

# Comparative genetic architectures of schizophrenia in East Asian and European populations

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## Introduction

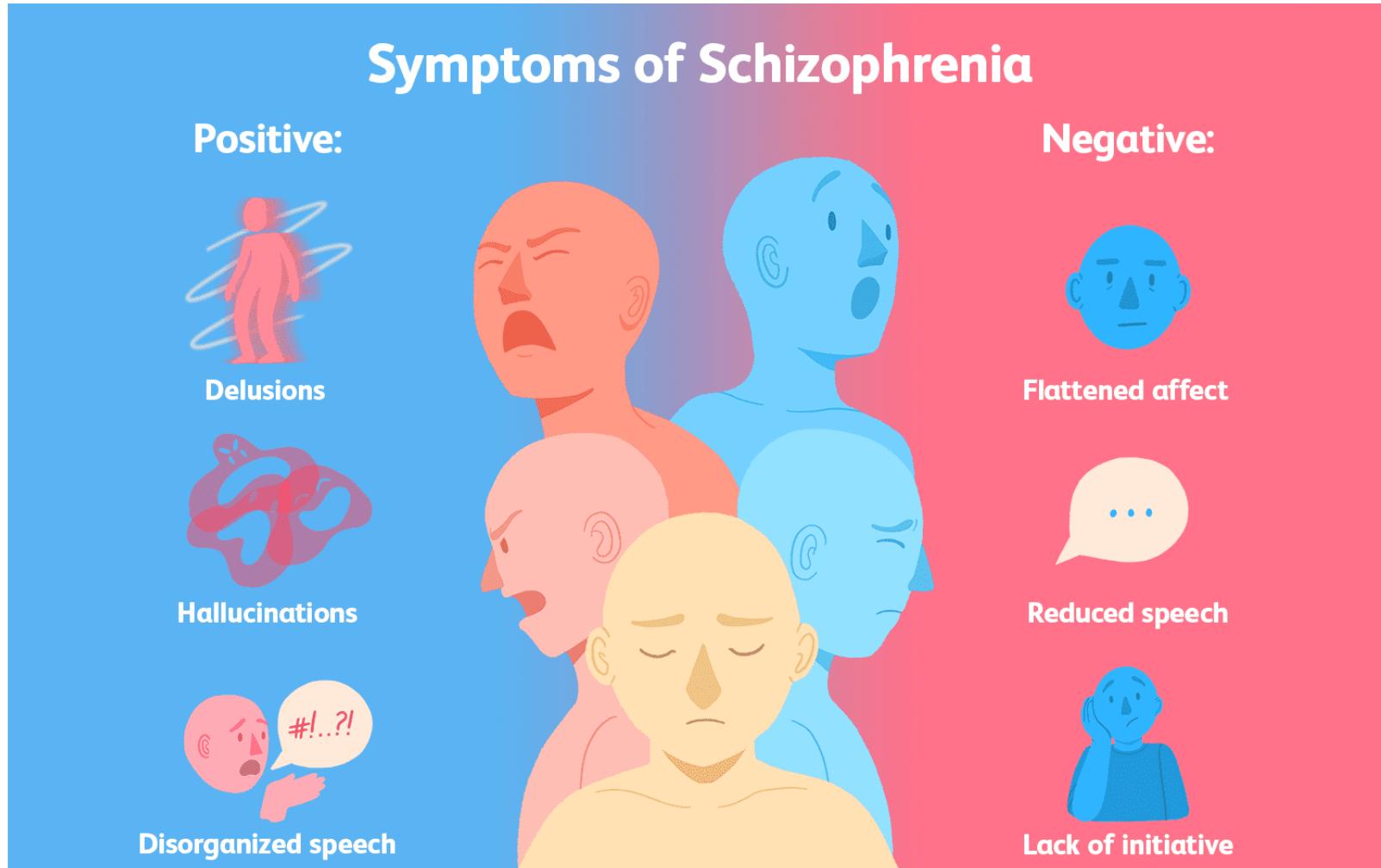
## Samples

## Results

1. Schizophrenia genetic associations in EAS population
2. Genetic effects across populations
3. Schizophrenia genetic associations from the meta-analysis of EAS and EUR
4. Population diversity and fine-mapping
5. Transferability of genetics across populations

