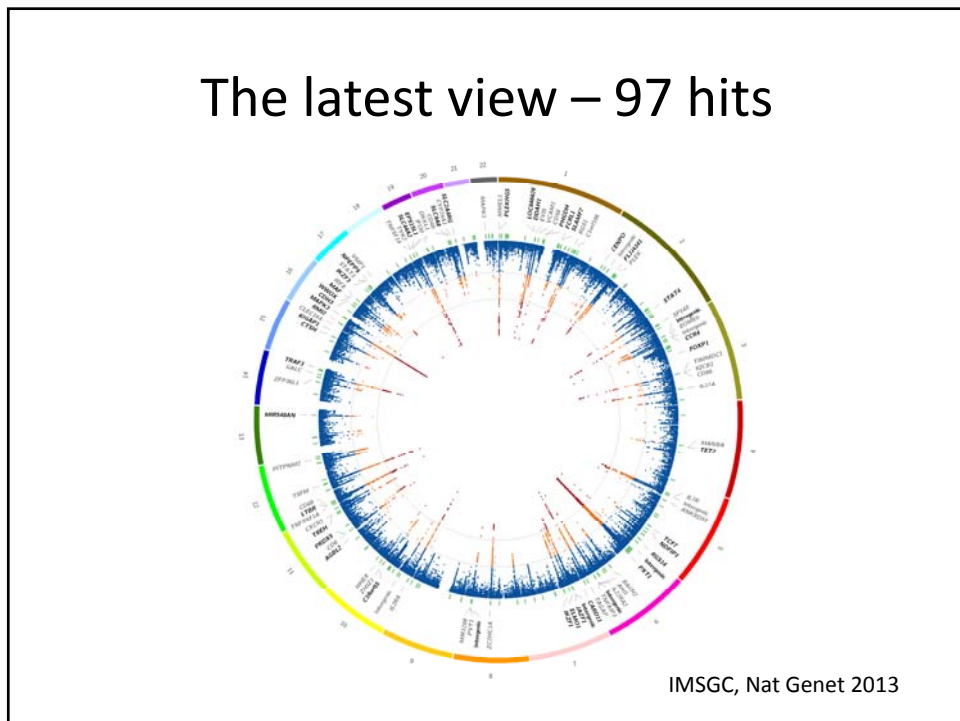
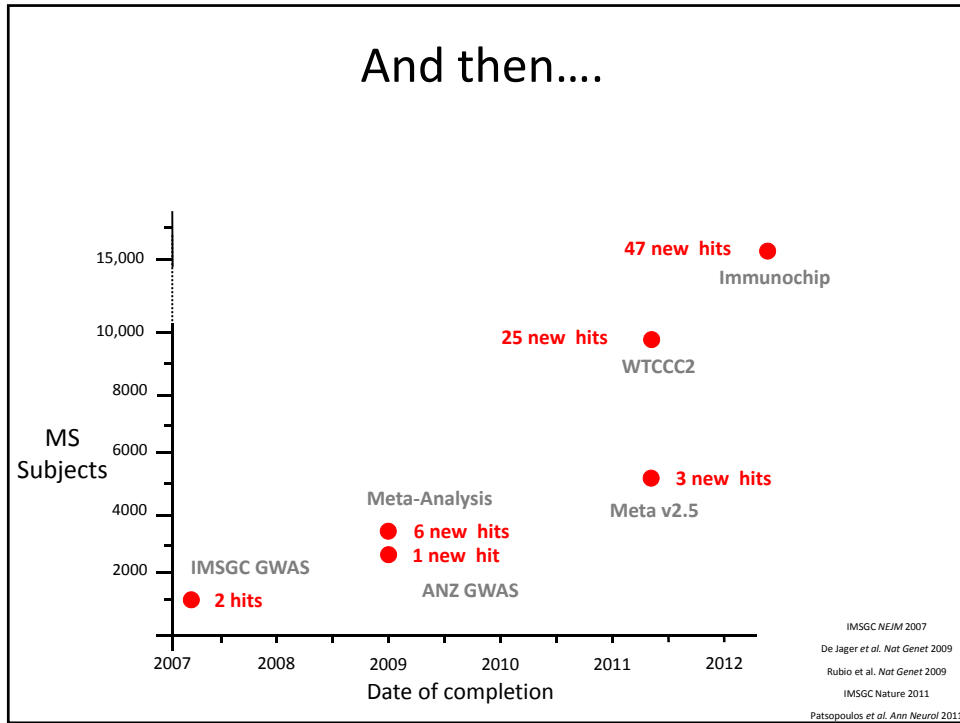


