SUPPLEMENTARY METHODS

Genotyping, imputation, and ancestry inference

Participants were genotyped using the Multi-Ethnic Global Array (MEGA), which includes approximately 2 million SNPs or the Global Screening Array (GSA), which includes 654,027 SNPs.(1,2) Genotyping was conducted following protocols specified by The Centre for Applied Genomics (TCAG) at SickKids. Quality control (QC) measures included comparing genotype inferred sex chromosome composition (X chromosome heterozygosity and Y chromosome call rate) with self-reported sex, sample call rates>90%, autosomal heterozygosity to detect potential sample contamination, SNP call rate >97%, and a Hardy-Weinberg equilibrium threshold of $1x10^{-6}$. SNPs not genotyped were imputed using the Sanger Imputation Server and the Haplotype Reference Consortium (HRC) and 1000 Genomes Project (1KGP) phase 3 as references.(3) HLA allele dosages in inferred European participants only were imputed using SNP2HLA and Type 1 Diabetes Genetics Consortium as a reference.(4,5)

Ancestry was inferred for each participant using 1KGP and the Human Genome Diversity Project (HGDP) as referents.(3,6) Individuals were inferred to be of a specific ancestry if their first three principal components (PCs) were within the range (mean ± standard deviation) of the first 3 PCs of the referent group with the corresponding ethnicity. If there were discordances between 1KGP or HGDP, the software tool ADMIXTURE was used to estimate relative proportions of ancestral groups within discordant subjects.(7) Participants with single ancestral proportions ≥80% were classified into one of five ancestral groups: African, Amerindian, East Asian, European, or South Asian. Participants displaying ancestral proportions <80% were classified as “Admixed”. Due to sample size restrictions, for our analyses, participants in the Amerindian ancestral group were combined with the “Admixed” group.

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Polygenic risk score (PRS) calculations

We selected SNPs for inclusion in schizophrenia PRSs based on the most recent, comprehensive schizophrenia GWAS conducted to-date by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG-PGC).(8) The study of up to 36,989 cases with schizophrenia and 113,075 controls identified 128 independent genome-wide significant SNPs ($P<5x10^{-8}$) and over 100,000 SNPs showing modest association with schizophrenia.(8) We computed two PRSs using: 1) genome-wide significant SNPs ($P<5x10^{-8}$) and 2) an expanded list of SNPs significant at a threshold of $P<0.05$. The SWG-PGC paper also calculated PRSs for schizophrenia and we used their QC procedures as guiding principles in creating our PRSs.(8) We excluded the following SNPs from our calculations: insertions/deletions, sex chromosomes, uncommon SNPs (minor allele frequency [MAF] <10%) and low-quality variants (imputation INFO <0.9) on either array, SNPs in the extended major histocompatibility complex (MHC) region (chr6:25-34 Mb) and variants within 500 kb of and with evidence for linkage disequilibrium (LD, $r^2 \geq 0.1$) with another more significant marker. For the expanded PRS only, we removed all ambiguous SNPs (i.e., those with complementary alleles such as A/T or C/G) for which we were unable to use allele frequencies to infer which alleles matched. All SNPs retained in the analyses were independent of each other, allowing their effects to be summed.(8,9) After exclusions, a total 76/128 SNPs were included in the GWAS PRS calculations and a total 15,305/24,850 SNPs were included in the extended PRS calculations for schizophrenia.

We calculated additive, allelic schizophrenia PRSs, for each participant by identifying the risk alleles, weighting the allele dosages by the log odds ratios (log(ORs)) from the SWG-PGC study, and summing up the values to derive the PRS.(8,9)

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SUPPLEMENTARY TABLES

Supplementary Table 1. Association between NPSLE, NPSLE subtypes and schizophrenia expanded PRS*

	OR (95% CI) p-value					
Variable	Any NPSLE†		Psychosis‡		Non-psychosis NPSLE‡	
Unadjusted expanded PRS	1.19 (1.00 - 1.43)	0.06	0.97 (0.74 - 1.29)	0.86	1.30 (1.06 - 1.59)	0.01
Ancestry adjusted expanded PRS	1.08 (0.89 – 1.32)	0.43	0.92 (0.68 - 1.24)	0.57	1.16 (0.93 - 1.45)	0.18
Full multivariable adjusted expanded PRS§	1.07 (0.87 - 1.31)	0.53	0.91 (0.67 - 1.24)	0.55	1.15 (0.91 - 1.44)	0.24

* Reference category is absence of any NPSLE feature.

