

128 genome-wide significant associations for schizophrenia

The Psychiatric Genomics Consortium

Psychiatric Genomics Consortium

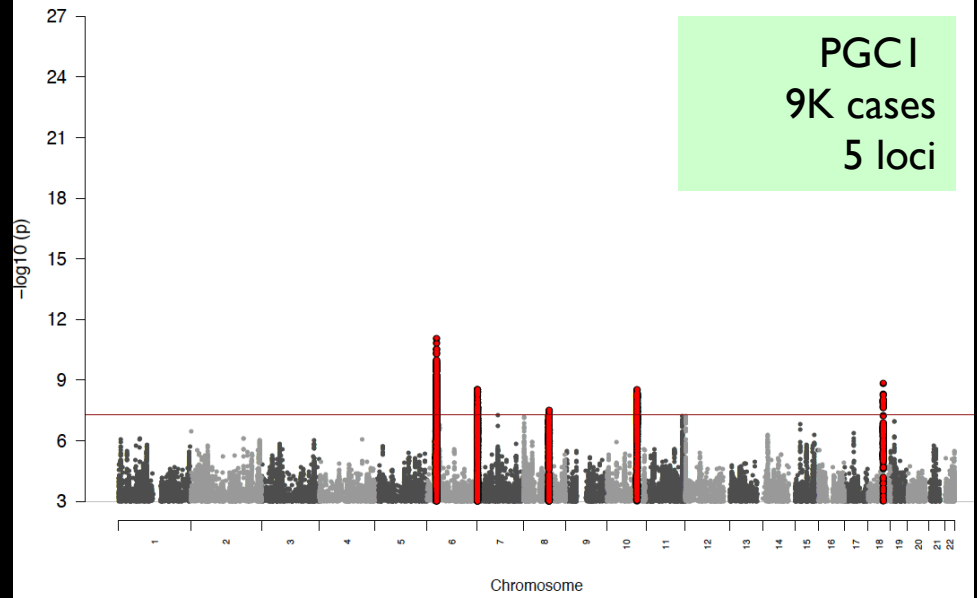
- Since 2007
- Open, democratic, participatory, rapid
- 400+ scientists
- Individual GWAS data on 172,000 subjects
- Schizophrenia, ADHD, anorexia nervosa, autism, bipolar disorder, drugs/alcohol, major depression, OCD/Tourette's, PTSD
- N's will increase by 100,000+ in 2014

Schizophrenia

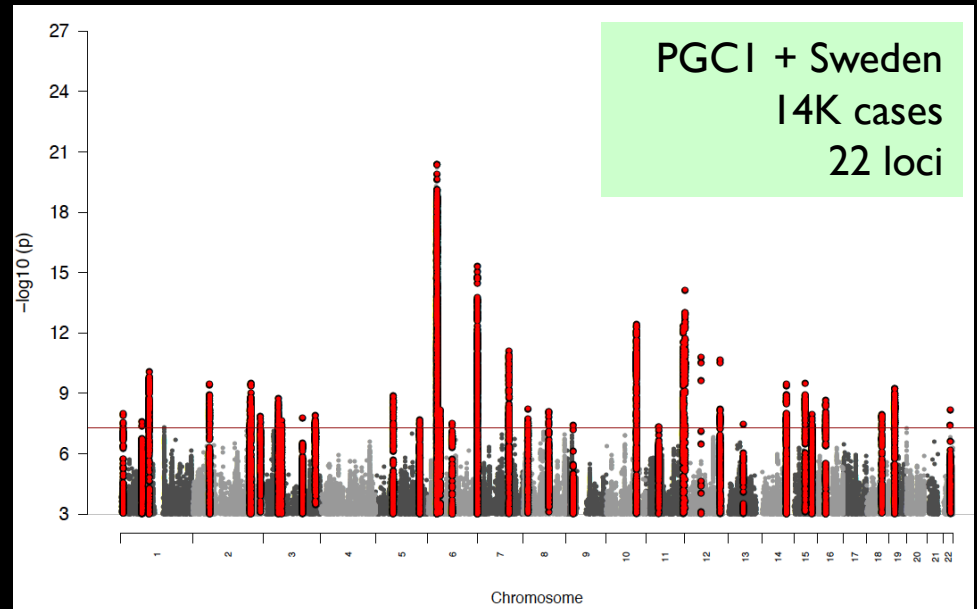
- Lifetime prevalence 0.7%
- Life expectancy 10-15 years less
- Life cost \$US 1.4 million/person
- Clinical, epidemiological, biological investigations less successful
- Heritability 65% (SW & DK), 81% twin