## Discussion

# Introduction. Schizophrenia



# Introduction. The limitations of only using European ancestry samples

- It **hinders the discovery of biological clues** about schizophrenia.
- **Associations** that can be **detected in one population** may **not be detected in others**.
- Impossible to determine if **differences** between populations **represent etiologic heterogeneity** on the illness.
- **Prediction accuracy of Polygenic Risk Scores (PRS) decays with increasing genetic divergence** between **the risk allele discovery** (i.e. Europeans) and **target datasets** (i.e. East Asians)

# Samples. East Asian

Study	Case	Control	Chip	Design	Population	Raw data	Stage	X chr
IMH-1	856	946	I_1M	CC	Han Chinese	Y	1	Y
IMH-2	766	913	I_OZH	CC	Han Chinese	Y	1	Y
HNK-1	476	2018	I_610	CC	Han Chinese	Y	1	Y
JPN-1	547	540	A_SNP5.0	CC	Japanese	Y	1	Y
BIX-1	1045	2272	A_SNP6.0	CC	Han Chinese	Y	1	N
BIX-2	1021	1001	A_SNP6.0	CC	Han Chinese	Y	1	N
BIX-3	489	679	A_SNP6.0	CC	Han Chinese	Y	1	N
XJU-1	1846	947	I_OZH	CC	Han Chinese	Y	1	Y
UMC-1	2260	2241	I_Psyc	CC	Han Chinese	Y	1	Y
UWA-1	988	1001	I_Psyc	CC	Indonesia	Y	1	Y
BJM-1	1312	1987	I_OZH	CC	Han Chinese	Y	1	Y
TAI-1	1109	1109	I_Psyc	TRIO	Han Chinese	Y	1	Y
TAI-2	590	590	I_Psyc	TRIO	Han Chinese	Y	1	Y
KOR-1	687	492	A_KB	CC	Korean	Y	2	N
SIX-1	192	47	I_Psyc	CC	Han Chinese	Y	2	N
BIX-4	399	478	I_GSA	CC	Han Chinese	Y	2	N
BJM-2	746	1599	I_610	CC	Han Chinese	N	2	N
BJM-3	1595	1447	I_660W	CC	Han Chinese	N	2	N
BJM-4	710	680	I_OZH	CC	Han Chinese	N	2	N
BIX-5	5144	14375	A_SNP6.0, A_CHB1, I_1M	CC	Han Chinese	N	2	N
<b>Total</b>	<b>22,778</b>	<b>35,362</b>						



Cases (n): 22,778  
Controls (n): 35,362

Samples. European

nature

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Article | Published: 22 July 2014

# Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium

*Nature* 511, 421–427(2014) | Cite this article

35k Accesses | 3171 Citations | 1086 Altmetric | Metrics

# Samples. European

Note	PI	PMID	Site	QC score	Array	Cases	Controls	Male	Tag
●									
●									
●									
PGC1	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw1)	3	A5.0	215	210	0.527	scz_swe1_eur
PGC1/New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw234)	3	A6.0	1980	2274		scz_s234_eur
New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw5)	3	omni	1764	2581	0.553	scz_swe5_eur
New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw6)	3	omni	975	1145	0.543	scz_swe6_eur
New CC	Walters, J	21850710	Cardiff, UK (CogUK)	9	omni	530	678	0.554	scz_cog3_eur
New CC	Weinberger, D	11381111	NIMH CBDB	5	O25	133	269	0.547	scz_lie2_eur
New CC	Weinberger, D	11381111	NIMH CBDB	5	I550	497	389	0.627	scz_lie5_eur
PGC1	Werge, T	19571808	Denmark	8	I650	471	456	0.583	scz_denm_eur
<b>Total EUR CC</b>						<b>32,405</b>	<b>42,221</b>		
Trios	Kirov, G/Owen M	22083728	Bulgaria	8	A6.0	649	649	0.502	ms.scz_butr_eur
Trios	Levinson, D	22885689	Six countries	4	I650	516	516	0.556	ms.scz_lemu_eur
Trios	Kirov, G/Owen M	NP	Bulgaria	8	omni	70	70	0.595	ms.scz_uktr_eur
<b>Total Trios</b>						<b>1,235</b>	<b>1,235</b>		
East Asia	Iwata, N	20832056	Japan	3	A5.0	492	427	0.507	scz_jpn1_asn
East Asia	Liu, J	NP	Singapore (STCRP)	8	I1M	868	938		scz_tcr1_asn
East Asia	Sham, P	24043878	China	6	I550	476	2018	0.398	scz_hok2_asn
<b>Total Asia CC</b>						<b>1,836</b>	<b>3,383</b>		
<b>Total Discovery</b>						<b>35,476</b>	<b>46,839</b>		
Replication	Stefánsson, H	19571808	Iceland (SGENE+, deCODE)		ILMN*	628	65,312		N/A
Replication	Stefánsson, H	23164818	Non-Icelandic (SGENE+, deCODE)		ILMN*	885	924		N/A

Cases (n): 33,640

Controls (n): 43,456

# Samples. Preprocessing

20 samples in total from EAS

- Quality control, phasing and imputation (**same method for EUR samples**) for **16** samples for which they had individual genotype data (raw data = Y)
- **Two** of the samples from these 16 were from a trio design so pseudo-controls were used.
- For the **4** remaining samples only summary statistics were available.

Two-stage study design

Discovery (13 samples)

Replication (7 samples)

