Needles, haystacks and genetic causes of disease

Chris Wallace chr1swallace chr1swallace.github.io

Jenn Asimit

Mary Fortune

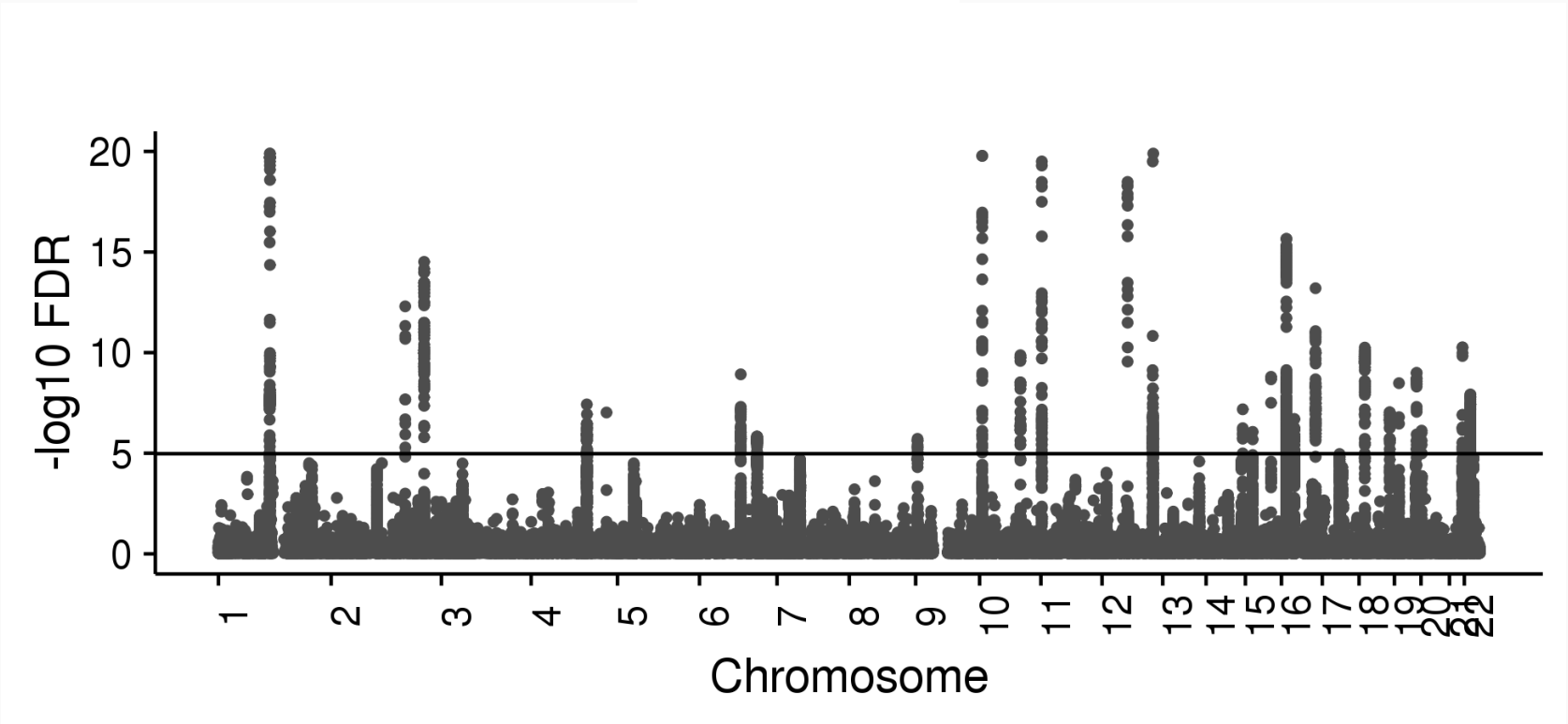
Dan Rainbow

wellcome

UNIVERSITY OF CAMBRIDGE

MRC | Biostatistics Unit

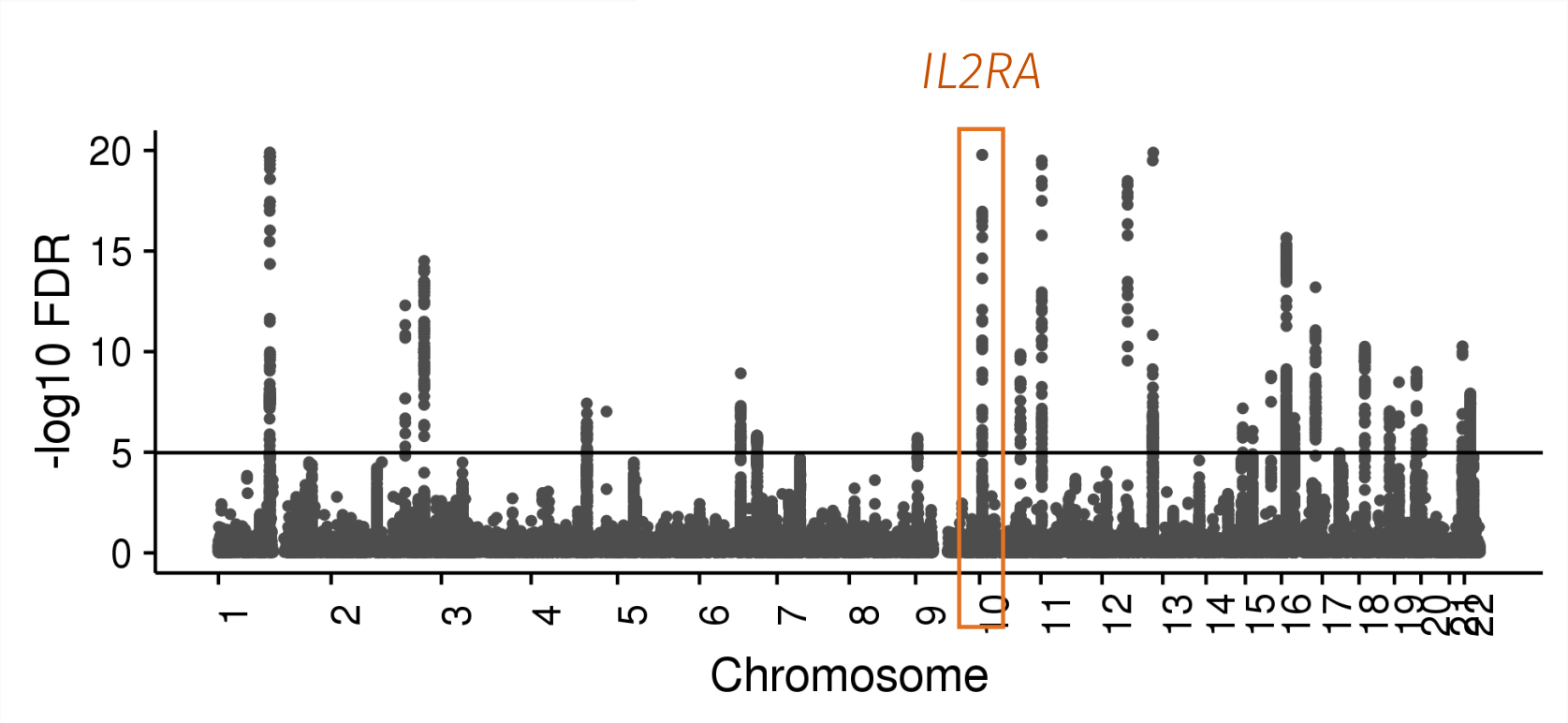
Manhattan plots (haystack plots?)



How do we use GWAS to identify disease genes/proteins and drug targets?

Onengut et al, Nat Genet 2015

Manhattan plots (haystack plots?)



How do we use GWAS to identify disease genes/proteins and drug targets?

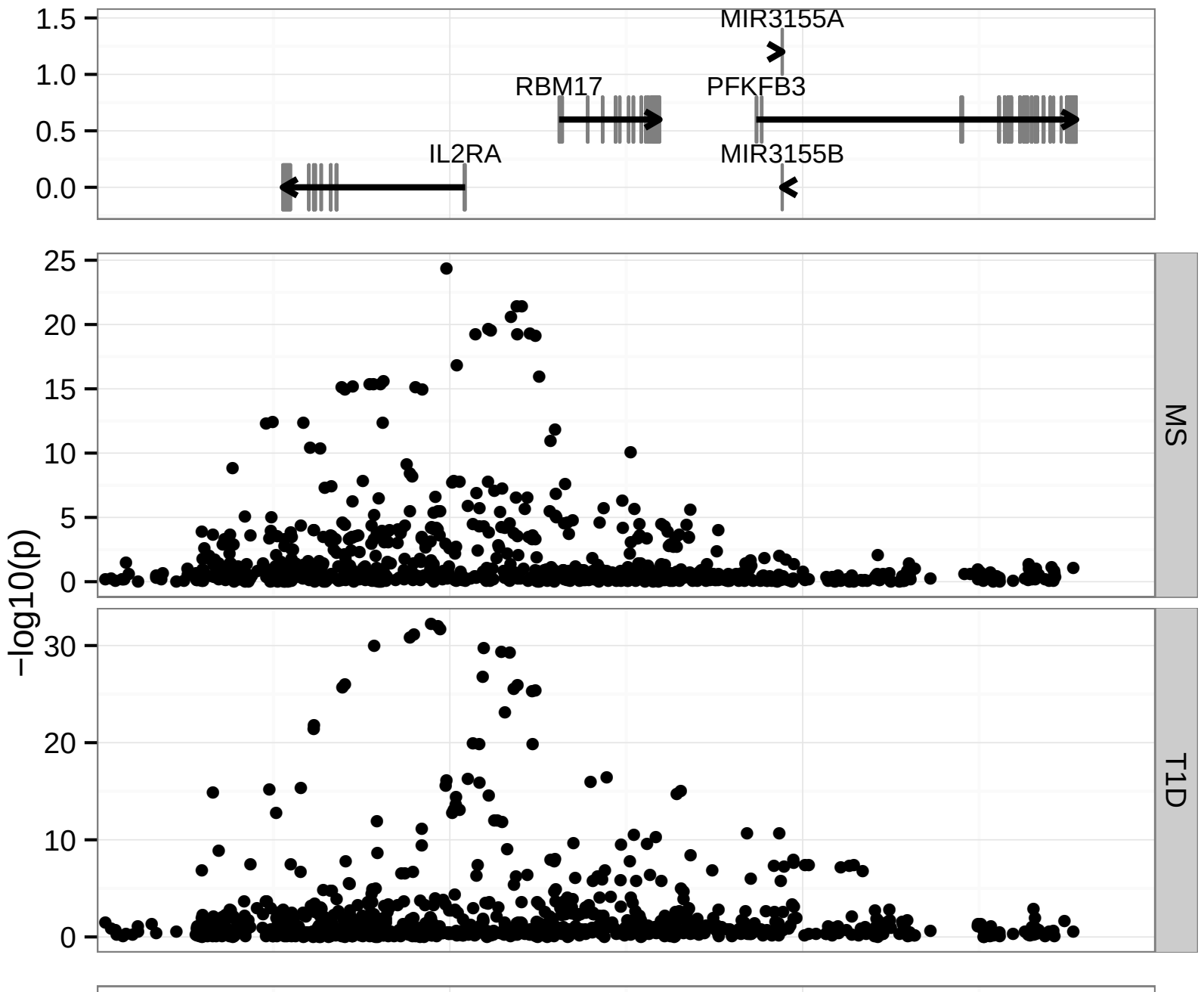
Onengut et al, Nat Genet 2015

Overview

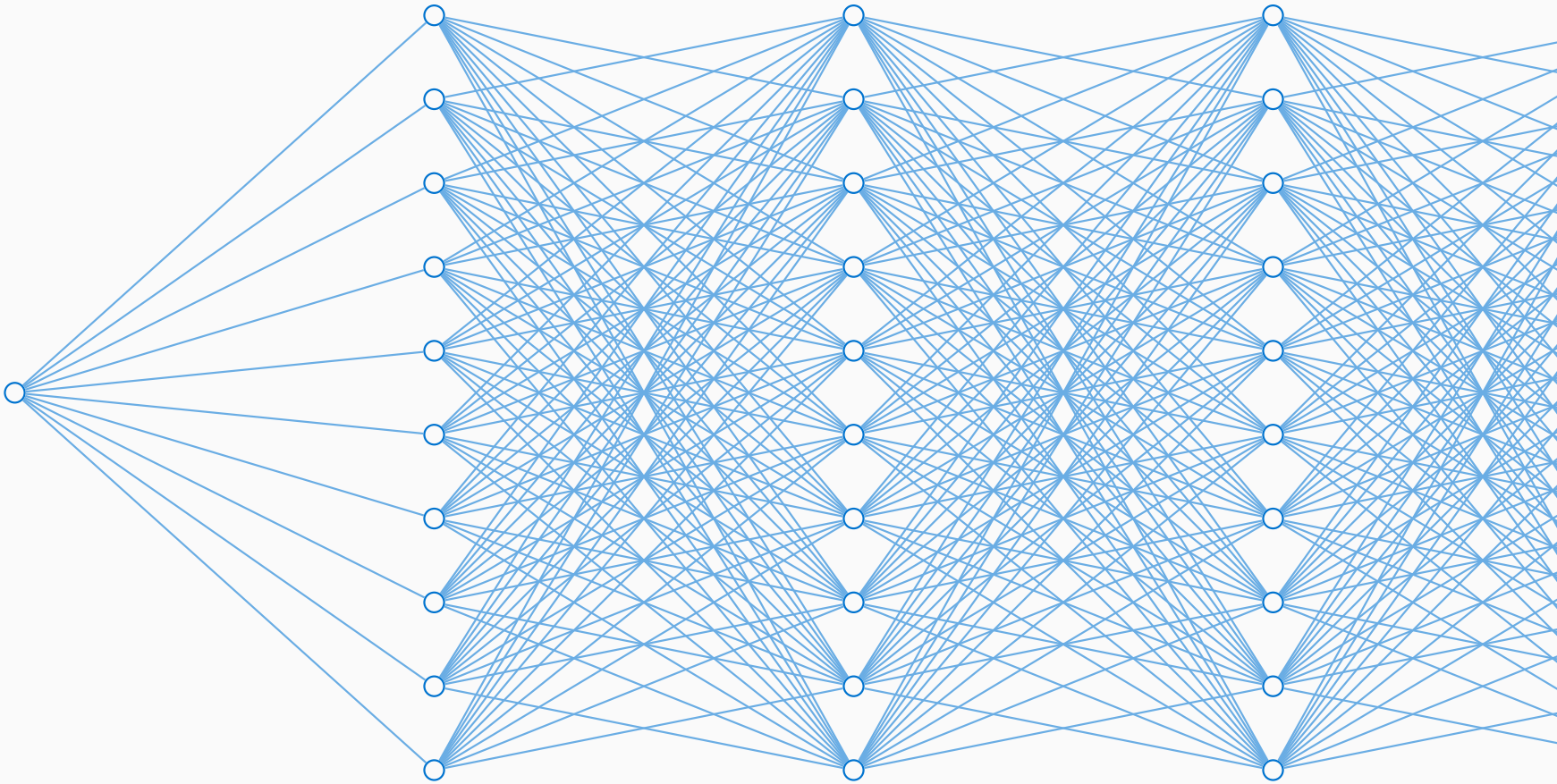
- Fine mapping causal variants
- Joint tagging of causal variants
- Improved fine mapping by exploiting shared aetiology
- Functional validation of causal effects on *IL2RA*

Fine mapping causal variants

Association of MS and T1D in *IL2RA* region



Stepwise search



no SNPs 1 SNP 2 SNPs 3 SNPs

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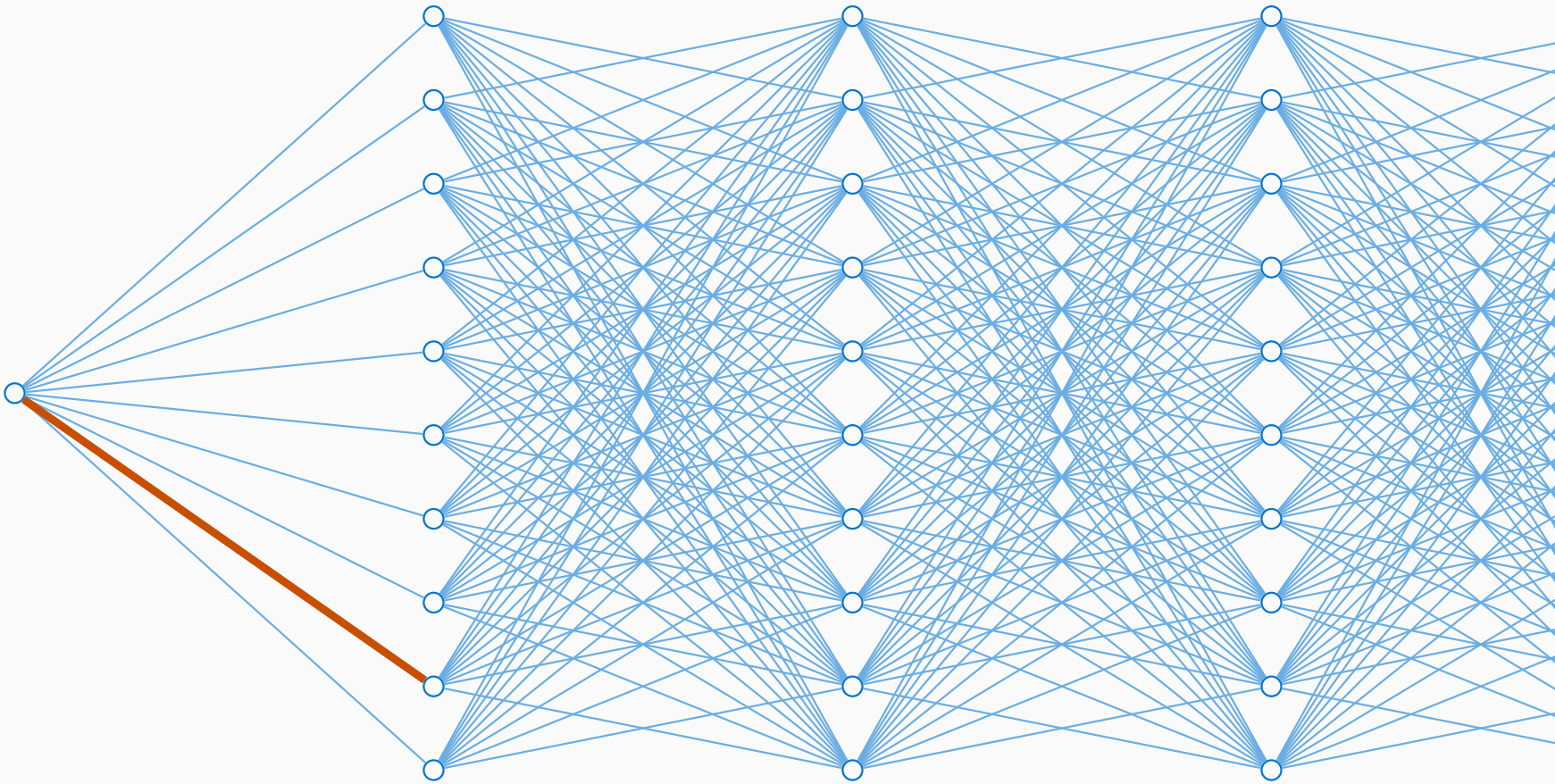

