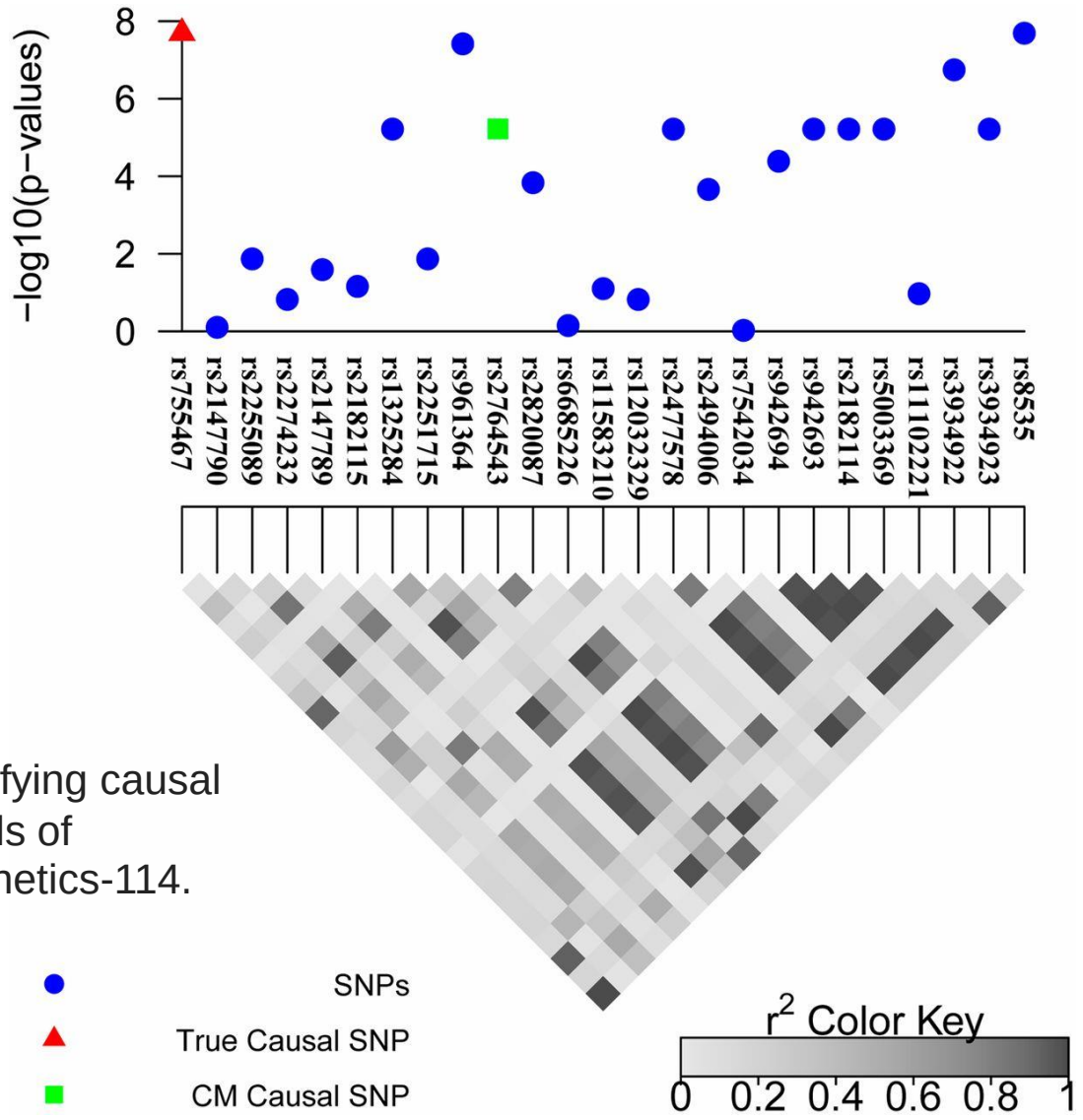


GWAS SNPs: Cause of disease?



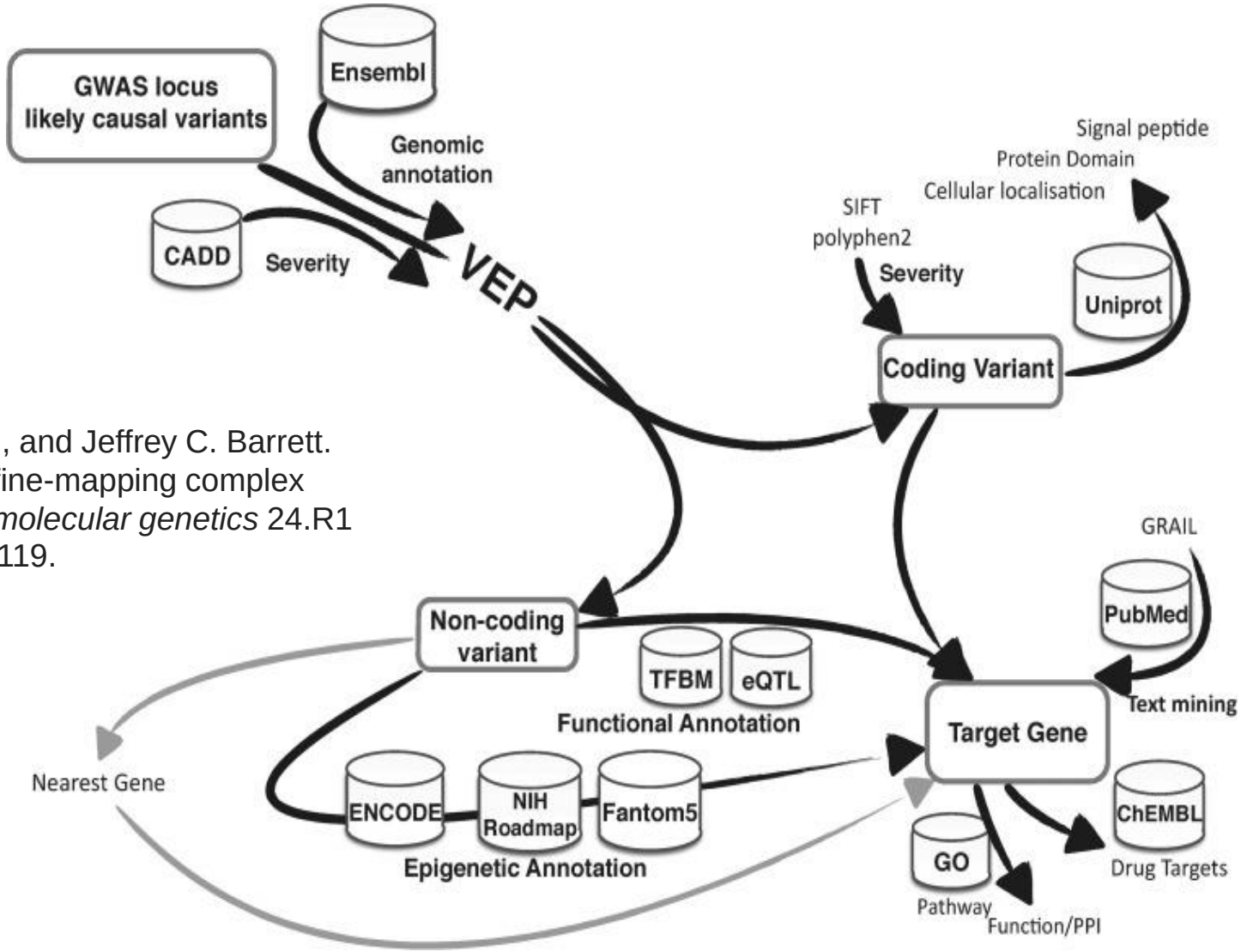
GWAS fine mapping

Statistical



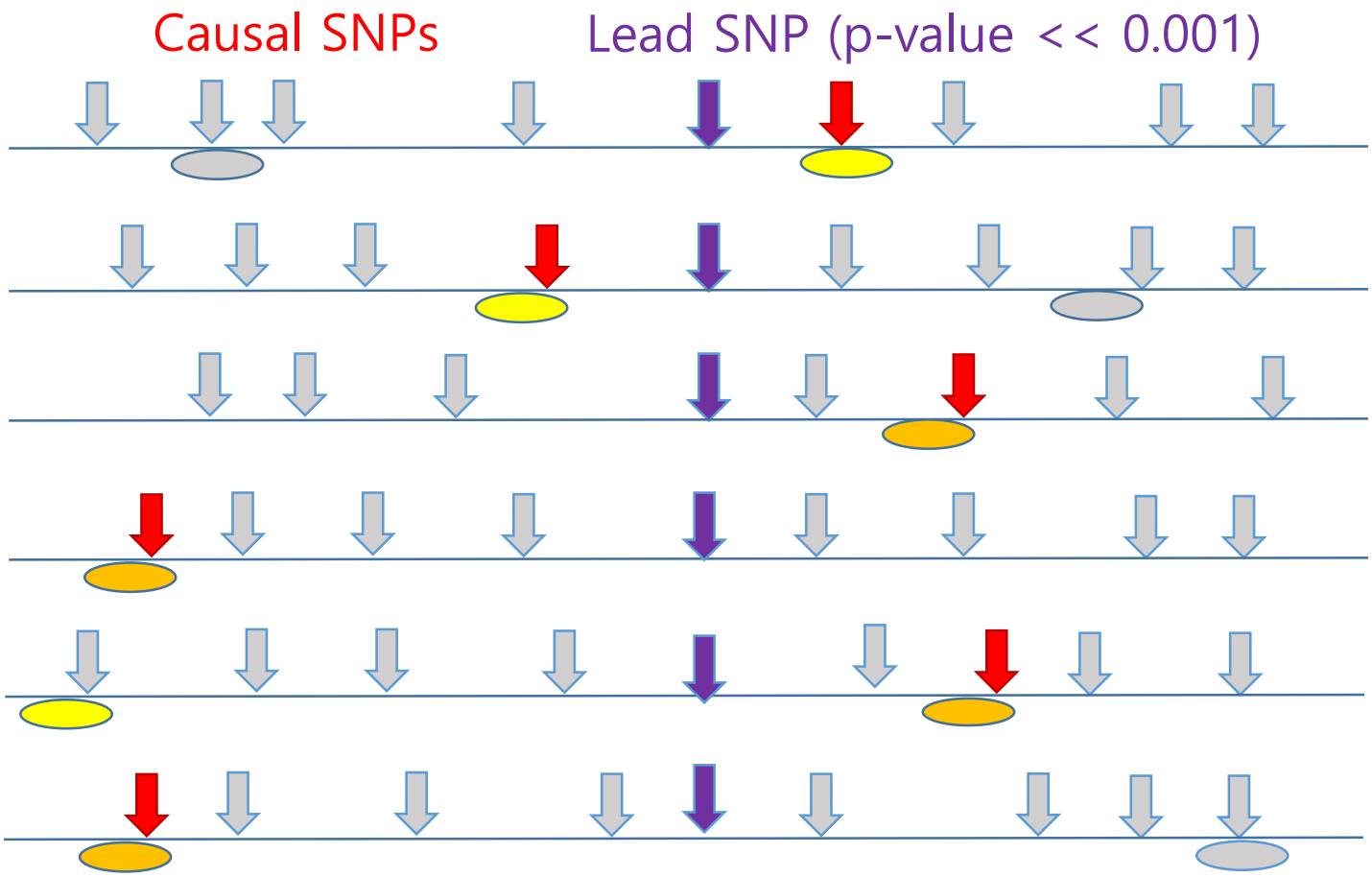
Hormozdiari, Farhad, et al. "Identifying causal variants at loci with multiple signals of association." *Genetics* (2014): genetics-114.

Functional fine mapping



Spain, Sarah L., and Jeffrey C. Barrett. "Strategies for fine-mapping complex traits." *Human molecular genetics* 24.R1 (2015): R111-R119.

Causal Variant Prediction by CNN-based Fine Mapping

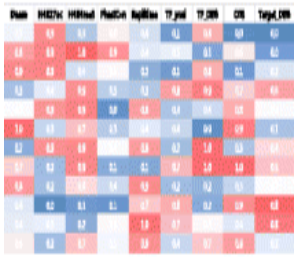


Common feature?

What to train: The features

Disease related variants

Features



Training

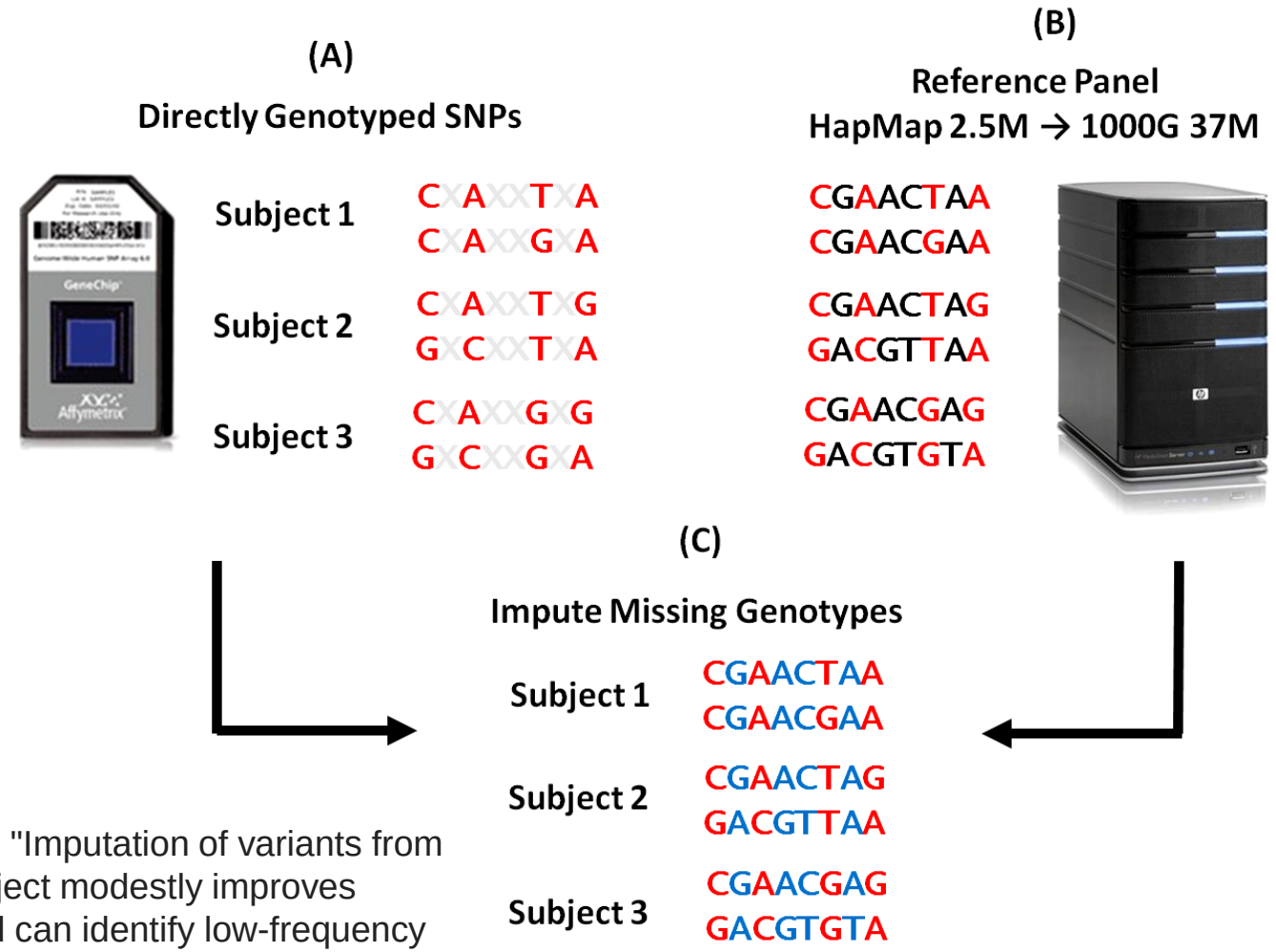
Model

Machine learning

SNPs to features

	Number of associations		
Disease	**ADHD**	**ASD**	**BPD**
Significant tag SNPs (P < 5x10-4)	642	943	1,424
Disease	**MDD**	**SCZ**	**RA**
Significant tag SNPs (P < 5x10-4)	832	601	435
Disease	**SLE**	**CD**	**UC**
Significant tag SNPs (P < 5x10-4)	849	431	383

