Title: Schizophrenia Genetics and Neuropsychiatric Features in Childhood-Onset Systemic Lupus Erythematosus

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Abstract

Objectives: We examined the association between schizophrenia genetic susceptibility loci and neuropsychiatric systemic lupus erythematosus (NPSLE) features in childhood-onset SLE (cSLE) participants.

Methods: Study participants from the Lupus Clinic at the Hospital for Sick Children, Toronto, met ≥4 of the ACR and/or SLICC SLE classification criteria and were genotyped using the Illumina MEGA or GSA arrays. Ungenotyped SNPs were imputed, and ancestry was genetically inferred. We calculated two additive schizophrenia weighted polygenic risk scores (PRSs) using: 1) genome-wide significant SNPs ($P<5x10^{-8}$) and 2) expanded list of SNPs with significance $P<0.05$. We defined two outcomes compared to absence of NPSLE features: 1) any NPSLE feature and 2) subtypes of NPSLE features: psychosis and non-psychosis NPSLE. We completed logistic and multinomial regressions, first adjusted for inferred ancestry only and second including variables significantly associated with NPSLE in our cohort ($P<0.05$).

Results: We included 513 participants with cSLE. Median age at diagnosis was 13.8 years (IQR, 11.2-15.6), 83% were female, and 31% were of European ancestry. An increasing schizophrenia GWAS PRS was not significantly associated with NPSLE (OR=1.04, [95%CI 0.87,1.26];*P=0.62*), nor with NPSLE subtypes: psychosis (OR=0.97, [95%CI 0.73,1.29];*P=0.84*) and other non-psychosis NPSLE (OR=1.08, [95%CI 0.88,1.34];*P=0.44*) in ancestry adjusted models. Results were similar for the model including covariates (ancestry, malar rash, oral/nasal ulcers, arthritis, lymphopenia, Coombs-positive hemolytic anemia, lupus anticoagulant and anticardiolipin antibodies), and for the expanded PRS estimates.

Conclusion: We did not observe an association between known risk loci for schizophrenia and NPSLE in a multiethnic cSLE cohort. This work warrants further validation.

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Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune disease with varying clinical presentations that can affect virtually any organ system. Genetics plays and important role in SLE susceptibility with heritability estimates of up to 66% and over 100 susceptibility single nucleotide polymorphisms (SNPs).(1) Genetics also contribute to the risk of developing certain SLE clinical features, including neuropsychiatric SLE (NPSLE).(2)

NPSLE features are heterogeneous, can involve the peripheral or central nervous system, and include psychosis, other non-psychosis features (e.g., acute confusional state, cerebrovascular diseases, seizures) and less SLE-specific symptoms such as headaches and mood or anxiety disorders.(3) The prevalence of NPSLE in childhood-onset SLE (cSLE) is estimated to be up to 95% depending on the NPSLE case definition used.(4) While there is no gold-standard for NPSLE diagnosis, the American College of Rheumatology (ACR) published case definitions for NPSLE in 1999.(3)

Morbidity and mortality vary across cSLE cohorts. Some studies of cSLE participants show that when compared to cSLE without NPSLE, NPSLE is associated with disease-associated damage. Damage most frequently occurring includes cataracts, the musculoskeletal, neuropsychiatric, and renal systems.(5–7)

Schizophrenia is a severe, chronic psychiatric disorder with heterogeneous manifestations including hallucinations, delusions, cognitive impairment and disorganized or abnormal motor behaviour. It is strongly influenced by genetics, with heritability estimates of nearly 80% and over 100 risk loci identified using genome-wide association studies (GWAS).(8) These prior GWAS demonstrate that schizophrenia is a polygenic disease, with many risk loci also linked

with other disorders such as autism spectrum disorder, bipolar disorder and major depressive disorder.(8,9)

Large-scale studies have also demonstrated significant comorbid and genetic associations between schizophrenia and several autoimmune diseases, including SLE.(10,11) Schizophrenia GWAS have identified risk loci in the major histocompatibility complex (MHC), which encodes numerous immune-related genes involved in antigen presentation and inflammation. Other schizophrenia genetic risk loci associated with immunity outside of the MHC region have also been found, such as those encoding for CD19 and CD20 B-lymphocytes. These suggest that inflammation and immune dysregulation may be important disease mechanisms for schizophrenia.(8) No study to date has examined the relationship between genetic risk loci for schizophrenia and NPSLE risk. The purpose of this study was to examine the association between polygenic risk scores (PRS) for schizophrenia and NPSLE and specific NPSLE features, in a multi-ethnic cohort of participants with cSLE. This approach enabled testing for pleiotropy (one gene influences two or more unrelated phenotypes) with schizophrenia and NPSLE, as well a link between schizophrenia genetic risk and NPSLE in children and adolescents with SLE.

