Assessing colocalisation of causal variants for complex and molecular traits

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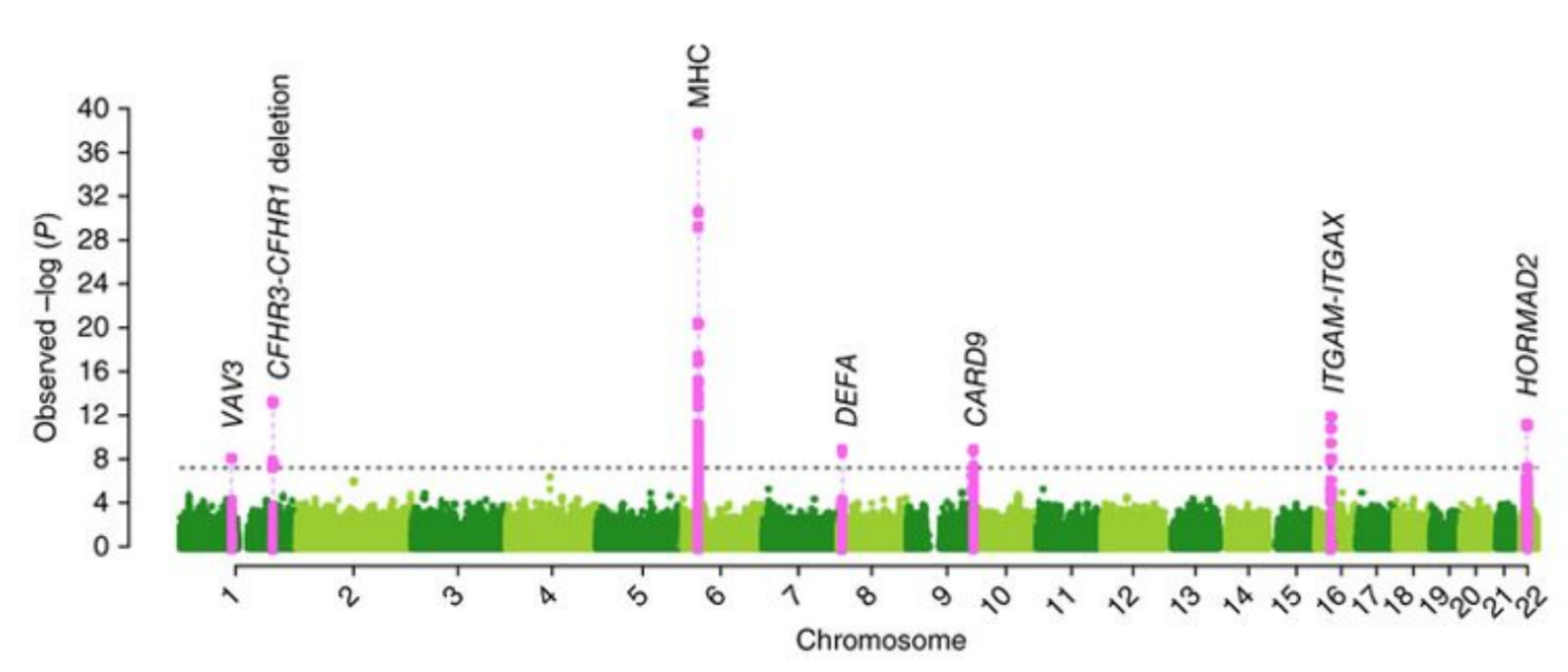
University of Cambridge

Identifying molecular traits that mediate a disease association



GWAS of IgA Nephropathy (Kiryluk et al, Nat Genet 2014)

Testing whether a trait is causal for disease

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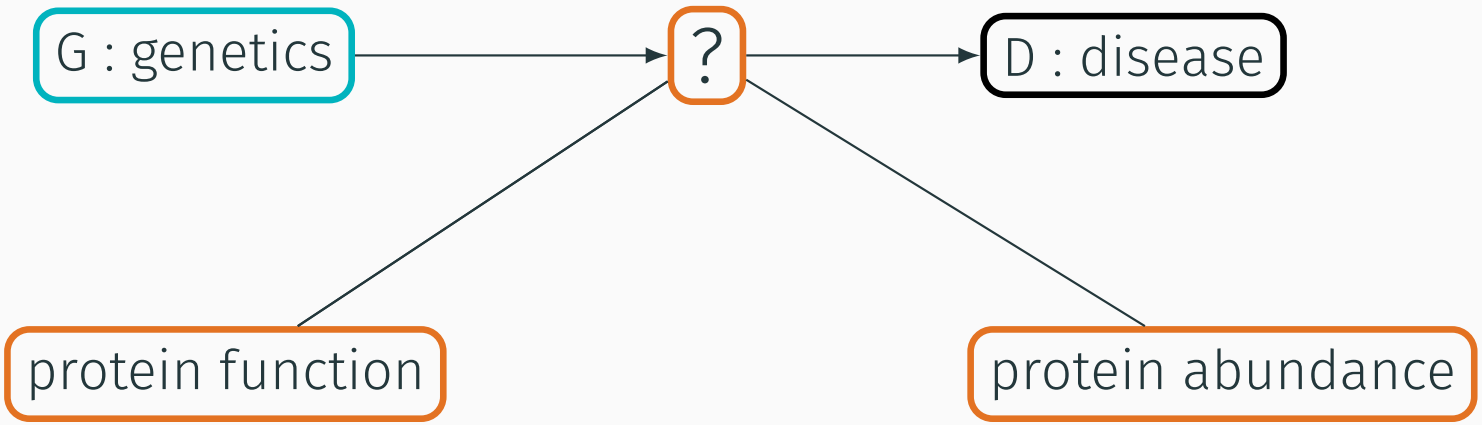
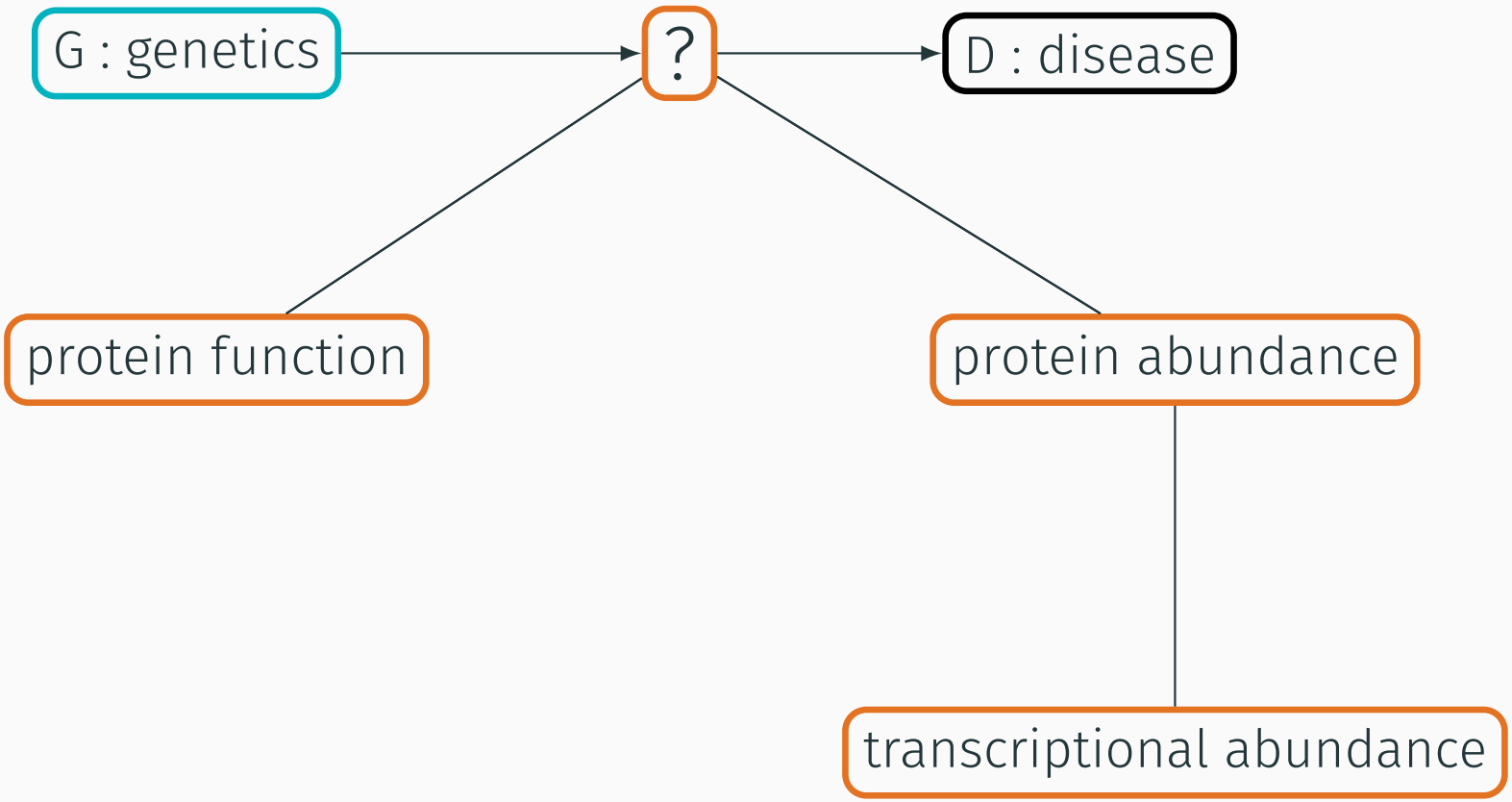


Testing whether a trait is causal for disease



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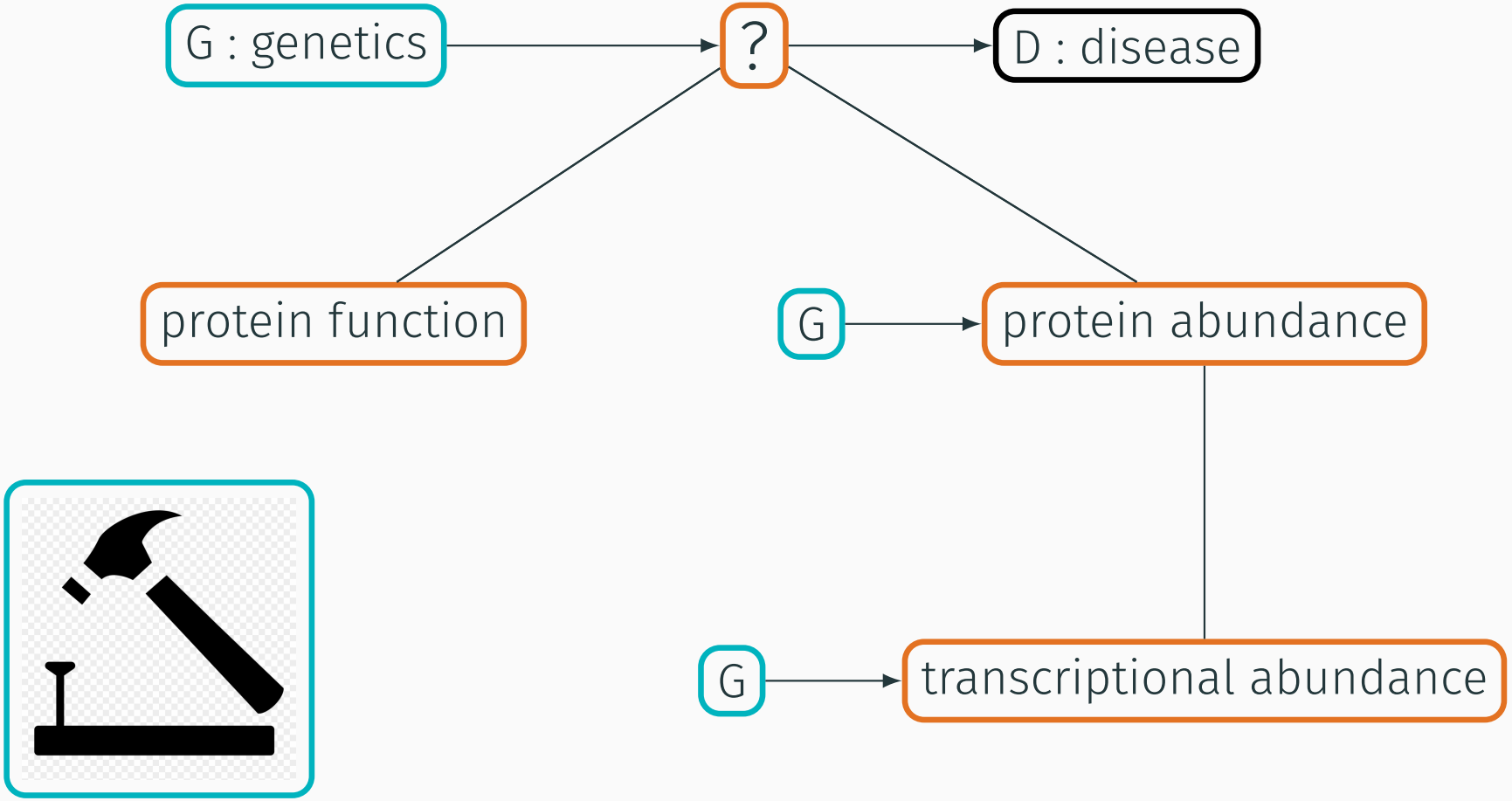

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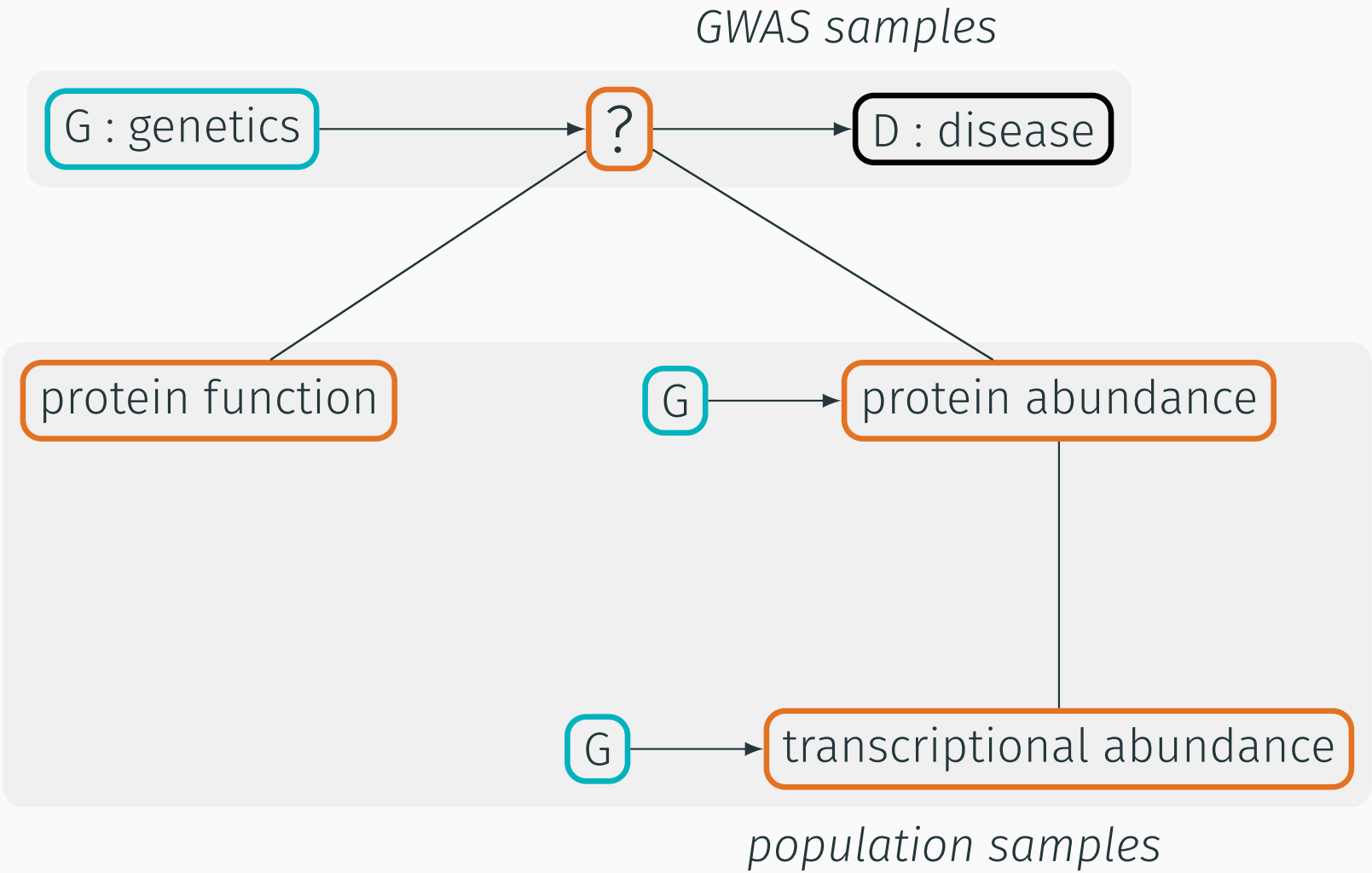