† Binomial logistic regression model

‡Multinomial logistic regression model

§ Model adjusted for inferred ancestry categories (Admixed, African, East Asian, South Asian), malar rash, oral or nasal ulcers, arthritis, lymphopenia, Coombs-positive hemolytic anemia, and lupus anticoagulant and/or anticardiolipin antibodies.

Abbreviations: CI: confidence interval; GWAS: genome-wide association studies; NPSLE: neuropsychiatric systemic lupus erythematosus; OR: odds ratio; PRS: polygenic risk scores

Supplementary Table 2. Single schizophrenia GWAS SNPs ancestry-adjusted analysis (N=513)*

				SLE Cohort				SWG-PGC Cohort†			
rsID	chr	bp	Ref Allele‡	Frq (cases)	Frq (controls)	OR (95% CI)	P-value	Frq (cases)	Frq (controls)	OR (95% CI)	P-value
rs1498232	1	30433951	T	0.17	0.12	0.87 (0.66 - 1.16)	3.50E-01	0.31	0.30	1.07 (1.05-1.09)	2.86E-09
rs11210892	1	44100084	A	0.11	0.08	1.11 (0.84 - 1.46)	4.81E-01	0.66	0.68	0.93 (0.91-0.95)	3.39E-10
rs12129573	1	73768366	A	0.17	0.12	1.11 (0.84-1.47)	4.59E-01	0.38	0.36	1.08 (1.06-1.10)	2.03E-12
rs1702294	1	98501984	T	0.19	0.12	0.84 (0.59-1.19)	3.36E-01	0.18	0.19	0.89 (0.87-0.91)	3.36E-19
rs6670165	1	177280121	T	0.15	0.09	1.12 (0.80-1.56)	5.01E-01	0.20	0.18	1.08 (1.05-1.10)	4.45E-08
rs7523273	1	207977083	A	0.14	0.08	0.96 (0.71-1.30)	7.86E-01	0.70	0.69	1.06 (1.04-1.09)	4.47E-08
rs11682175	2	57987593	T	0.11	0.09	0.90 (0.68-1.20)	4.74E-01	0.52	0.54	0.93 (0.91-0.95)	1.47E-11
rs2909457	2	162845855	A	0.25	0.16	0.94 (0.71-1.26)	6.83E-01	0.57	0.59	0.94 (0.93-0.96)	4.62E-08
rs11693094	2	185601420	T	0.13	0.10	1.04 (0.79-1.38)	7.71E-01	0.44	0.46	0.93 (0.91-0.95)	1.53E-12
rs59979824	2	193848340	A	0.16	0.10	0.82 (0.61-1.08)	1.60E-01	0.32	0.34	0.94 (0.92-0.96)	8.41E-09
rs6434928	2	198304577	A	0.21	0.14	1.18 (0.90-1.54)	2.37E-01	0.64	0.64	0.93 (0.91-0.95)	2.06E-11
rs6704641	2	200164252	A	0.18	0.13	0.97 (0.72-1.30)	8.20E-01	0.82	0.81	1.08 (1.05-1.11)	8.33E-09
rs11685299	2	225391296	A	0.12	0.10	1.20 (0.89-1.62)	2.22E-01	0.31	0.33	0.94 (0.92-0.96)	1.12E-08
rs6704768	2	233592501	A	0.32	0.19	0.94 (0.72-1.22)	6.28E-01	0.54	0.55	0.93 (0.91-0.95)	2.32E-12
rs4330281	3	17859366	T	0.27	0.16	0.82 (0.61-1.10)	1.84E-01	0.48	0.48	0.94 (0.92-0.96)	4.64E-09
rs75968099	3	36858583	T	0.24	0.18	1.07 (0.77-1.49)	6.83E-01	0.35	0.32	1.09 (1.06-1.11)	1.05E-13