Materials and Methods

Study population

The study cohort included participants diagnosed and followed for cSLE between 1983 and 2018 in the Lupus Clinic at the Hospital for Sick Children (SickKids), a tertiary care centre in Toronto, Canada. Participants met 4 or more of the 1997 ACR revised criteria for SLE diagnosis and/or the 2012 SLE International Collaborating Clinics (SLICC) criteria.(12,13)

Genotyping and imputation

Participants were genotyped using the Illumina Multi-Ethnic Global Array (MEGA) or the Global Screening Array (GSA).(14,15) Genotyping was conducted following protocols specified by The Centre for Applied Genomics (TCAG) at SickKids (Please find quality control [QC] measures in the Supplementary Methods). 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.(16) For participant with inferred European ancestry, human leukocyte antigen (HLA) allele dosages were imputed using SNP2HLA and Type 1 Diabetes Genetics Consortium as a reference.(17,18)

Polygenic risk score (PRS) calculations

We selected SNPs for inclusion in schizophrenia PRSs based on the most comprehensive schizophrenia GWAS conducted to date by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG-PGC).(8) Utilizing the SWG-PGC PRS calculation for schizophrenia, and QC procedures as guiding principles (Supplementary Methods), we computed two PRSs using: 1) genome-wide significant SNPs ($P<5x10^{-8}$) and 2) an expanded set of SNPs showing significance at a threshold of $P<0.05$. After excluding SNPs via QC procedures, the GWAS PRS included 76/128 SWG-PGC SNPs and the extended PRS included 15,305/24,850 SNPs.

We used these SNPs to calculate 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)

Outcome measures

Demographic, clinical and laboratory features for all participants were extracted from the SickKids Lupus Database, with details supplemented by medical records when required. NPSLE features were defined using the 1999 ACR list of case definitions for NPSLE.(3) Features were independently validated by two pediatric rheumatologists (R.C. and T.D.). In the case of discrepancies, additional pediatric rheumatologist (L.H., A.K., D.L.) acted as tiebreakers. We defined two outcomes compared to absence of NPSLE features: 1) Any NPSLE feature and 2) Subtypes of NPSLE features: psychosis and non-psychosis NPSLE features.

Covariates

Ancestry was inferred using 1KGP and the Human Genome Diversity Project (HGDP) as referents (Supplementary Methods). The software tool ADMIXTURE was used to estimate relative proportions of ancestral groups within discordant subjects.(19) 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".

We also calculated SLE non-HLA PRSs in all participants and SLE HLA PRSs in ancestral European participants, by weighting allele dosages using log(ORs) obtained from the largest multi-ethnic SLE GWAS study conducted to-date.(1)

Statistical analyses

We calculated counts and proportions for categorical variables and median and interquartile range (IQR) for continuous variables. We compared the characteristics of those with and without NPSLE using Chi-squared statistics for categorical values and Wilcoxon rank sum test for continuous variables.

We tested the association between PRSs for schizophrenia and NPSLE using logistic and multinomial logistic regression. We ran univariate models and multivariable models adjusted for: 1) inferred ancestry categories (European, Admixed, African, East Asian, South Asian) and 2) variables significantly associated with NPSLE in our cohort ($P<0.05$). We conducted the multivariable adjusted analysis to account for NPSLE risk and increase power to detect genetic effects in our cohort. We calculated ORs, 95% confidence intervals (CIs) and P-values.

We also tested the association between each of the following and NPSLE: each individual genome-wide significant SNP (using a Bonferroni-corrected P-value threshold of $6.58x10^{-4}$ [0.05/76]) and two SNPs located in the major histocompatibility complex (MHC) region (rs115329265 and rs114541829) that were significant at a threshold of $P<0.05$ in the SWG-PGC study but not included in their PRS calculations. To test the association between known SLE susceptibility loci and NPSLE, we regressed SLE non-HLA PRSs and NPSLE, and SLE HLA PRSs and NSPLE among European participants.

