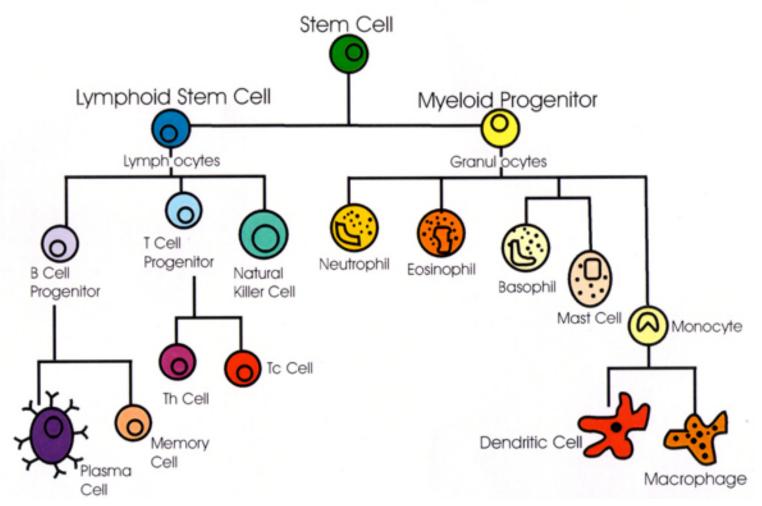
### Identifying Dysregulated Genes in Autoimmune Disease

Chris Cotsapas PhD Yale Neurology/Genetics Broad Institute cotsapas@broadinstitute.org

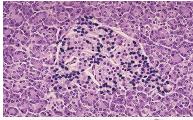
#### Causal Identifying <del>Dysregulated</del> Genes in Autoimmune Disease

Chris Cotsapas PhD Yale Neurology/Genetics Broad Institute cotsapas@broadinstitute.org

#### Cells of the Immune System



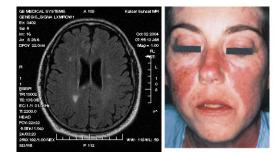


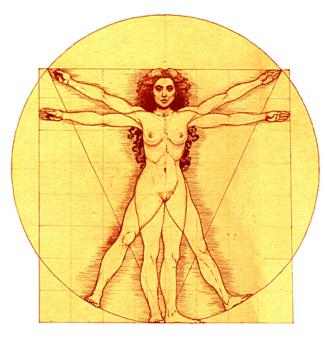






Enlarged, inflamed hypofunctioning thyroid (goiter)