Genome-wide association study identifies five new schizophrenia loci

The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium¹



Genome-wide association analysis identifies 13 new risk loci for schizophrenia

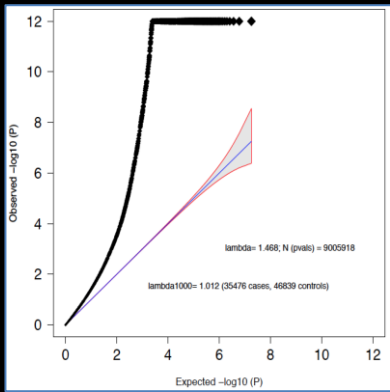


Subjects

- Schizophrenia or schizoaffective disorder
- 49 case-control samples (46 EUR, 3 ASI)
- 3 family-based samples (EUR)
- 2 replication samples (EUR, deCODE)
- **Cases: 38,131**
- **Controls: 48,438 + deCODE 66,236**

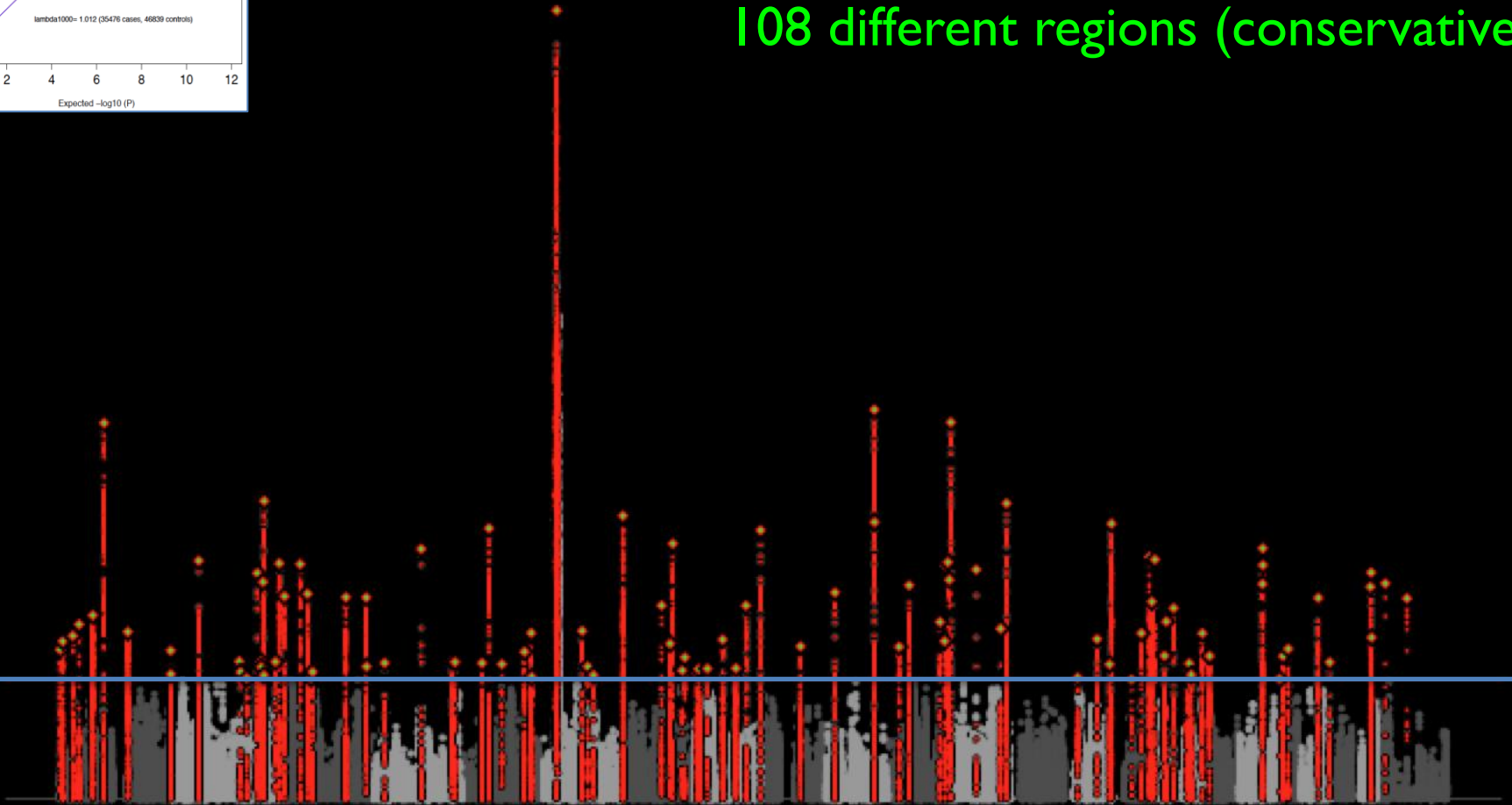
Genotypes

