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Evaluation of HLA Polymorphisms in Relation to Schizophrenia Risk and Infectious Exposure

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Background: **Genome-wide association studies (GWAS) implicate single nucleotide polymorphisms (SNPs) on chromosome 6p21.3-22.1, the human leukocyte antigen (HLA) region, as common risk factors for schizophrenia (SZ). Other studies implicate viral and protozoan exposure. Our study tests chromosome 6p SNPs for effects on SZ risk with and without exposure.** ***Method:*** **GWAS-significant SNPs and ancestry-informative marker SNPs were analyzed among African American patients with SZ (n = 604) and controls (n = 404). Exposure to herpes simplex virus, type 1 (HSV-1), cytomegalovirus (CMV), and *Toxoplasma gondii* (TOX) was assayed using specific antibody assays. Results: Five SNPs were nominally associated with SZ, adjusted for population admixture (P < .05, uncorrected for multiple comparisons). These SNPs were next analyzed in relation to infectious exposure. Multivariate analysis indicated significant association between rs3130297 genotype and HSV-1 exposure; the associated allele was different from the SZ risk allele.** ***Conclusions:*** **We propose a model for the genesis of SZ incorporating genomic variation in the HLA region and neurotropic viral exposure for testing in additional, independent African American samples.**

Key words: HLA/gene/HSV-1/cytomegalovirus/schizophrenia/African American

Introduction

Recent genome-wide association studies (GWAS) have detected risk for schizophrenia (SZ) associated with polymorphisms in the chromosome 6p/human leukocyte antigen (HLA) region.[1–3] Combined data from independent Caucasian ancestry samples, comprising SZ cases (n = 12 945) and controls (n = 34 591) indicated significant associations corrected for multiple comparisons at 5 SNPs, localized to chromosome 6p21.3-22.1; genomic locations from 27.2 Mb to 32.3 Mb (National Center for Biotechnology Information map, Build 36).[1–3] Follow-up studies using additional Caucasian samples

continue to support associations with these and additional SNPs in the HLA region.[4,5] Our prior candidate gene studies have also reported associations with different HLA polymorphisms in several ethnic groups.[6–11] The risk conferred by individual variants in the HLA region is modest, with most odds ratios (ORs) in the 1.15–1.80 range. The risk due to any one marker could not account for all the associations, suggesting multiple risk loci.[2] Further, no functional significance could be ascribed to the associated SNPs, although some of them are in linkage disequilibrium (LD) with HLA markers and other SNPs associated with infectious exposure and autoimmune diseases.[2]

In this study, we further investigated the HLA associations with SZ as they are related to exposure to infectious agents. HLA polymorphisms are known to influence immune surveillance and there are reports of neurotropic infectious agents as risk factors for SZ.[12,13] Although a variety of viral agents have been proposed as putative SZ risk factors, including *Toxoplasma gondii* (TOX), a protozoan parasite,[14,15] many of the studies have not been consistent. It is possible that the lack of consistency stems from the failure to investigate host genetic variations. In support, our prior analyses suggest interactions between host HLA polymorphisms and exposure to herpes simplex virus type 1 (HSV-1) and cytomegalovirus (CMV).[10,11] We reported that exposure to CMV is increased among multiplex SZ families versus simplex families (OR 2.47, 95% confidence interval, CI = 1.48–5.33).[10] In those earlier studies, we further suggested that CMV exposure increases risk for SZ among Caucasians when considered in conjunction with host genetic variability in the HLA region.[10,16] Therefore, in this study variation in the HLA region was analyzed in conjunction with exposure to TOX, as well as HSV-1 and CMV. We investigated cases and controls from an African American multisite collaborative study called the Project Among African Americans to Explore Risks for Schizophrenia (PAARTNERS).[17]

Methods

Design of the Study

Our goal was to evaluate published HLA/SZ associations. Using a case-control design and a nominal threshold of statistical significance, we initially evaluated individual SNPs previously reported to be associated with SZ (see online supplementary table 1). The associated SNPs were then individually screened in relation to exposure to 3 putative infectious risk agents for SZ.

Participants

Unrelated SZ/schizoaffective disorder (SZA) cases (n = 604) and screened adult controls (n = 404) with self-reported African American ancestry were evaluated through the PAARTNERS study.[17,18] Briefly, all participants were interviewed using the Diagnostic Interview for Genetic Studies. Additional clinical information was obtained from medical records and consenting relatives. The detailed information was used to obtain consensus diagnoses based on DSM-IV criteria. All participants provided blood samples.