				SLE Cohort				SWG-PGC Cohort†			
rsID	chr	bp	Ref Allele‡	Frq (cases)	Frq (controls)	OR (95% CI)	P-value	Frq (cases)	Frq (controls)	OR (95% CI)	P-value
rs2535627	3	52845105	T	0.06	0.05	1.04 (0.81-1.35)	7.55E-01	0.55	0.53	1.07 (1.05-1.09)	4.26E-11
rs832187	3	63833050	T	0.17	0.12	1.02 (0.79-1.32)	8.63E-01	0.61	0.62	0.94 (0.92-0.96)	1.43E-08
rs7432375	3	136288405	A	0.18	0.14	1.09 (0.82-1.45)	5.40E-01	0.42	0.45	0.93 (0.91-0.95)	7.26E-11
rs10520163	4	170626552	T	0.26	0.18	0.73 (0.55-0.96)	2.60E-02	0.49	0.47	1.07 (1.04-1.09)	1.47E-09
rs1106568	4	176861301	A	0.27	0.18	1.37 (1.02-1.85)	3.55E-02	0.75	0.76	0.93 (0.91-0.96)	9.47E-09
rs1501357	5	45364875	T	0.10	0.09	0.97 (0.73-1.27)	8.00E-01	0.79	0.80	0.93 (0.90-0.95)	5.05E-09
rs4391122	5	60598543	A	0.21	0.14	1.03 (0.79-1.35)	8.10E-01	0.51	0.53	0.92 (0.90-0.94)	1.10E-14
rs16867576	5	88746331	A	0.20	0.16	1.21 (0.83-1.77)	3.23E-01	0.89	0.88	1.10 (1.07-1.14)	4.61E-09
rs4388249	5	109036066	T	0.32	0.20	0.99 (0.74-1.32)	9.28E-01	0.21	0.21	1.08 (1.05-1.10)	3.05E-08
rs3849046	5	137851192	T	0.23	0.15	1.03 (0.79-1.34)	8.29E-01	0.54	0.52	1.06 (1.042-1.09)	4.67E-09
rs11740474	5	153680747	A	0.10	0.10	1.20 (0.88-1.62)	2.48E-01	0.60	0.62	0.94 (0.92-0.96)	3.15E-08
rs1339227	6	73155701	T	0.07	0.06	0.85 (0.64-1.13)	2.76E-01	0.35	0.37	0.94 (0.92-0.96)	2.69E-08
rs6466055	7	104929064	A	0.23	0.16	1.03 (0.78-1.36)	8.48E-01	0.35	0.33	1.07 (1.05-1.09)	1.13E-09
rs211829	7	110048893	T	0.09	0.05	1.07 (0.79-1.43)	6.74E-01	0.64	0.63	1.06 (1.04-1.08)	3.71E-08
rs13240464	7	110898915	T	0.31	0.20	1.12 (0.86-1.45)	3.96E-01	0.67	0.65	1.08 (1.06-1.11)	3.03E-13
rs7801375	7	131567263	A	0.05	0.04	0.66 (0.45-0.94)	2.21E-02	0.15	0.15	0.92 (0.90-0.95)	4.42E-08

				SLE Cohort				SWG-PGC Cohort[†]			
rsID	chr	bp	Ref Allele[‡]	Frq (cases)	Frq (controls)	OR (95% CI)	P-value	Frq (cases)	Frq (controls)	OR (95% CI)	P-value
rs3735025	7	137074844	T	0.18	0.14	1.05 (0.79-1.40)	7.24E-01	0.66	0.64	1.07 (1.04-1.09)	3.28E-09
rs10503253	8	4180844	A	0.11	0.08	0.93 (0.70-1.24)	6.14E-01	0.22	0.22	1.07 (1.05-1.10)	1.06E-08
rs6984242	8	60700469	A	0.21	0.15	0.96 (0.74-1.23)	7.31E-01	0.59	0.60	0.94 (0.92-0.96)	5.97E-09
rs7819570	8	89588626	T	0.25	0.16	1.13 (0.79-1.62)	5.06E-01	0.19	0.17	1.08 (1.05-1.11)	1.22E-08
rs36068923	8	111485761	A	0.28	0.22	0.81 (0.59-1.12)	1.97E-01	0.79	0.80	0.92 (0.90-0.94)	2.61E-11
rs4129585	8	143312933	A	0.16	0.12	0.98 (0.72-1.33)	8.77E-01	0.45	0.42	1.09 (1.07-1.11)	1.74E-15
rs11139497	9	84739941	A	0.12	0.09	1.08 (0.81-1.45)	6.05E-01	0.35	0.34	1.07 (1.05-1.09)	3.61E-09
rs11191419	10	104612335	A	0.21	0.14	0.93 (0.72-1.22)	6.18E-01	0.34	0.36	0.91 (0.89-0.93)	6.20E-19
rs11027857	11	24403620	A	0.07	0.04	1.14 (0.88-1.47)	3.33E-01	0.52	0.50	1.06 (1.04-1.09)	2.55E-09
rs9420	11	57510294	A	0.13	0.08	0.87 (0.64-1.16)	3.41E-01	0.33	0.31	1.07 (1.05-1.09)	2.24E-09
rs12421382	11	109378071	T	0.13	0.08	0.68 (0.50-0.94)	1.91E-02	0.32	0.33	0.94 (0.92-0.96)	3.70E-08
rs2514218	11	113392994	T	0.31	0.22	0.97 (0.71-1.33)	8.51E-01	0.31	0.31	0.93 (0.91-0.95)	2.75E-11
rs77502336	11	123394636	C	0.25	0.14	0.75 (0.56-1.00)	4.92E-02	0.34	0.32	1.07 (1.04-1.09)	7.54E-09
rs55661361	11	124613957	A	0.29	0.20	0.67 (0.50-0.89)	5.28E-03	0.32	0.34	0.93 (0.91-0.95)	2.80E-12
rs10791097	11	130718630	T	0.14	0.09	0.94 (0.72-1.23)	6.42E-01	0.48	0.46	1.08 (1.06-1.10)	1.09E-12
rs75059851	11	133822569	A	0.20	0.14	0.63 (0.41-0.97)	3.71E-02	0.81	0.80	1.09 (1.06-1.12)	3.87E-11