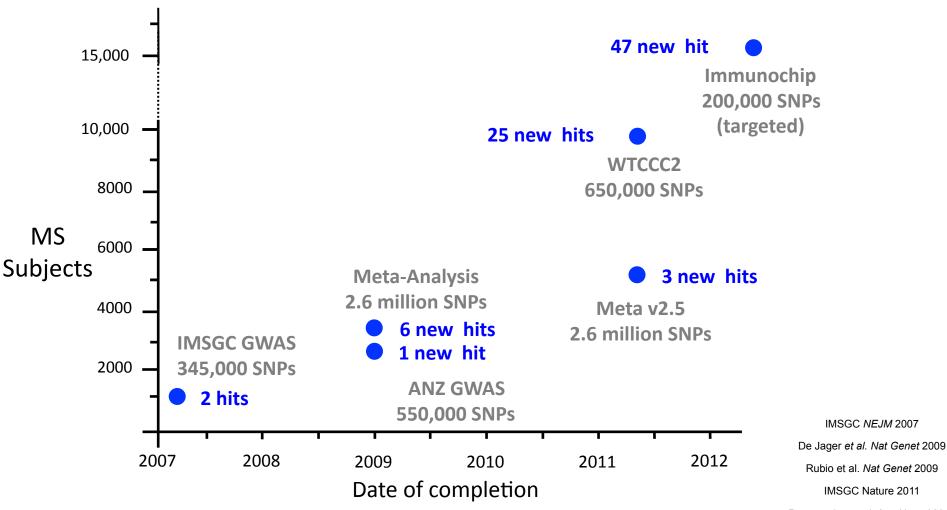




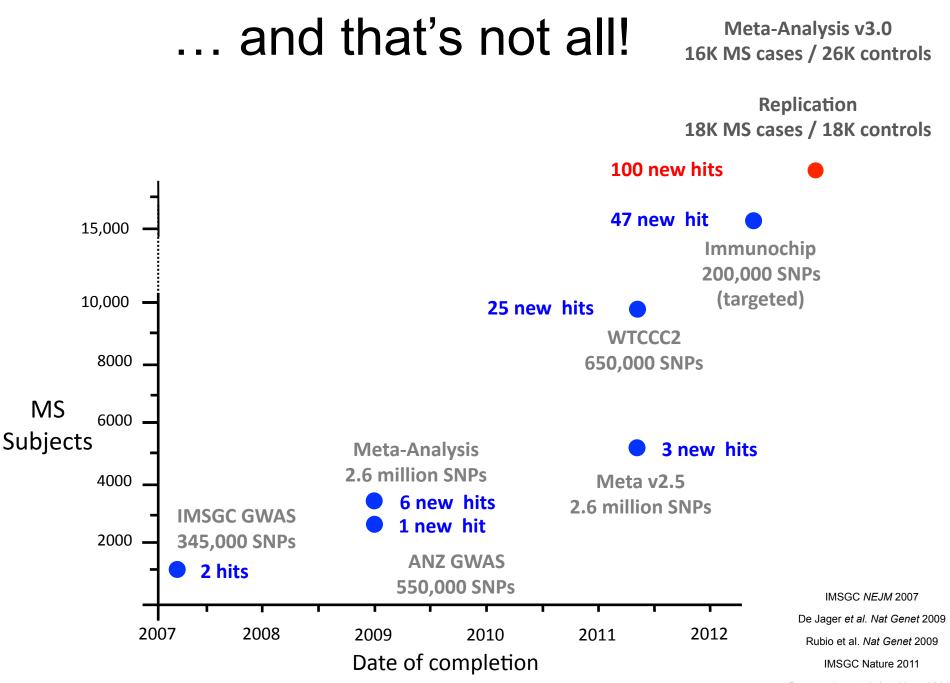


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#### **Multiple sclerosis GWAS**

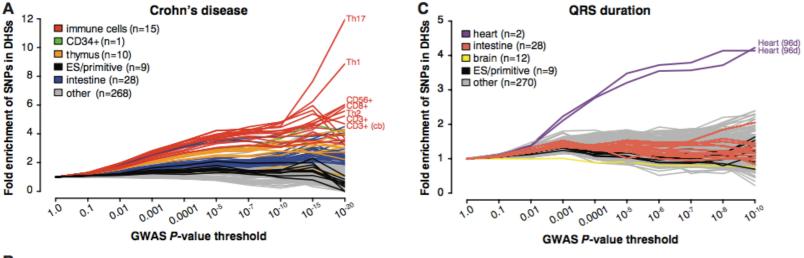


Patsopoulos et al. Ann Neurol 2017

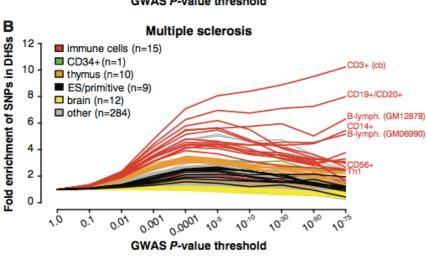


Patsopoulos et al. Ann Neurol 2017

## GWAS signals are enriched in regulatory DNA

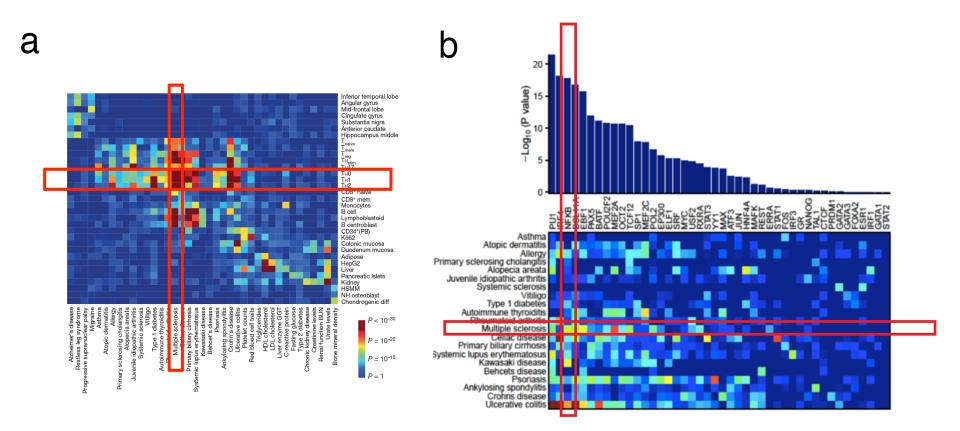


**Fig. 5.** De novo Identification of pathogenic cell types. GWAS SNPs are systematically enriched in the regulatory DNA of disease-specific cell types throughout the full range of significance (*P*-values). Shown are SNPs tested for association with the autoimmune disorders Crohn's disease (**A**) and multiple sclerosis (**B**), and the cardiovascular trait QRS duration (**C**). Note the increasingly selective enrichment of disease-associated variants within DHSs of specific pathogenic or trait-determining cell or tissue types. Note also that enrichment within cell-selective regulatory DNA persists well below conventional *P*-value thresholds for genome-wide significance.