## Uncovering MS Susceptibility Pathways from Large-Scale Genetic Studies

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

### Multiple sclerosis genetics ca. 2002

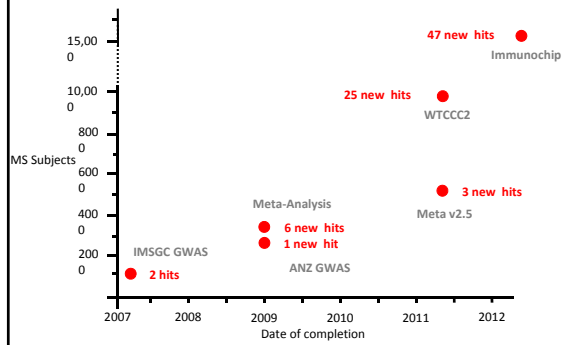
- MS risk is heritable (sib risk ~8-14)
- *HLA DRB1\*1501* known for 2 decades
  - cf. *APOEε4* in Alzheimer's disease
- No other genes known
- Very large pedigree-based studies were uninformative



... and that's not all!

Meta-analysis v3 + Replication  
34K MS cases / 44K controls  
100+ new loci

Exome chip  
38K MS cases / 55K controls

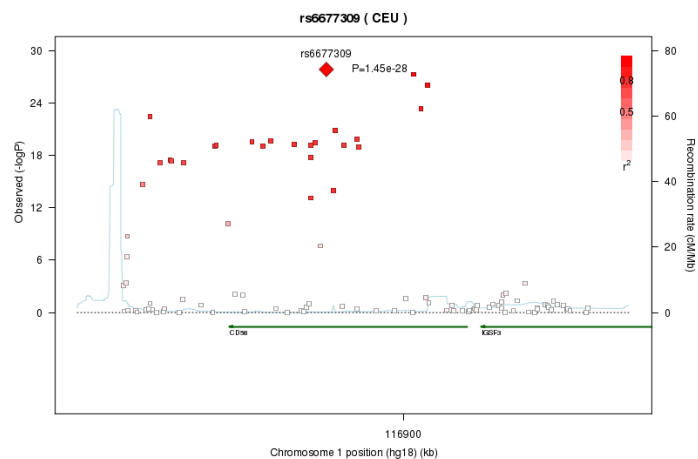


What on earth do we do now?

## The next five (??) years

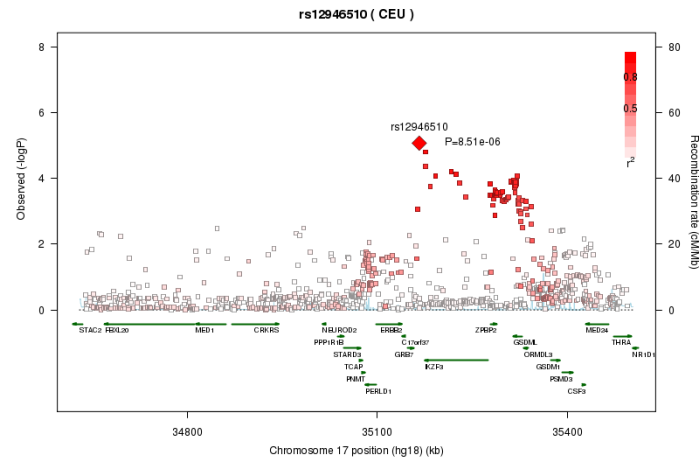
- More genetic studies
  - More GWAS
  - Sequence extremes
  - Low frequency variation in common disease
  - Rare diseases
- Patient heterogeneity
  - Progression/severity studies
  - Therapy
- Risk/outcome prediction
- **Underlying biology**

## Let's zoom into a locus (CD58)



IMSGC, Nat Genet, 2013

... and another



IMSGC, Nat Genet, 2013

## What we know now

- ~800 risk loci projected
  - None is necessary or sufficient for disease
- Several immune tissues likely involved

