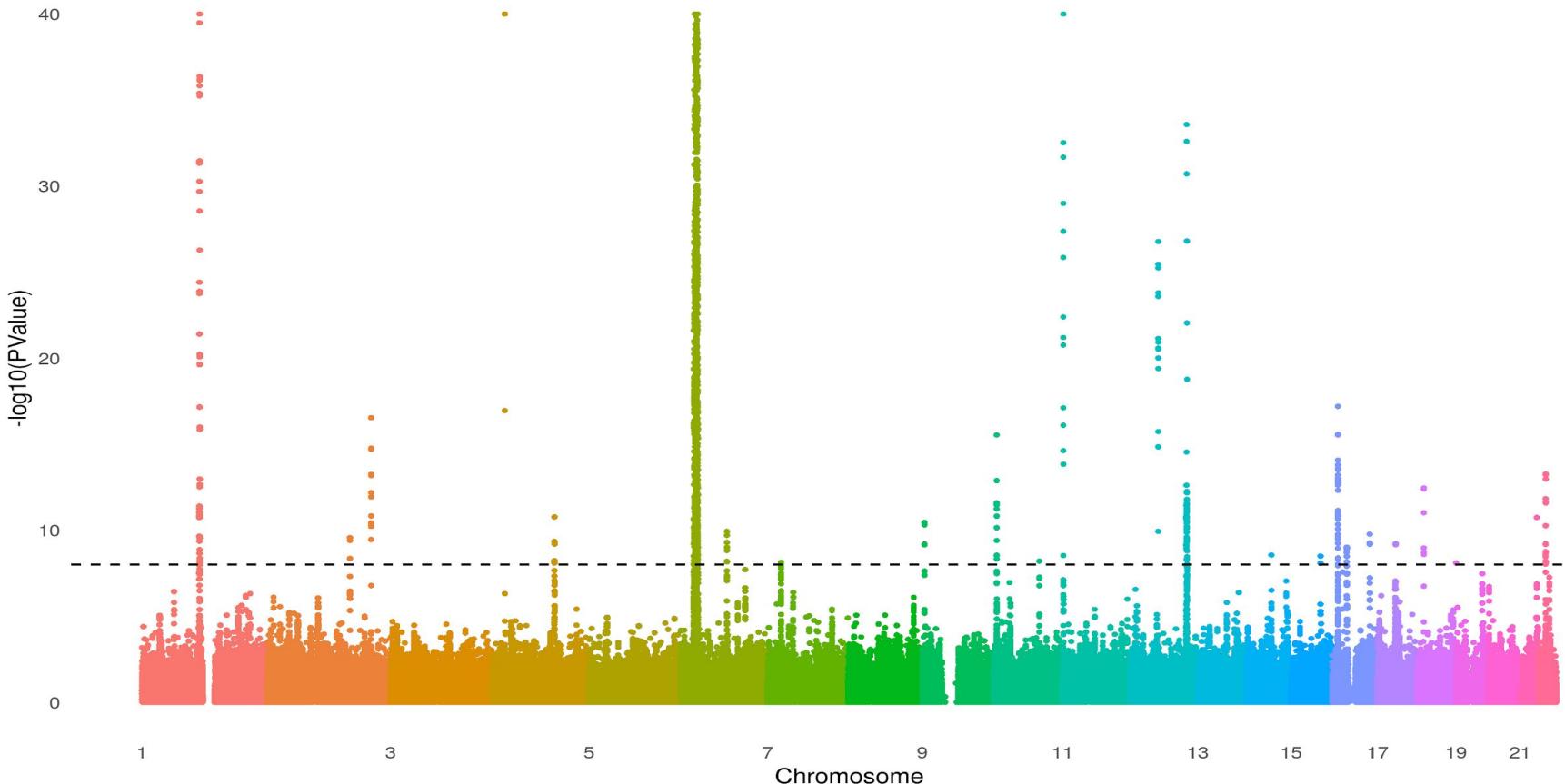


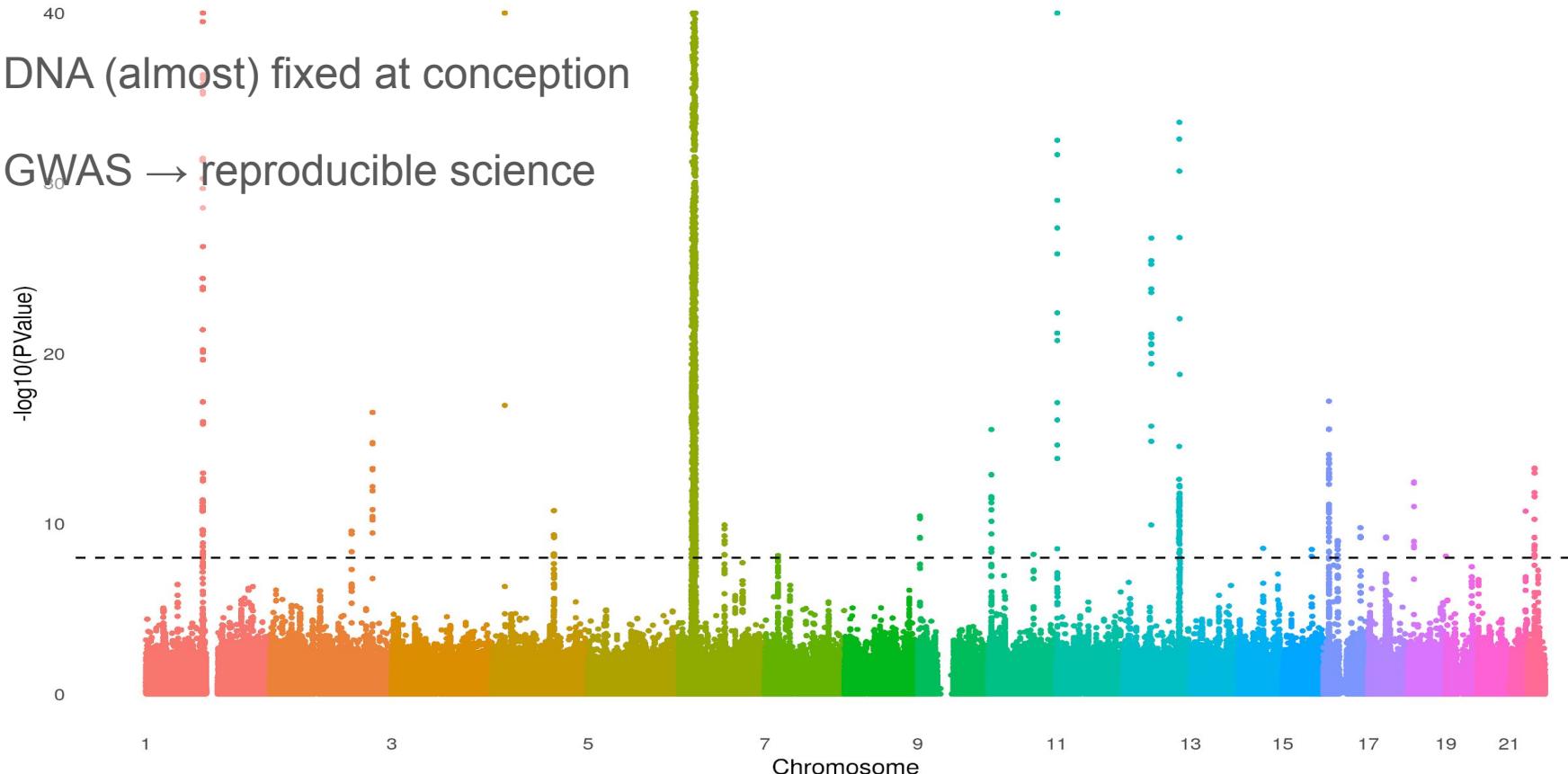
Integrative genomics in immune mediated diseases



