Comparative genetic architectures of schizophrenia in East Asian and European populations

Armand González Escalante
Ana Sánchez Fernández

Index

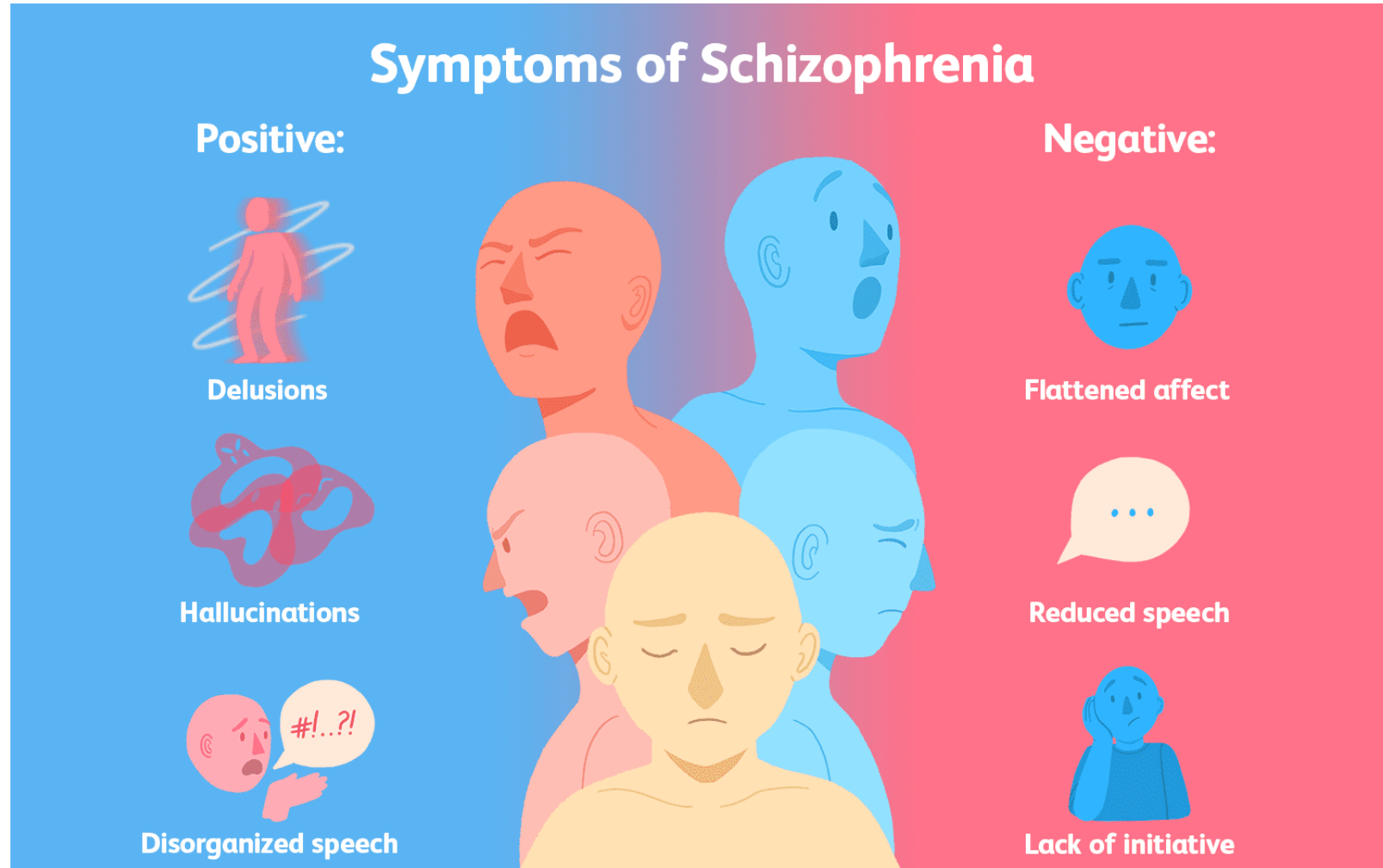**Introduction**

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
Total	**22,778**	**35,362**						