- II GWAS arrays (affy6 & omni express)
- Individual genotype data
 - Mature technology, standard pipeline
 - Major QC: $INFO \geq 0.6$, $MAF \geq 0.1$, ≥ 20 studies, missingness. Many minor QC steps.
 - 1000 Genomes imputation
 - Covariates 10 PCs plus study indicator
 - 9.3M SNPs (include chrX)
- Inverse-weighted meta-analysis



128 independent SNPs
($p < 5e-8$, $r^2 < 0.1$, 3 Mb windows)

108 different regions (conservative)



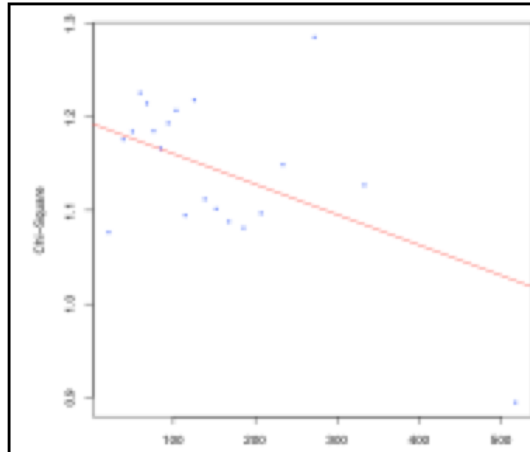
A team of 20+ statistical geneticists, analysts, & bioinformatics worked on this for 1.5 years