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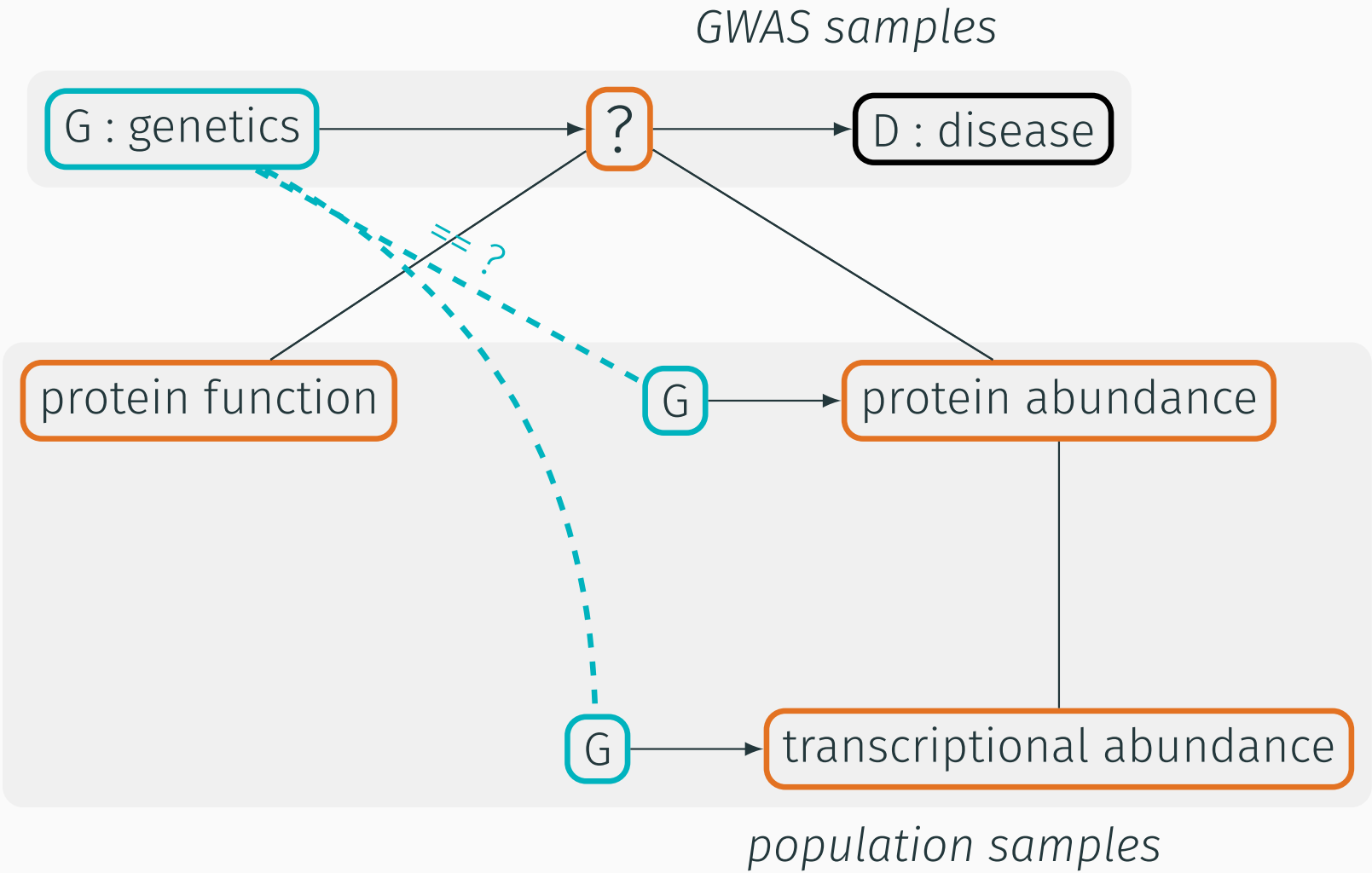

Testing whether an exposure causally affects outcome

Mendelian Randomisation

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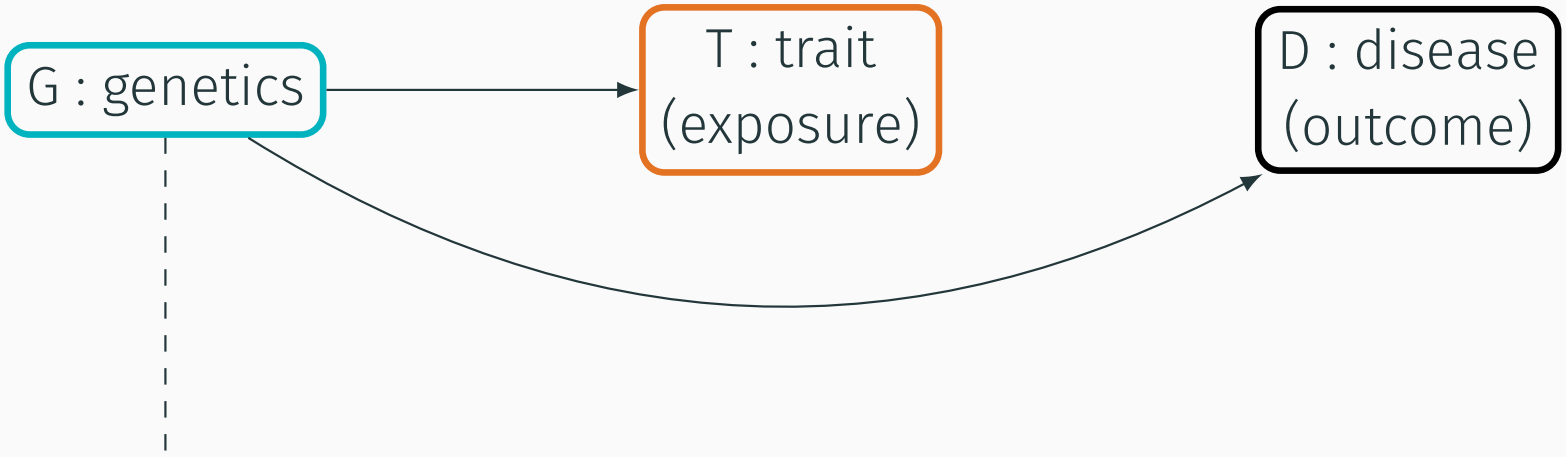


Instrumental variable

- potentially multiple IVs

Test significance of effects

$G \rightarrow D$

Particular issues for finding mediating molecular traits

trait/IV not generally known in advance

- Need to use the same data for discovery and testing

May only be one variant affecting molecular trait

Need to distinguish

- molecular variant in LD with disease variant

OR

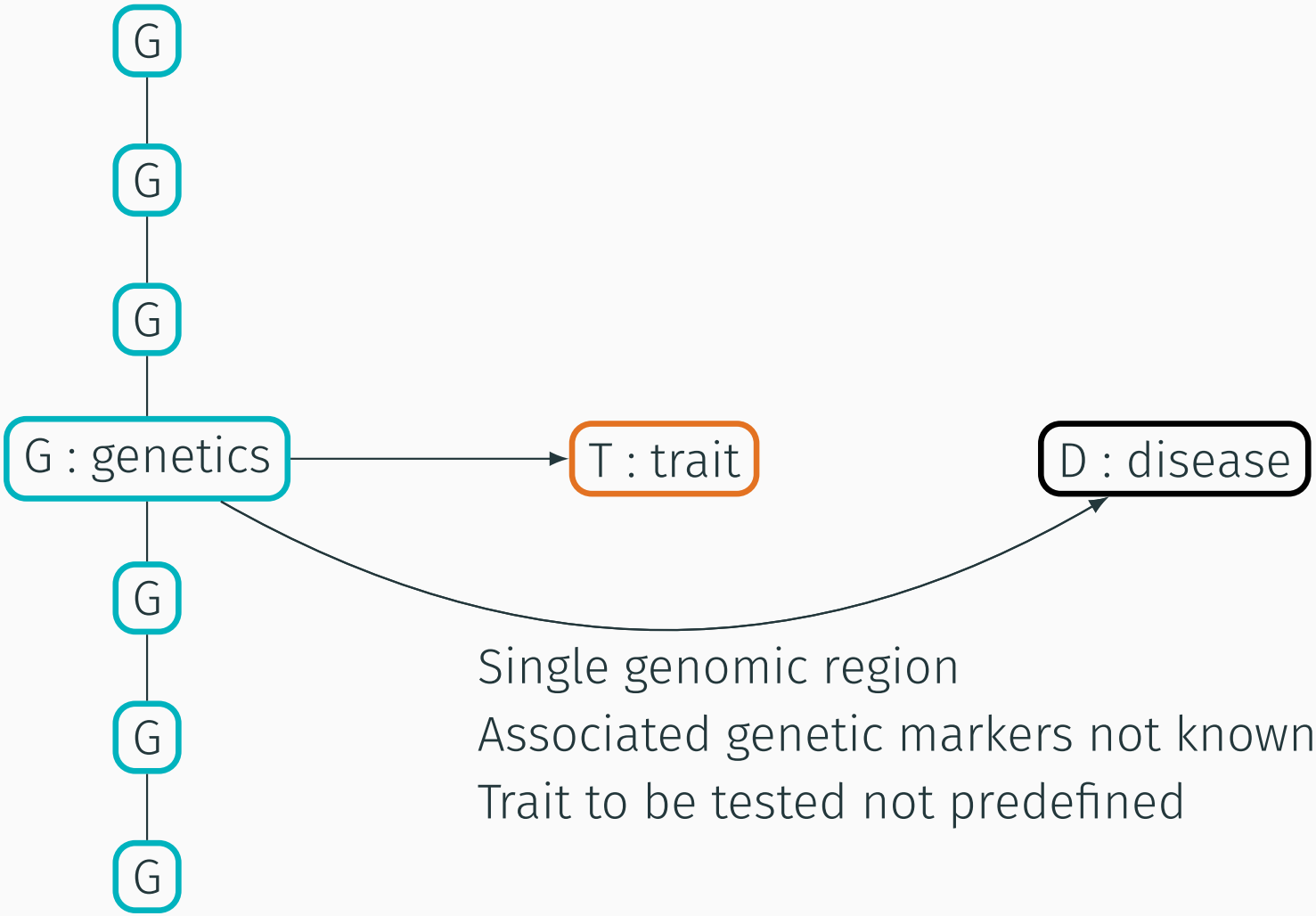
- molecular variant coincident with disease variant

Identifying molecular traits that mediate a disease association

Identifying molecular traits that mediate a disease association

Colocalisation

Genetic discovery **and** test joint relationship



Single genomic region

Associated genetic markers not known *a priori*

Trait to be tested not predefined

Identifying molecular traits that mediate a disease association

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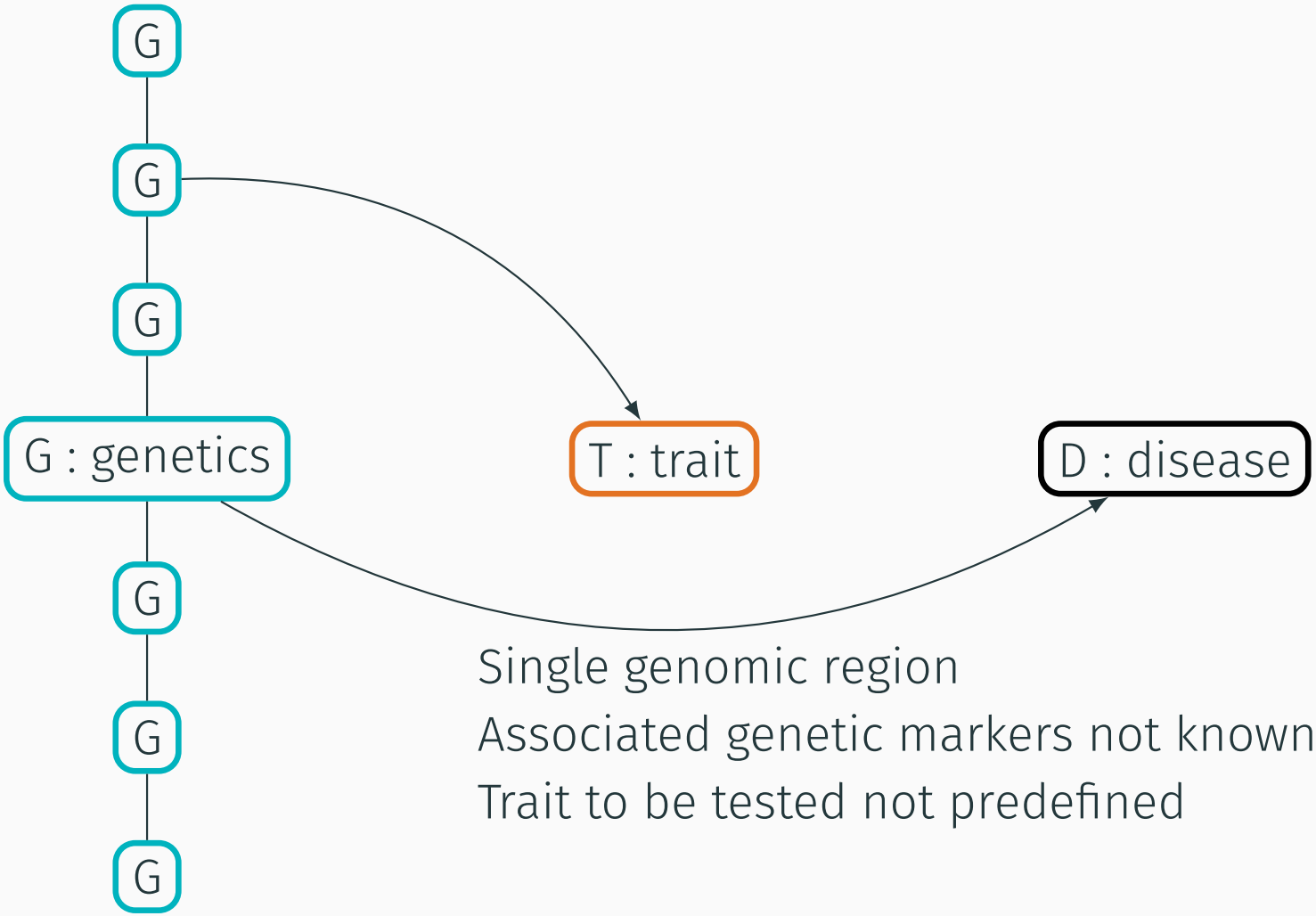