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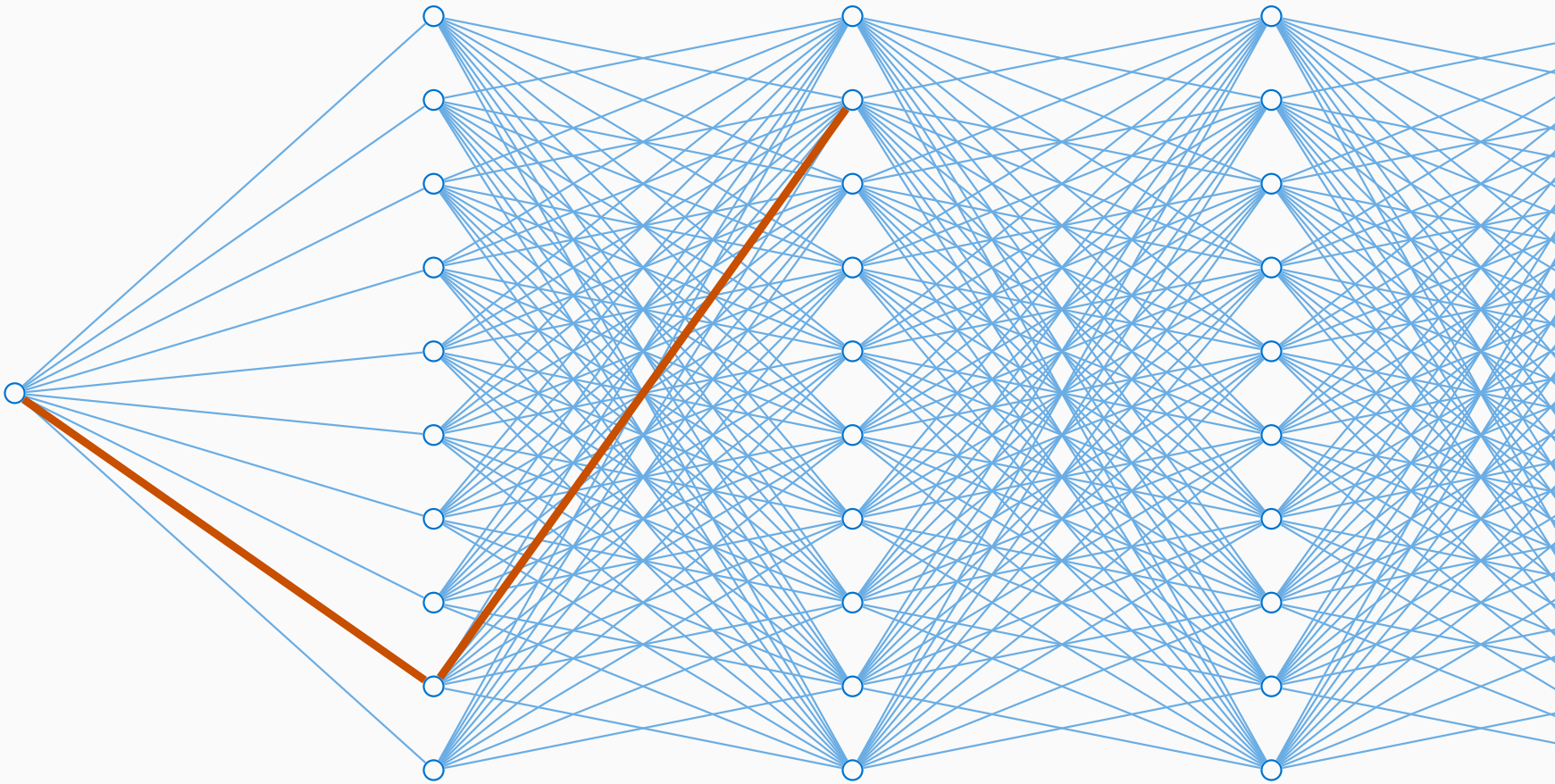

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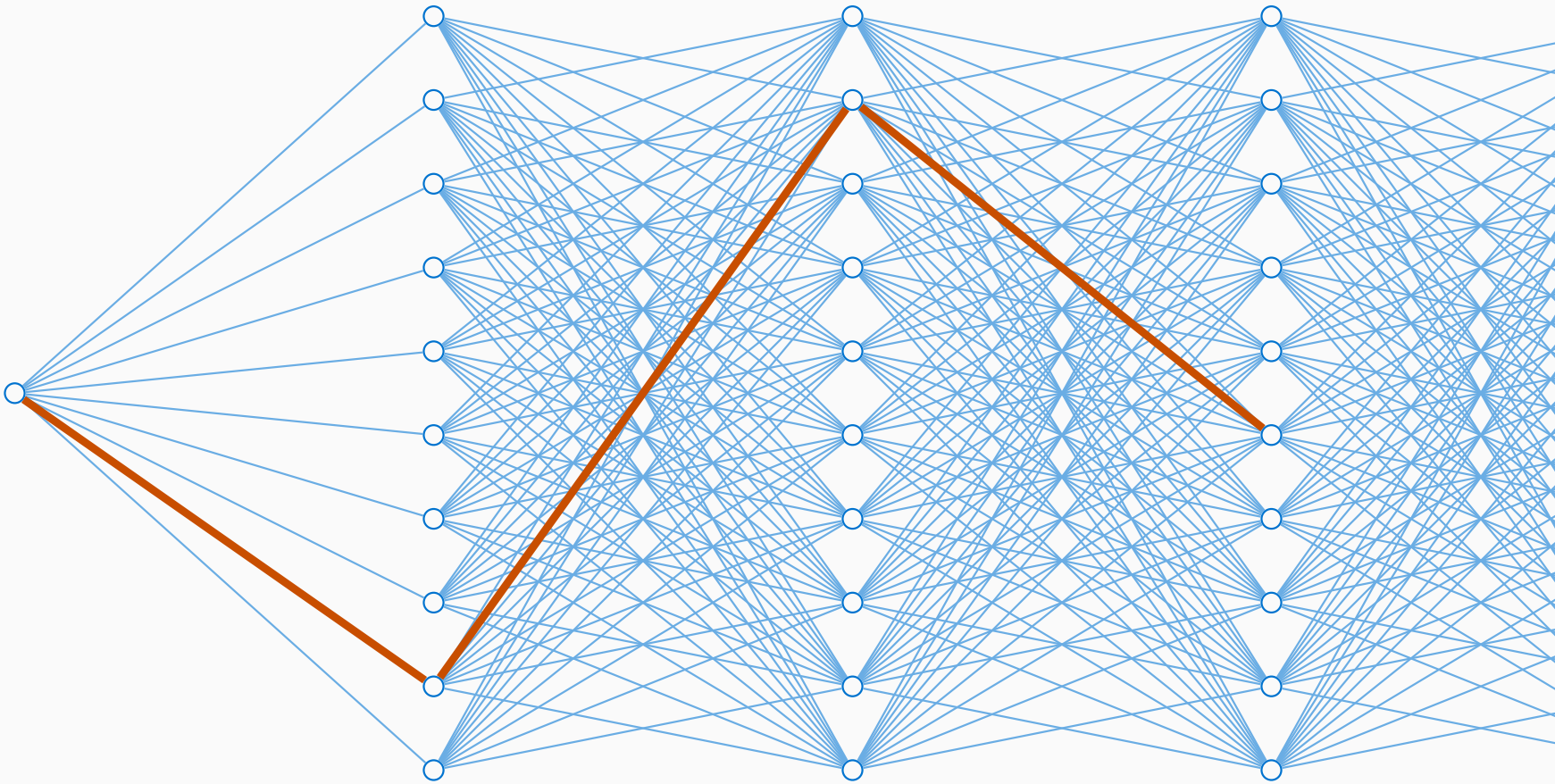

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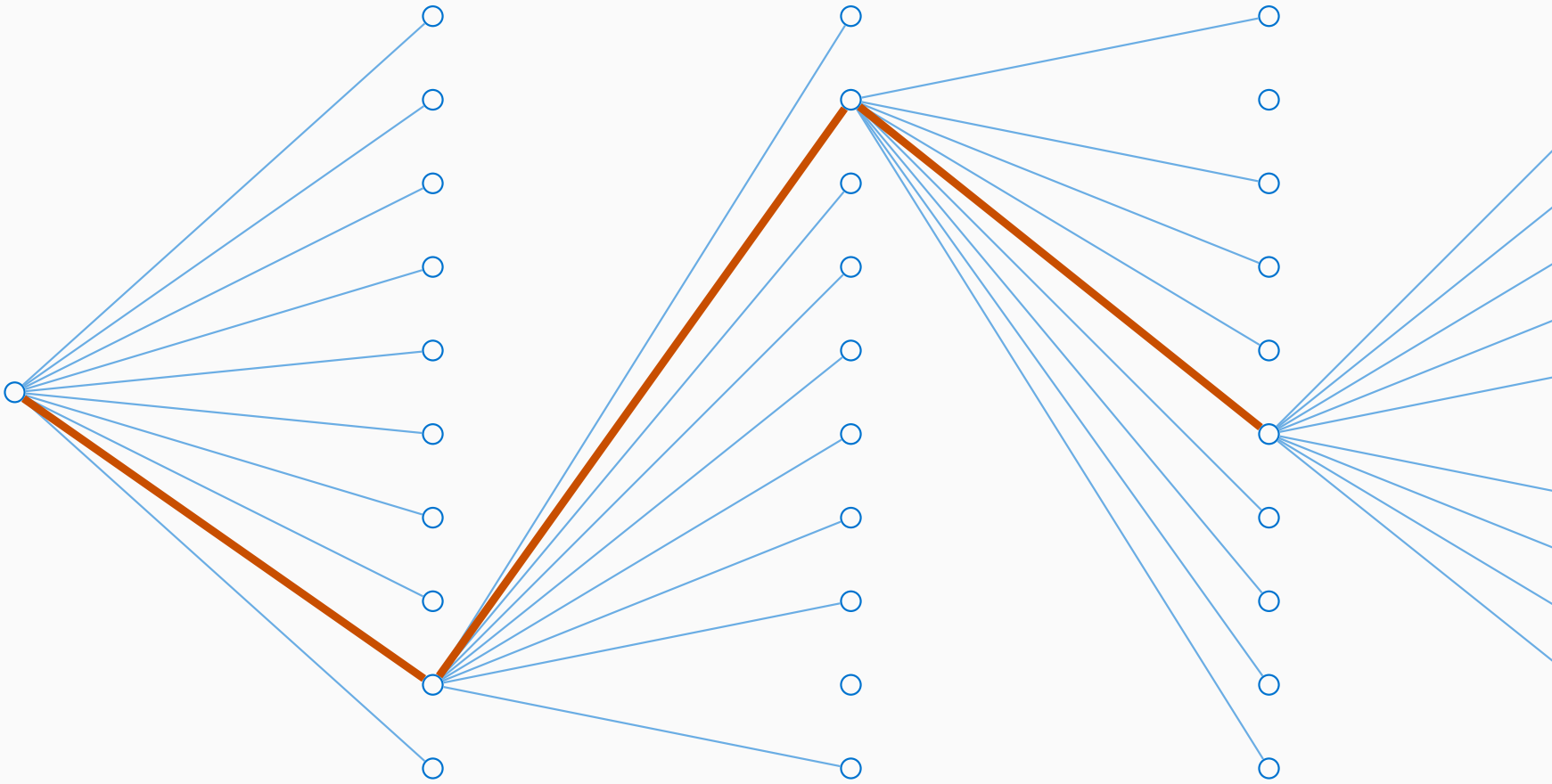

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Stepwise search of IL2RA region

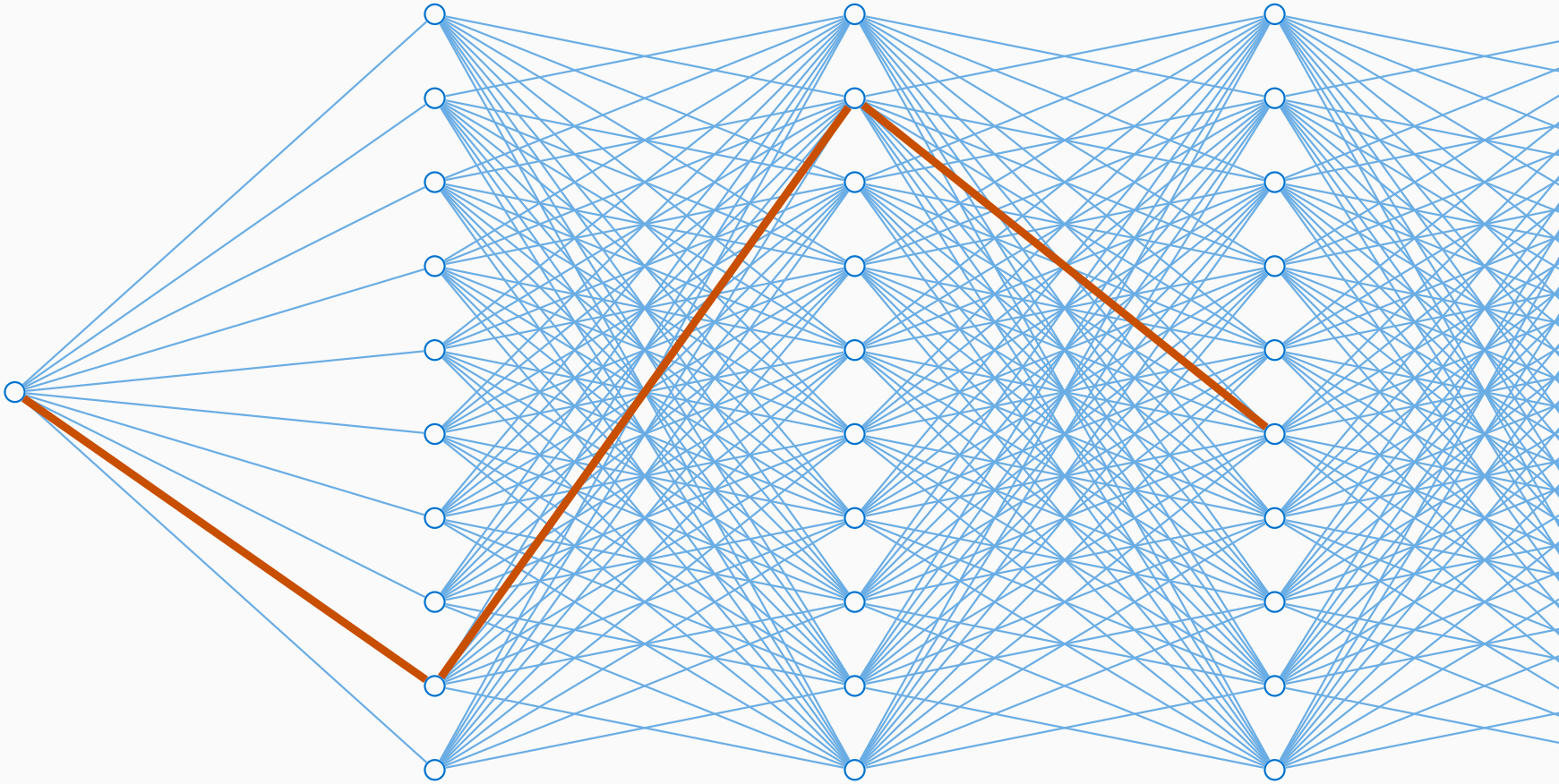
MS

SNP	p
rs2104286	$< 2 \times 10^{-16}$
rs11256593	1×10^{-5}

T1D

SNP	p
rs61839660	$< 2 \times 10^{-16}$
rs11594656	7×10^{-12}
rs12220852	1×10^{-9}
rs41295159	1×10^{-7}

Alternative: evolutionary stochastic search



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Botolo et al, PLoS Genet 2013; Wallace et al, PLoS Genet 2015

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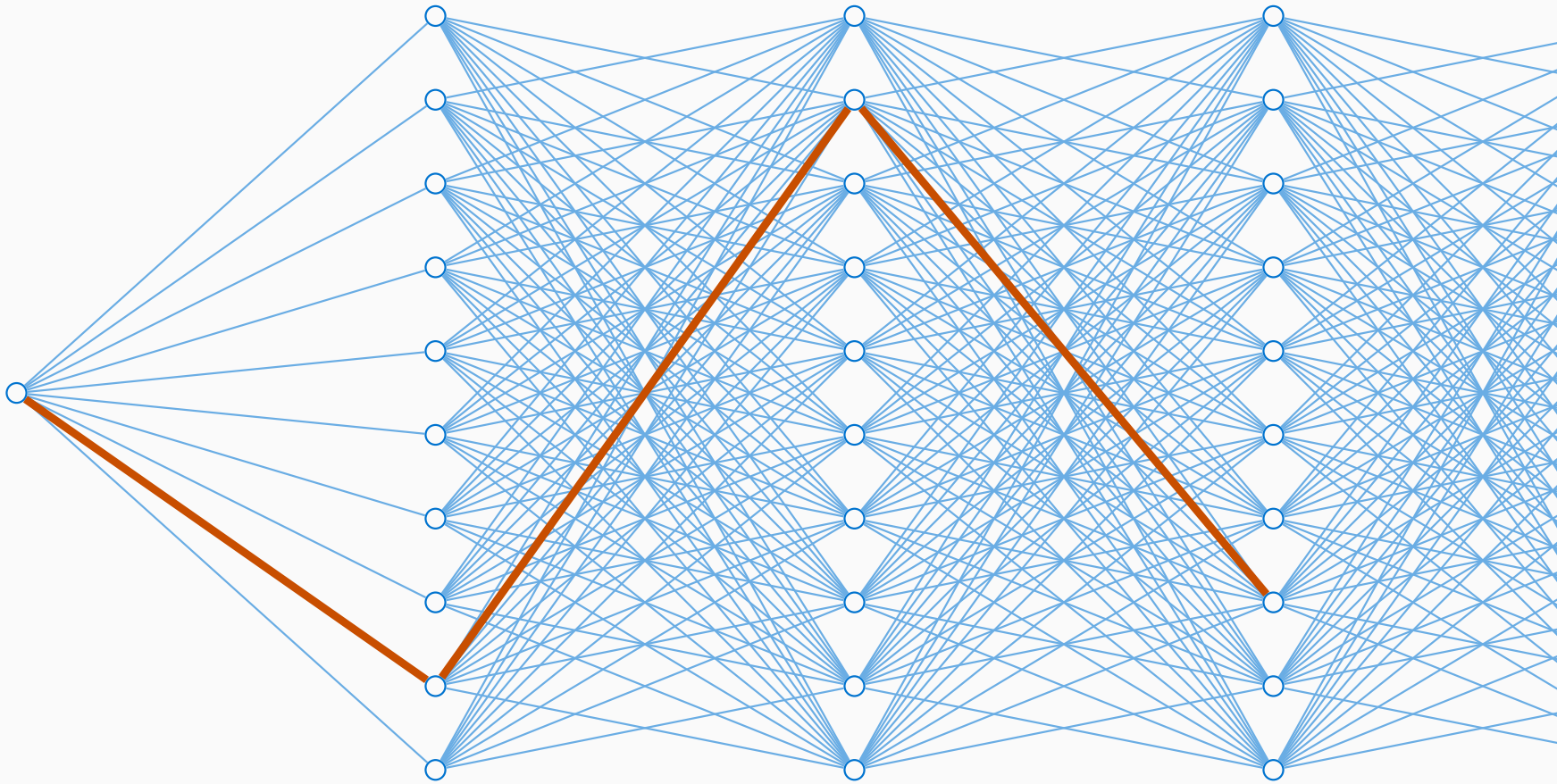

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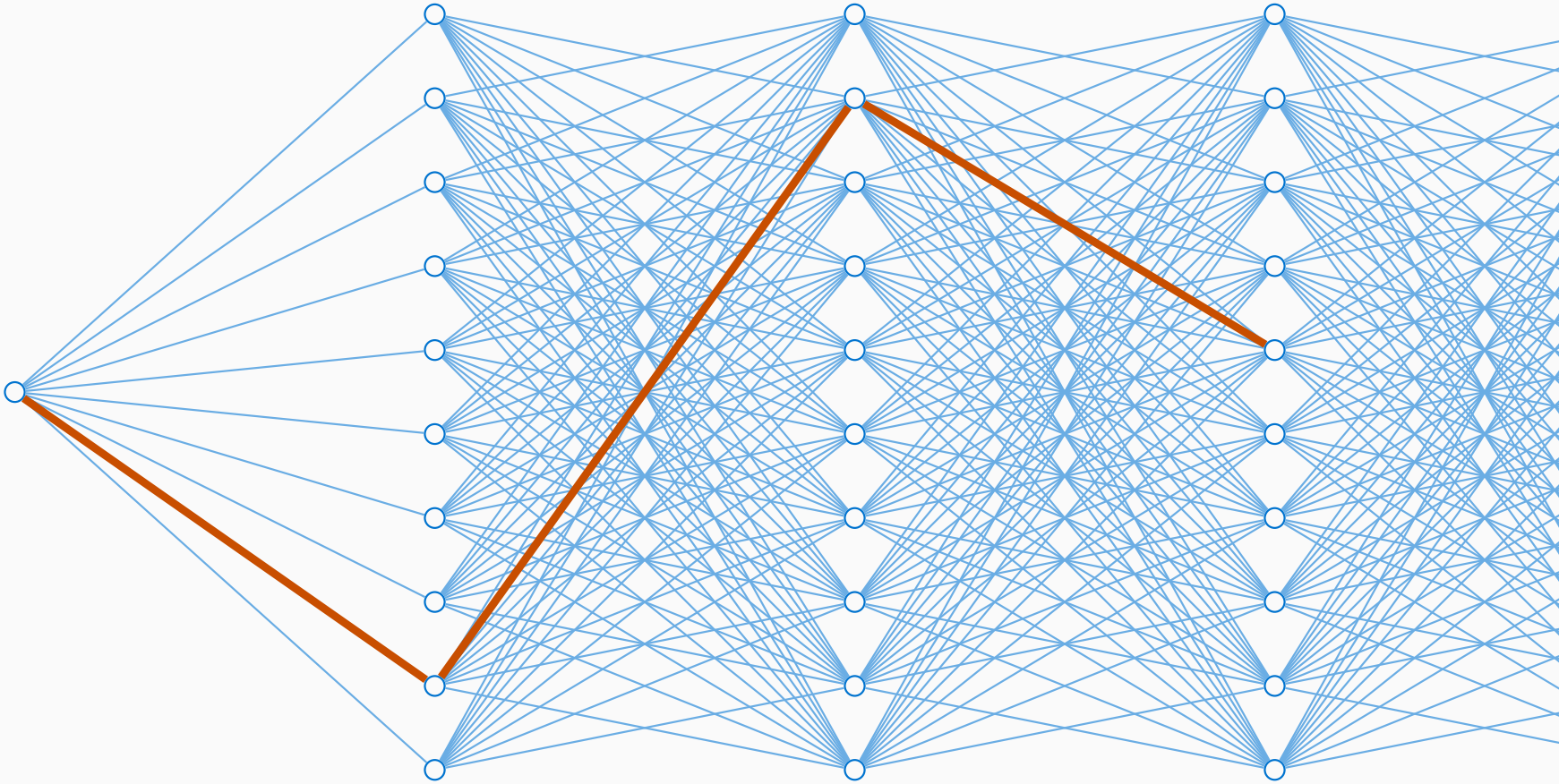