Imputation with 1000 genomes



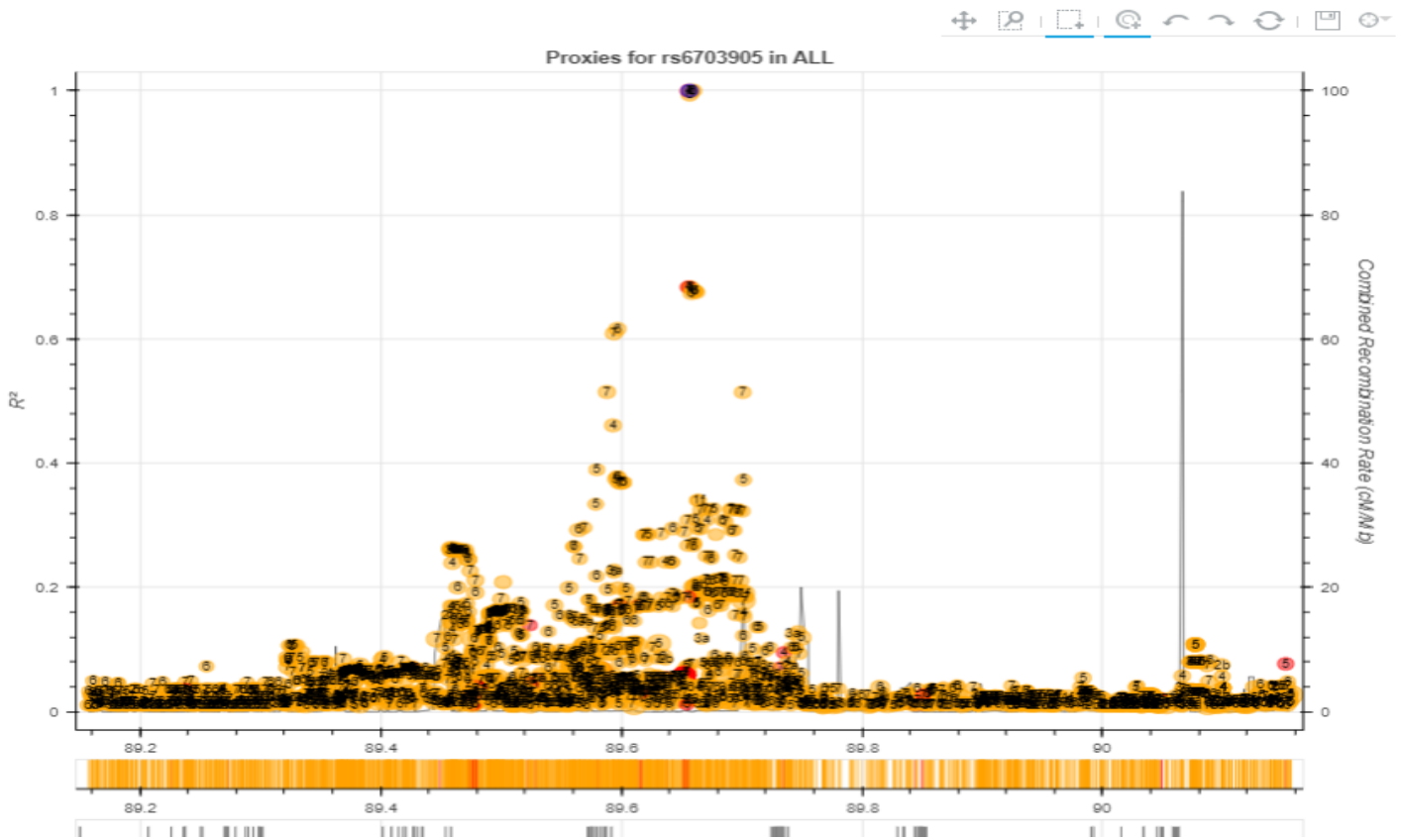
Wood, Andrew R., et al. "Imputation of variants from the 1000 Genomes Project modestly improves known associations and can identify low-frequency variant-phenotype associations undetected by HapMap based imputation." *PLoS One* 8.5 (2013): e64343.

LD proxy calculation

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Epidemiology & Genetics

Home | LDassoc | LDhap | LDmatrix | LDpair | **LDproxy** | SNPchip | SNPclip | Help

rs6703905 | All Populations | R^2 | D' | Calculate



LD proxy calculation

Proxy Variants

Show 10 ▼ entries

Search:

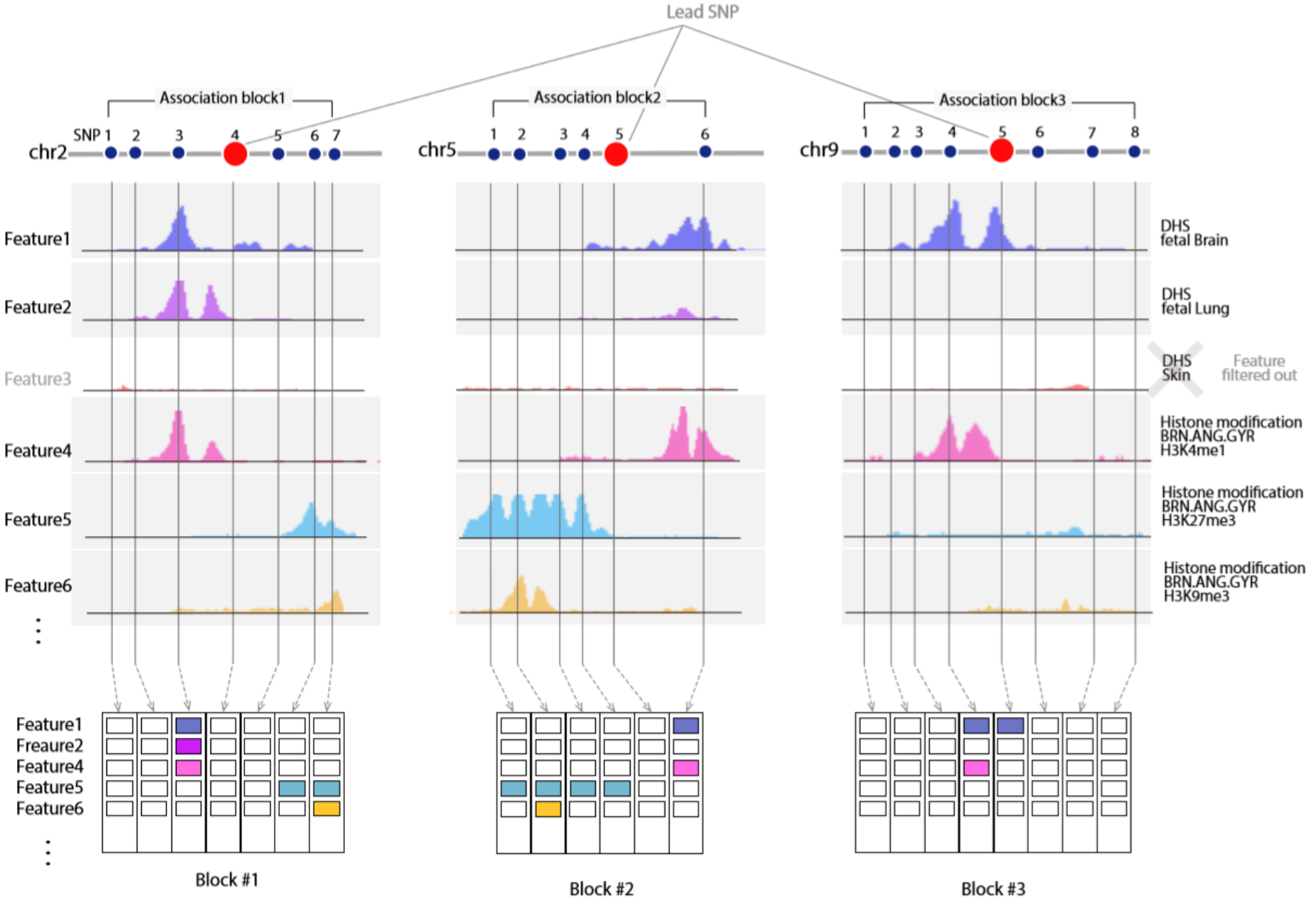
RS Number	Chr	Position (GRCh37)	Alleles	MAF	Distance	D'	R^2	Correlated Alleles	RegulomeDB	HaploReg	Functional Class
rs12077011	1	89659652	(G/A)	0.1072	2903	1.0	1.0	C=G,T=A	6		NA
rs12069631	1	89657754	(A/C)	0.1072	1005	1.0	1.0	C=A,T=C	6		NA
rs1410871	1	89655994	(C/T)	0.1072	755	1.0	1.0	C=C,T=T	4		synonymous
rs6667970	1	89656861	(A/G)	0.1078	112	1.0	0.9938	C=A,T=G	6		NA
rs1831240	1	89655783	(T/C)	0.0759	966	1.0	0.6836	C=T,T=C	4		missense
rs12084701	1	89657679	(C/A)	0.0759	930	1.0	0.6836	C=C,T=A	6		NA
rs1324333	1	89656534	(C/T)	0.0759	215	1.0	0.6836	C=C,T=T	7		NA
rs1324331	1	89661163	(A/G)	0.0761	4414	0.9941	0.6775	C=A,T=G	5		NA
rs1324332	1	89660833	(T/A)	0.0761	4084	0.9941	0.6775	C=T,T=A	6		NA
rs7537509	1	89660405	(T/A)	0.0761	3656	0.9941	0.6775	C=T,T=A	6		NA
RS Results	Chr	Position (GRCh37)	Alleles	MAF	Distance	D'	R^2	Correlated Alleles	RegulomeDB	HaploReg	Functional Class