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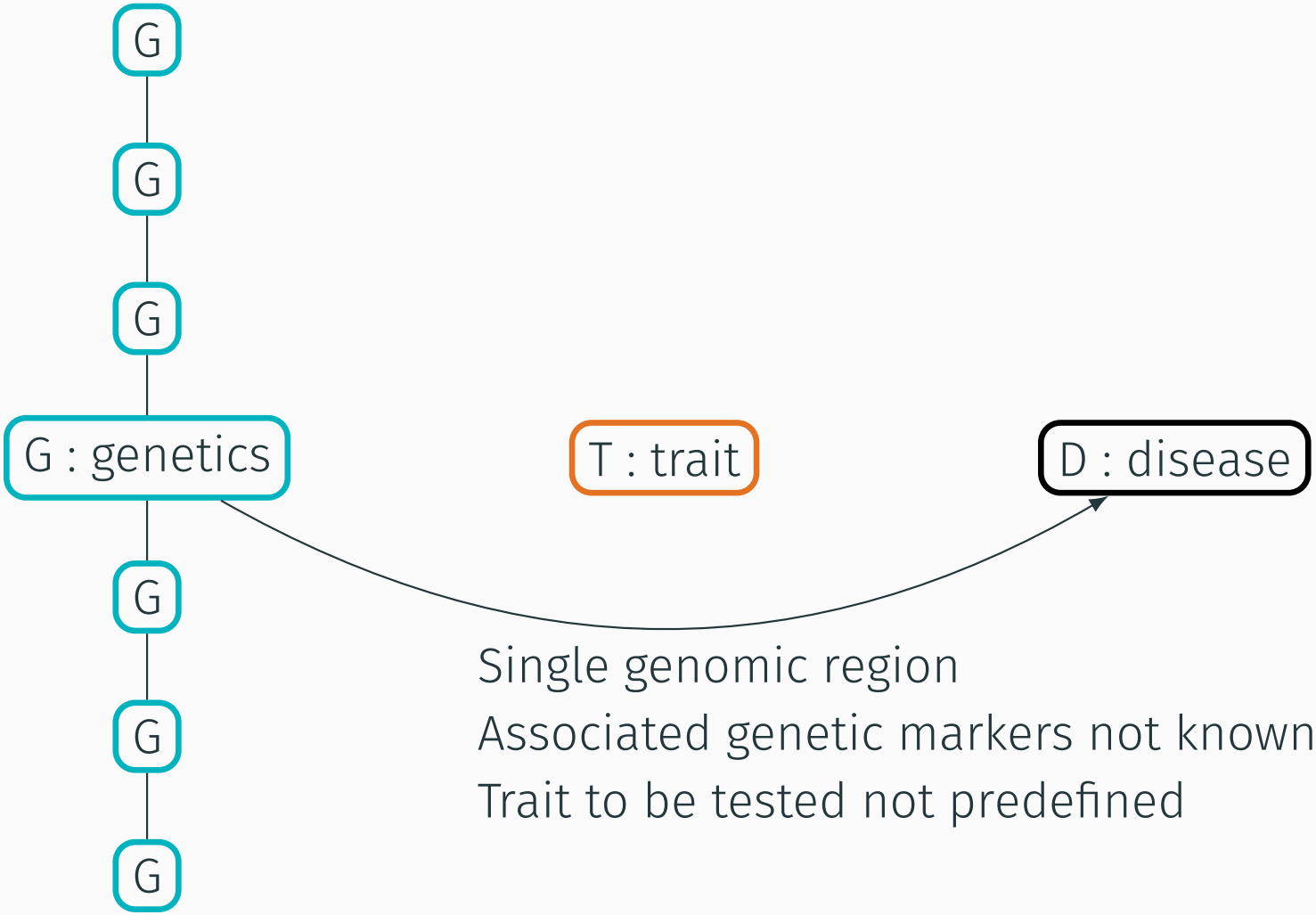

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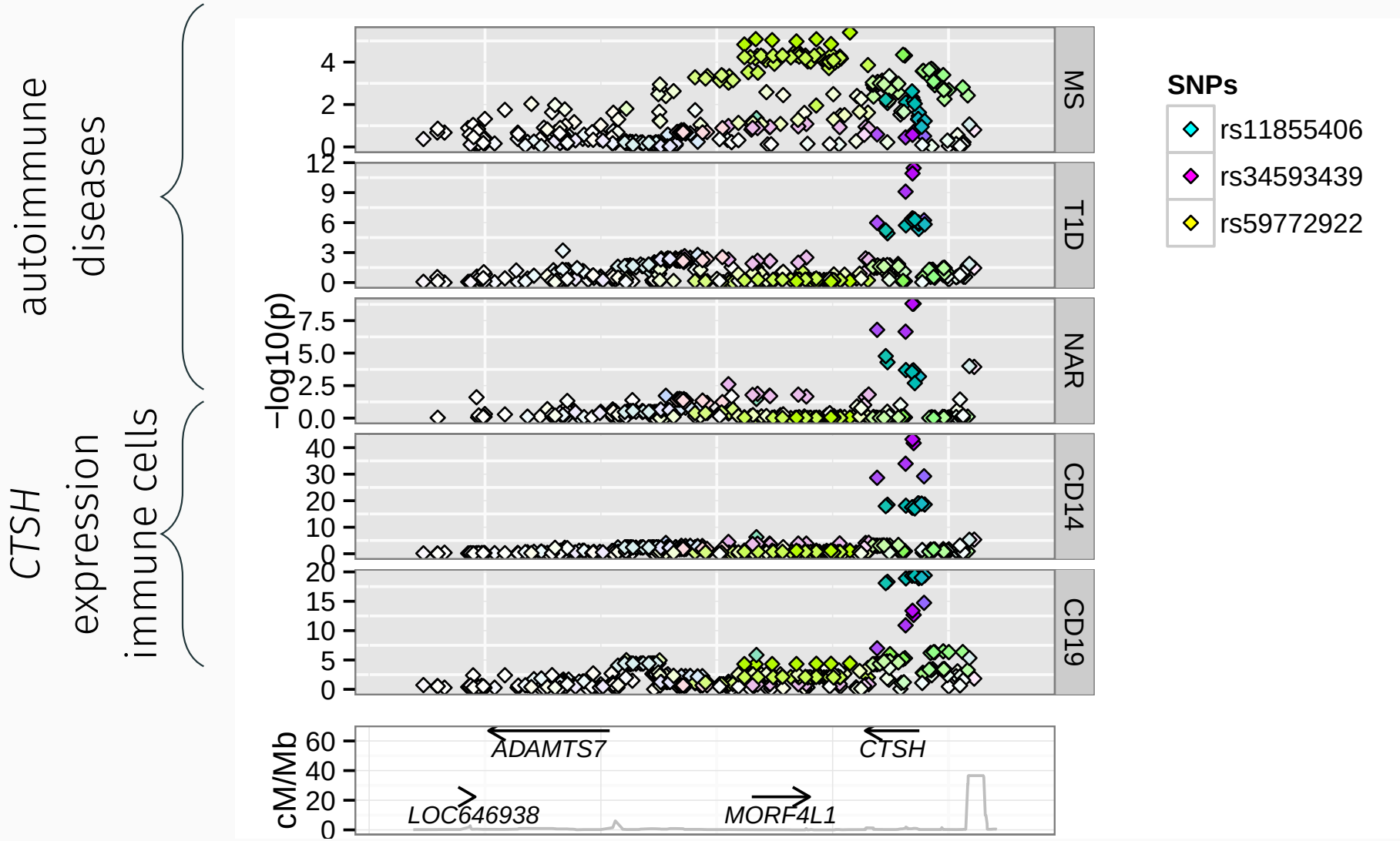
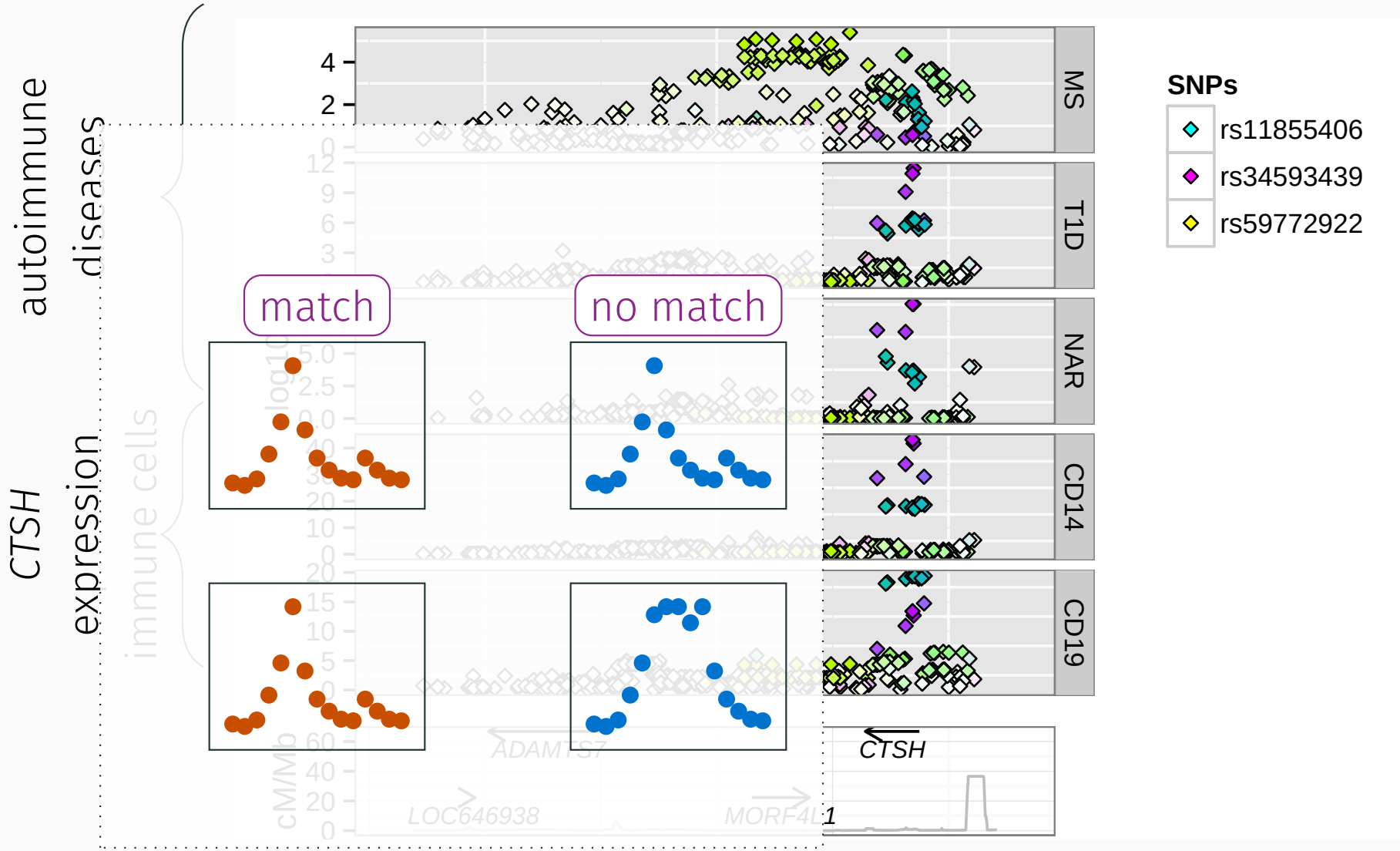
Colocalisation:
the coloc approach

Coloc: at essence a pattern matcher



Coloc: at essence a pattern matcher



Giambartolomei et al, 2014. Guo et al, 2016. chr1swallace/coloc

Coloc enumerates hypotheses

We have a pair of traits.

For a single, LD-defined, genomic region, assume at most one association per trait.

Then exactly 5 possibilities:

H_0 : no association

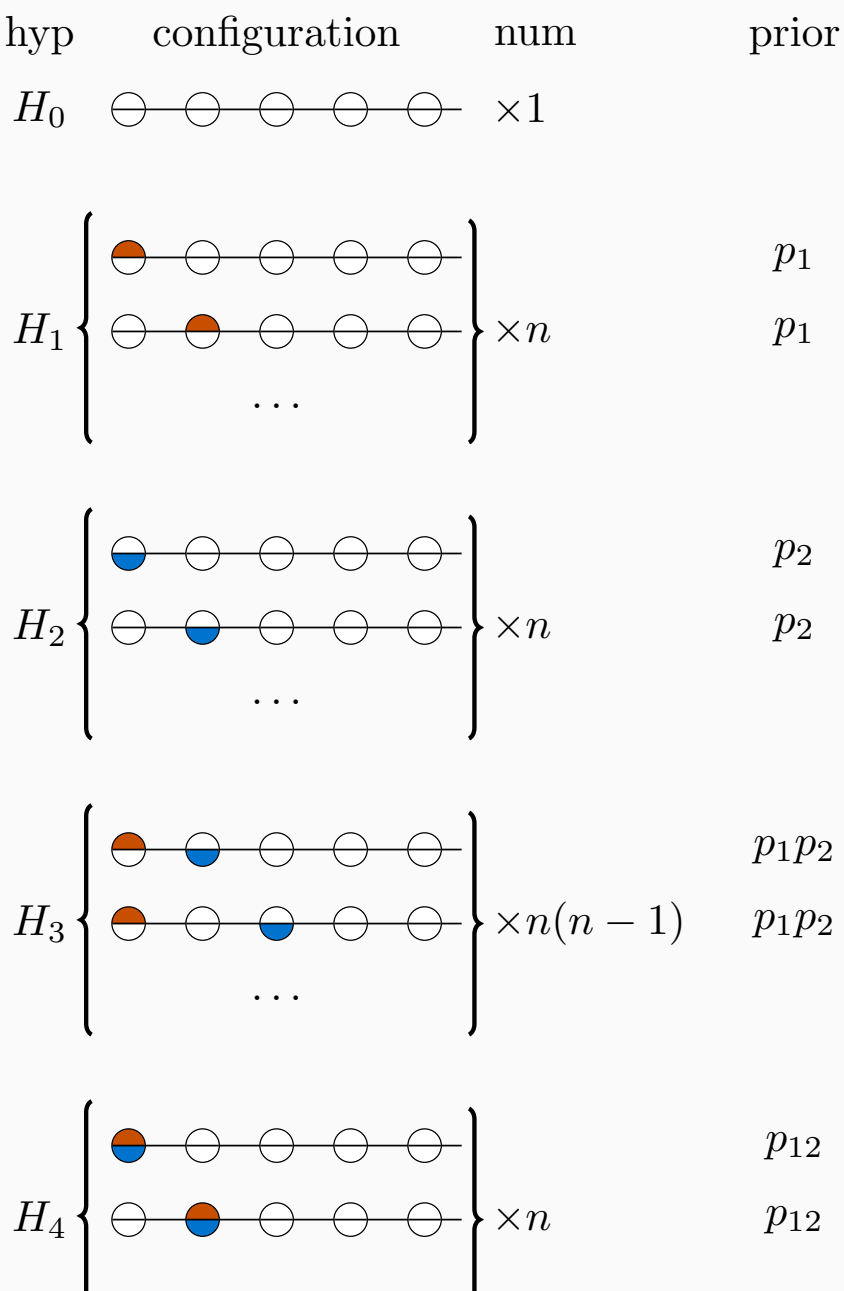
H_1 : association to trait 1 only

H_2 : association to trait 2 only

H_3 : association to both traits, distinct causal variants

H_4 : association to both traits, shared causal variant

Coloc enumerates hypotheses



Values of prior parameters

Original context:

- GWAS of lipid traits (100,000 individuals)
- Liver eQTLs (1000 individuals)

i.e. two large studies, *a priori* biologically relevant to each other

$$p_1 = p_2 = 10^{-4} \qquad p_{12} = 10^{-5}$$

For a 1000 SNP region, this gives

$$P(H_1) = 0.1 \qquad P(H_2) = 0.1$$
$$P(H_3) = 0.01 \qquad P(H_4) = 0.01$$

Giambartolomei et al, PLoS Gen 2014

Review of current practice

Out of 25 papers which used coloc in 2018 ...