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Total	22,778	35,362						

# Schizophrenia genetic associations in EAS population

## METANALYSIS

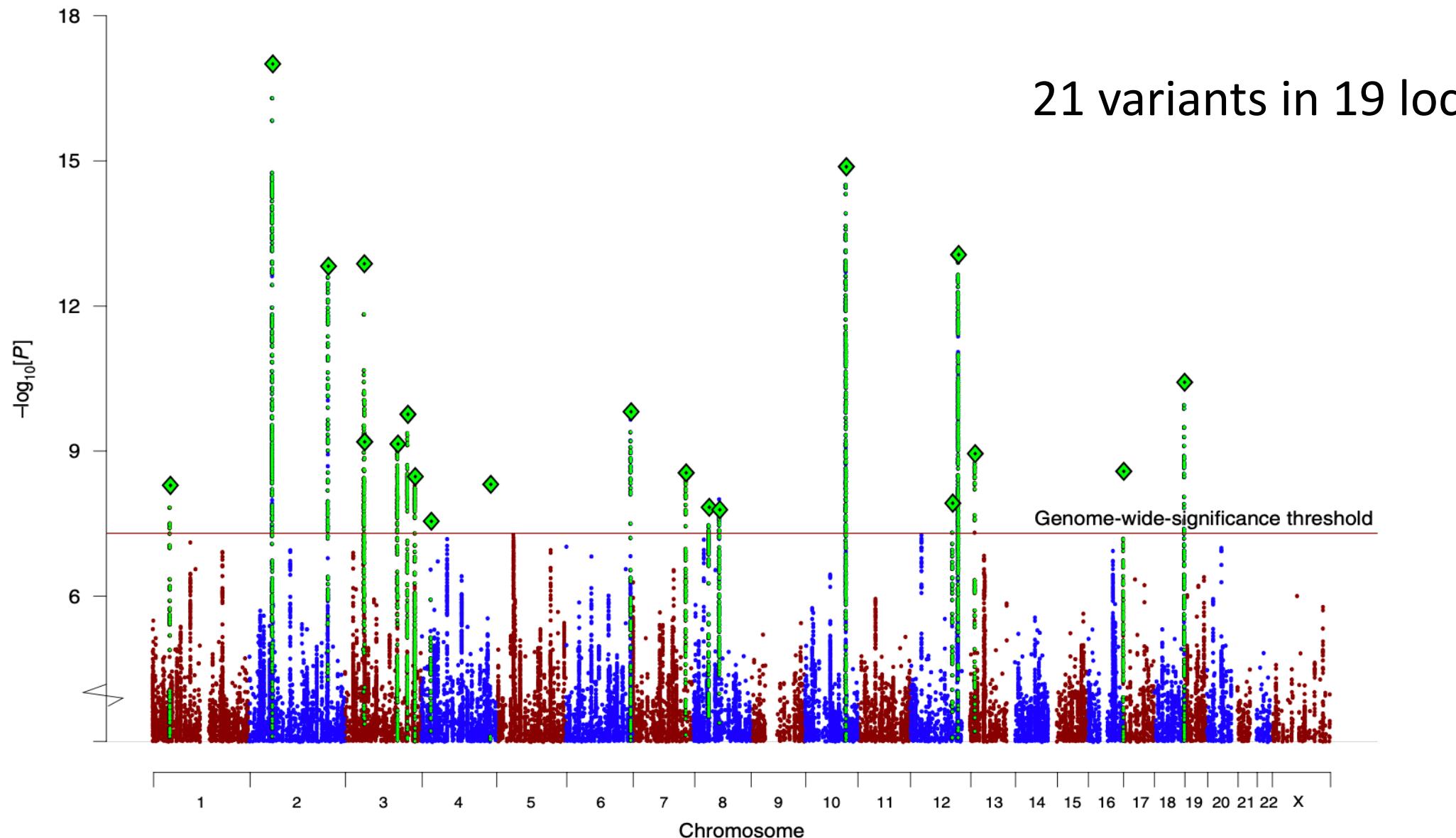
**Fixed-effect** model with  
inverse-variance weighting