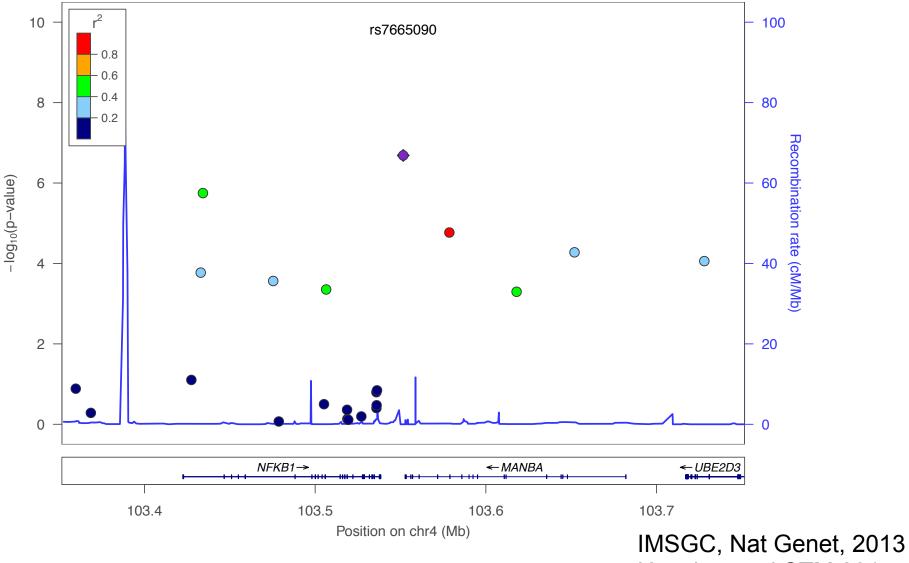
#### Maurano et al Science 2012

# MS GWAS hits enriched in transcription factor binding sites



Farh et al Nature 2015

### NFKB1 locus in MS GWAS



Housley et al STM 2015

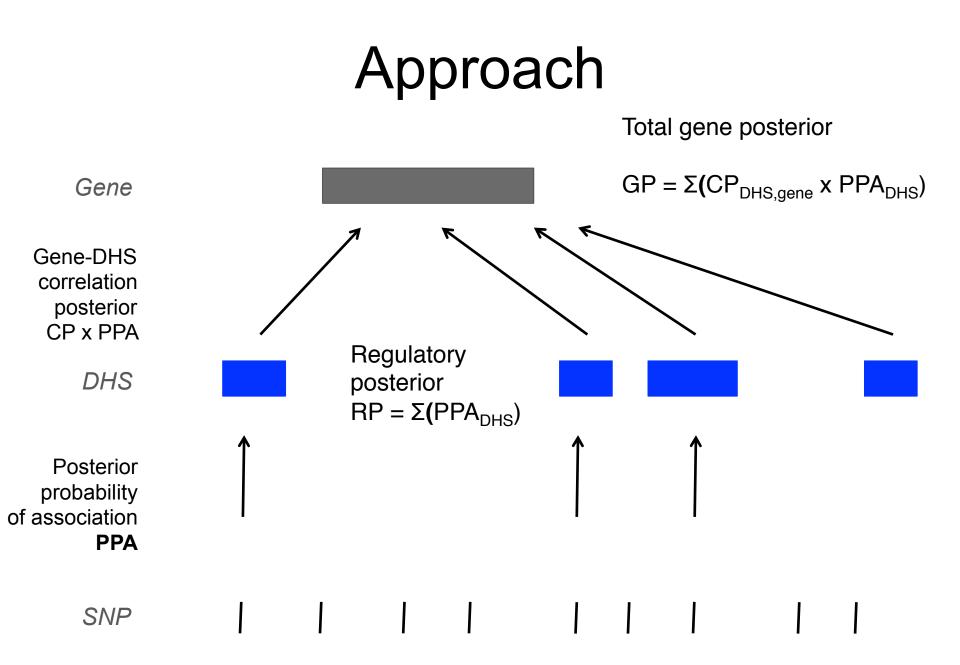
#### IKZF3/ORMDL3 locus in MS GWAS

rs12946510 (CEU)

8 80 0.56 60 rs12946510 P=8.51e-06 Recombination rate (cM/Mb) Observed (-logP) r² 4 40 ч, T) 2 20 R □, 0 0 NEUROD2 ZPBP2 STAC2 FBXL20 MED 1 CRKRS MED<sub>24</sub> ERBB2 GSDML ORMDL3 PPP1R1B C 17orf37 THRA NR1D1 STARD3 GRB7 TCAP **KZF3** GSDM PNMT PSMD3 PERLD1 CSF3 35100 34800 35400

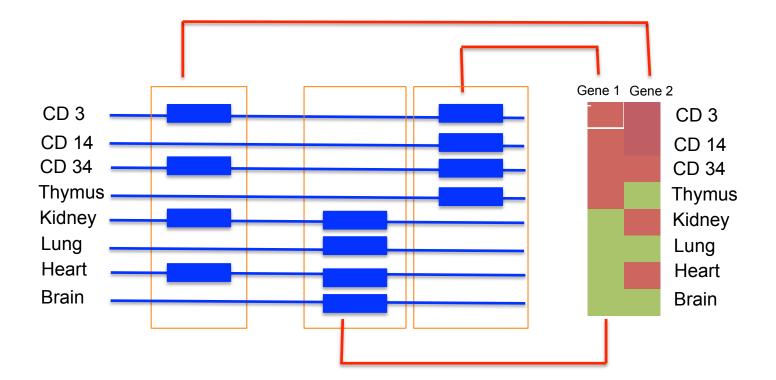
Chromosome 17 position (hg18) (kb)

IMSGC, Nat Genet, 2013



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#### Problem 1: DHS-gene correlations