Showing 1 to 10 of 3,033 entries

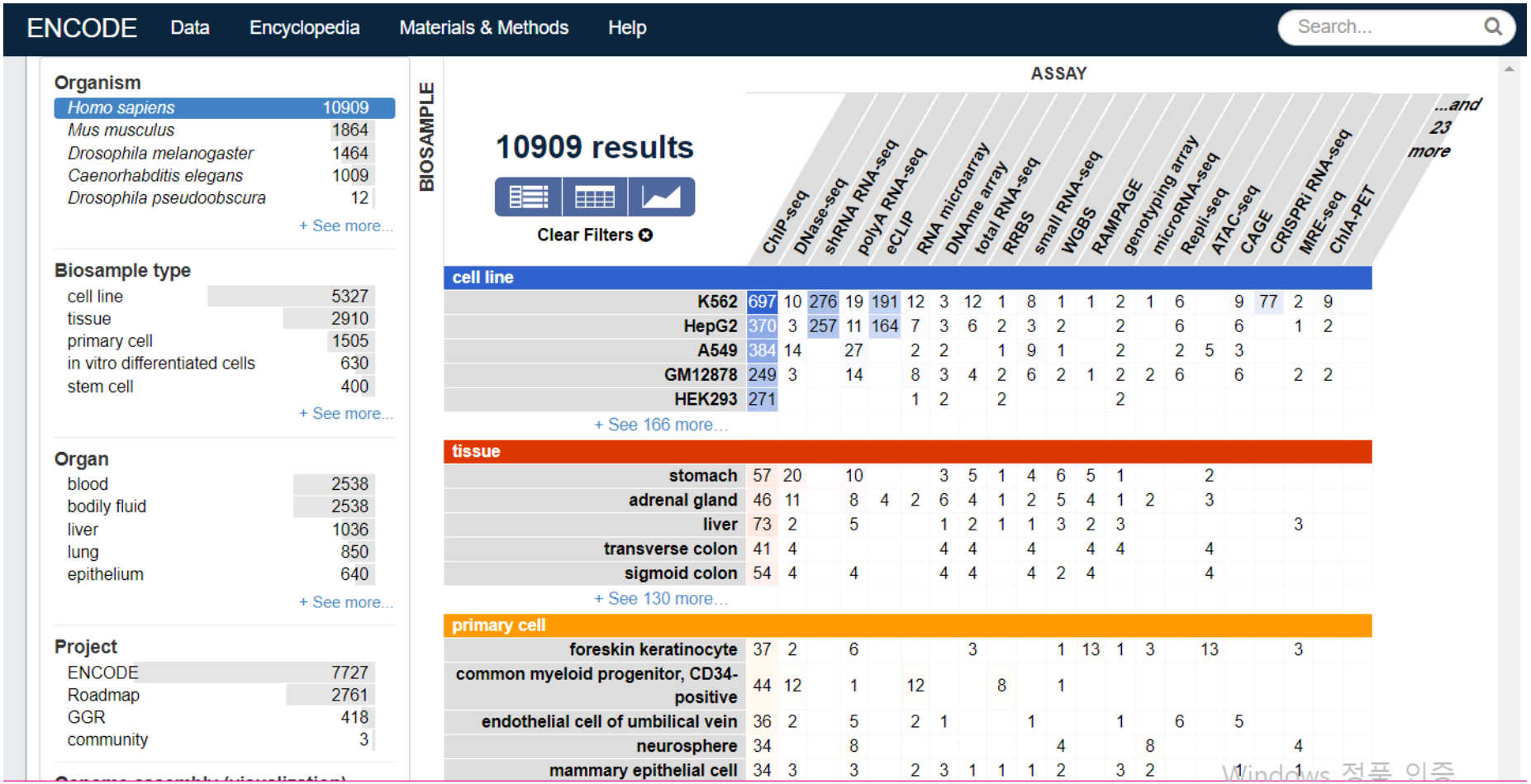
Previous 1 2 3 4 5 … 304 Next

Download all proxy variants

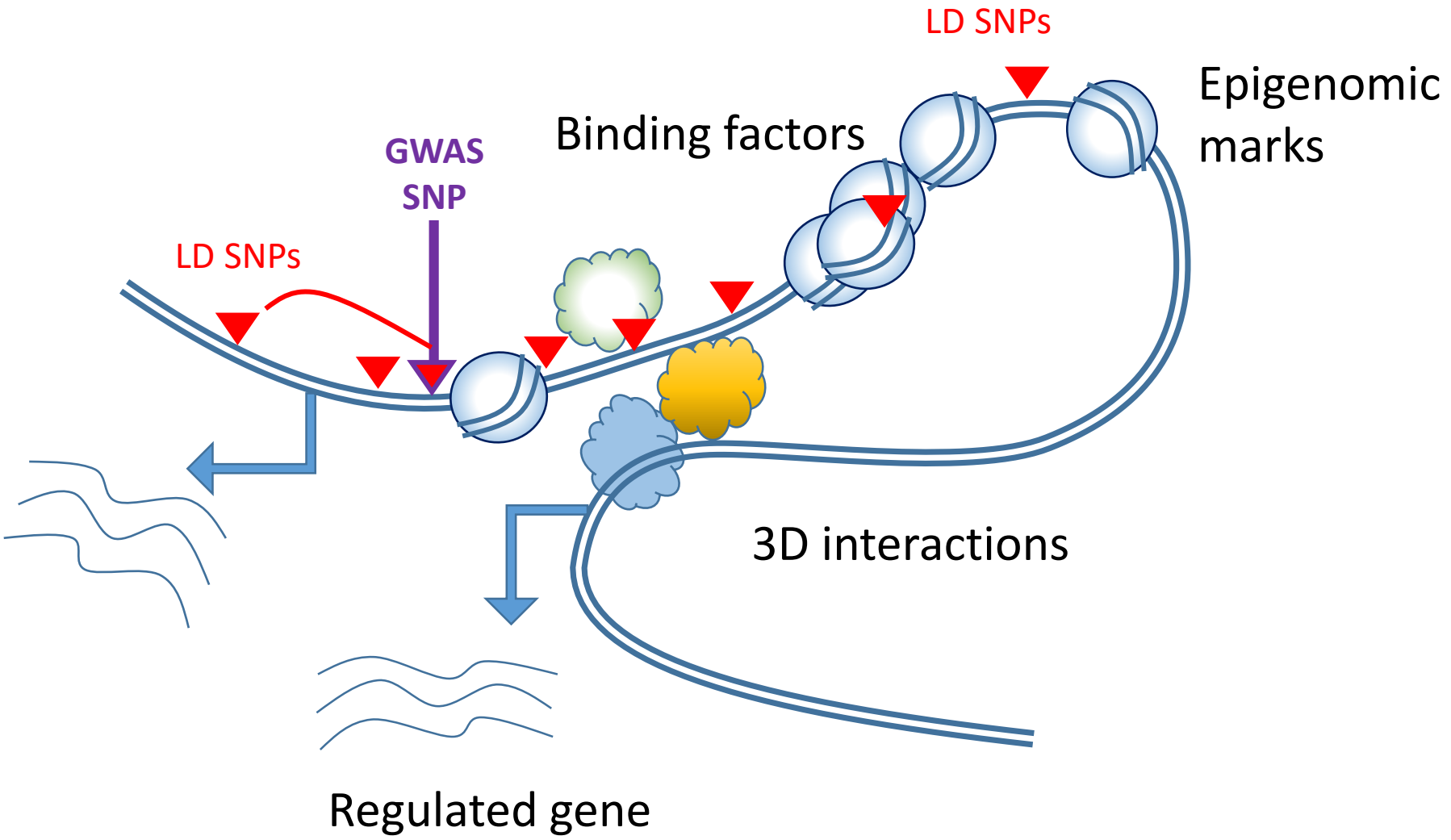
SNPs to features



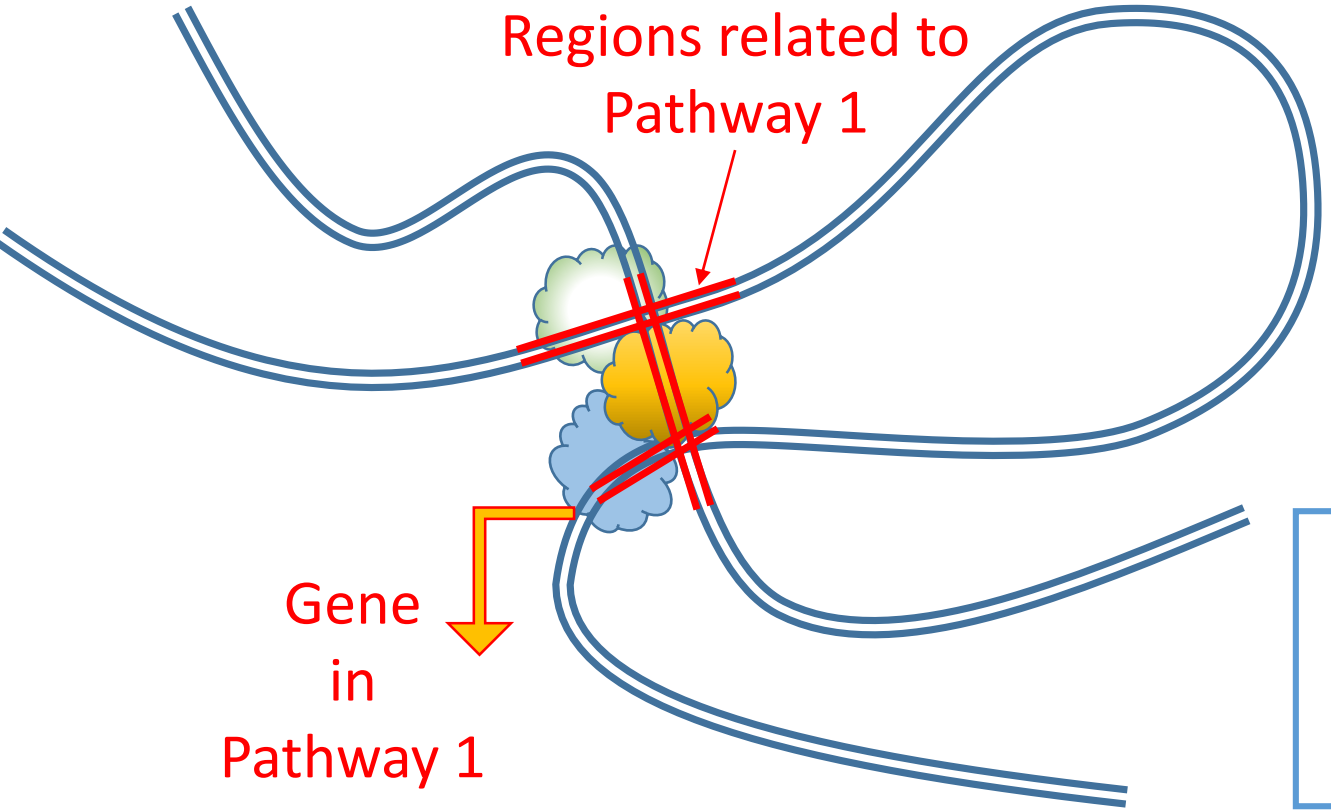
Epigenetic data



Regulatory effect of variants



Pathway data



3D structure data

chr | pos | gene_name

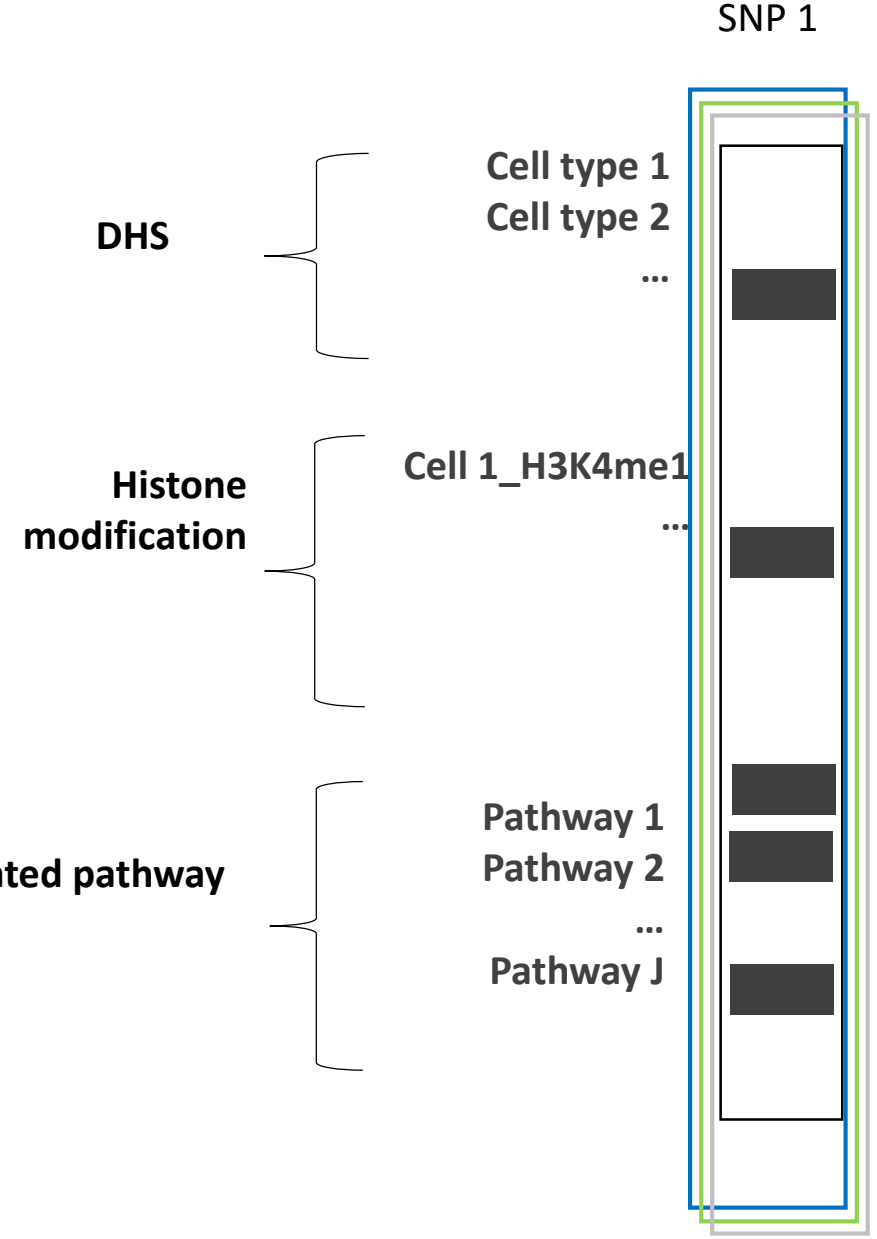
Join by gene

Pathway data

gene_name | pathway

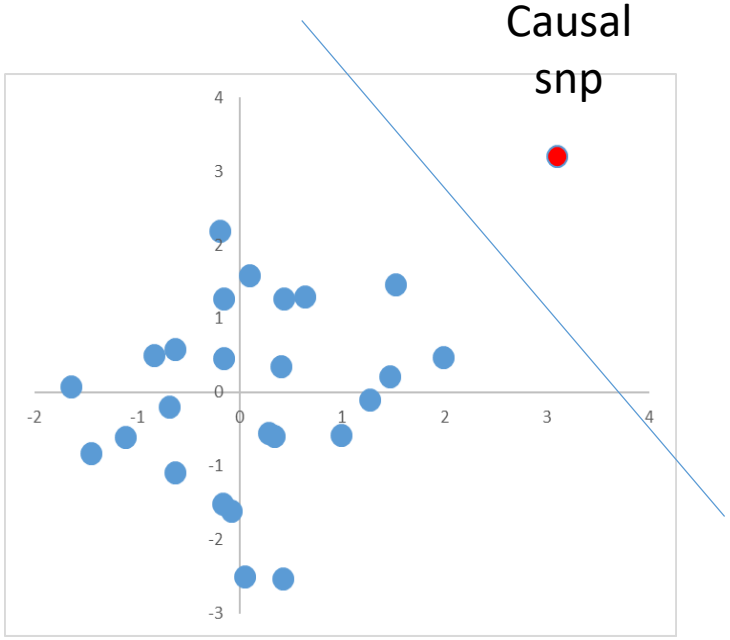
Data merging

Binding factor data?