## ASSUMPTION

There exists a **true effect size** shared by all the studies

# Schizophrenia genetic associations in EAS population

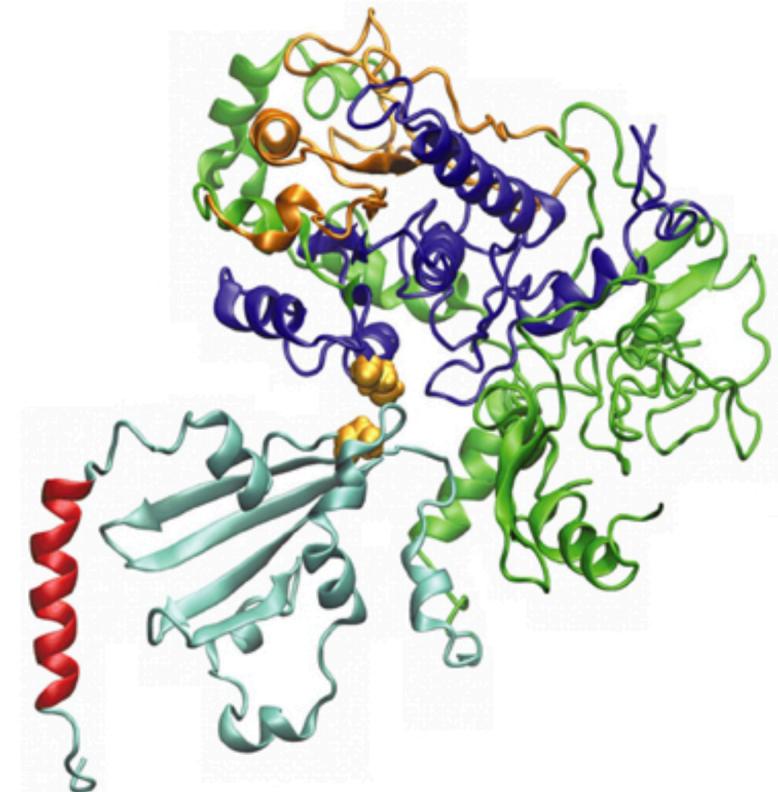


# Schizophrenia genetic associations in EAS population

- **15 of 21 loci found had higher MAFs in EAS compared to EUR:**

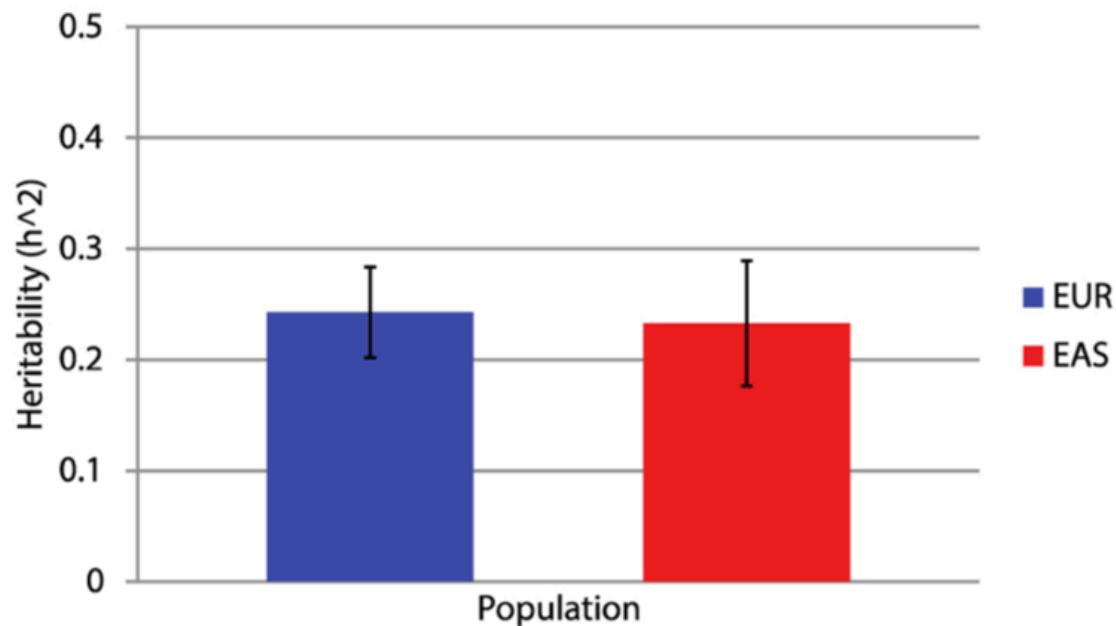
Example: **rs374528934** (the top association) has a MAF of **45%** in EAS but only **0.7%** in EUR . It wasn't detected on the EUR association study.

This locus contains **CACNA2D2** that codes for a **protein** subunit associated to **childhood epilepsy** and to which the anticonvulsant medication **gabapentin** binds, suggesting a future **possible therapeutic investigation**.



# Results. Genetic effects are consistent across populations

**Linkage Disequilibrium Score Regression (LDSC)** was used in order to quantify the **SNP heritability** for schizophrenia in both EUR and EAS populations and was found to be very similar,  $0.24 \pm 0.02$  against  $0.23 \pm 0.03$



Using the same set of variants the **genetic correlation** between schizophrenia at EUR and EAS was found to be very close to 1 ( $r = 0.98 \pm 0.03$ )