... 22 used software default priors

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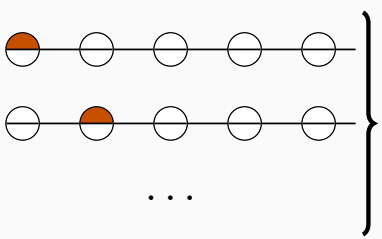
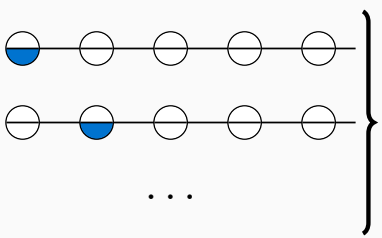
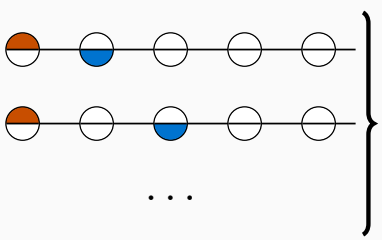
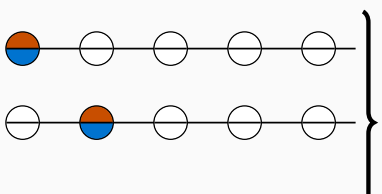
Varied trait pairs:

GWAS-eQTL	GWAS-meQTL	eQTL-pQTL	GWAS-chromatinQTL
15	3	2	2
GWAS-GWAS	GWAS-molecular QTL	GWAS-pQTL	
1	1	1	

Marginal priors: q_1, q_2

Colocalisation priors

hyp	configuration	num	prior
H_0		$\times 1$	
H_1		$\times n$	p_1 p_1
H_2		$\times n$	p_2 p_2
H_3		$\times n(n-1)$	p_1p_2 p_1p_2
H_4		$\times n$	p_{12} p_{12}

Marginal prior

$q_1 = p_1 + p_{12}$

$q_2 = p_2 + p_{12}$

Prior explorer for coloc

Input: Type of Per SNP priors

select one

Raw
Marginal/Conditional

Input: Parameter values

Number of SNPs in region 1000

p12 0.000001

p1 0.0001

p2 0.0001

nsnps > 0
p1 * p2 < p12 < min(p1,p2)
0 < p1 < 1/nsnps
0 < p2 < 1/nsnps

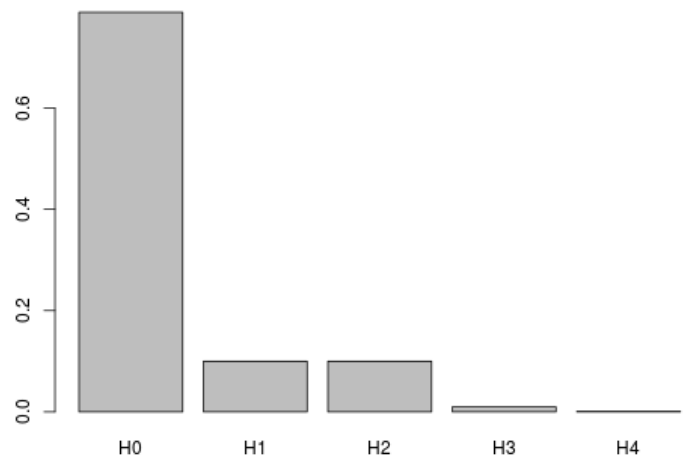
Result

Per-SNP priors

p12	p1	p2	q1|2	q1	q2
1.0E-06	1.0E-04	1.0E-04	9.9E-03	1.0E-04	1.0E-04

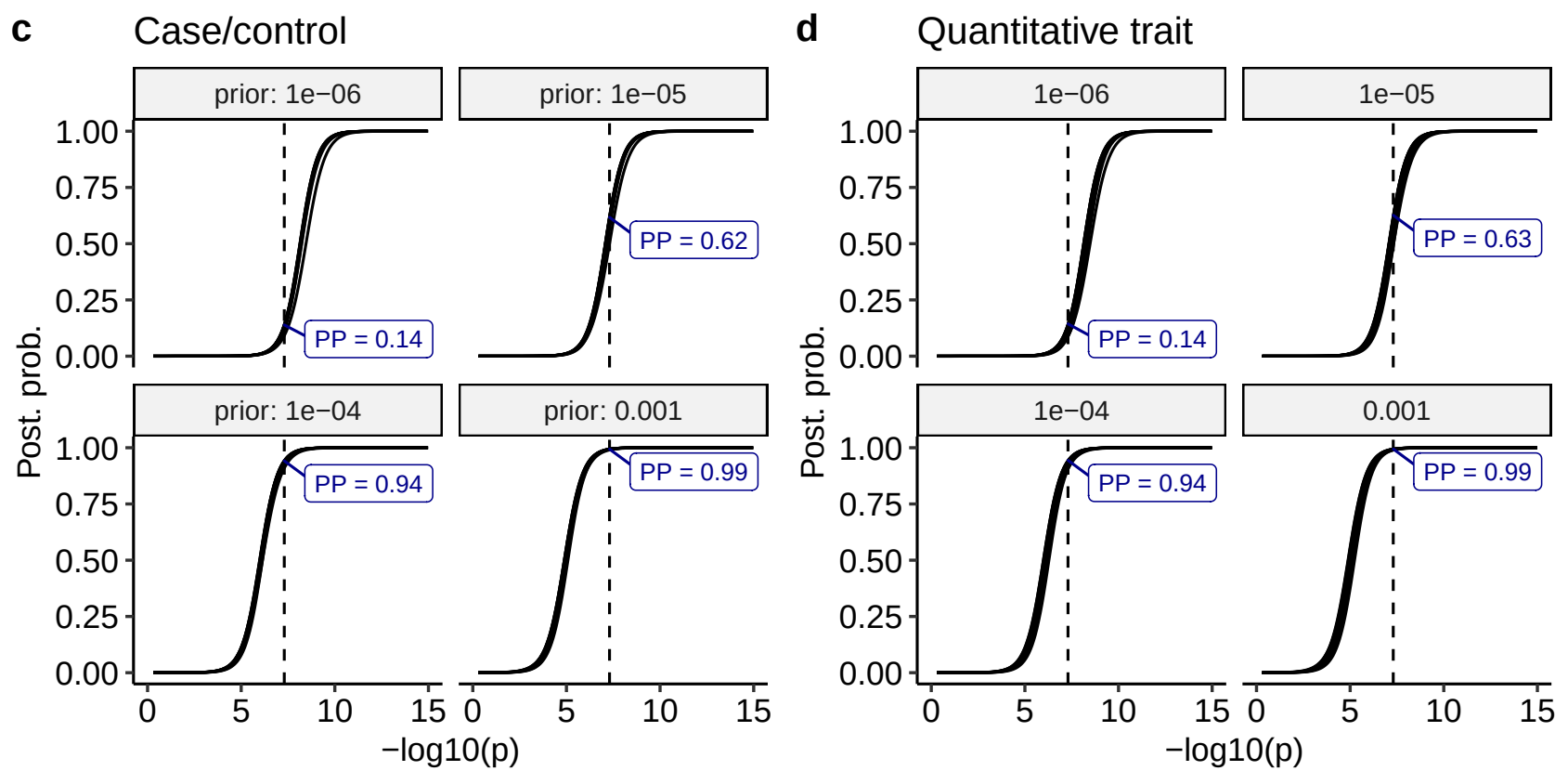
Per-hypothesis priors

H0	H1	H2	H3	H4
0.789	0.100	0.100	0.010	0.001



https://chr1swallace.shinyapps.io/coloc-priors/

Pragmatic prior for single trait



Empirical prior for single trait

Largest relevant GWAS disease studies:

eg IBD, 60,000 subjects[†]
$\sim$ 200 "hits" from 2 million common SNPs $\rightarrow$

$$q_i = \frac{200}{2,000,000} = \frac{1}{10,000}$$

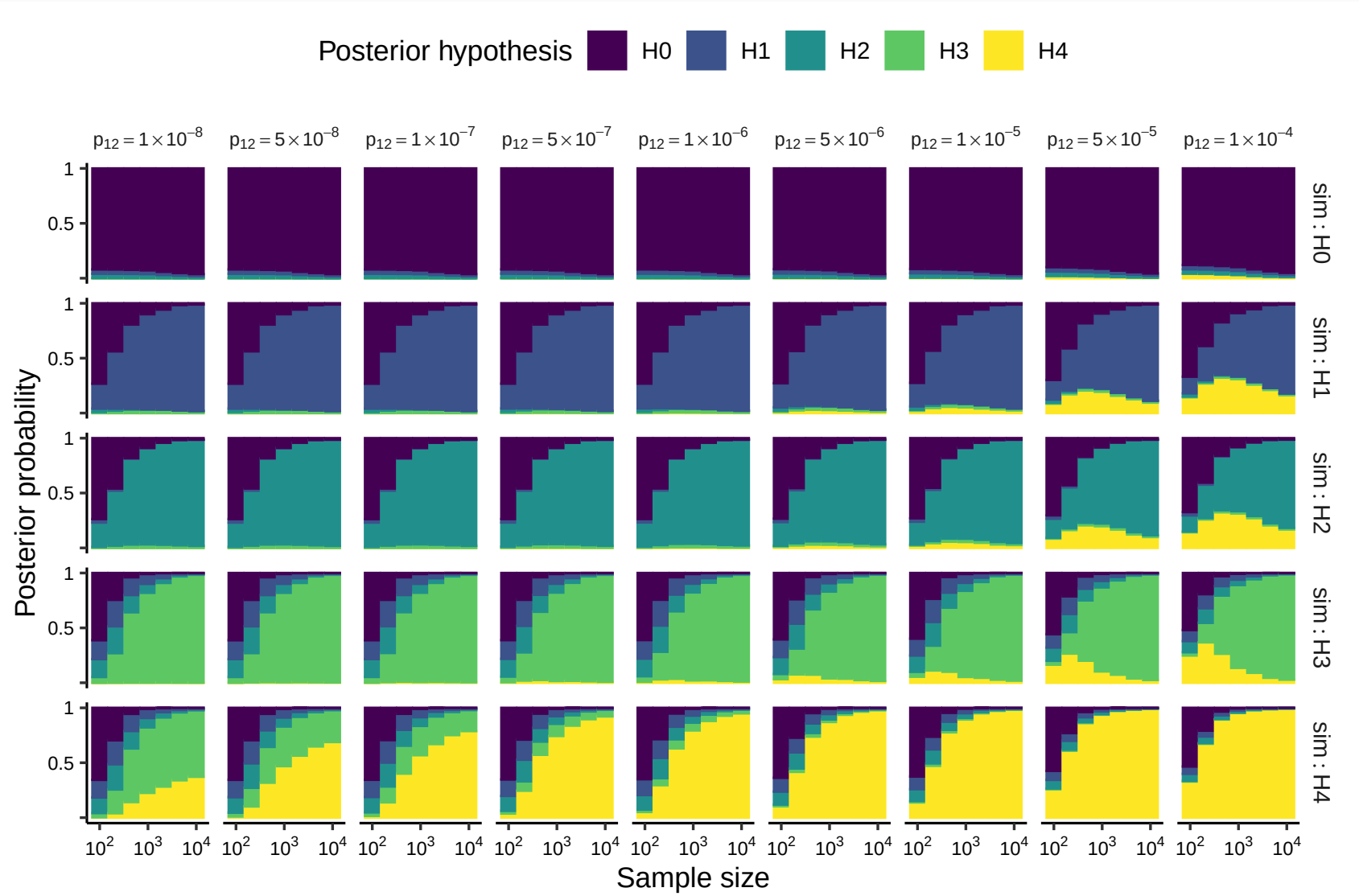
GTeX whole blood:

Fraction of SNPs in 1 mb window around TSS that are genome-wide significant $\approx \frac{1}{10,000}$