Why we think it's **real** & relevant

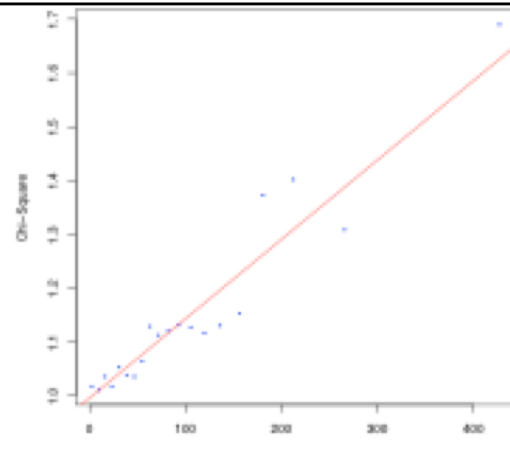
I of III

II=Ben & III=Tune

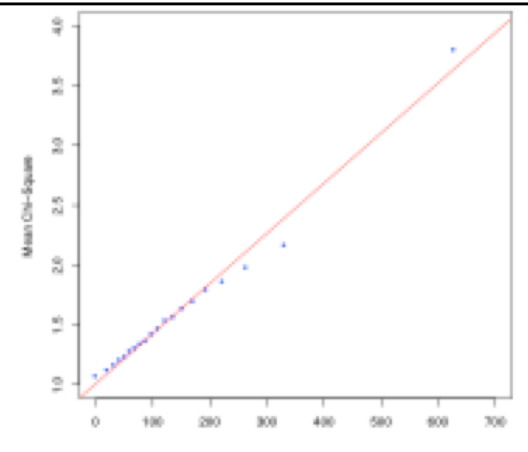
Inconsistent with pop strat



(a) LD regression results in scenario where test statistic inflation due to population stratification. $\lambda_{GC}=1.16$.



(b) LD regression results from a simulation where test statistic inflation is due to polygenic inheritance. $\lambda_{GC}=1.16$.



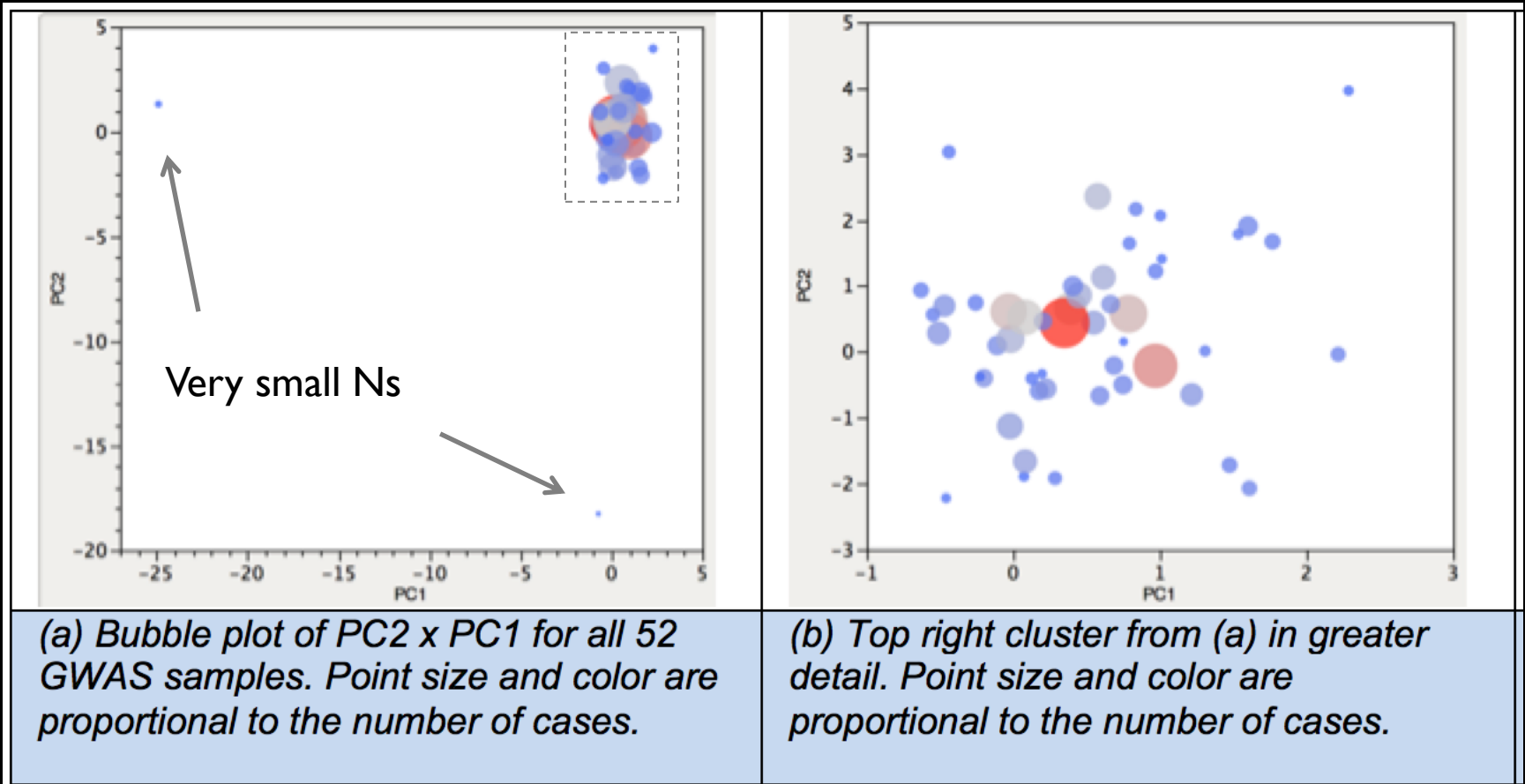
(c) LD regression applied to PGC schizophrenia results. Results consistent with polygenic inheritance not bias.