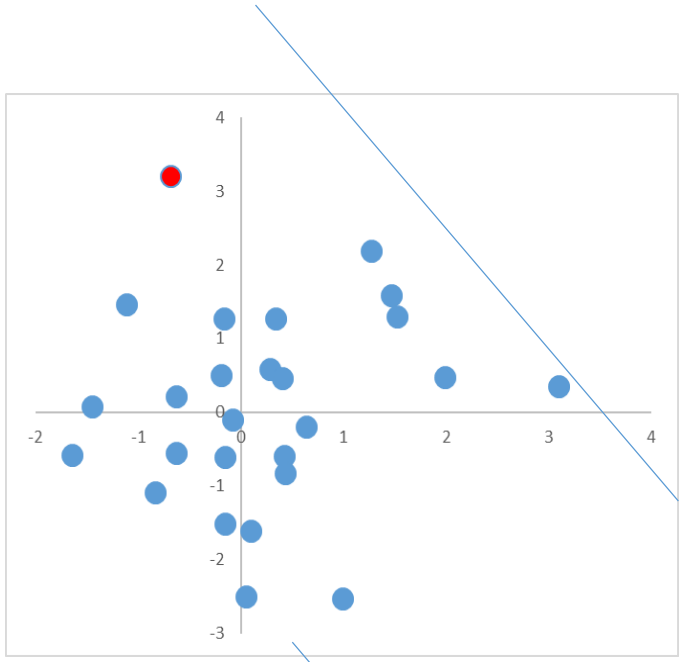


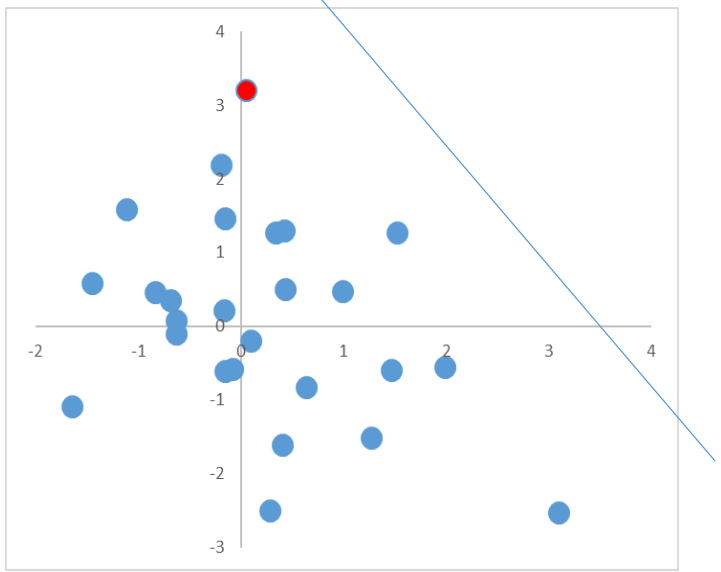
Make false set

maybe Causal snp

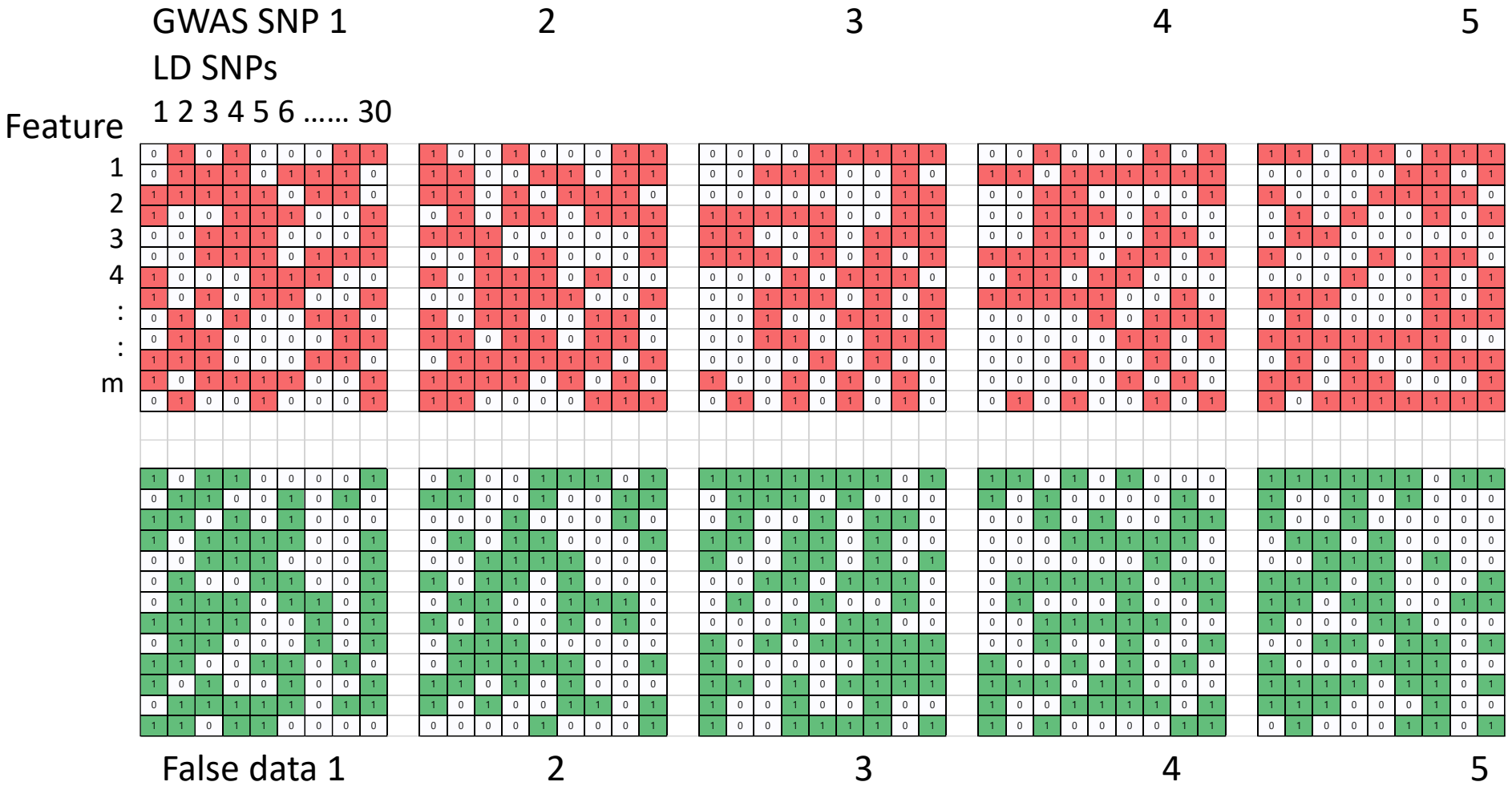


Shuffle x and y

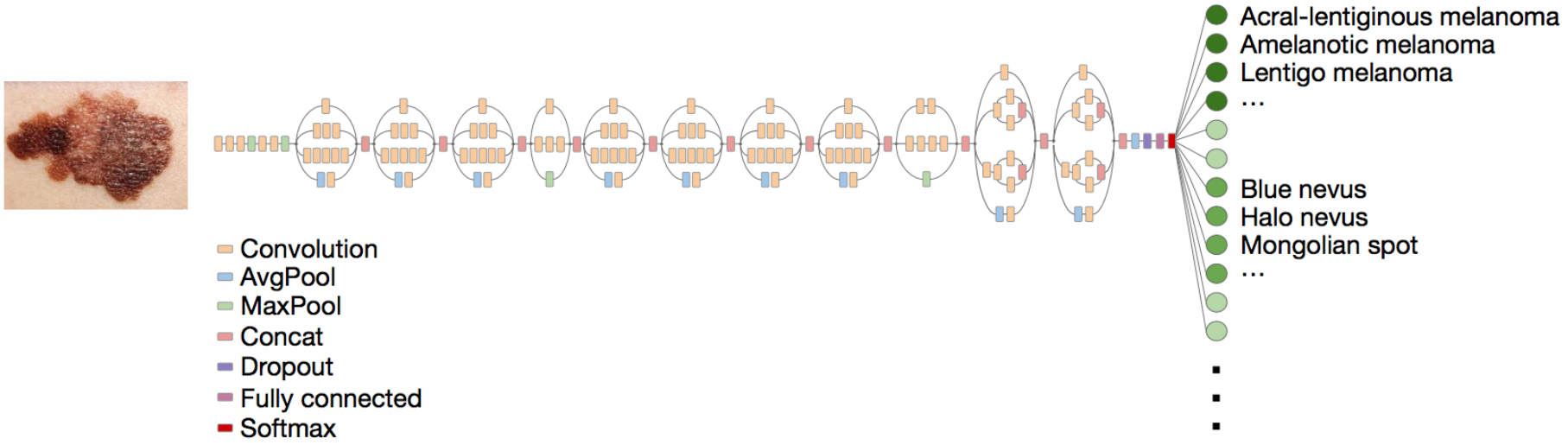




Datasets to train

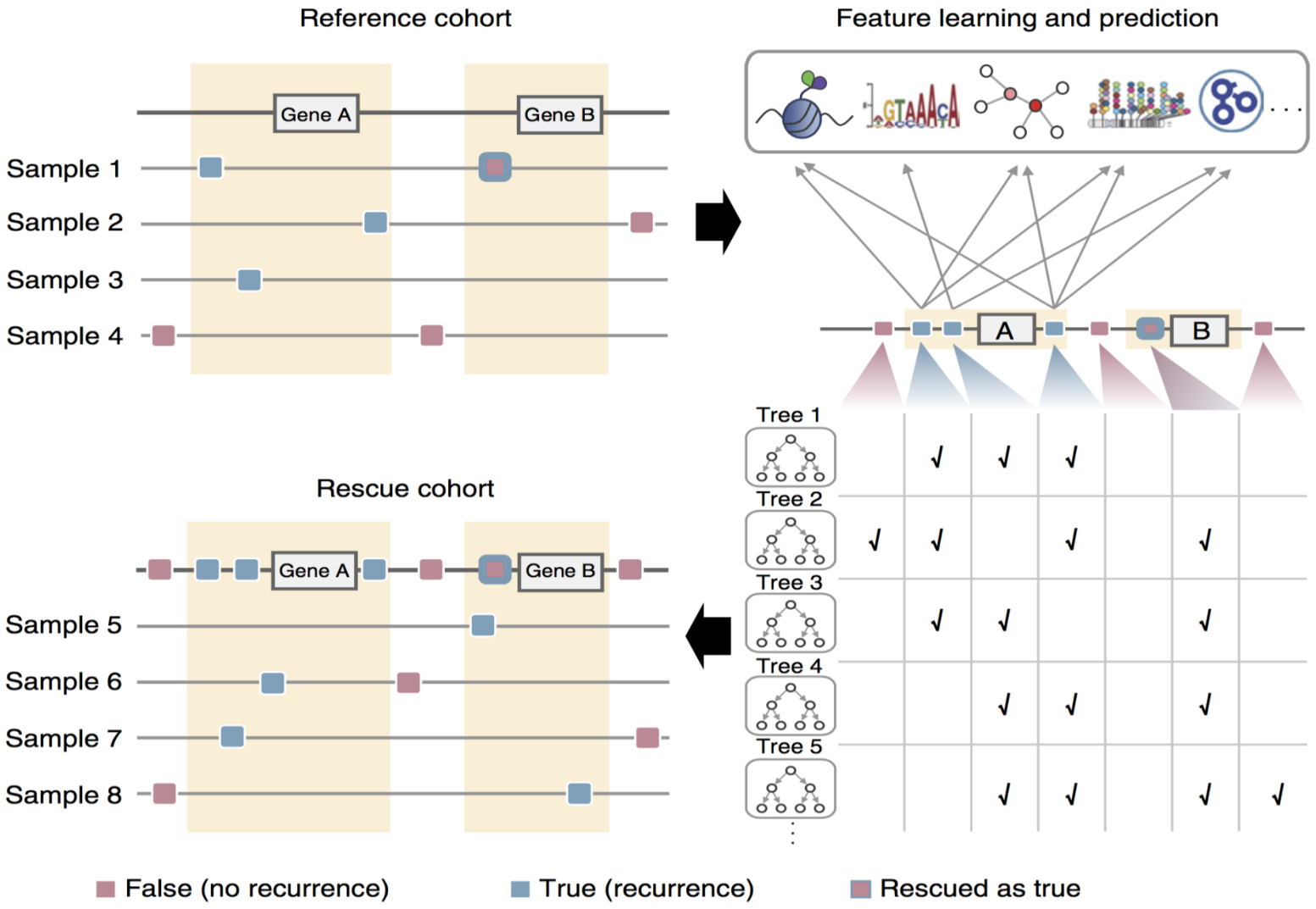


How to train: The model

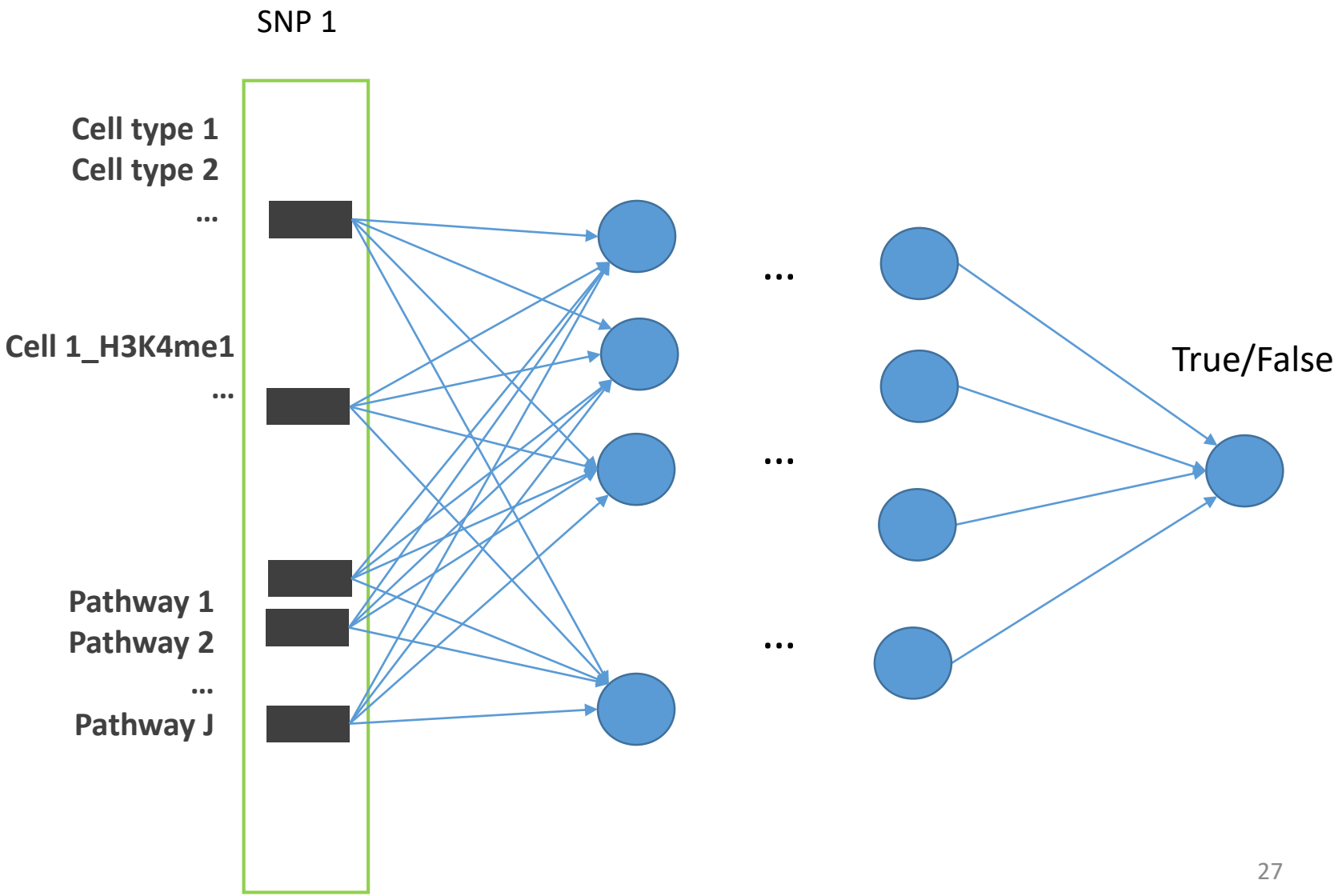


Esteva, Andre, et al. "Dermatologist-level classification of skin cancer with deep neural networks." *Nature* 542.7639 (2017): 115.