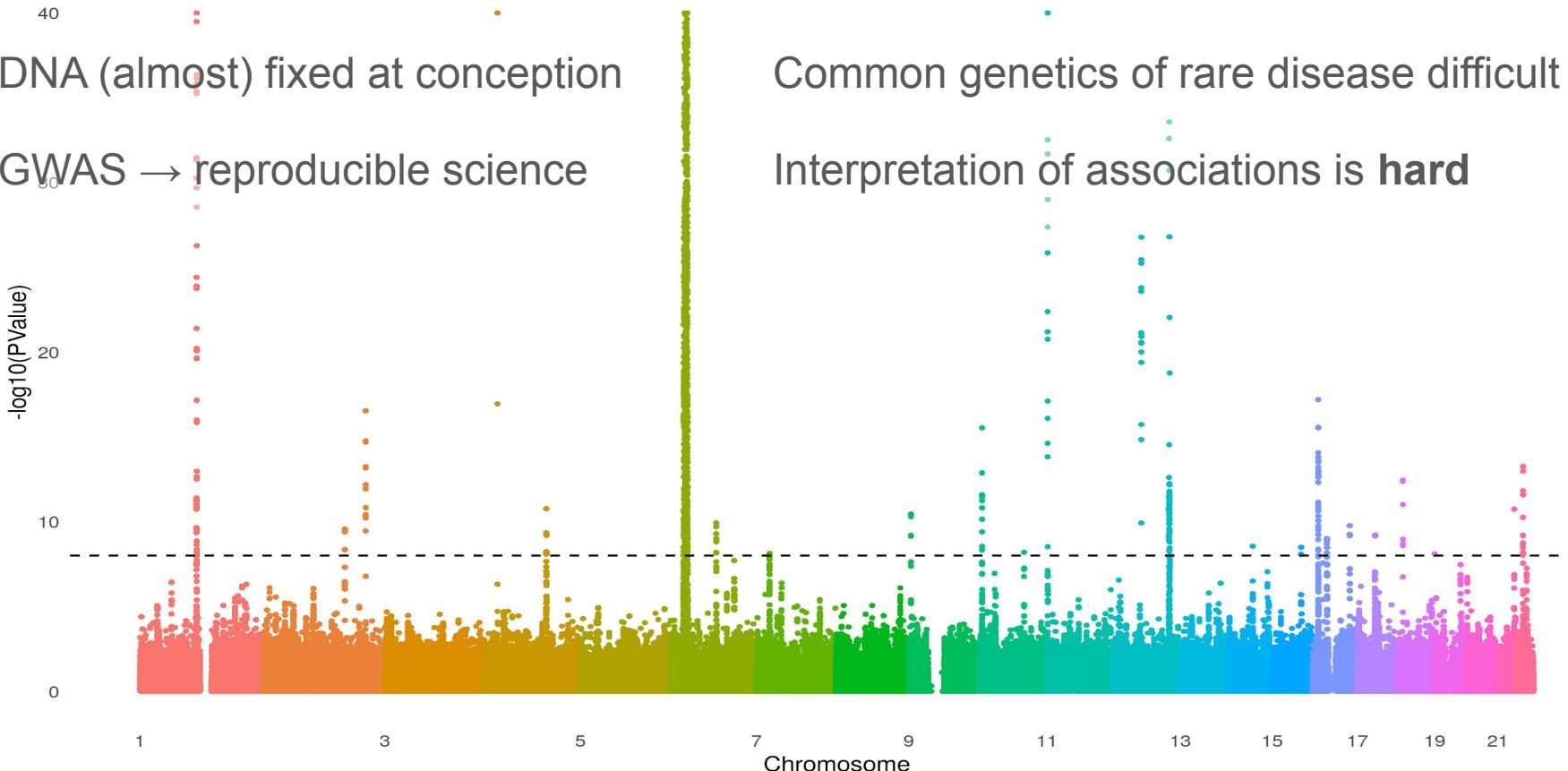
Genomewide association studies



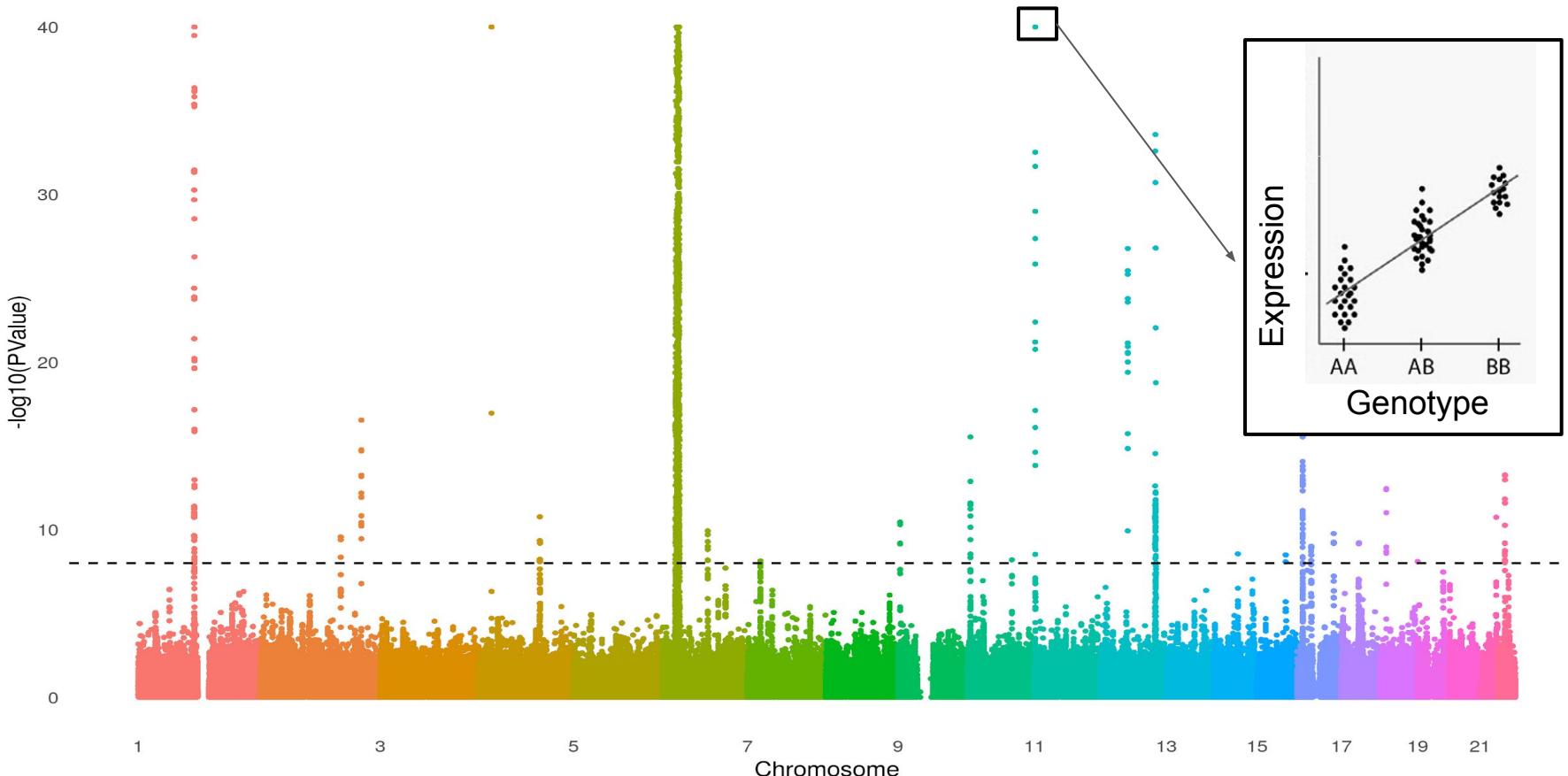
Genomewide association studies



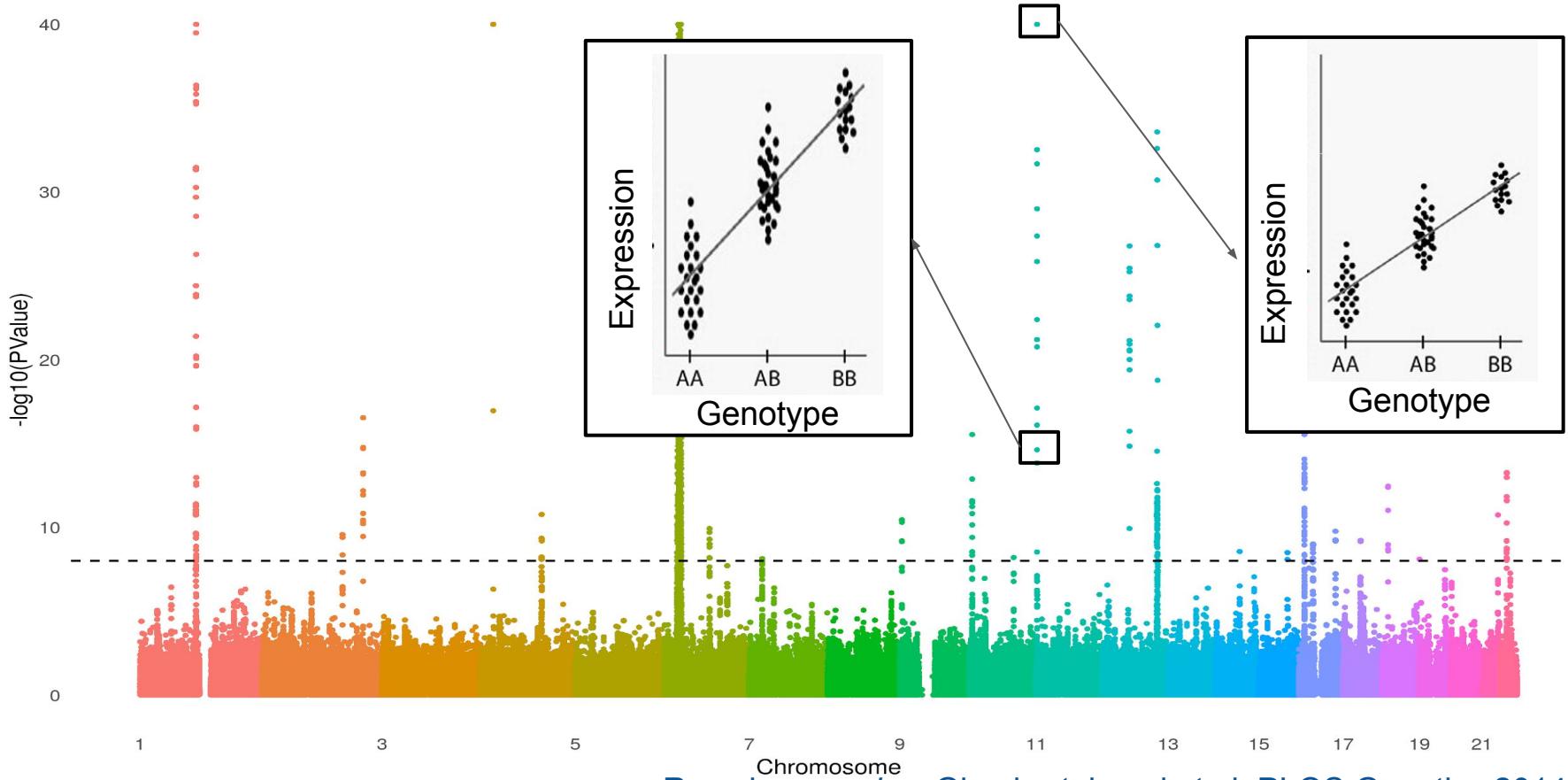
Genomewide association studies



Breadth of genetics studies: improve interpretation through joint analysis

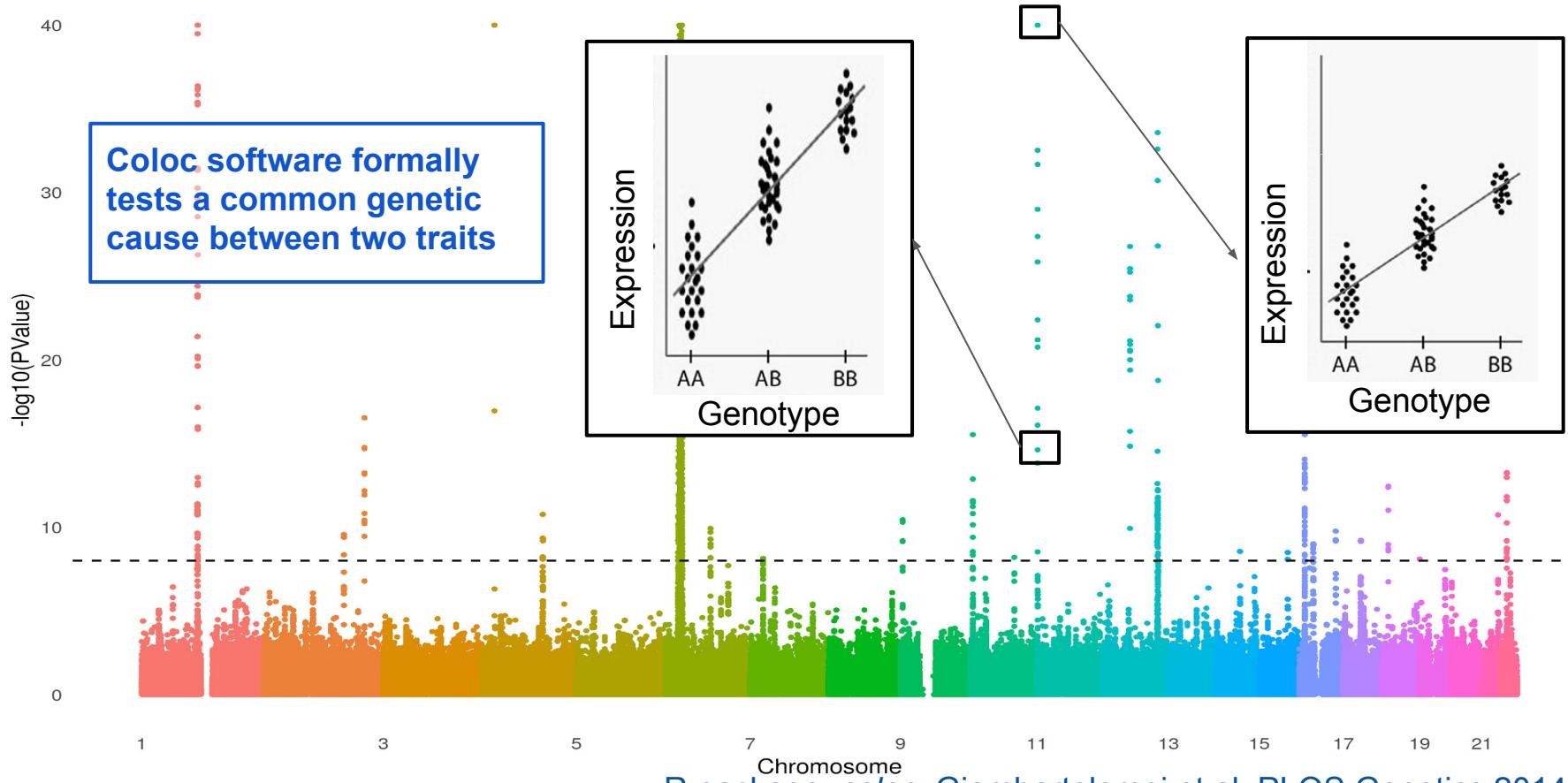


Breadth of genetics studies: improve interpretation through joint analysis



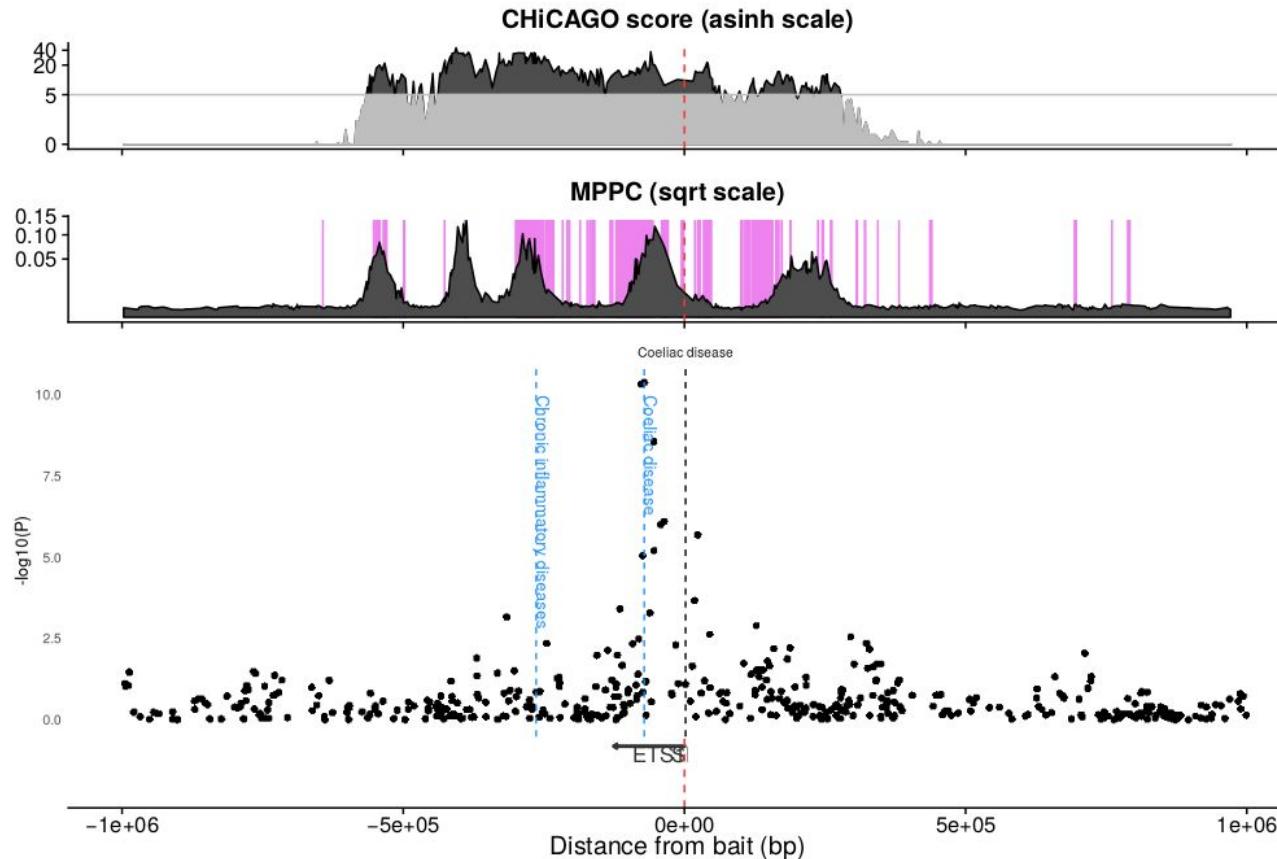
R package: *coloc*; Giambartolomei et al, PLOS Genetics 2014

Breadth of genetics studies: improve interpretation through joint analysis



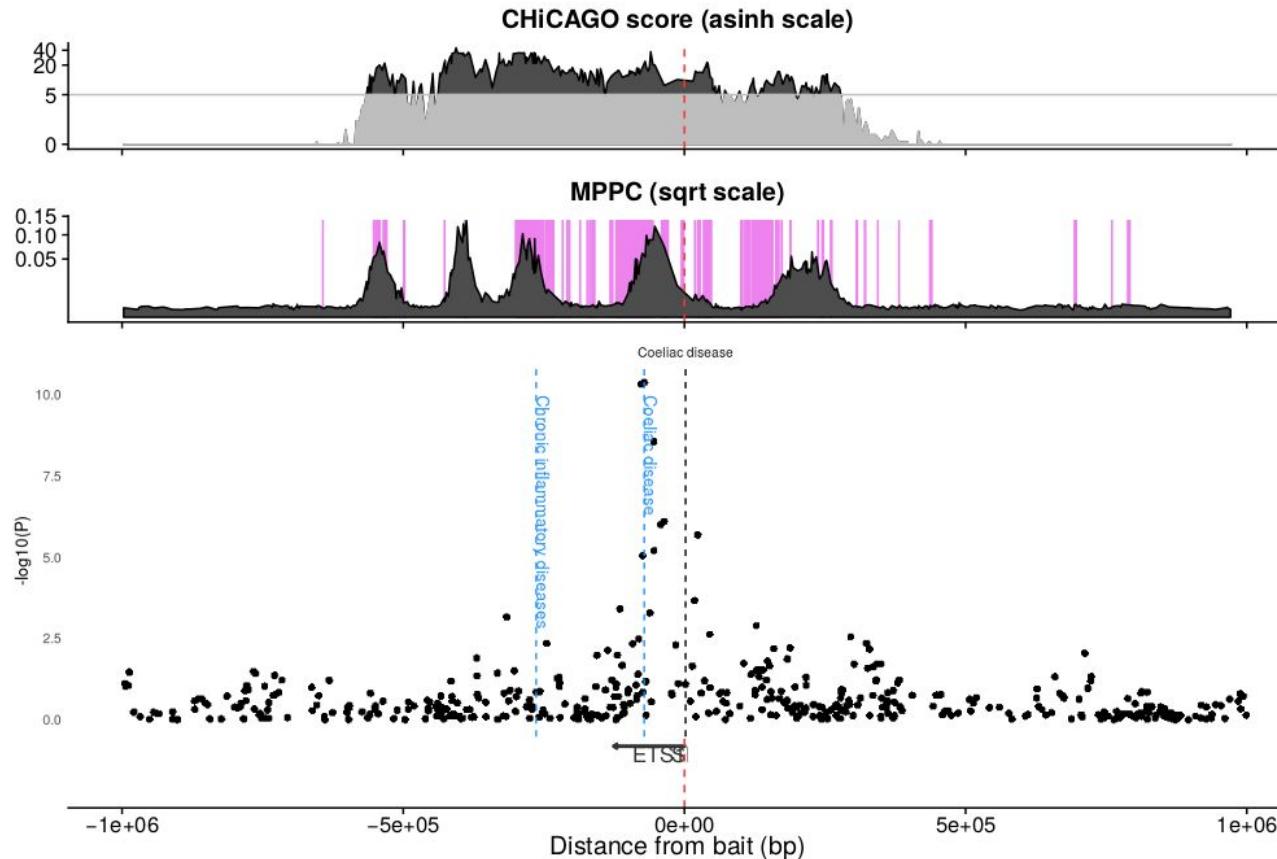
Linking gene regulatory regions and their target genes