Consistent Effects

- Between case-control & trio samples
 - Trio design protects against pop strat
 - 69% of 263 SNP alleles transmitted, $p=1e-9$
- Asian samples consistent with European

Consistent effects

PCA on sample x SNP matrix of 105 top betas – how similar are samples?



Why we think it's real & relevant

Specific associations

- *DRD2*, $p=3e-11$
- NMDA receptor, *GRIN2A GRM7 SRR*
- *KCTD13*, driver gene in 16p11 CNV, 2.5kb away, $p=5e-11$
- Calcium: *CACNA1C CACNB2* *CACNA1I*
ATP2A2

Among others

Implicate biological pathways

- Shaun's talk this afternoon
- Several biological pathways implicated by more than one of GWAS, exome sequencing, or CNVs

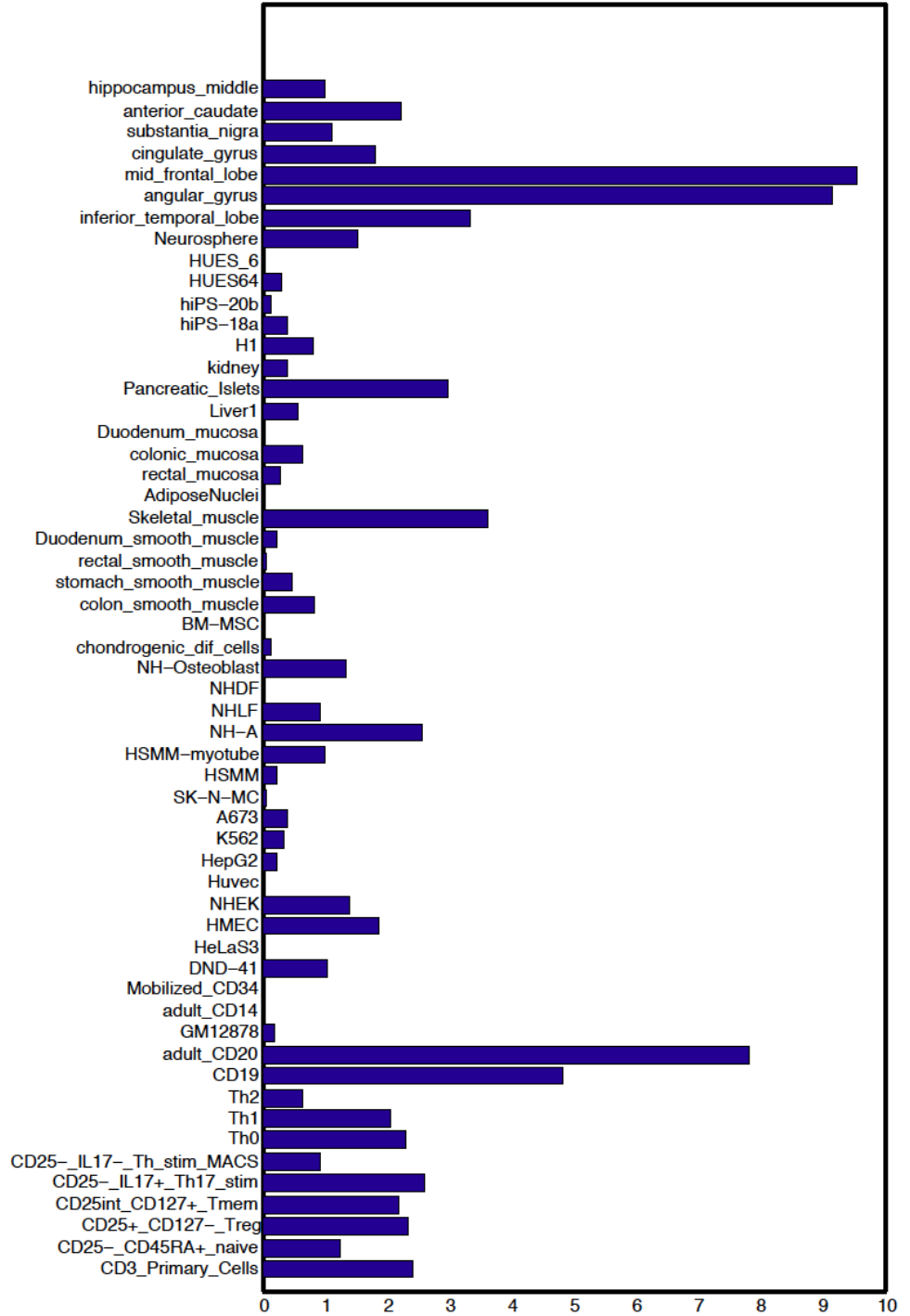
“Credible causal SNPs” from GWAS results