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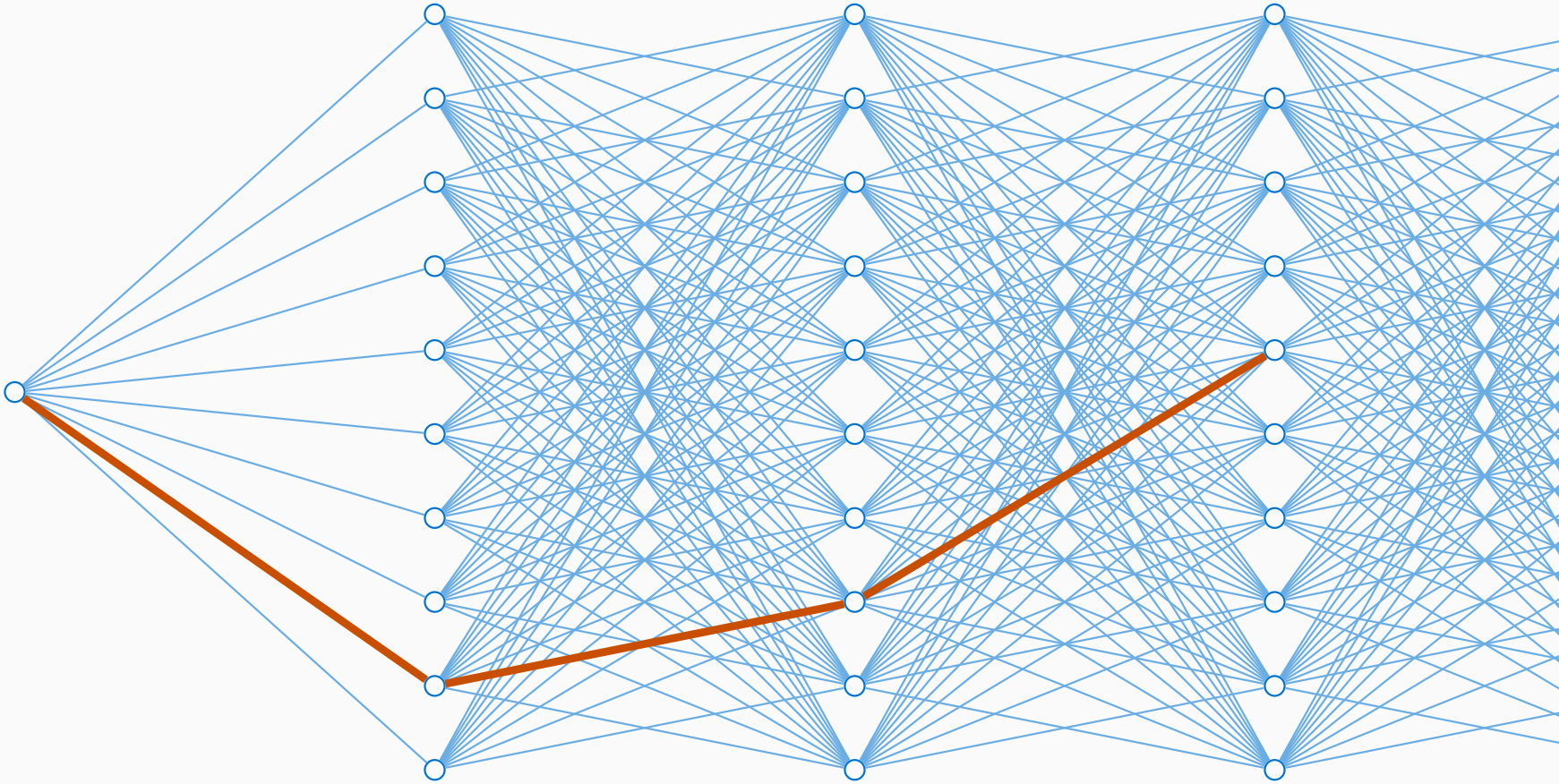

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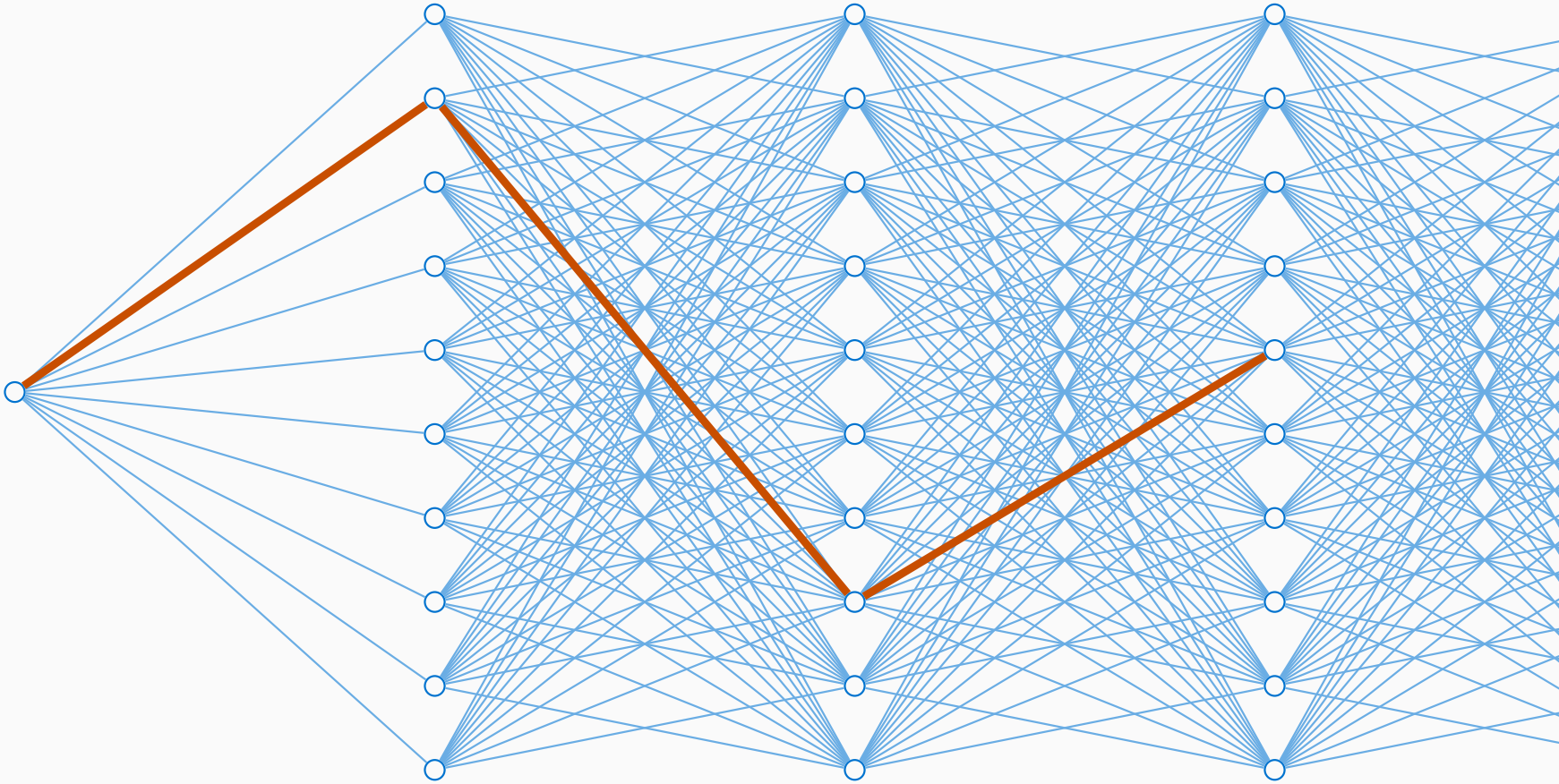

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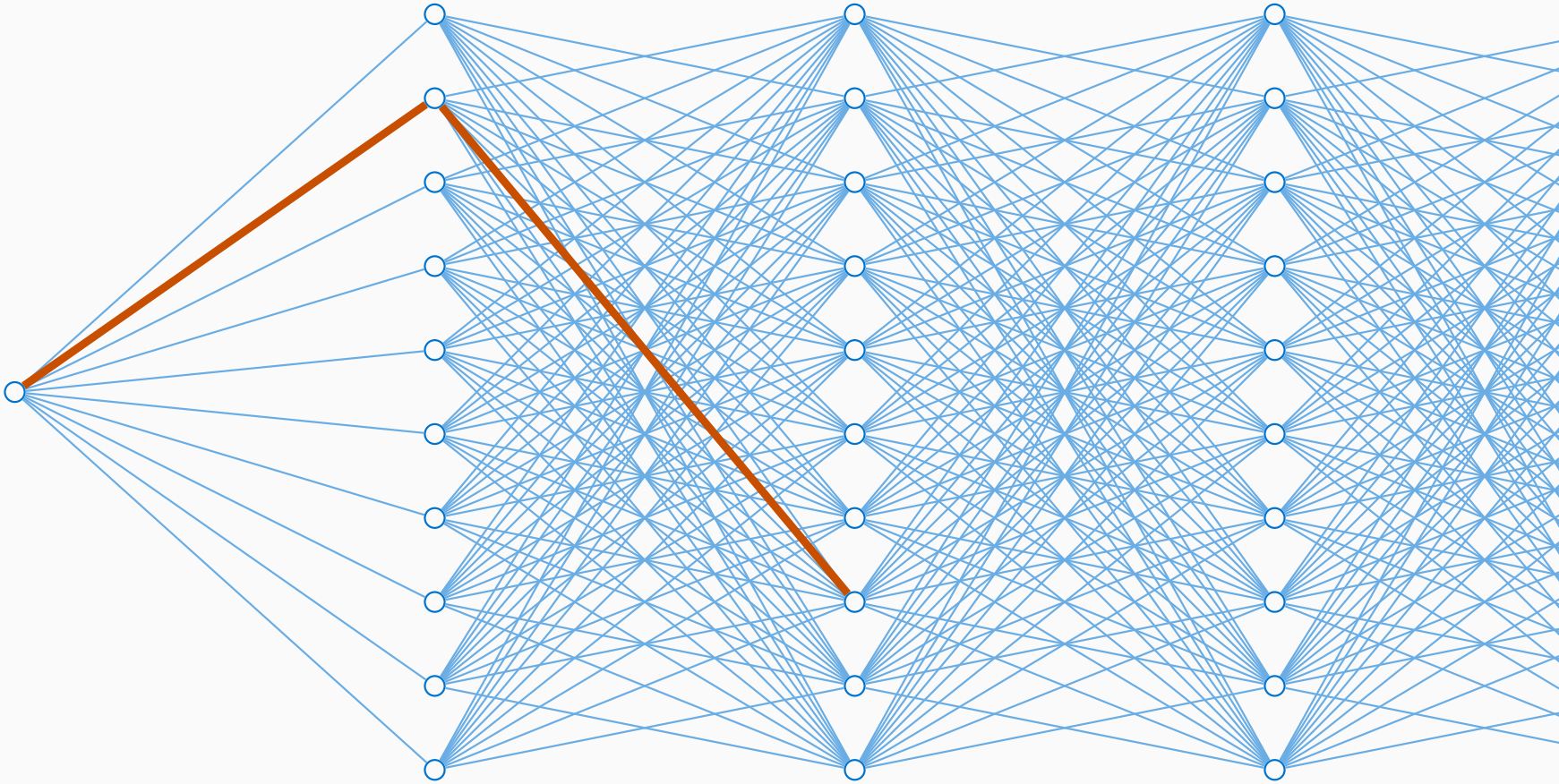

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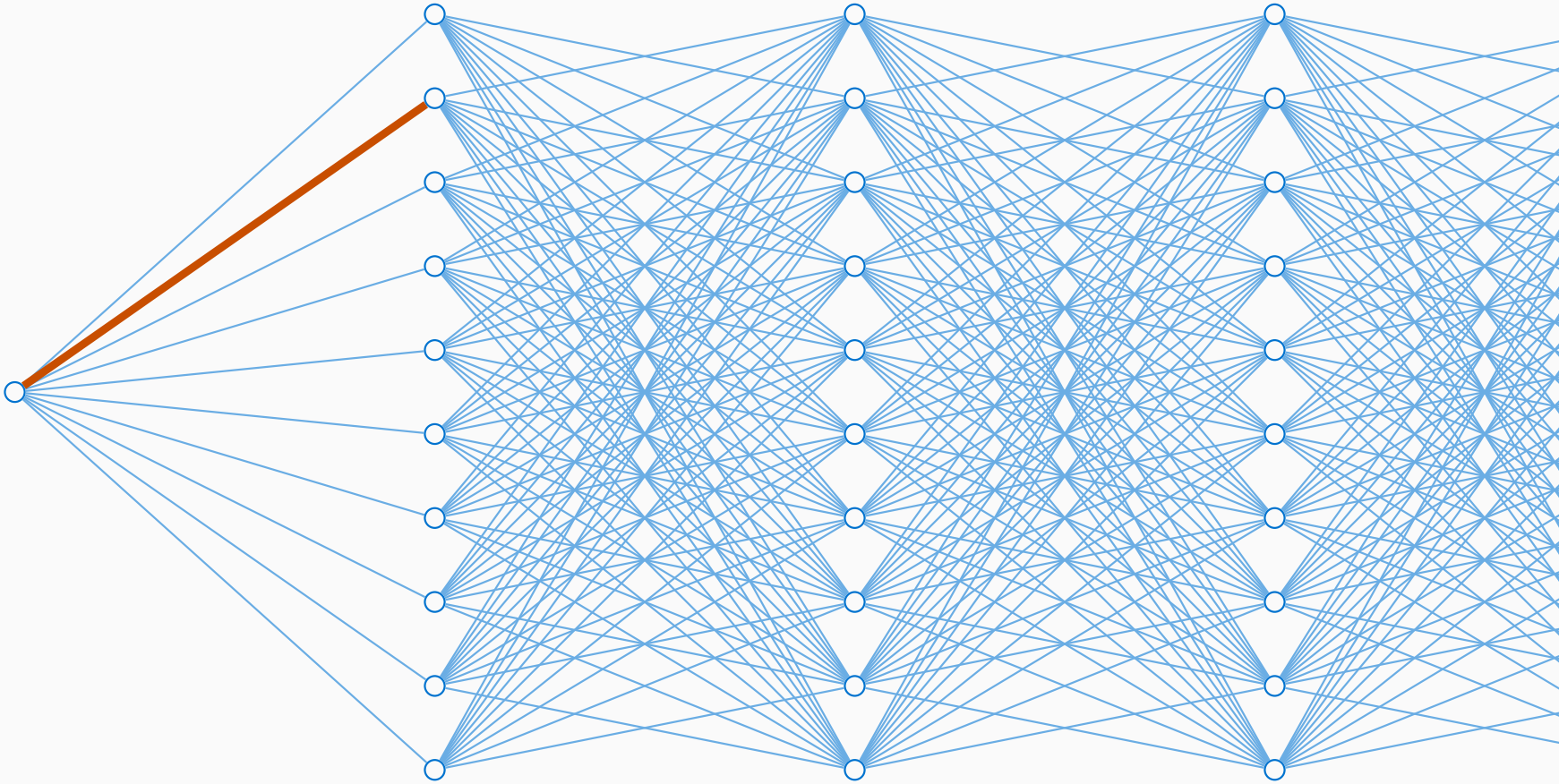

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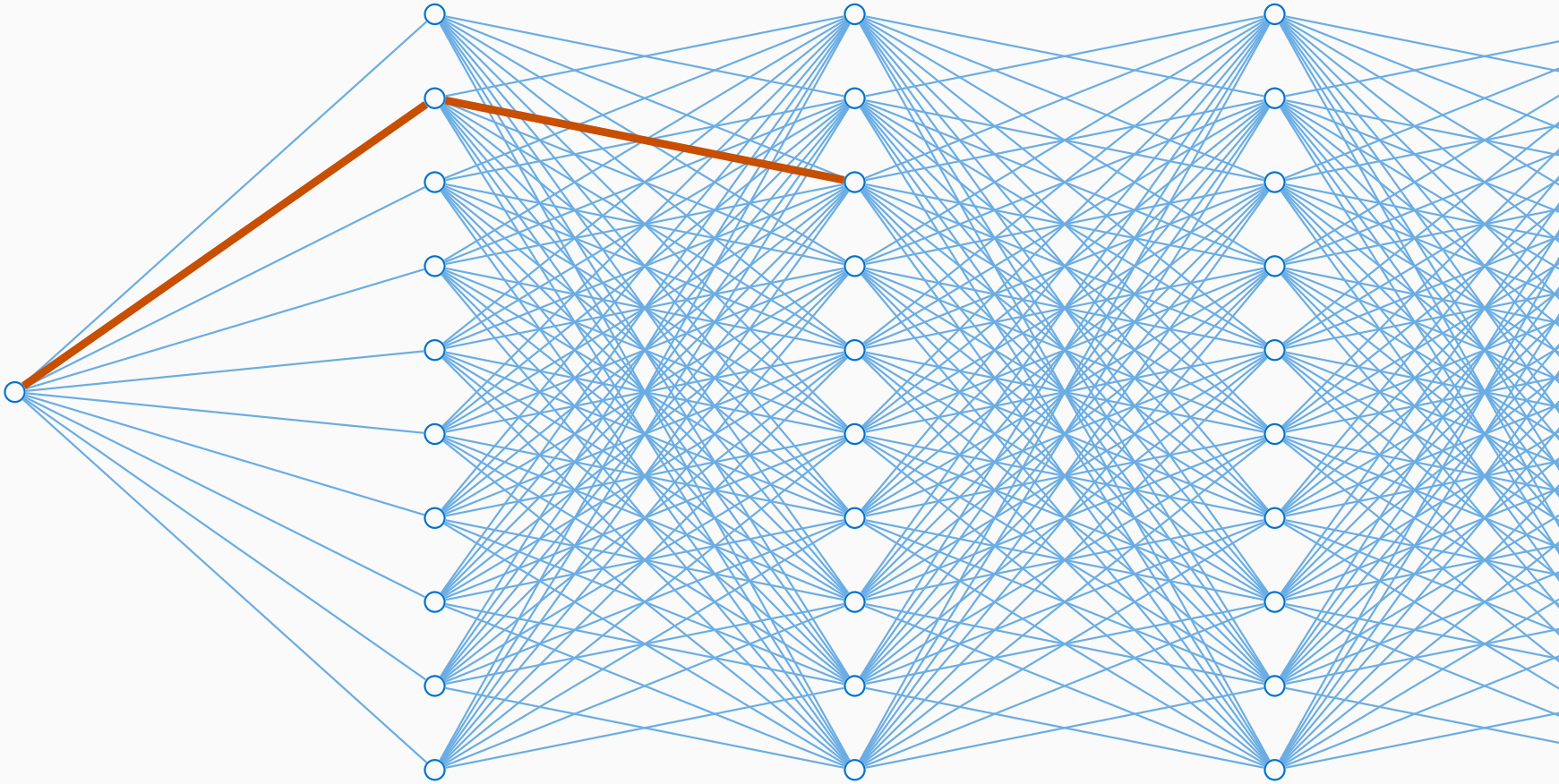