Venous Blood Collection and DNA Extraction

Venous blood was obtained from participants and genomic DNA extracted using the phenol chloroform method as described.[19] Serum was extracted from coagulated blood following centrifugation.

Genotype Assays

SNPs were genotyped primarily using iPLEX, a multiplexed single base extension method using the MassArray MALDI-TOF MS detection platform (SequenomInc.) (http://www.sequenom.com/getdoc/197b98fa-93f7-40e8-9deb-a8dcfecf899e/iPLEX-brochure_web/). SNPs unsuitable for iPLEX were assayed using the multiplexed SNaPshot platform (Applied Biosystems, New Jersey)

Table 1. Comparisons Between Cases and Controls

				Exposure Rates#[a]			
	N	Age (Years)	Gender (Male/Female)	CMV	HSV-1	TOX	Population Admixture
Controls	404	41.0 (14.6)[*]	178/226 (44%)[**]	77.50%	67%	20.60%	0.185 (0.068)
Cases	604	38.5 (11.4)	393/211 (65%)	66.80%	69.90%	26.30%	0.182 (0.067)

Note: Continuous variables shown as mean (standard deviation). Gender proportions shown as male/female, with proportion of men in brackets. Population admixture was estimated using LAMP software.
[a]Exposure to cytomegalovirus (CMV), herpes simplex virus, type 1 (HSV-1) and *Toxoplasma gondii* (TOX) not significantly different between cases and controls, after correcting for age and gender.
[*]Controls significantly older than cases, $P = .005$, $t = 2.83$, $P = .005$, equal variances not assumed.
[**]Significantly higher proportion of men among cases, $P = 4.96 \times 10^{-11}$; $\chi^2 = 43.5$, 1 degree of freedom.
[***]$P = 9.72 \times 10^{-25}$, $t = 10.76$, equal variances not assumed.

(http://www3.appliedbiosystems.com/cms/groups/mcb_support/documents/generaldocuments/cms_041203.pdf). One SNP (rs2517614) was genotyped by Sanger sequencing. All assays included Centre d'Etude du Polymorphisme Humain (CEPH) samples with known genotypes, as well as blind duplicates and negative samples. Genotypes were read blind to case/control status. Assays were repeated for ambiguous genotypes.

SNP Selection

(i) SNPs that showed the most significant associations in GWAS studies were selected (n = 16, see online supplementary table 1); (see table 2 in Shi et al).[1] This list includes rs2517614, a SNP which is in substantial LD with rs2021722 (r^2 = 0.93), the most significantly associated SNP in a recent mega analysis.[5]
(ii) Ancestry-informative markers (AIMs) suitable for analysis of African ancestry were assayed (n = 22) (see online supplementary table 2).[20]

SNPs for which satisfactory genotypes could not be generated were replaced with tag SNPs in LD (r^2 > 0.9). The relative locations of chromosome 6p SNPs and their LD patterns are provided in figure 1 and online supplementary figure 1, respectively.

Serological Assays

The titers of IgG antibodies to HSV-1, CMV, and TOX were estimated using solid phase enzyme immunoassay kits (obtained from KMI Diagnostics Inc, Minneapolis).[21,22] Using cutoff values based on internal controls and the manufacturer's recommendations, individuals were classified as exposed (raised titers) or unexposed to the appropriate infectious agent.[16]

The study was approved by the Institutional Review Boards (IRB) at the participating collaborative sites. Written informed consent was obtained from all participants in accordance with IRB guidelines.

Statistical Analysis

Associations between individual SNPs and SZ risk were initially tested among the cases and controls using logistic regression analysis. Case-control status was the outcome, with SNP minor allele dosage as the predictor variable, co-varying for admixture proportion. Logistic regression analyses were also used to evaluate interactions between SNPs and exposure variables in relation to SZ risk using case/control status as the outcome and individual SNP genotype, exposure variable, admixture proportion, and demographic variables as covariates. Corrections for multiple comparisons were not applied.