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

Samples. European

nature

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium

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_cou3_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
Total EUR CC						**32,405**	**42,221**		
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
Total Trios						**1.235**	**1.235**		
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
Total Asia CC						**1.836**	**3.383**		
Total Discovery						**35,476**	**46,839**		
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)

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
Total	**22,778**	**35,362**						

Schizophrenia genetic associations in EAS population
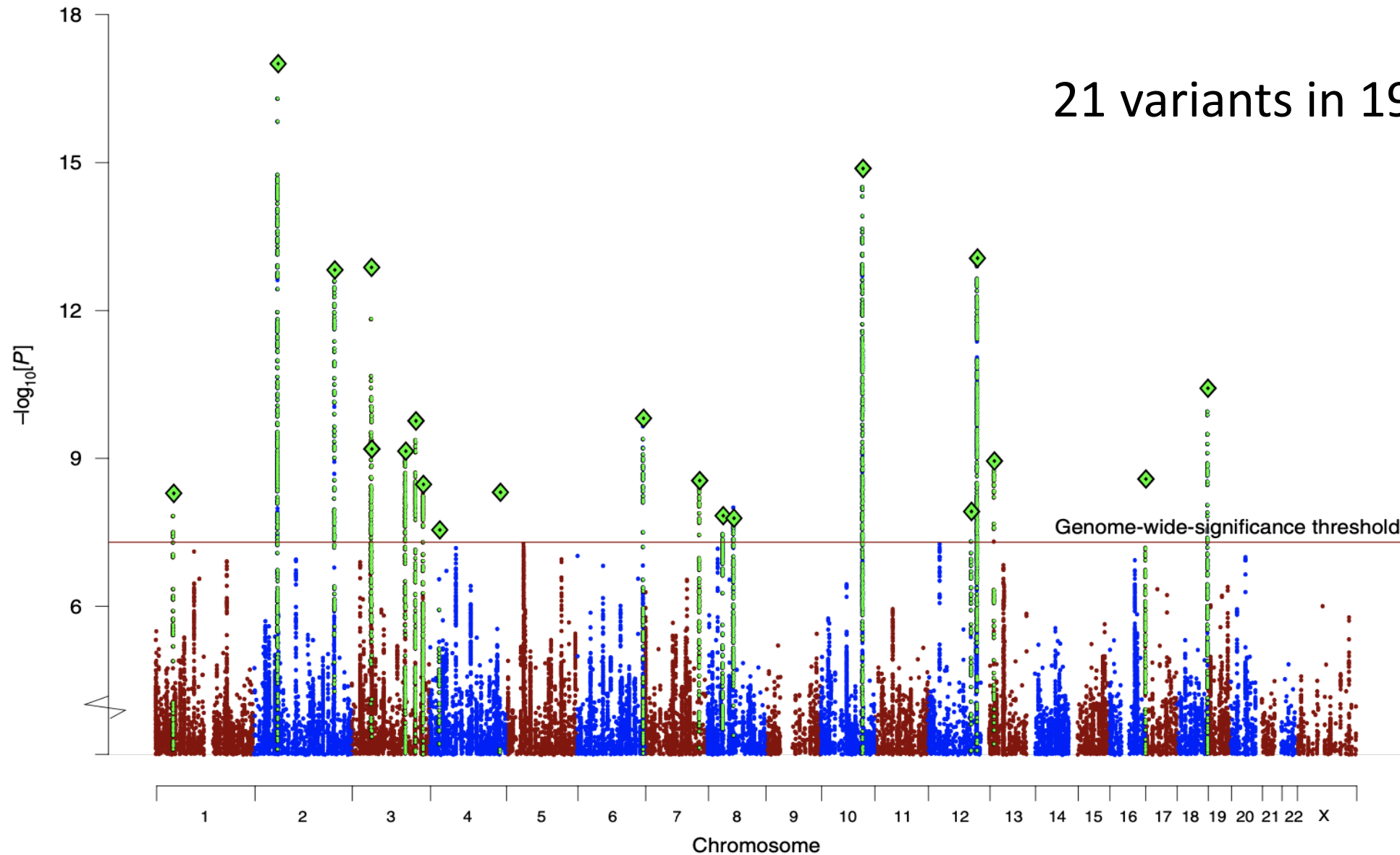
METANALYSIS