Compare to ChIP-seq from 56 cell lines and tissues

H3K27ac, enhancer mark

Schizophrenia associations enriched at enhancers active in brain

But not in tissues are unlikely to be relevant to schizophrenia



Epidemiology

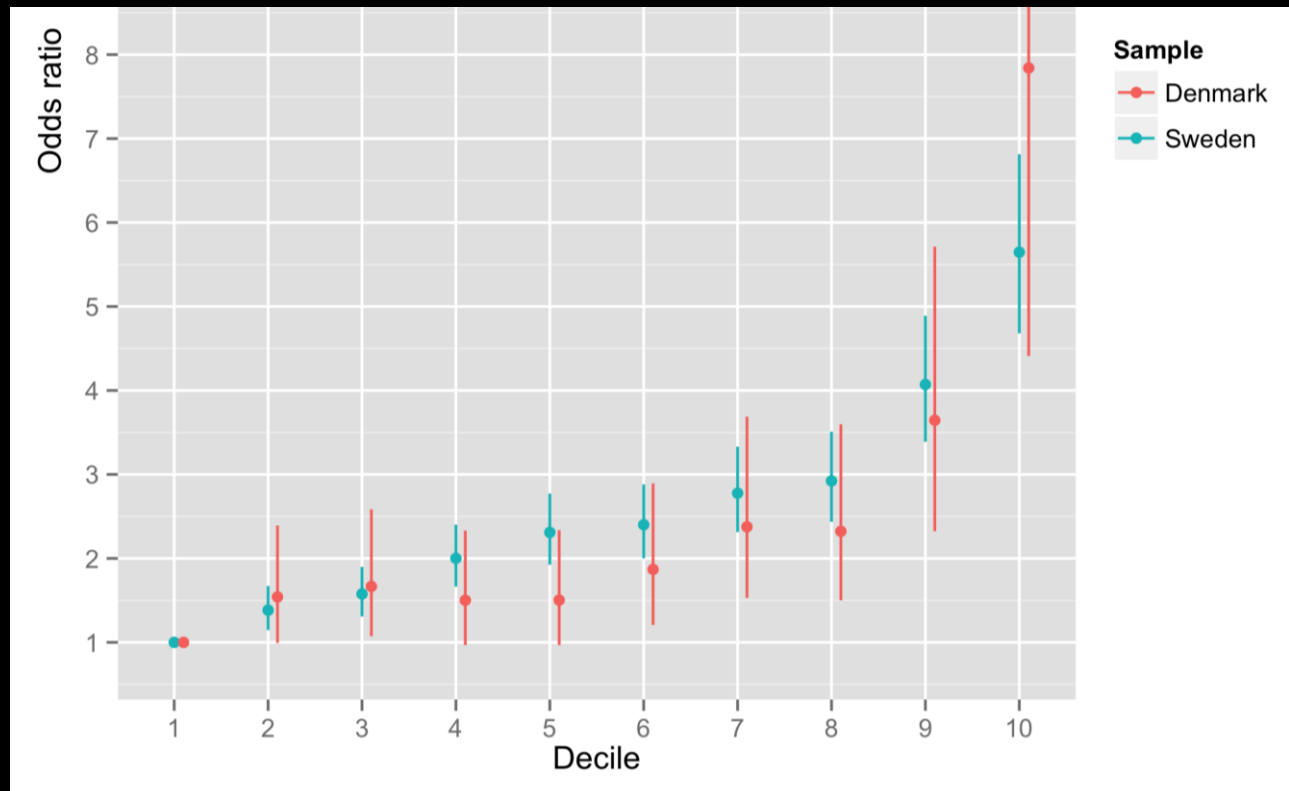
- Risk profile score – sum of number of common risk alleles from GWAS
- One number per person
- Independent “discovery” & “testing” samples