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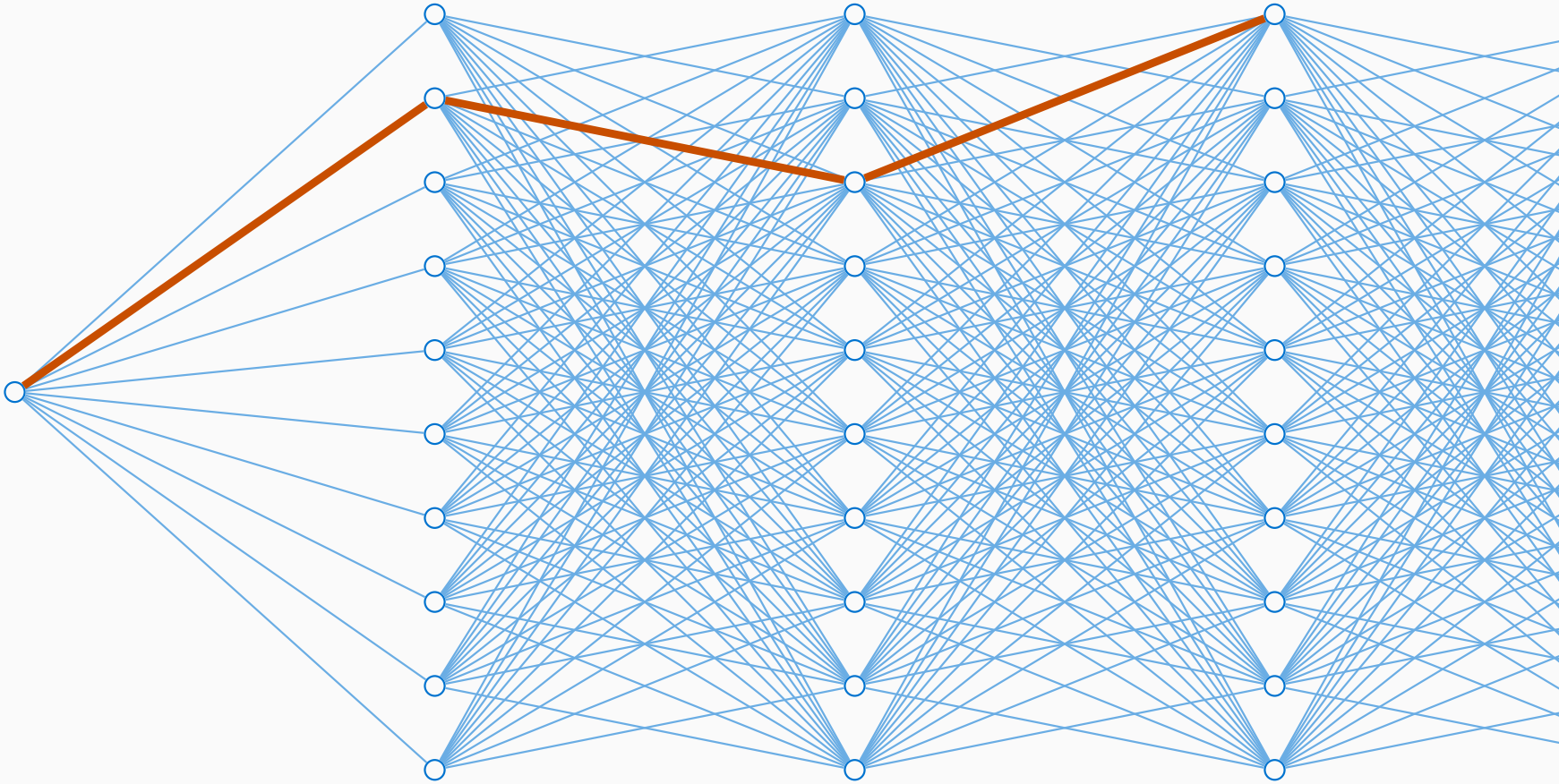

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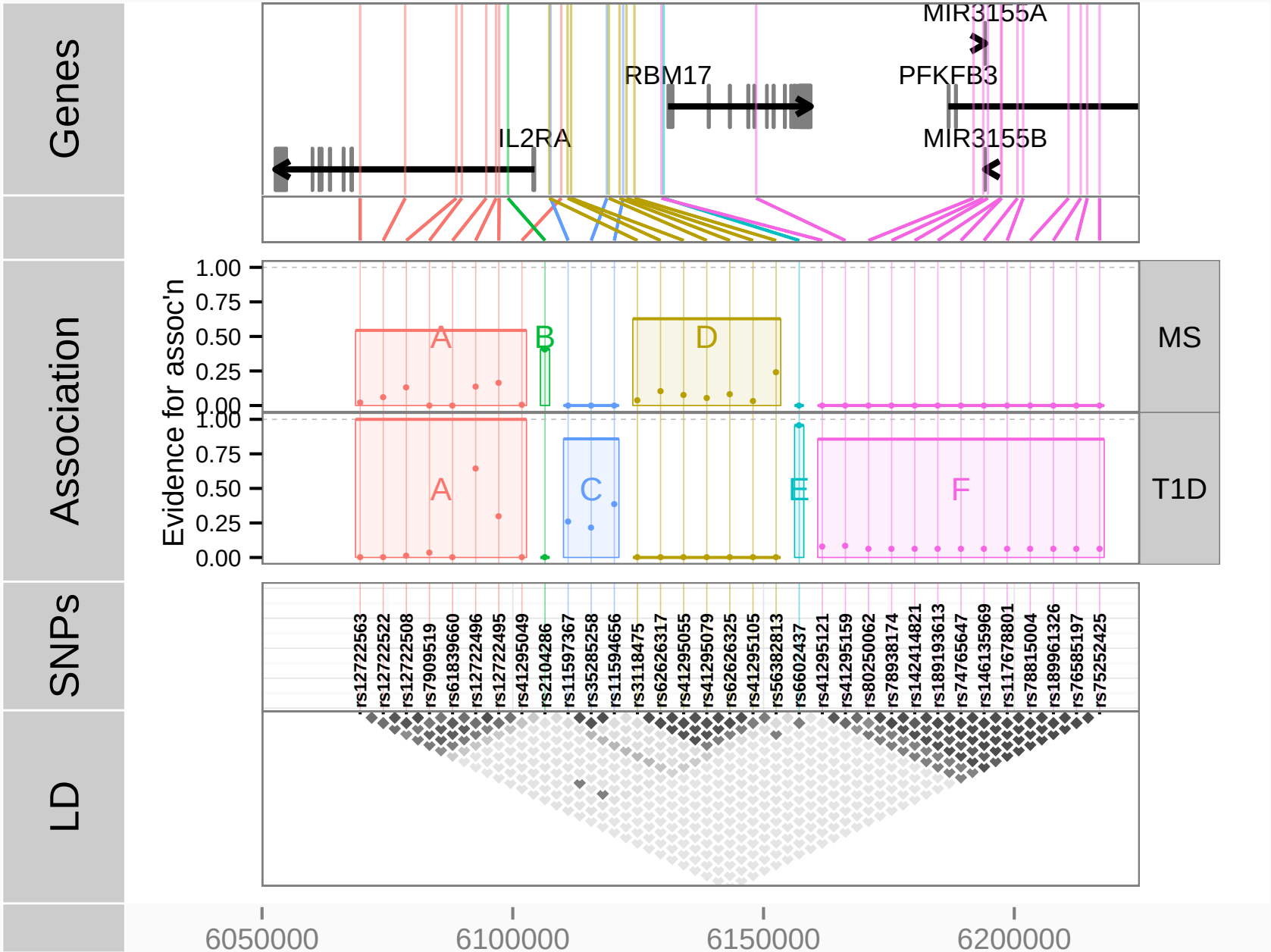
Stochastic search of IL2RA region



(Dis-) agreement between stepwise and stochastic search

MS

Stepwise Stochastic	rs2104286 (B)	rs11256593
M1: rs2104286 (B)	**1.00**	0.33
M2: rs12722496 (A)	0.33	0.08
M2: rs56382813 (D)	0.31	0.29

r^2 between SNPs

T1D

Stepwise Stochastic	rs61839660 (A)	rs11594656 (C)	rs12220852 (E)	rs41295159 (F)
rs12722496 (A)	**0.88**	0.02	0.02	0.00
rs11594656 (C)	0.02	**1.00**	0.26	0.02
rs6602437 (E)	0.05	0.25	**0.62**	0.01
rs41295159 (F)	0.00	0.02	0.00	**1.00**

Wallace et al, PLoS Genet 2015

Systematic comparison: 89 genetic regions, 6 diseases

Group	Number	Group	Number
Autoimm. Thyroid Disease, ATD	2772	Celiac Disease, CEL	12041
Juvenile Idiopathic Arthritis, JIA	1214	Multiple Sclerosis, MS	4461
Rhemuatoid Arthritis, RA	11475	Type 1 Diabetes, T1D	6681
CONTROL	22997		

201 region/disease pairs showing association (min. $p < 10^{-6}$)

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Regions	Region-disease pairs	
62	171	matched
2	2	stochastic null ($p \simeq 1 \times 10^{-6}$)
15	17	stepwise nested in stochastic
5	5	different top SNP (two weak signals)
5	6	non-nested mismatch

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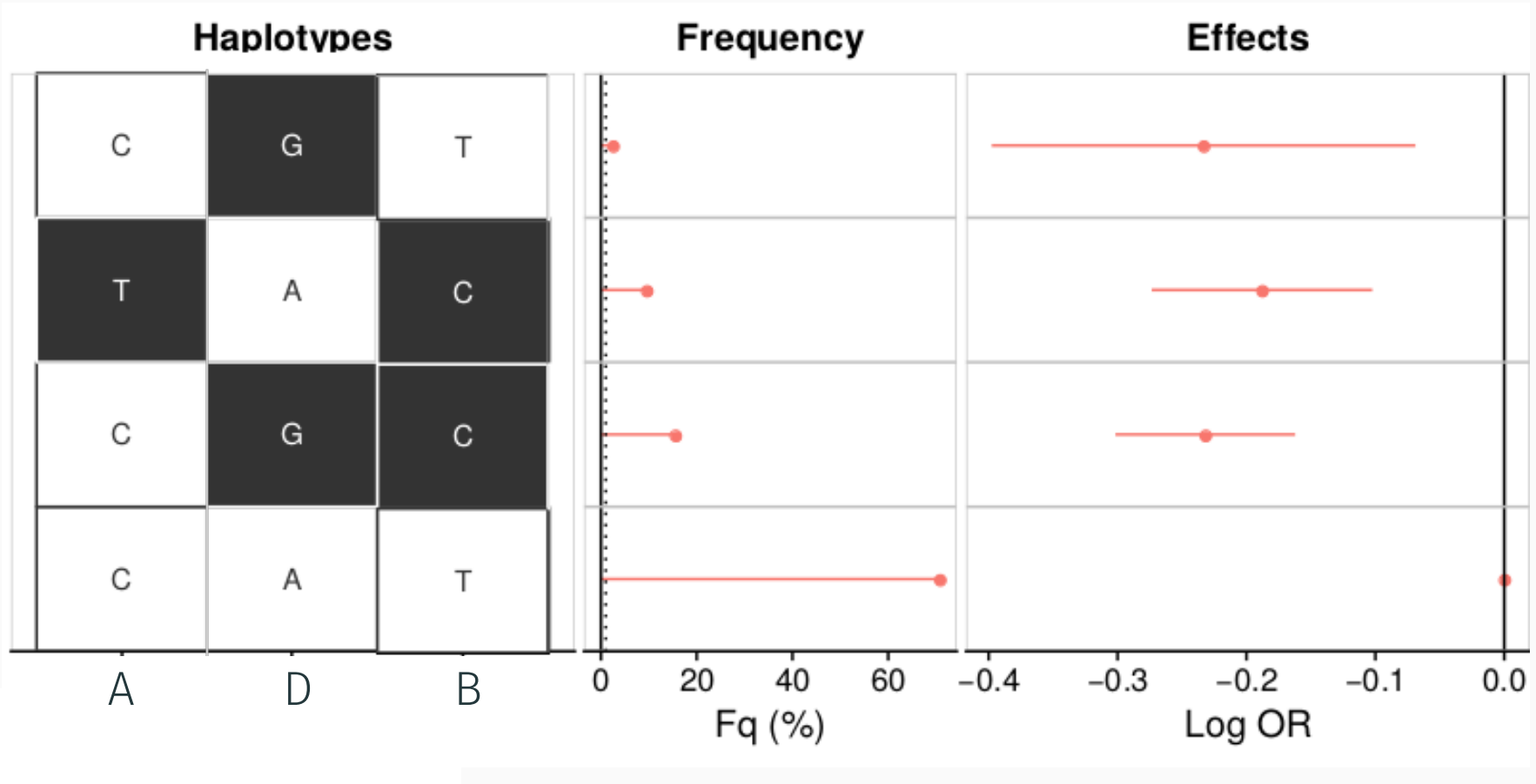
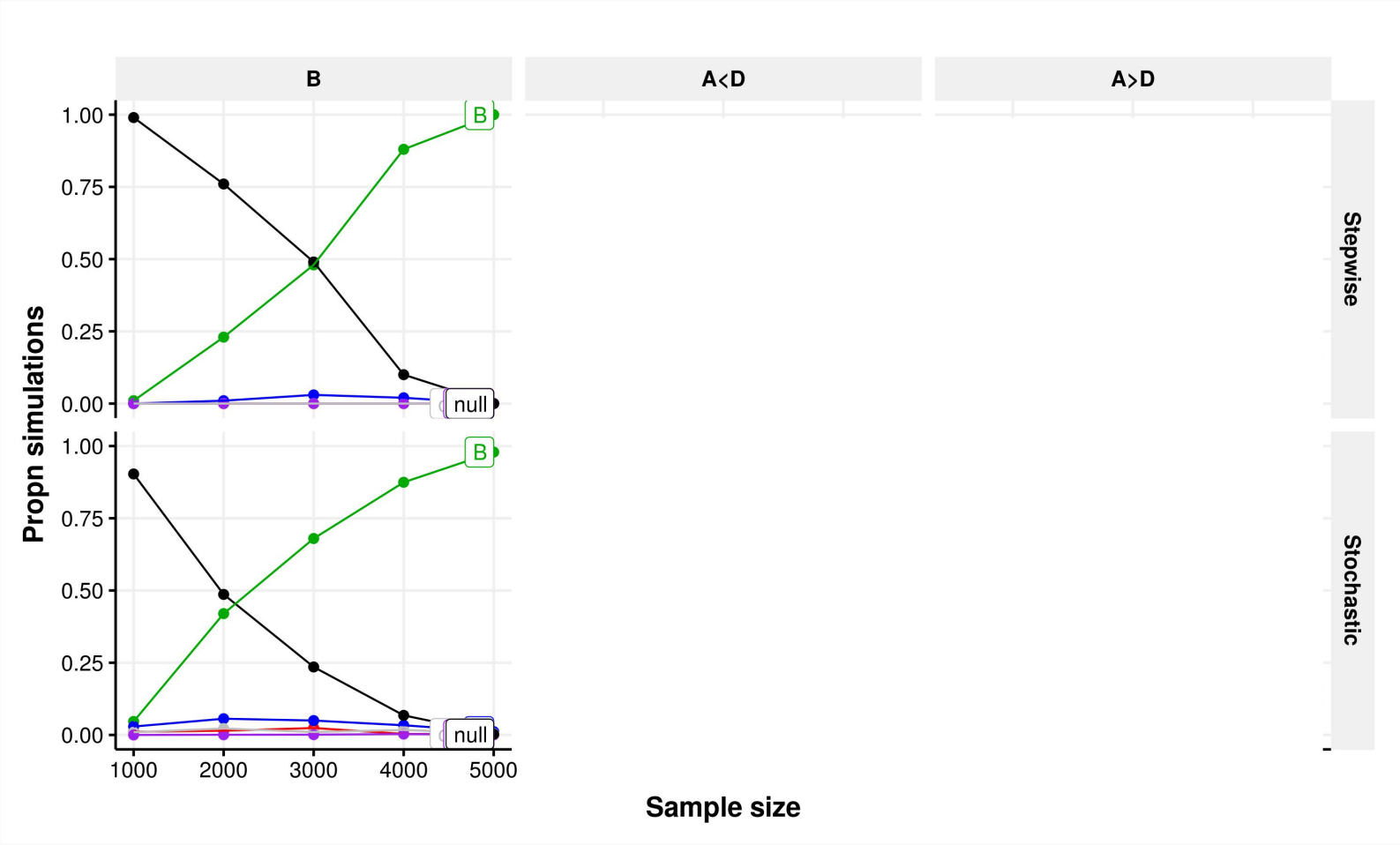
20/30 regions with > 1 associated disease had a shared signal

Joint tagging of causal variants

Haplotype analysis of MS



Stochastic search “correctness” sample size dependent



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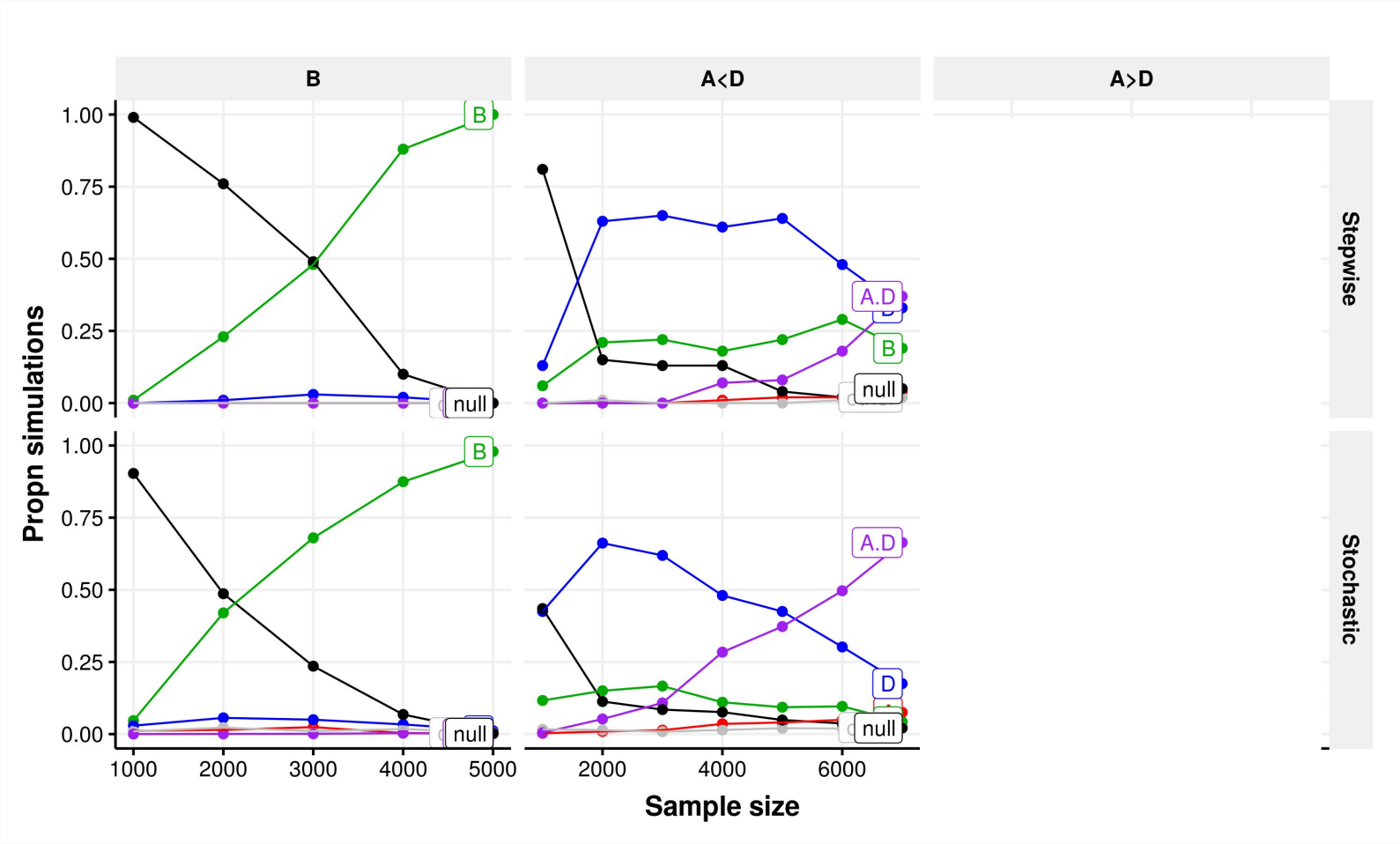