Chromatin conformation (capture Hi-C) links regulatory regions to gene promoters



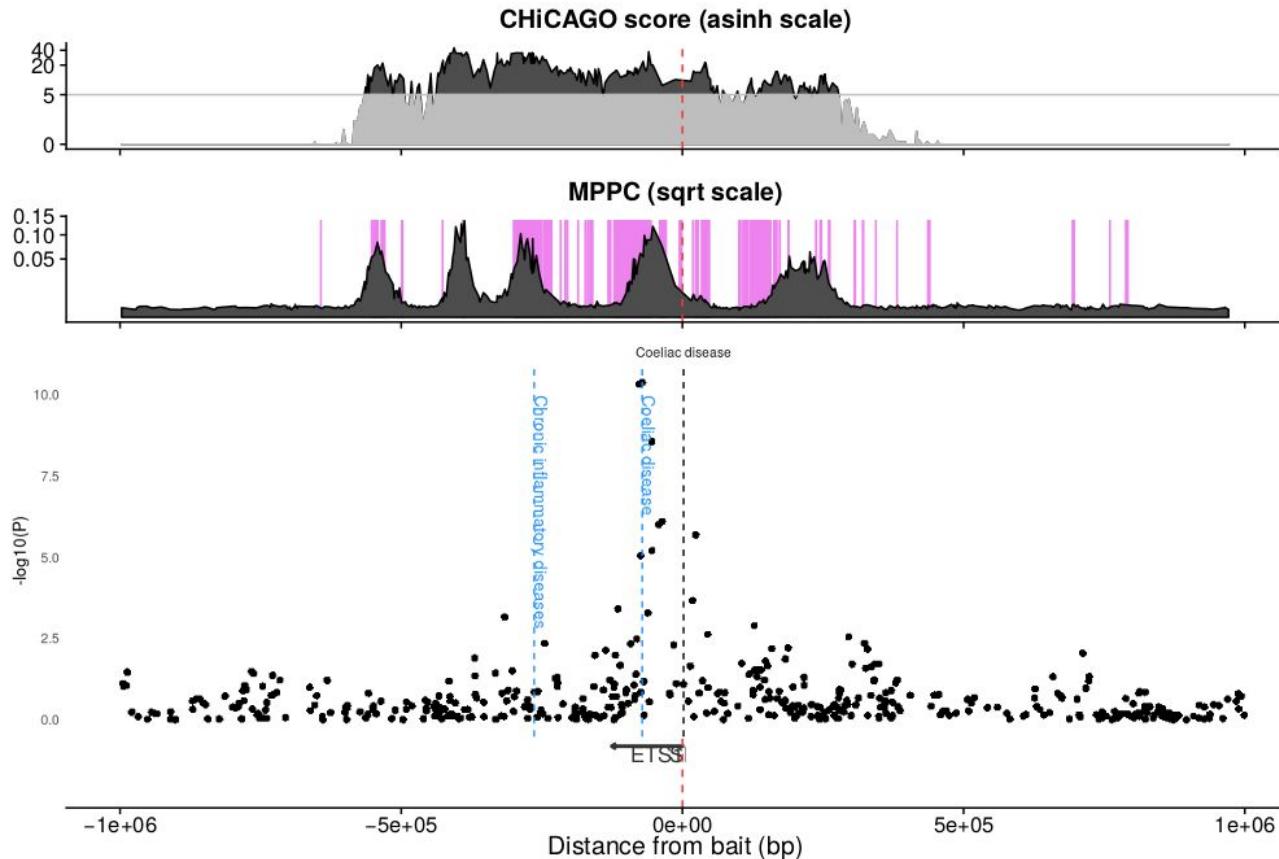
Javierre et al, Cell 2016; Burren et al, Genome Biology 2017; Eijsbouts et al, BMC Genomics 2019

Chromatin conformation (capture Hi-C) links regulatory regions to gene promoters



Standard analysis:
800kb of regulatory
contacts

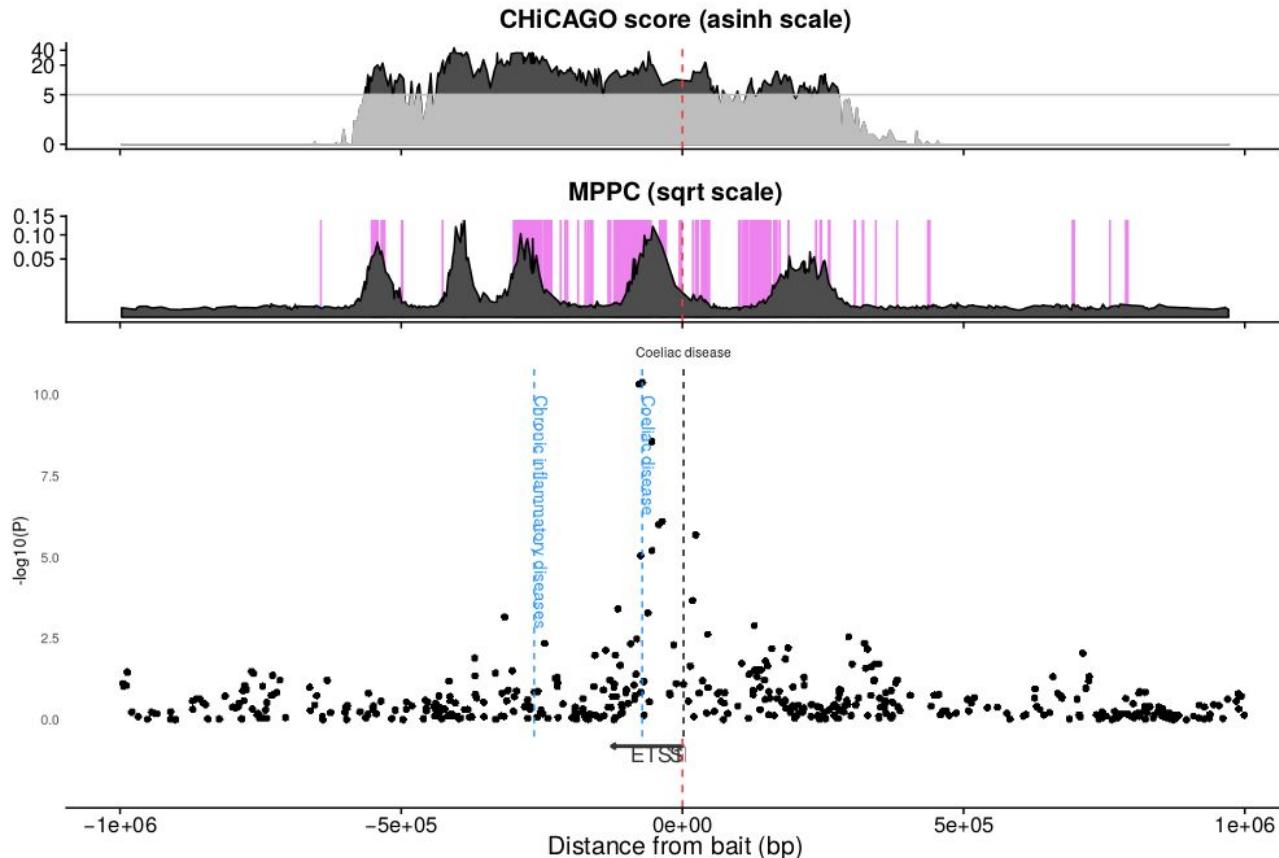
Chromatin conformation (capture Hi-C) links regulatory regions to gene promoters



Standard analysis:
800kb of regulatory
contacts

Hi-res analysis: 5
regulatory contacts

Chromatin conformation (capture Hi-C) links regulatory regions to gene promoters



Standard analysis:
800kb of regulatory
contacts

Hi-res analysis: 5
regulatory contacts

Coeliac and
chronic
inflammatory
diseases link to
ETS1

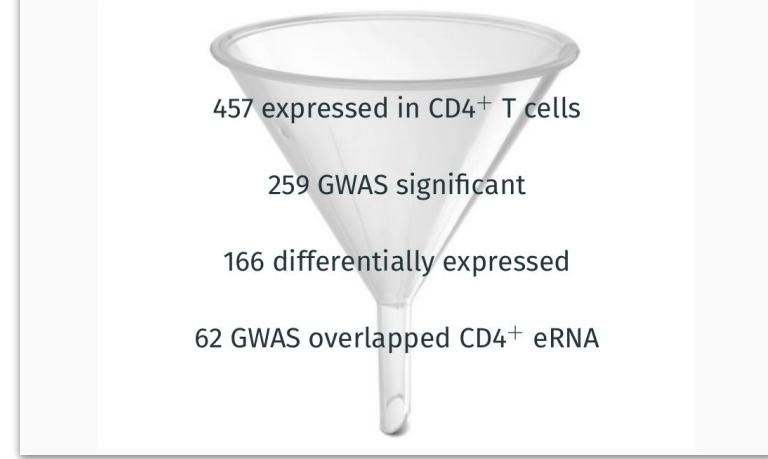
BUT

Convincing colocalisation seems rare

Gene	Disease(s)	Direction
<i>Resting B cells + monocytes</i>		
RGS1	Celiac, MS	-
SYNGR1	Primary Biliary cirrhosis	+
<i>Resting + activated monocytes</i>		
ADAM15	Crohn's	?
CARD19	Crohn's, ulcerative colitis	+
LTBR	Primary Biliary cirrhosis	+
CTSH	T1D, narcolepsy	-

Hi-C links *too many* genes to be plausible

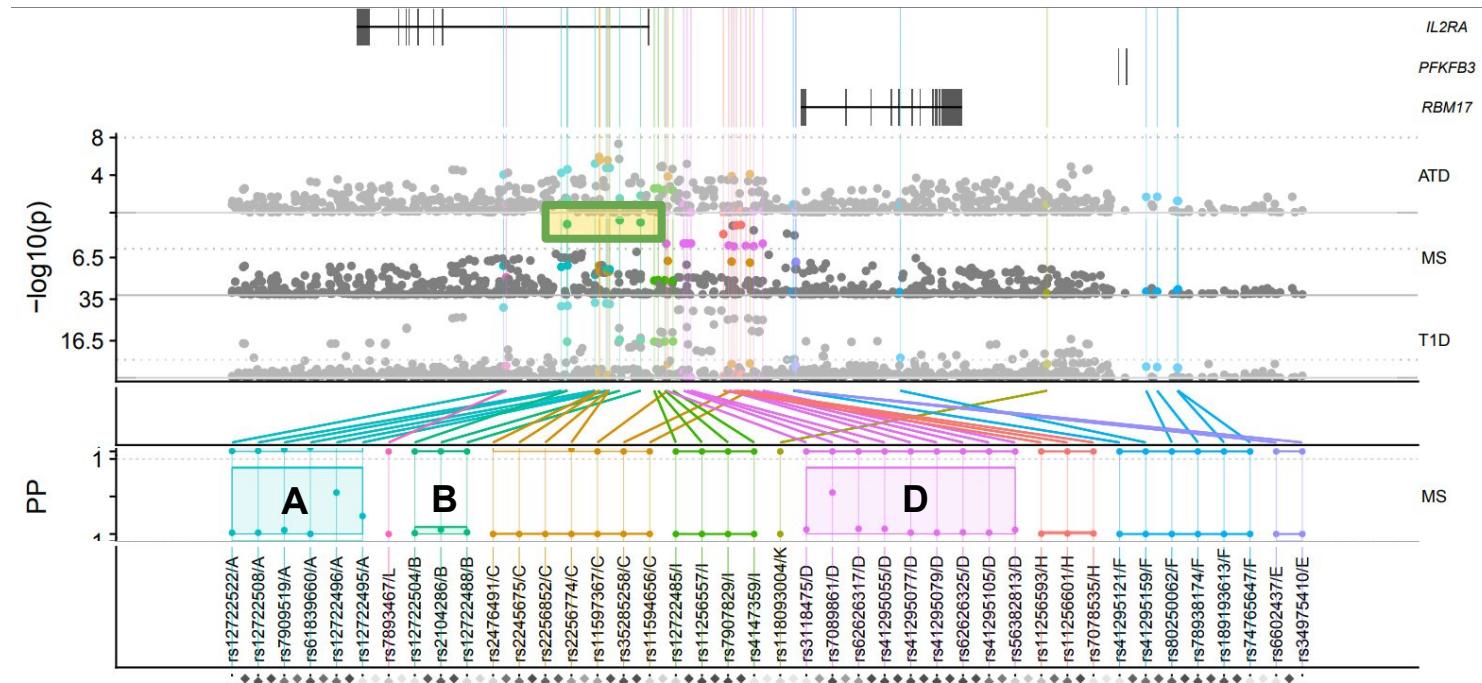
602 autoimmune disease prioritised genes in CD4⁺ T cells



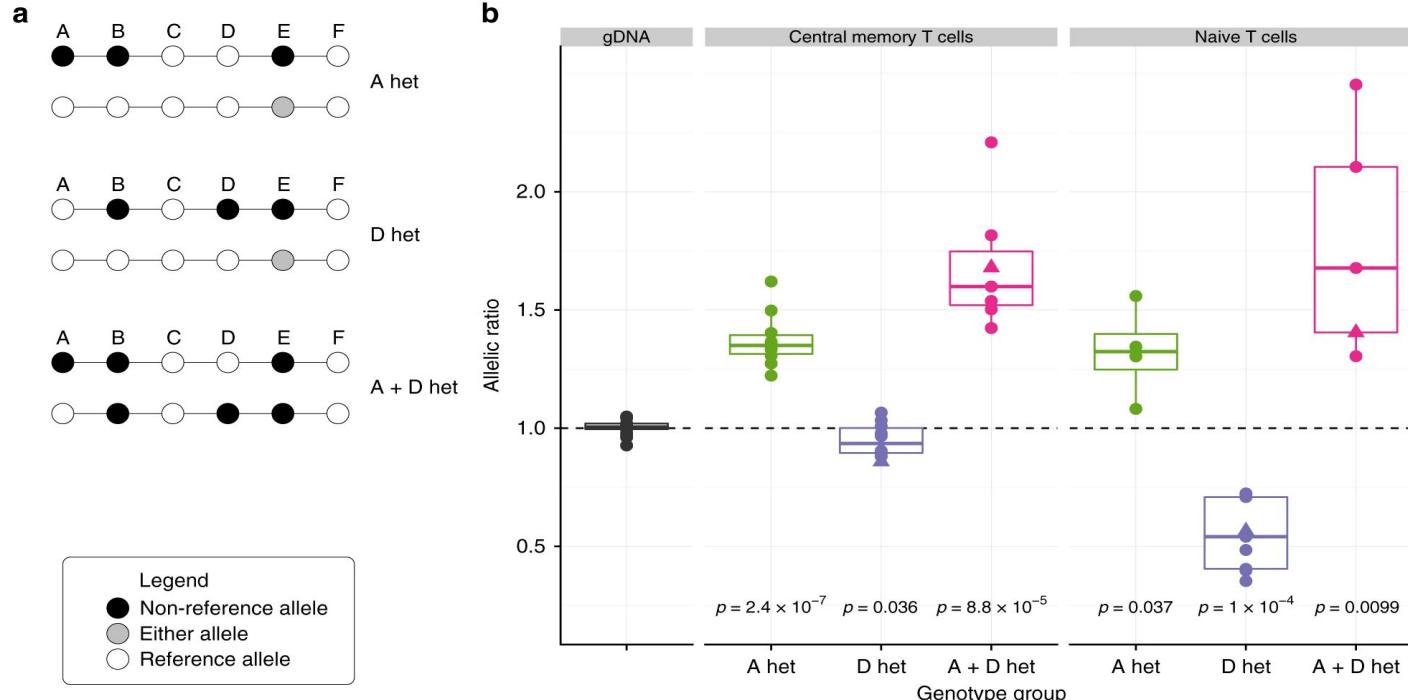
Resolution too low : cannot pinpoint genetic causes of disease, or their mediating effects