We completed three sensitivity analyses for less NPSLE-specific features of headache, anxiety and/or mood disorders. First, we censored these participants from analyses. Second, we included them as controls, and third, we included them in their own subcategory of NPSLE features. All analyses were conducted in R version 3.6.3.(20) This project was approved by the SickKids Institutional Research Ethics Board (REB #1000058324).

Results

Our study cohort consisted of 513 participants, of which 424 (83%) were female, with a median age at SLE diagnosis of 13.8 years (IQR, 11.2-15.6 years) and a median duration of follow-up of 4.6 years (IQR, 2.8-7.5 years). Genetically inferred ancestry indicated that most

participants were European (N=157, 31%) or East Asian (N=143, 28%). Four-hundred and seventy-one participants were genotyped on the MEGA array, and 42 were genotyped on the GSA array. A total of 201 had any NPSLE feature (39%) (Table 1). Inferred ancestry categories, malar rash, oral or nasal ulcers, arthritis, lymphopenia, Coombs-positive hemolytic anemia, and lupus anticoagulant (LAC) and/or anticardiolipin (aCL) antibodies were all significantly associated with NPSLE in our cohort (P<0.05) (Table 1). Of the 201 participants with NPSLE, subtype classification resulted in 60 (30%) participants with psychosis as a feature and 141 (70%) with non-psychosis features (Table 2).

An increase in the GWAS PRS for schizophrenia was not significantly associated with increased odds of having any NPSLE feature versus no features (OR=1.04, [95% CI 0.87, 1.26]; *P=0.62*) in ancestry adjusted models (Table 3). Similarly, an increase in the GWAS PRS for schizophrenia was not significantly associated with increased odds of having psychosis (OR=0.97, [95% CI 0.73,1.29]; *P=0.84*) or other non-psychosis NPSLE features (OR=1.08, [95% CI 0.88,1.34], *P=0.45*) compared to no NPSLE. Results did not differ significantly in the univariate or full multivariable adjusting models (Table 3), nor for the expanded schizophrenia PRS which remained non-significant (Supplementary Table 1).

Analyses of individual schizophrenia GWAS SNPs with NPSLE risk in ancestry adjusted models indicated no significant associations with NPSLE (Supplementary Table 2). Additional analyses of two schizophrenia risk SNPs in the MHC region that were excluded from the PRS calculations demonstrated a marginally significant association with NPSLE for rs115329265, (Allele G OR=0.69, [95% CI 0.48, 0.97] *P*=0.04) and no significant association for rs114541829 (Allele G, OR=1.00, [95% CI 0.58,1.73]; *P*=1.00). We repeated these analyses in the European subset of our cohort (N=157) however, results were not significant (Results not shown).

SLE non-HLA PRSs were normally distributed across our study population (P=0.86). There was no significant association between SLE non-HLA PRS and NPSLE in the total cohort in ancestry adjusted models (OR=1.21, [95% CI 0.98, 1.49]; *P=0.07*). Results were similar when adjusted for all significant covariates (Results not shown).

Of the 157 participants of European inferred ancestry, 76 (48%) had at least one NPSLE feature. SLE HLA PRSs were not normally distributed across this population ($P=1.04x10^{-5}$). The distribution of SLE HLA PRSs was not significantly different between participants without NPSLE and those with NPSLE (P=0.64). There was no significant association between SLE HLA PRS and NPSLE (OR=1.17, [95% CI 0.83, 1.67]; *P*=0.37) in the multivariable adjusted model.

In sensitivity analyses, by (1) censoring participants with headaches, anxiety and/or mood disorders as their only NPSLE features, (2) including them as controls, or (3) including them in their own subcategory of NPSLE features, we did not find an association between the schizophrenia PRSs and NPSLE (Results not shown).

Discussion

Our study found no significant association between schizophrenia PRSs and overall NPSLE risk, or with specific NPSLE features. We also did not find a significant association between SLE susceptibility loci and NPSLE. In this multiethnic cohort of patients with cSLE, there was no evidence for shared risk between schizophrenia genetic susceptibility loci and NPSLE.