[†] *de Lange et al, Nat Genet 2017*

Joint prior p_{12}

Pragmatic p_{12}



Empirical prior for p_{12}

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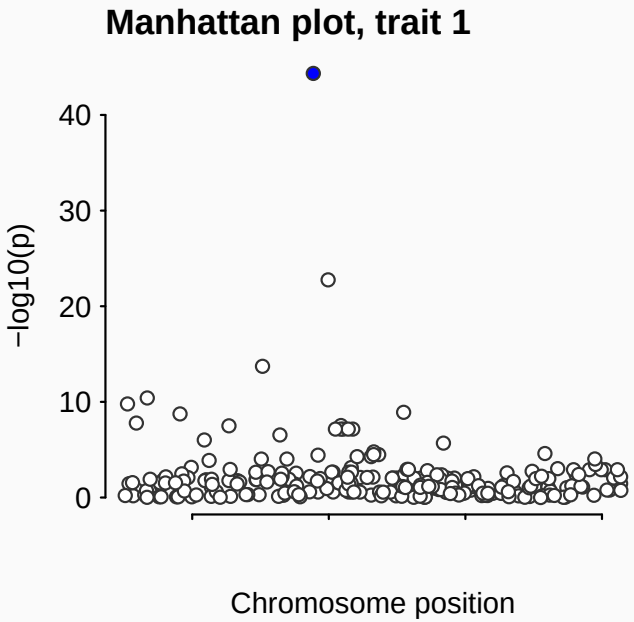
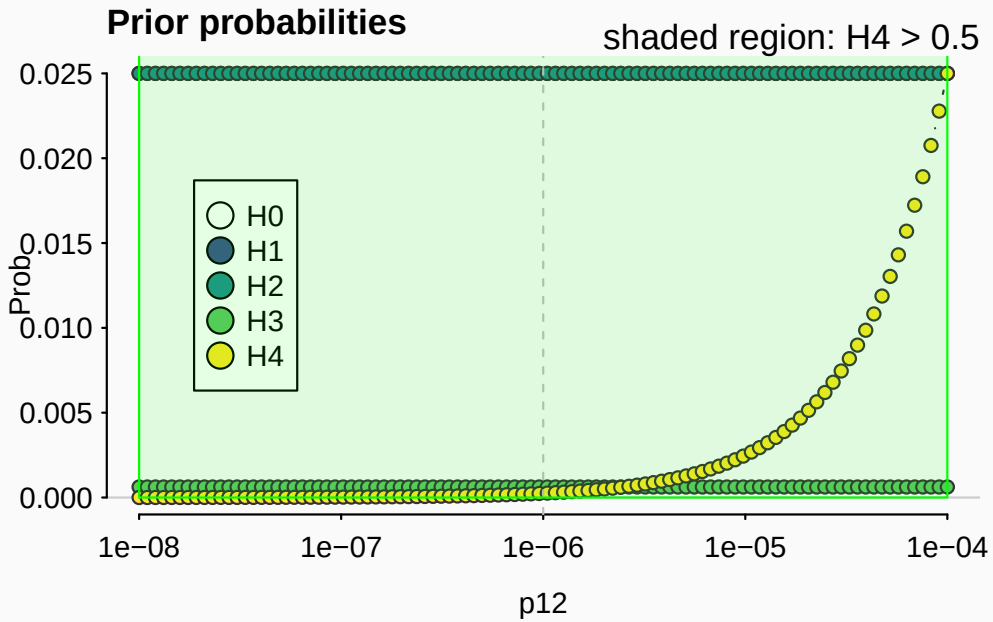
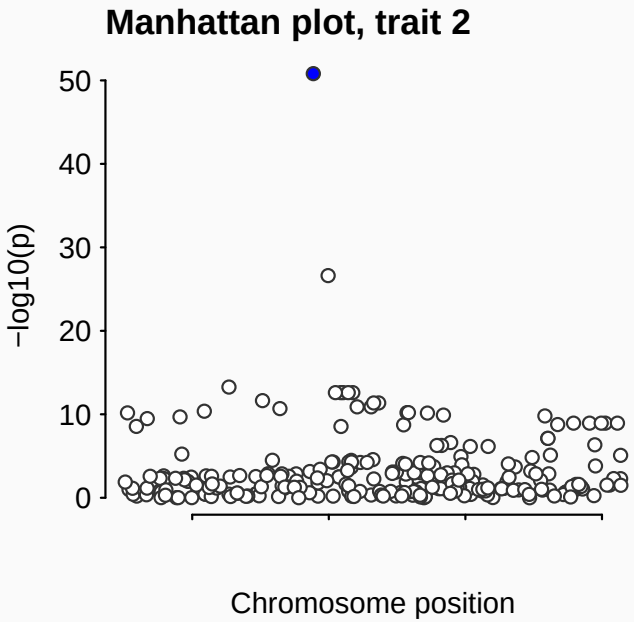
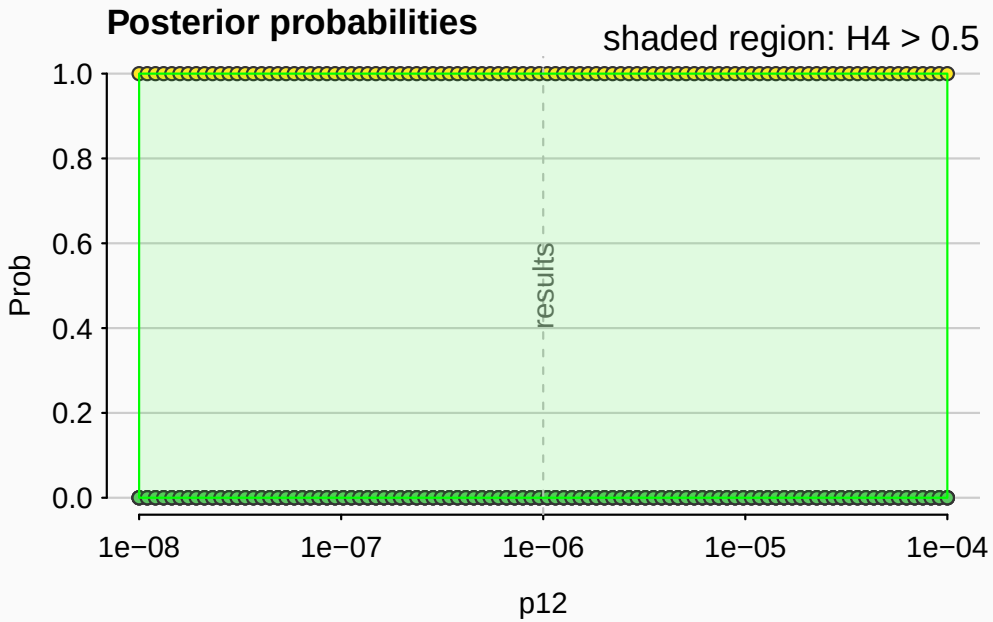
?

Sensitivity analysis









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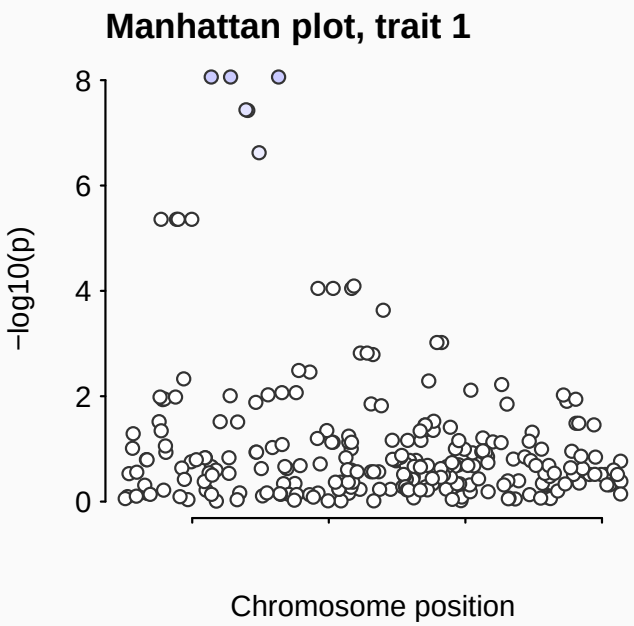
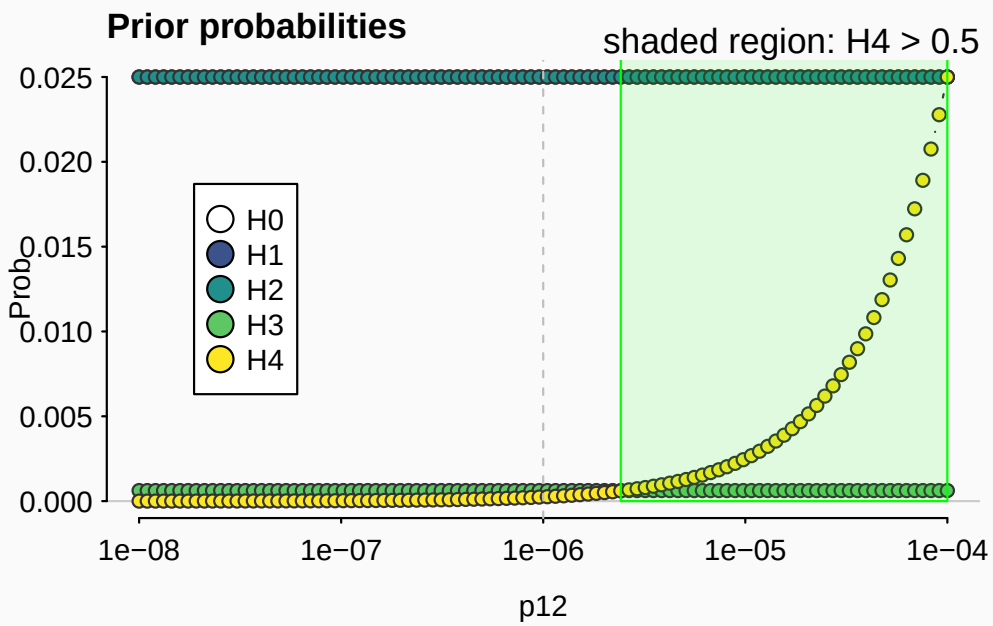
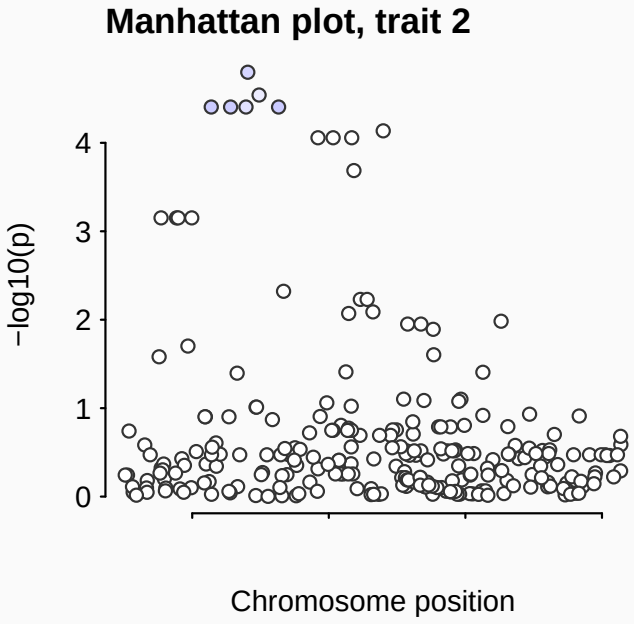
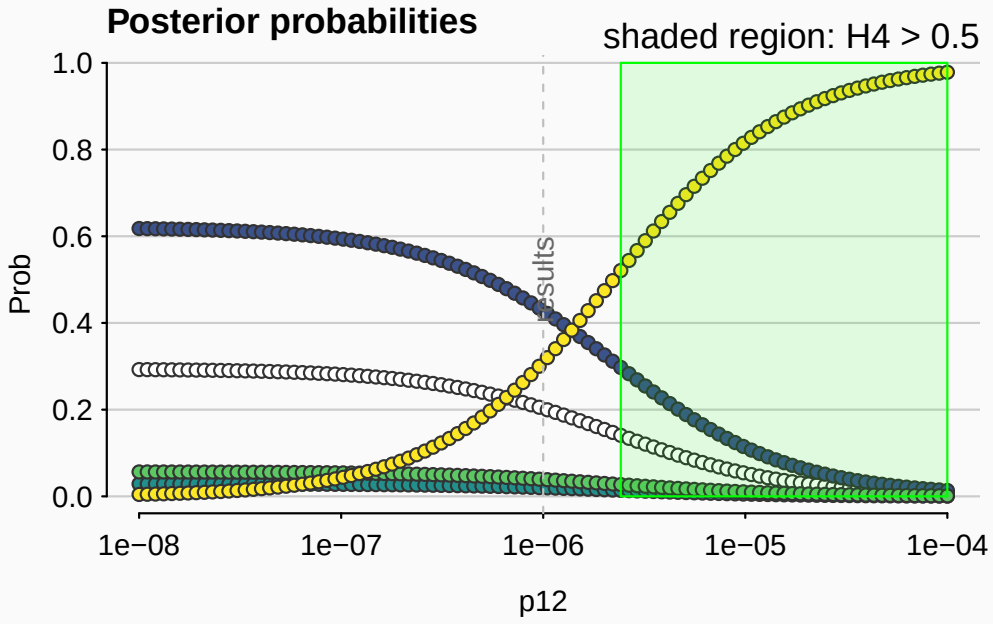


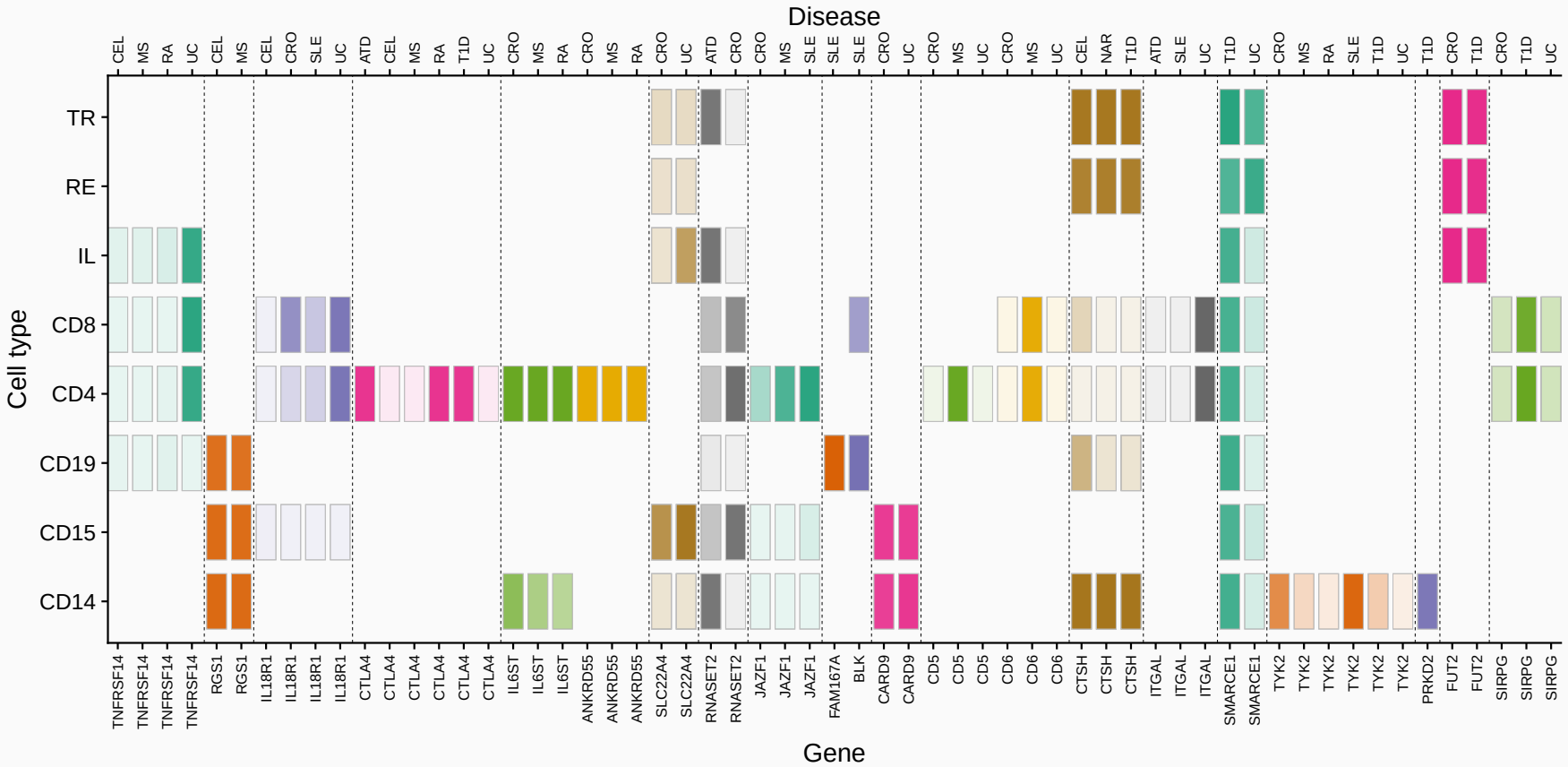






Transcripts colocalising with immune mediated disease risk

Colocalisation of eQTL (8 cell types) vs 11 diseases



All genes with $P(H_4) > 0.9$ in at least one cell type/disease shown.