- Testing → population-based samples, Sweden & Denmark

Risk Profile Scores

- Normally distributed, uncorrelated with PCs
- Predicts case-control status ($p=4 \times 10^{-175}$)
- AUC 0.7

Risk Profile Scores

- Normally distributed, uncorrelated with PCs
- Predicts case-control status ($p=4 \times 10^{-175}$)
- AUC 0.7



Higher Risk Profile Scores

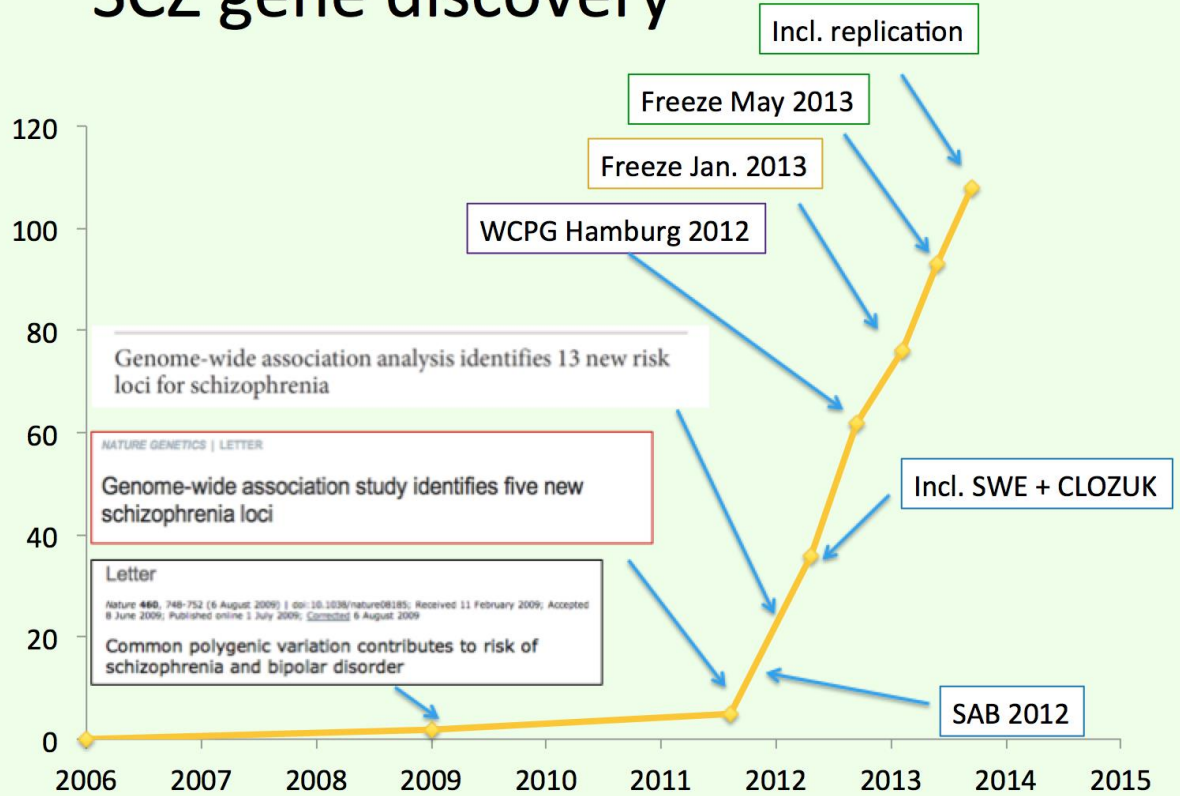
- + family history
- Greater disease severity
- Lesser survival