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


21 variants in 19 loci

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**.
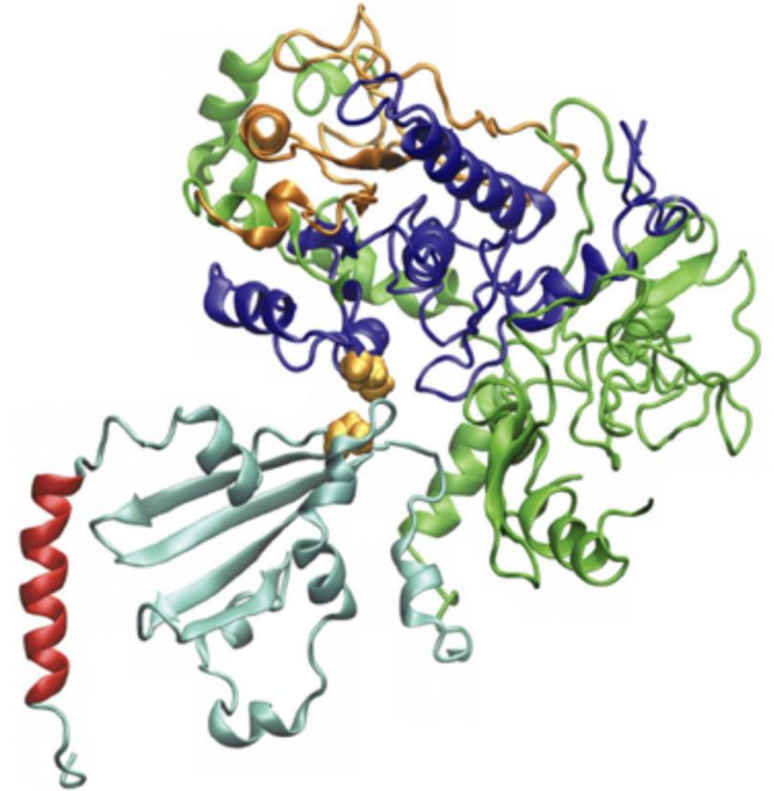
Results. Genetic effects are consistent across populations

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 ± 0.02 against 0.23 ± 0.03
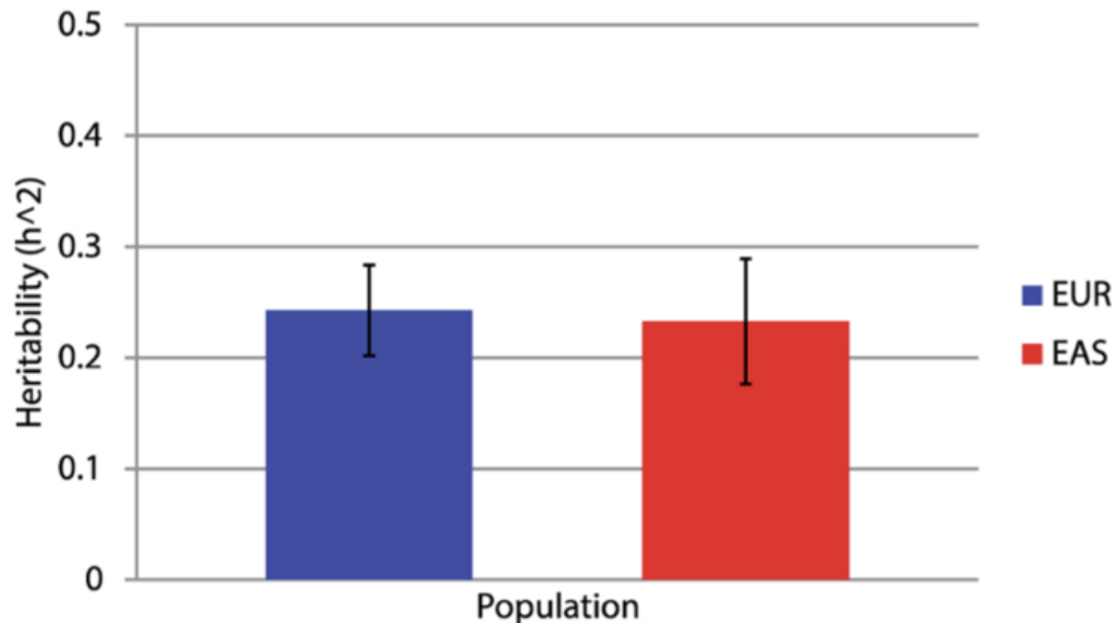
Using the same set of variants the **genetic correlation** between schizophrenia at EUR and EAS was found to be very close to 1 ($r = 0.98 \pm 0.03$)