Momozawa et al, Nat Genet 2018

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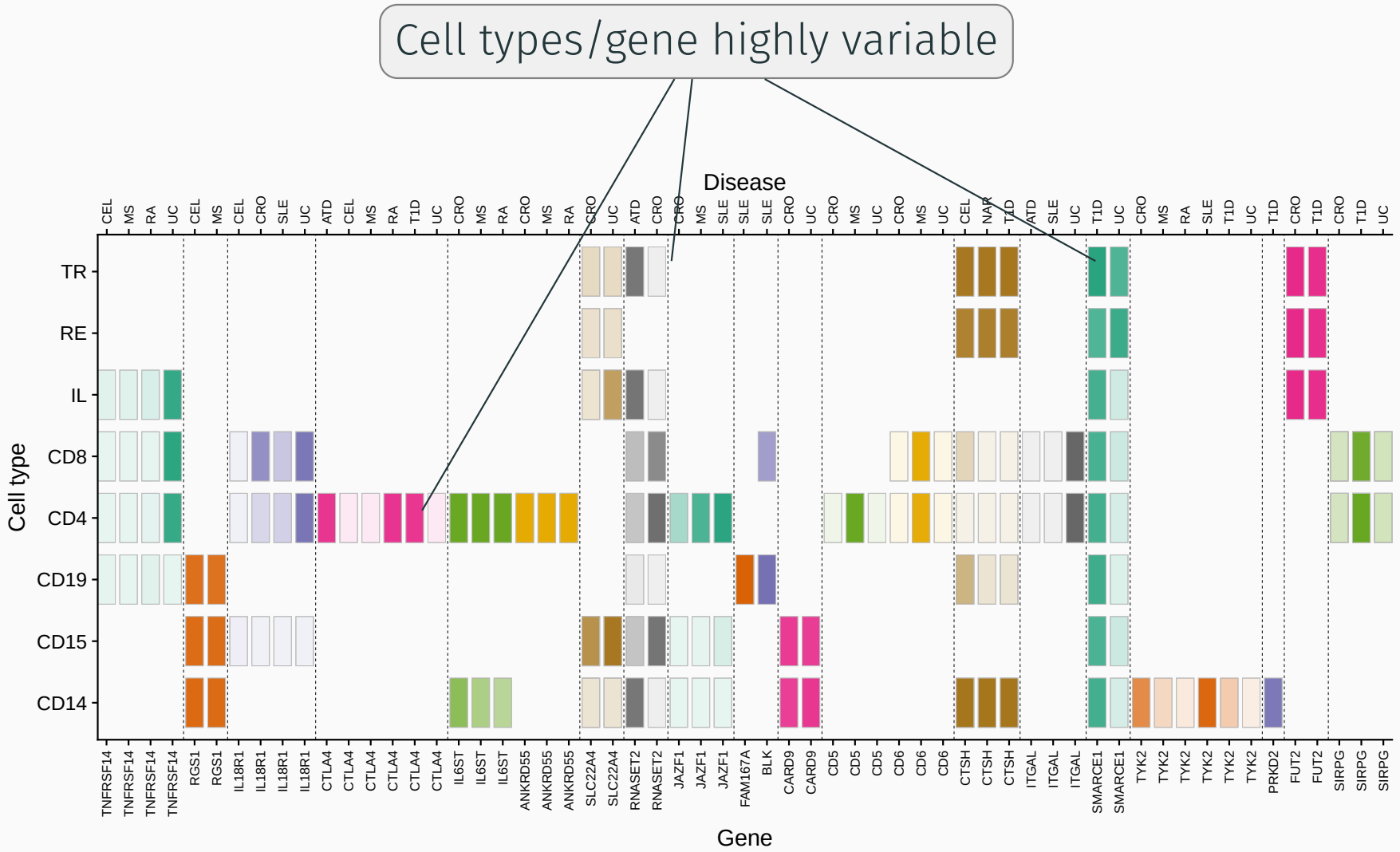

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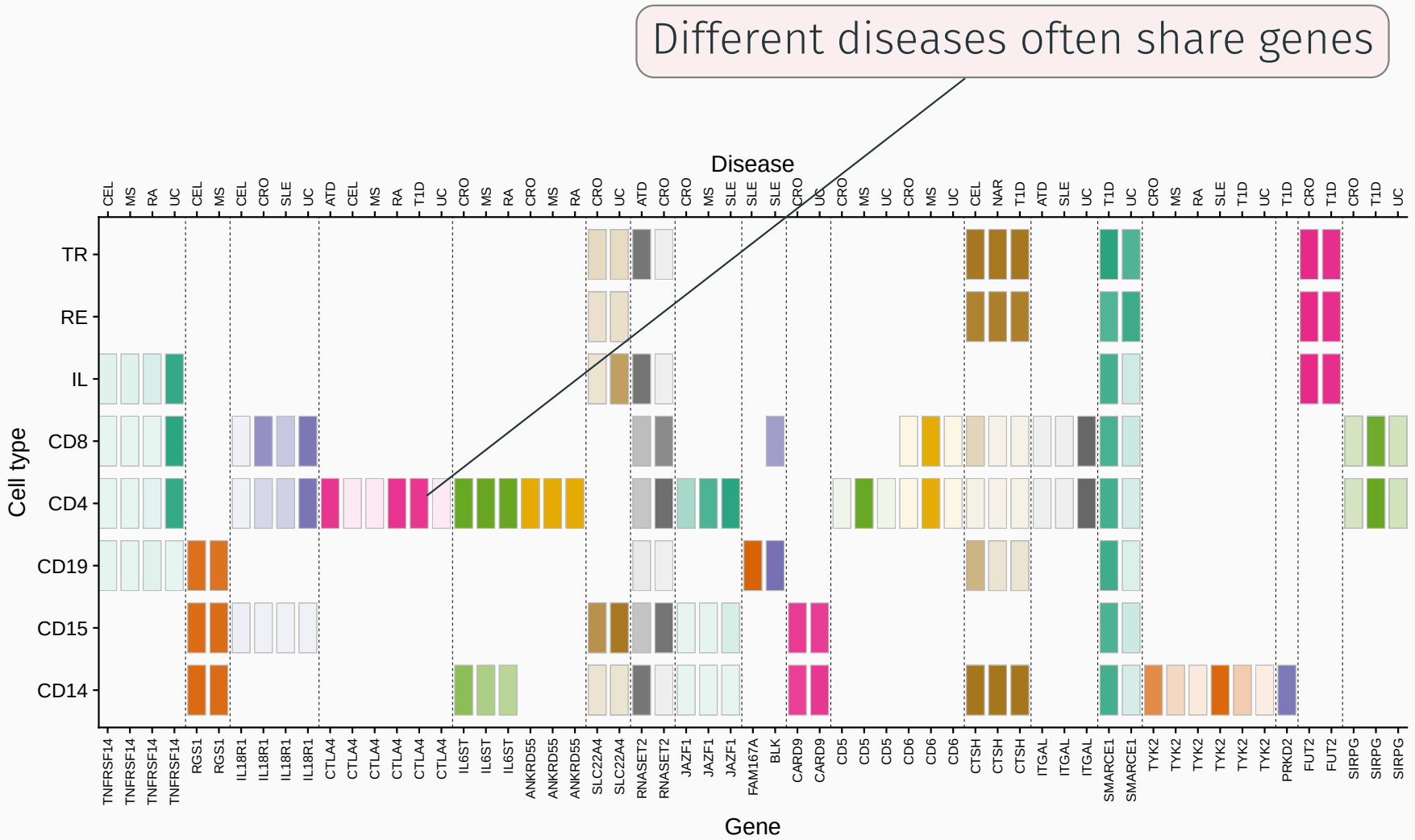

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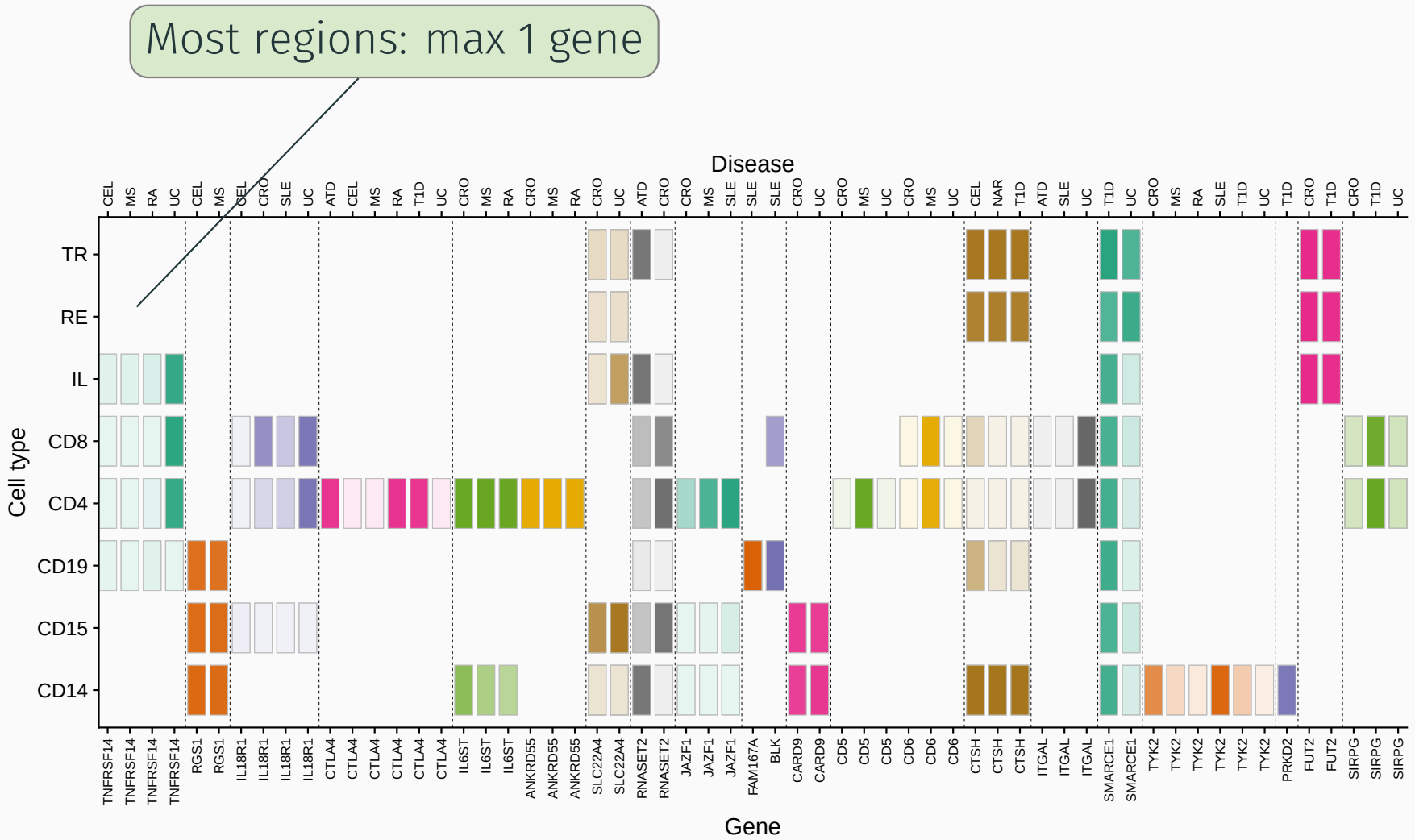

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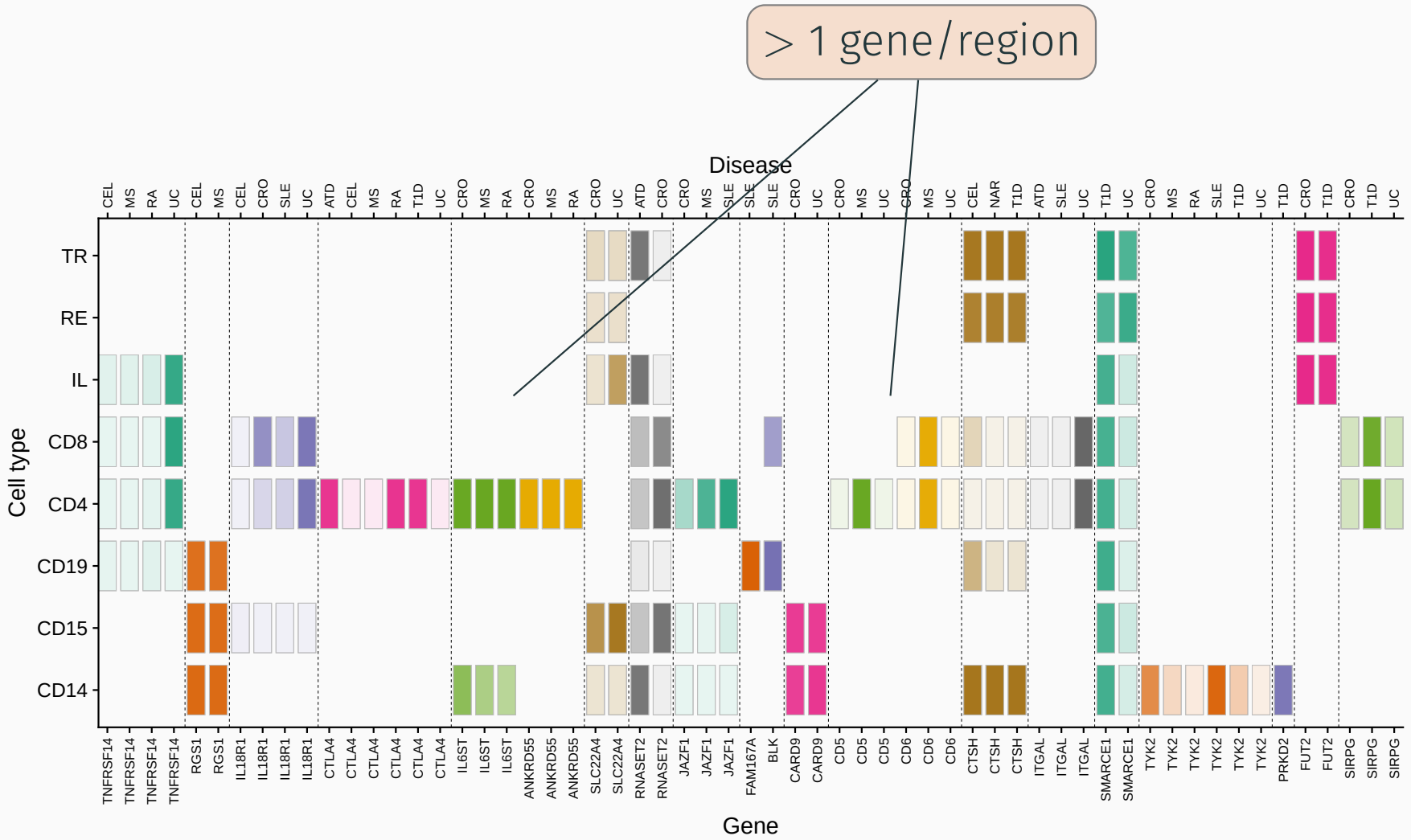