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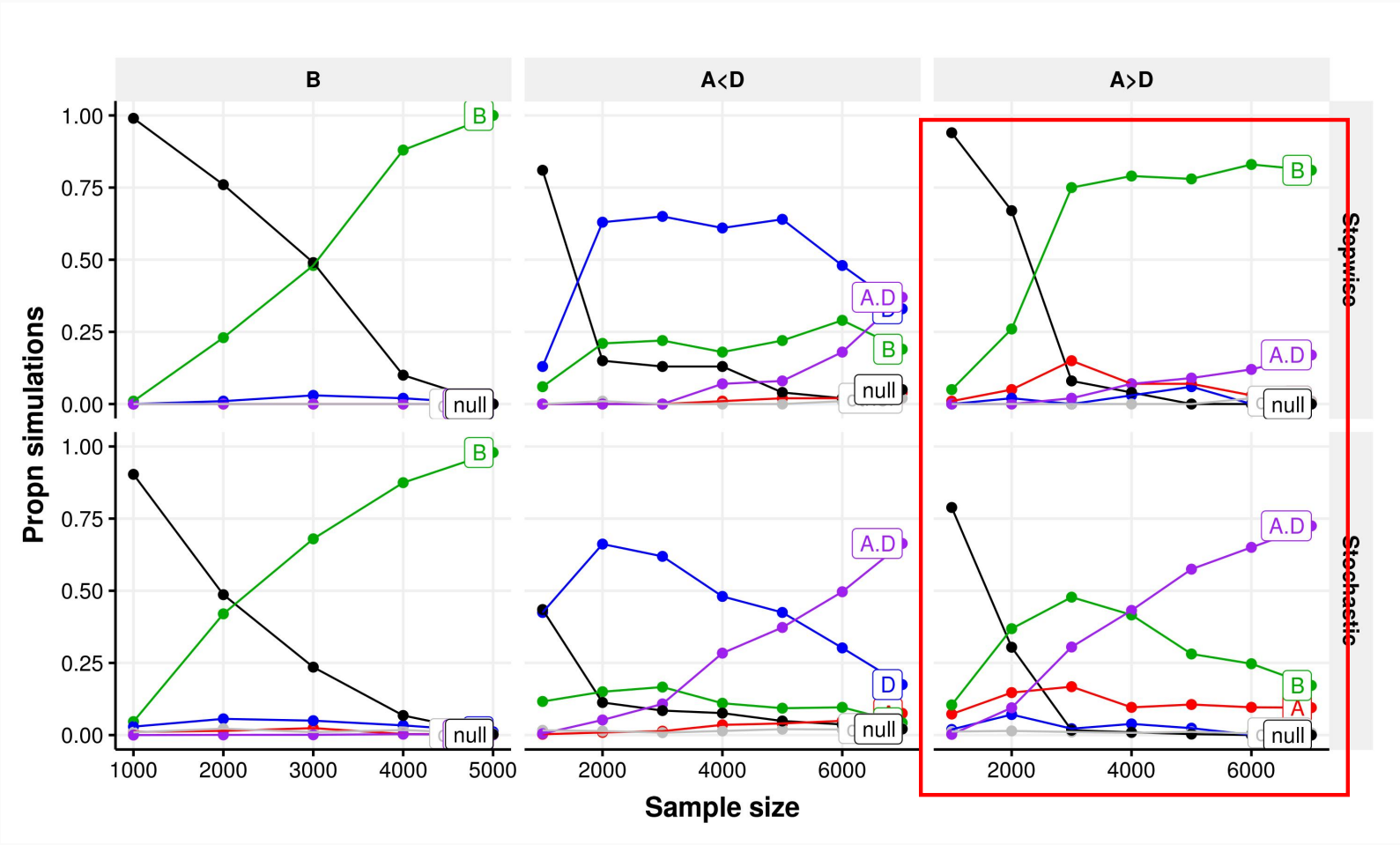


Conditions for joint tagging

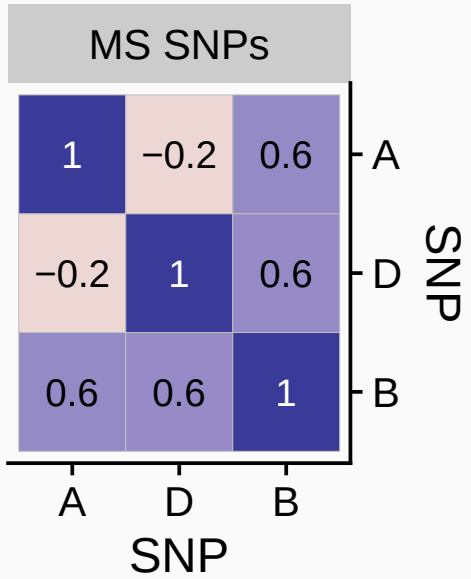
SNPs X_i, $i = 1, .., p$. $X_1, .., X_k$ are causal ($k < p$) correlation matrix is Σ

Expected Z score from a joint model is μ

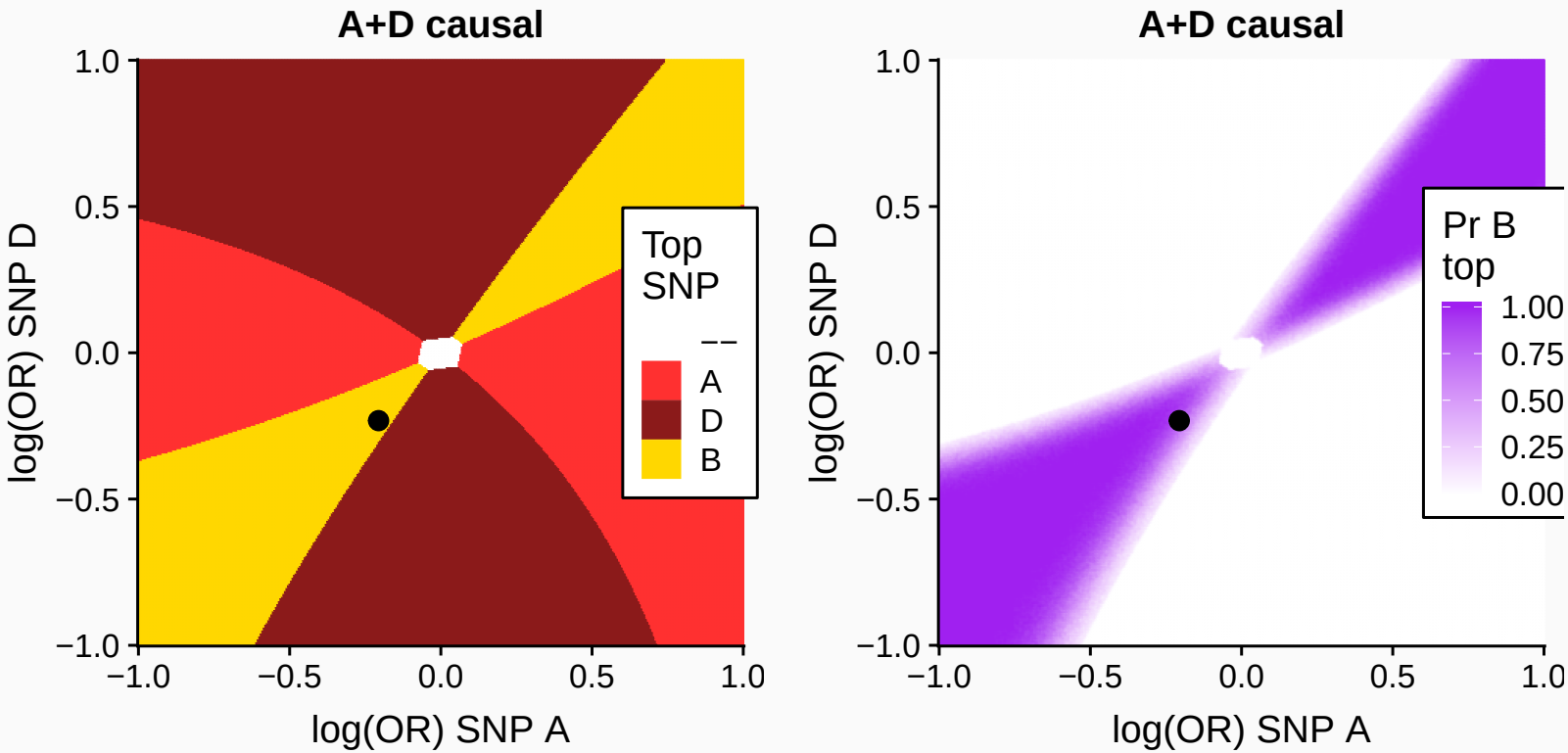
$$\mu_i = \begin{cases} f(\text{MAF, OR, N}) & i \leq k \\ 0 & i > k \end{cases}$$

Marginal Z scores across all SNPs:

$$Z \sim N(\Sigma\mu, \Sigma)$$

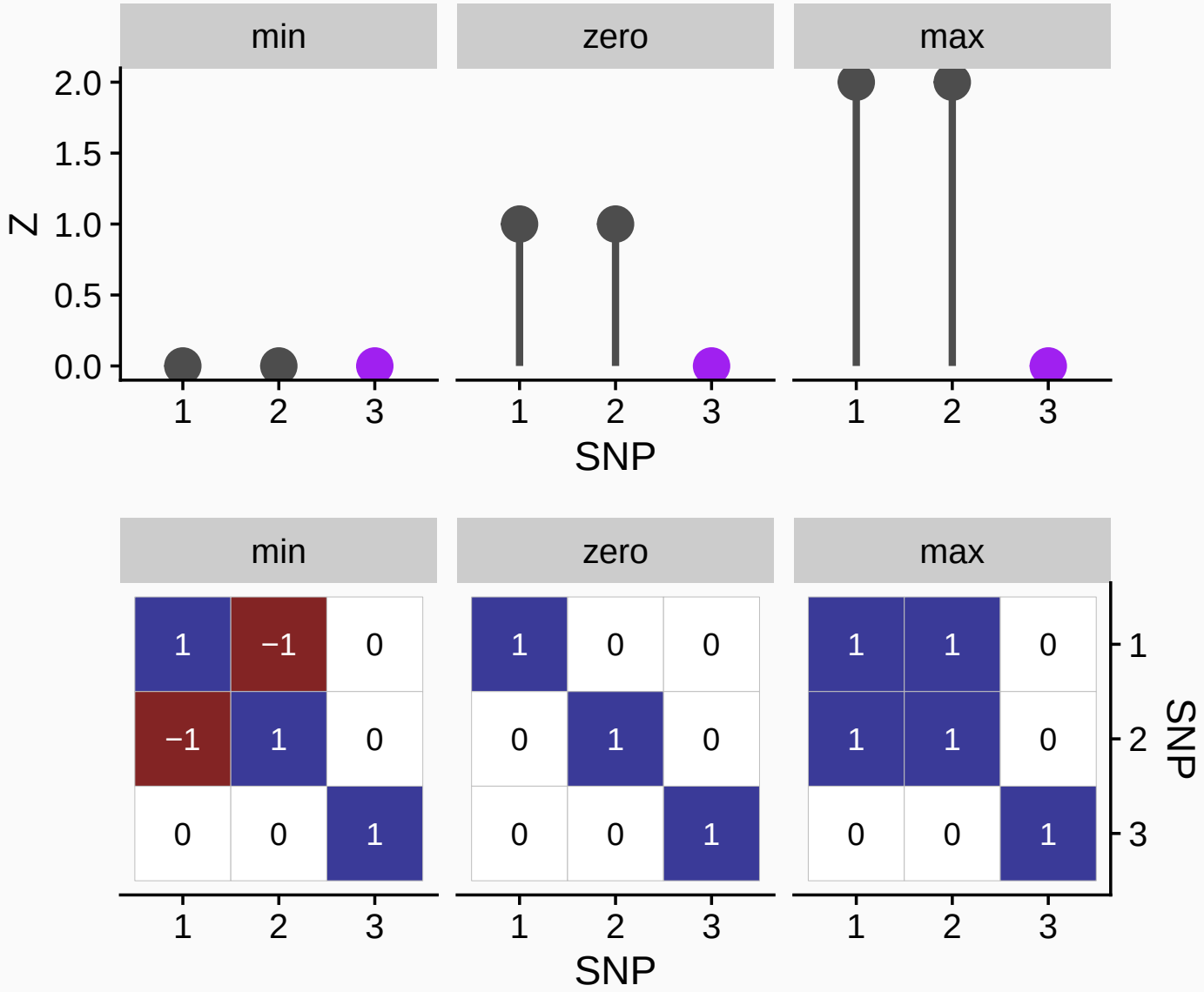


A, D causal, similar effects: expect B to have smallest p value



Effect of Σ on potential for joint tagging

SNPs 1, 2 causal. SNP 3 potential tag. $\mu = (1, 1, 0)'$



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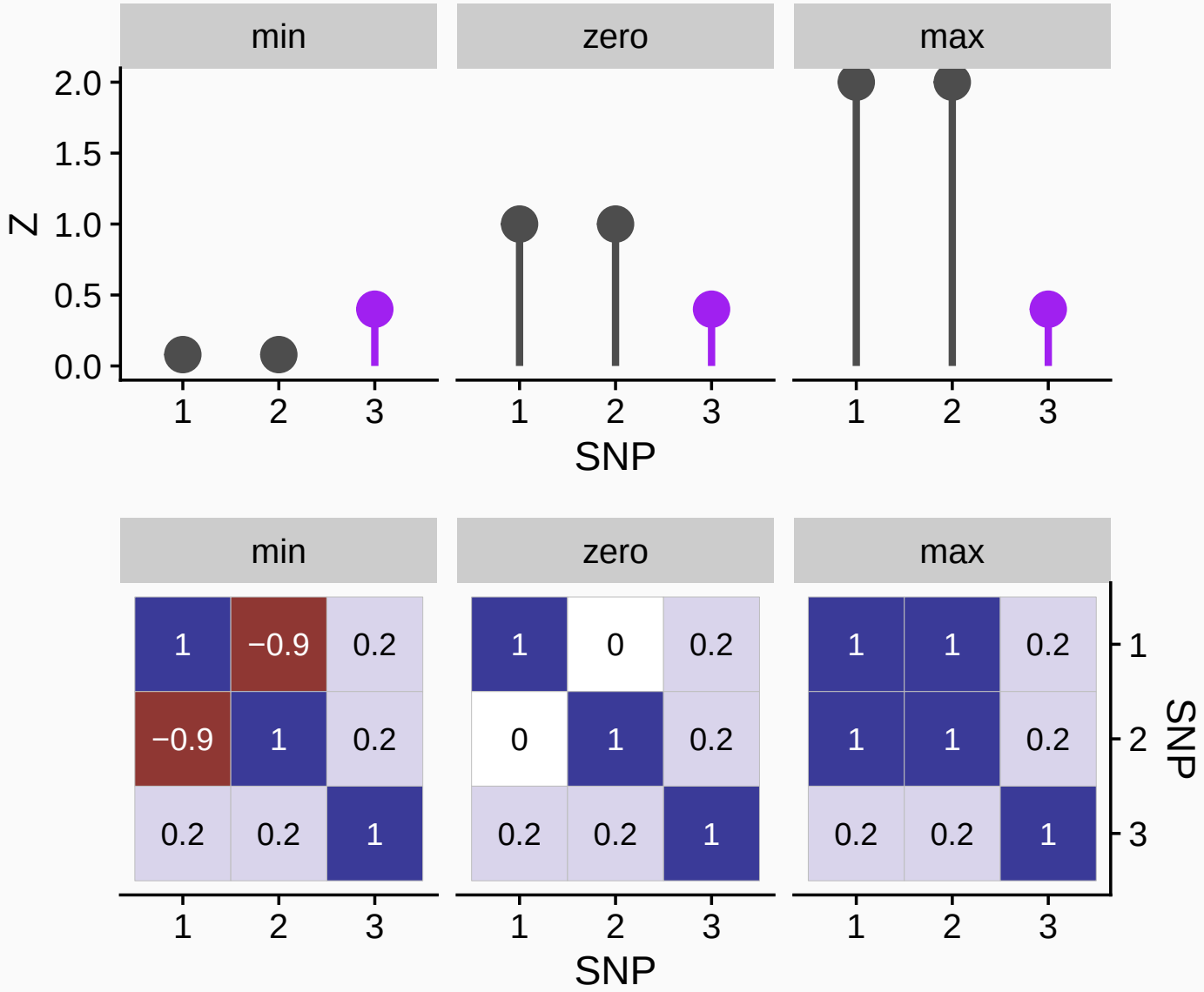

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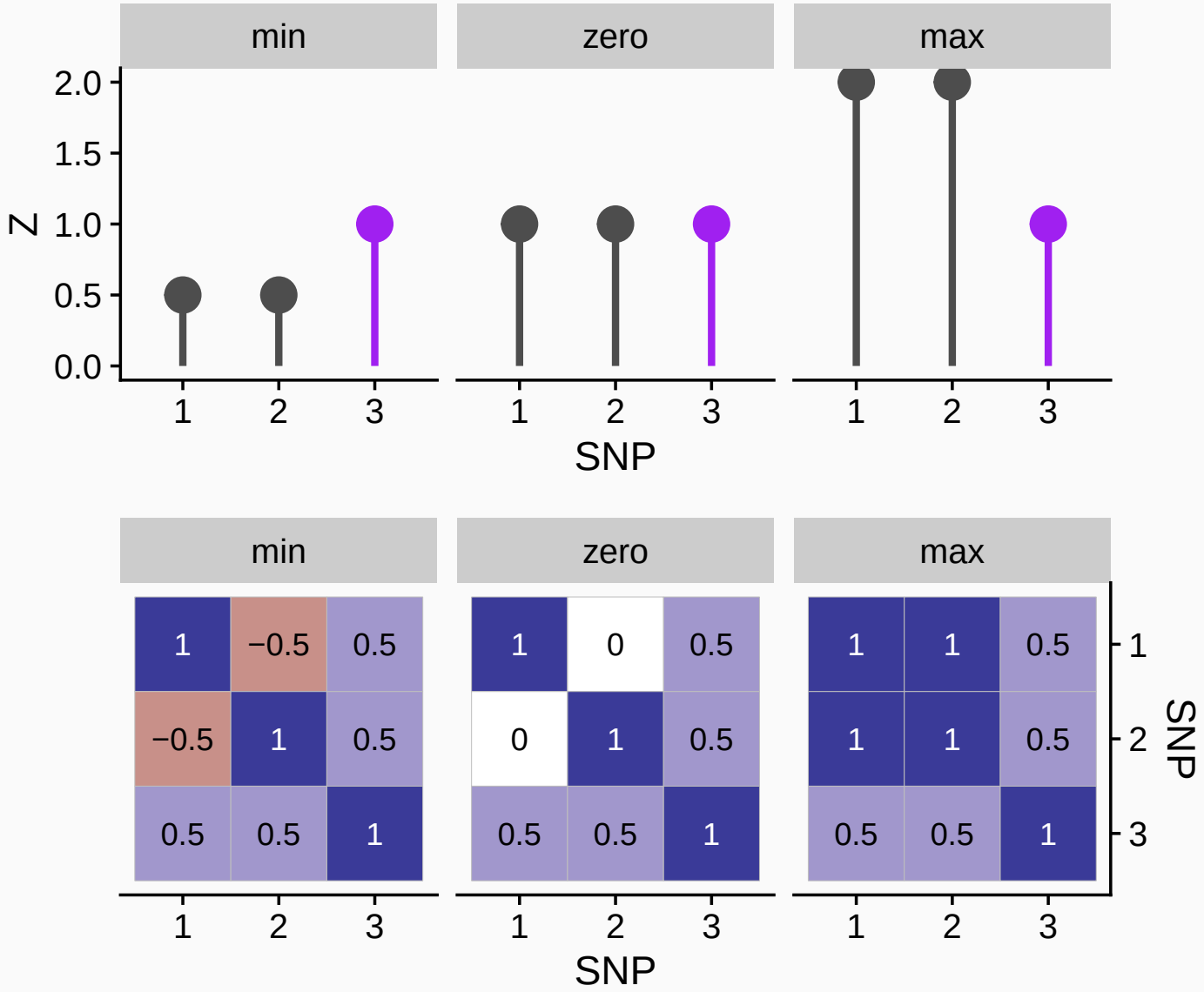