To test for associations with viral and TOX exposure, separate logistical regression analyses were conducted for each infectious agent with serological status (exposed/unexposed) as the outcome. Minor allele dose for each SZ-associated SNP, age, gender, group status (case/control), and admixture proportion were used as covariates. These analyses were conducted using participants with available serological data (n = 749). Population admixture was estimated from the AIMs using LAMP software,[23] assuming 2 populations. Ancestral allele frequencies were estimated using HAPMAP CEU and YRI genotypes.

Results

Case-Control Comparisons for Demographic, Serological and Admixture Variables

Cases were significantly younger than controls. There were proportionately more men among the cases. Cases and controls did not differ significantly with respect to exposure rates for CMV, TOX, or HSV-1, following

Table 2. Chromosome 6p Single Nucleotide Polymorphisms With Nominally Significant Associations

						CMV Exposure		HSV-1 Exposure		TOX Exposure	
SNP	Gene	Position	Minor Allele	OR	*P*	OR	*P*	OR	*P*	OR	*P*
rs9393709*	*BTN3A2*	26365147	T	0.79	0.01	0.99	0.94	1.02	0.87	1.08	0.54
rs12199613*	*BTN3A2*	26367218	T	0.79	0.02	0.99	0.96	1.022	0.86	1.08	0.56
rs12214031*	*BTN3A2*_3UTR	26376628	C	0.76	0.0043	0.99	0.92	1.014	0.91	1.11	0.42
rs6932590	Intragenic	27248931	C	0.76	0.0074	1.16	0.27	1.011	0.93	1.03	0.81
rs3130297**	Intragenic	32198981	A	0.41	0.0007	1.55	0.28	4.76	0.004	1.00	1.00

Note: SNP, single nucleotide polymorphism, OR, odds ratio; CMV, cytomegalovirus; HSV-1, herpes simplex virus, type 1; TOX, *Toxoplasma gondii*. Nucleotide positions are based on NCBI build 36.1. Associations with individual SNPs were tested using logistic regression analysis, with case-control status as the outcome, genotypes for the relevant SNP and estimates for admixture proportion as covariates. Only SNPs associated with schizophrenia at P = .05 or better are listed.
*rs3734536, one of the associated SNPs in the published GWAS could not be assayed reliably, so these surrogates were selected (linkage disequilibrium, r^2 > 0.9).
**rs3130297: Allele G associated with schizophrenia risk; allele A (minor allele) associated with exposure to HSV-1.