				SLE Cohort				SWG-PGC Cohort†			
rsID	chr	bp	Ref Allele‡	Frq (cases)	Frq (controls)	OR (95% CI)	P-value	Frq (cases)	Frq (controls)	OR (95% CI)	P-value
rs2007044	12	2344960	A	0.28	0.21	1.01 (0.77-1.32)	9.57E-01	0.60	0.62	0.91 (0.89-0.93)	3.22E-18
rs679087	12	29917265	A	0.29	0.20	0.98 (0.72-1.31)	8.75E-01	0.32	0.34	0.94 (0.92-0.96)	3.91E-08
rs4240748	12	92246786	C	0.12	0.11	0.99 (0.75-1.30)	9.25E-01	0.36	0.37	0.94 (0.92-0.96)	4.59E-08
rs10860964	12	103596455	T	0.06	0.05	1.14 (0.83-1.55)	4.24E-01	0.65	0.65	1.06 (1.04-1.08)	4.84E-08
rs2851447	12	123665113	C	0.26	0.16	1.02 (0.77-1.36)	8.88E-01	0.72	0.74	0.92 (0.89-0.94)	1.86E-14
rs2068012	14	30190316	T	0.13	0.08	1.18 (0.88-1.59)	2.67E-01	0.76	0.77	0.93 (0.91-0.96)	1.41E-08
rs2332700	14	72417326	C	0.17	0.11	0.86 (0.61-1.20)	3.73E-01	0.26	0.25	1.07 (1.05-1.10)	4.86E-09
rs2693698	14	99719219	A	0.24	0.18	1.08 (0.80-1.47)	6.06E-01	0.41	0.42	0.94 (0.92-0.96)	4.80E-09
rs12887734	14	104046834	T	0.24	0.15	0.91 (0.68-1.23)	5.55E-01	0.30	0.29	1.09 (1.06-1.11)	1.36E-13
rs12903146	15	61854663	A	0.30	0.19	0.91 (0.70-1.19)	4.87E-01	0.54	0.52	1.07 (1.05-1.09)	3.38E-10
rs12148337	15	70589272	T	0.28	0.21	1.01 (0.78-1.32)	9.15E-01	0.48	0.47	1.06 (1.04-1.08)	1.79E-08
rs8042374	15	78908032	A	0.06	0.05	0.94 (0.72-1.25)	6.89E-01	0.75	0.73	1.09 (1.07-1.12)	2.44E-13
rs950169	15	84706461	T	0.31	0.21	0.66 (0.45-0.94)	2.48E-02	0.25	0.26	0.92 (0.90-0.95)	1.62E-11
rs9922678	16	9946319	A	0.06	0.04	0.92 (0.68-1.25)	5.97E-01	0.30	0.28	1.07 (1.04-1.09)	1.28E-08
rs7405404	16	13749859	T	0.06	0.05	0.87 (0.63-1.19)	3.88E-01	0.24	0.22	1.08 (1.05-1.10)	1.01E-09
rs12691307	16	29939877	A	0.11	0.11	0.97 (0.75-1.27)	8.37E-01	0.52	0.51	1.07 (1.05-1.10)	4.55E-11