Resolution of genetic causal variants

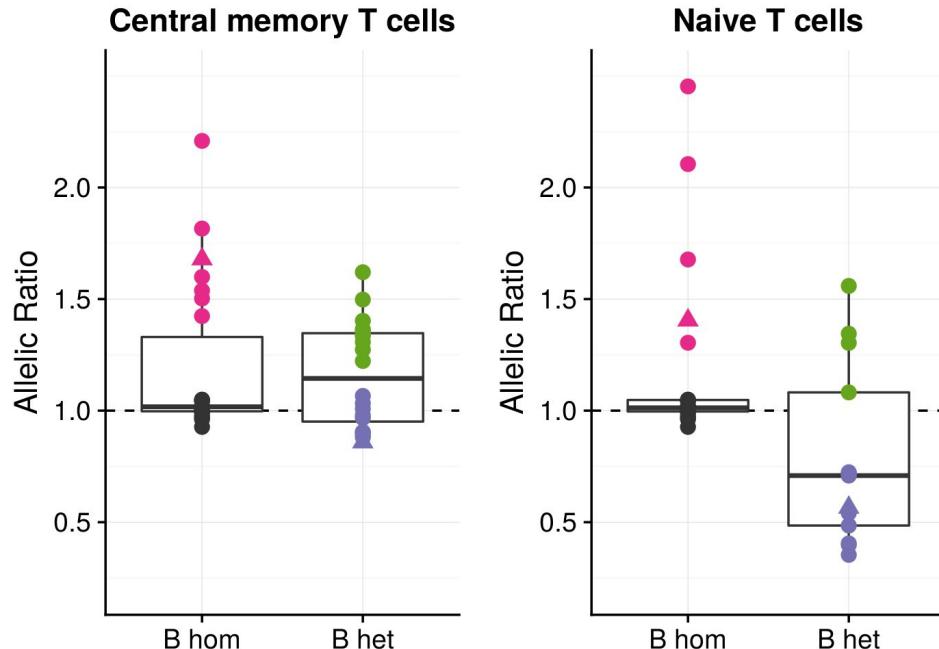
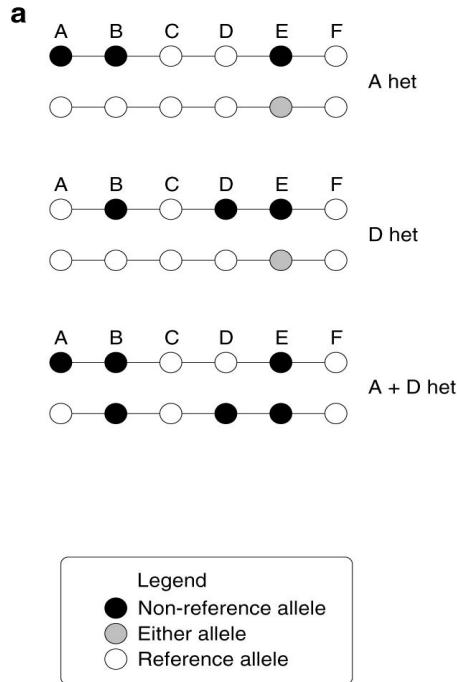
Improve genetic fine mapping resolution by sharing information between diseases



A and D variants have distinct effects on *IL2RA* expression in naive and central memory CD4⁺ T cells



A and D variants have distinct effects on *IL2RA* expression in naive and central memory CD4⁺ T cells



Resolution of effects on gene expression

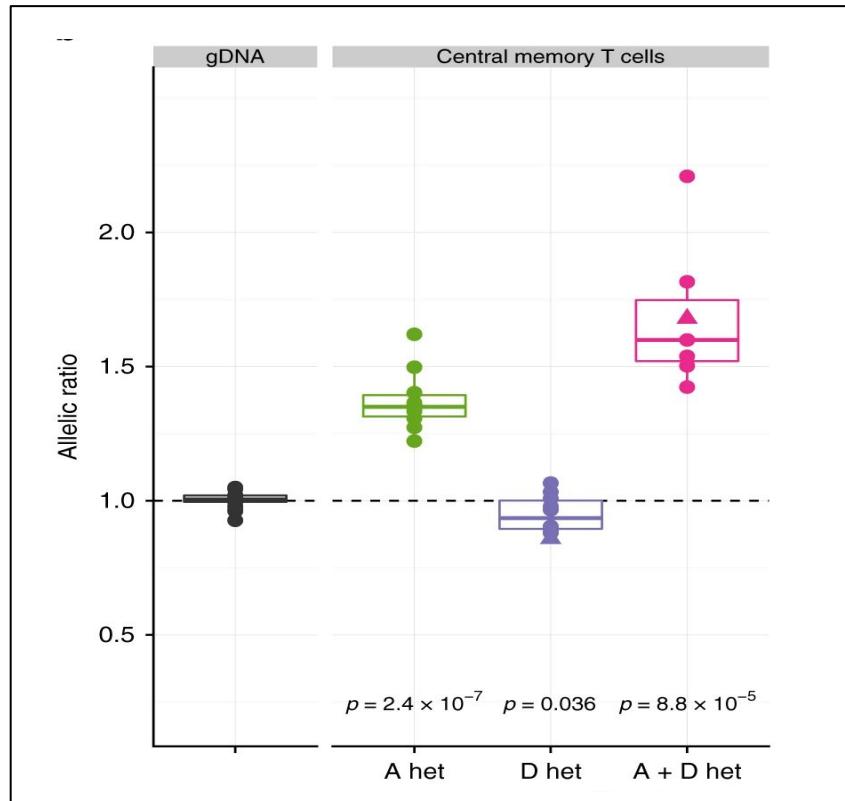
Allele specific expression assays in patient transcriptomes

Most studies that connect genetics and transcriptome focus on healthy cohorts

Expression effects of GWAS variants better seen in people with active disease

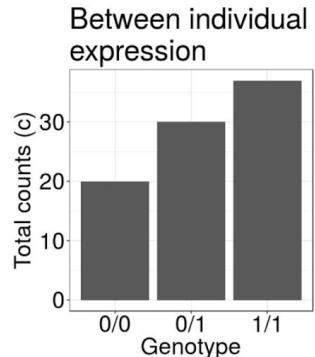
Disease cohorts generally smaller, biomarker-focused, may not sample DNA

Within individual comparisons much less noisy than between individual



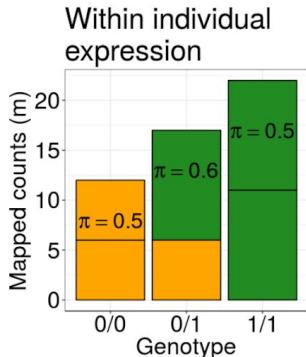
Allele specific expression assays in patient transcriptomes

a. Known genotypes and phase

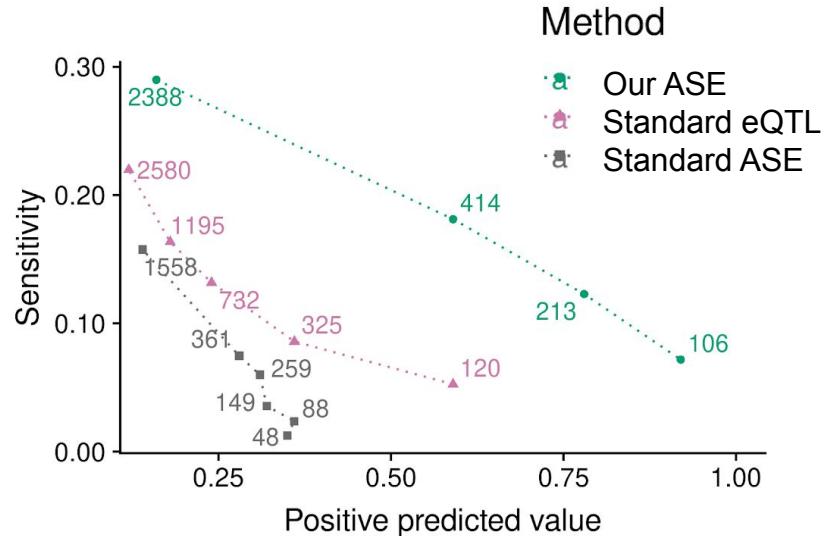


allelic Fold Change:

$$\frac{\mu_{1/1}}{\mu_{0/0}} = \frac{\pi}{1-\pi}$$

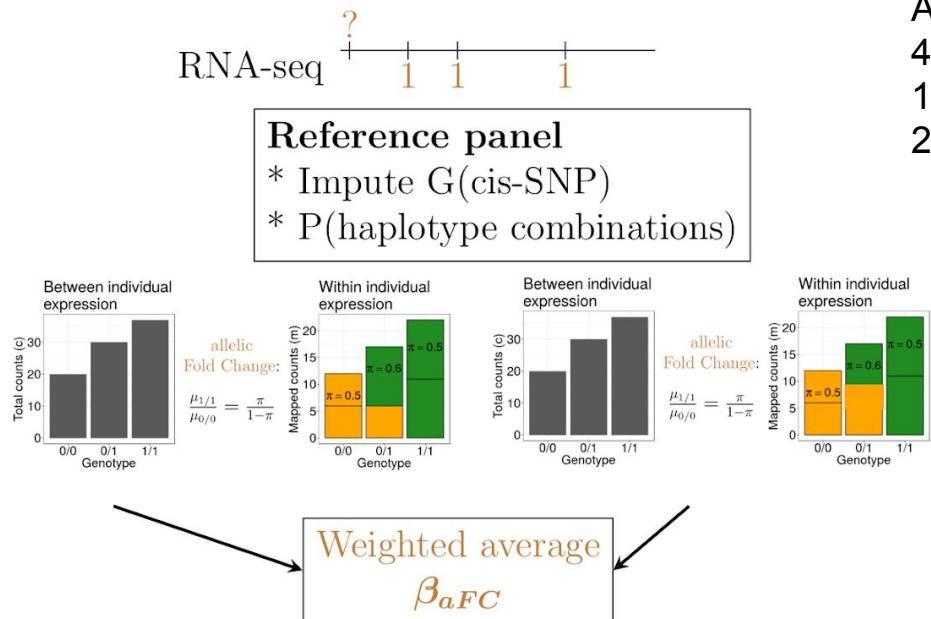


$$\beta_{aFC}$$

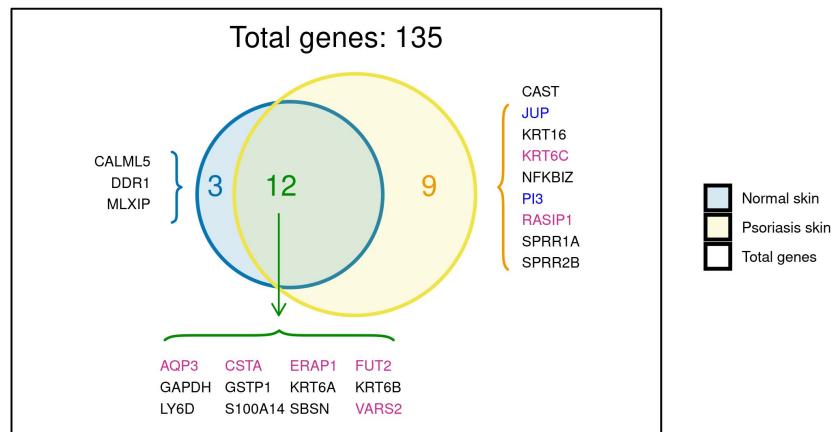


Allele specific expression assays in patient transcriptomes

b. Unknown genotypes

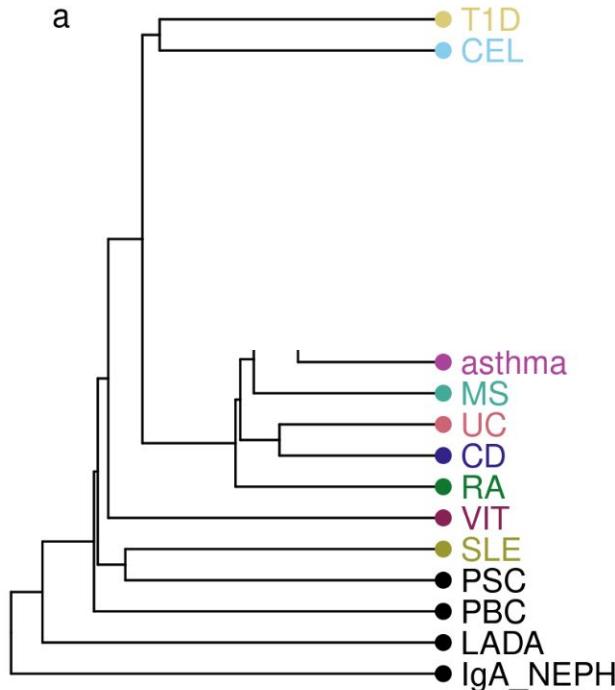


Analysis of 92 psoriatic, 80 normal skin biopsies
429 differentially expressed genes
135 testable
24 significant (FDR < 1%)

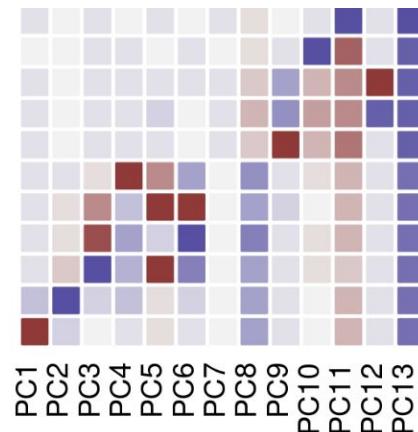


Focus on genetic components of
immune mediated disease

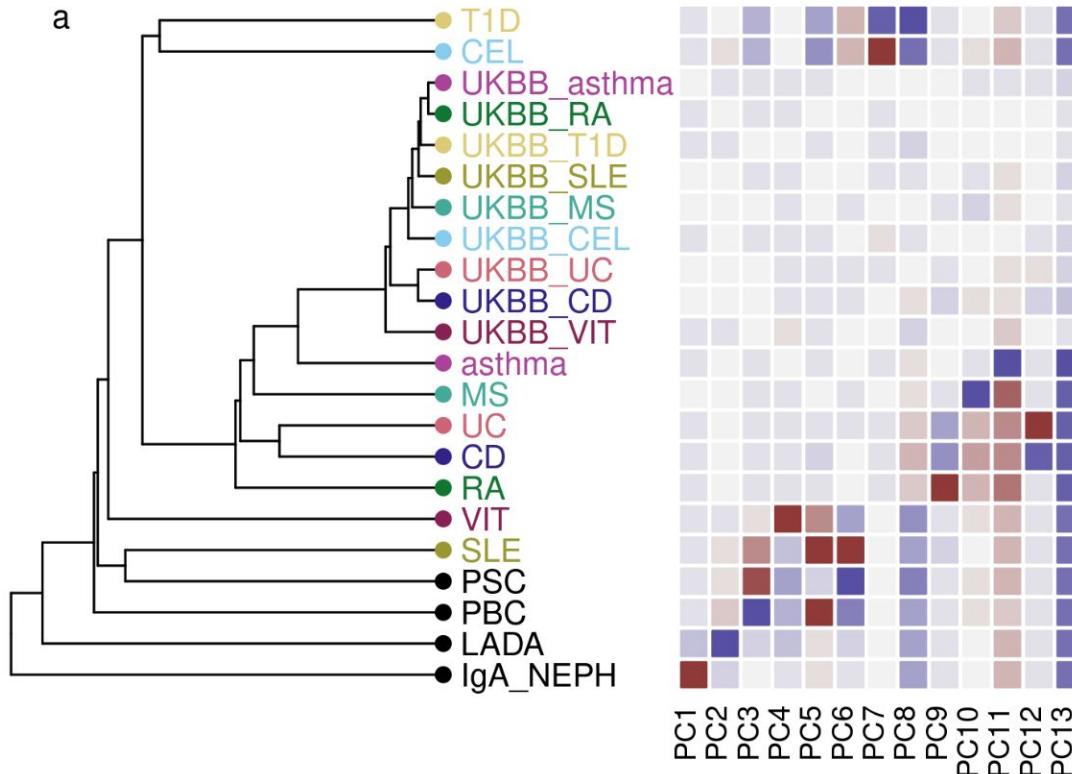
A 13-dimensional genetic basis for immune mediated disease