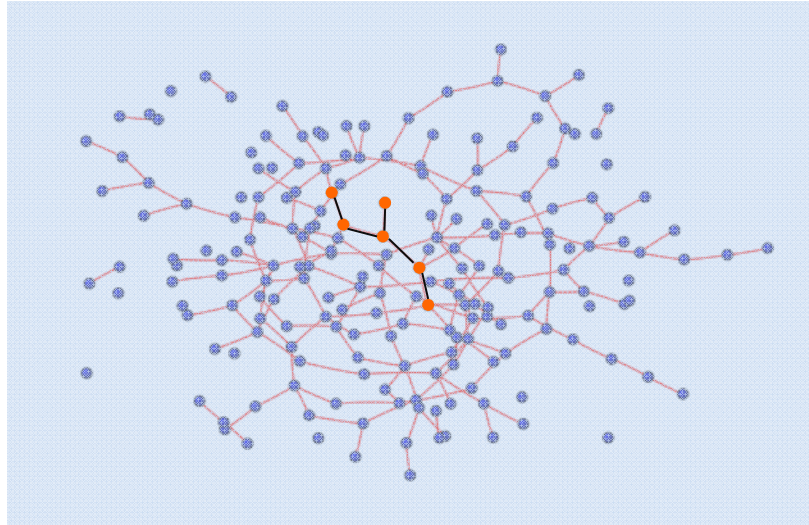
## What we know now

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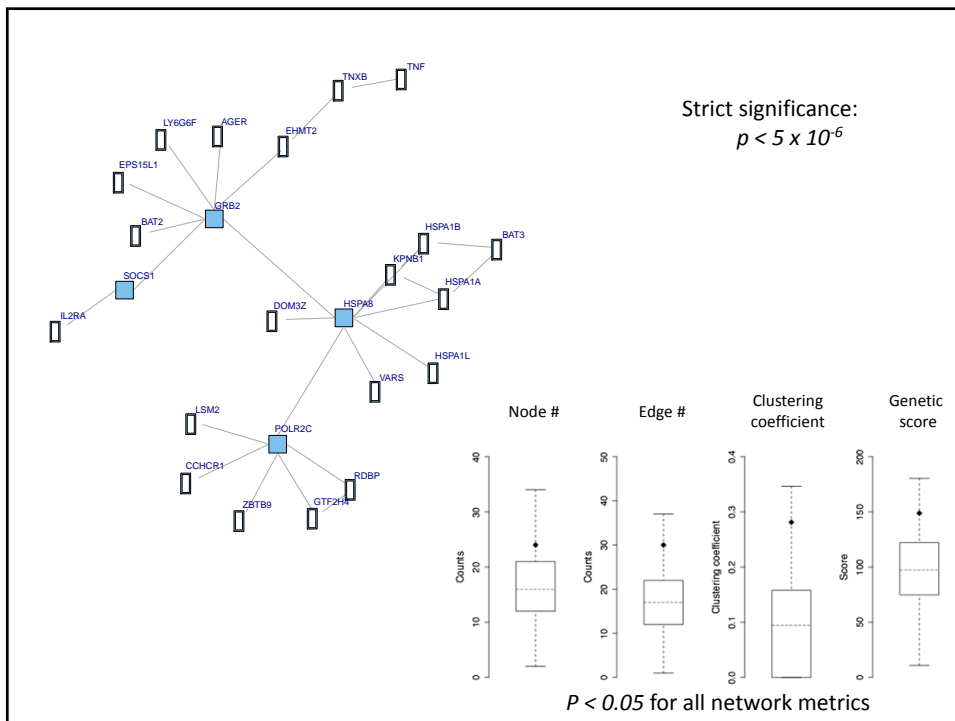
## What we know now