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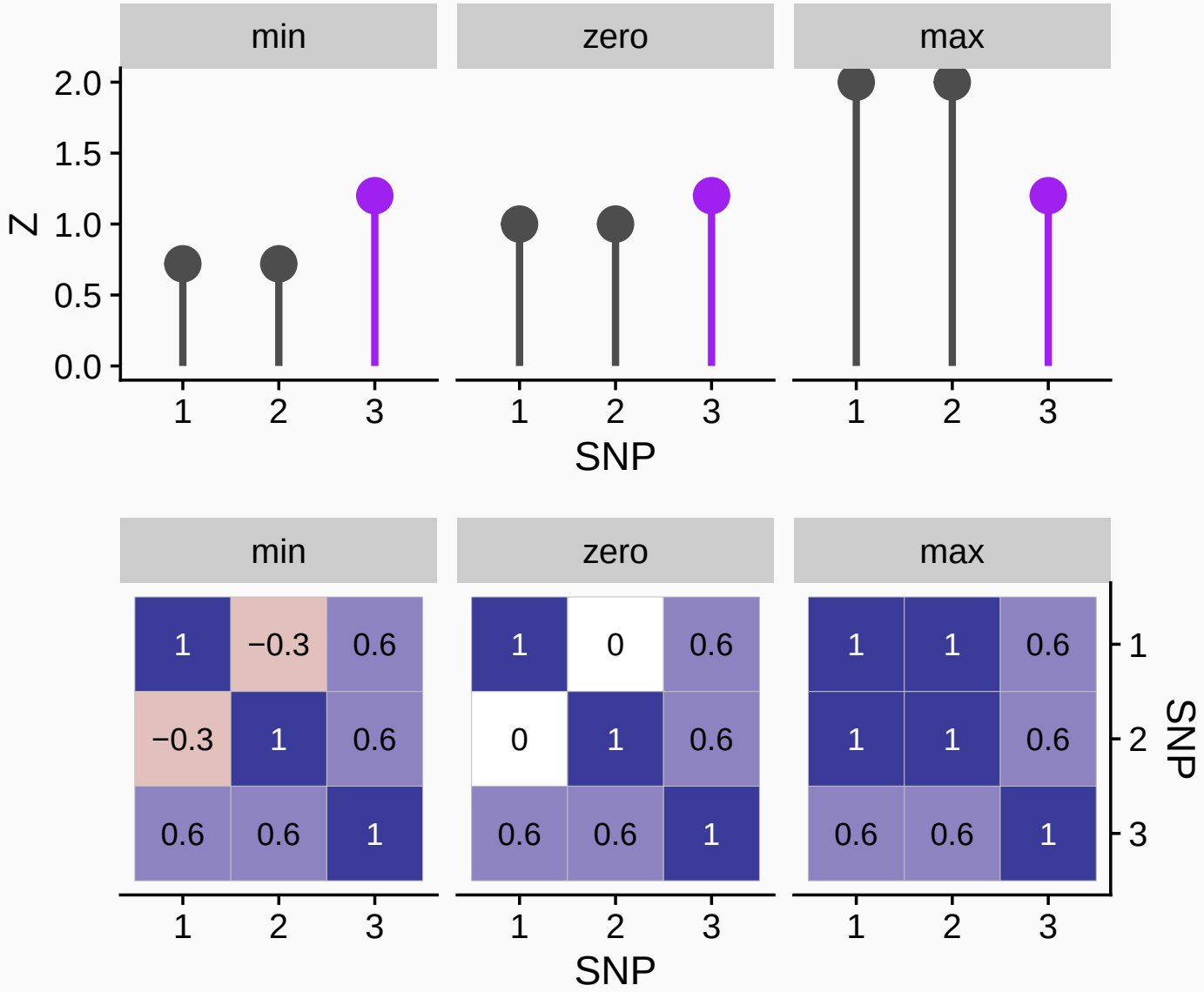

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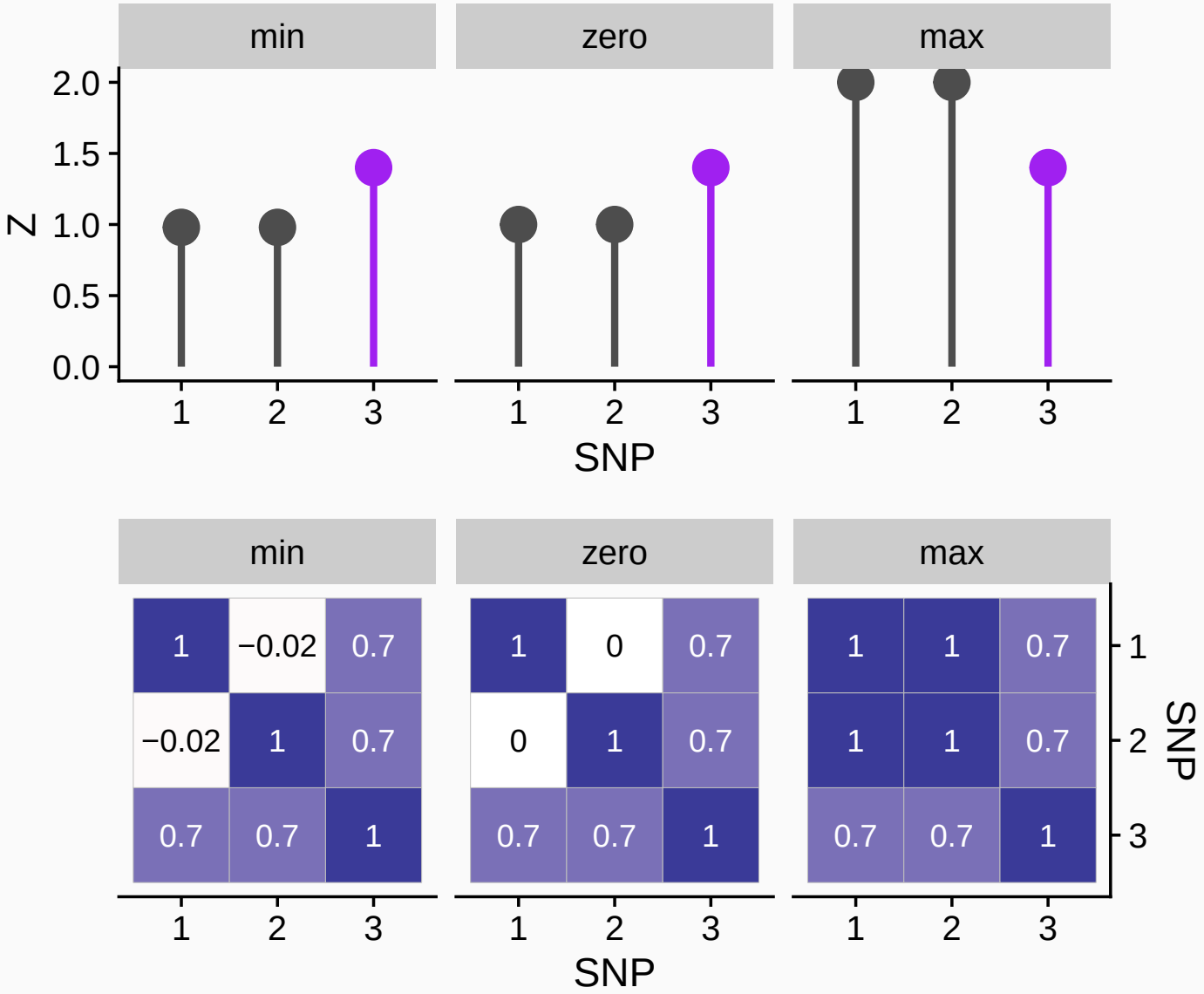
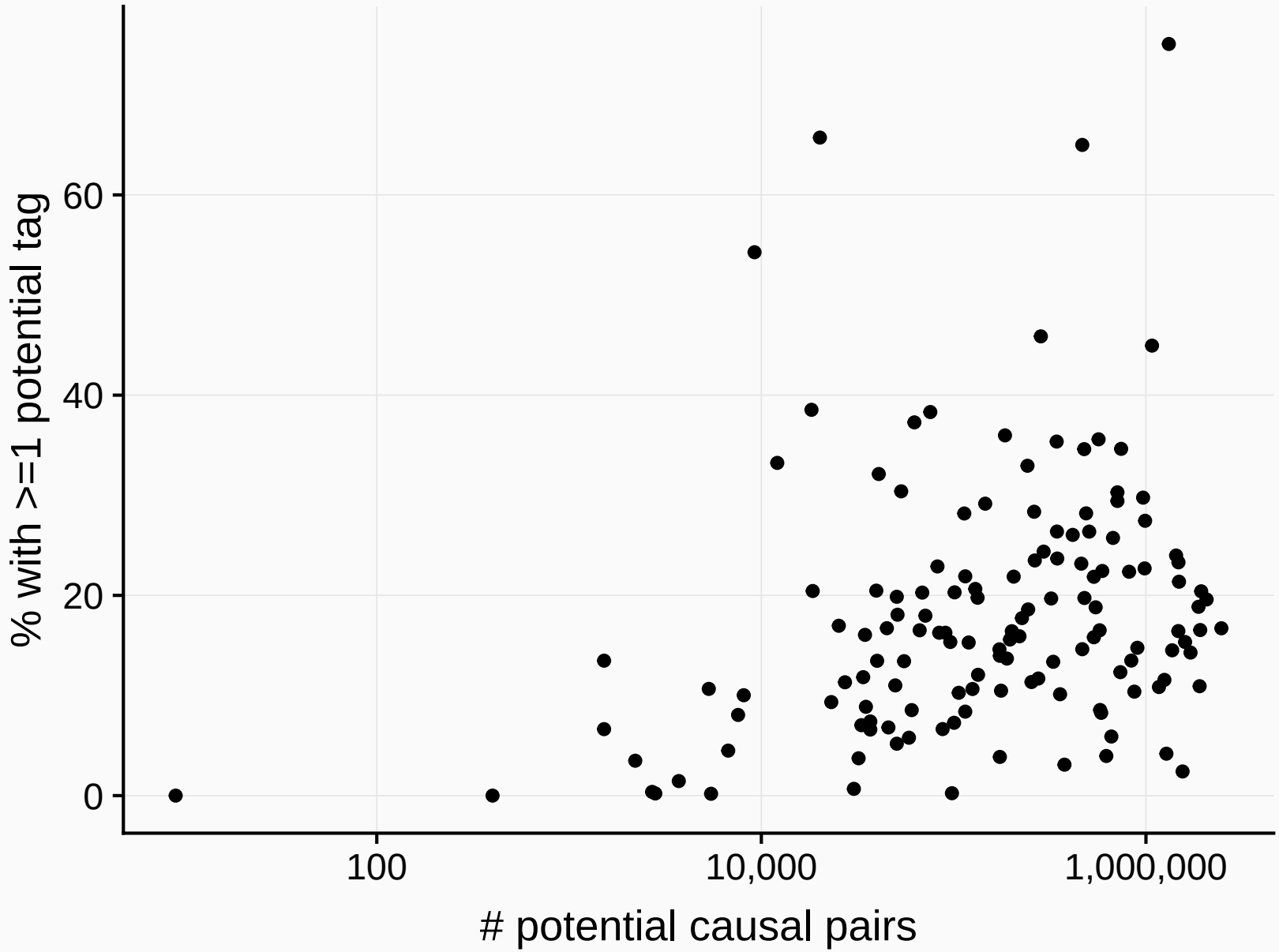


Potential tags by LD pattern at 20% of variant pairs



Improved fine mapping by exploiting shared aetiology

Bayesian fine mapping

Single disease

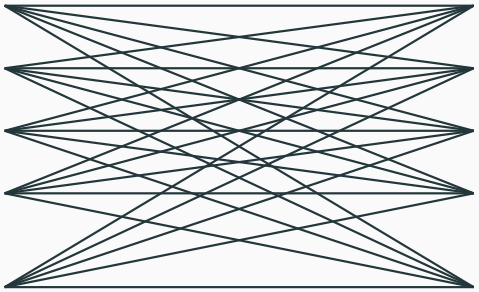
Model	Prior	Data	Posterior
A	π_A	BF_A	$\propto \pi_A BF_A$
B	π_B	BF_B	$\propto \pi_B BF_B$
D	π_D	BF_D	$\propto \pi_D BF_D$
B+D	π_{B+D}	BF_{B+D}	$\propto \pi_{B+D} BF_{B+D}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$

Bayesian fine mapping

Two diseases

Disease 1

Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮



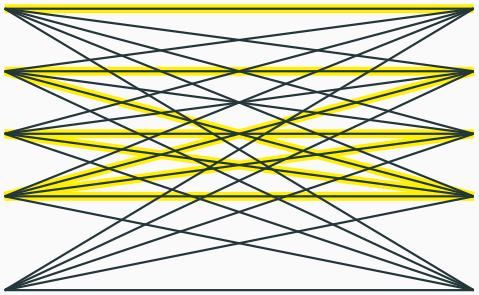
Disease 2

Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮

Bayesian fine mapping

Two diseases

Disease 1	
Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮



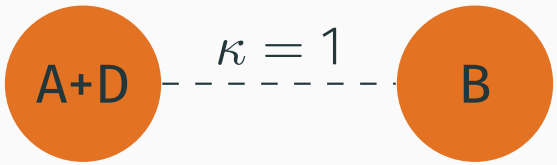
Disease 2	
Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮

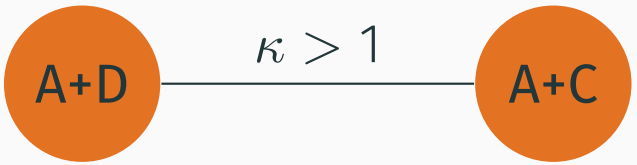
Use prior to borrow information between diseases

Define configurations: sets of models for each disease

$$C_{i,j} = \{M_i \text{ for disease 1}, M_j \text{ for disease 2}\}$$

$$Pr(C_{i,j}) = \begin{cases} Pr(M_i)Pr(M_j) \times \kappa \times \tau_{ij} & M_i \cap M_j \neq \varnothing \\ Pr(M_i)Pr(M_j) \times 1 \times \tau_{ij} & M_i \cap M_j = \varnothing \end{cases}$$





κ: upweighting factor

τ_{ij}: normalisation factor, fixes prior on the number of causal variants

Computational challenges of Bayesian fine mapping

Single disease

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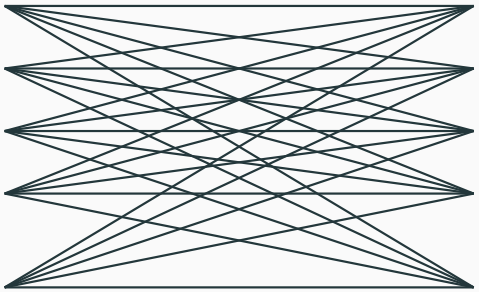
B	π_B	BF_B	$\propto \pi_B BF_B$
D	π_D	BF_D	$\propto \pi_D BF_D$
B+D	π_{B+D}	BF_{B+D}	$\propto \pi_{B+D} BF_{B+D}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$

Model space: exponential in number of causal variants

Computational challenges of Bayesian fine mapping

Two diseases

Disease 1	
Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮



Disease 2	
Model	Data
A	BF_A
B	BF_B
D	BF_D
B+D	BF_{B+D}
⋮	⋮

Model space: (exp. causal variants)$^{\text{number of diseases}}$

Challenges: memory, computational time

Fast, memory efficient calculation of marginal posteriors

Speed: Joint Bayes factor approximated by function of single disease Bayes factors

$$BF(\{M_i, M_j\}) \underset{\sim}{\propto} BF(M_i) \times BF(M_j) \times \eta$$

η function of numbers of cases, shared controls and causal variants

Memory: linear (not exponential) in number of diseases, by storing only marginal single disease posteriors

Fast, memory efficient calculation of marginal posteriors

Speed: Joint Bayes factor approximated by function of single disease Bayes factors

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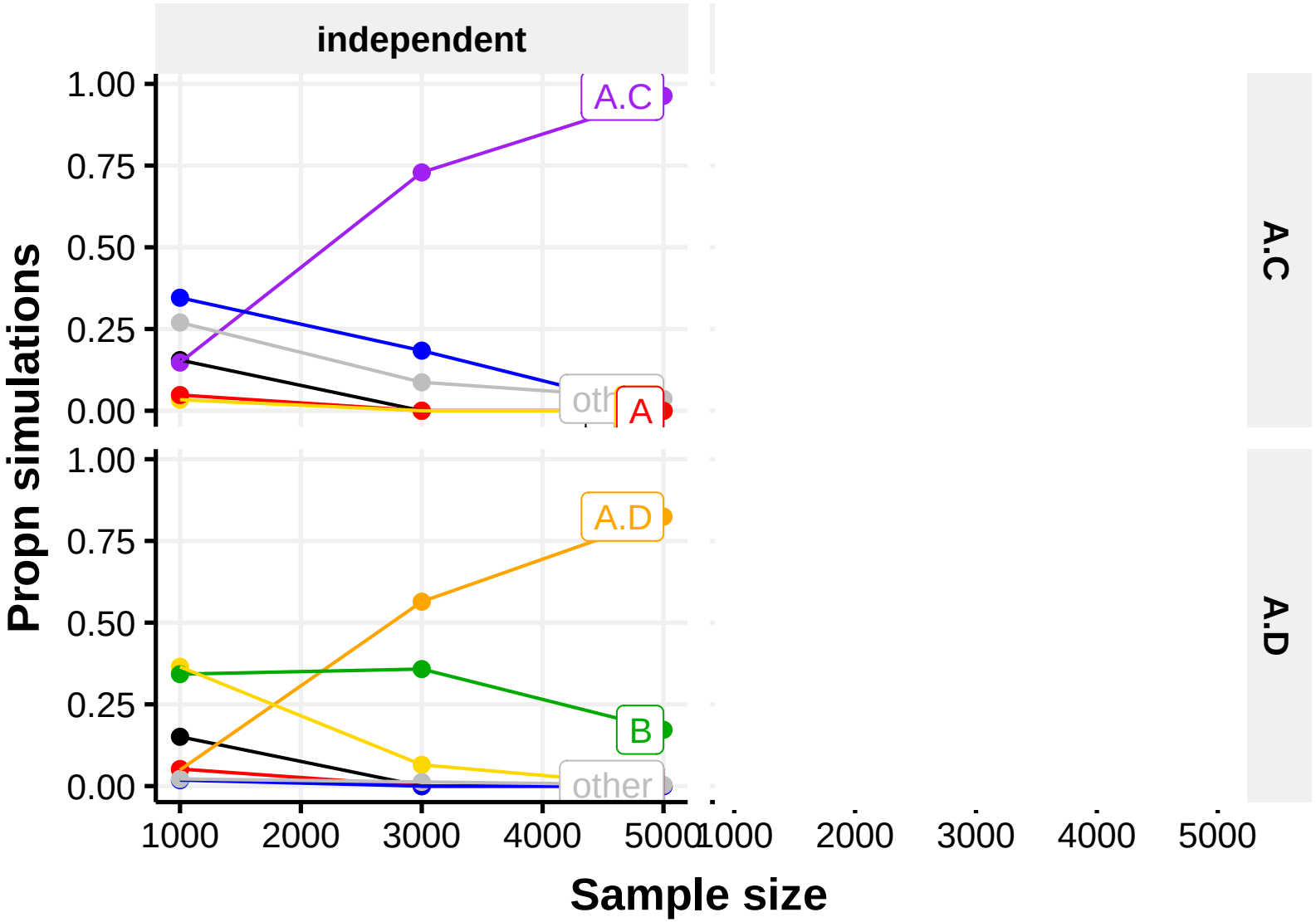
η function of numbers of cases, shared controls and causal variants

Memory: linear (not exponential) in number of diseases, by storing only marginal single disease posteriors