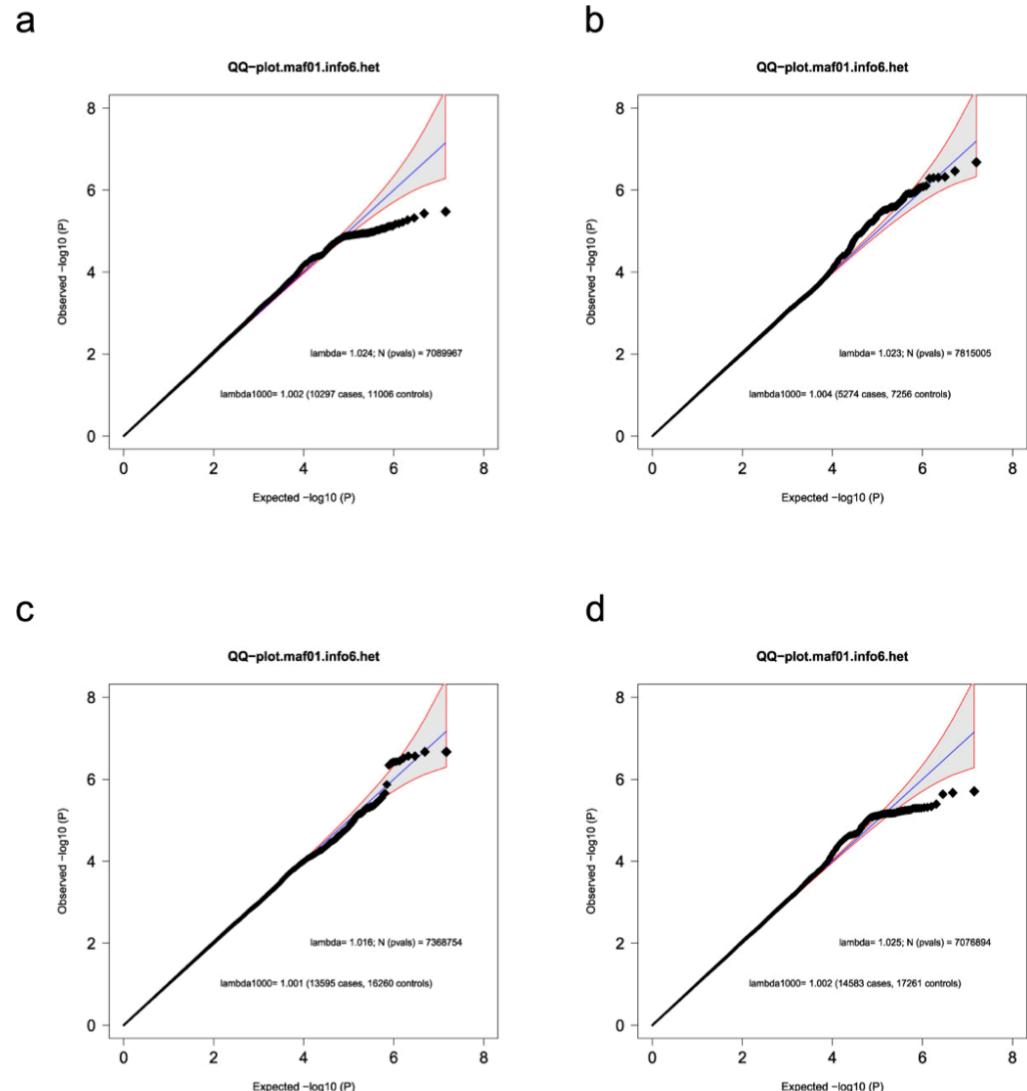
This implies that the **common variant genetic architecture of schizophrenia is highly consistent** across EUR and EAS samples.

# Genetic effects are consistent across populations

**Gene set enrichment analysis** was also performed for EUR and EAS samples. There was **no significant difference** between gene set ranks( $P = 0.72$ , two-sided Wilcoxon test).