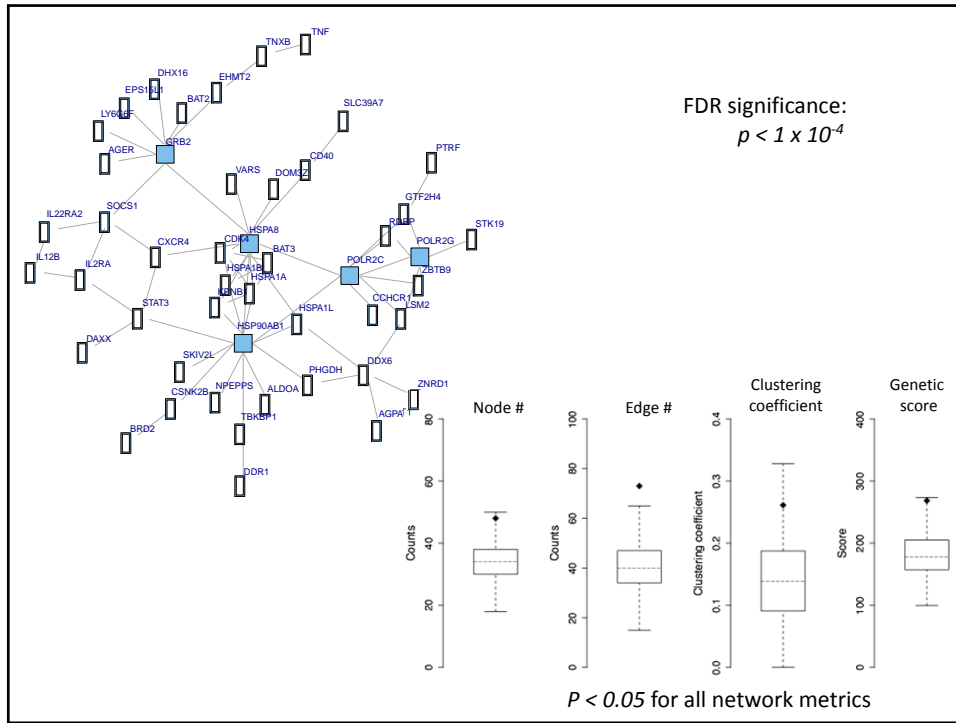
- ~800 risk loci projected
  - None is necessary or sufficient for disease
- Several immune tissues likely involved
- Do these act independently?

# New pathway tools

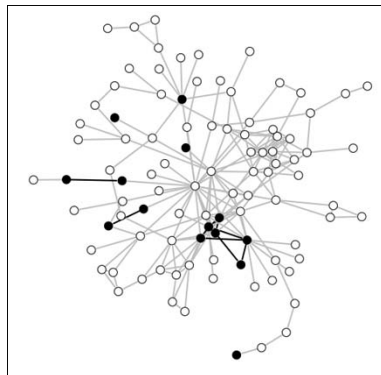


InWeb, ~12K proteins, ~127K interactions. Lage et al Nat Bio 2007; Rossin et al PLoS G 2011

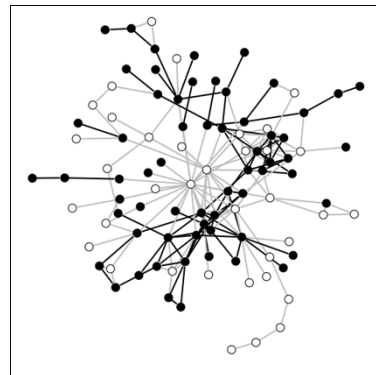




## Finding relevant tissues



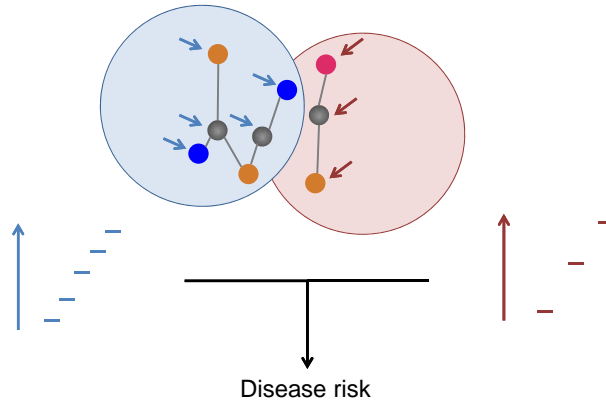
Network gene expression in a  
random ENCODE tissue



Network gene expression in an  
immune ENCODE tissue

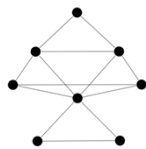


## A pathway burden model

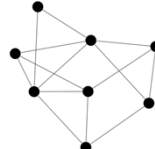


## Identifying patient subsets

Pathway 1



Pathway 2



Different outcomes?

## Acknowledgements

- IMSGC
  - Phil De Jager
  - Nikos Patsopoulos
  - Jake McCauley
  - David Hafler
  - Adrian Ivinson
  - Many, many others
- Epigenomics
  - John Stamatoyannopoulos
- Networks
  - Kasper Lage
- IIBDGC
  - Mark Daly
  - Hailieng Huang
- Lab folks
  - **Jinmyung Choi**
  - **Parisa Shooshtari**
  - Mitja Mitrovic
  - Lizzy Rossin
  - Ioanna Pagani
  - Boel Brynedal
  - Jason Vander Heiden