Naive decomposition of
GWAS summary statistics
learns some structure



A 13-dimensional genetic basis for immune mediated disease

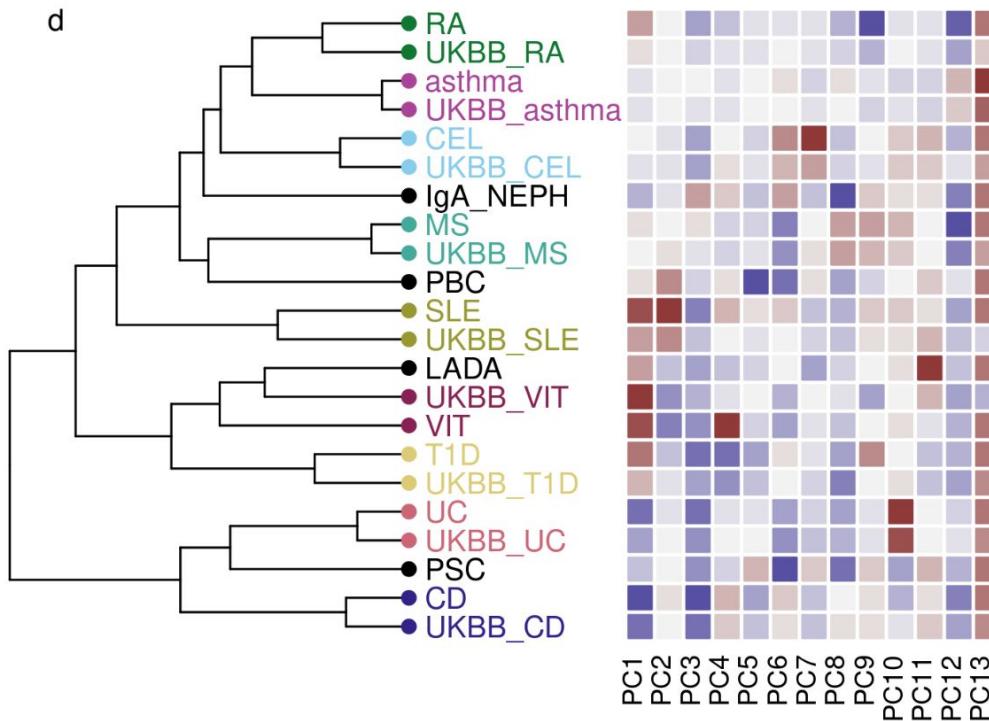


Projection of UK Biobank datasets show the structure is not disease-related

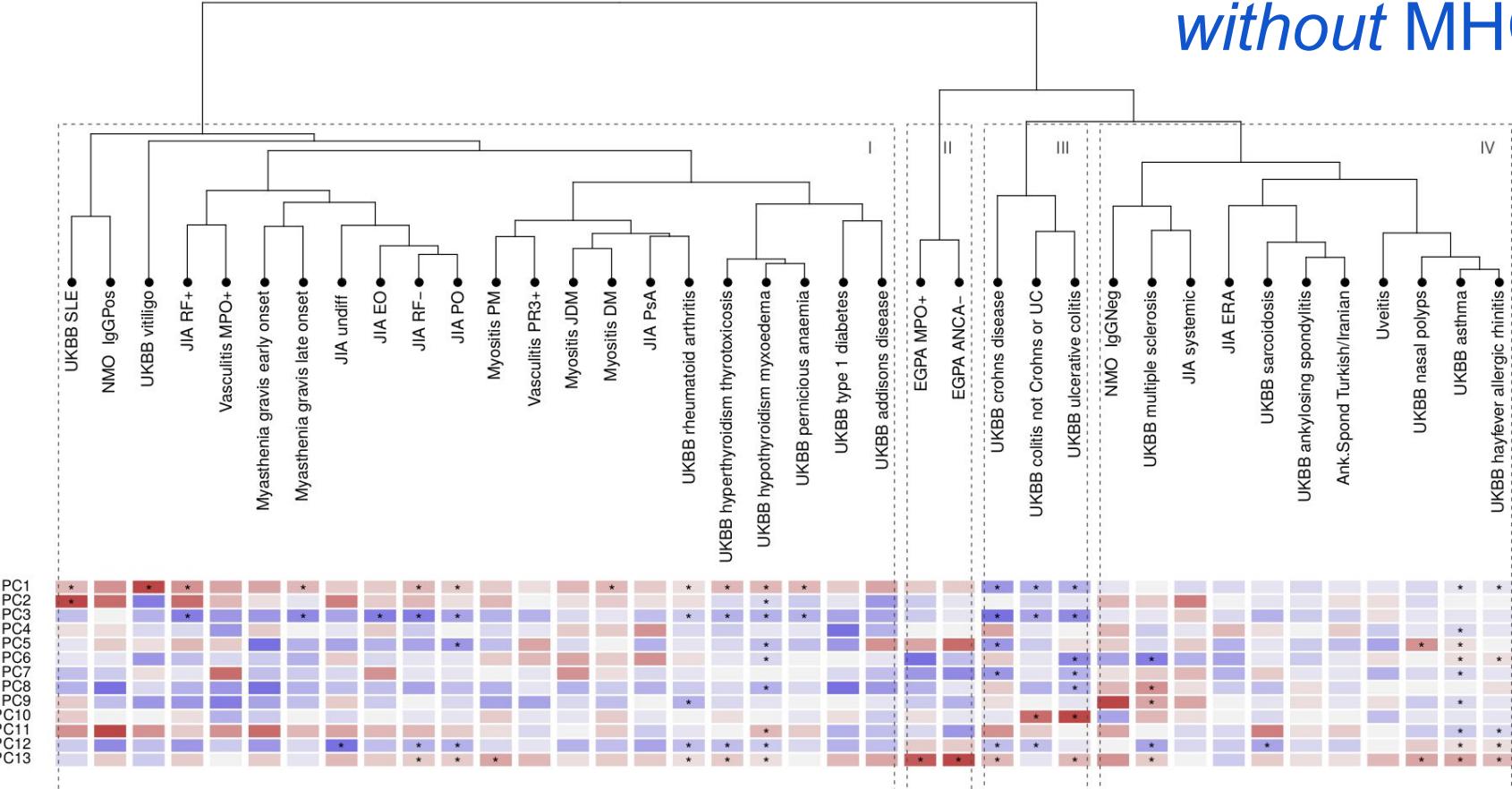
A 13-dimensional genetic basis for immune mediated disease

Exploiting fine mapping methodology we construct a “lens” to focus on disease-relevant genetics

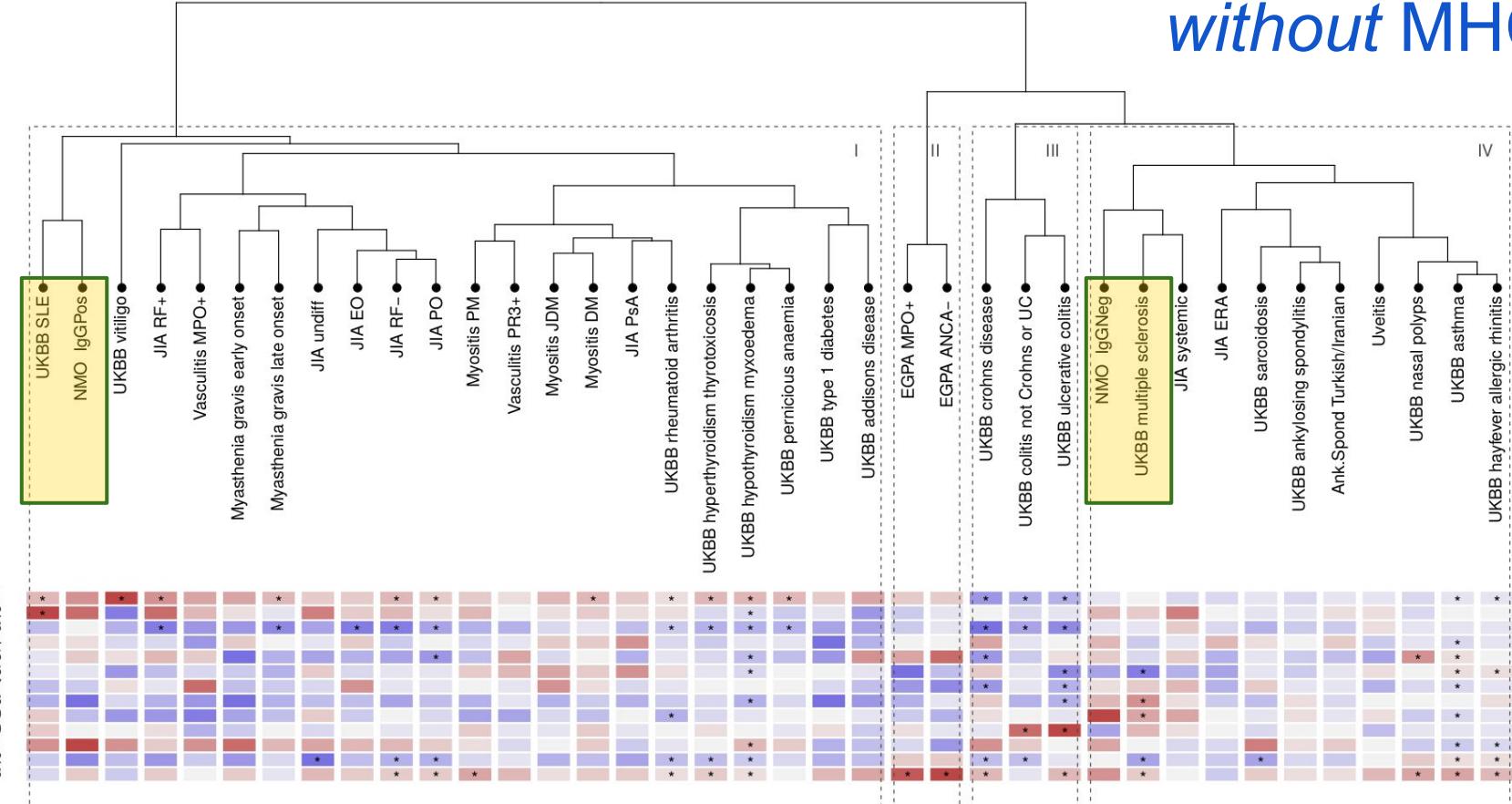
Independent datasets fall on same axes as their GWAS counterparts



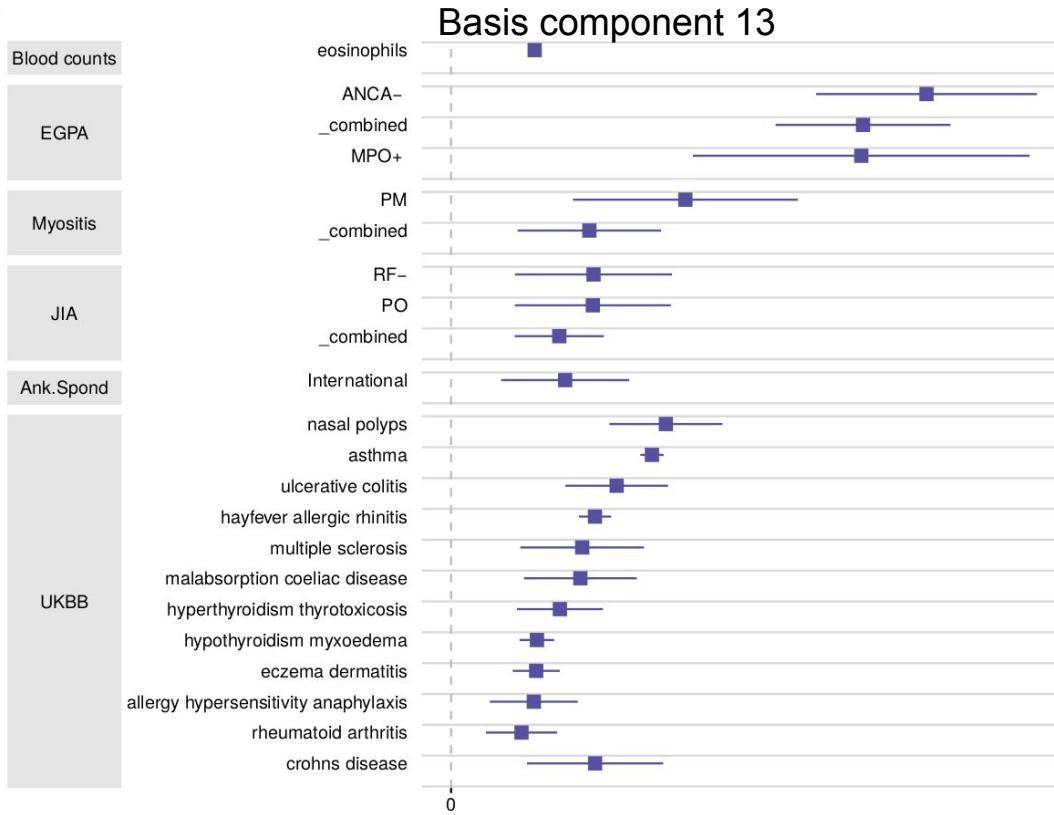
An overview of immune mediated disease genetics *without* MHC