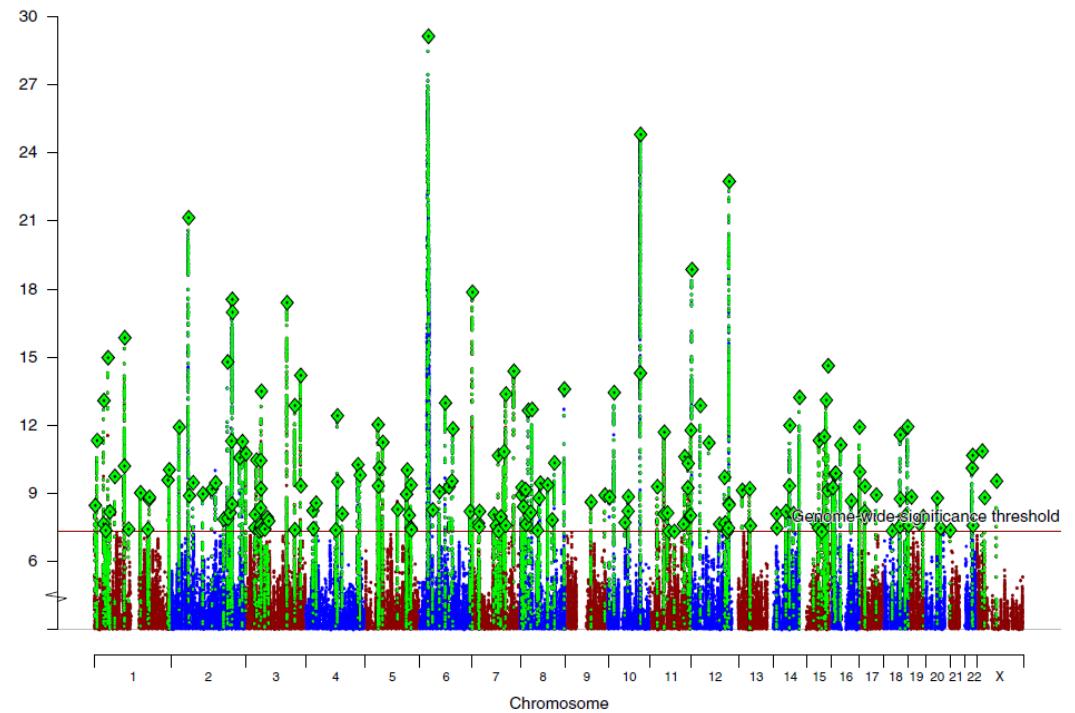
An **evaluation of the heterogeneity of schizophrenia genetic effects within EAS samples** was performed (Cochran's  $Q$ ). None of the 21 associations showed significant heterogeneity across samples.

Using **PCA**, the samples were grouped into Northeast Asian, Southeast Asian and Indonesian subpopulations. A heterogeneity test (Cochran's  $Q$ ) was then performed and found **no significant heterogeneity among the three subpopulations**.



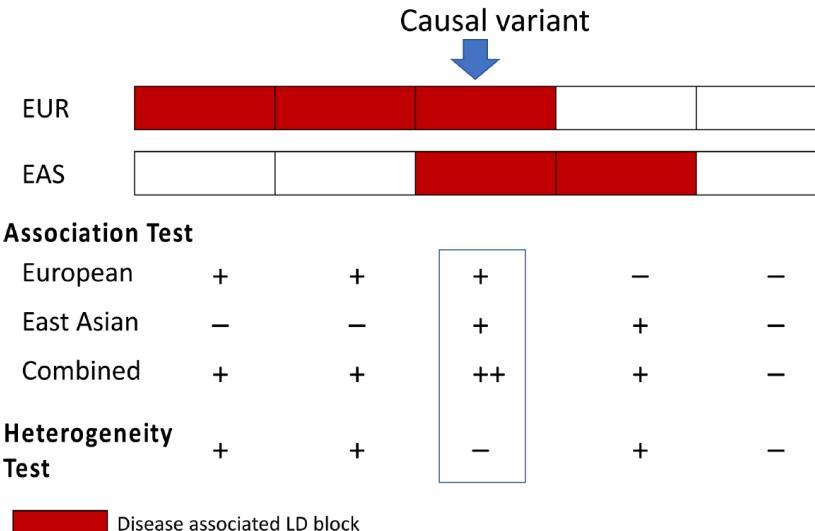
# Schizophrenia genetic associations from the meta-analysis of EAS and EUR