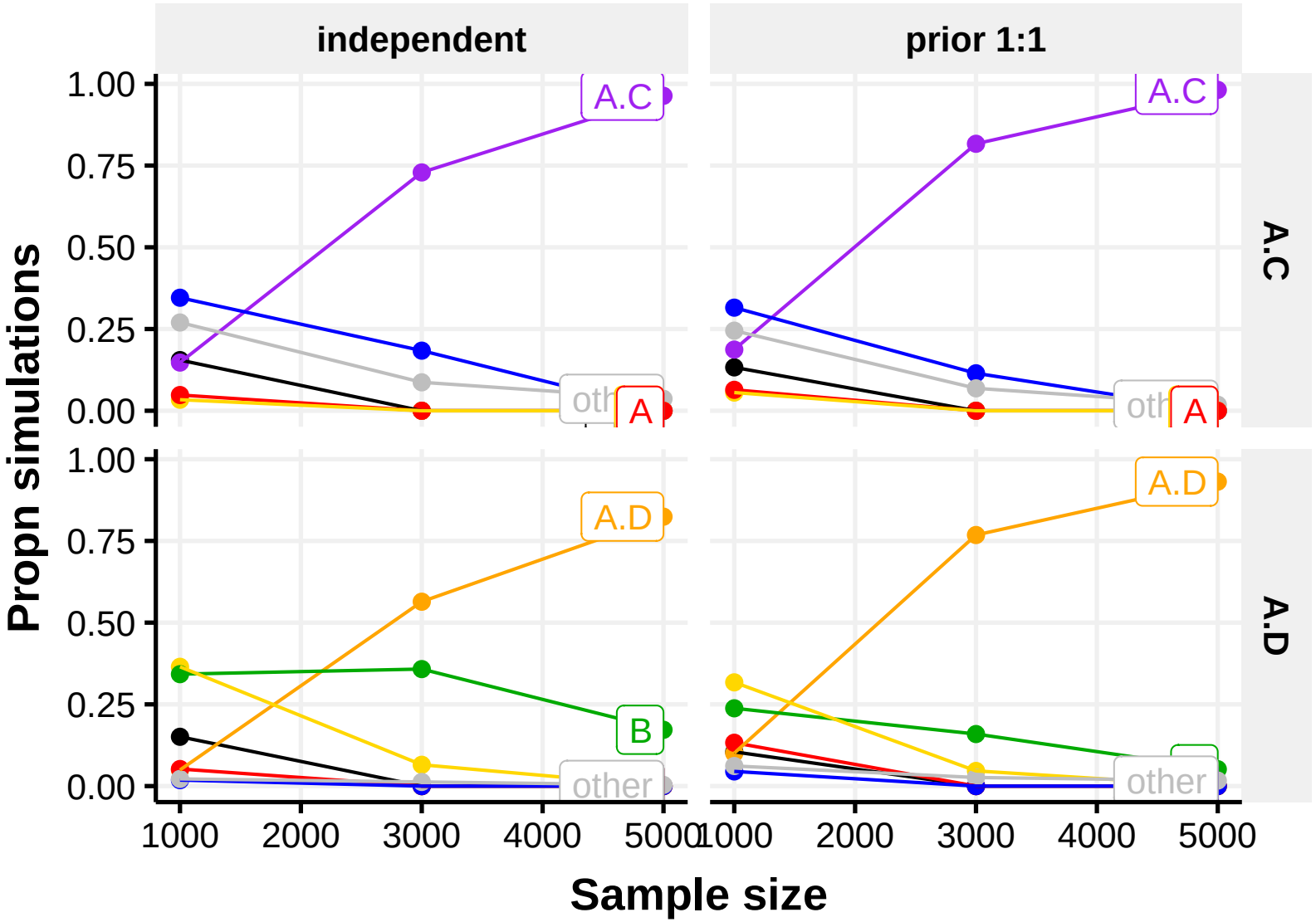
- Running time: 15 seconds (2 diseases) — 83 seconds (6 diseases)

`https://github.com/jennasimit/MTFM`

Joint fine mapping improves accuracy at smaller sample sizes



Joint fine mapping improves accuracy at smaller sample sizes



Joint fine mapping of 30 regions

7/30 regions differed between single and multi-disease analysis

4/4 cases: MFM results matched single disease analysis in larger international dataset

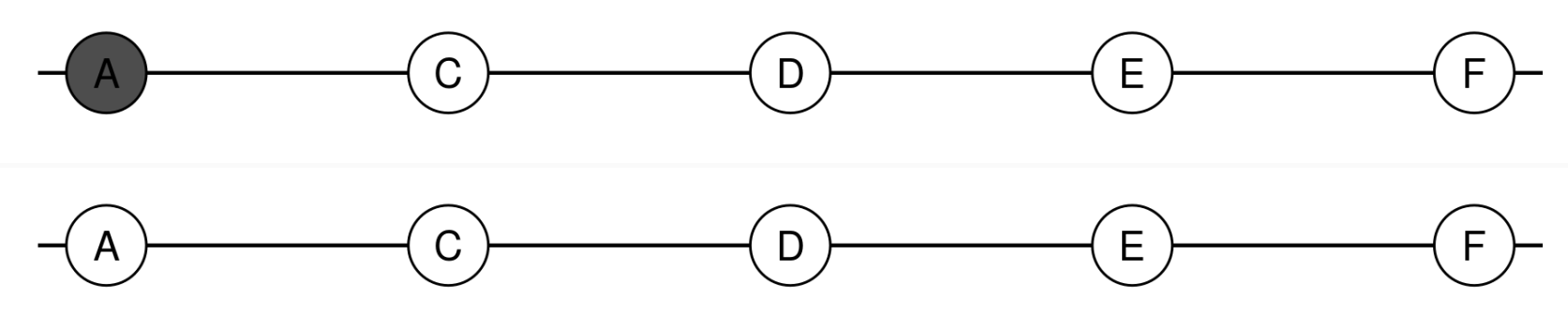
Region	Disease	Stochastic	MFM	Mean r^2
1p	RA	D/rs4648662	C/rs10752749	0.36
	iRA	C/rs141426426	C/rs10797431	
6q	RA	G/rs56258221	C/rs72928038	0.33
BACH2	iRA	C/rs72928038	C/rs72928038	
18p	CEL	F/rs34799913	C/rs12967678	0.4
PTPN2	iCEL	C/rs67878610	C/rs12967678	
10p	MS	B/rs2104286	A/rs12722496 + D/rs7089861	0.2, 0.3
IL2RA	iMS	A/rs12722496 + D/rs56382813	A/rs12722496 + D/rs7089861	

Functional validation of causal effects on *IL2RA*

Allele specific expression

Allele specific expression: quantify relative expression of two chromosomes using targetted PCR and sequencing

Within-individual: controls for between individual variation in environment, other genetics etc



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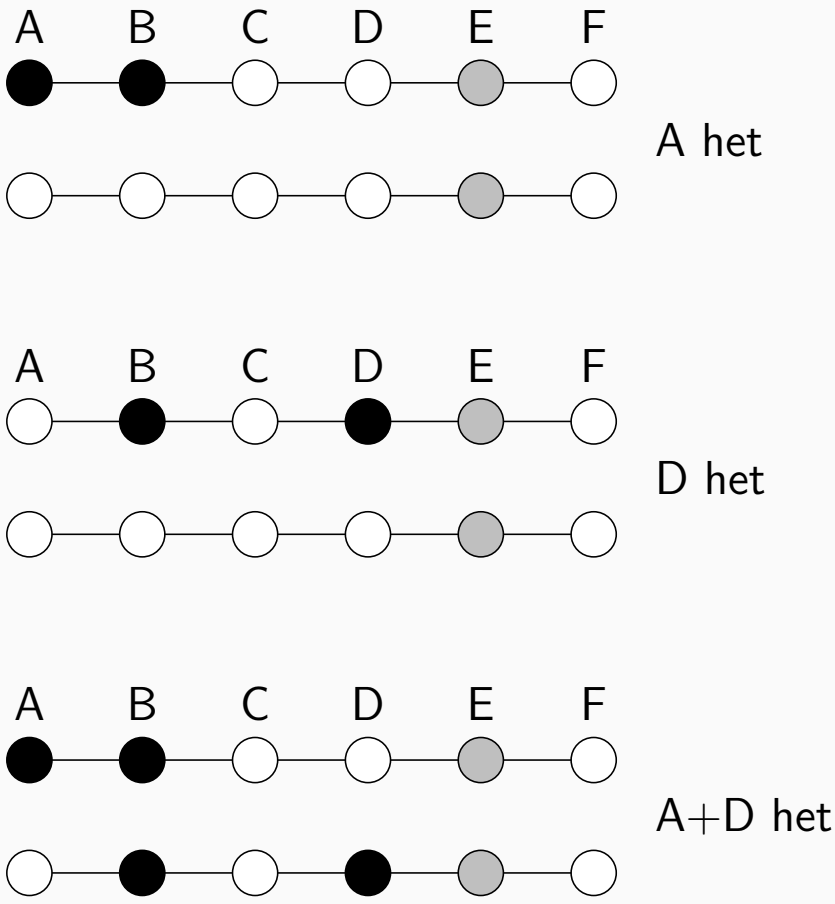
Effects of A, D and B

a



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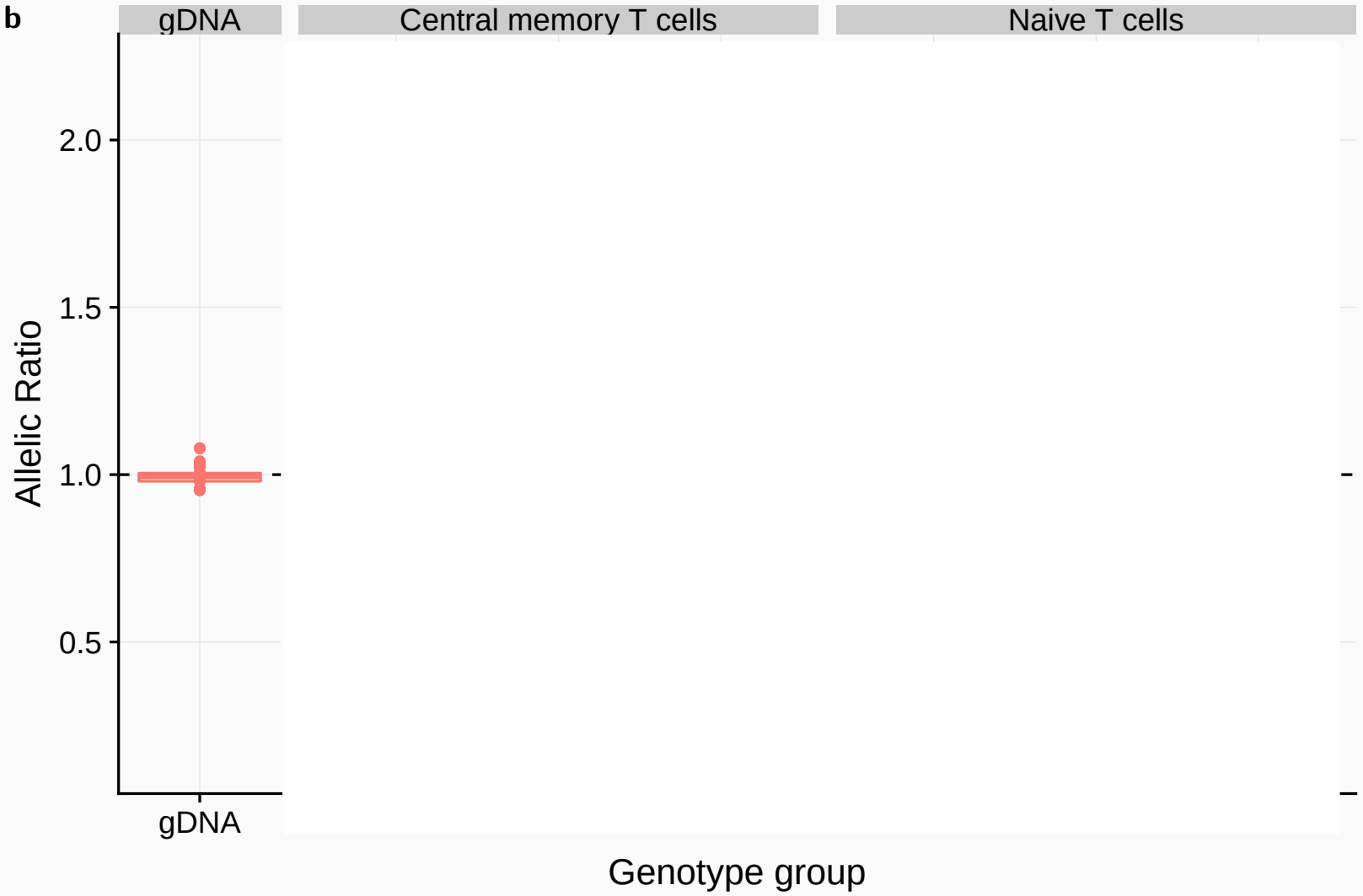

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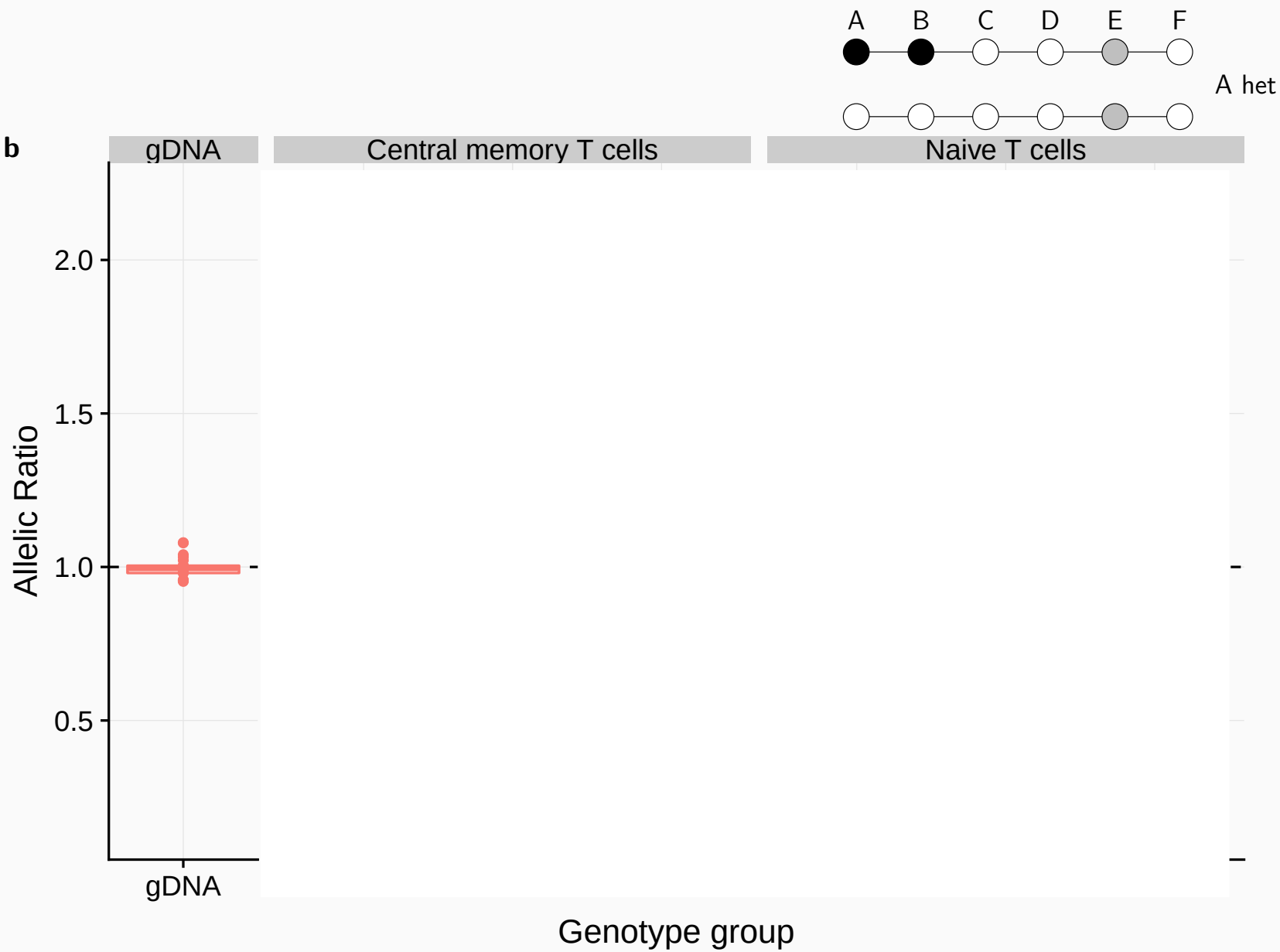

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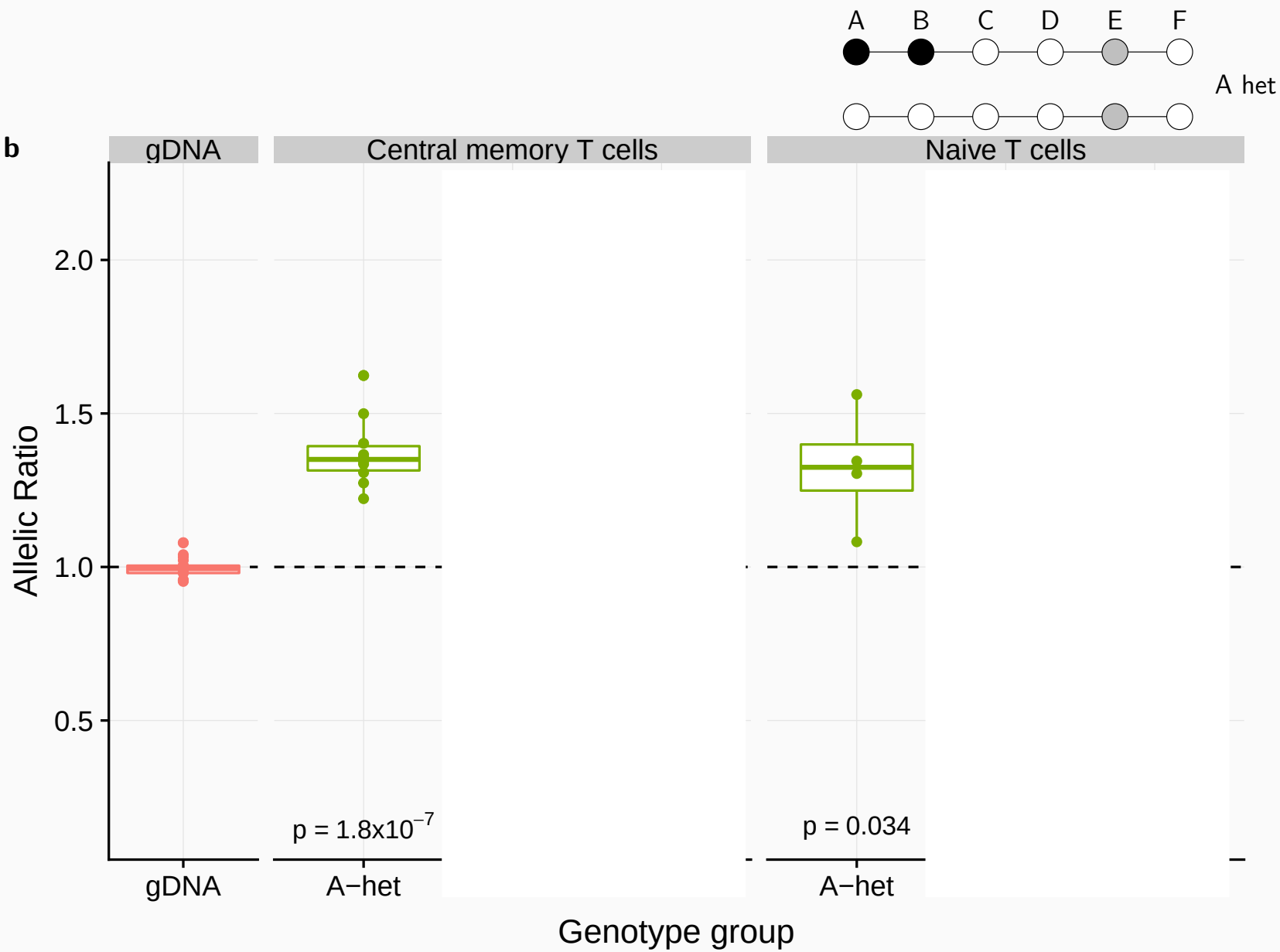