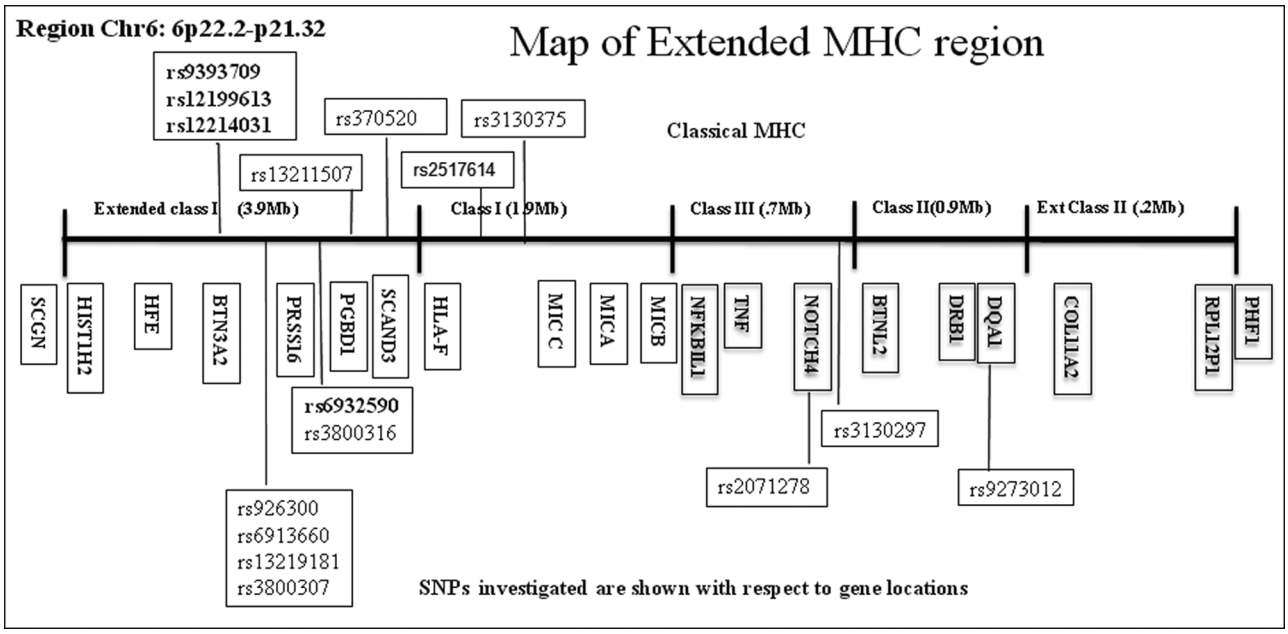

Fig. 1. Single nucleotide polymorphisms in the human leukocyte antigen region analyzed in this study.

correction for age and gender. There were no significant case-control differences with respect to the individual estimates for admixture (table 1).

Associations Between SZ and Individual SNP Genotypes

Nominally, significant associations with SZ were noted for 5 SNPs (see table 2; rs12214031—*BTN3A2*_3UTR, $P = .004$; rs9393709—*BTN3A2*, $P = .015$; rs12199613—*BTN3A2*, $P = .016$, rs6932590, $P = .007$; rs3130297, $P = .0007$; uncorrected for multiple comparisons).

Associations Between Infectious Agent Exposure and SZ-associated SNPs

To evaluate associations between infectious agent exposure and SNPs associated with SZ from table 2, logistic regression analysis was used for each SNP that was associated with SZ, with exposure status as the outcome. HSV-1 exposure was nominally associated with rs3130297, one of the SNPs associated with SZ ($P < .05$, table 2). At this SNP, allele A (minor allele) was associated with HSV-1, while the major allele (G) was associated with SZ risk. None of the other SNPs were significantly associated with HSV-1, CMV, or TOX exposure.

Discussion

Our goal was to evaluate previously reported GWAS results in the HLA region. We detected nominally significant associations between SZ and 5 SNPs. The associated alleles are consistent with the published GWAS reports, although an earlier GWAS study of African Americans did not detect genome-wide significant associations in the HLA region.[1] rs3130297, one of the SZ-associated SNPs is also associated with exposure to HSV-1 but the risk alleles differ. The allelic differences are reminiscent of a Caucasian ancestry sample in which we reported that the alleles of an exonic SNP at the *MICB* locus in the HLA region were associated with SZ or with CMV exposure.[11]. The basis for such associations is uncertain as there is no known functional effect of the sequence variation at rs3130297. They could indicate an epistatic effect at rs3130297 or a SNP in LD with it. Published studies indicate that exposure to HSV-1 is associated with impairment in specific cognitive domains among SZ patients and community-based control individuals,[16,24–27] although an association between HSV-1 exposure and SZ risk per se has not been convincingly demonstrated.[28] Nevertheless, our results provide a testable model summarized in figure 2.

There are some shortcomings in our analyses. We did not correct the initial genetic association analyses for multiple comparisons, as the type of correction necessary for previously associated GWAS SNPs is uncertain. Further evaluations of our results are therefore necessary in other independent samples, preferably with African American ancestry. The replicate samples would necessarily require available DNA and serum samples. Another concern is that exposure to infectious agents was indexed indirectly using antibody titers in the serum because demonstration of the viruses in the host target tissues is difficult.[29,30] The serological assays clearly indicate infectious exposure, but do not reveal when it occurred. The timing of the exposure may be a critical determinant of viral effects

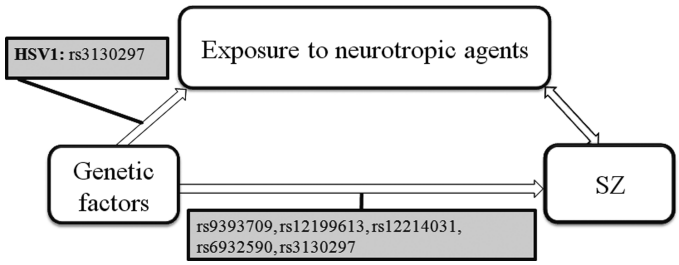

Fig. 2. Model incorporating genetic variation, viral exposure, and schizophrenia risk.

on neurodevelopment thought to be critical for SZ pathogenesis.

In conclusion, our analyses suggest a complex relationship between individual genomic variability, exposure to infectious agents, and SZ risk. The associations suggest a testable model of SZ genesis.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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