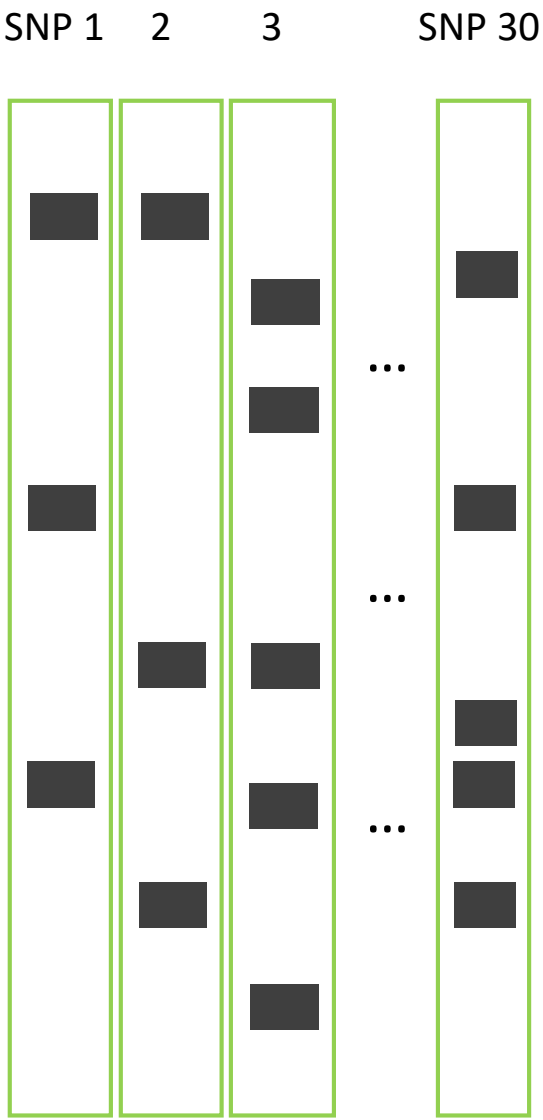
Machine Learning for Recurrent Mutations



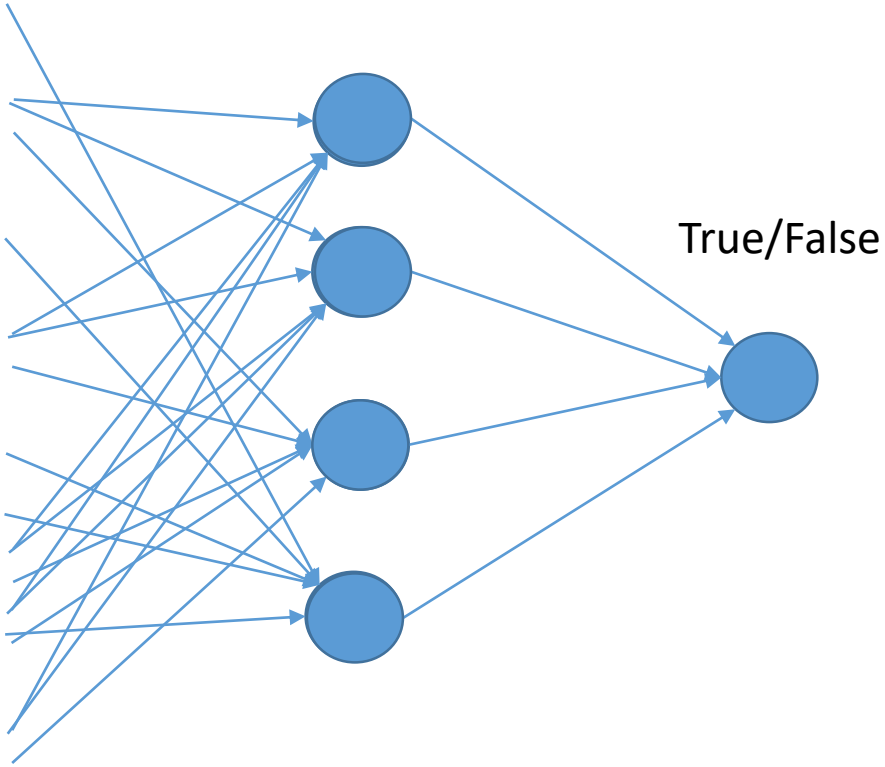
Classify single SNP



Classify group of SNP

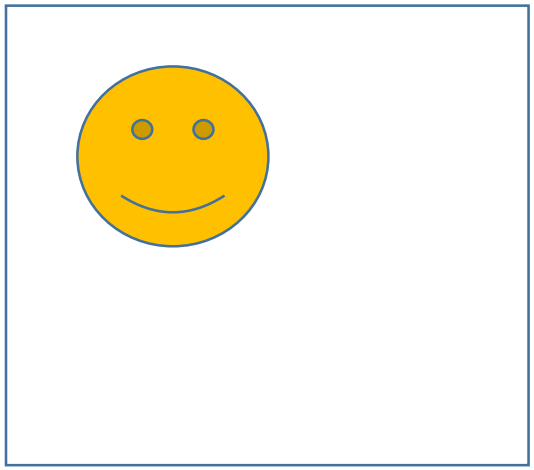


?