The prevalence of NPSLE in our cohort was consistent with previous reports of NPSLE among cSLE cohorts at 39%, with a high prevalence of headaches (31%), psychosis (12%), and

cognitive dysfunction (10%).(21) While several studies utilize the 1999 ACR classification criteria to define NPSLE features, there remains a lack of case definition standardization.(21) Depending on the manifestations and diagnostic methods, the prevalence of NPSLE reported varies between 22%-95% among cSLE cohorts.(21) Recognizing these discrepancies, we examined not only overall NPSLE risk, but also NPSLE risk by subtypes, given our large cohort and detailed clinical and laboratory data to classify participants into specific subtypes. We defined two NPSLE subphenotypes: psychosis and non-psychosis NPSLE, focusing on the clinical similarity between psychosis in NPSLE and schizophrenia to define subtypes.(22) Our sensitivity analyses accounted for potential misclassifications of NPSLE status. With these groupings, we assumed similar relationships between genetic risk and each of the features within each category.

The SWG-PGC study from which we selected SNPs for inclusion in our study represents the largest schizophrenia GWAS study conducted to date, including almost 37,000 cases and over 113,000 controls and it tested over 9 million SNPs.(8) More recently, other GWAS studies have looked at endophenotypes (referring to phenotypes associated with a particular disease with a strong genetic component) associated with schizophrenia and cross-disorder analyses have looked at the genetic association between schizophrenia and other psychiatric or immune-mediated disorders, yet the SWG-PGC study remains the largest cohort to date as well as the one to have tested the most SNPs to date.(9–11) Some of these studies have found shared genetic risks between SLE and schizophrenia to be mediated primarily by HLA alleles.(10,23) We found non-significant and marginally significant associations between two individual schizophrenia SNPs in the MHC region and overall NPSLE risk in our cohort suggesting a distinct

pathobiology for schizophrenia and NPSLE in cSLE; however, our findings warrant further validation.

Our study findings should be considered in light of some limitations. Our cSLE cohort was multi-ethnic, yet susceptibility loci for schizophrenia were derived from a primarily European GWAS.(8) As a result, we may have excluded important non-European susceptibility loci from our PRSs. In recent years, there has been an effort to improve representation of ancestral diversity world populations in genetic studies. However, until the sample sizes for these studies are sufficient, our ability to draw inferences from non-European populations are limited.(24,25) A multiethnic schizophrenia meta-GWAS in East Asian and European populations found 53 novel loci.(24) Yet, the total number of cases included this meta-GWAS was still 15,000 less than the GWAS in Europeans that we used to select SNPs for our PRSs. By using the largest GWAS to date, we are including the most robust risk loci for schizophrenia. Due to the highly polymorphic nature of the MHC region, and lack of reliable non-European HLA reference populations, we could only examine HLA alleles in Europeans.(10,23) Neuropsychological evaluations were not routinely completed in all patients. Neurocognitive function was determined by physician diagnosis. Efforts were made to avoid diagnostic biases by having two pediatric rheumatologists independently validate NPSLE features as described in the methods. Finally, our analyses may have lacked sufficient power to detect significant associations, particularly, in the NPSLE subtypes analyses, and analyses stratified by ancestry.

Our study had several strengths. It is the first to examine the association between genetic risk loci for schizophrenia and NPSLE specifically. The detailed clinical, laboratory and genetic data for this large multi-ethnic cSLE cohort allowed us to look not only at overall NPSLE risk

but also at specific subtypes, and to control for covariates associated with NPSLE in our cohort including ancestry, the presence of arthritis, lymphopenia, and antiphospholipid antibodies.

We did not observe a significant association between genetic risk loci for schizophrenia and NPSLE in a multiethnic cohort of children and adolescents with SLE. Our study is the first of its kind and requires additional validation in adult-onset SLE cohorts and independent childhood-onset SLE cohorts. Our observed lack of association between schizophrenia risk loci and NPSLE, does not obviate a role for genetics for NPSLE risk. A genome-wide interrogation of NPSLE specific manifestations is warranted. Knowledge of the genetics of NPSLE will provide a better understanding of the molecular mechanisms driving this complex disease, ultimately improving therapy and outcomes for people with SLE.