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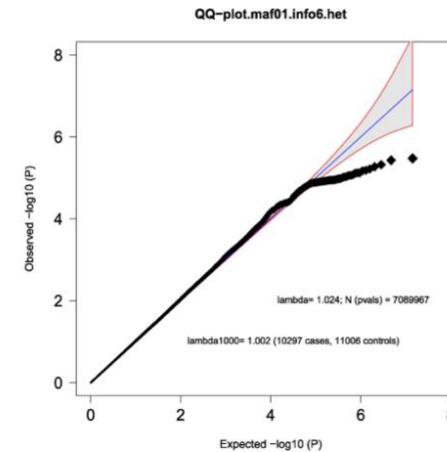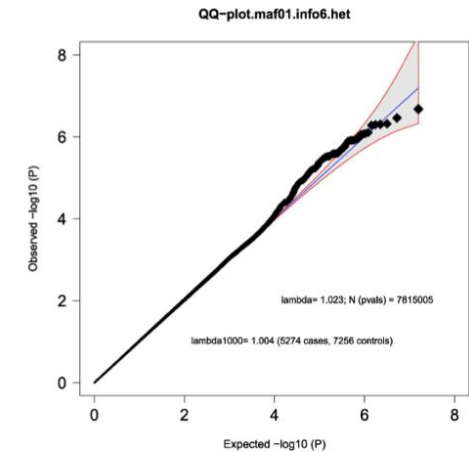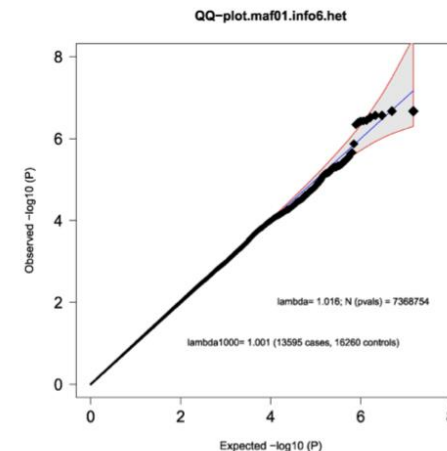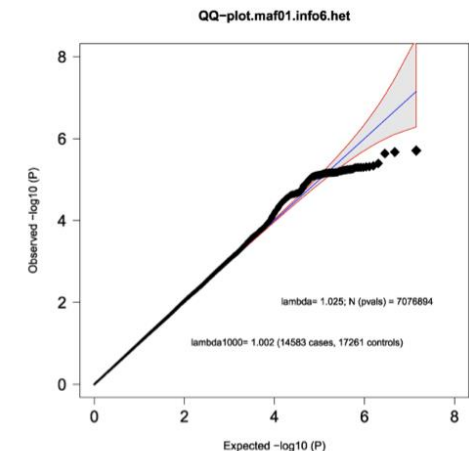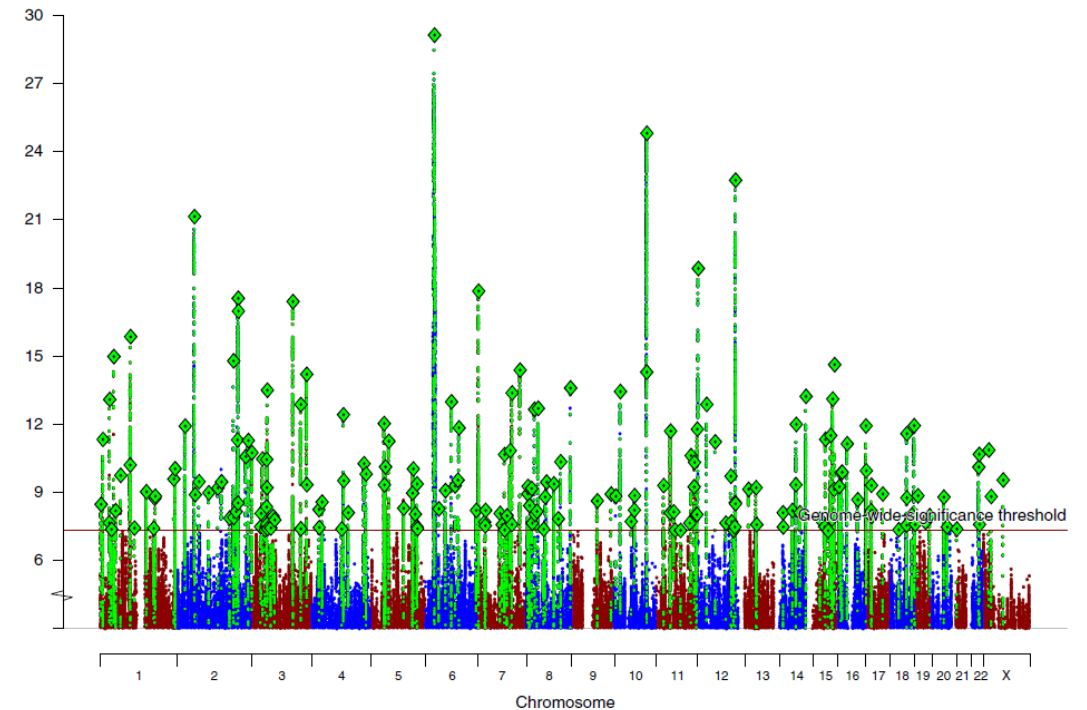
Schizophrenia genetic associations from the meta-analysis of EAS and EUR