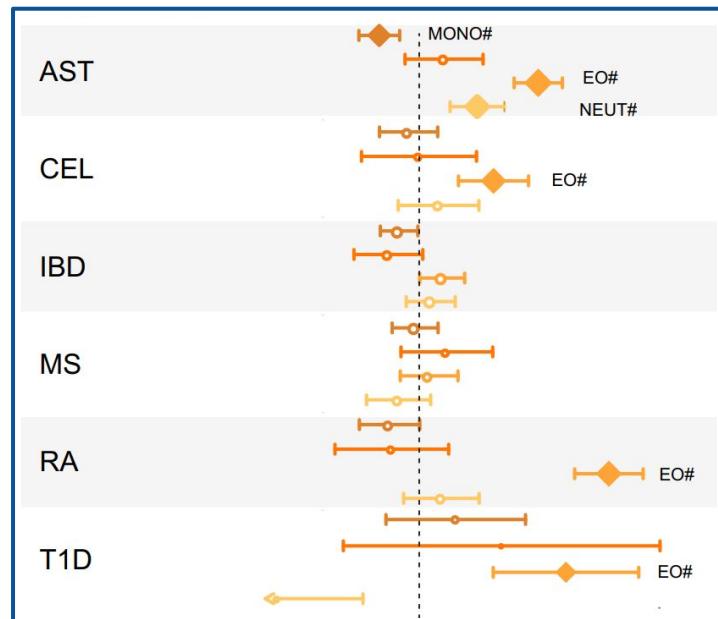
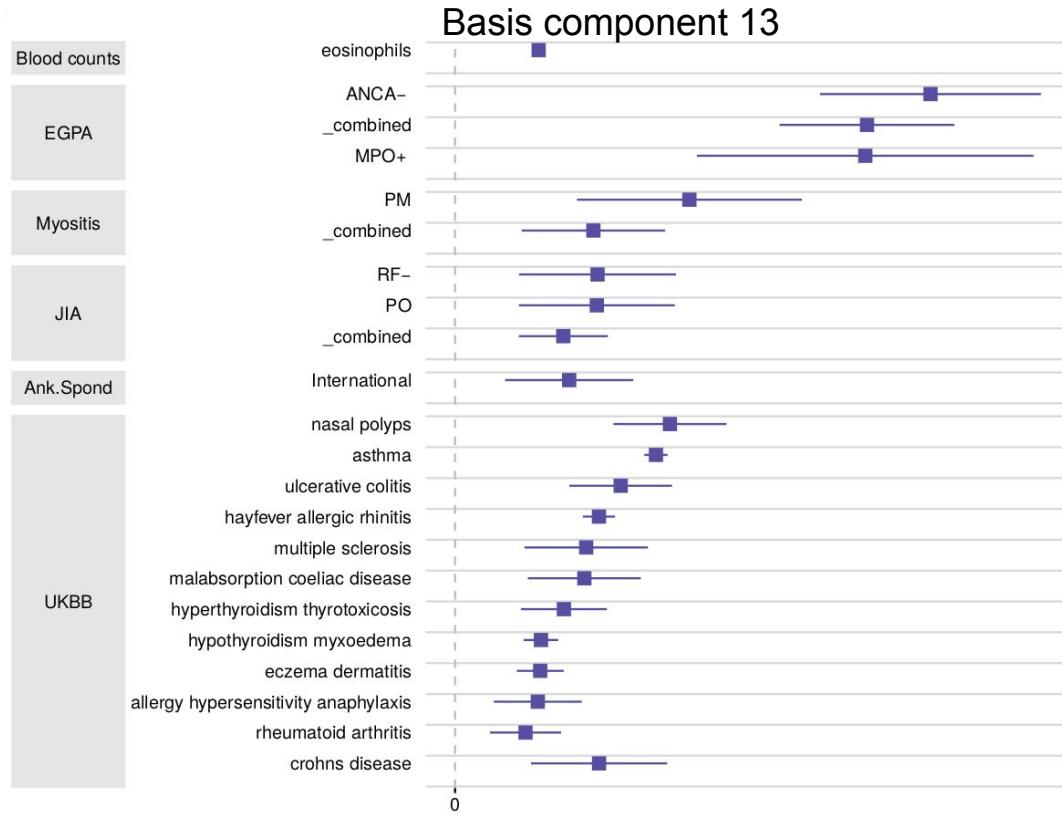
An overview of immune mediated disease genetics *without* MHC



Eosinophils relevant to range of IMD

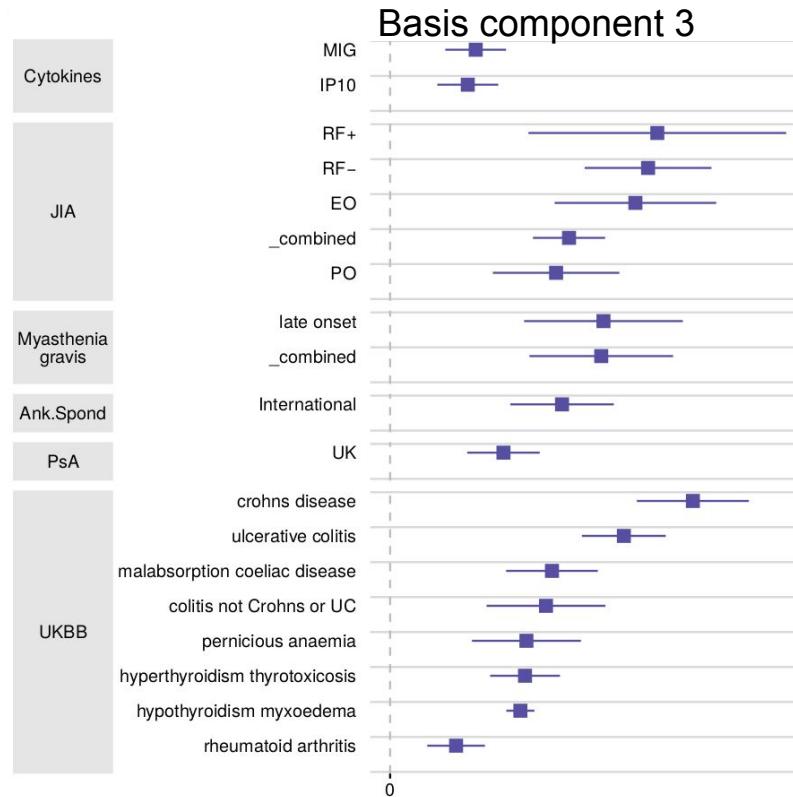


Eosinophils relevant to range of IMD



Astle et al. Cell 2016

Genetically link raised serum IP-10 and MIG to IMD



Th1 chemoattractants, ligands to the regulator of leukocyte trafficking CXCR3

- upregulated in myasthenia gravis, recent onset type 1 diabetes, Graves' disease
- correlate with disease activity in SLE, ankylosing spondylitis

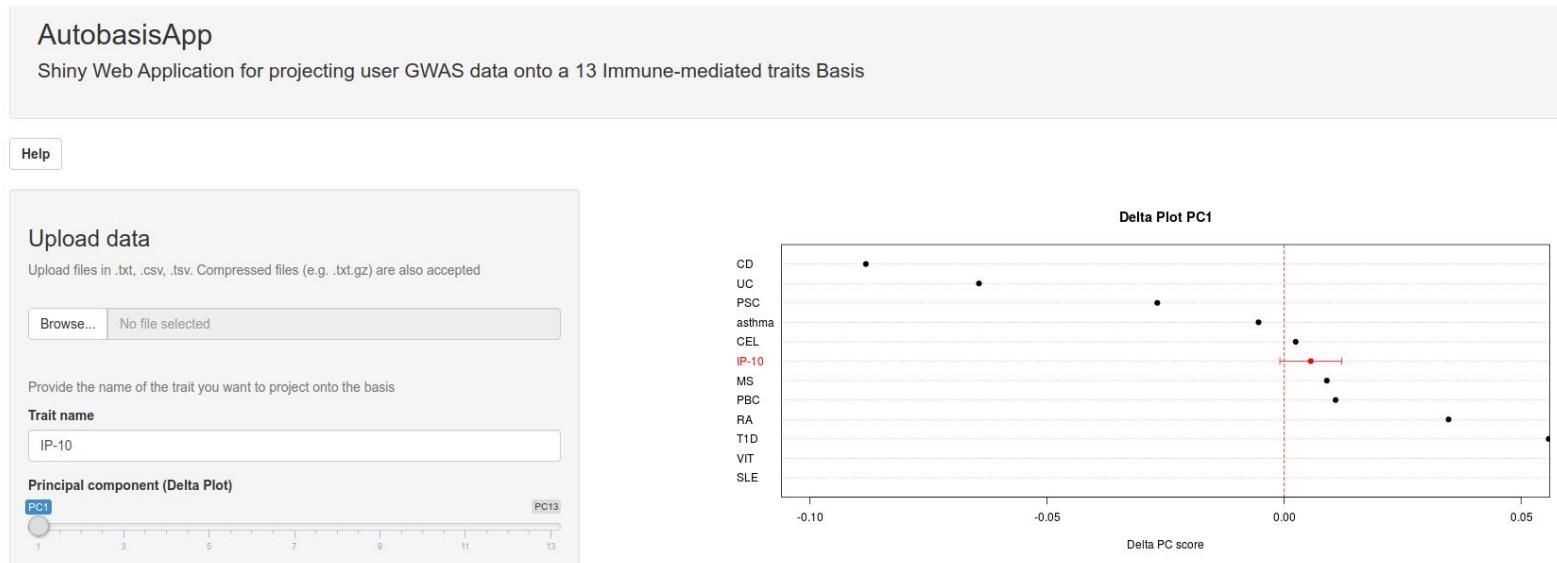
MDX1100, monoclonal antibody to IP-10

- dose-response relationship in ulcerative colitis¹
- clinically efficacious in RA²

¹Mayer et al. *Gut* 2014 ²Yellin et al. *Arthritis Rheum* 2012

Genetic basis for immune mediated disease

<https://grealesm.shinyapps.io/AutobasisApp/>



Compare multiple traits in manageable dimensions
Inclusive of small studies / rare diseases

Integrative genomics in immune mediated diseases

Improve discovery, resolution and interpretation



Martin
Keleman



Guillermo
Reales



Kath
Nicholls



Stasia
Grinberg



Wei-Yu
Lin



Anna
Hutchinson



Jenn
Asimit



Elena
Vigorito



Stephen
Coleman



Olly
Burren

Collaborators

JIA: Wendy Thomson, John Bowes

Myositis: Lucy Wedderburn, MYOGEN

EGPA, vasculitis: Limy Wong, Paul Lyons, Ken Smith

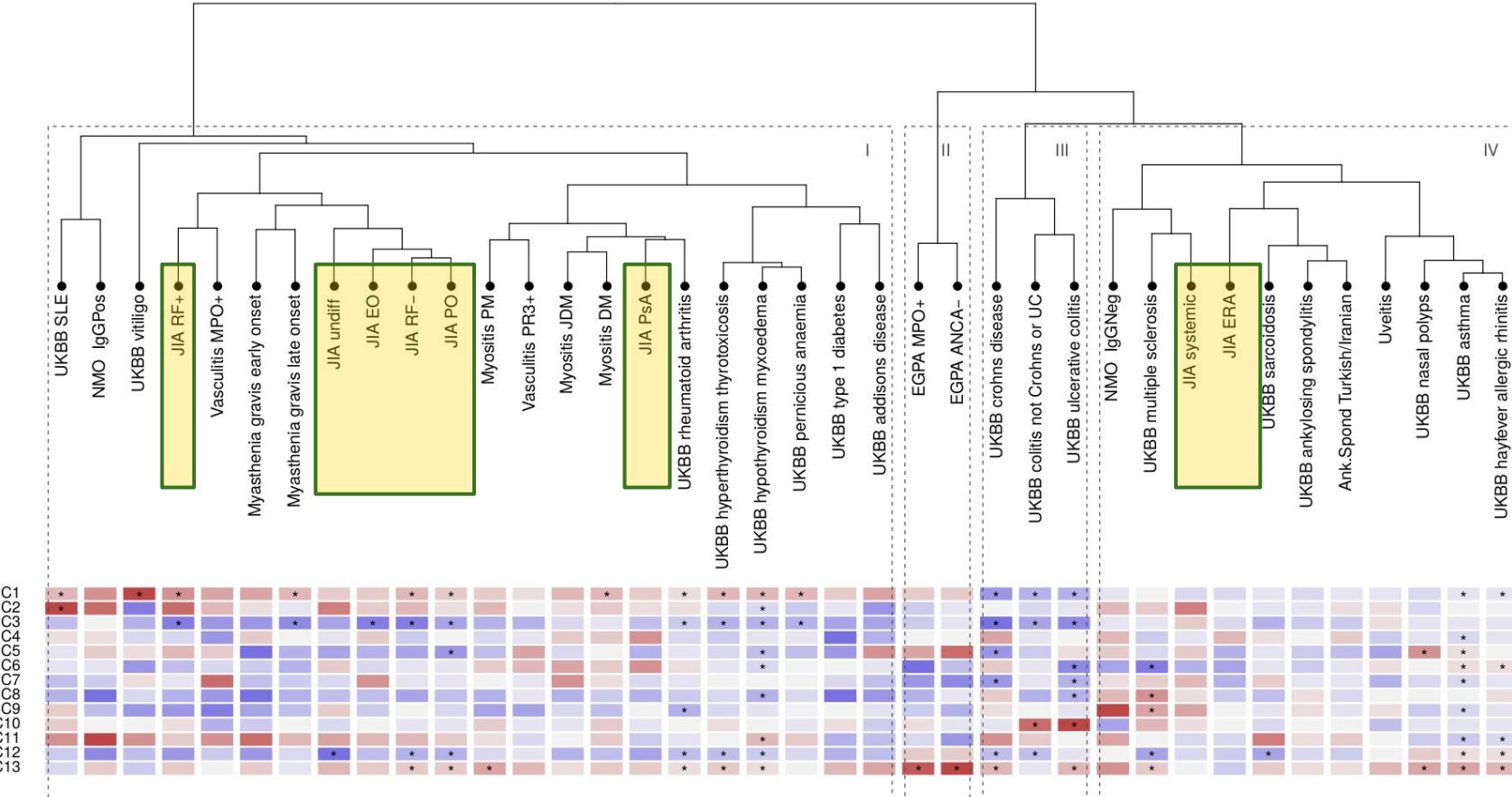
Chi-C: Mikhail Spivakov, Biola Javierre, Peter Fraser

IMD genetic basis: James Lee

Immune disease genetic basis: <https://grealesm.shinyapps.io/AutobasisApp/>

Capture Hi-C Browser for 17 immune-related cell types: <https://www.chicp.org>

An overview of immune mediated disease genetics



Integration of genomic studies with GWAS to improve interpretation

Reduce dimensions/borrow information to extend GWAS to rarer diseases

Jenn Asimit

Olly Burren

Hui Guo

Guillermo Reales

Elena Vigorito

Collaborators:

JIA: Wendy Thomson, John Bowes

Myositis: Lucy Wedderburn, MYOGEN

EGPA, vasculitis: Limy Wong, Paul Lyons, Ken Smith

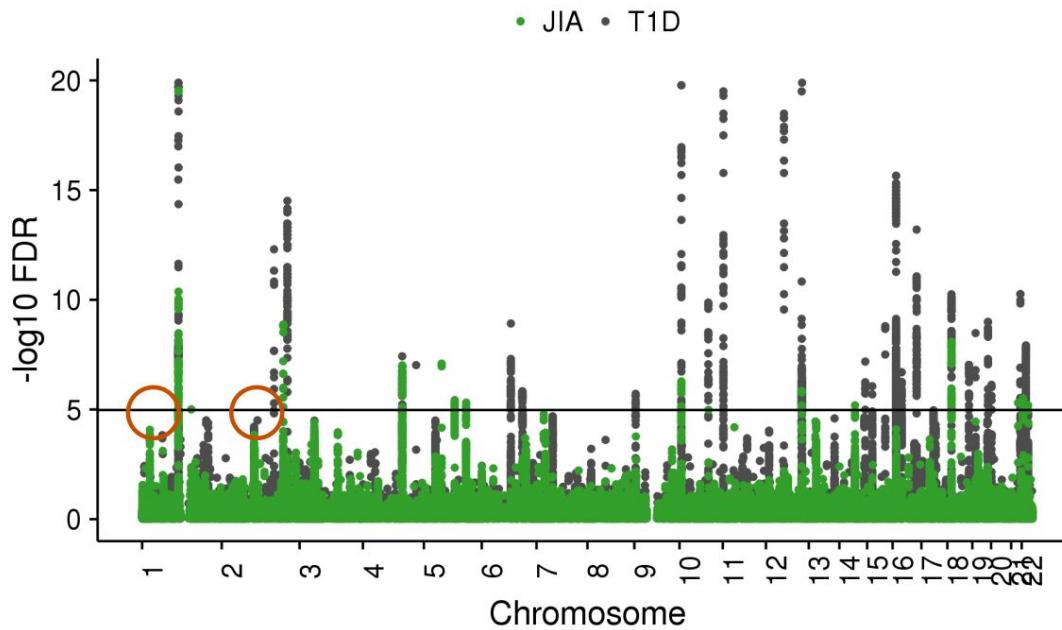
CHi-C: Mikhail Spivakov, Biola Javierre, Fraser