- Index heterogeneity (paternal age, epilepsy)

PGC Psych Chip

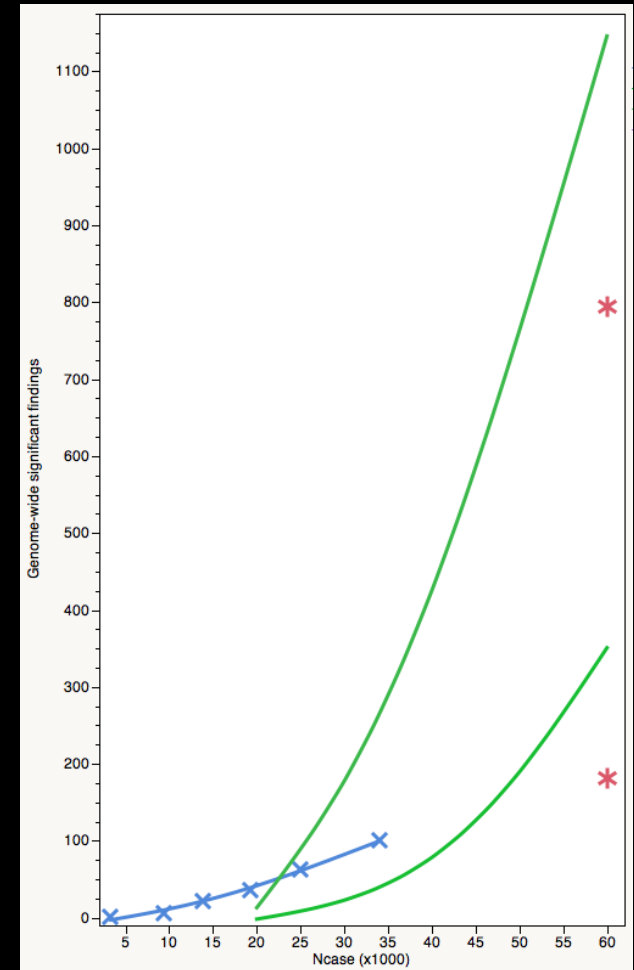
- Pamela Sklar & Ben Neale
- Illumina, GWAS + exome + custom content
- Will genotype 100K more people
- Should increase schizophrenia cases to 60K

SCZ gene discovery



10/2013 25K cases 62 gwsig

07/2014 38K cases 128 gwsig



thanks