- Fixed effect meta-analysis **EAS + EUR**:

  56,418 cases – 78,818 controls

- **208** independent **variants associated**

  with schizophrenia in **176 loci**

- **53 novel loci**

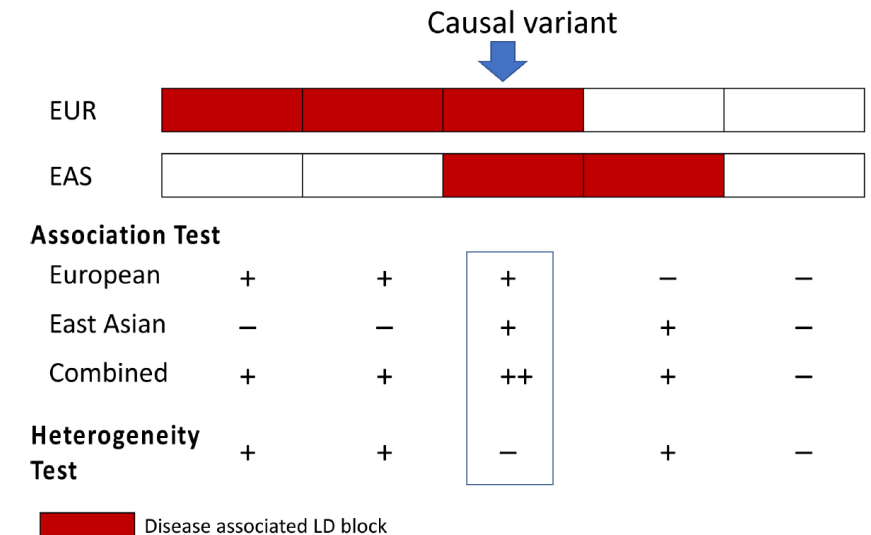- 89 variants of the only EUR study

  remained significant

Trans-ethnicity bayesian fine-mapping

- **Fine-mapping** defines a 'credible set' of variants that contains the **causal variant** with certain probability