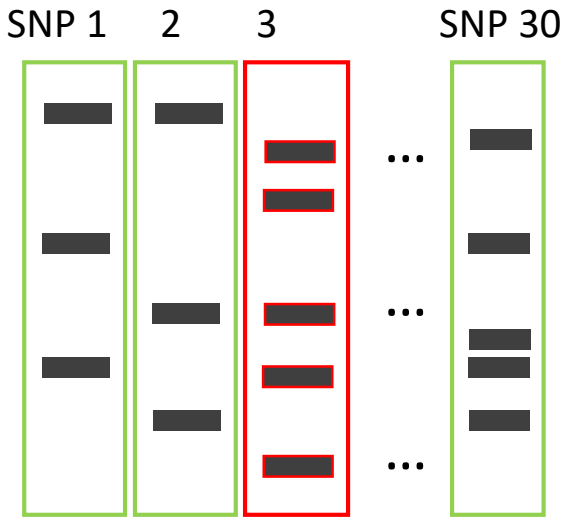


Use of convolutional neural network

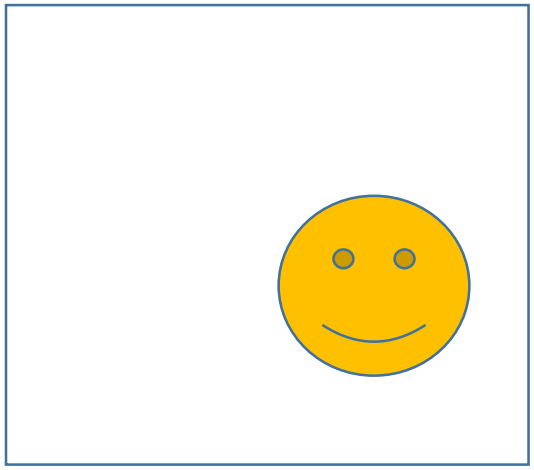
smile



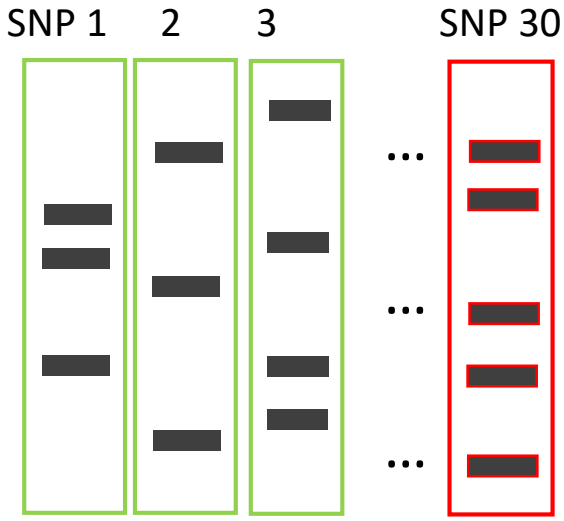
Find same pattern of image



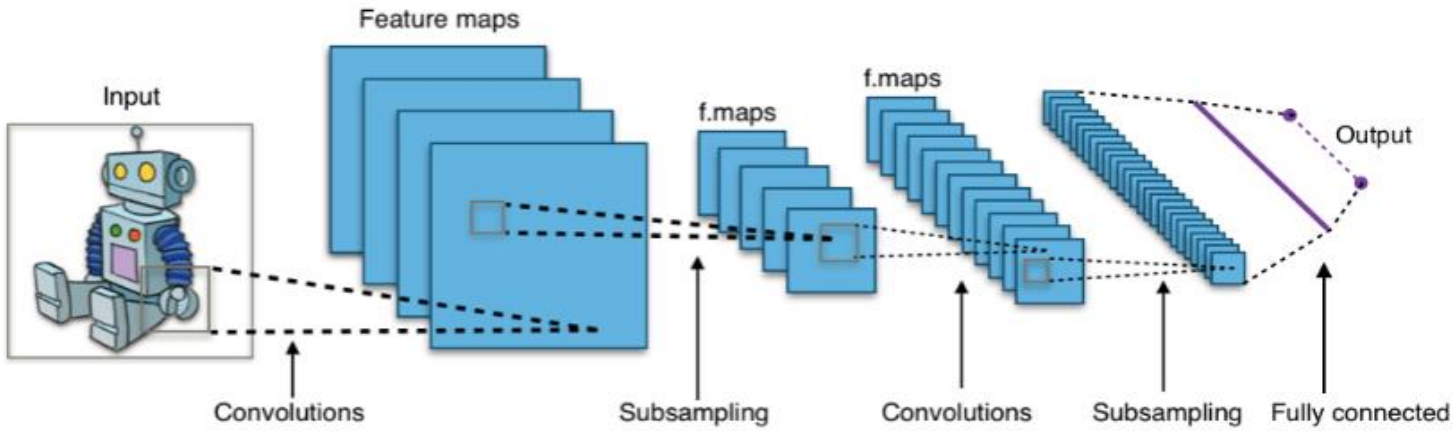
smile



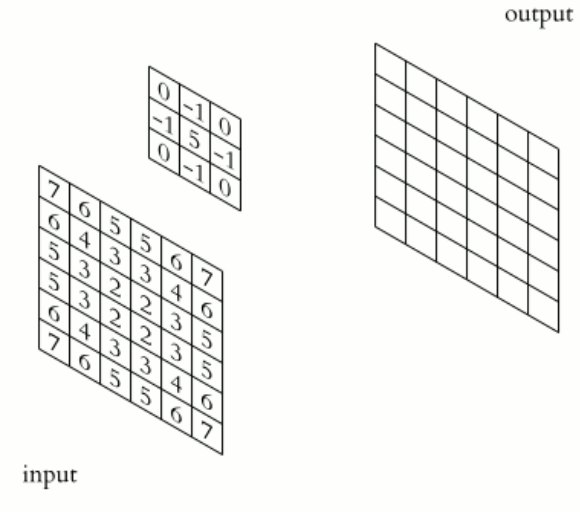
Not sensitive to position



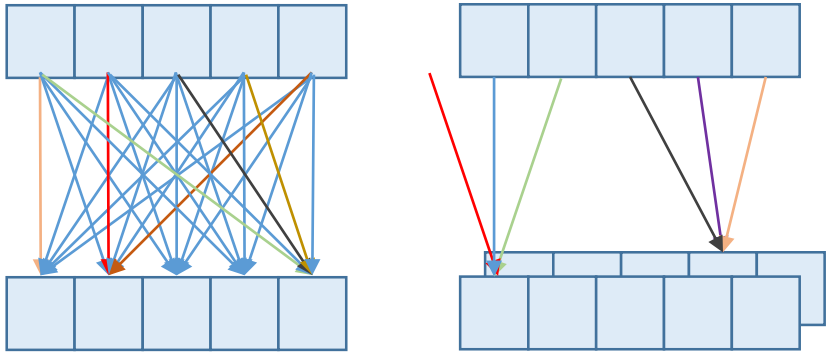
Convolutional neural network



Convolution



Fully-connected vs convolutional layer

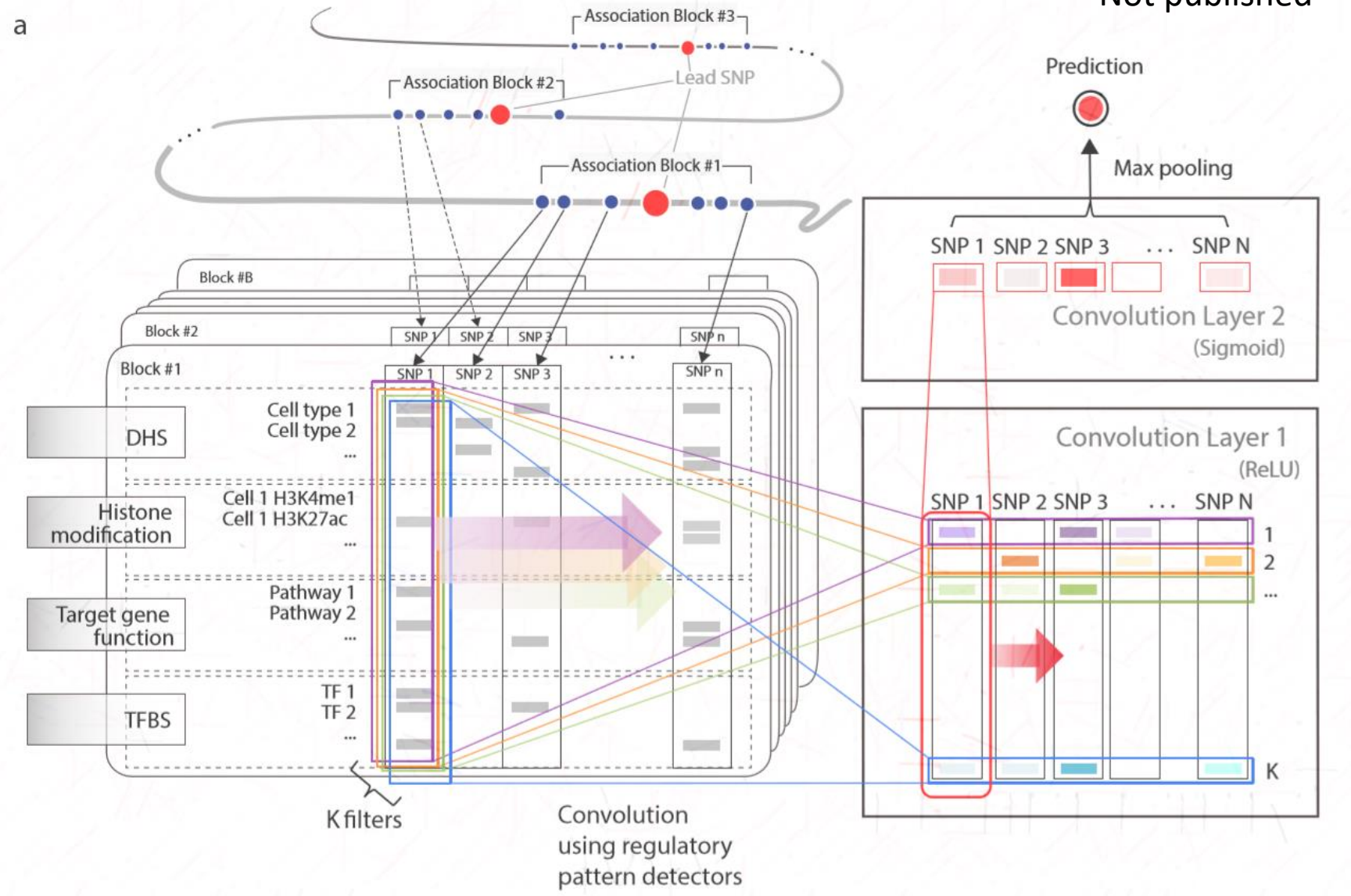


Weight of all links are different (parameters to learn)

Num of weights
= num of kernels
* size of kernel

Model using CNN

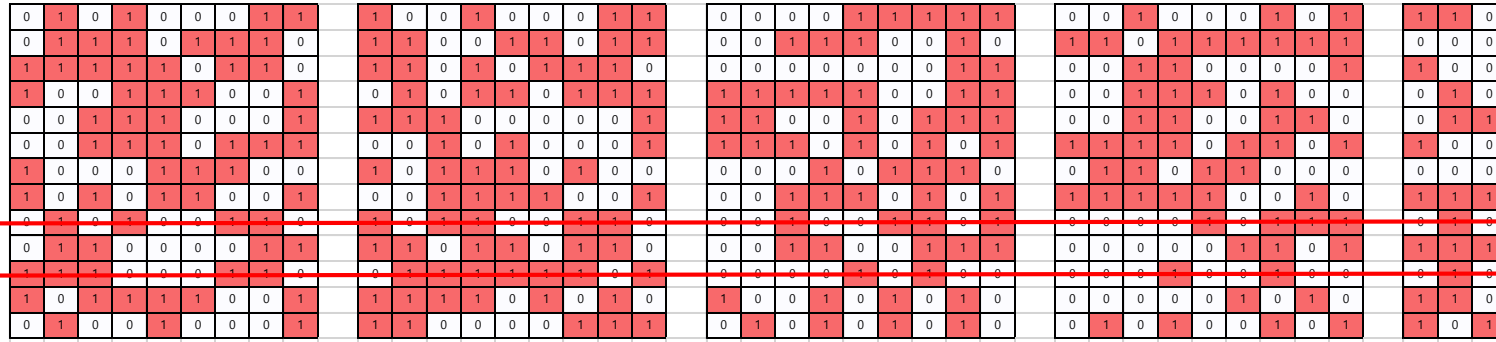
Not published



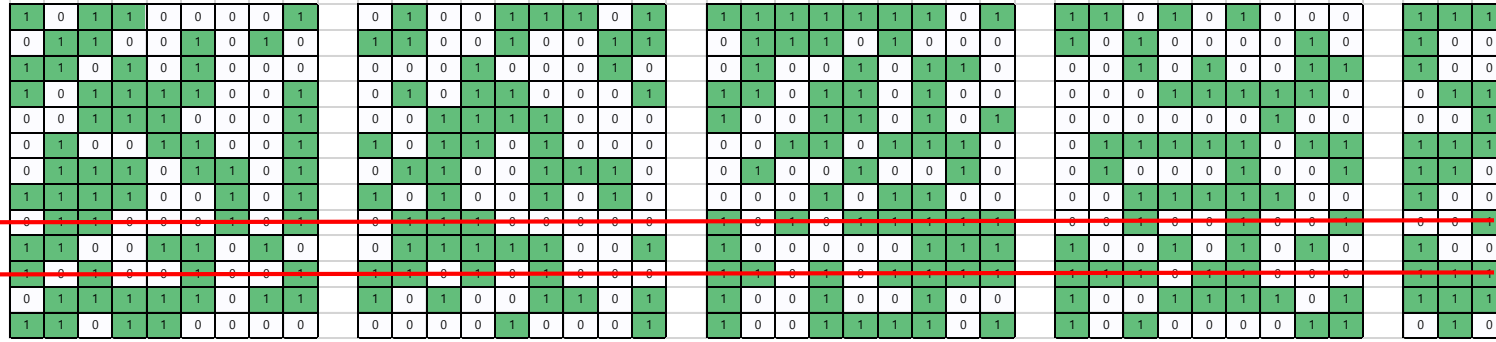
Feature reduction

Small number of samples ~ 500

Too many and sparse features

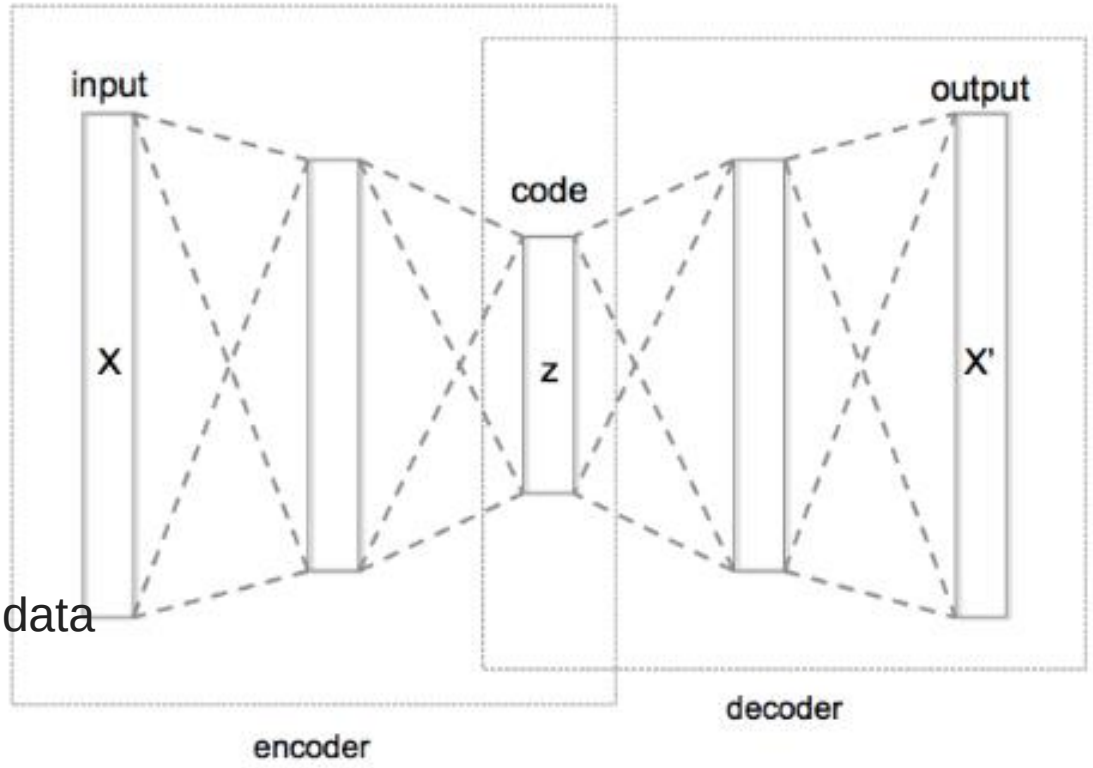


Remove sparse features < 1%



Binding features are removed

Autoencoder



Unsupervised learning

ANN

For efficient encoding of input data

Good tool for dimension reduction

Feature extraction

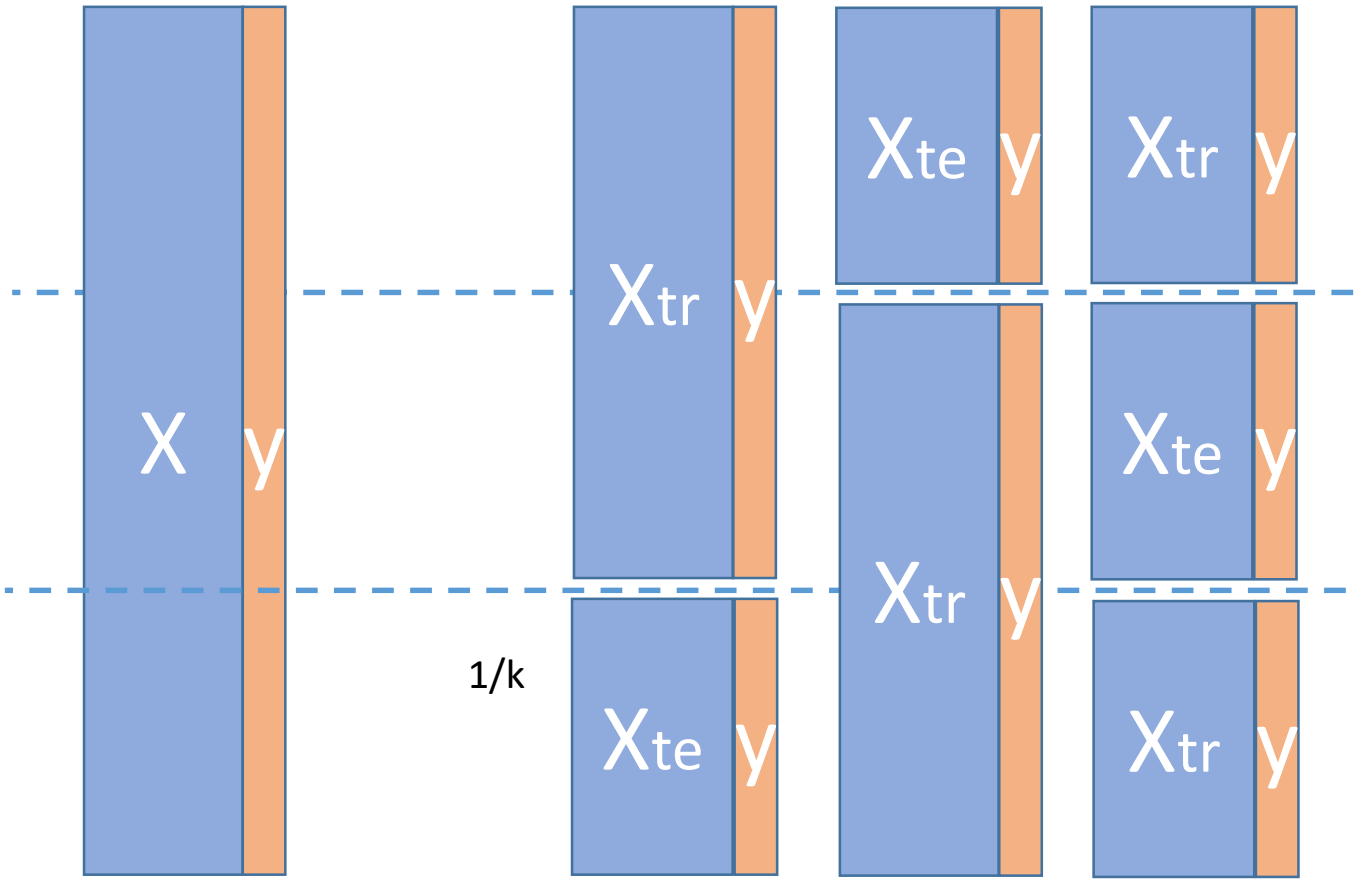
Non-linear (if 2 or more encoding layers are used)