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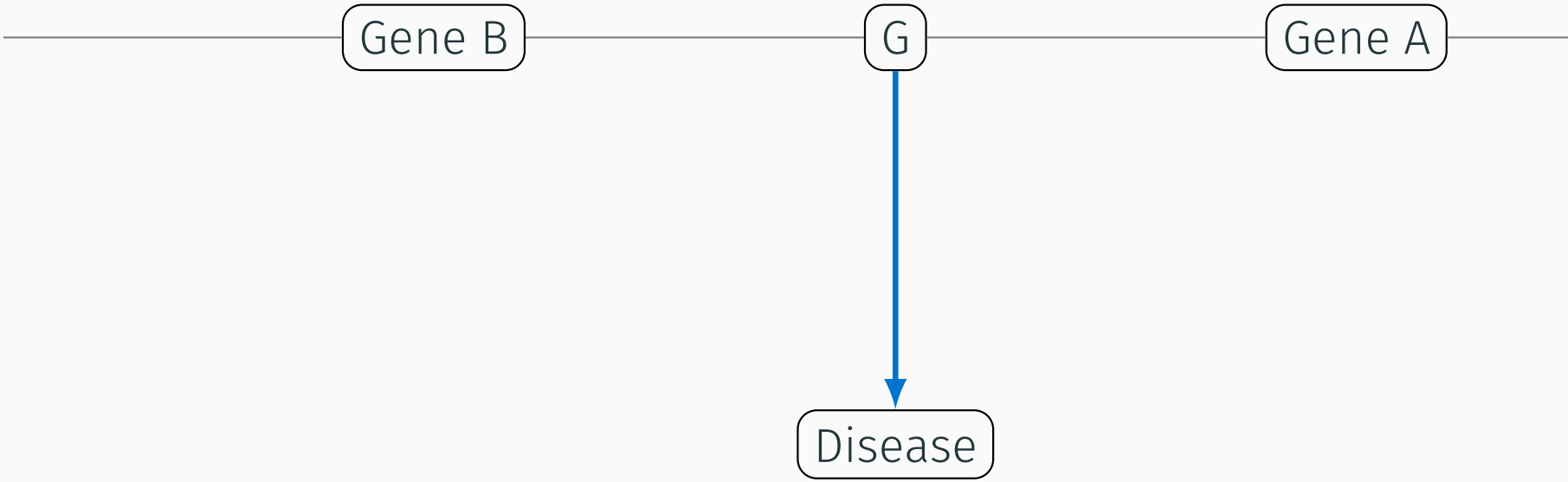
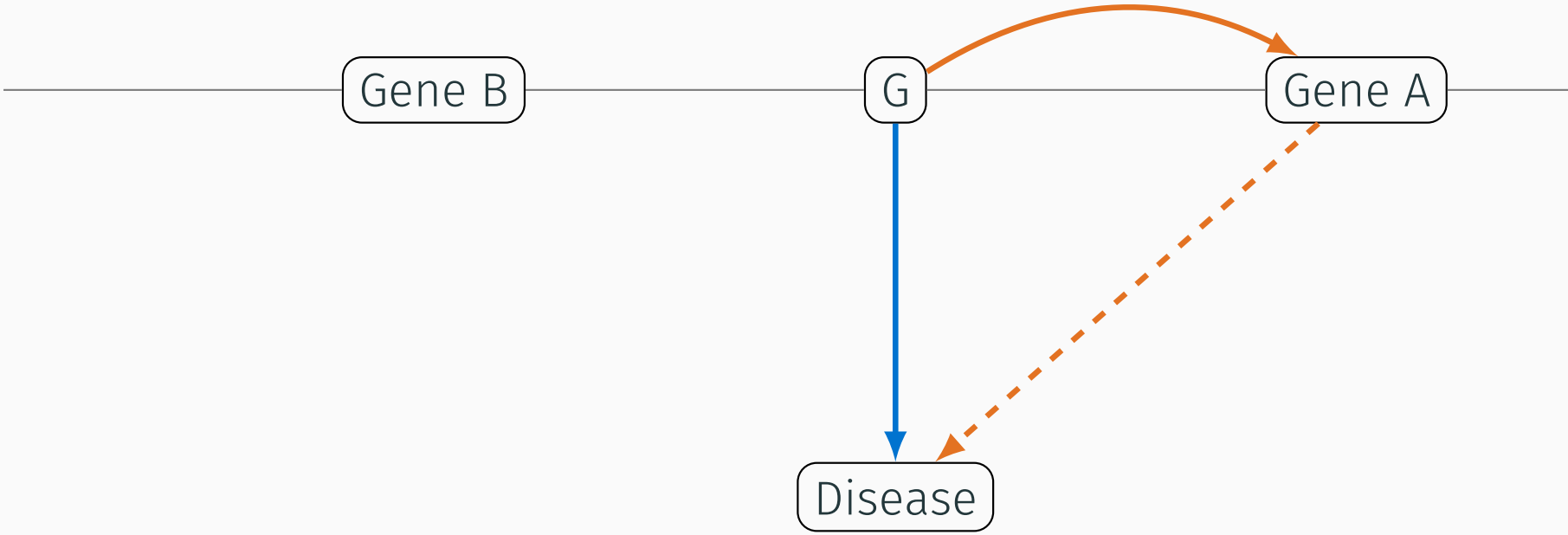

Gene B
G
Gene A
Disease


Gene B
G
Gene A
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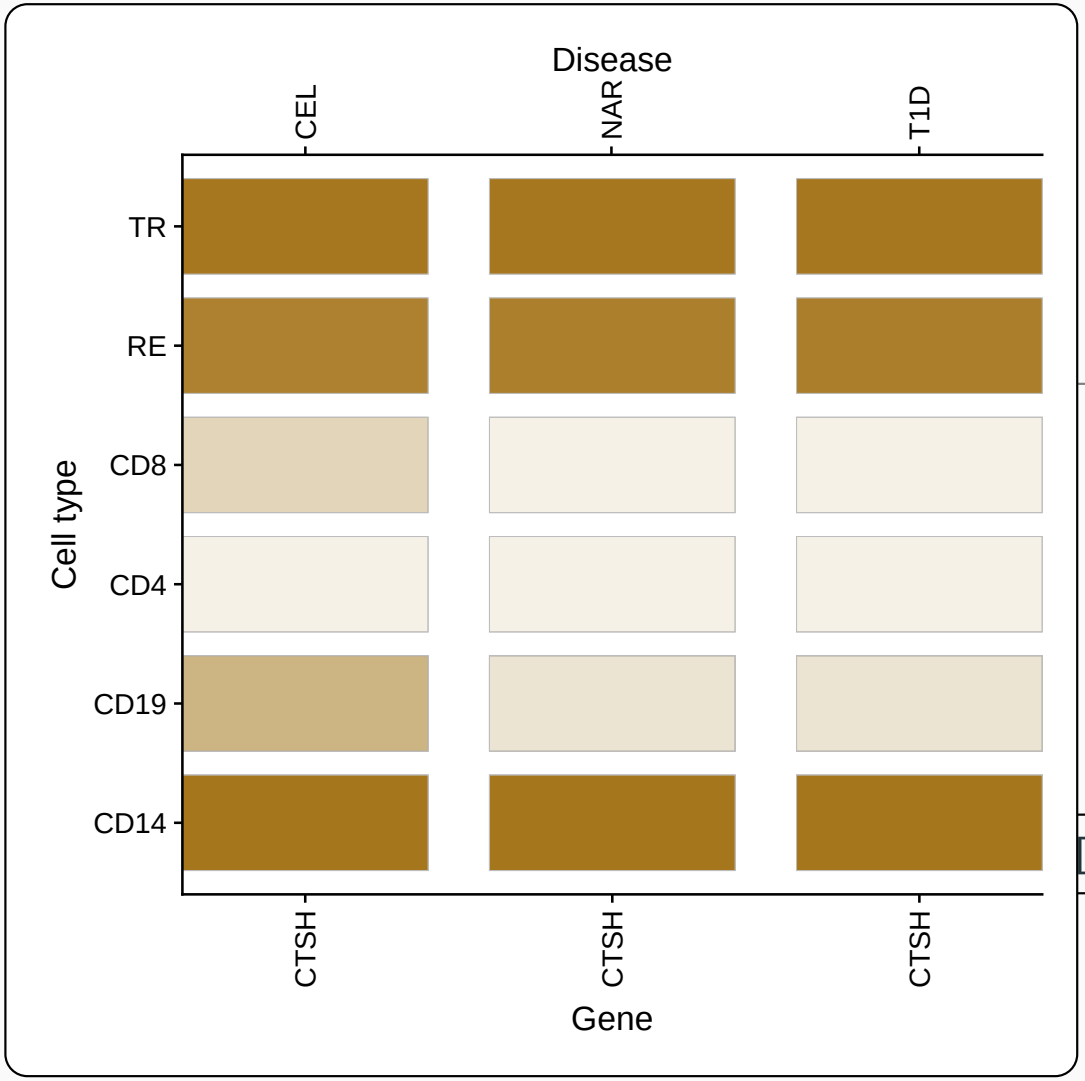
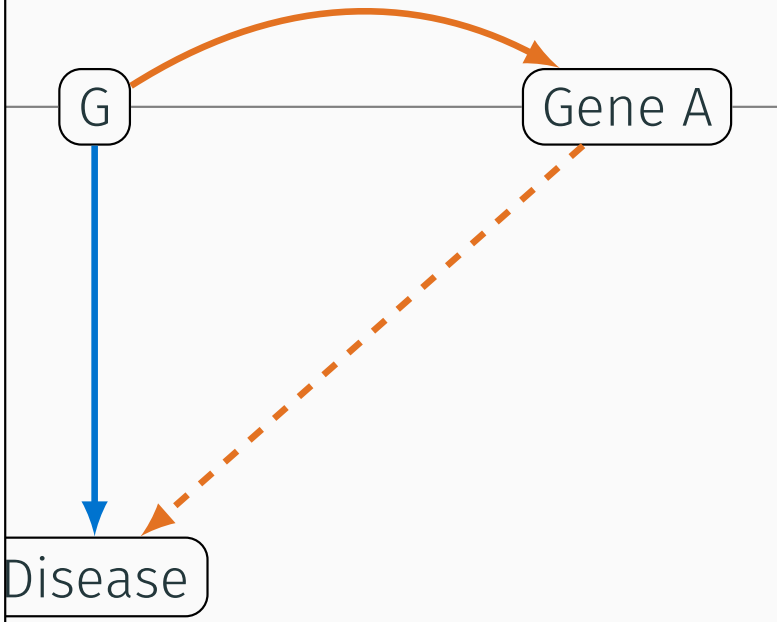
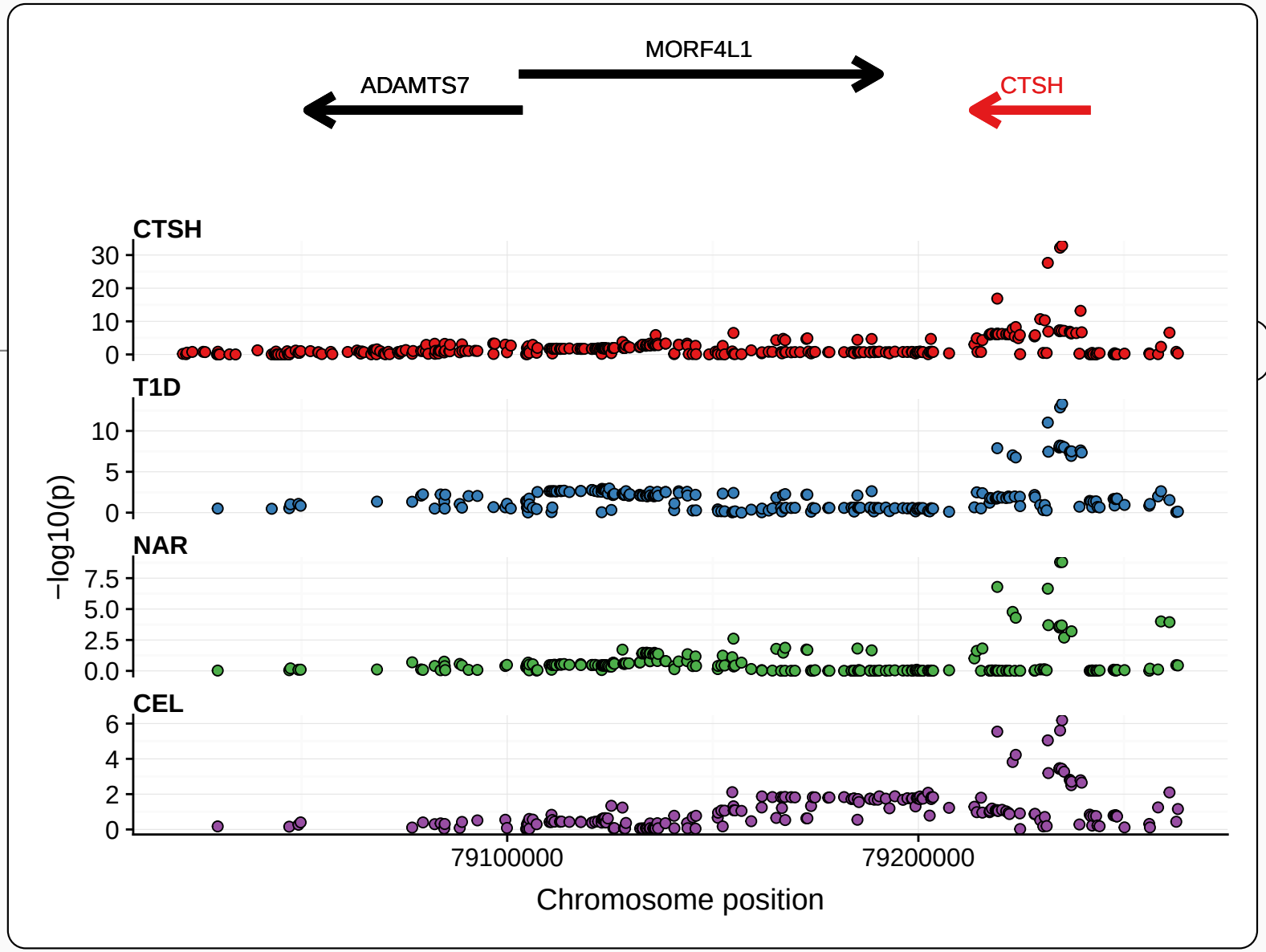
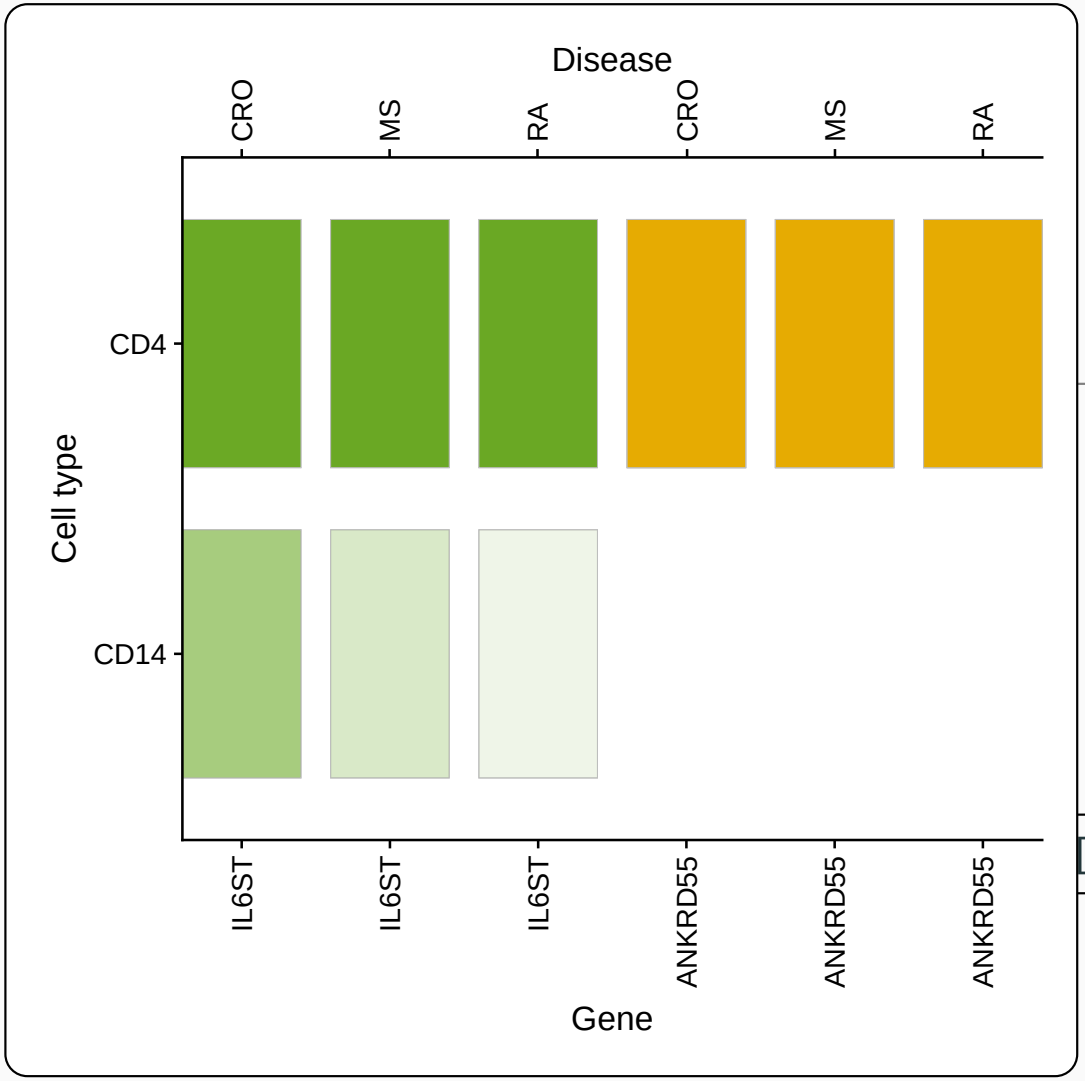