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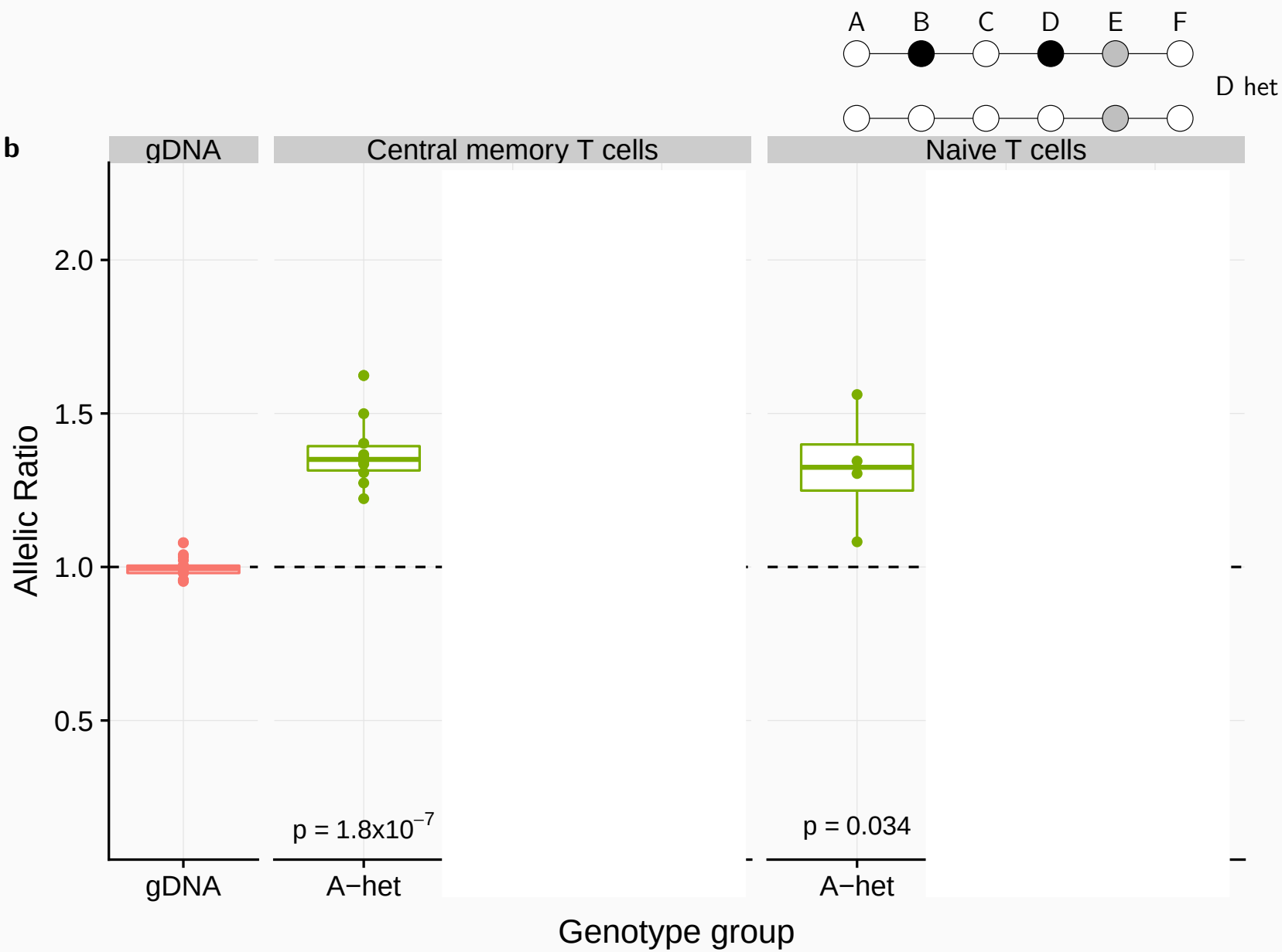

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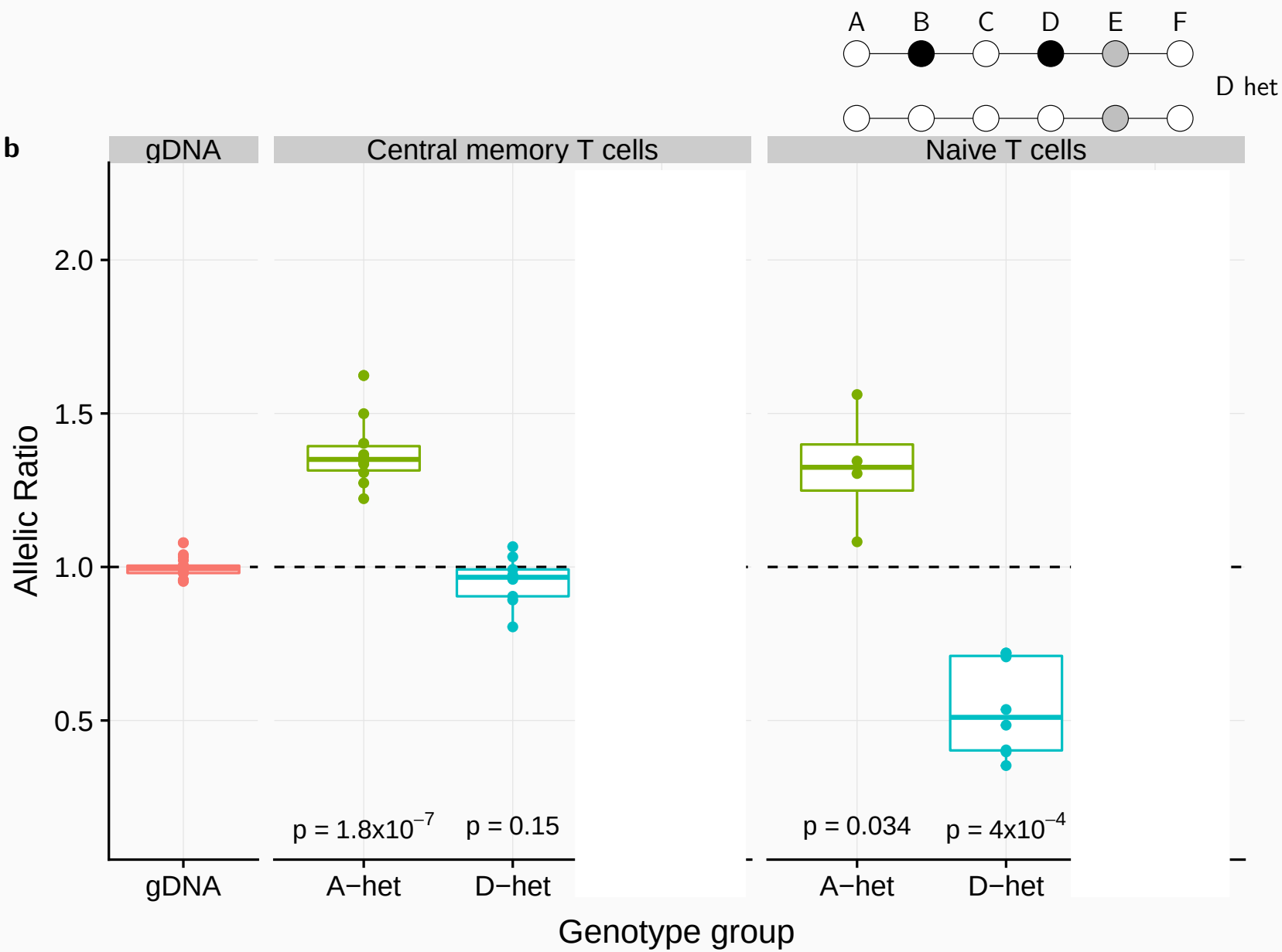

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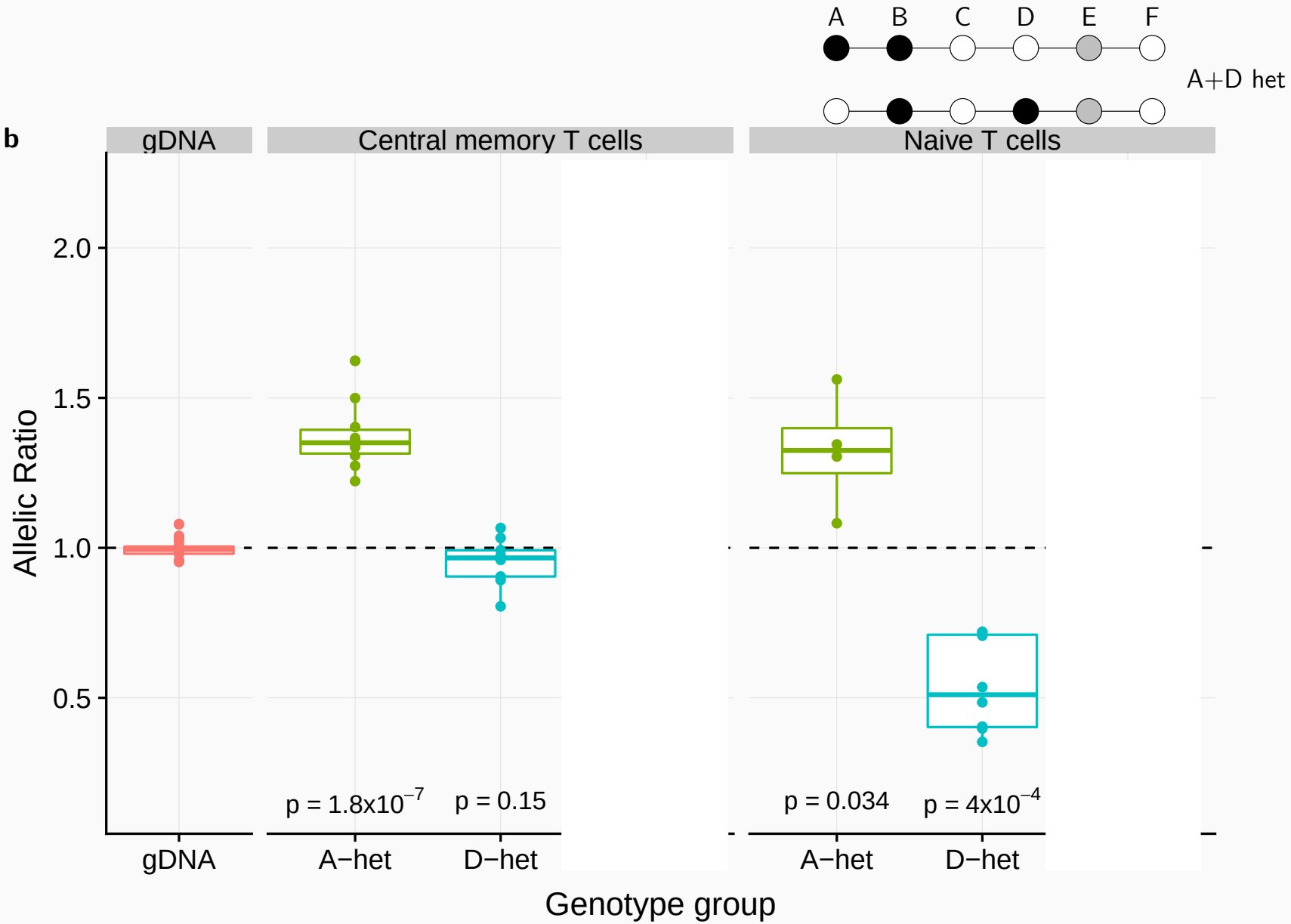

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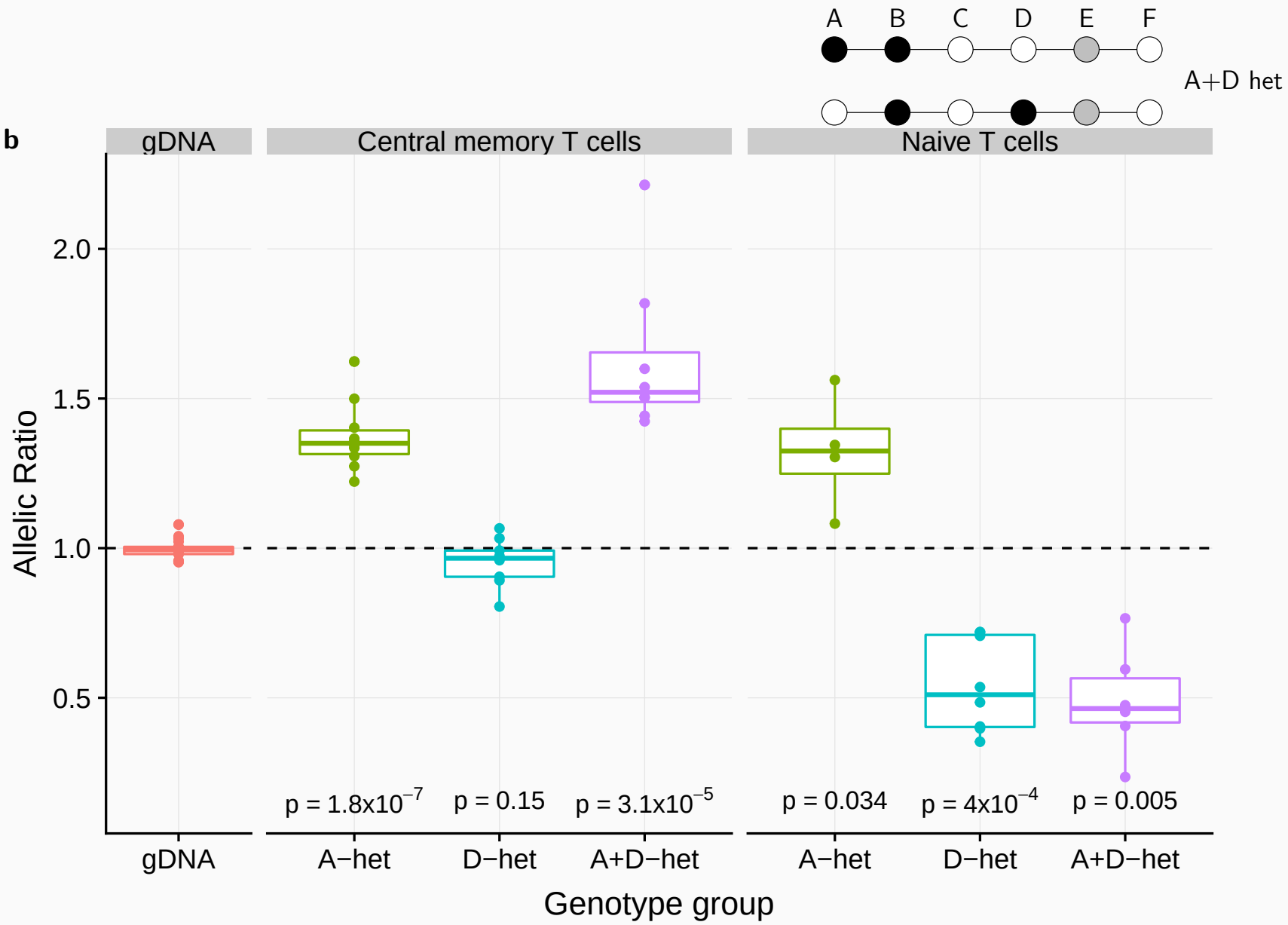

Summary

- Finding associated variants by GWAS variants is “easy”
- Fine mapping is harder
- Knowing causal variants, mechanism can be explored, or explicitly tested (ASE, Hi-C, eQTL, chipseq, CRISPR)

Joint tagging is a thing

- Most regions likely to contain > 1 causal variants
- Joint tagging might affect $\sim 20\%$ of causal variant pairs
- Key assumptions in stepwise search are not about number of / LD between causal variants, but about whether another SNP exists which acts as a lower dimensional summary of disease effect

Reasons for caution

- *IL2RA* “famous”: multiple, complex associations
- Other regions of greatest a-priori interest show strongest associations, learning they are also complex (e.g. *IL2*, *CTLA4*)

What if all regions are “complex”?

Reasons for optimism

- Borrowing information between related diseases can help overcome sample size limitations
- Inference on shared/distinct genetic causality comes “for free”

Thanks to

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`chr1swallace/GUESSFM` `jennasimit/MFM`

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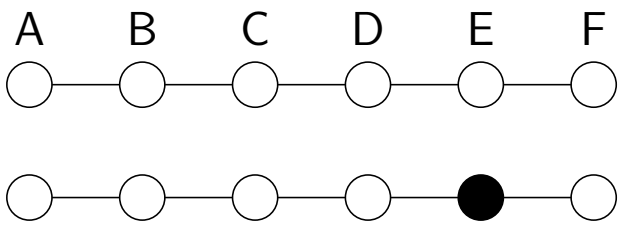
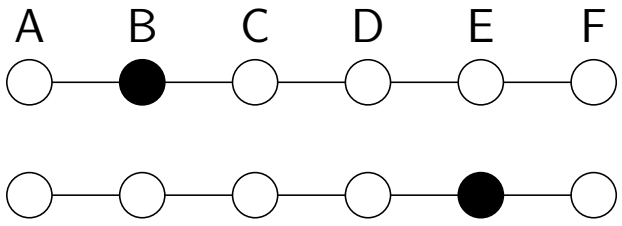
MRC Biostatistics Unit

Individuals with rare recombination events



Donor 1



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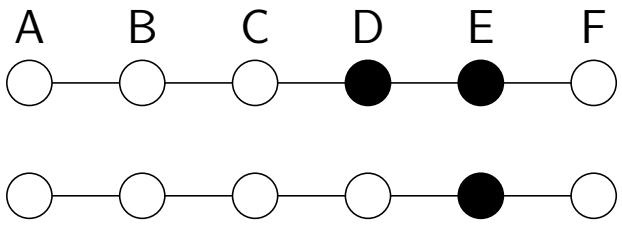

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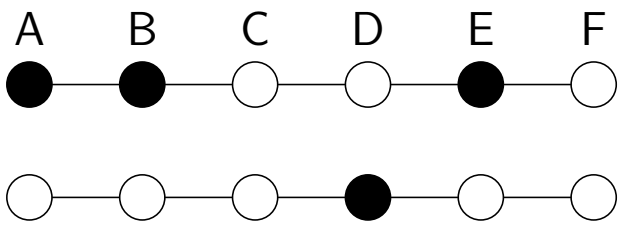
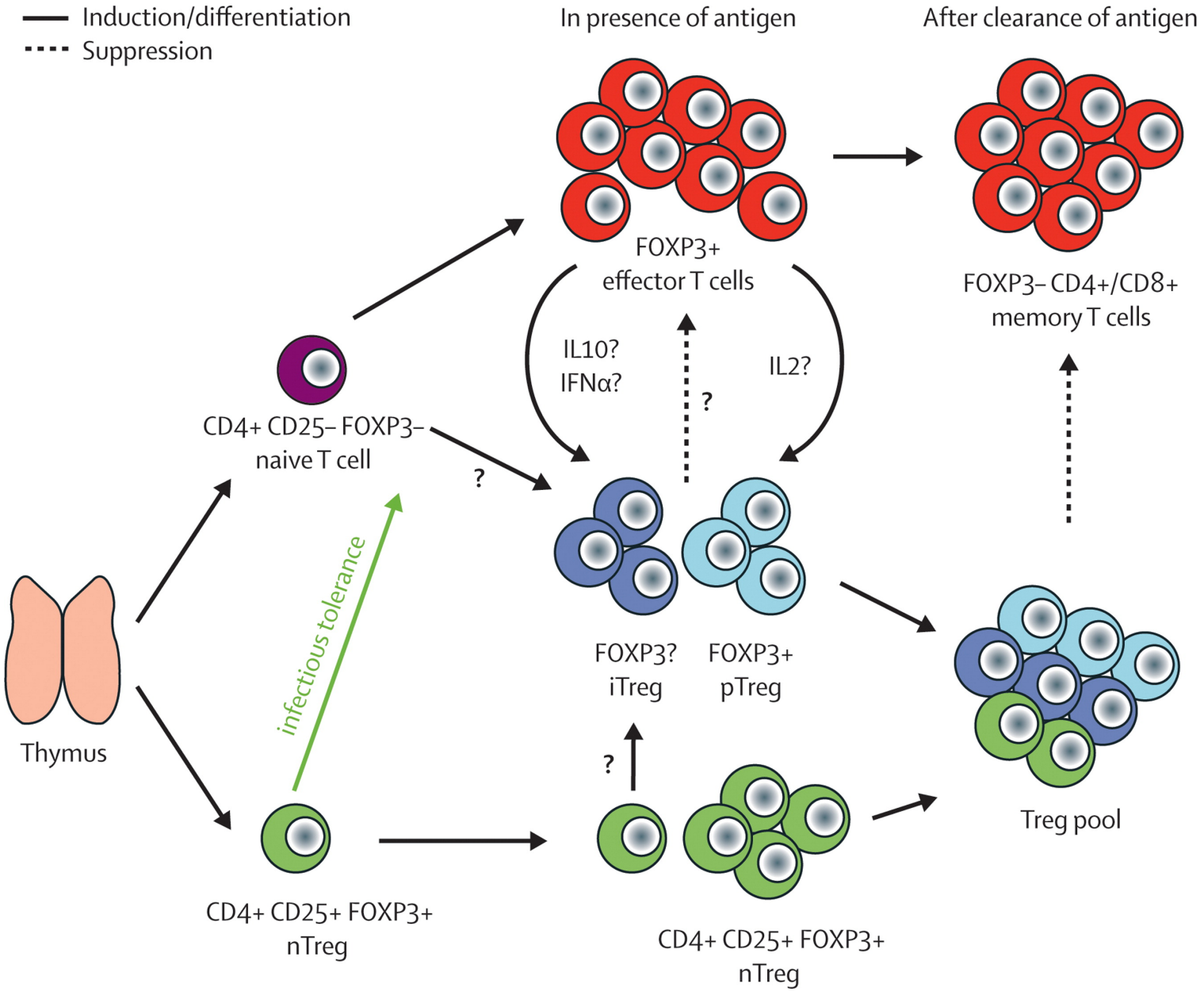


Donor 4

Individuals with rare recombination events

T cell subsets in immune-mediated diseases



T cell subsets in immune-mediated diseases

Disease	Model
T1D	A + C + E + F
MS	A + D
ATD	A + other
Celiac	A+C? / A / C / other