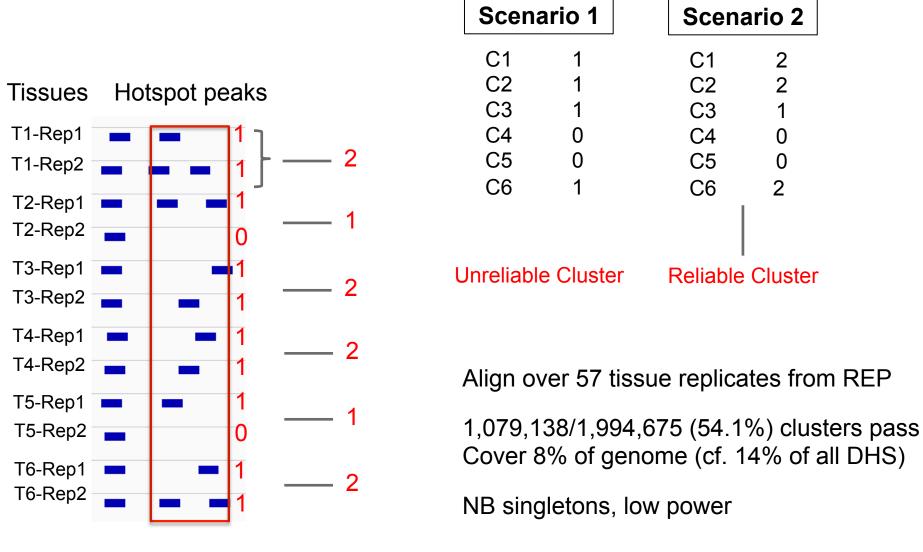


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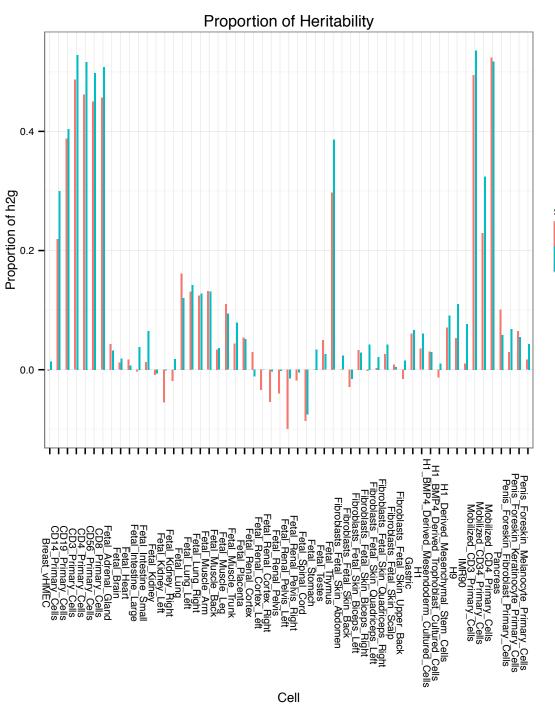
### Aligning DHSs Over Samples

	chr1 p36.31	p36.13 p35.3	3 p34.2	p32.3	p31.3	p31.1	p22.3	p21.3	p13.3	p12 q1	11 q12	q21.1	q22	q24.1	q25.2
		933,000 bp 	1	934,000 bp 			935,000 bp 		1	— 7,266 b 936,000 bp 	-	1	937,000 bp 		<u> </u>
RefSeq Genes						< <	HES4	<	-						
UW.Fetal_Intestine_Small.Chroma ibility.H-23604.DS16559.fdr0.01.p				-	-		-			- [					
UW.Fetal_Intestine_Small.Chroma ibility.H-23640.DS16712.fdr0.01.p				-	-		-						-	-	
UW.Fetal_Intestine_Small.Chroma ibility.H-23663.DS16822.fdr0.01.p					-	-	-		-		-	-	-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23724.DS16975.fdr0.01.p					-	- /			-		-			-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23744.DS17092.fdr0.01.p					-		-		-		-		-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23758.DS17150.fdr0.01.p					-		-		-		-	-	-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23769.DS17317.fdr0.01.p					-		-		-	-	-		-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23808.DS17425.fdr0.01.p					-		-		-		-	-	-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23864.DS17844.fdr0.01.p					-	-	-		-		-	-		-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23887.DS17643.fdr0.01.p					-	-	-		-		-			-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23914.DS17763.fdr0.01.p					-	-	-		-		-		-	-	
UW.Fetal_Intestine_Small.Chrom ibility.H-23941.DS17808.fdr0.01.p					-	-	-				-	-		-	
UW.Fetal_Intestine_Small.Chrom ibility.H-24111.DS18495.fdr0.01.p					-		-	1		-	-	Ļ			
/												Pa	arisa	Sho	oshta

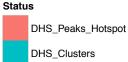
#### Identify detectable DHS clusters



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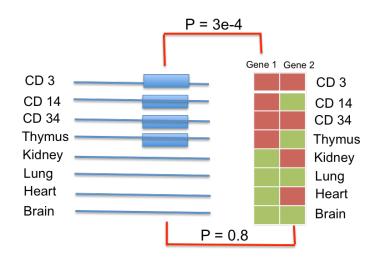
## QC+ DHS clusters capture most MS heritability



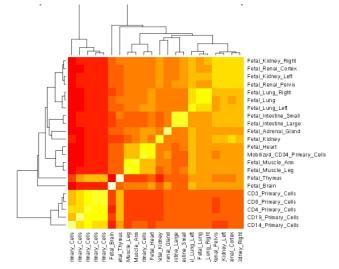
*Caveat* DHS clusters are wider than DHS peaks (250-400bp vs 150bp