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Table 1. Demographic characteristics, clinical and laboratory features of cohort (N=513)

Variable	Participants with any NPSLE feature (N=201)	Participants with no NPSLE features (N=312)	P-value
Female sex [n (%)]	166 (83)	258 (83)	1.00
Age at SLE diagnosis, years [median (IQR)]	14.2 (11.7-15.7)	13.5 (11.2-15.5)	0.17
Duration of follow-up, years [median (IQR)]	5.2 (3.0-7.8)	4.5 (2.5-7.3)	0.12
Inferred ancestry [n (%)]			<0.01
European	76 (38)	81 (26)	
Admixed*	51 (25)	69 (22)	
East Asian	41 (20)	102 (33)	
African	17 (8)	37 (12)	
South Asian	16 (8)	23 (7)	
Clinical Features (ever) [n (%)]			
Malar rash	170 (85)	236 (76)	0.02
Oral or nasal ulcers	96 (48)	114 (37)	0.02
Arthritis	161 (80)	206 (66)	<0.01
Serositis†	36 (18)	50 (16)	0.66
Myositis	17 (8)	15 (5)	0.14
Lupus nephritis (any)	80 (40)	133 (43)	0.59
Mesangial LN	11 (5)	12 (4)	0.52
Proliferative LN	61 (30)	103 (33)	0.59

Membranous LN	19 (9)	47 (15)	0.09
Mixed proliferative/membranous LN	8 (4)	25 (8)	0.10
SLE laboratory features [n (%)]			
Thrombocytopenia	60 (30)	90 (29)	0.88
Lymphopenia	161 (81)	213 (68)	<0.01
Coombs-positive hemolytic anemia	79 (39)	94 (30)	0.04
Specific autoantibodies [n (%)]			
Anti-dsDNA	134 (67)	229 (73)	0.12
Anti-Sm	89 (44)	117 (38)	0.15
Anti-RNP	95 (47)	136 (44)	0.47
Anti-Ro	82 (41)	111 (36)	0.27
Anti-La	27 (13)	64 (21)	0.05
LAC and/or aCL antibodies	106 (53)	132 (42)	0.03
Lupus anticoagulant	40 (20)	39 (13)	0.03
Anticardiolipin	95 (47)	115 (37)	0.02

* Admixed category includes participants with <80% single ancestral proportion as well as those of Amerindian (N=15) ancestral proportion due to sample size restrictions.

† Pericarditis and/or pleuritis.

Abbreviations: aCL: anticardiolipin; Anti-dsDNA: anti-double-stranded DNA; aPL: antiphospholipid; IQR: interquartile range; LAC: lupus anticoagulant; LN: lupus nephritis; NPSLE: neuropsychiatric SLE; SLE: systemic lupus erythematosus

Table 2. Characteristics of NPSLE features among study cases by category

NPSLE features*		N=201 (%)
Psychosis†		60 (30)
Non-psychosis NPSLE		141 (70)
	Headaches	117 (58)
	Cerebrovascular disease	23 (11)
	Cognitive dysfunction	16 (8)
	Seizure disorder	13 (6)
	Mood disorder	5 (3)
	Acute confusional state	4 (2)
	Anxiety	3 (1)
	Movement disorder	3 (1)
	Myelopathy	2 (1)
	Neuropathy, cranial	2 (1)
	Aseptic meningitis	1 (0.5)

* While NPSLE subtype categories are mutually exclusive, features within each category are not mutually exclusive.

† Participants with psychosis also had the following NPSLE features: headaches (N=44), cognitive dysfunction (N=36), mood disorder (N=25), anxiety (N=10), acute confusional state (N=6), cerebrovascular disease (N=6), seizure disorder (N=6) and movement disorder (N=2).

Table 3. Association between NPSLE, NPSLE subtypes and schizophrenia GWAS PRS*

	OR (95% CI) p-value					
Variable	Any NPSLE †		Psychosis ‡		Non-psychosis NPSLE ‡	
Unadjusted GWAS PRS	1.06 (0.89 - 1.26)	0.54	1.00 (0.76 – 1.32)	0.98	1.08 (0.89 – 1.32)	0.44
Ancestry adjusted GWAS PRS	1.04 (0.87 - 1.26)	0.62	0.97 (0.73 - 1.29)	0.84	1.08 (0.88 - 1.34)	0.45
Full multivariable adjusted GWAS PRS§	1.05 (0.87 - 1.28)	0.62	0.98 (0.73 - 1.32)	0.91	1.08 (0.87 - 1.34)	0.48

* 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