				SLE Cohort				SWG-PGC Cohort†			
rsID	chr	bp	Ref Allele‡	Frq (cases)	Frq (controls)	OR (95% CI)	P-value	Frq (cases)	Frq (controls)	OR (95% CI)	P-value
rs12325245	16	58681393	A	0.24	0.14	0.91 (0.65-1.28)	5.98E-01	0.85	0.86	0.92 (0.89-0.95)	1.87E-08
rs8044995	16	68189340	A	0.23	0.16	0.87 (0.63-1.19)	3.84E-01	0.17	0.16	1.08 (1.05-1.11)	1.51E-08
rs4523957	17	2208899	T	0.15	0.08	0.87 (0.65-1.15)	3.15E-01	0.64	0.63	1.07 (1.05-1.09)	2.86E-10
rs8082590	17	17958402	A	0.30	0.21	1.17 (0.85-1.59)	3.30E-01	0.61	0.61	0.94 (0.92-0.96)	1.77E-08
rs9636107	18	53200117	A	0.11	0.09	1.09 (0.82-1.45)	5.36E-01	0.49	0.50	0.93 (0.91-0.95)	3.34E-12
rs2905426	19	19478022	T	0.19	0.12	1.21 (0.92-1.58)	1.72E-01	0.61	0.63	0.93 (0.91-0.95)	3.63E-10
rs2053079	19	30987423	A	0.09	0.08	0.97 (0.70-1.36)	8.77E-01	0.76	0.77	0.93 (0.91-0.95)	4.49E-09
rs56873913	19	50091199	T	0.08	0.05	1.11 (0.83-1.49)	4.79E-01	0.78	0.77	1.07 (1.05-1.10)	4.69E-08
rs6065094	20	37453194	A	0.13	0.09	1.28 (0.98-1.67)	6.68E-02	0.31	0.32	0.93 (0.91-0.95)	1.46E-11
rs7267348	20	48131036	T	0.32	0.22	0.82 (0.61-1.09)	1.75E-01	0.74	0.75	0.94 (0.92-0.96)	4.56E-08
rs9607782	22	41587556	A	0.14	0.08	1.18 (0.86-1.64)	3.02E-01	0.25	0.23	1.09 (1.06-1.11)	2.07E-11
rs6002655	22	42603814	T	0.18	0.14	1.28 (0.98-1.68)	7.57E-02	0.46	0.44	1.07 (1.04-1.09)	1.71E-09

* Model adjusted for inferred ancestry categories (Admixed, African, East Asian, South Asian)

† Data obtained from the largest schizophrenia GWAS conducted to-date by the Schizophrenia Working Group of the Psychiatric Genomics Consortium(8).

‡ The allele shown is the reference allele for the frequency and odds ratios columns. Note that this is not necessarily the risk allele.

Abbreviations: bp: base pair position; chr: chromosome; CI: confidence interval; cSLE: childhood-onset systemic lupus erythematosus; frq: frequency; GWAS: genome-wide association studies; ref: reference; OR: odds ratio

References

1. Expanded Multi-Ethnic Genotyping Array [Internet]. Illumina; 2015 [cited 2020 Mar 3]. Available from: https://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/mega-ex-data-sheet-370-2015-004.pdf

2. Global Screening Array-24 v3.0 BeadChip [Internet]. Illumina; 2020 [cited 2020 Jul 15]. Available from: https://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/infinium-global-screening-array-data-sheet-370-2016-016.pdf

3. Mills RE, Walter K, Stewart C, Handsaker RE, Chen K, Alkan C, et al. Mapping copy number variation by population-scale genome sequencing. Nature 2011;470:59-65.

4. Rich SS, Akolkar B, Concannon P, Erlich H, Hilner JE, Julier C, et al. Overview of the Type I Diabetes Genetics Consortium. Genes Immun 2009;10 Suppl 1:S1-4.

5. Jia X, Han B, Onengut-Gumuscu S, Chen W-M, Concannon PJ, Rich SS, et al. Imputing amino acid polymorphisms in human leukocyte antigens. Tang J, editor. PLoS ONE 2013;8:e64683.

6. Jakobsson M, Scholz SW, Scheet P, Gibbs JR, VanLiere JM, Fung H-C, et al. Genotype, haplotype and copy-number variation in worldwide human populations. Nature 2008;451:998-1003.

7. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. Genome Res 2009;19:1655-64.

8. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511:421-7.

9. Choi SW, Heng Mak TS, O'Reilly PF. A guide to performing polygenic risk score analyses [Internet]. Genomics; 2018 Sep. Available from: http://biorxiv.org/lookup/doi/10.1101/416545