- **Bayes theorem** to calculate the probability of being causal for each associated variant in a locus
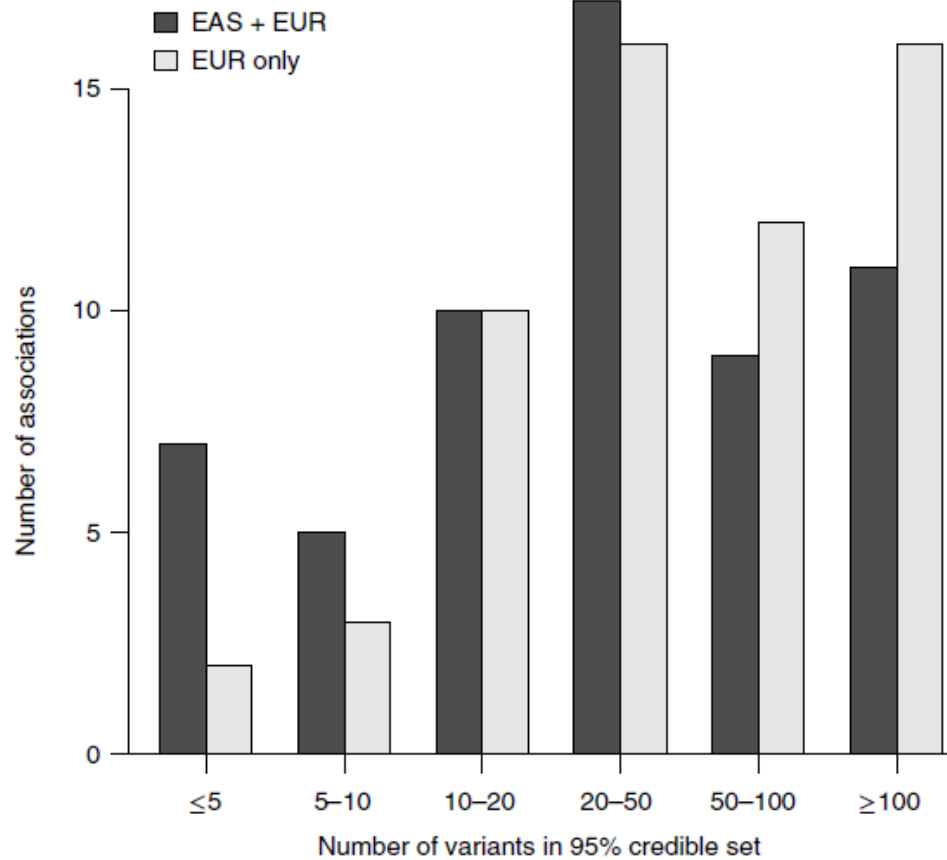
$$P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)}$$

- **Credible set:** variants for which sum of the probabilities ≥ 95%

- **Trans-ethnicity.** Heterogeneity was considered.