- Fixed effect meta-analysis EAS + EUR:  
56,418 cases – 78818 controls
- 208 independent variants associated with schizophrenia in 176 loci
- 53 novel loci
- 89 variants of the only EUR study remained significant

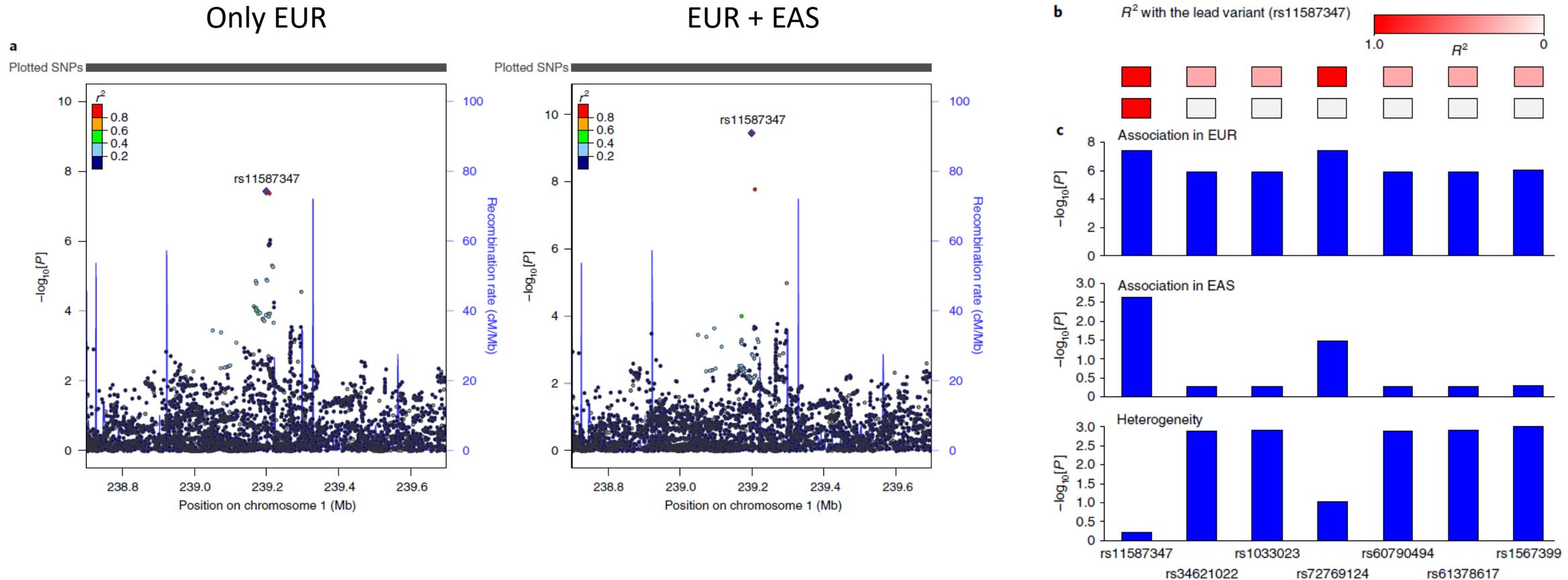


# Population diversity and fine-mapping

- Fine-mapping defines a ‘credible set’ of variants that contains the causal variant with certain probability (95 or 99 %)
- Consistent genetic effects across EAS and EUR
- Causal variants: ↑ statistical significance      ↓ heterogeneity



# Population diversity and fine-mapping



# Transferability of genetics across populations

- Comparing cause of variance across EUR and EAS populations for SNPs that explained > 0.05 % variance in SCHZ liability
- Most of them had similar odd ratio but different allele frequencies
- Even if different ancestries have the same risk alleles and effect sizes → predictive power not equivalent