Disease
CEL
NAR
T1D
TR
RE
CD8
CD4
CD19
CD14
Cell type
CTSH
CTSH
CTSH
Gene


G
Gene A
Disease

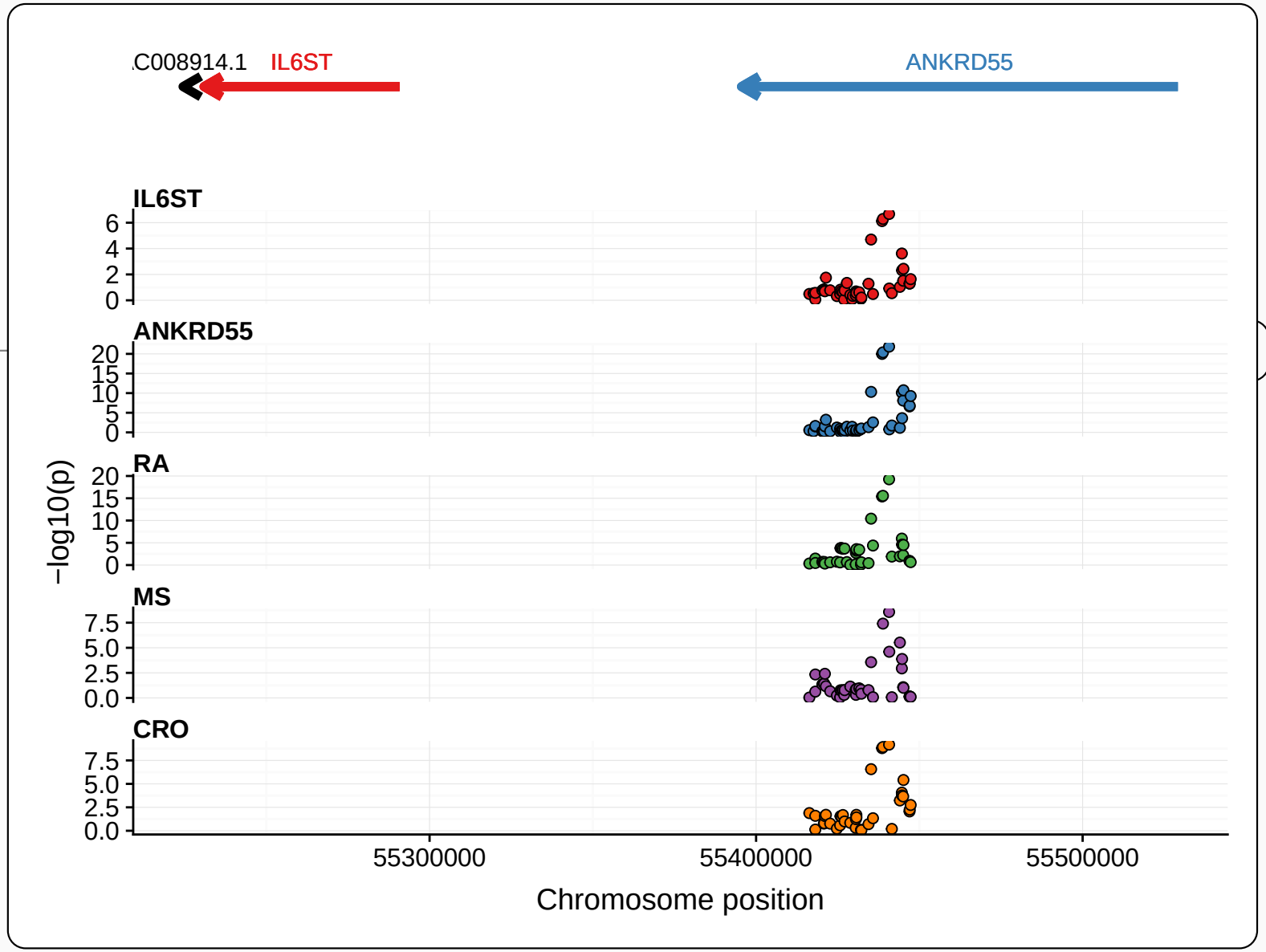

MORF4L1
ADAMTS7
CTSH
CTSH
30
20
10
0
T1D
10
5
0
NAR
7.5
5.0
2.5
0.0
CEL
6
4
2
0
−log10(p)
79100000
79200000
Chromosome position

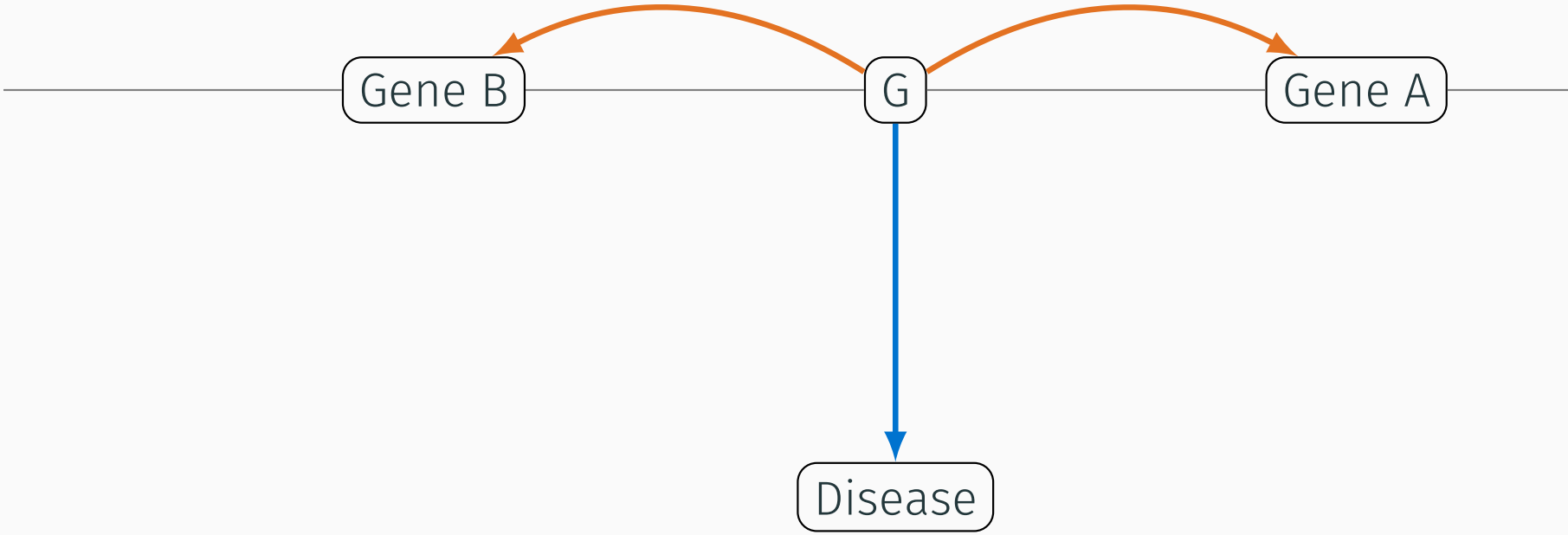


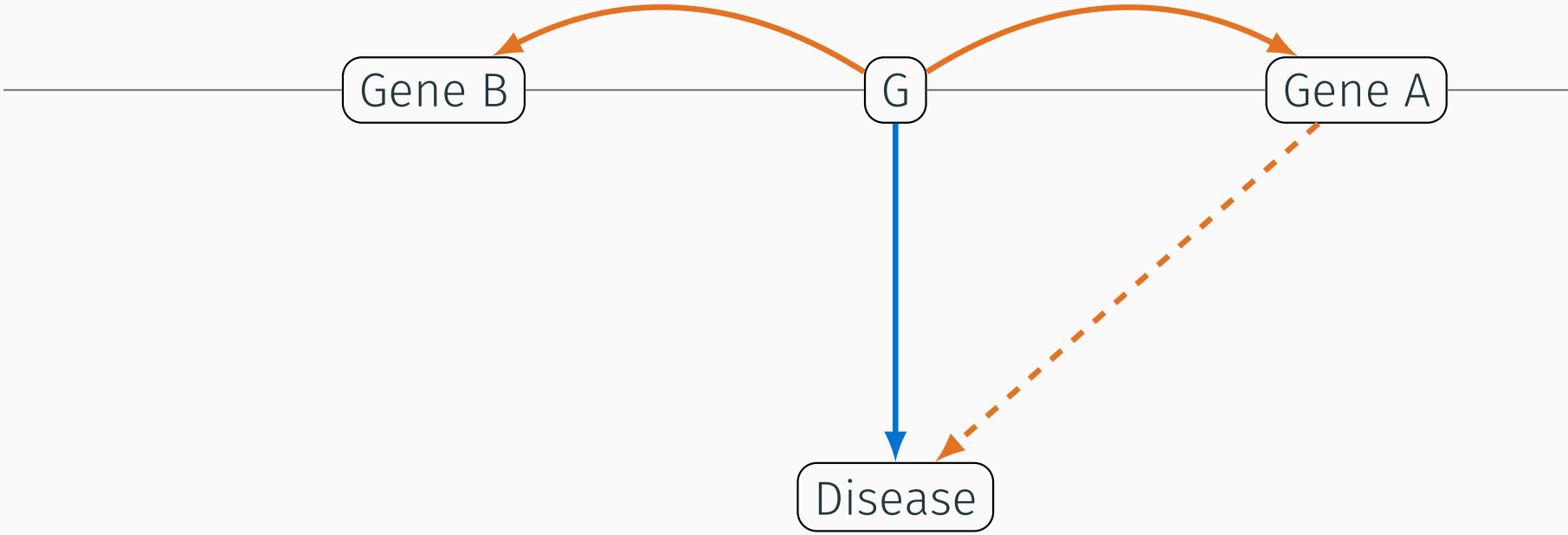
G

Gene A

Disease


.C008914.1
IL6ST
ANKRD55
IL6ST
ANKRD55
RA
MS
CRO
−log10(p)
55300000
55400000
55500000
Chromosome position


Gene B
G
Gene A
Disease


Gene B
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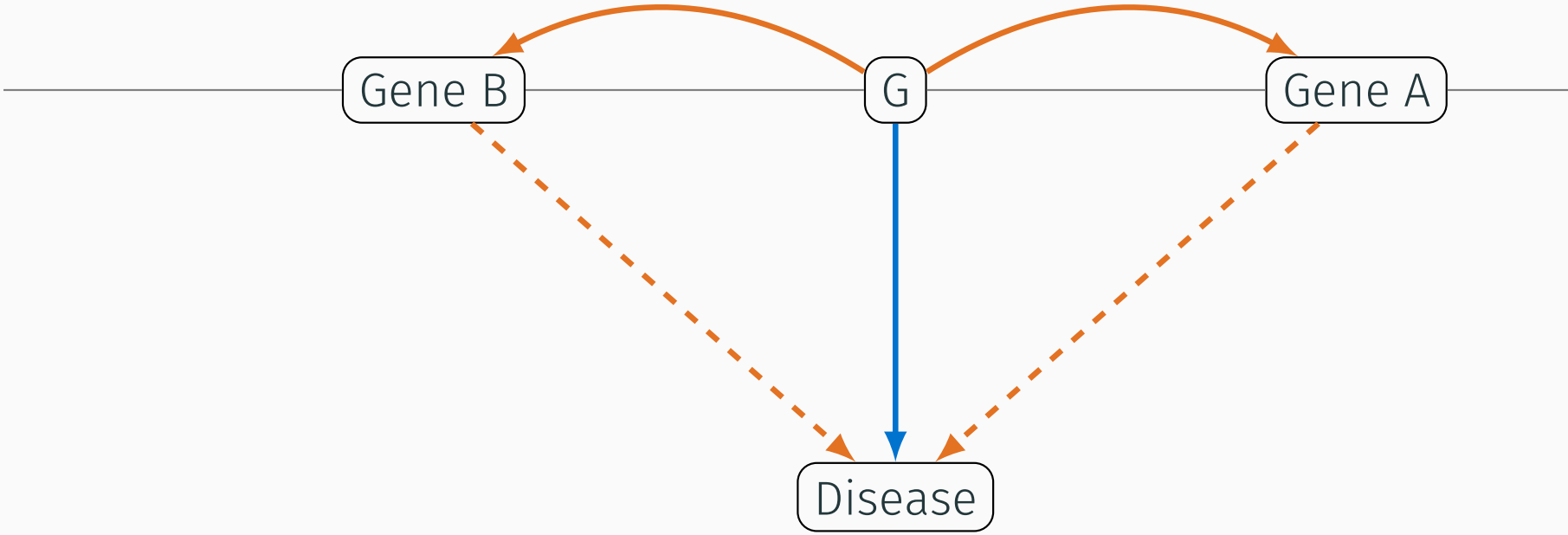
Gene B
G
Gene A
Disease

Summary

Colocalisation looks for shared genetic causes

- Search for 1+ traits that colocalise with trait of interest – potential mediators
- Or test for shared genetics for specific trait pair
- Pleitropy (one variant $\rightarrow$ two phenotypes) **is** colocalisation
- Co-regulation (one variant $\rightarrow$ two genes) detectable – interpretation: “more experiments/data needed”
- Single coloc gene might reflect only partial search

Bayesian method - informative priors

- Default values for marginal priors seem reasonable
- Always reasonable priors for joint causality not known (also situation dependent)

Thanks to...

Stasia Grinberg 

Cooper *HMG* 2012	Trynka *NG* 2011	Eyre *NG* 2012	Onengut-Gumuscu *NG* 2015
Faraco *PlosG* 2013	Liu *NG* 2012	Liu *NG* 2013	Momozawa *NG* 2018
Tsoi *NG* 2012	Hinks *NG* 2013	IMSGC *NG* 2013	Liu *NG* 2015

wellcome

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