Capture Hi-C Browser of 17 immune cells: <https://www.chicp.org>

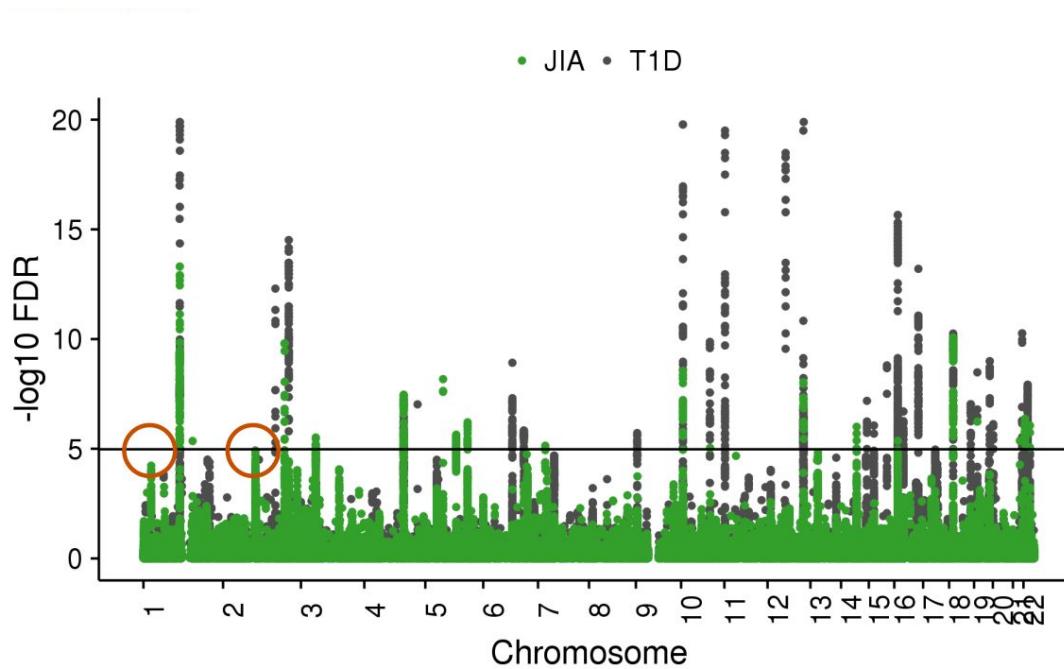
Immune disease genetic basis: <http://...>



Overcoming dimension: false discovery rate



Overcoming dimension: **conditional false discovery rate**



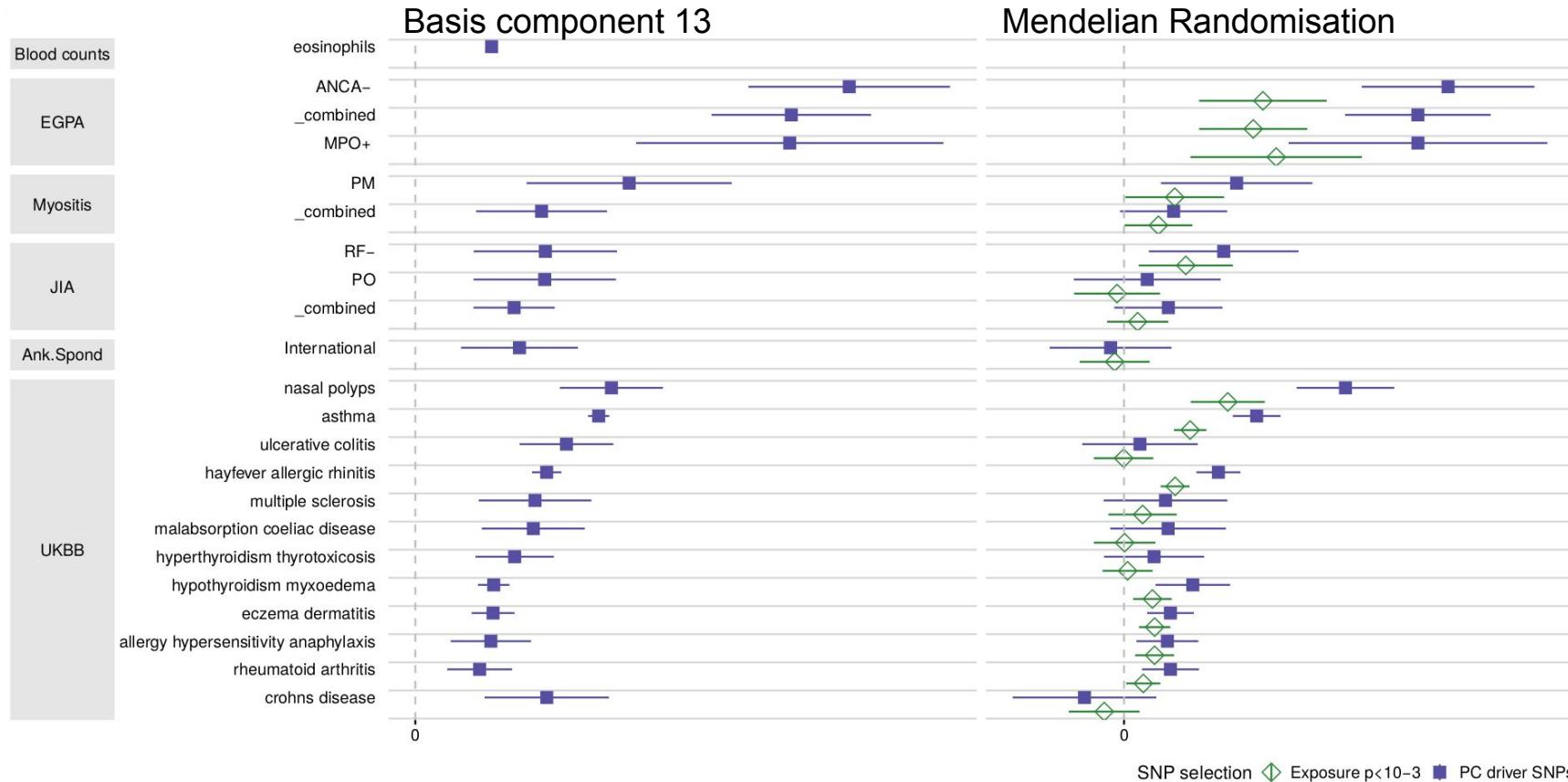
New associations with EGPA via conditioning on asthma, eosinophil counts

Chr	Gene/ Region	Total EGPA N = 534			MPO +ve EGPA N = 159		ANCA -ve EGPA N = 352		cFDR asthma analysis N = 10,365		cFDR EC analysis N = 175,000		
		OR	LMM P	Meta OR	Meta P	MPO OR	MPO P	OR	P	P asthma	cFDR ^ (EGPA asthma)	P EC	cFDR ‡ (EGPA EC)
2	BCL2L11	1.66	1.9x10 ⁻¹⁰	1.81	9.0x10 ⁻¹¹	1.89	7.7x10 ⁻⁵	1.76	3.6x10 ⁻⁷				
5	TSLP	1.42	1.5x10 ⁻¹⁰	1.52	5.2x10 ⁻¹¹	1.46	0.0008	1.53	1.2x10 ⁻⁸				
6	HLA-DQ	1.98	8.2x10 ⁻¹⁶	2.01	1.2x10 ⁻²⁰	5.68	1.1x10 ⁻²⁸	1.32	0.004				
10	10p14	0.73	8.0x10 ⁻⁸	0.7	2.9x10 ⁻⁸	0.66	0.0004	0.7	9.9x10 ⁻⁶				
7	CDK6	1.32	1.9x10 ⁻⁶			1.34	0.014	1.36	9.7x10 ⁻⁵			4.5 x10 ⁻⁸	0.0003
5	IRF1/IL5	1.31	2.1x10 ⁻⁷			1.16	0.17	1.47	1.8x10 ⁻⁸	0.002	1.9 x10 ⁻⁵	1.6 x10 ⁻²⁹	3.6x10 ⁻⁵
6	BACH2	0.8	2.2x10 ⁻⁶			0.81	0.024	0.74	3.8x10 ⁻⁶	0.002	0.0002	1.0 x10 ⁻¹⁸	0.0002
3	LPP	1.27	4.7x10 ⁻⁶			1.48	0.0007	1.24	0.0006			9.0 x10 ⁻¹⁴	0.0002

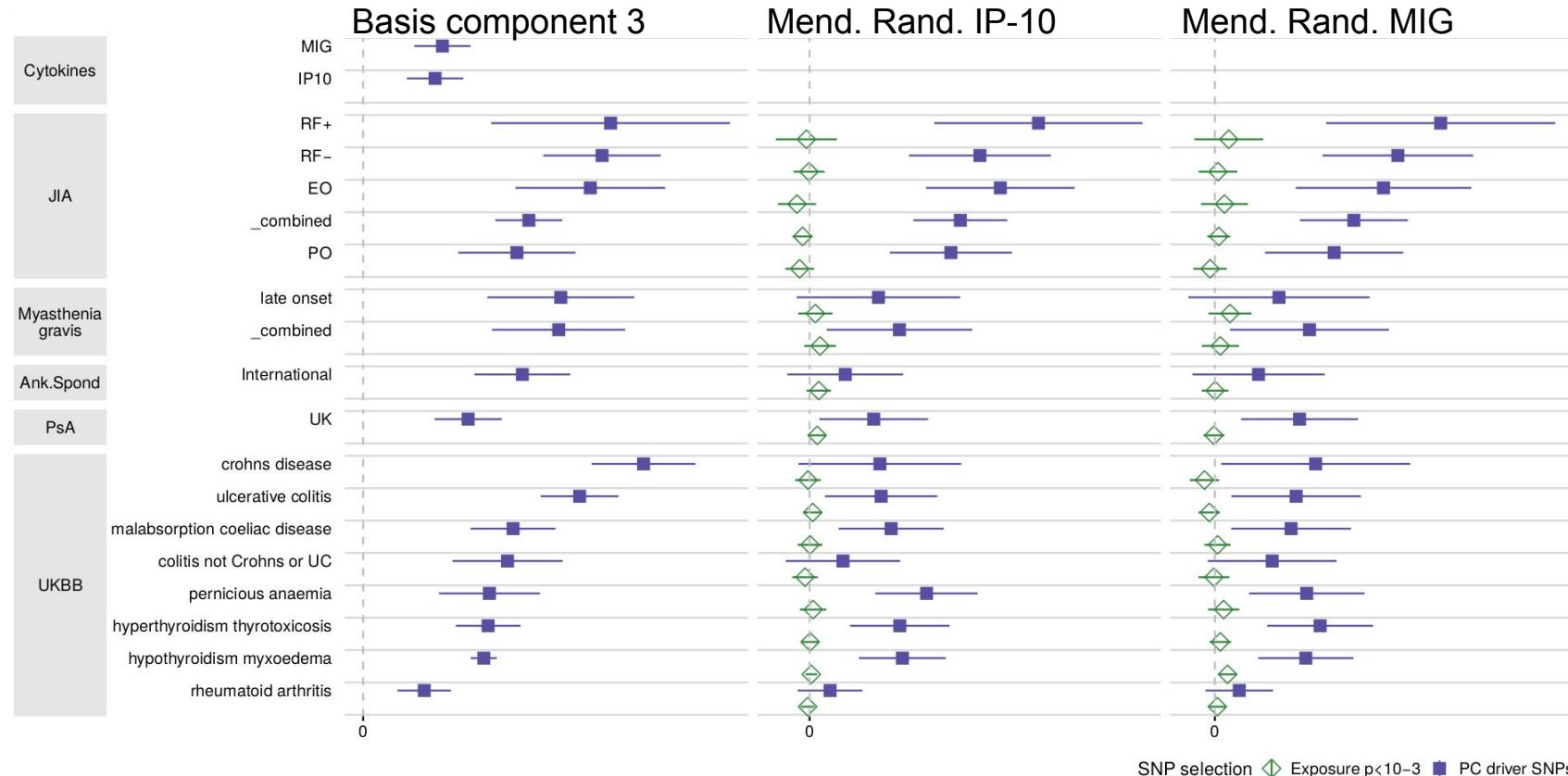
Collaboration with Ken Smith, Paul Lyons

Lyons et al, *Nat Commun* 2019

Eosinophils relevant to range of IMD



Genetically link raised serum IP-10 and MIG to IMD



Integrative genomics in immune mediated diseases



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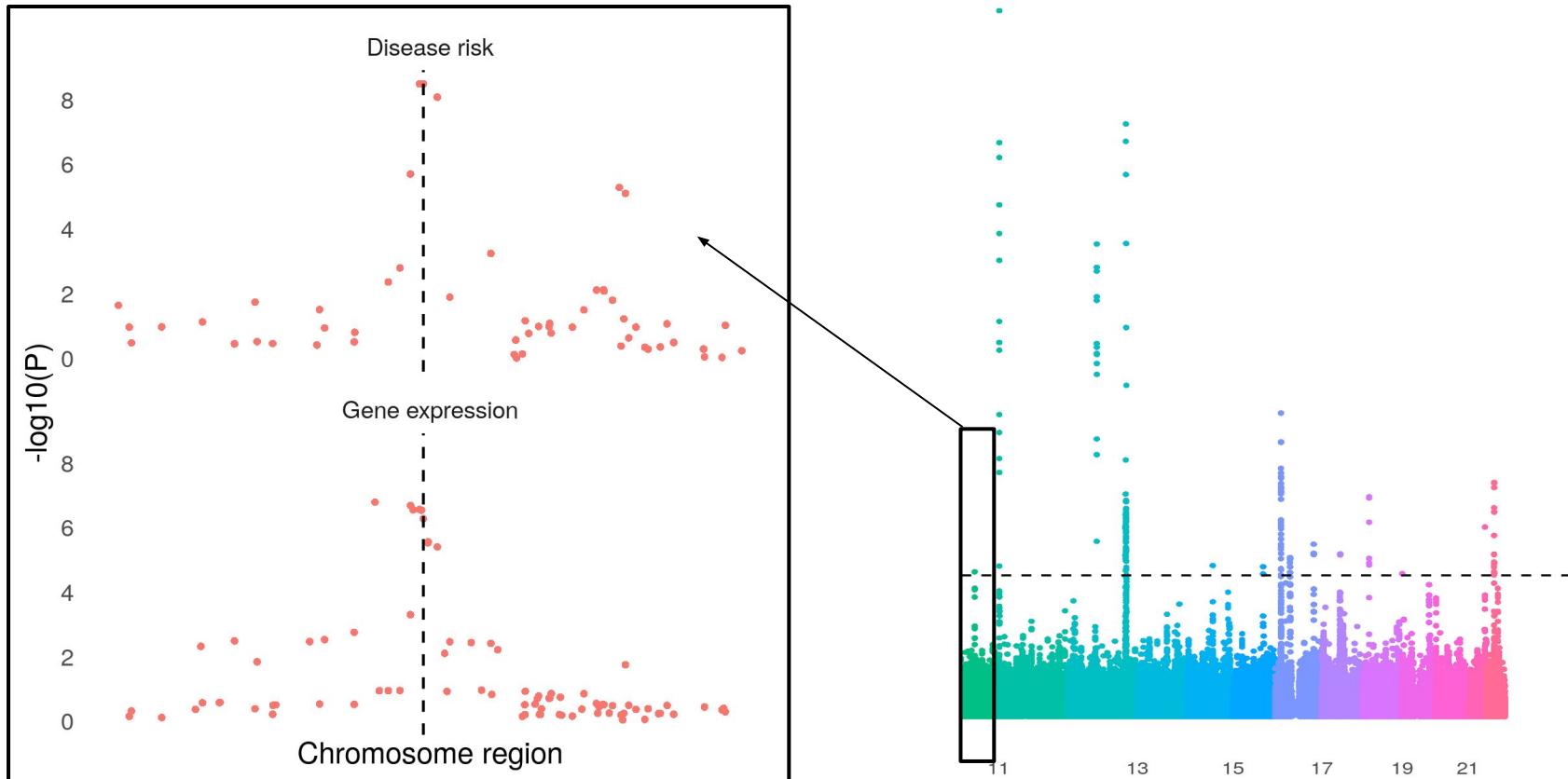