Cf. PCA

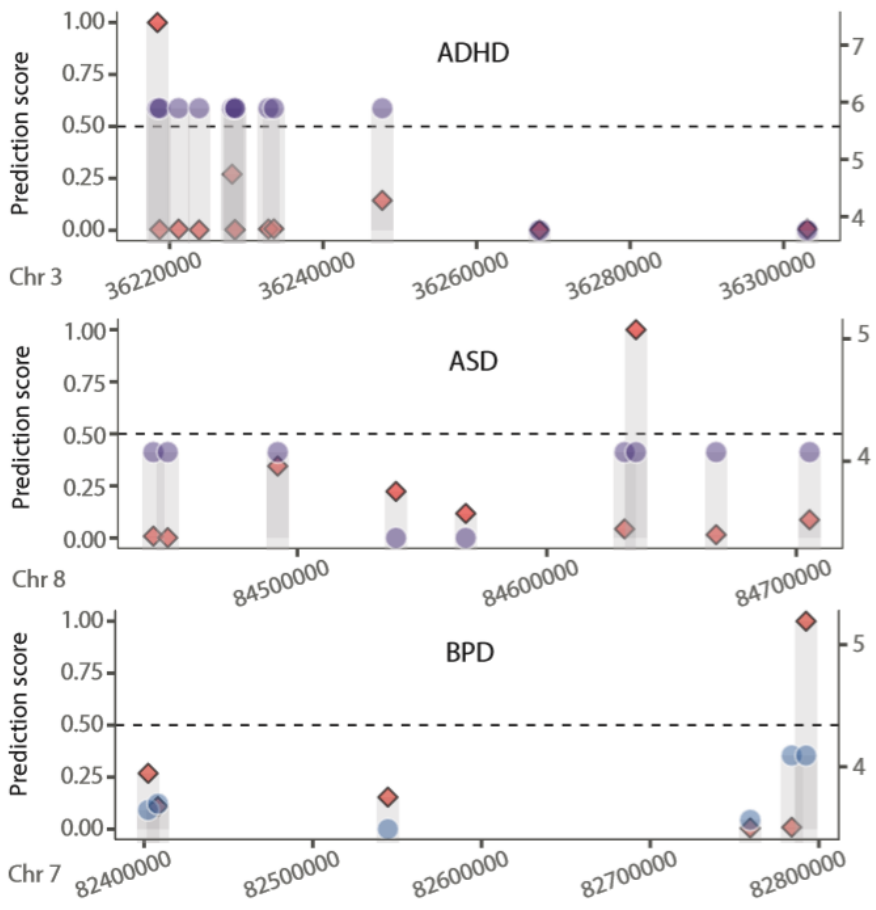
PCA is linear and greedy (1st PC explain more than 2nd)

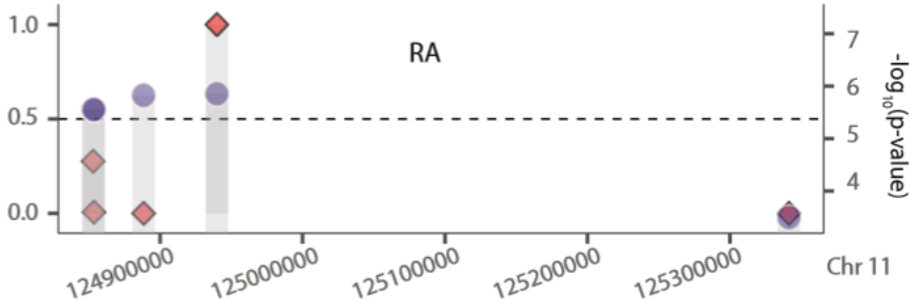
Result and validation

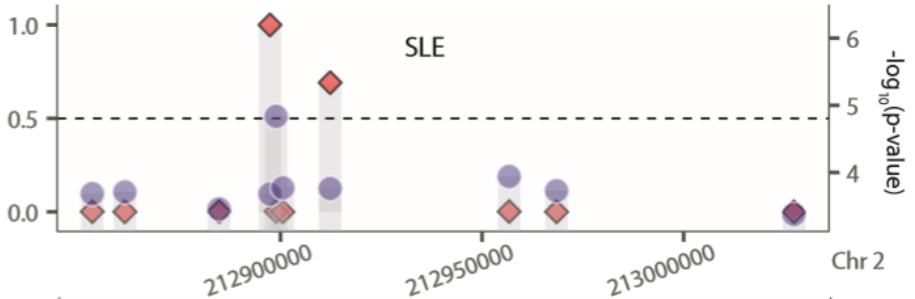
***k*-fold cross-validation**

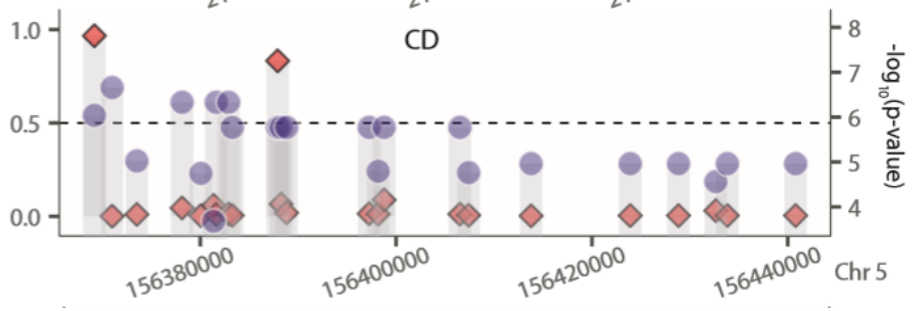


Distinguished SNPs









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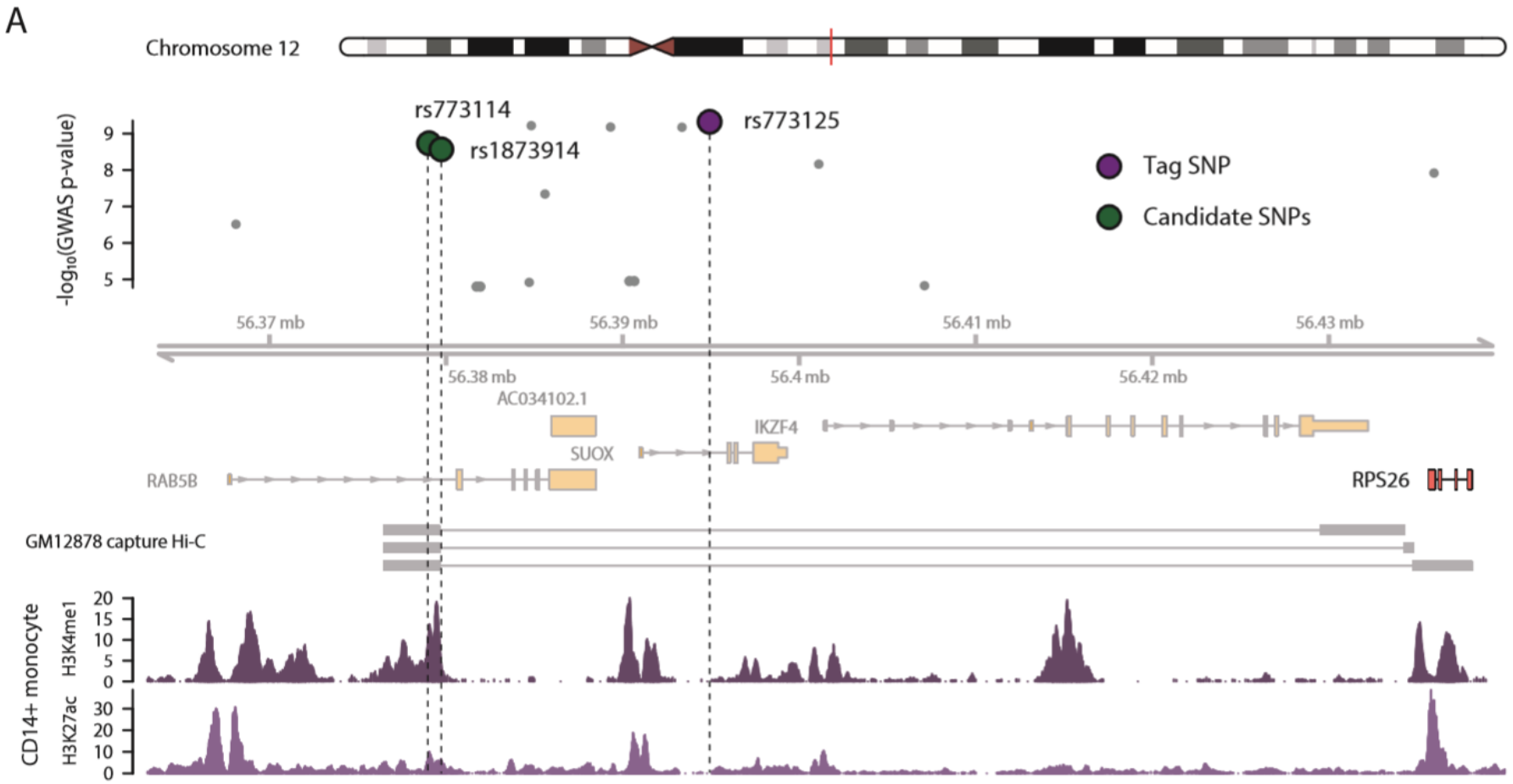
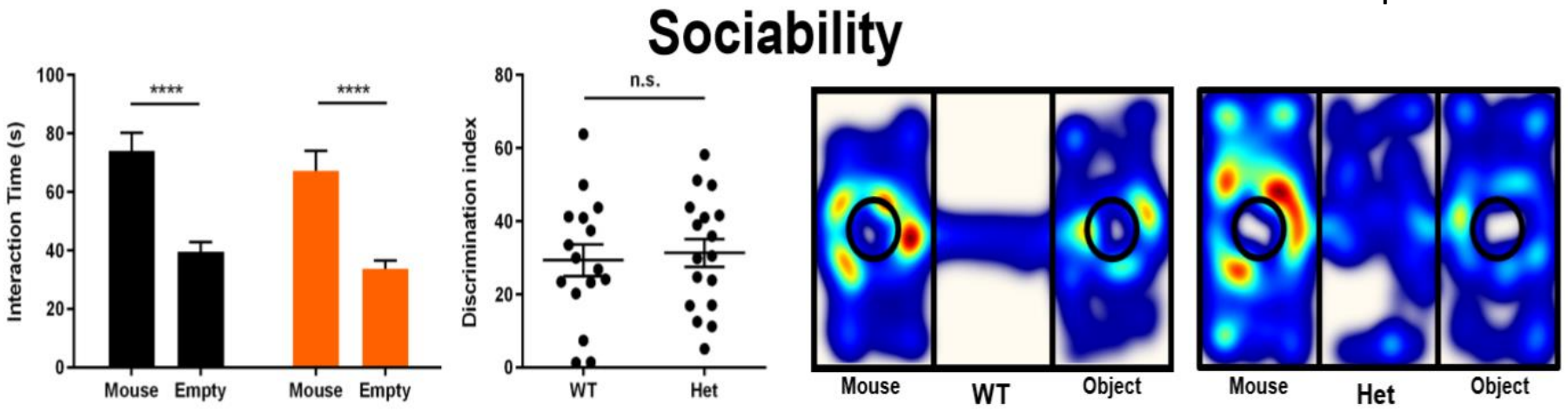
Biological validation

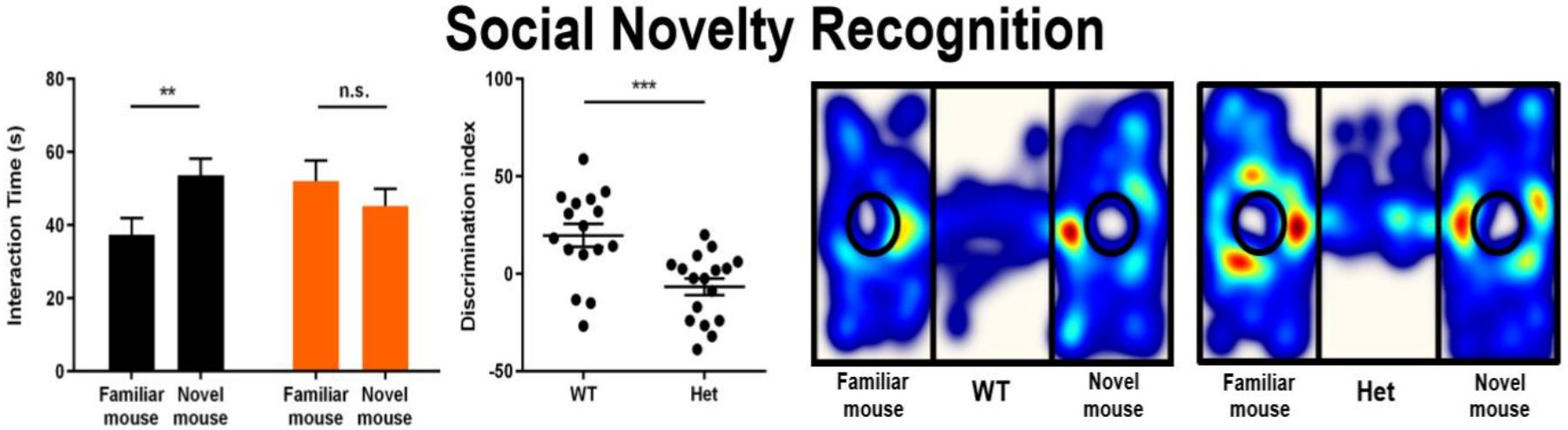


Not published

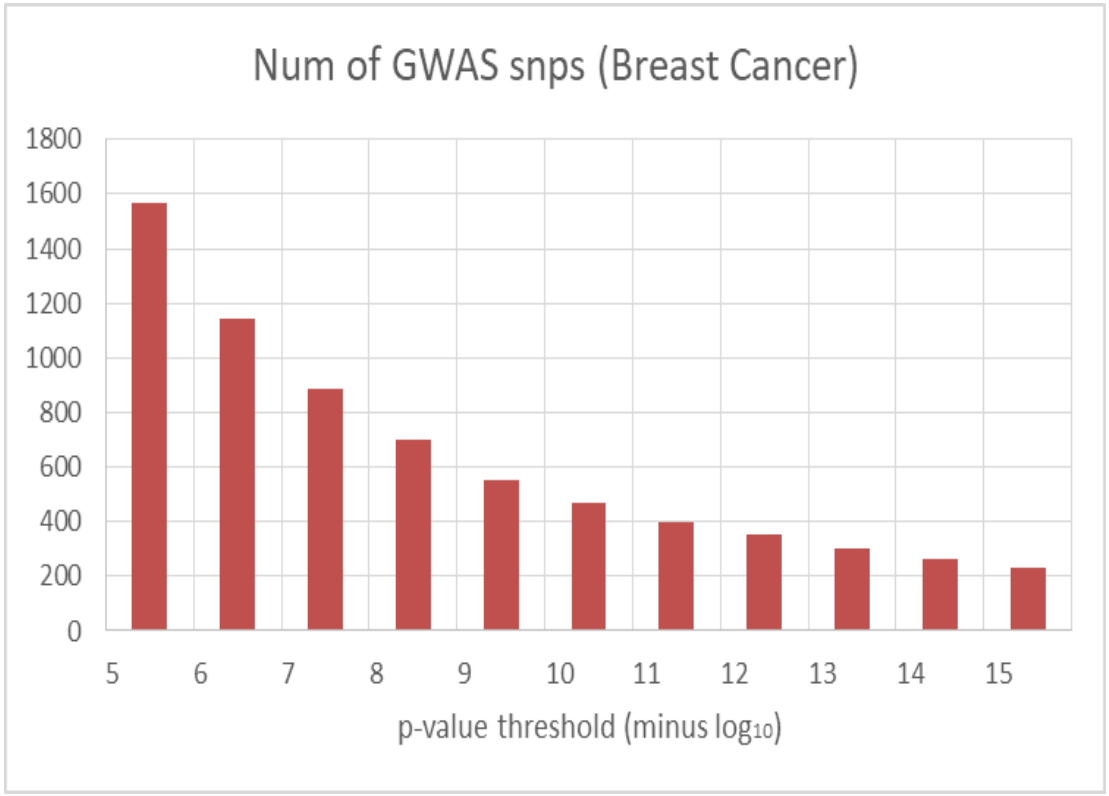
Knockout mice

Not published





! Lack of samples !