> Parisa Shooshtari Hilary Finucane Alkes Price

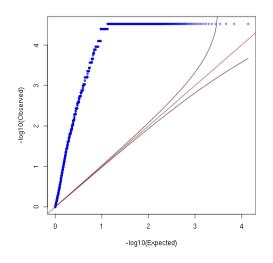
#### Challenge 2: Gene expression correlation



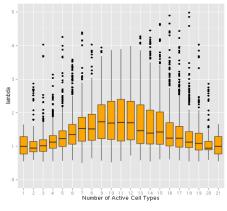
Correlation Structure of the Gene Expression Data



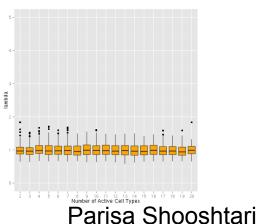
QQ plot for P Value of Correlation Between One DHS and 14000 Genes

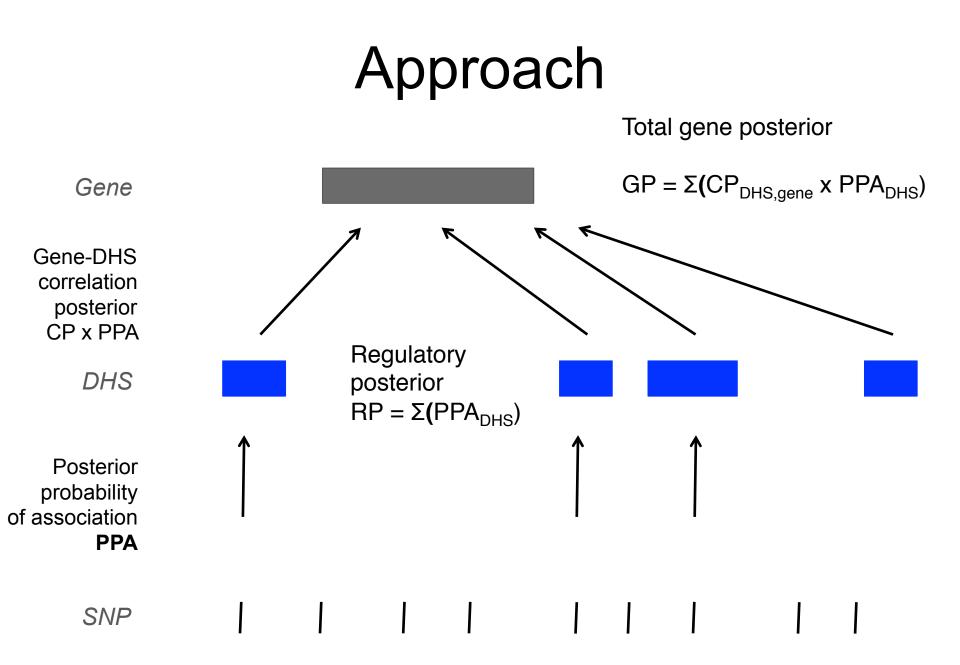


Before Correction









Parisa Shooshtari



## Application to MS GWAS

ц.	Gene	GP
Chr 6	MDN1	0.555
90.5-91.5Mb	BACH2	0.162
RP = 0.945	GABRR2	0.106
	RRAGD	0.065
	GJA10	0.029
	MAP3K7	0.028

Parisa Shooshtari IMSGC NG 2013

IKZF3/ORMDL3 locus			
		Gene	GP
	Chr 17	ORMDL3	0.029
	34.5-35.5Mb	PIP4K2B	0.022
	RP = 0.295	IGFBP4	0.018
		IKZF3	0.015
		GSDMB	0.014
		SMARCE1	0.013
rs12946510(CEU)		CCR7	0.013
	- 80	TNS4	0.01
	0.8	ZPBP2	0.009
rs12946510	0.5 - 60	MED1	0.009
► P=8.51e-06	Pecco m	MED24	0.009
	Pecombination rate (cM/Mb)	KRT24	0.009
	rate (cM	PNMT	0.008
	A/Mb)	CDK12	0.007
	99 1.at. – 0	RPL23	0.007
STAC2 FBXL20 MED 1 CRKRS NEUROD2 ERBB2 ZPBP2 MED24 PPP1R1B C17or137 GSDML THI STARD3 GRB7 ORMDL3	RA NR 1D 1	PSMD3	0.007
TCAP KZF3 GSDM1 PNMT PSMD3	וטואא	PLXDC1	0.006
PERLD1 CSF3		TOP2A	0.006
34800 35100 35400 Chromosome 17 position (hg18) (kb)		RARA	0.006