Elena
Vigorito



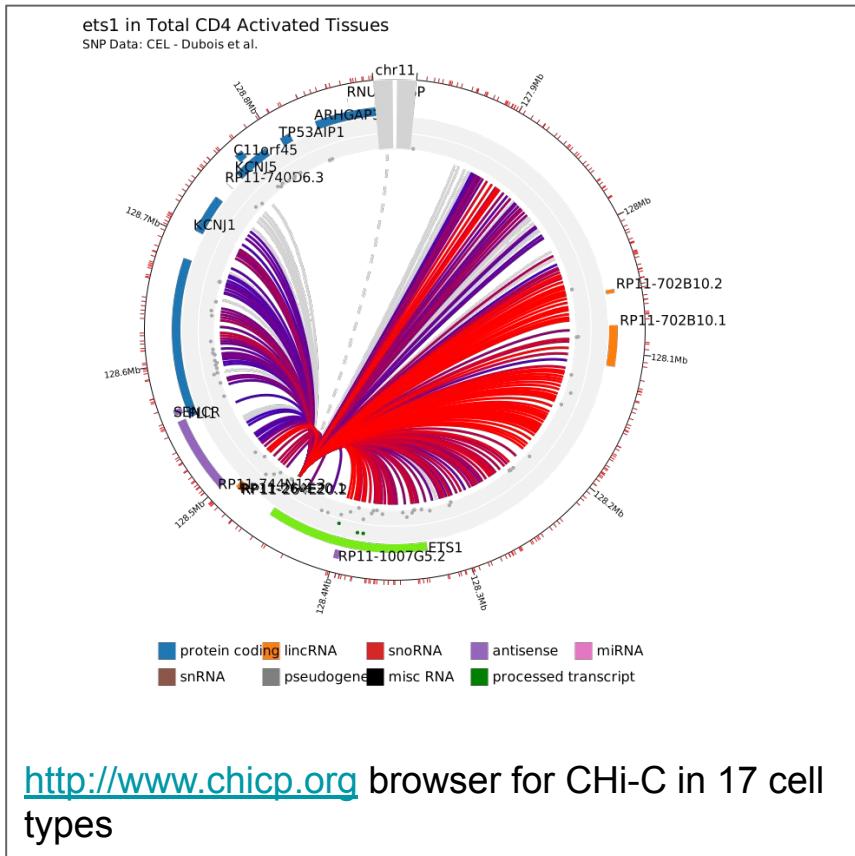
Stephen
Coleman

Colocalisation of two GWAS traits tests for shared causal variants

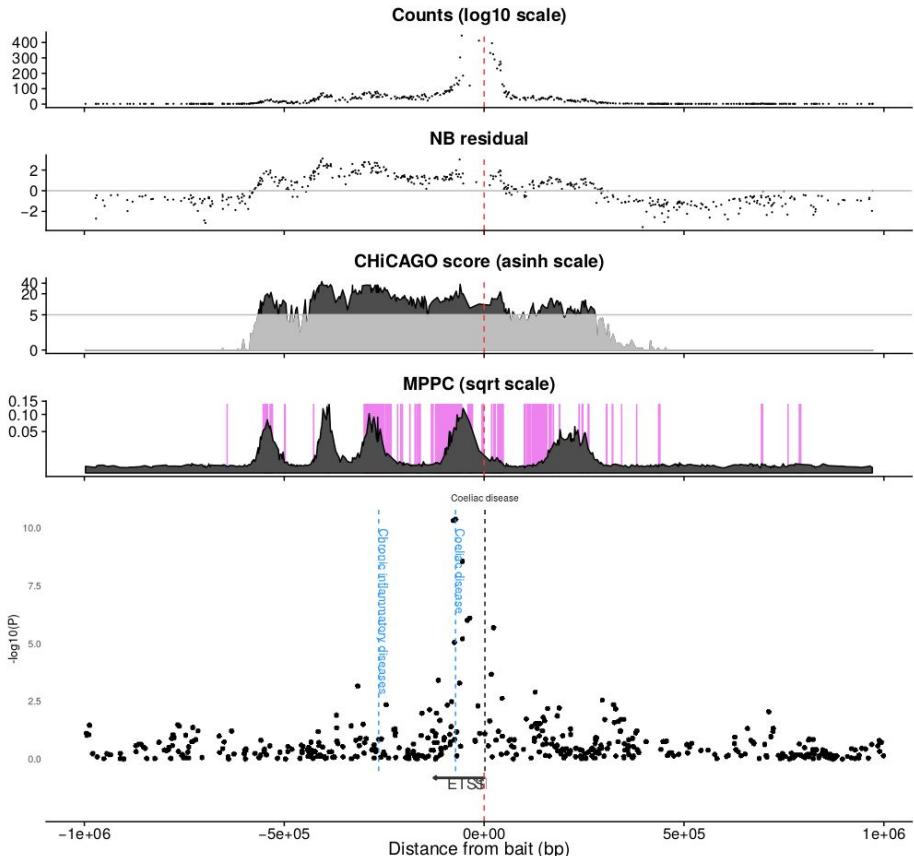


R package: *coloc*; Giambartolomei et al, PLOS Genetics 2014

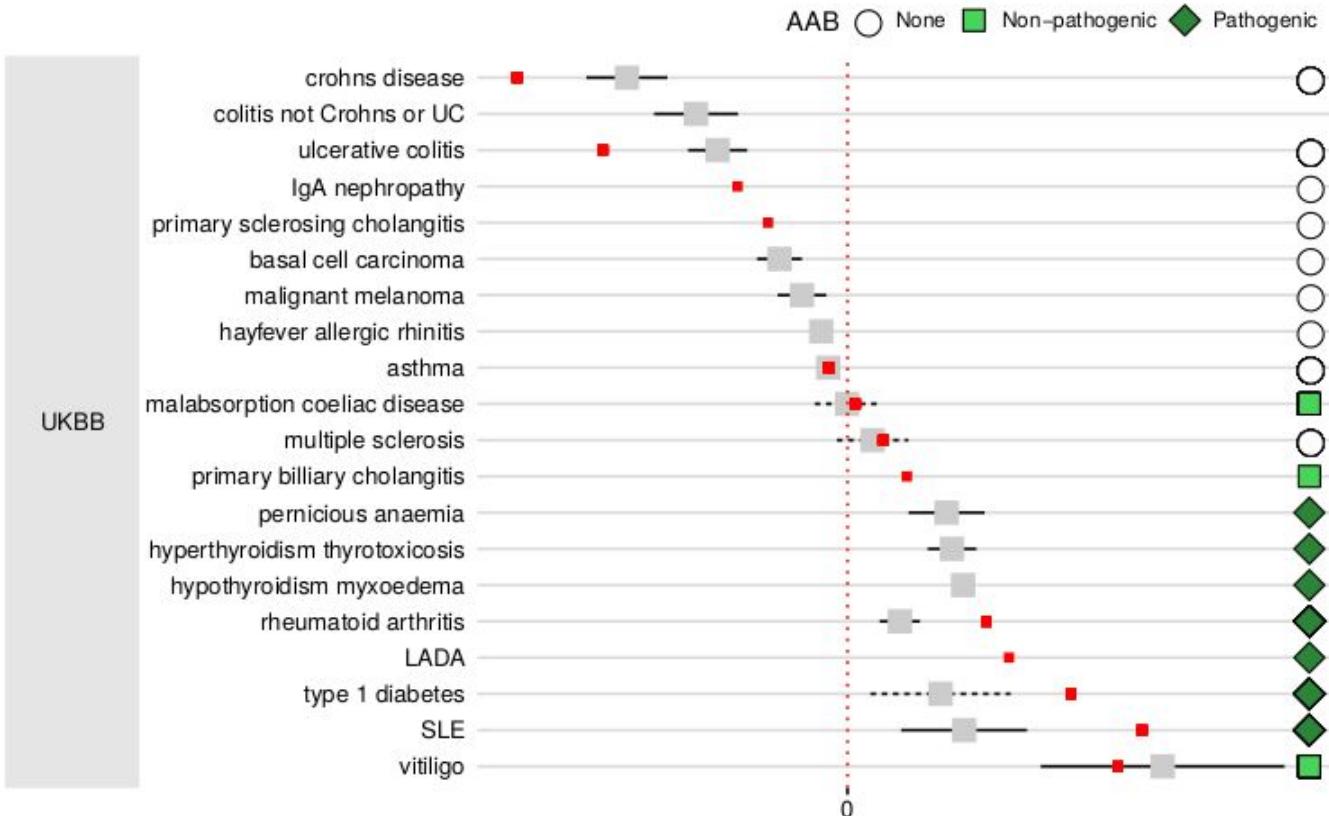
Chromatin conformation (capture Hi-C) links regulatory regions to gene promoters



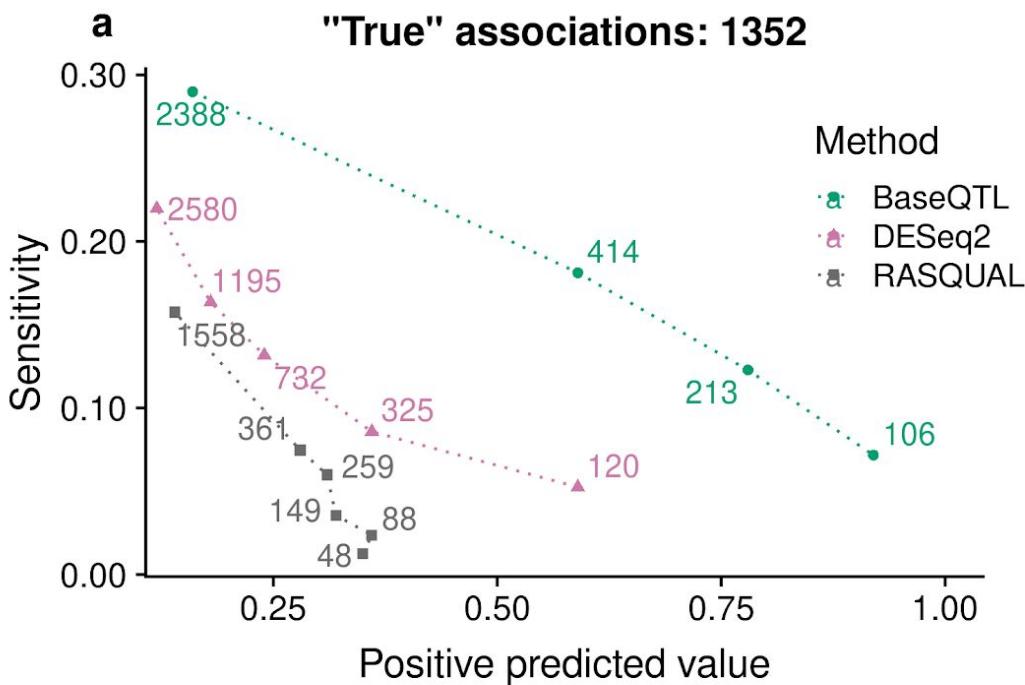
<http://www.chicp.org> browser for ChIP-C in 17 cell types



First component describes auto-antibody status



Bayesian ASE method improves power



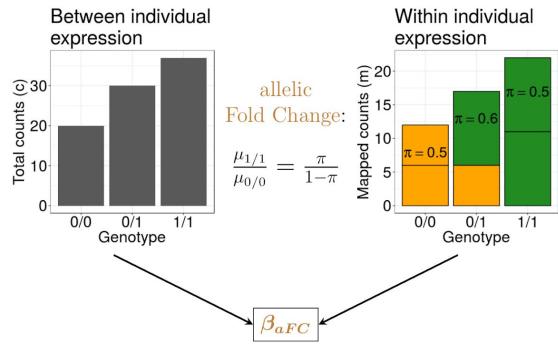
Can impute genotypes
from RNA-seq data alone

Reduces power

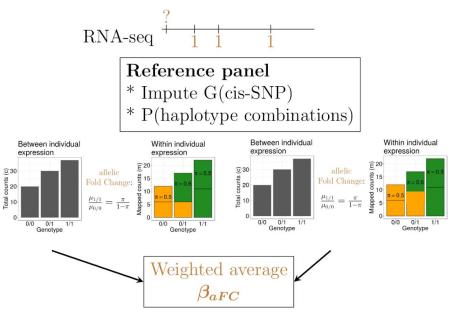
Results called are
consistent with/without
DNA genotypes

Allele specific expression assays in patient transcriptomes

a. Known genotypes and phase

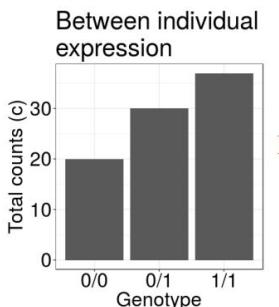
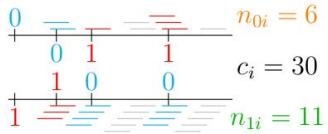


b. Unknown genotypes

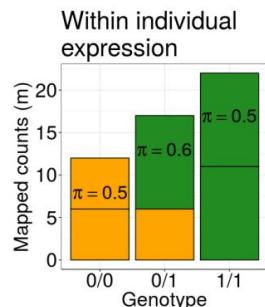


Allele specific expression assays in patient transcriptomes

a. Known genotypes and phase



$$\text{allelic Fold Change: } \frac{\mu_{1/1}}{\mu_{0/0}} = \frac{\pi}{1-\pi}$$



$$\beta_{aFC}$$

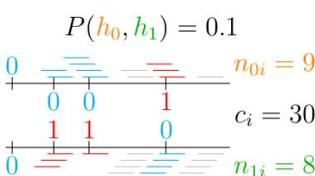
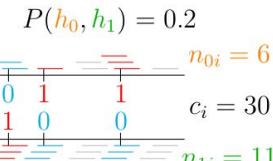
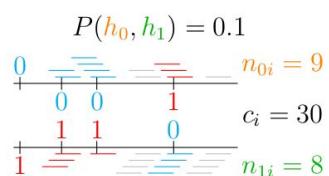
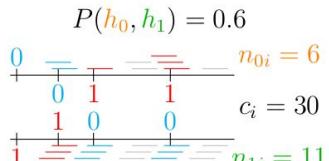
b. Unknown genotypes



Reference panel

- * Impute G(cis-SNP)

- * P(haplotype combinations)



Weighted average
 β_{aFC}