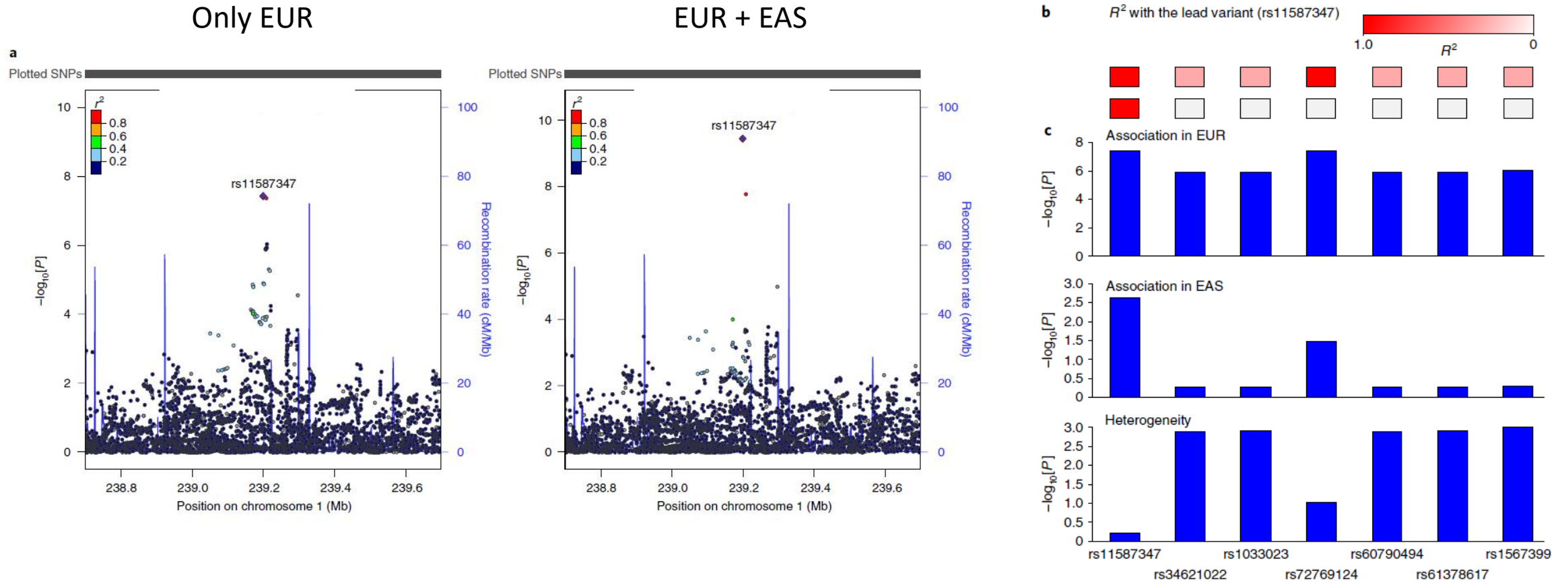 Causal variants: ↓ heterogeneity ↑ statistical significance

Causal variant

|	EUR				
	EAS				

Association Test

European	+	+	+	−	−
East Asian	−	−	+	+	−
Combined	+	+	++	+	−

Heterogeneity Test

	+	+	−	+	−

■ Disease associated LD block

Trans-ethnicity bayesian fine-mapping

44 out of 59 associations were improved by trans-ancestry fine mapping.

Population diversity and fine-mapping

Only EUR

EUR + EAS

Transeferability of genetics across populations

- Comparing cause of liability variance across EUR and EAS populations

- 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**

- Evaluation of PRS in EAS with EAS and EUR as training data
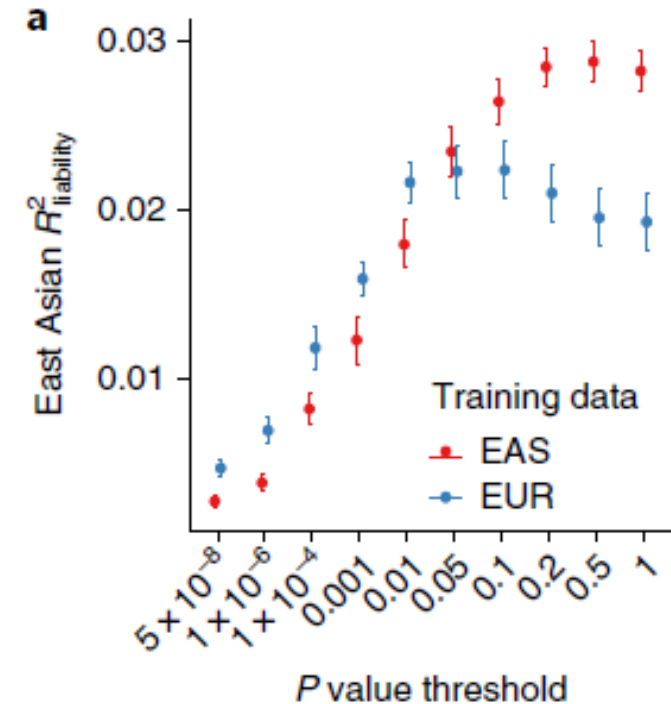
Discussion

- This study compiles the **largest non-EUR psychiatric cohort**

- **Single population** studies ➡ results **biased** toward higher **frequency alleles.** Including global samples increases discovery power

- Remarkable **genetic correlation** between EAS and EUR

- **Novel algorithm** for trans-ethnicity fine-mapping

- **Reduced performance predicting** PRS across populations due to different allele frequencies and LD patterns