Cf.
ImageNet
~ 14m images

MNIST
~ 60k hand-written

Recent trend of deep learning

Type	Classifier	Distortion	Preprocessing	Error rate (%)
Convolutional neural network	Committee of 5 CNNs, 6-layer 784-50-100-500-1000-10-10	None	Expansion of the training data	0.21[17]
Convolutional neural network	Committee of 35 CNNs, 1-20-P-40-P-150-10	elastic distortions	Width normalizations	0.23[8]
Convolutional neural network	6-layer 784-50-100-500-1000-10-10	None	Expansion of the training data	0.27[24]
Convolutional neural network	6-layer 784-40-80-500-1000-2000-10	None	Expansion of the training data	0.31[15]
Deep neural network	6-layer 784-2500-2000-1500-1000-500-10	elastic distortions	None	0.35[23]
K-Nearest Neighbors	K-NN with non-linear deformation (P2DHMDM)	None	Shiftable edges	0.52[19]
Support vector machine	Virtual SVM, deg-9 poly, 2-pixel jittered	None	Deskewing	0.56[21]

Data augmentation

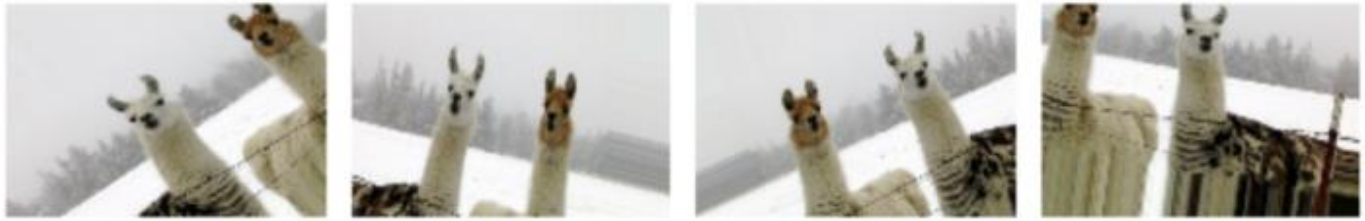


Figure I: Traditional Transformations

Figure II: Style Transformations via GANs

Perez, Luis, and Jason Wang. "The effectiveness of data augmentation in image classification using deep learning." *arXiv preprint arXiv:1712.04621* (2017).

Augmentation for multi-dimensional data

SNP	1	2	3	4	5	6	7	8
DHS	1.0							
CTCF								
H2AZ		1.0						
H3K27ac								
H3K27me3		1.0	1.0		1.0			
H3K36me3	1.0							
H3K4me1	1.0					1.0		
H3K4me3		1.0						
H3K9ac	1.0		1.0		1.0			1.0
H3K9me3				1.0	1.0		1.0	1.0
H4K20me1			1.0					

Traditional

SNP	1	2	3	4	5	6	7	8
DHS								
CTCF								
H2AZ								
H3K27ac								
H3K27me3								
H3K36me3								
H3K4me1								
H3K4me3								
H3K9ac								
H3K9me3								
H4K20me1								

Style transform

SNP	1	2	3	4	5	6	7	8
DHS								
CTCF	0.3							
H2AZ								
H3K27ac	0.3	0.3	0.3					
H3K27me3	0.3	0.3						
H3K36me3	0.5	0.4						
H3K4me1	0.5	0.3						
H3K4me3	0.5	0.4						
H3K9ac	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.5
H3K9me3		0.3	0.3	0.6	0.3	0.3	0.3	0.5
H4K20me1			0.3	0.5	0.3	0.3	0.3	0.5

It is not 2D image

Augmentation for multi-dimensional data

SNP	1	2	3	4	5	6	7	8
DHS	1.0							
CTCF								
H2AZ		1.0						
H3K27ac								
H3K27me3		1.0	1.0		1.0			
H3K36me3	1.0							
H3K4me1	1.0					1.0		
H3K4me3		1.0						
H3K9ac	1.0		1.0		1.0			1.0
H3K9me3				1.0	1.0		1.0	1.0
H4K20me1			1.0					

Add random features

X 10

SNP	1	2	3	4	5	6	7	8
DHS	1.0							
CTCF								
H2AZ		1.0						
H3K27ac								
H3K27me3		1.0	1.0		1.0			
H3K36me3	1.0							
H3K4me1	1.0					1.0		
H3K4me3		1.0						
H3K9ac	1.0		1.0		1.0			1.0
H3K9me3				1.0	1.0		1.0	1.0
H4K20me1			1.0					

SNP	1	2	3	4	5	6	7	8
DHS	1.0							
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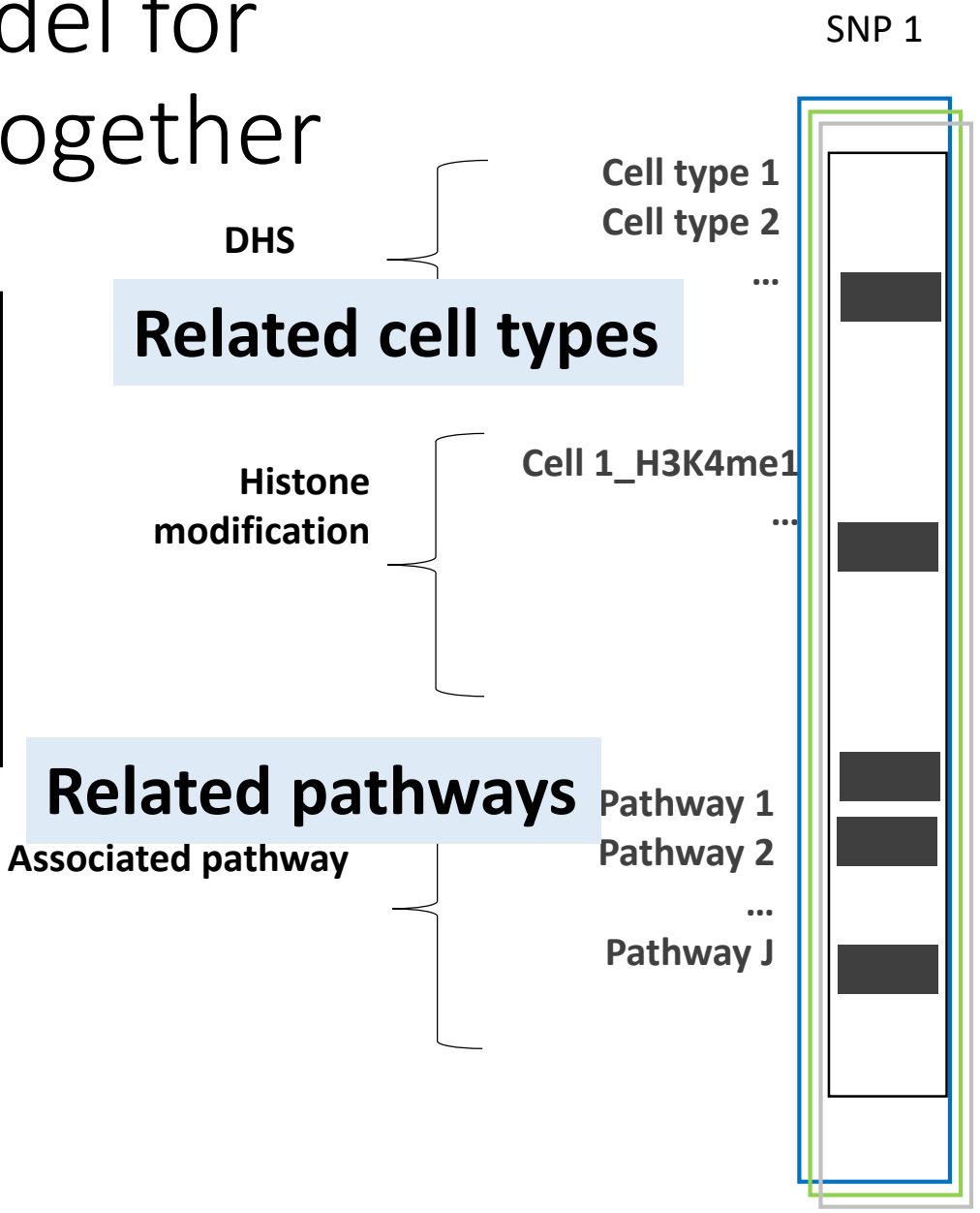
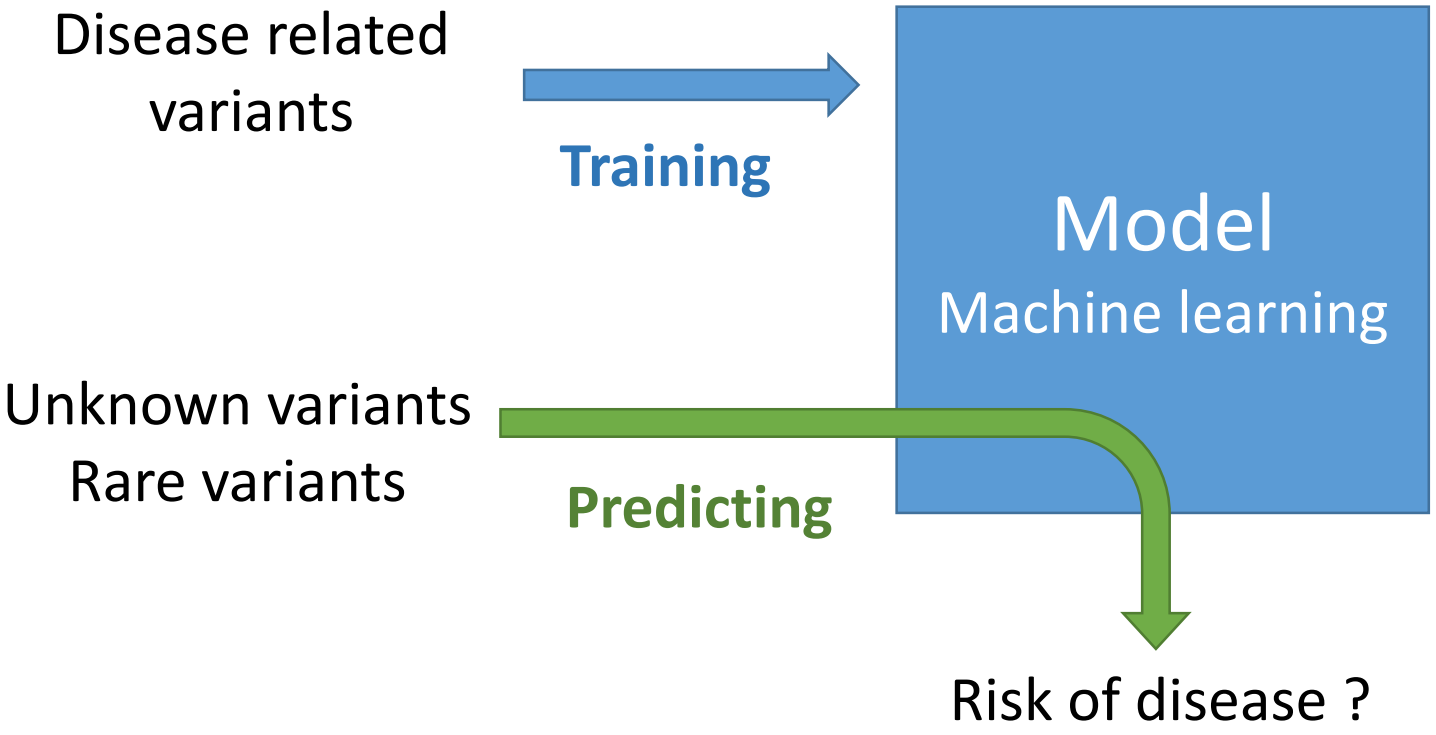
H3K27ac								
H3K27me3		1.0	1.0		1.0			
H3K36me3	1.0							
H3K4me1	1.0					1.0		
H3K4me3		1.0						
H3K9ac	1.0		1.0		1.0			1.0
H3K9me3				1.0	1.0		1.0	1.0
H4K20me1			1.0					

Generalized model for all GWAS SNPs together

Number of associations		
ADHD	**ASD**	**BPD**
642	943	1,424
MDD	**SCZ**	**RA**
832	601	435
SLE	**CD**	**UC**
849	431	383



Summary


Disease related variants
Training
Model
Machine learning
Unknown variants
Rare variants
Predicting
Risk of disease ?

History

1943 MCP artificial neuron

1958 Perceptron (machine learning)

1969 Multi-layer perceptron (ANN)

1986 Backpropagation

1997 LSTM
1998 LeNet (CNN)

2012 …
2016 AlphaGo

2025 My work?

Tools

2006 CUDA

2008 Python3

2010 Theano

2015 Tensorflow
Keras

Thank you