8 -

6

4

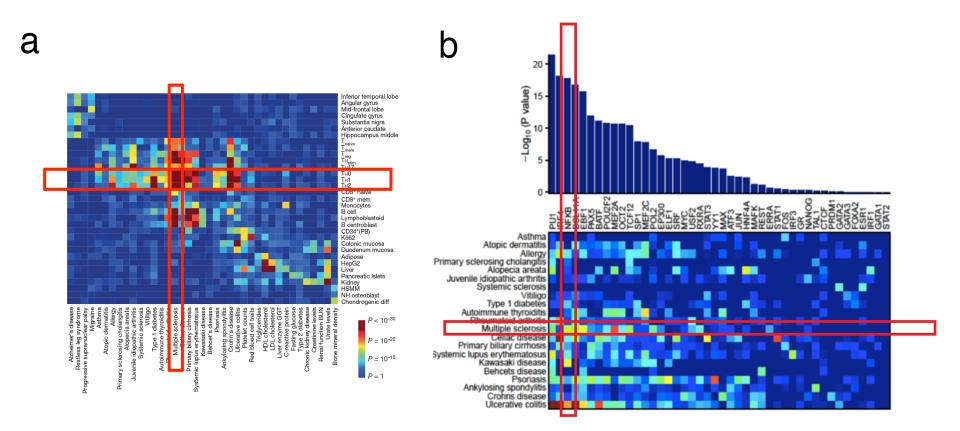
2

0 -

Observed (-logP)

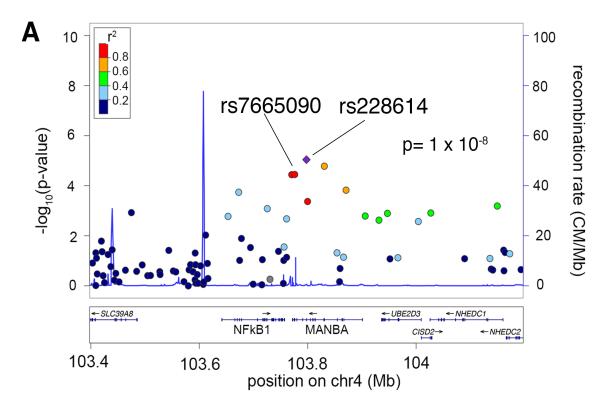


# MS GWAS hits enriched in transcription factor binding sites

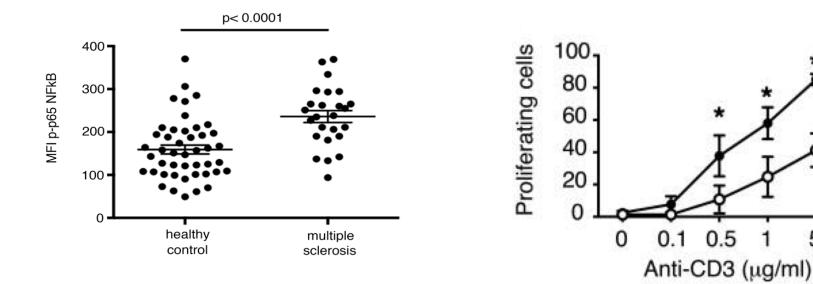


Farh et al Nature 2015

### MS GWAS risk effect: NFKB1 locus



### MS patients show altered NFkB signaling in CD4<sup>+</sup> T cells



ex vivo CD4<sup>+</sup> T cells show higher p-p65 (Housley et al, STM 2015)

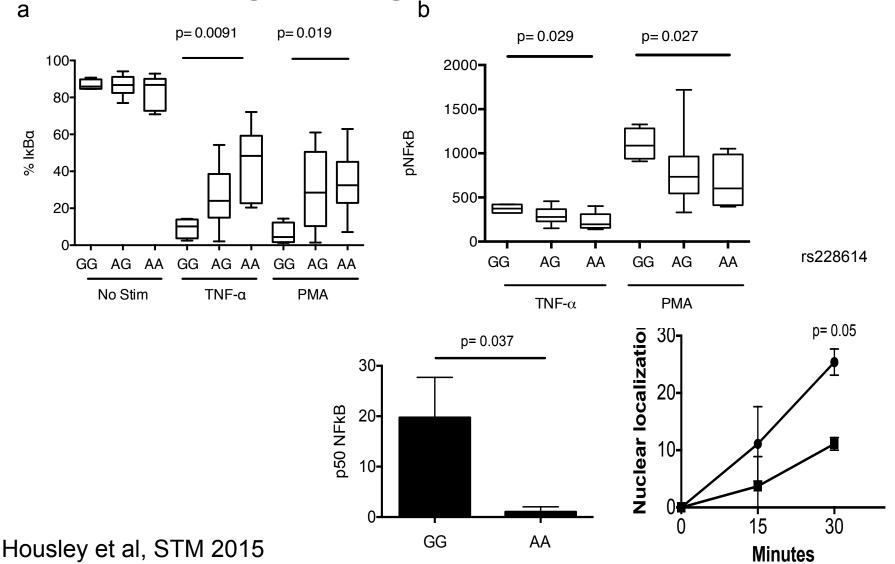
CD4<sup>+</sup> T cells from MS patients proliferate more rapidly after stimulus (Kofler et al JCI 2014)

0.5

MS

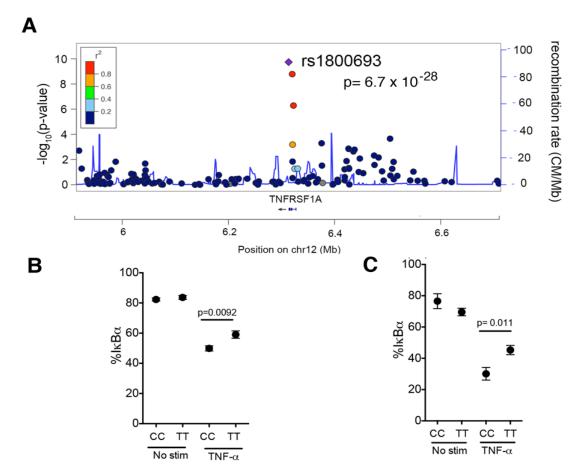
HC

### MS risk effect near NFKB1 alters signaling in CD4+ cells



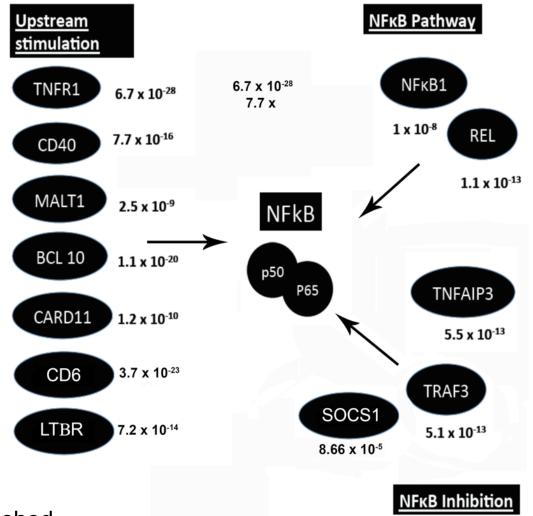
← GG ← AA

# MS variant in TNFRSF1A alters TNF $\alpha$ -dependent NF $\kappa$ B signaling



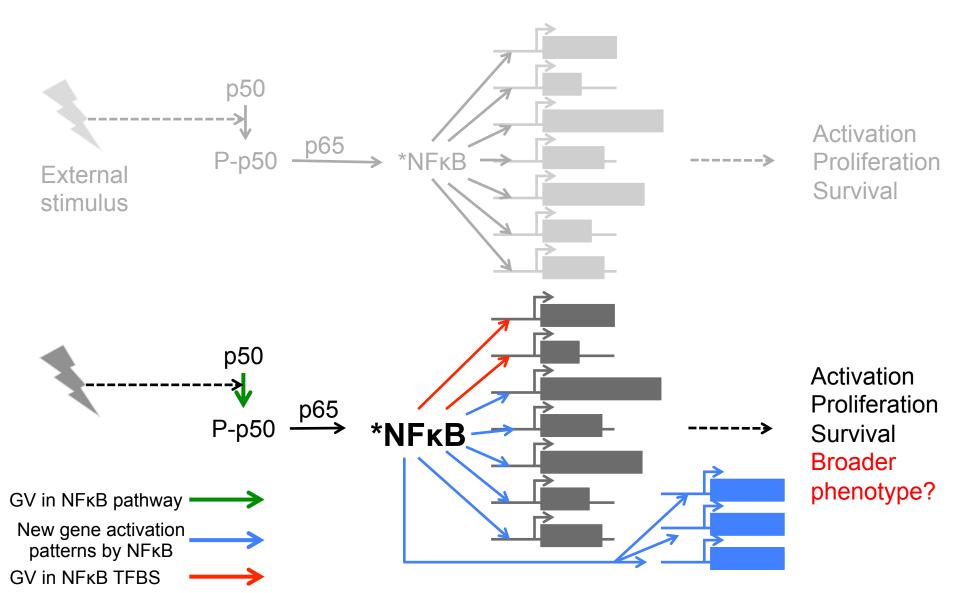
Housley, unpublished

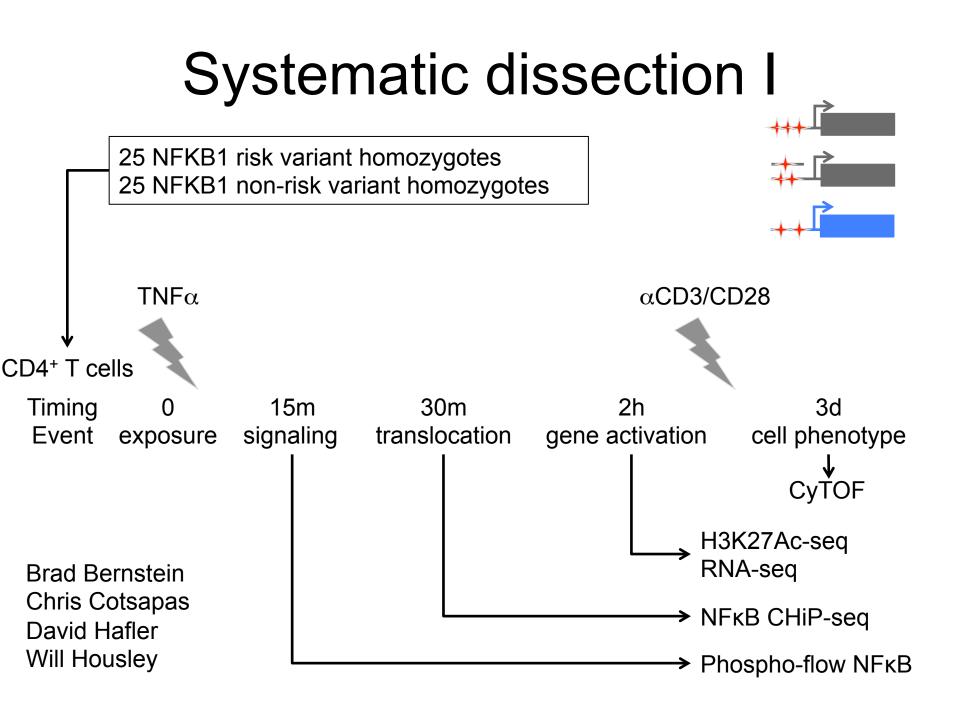
## GWAS loci harbor many NFkB genes



Housley, unpublished

## Model: NFkB signaling variation





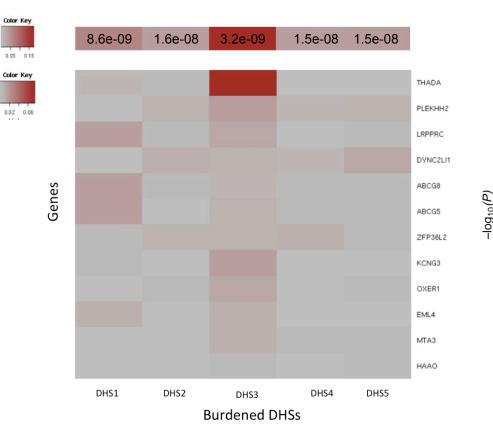
## Acknowledgements

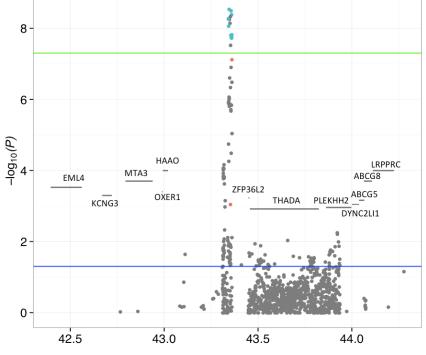
#### • IMSGC

- David Hafler
- Phil De Jager
- Steve Hauser
- Adrian Ivinson
- Nikos Patsopoulos
- Many, many others
- Partners
  - David Hafler
  - Phil De Jager
  - Brad Bernstein
  - John Stamatoyannopoulos

- Yale labs
  - Parisa Shooshtari
  - Mitja Mitrovic
  - Alex Casparino
  - Will Housley







In credible interval 🔶 No 🔶 Yes

Position on Chromosome 2

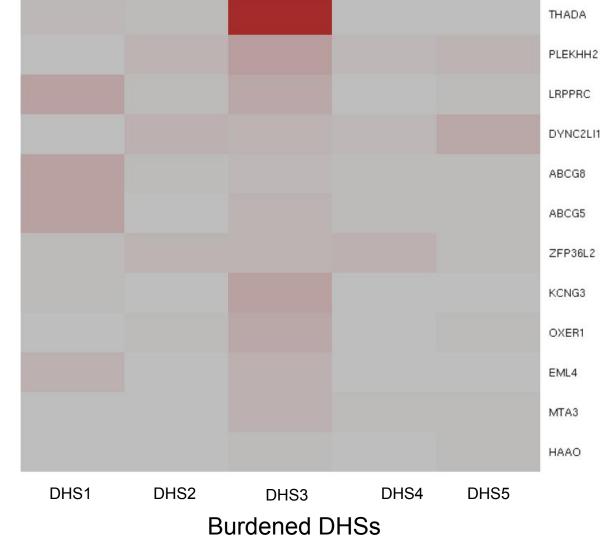
#### Color Key



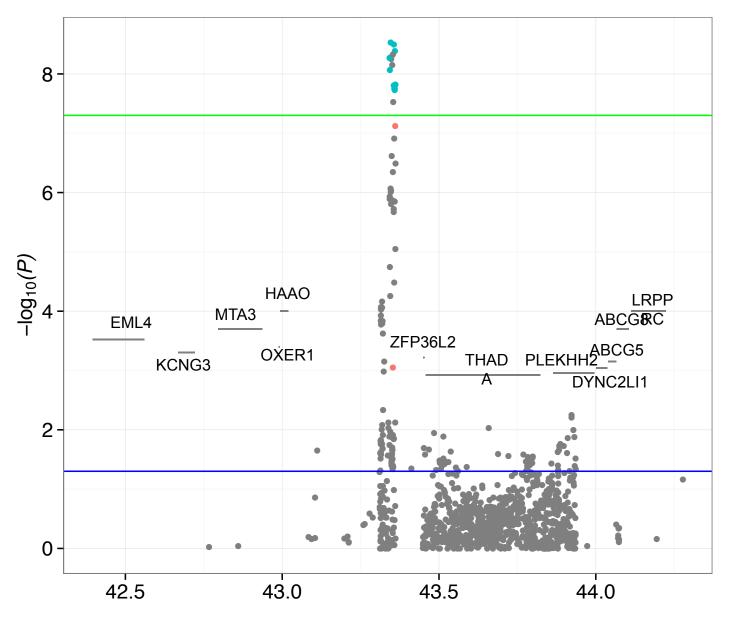


Genes









Position on Chromosome 2