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Primary sclerosing cholangitis in genetically diverse populations listed for liver transplantation: Unique clinical and HLA associations

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Abstract

Primary sclerosing cholangitis (PSC) is well characterized in European populations. We aimed to characterize clinical characteristics and human leukocyte antigen (HLA) associations in a population of European American, Hispanic and African-American PSC patients listed for liver transplantation. Demographic, clinical, and HLA data stratified by population from 6,767 liver transplant (LT) registrants of the United Network for Organ Sharing (UNOS) with a diagnosis of PSC (4.7% of registrants) were compared to registrants with other diagnoses. Compared to European Americans and Hispanics, African American cases were significantly younger (46.6 ± 13.7, 42.3 ± 15.9, and 39.7 ± 13.1, respectively; $p = 0.002$), listed with a higher Model of End Stage Liver Disease (MELD) score (15.2 ± 7.5, 14.9 ± 7.6, and 18.1 ± 9.3, respectively; $p = 0.001$), and less frequently noted to have inflammatory bowel disease (71.4% versus 60.5%, $p < 0.01$) compared to European Americans. In multivariate analysis, African origin was a significant factor associated with listing for LT with PSC (OR relative to European Americans 1.33, 95% C.I. 1.27 – 1.41). HLA associations in European Americans, Hispanics and African Americans with PSC compared to alcoholic liver disease were detected for HLA-B8, HLA-DR13 and the protective HLA-DR4. However, HLA-DR3, which is in linkage disequilibrium with HLA-B8, only showed associations in European Americans and Hispanics. African Americans with PSC listed for LT differ clinically from European Americans and Hispanics. The association with HLA-B8 but not HLA-DR3 in African Americans should make possible the refinement of the HLA associations in PSC.

Keywords

Primary sclerosing cholangitis; Epidemiology; Genetics; Human leukocyte antigen; Liver transplantation

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Introduction

Primary sclerosing cholangitis (PSC) is a progressive, chronic inflammatory disease of the biliary tree for which there is no established therapy other than liver transplantation (LT) [1]. Several large case series and a few population based studies have established that PSC affects men more commonly than women and that coexisting inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC), is diagnosed in approximately 60–80% of PSC cases. All age groups are affected by PSC with the peak incidence typically in the fourth decade of life and an average time from diagnosis to death or LT of 10–18 years [2,3]. The prevalence of PSC seems to be approximately 1/10,000 in populations of Northern European descent [4–8], whereas in Southern Europe and Asia 10 to 100-fold lower numbers have been reported [9,10].

Several small case series have assessed the clinical characteristics of PSC in Asia, South America and the Middle East [11–14] showing that the most prominent difference versus Northern Europe is a low frequency of IBD. Similarly, variable prevalence of IBD and IBD phenotypes in different populations has been firmly established [15]. So far, the genetic predisposition to PSC outside Europe has not been studied. In populations of Northern European origin, recent genome-wide association studies have pointed out that the HLA complex on chromosome *6p21* by far constitutes the most important risk locus [16], and a series of previous studies have established associations with several class I and class II alleles. The HLA variants are closely correlated, and as exemplified in other diseases [17], assessment of HLA associations in the admixed African American population may help to conclusively define the causative genes in this region.

On this basis we set out to determine whether population differences exist in the clinical characteristics of PSC patients listed for LT in the US. In addition, we aimed to define shared and distinct features with regard to the distribution of HLA alleles in the different groups. Because PSC does not have a unique ICD-9 code, epidemiologic studies of large medical databases have been problematic. Thus, to accomplish our goals we utilized the United Network for Organ Sharing (UNOS) database for LT listings. Despite the biases inherent in this database including access to LT and disease severity, its large size and comprehensive data collection allowed us to assess population differences in patients listed for liver transplantation with and without a diagnosis of PSC.

Patients and Methods

Patient dataset

The study was performed with data from LT registrants (n = 175,302) captured by the United Network for Organ Sharing (UNOS) database as of May 26, 2009. We limited the dataset to cases registered after 1995 ($n = 144,208$) because diagnosis at listing was not consistently specified prior to that time. The diagnosis of PSC was based upon the diagnosis at listing. IBD diagnosis was based upon the specific PSC diagnosis code that designates each PSC case as having UC, Crohn's disease (CD), no bowel disease, or other. To adjust for potential socioeconomic factors, the zip code of residency at the time of registration was used to impute socioeconomic status based on 2000 US Census data. Specifically, zip codes were associated with the percentage of household ownership and the percentage of the population living in urban areas as defined by the US Census Bureau. Although educational status, insurance status and working status are collected in the UNOS registry, data was missing in greater than 50% of cases for each of these variables and therefore were not included in our analysis.

In the comparison of HLA alleles, only cases with available HLA-typing were included (n = 3,755). For controls we used ethnically-matched listings with a primary diagnosis at listing of alcoholic liver disease (ALD) (n = 6,991) as opposed to organ donors because of the lack of association of HLA genes with ALD [18]. We excluded controls with any secondary diagnosis, positive hepatitis C antibody or positive hepatitis B surface antigen.

Statistical analysis

Statistical analyses were performed using SPSS Statistics v 17.0 (SPSS, Inc., IL). For non-normally distributed data, comparisons of group medians among ethnic groups were made using Kruskal-Wallis test followed by the Bonferroni correction for multiple hypothesis testing (significant if $P < 0.05/3$ for pair-wise comparisons). Categorical patient characteristics among the different populations were compared using the Chi squared test. Multiple logistic regressions were used to determine the independent effects of age at listing, ethnicity, gender, and socioeconomic status on the relative odds of listing for LT with a diagnosis of PSC.

The frequencies of HLA alleles in patients and controls were compared by the Chi squared test. Haplotype frequencies were estimated using PHASE v2.1 [19]. The P values were corrected for the number of comparisons only for associations not previously published.

Results

Liver transplant listing for PSC

A total of 6,767 patients were listed for LT with the diagnosis of PSC during the study period and accounted for 4.7% of all listings (Table 1). European Americans and African Americans were more frequently listed with a diagnosis of PSC relative to Hispanics and other ethnic groups. PSC accounted for 5.4% and 6.4% of all LT listings in European Americans and African Americans, respectively, compared to less than 2% in any other group.

Characteristics of PSC Patients Listed for LT

Comparisons between European American, African American and Hispanic groups of PSC patients listed for LT demonstrated significant differences in several important features (Table 2). African American patients were significantly younger at the time of listing than European American and Hispanic patients who were in turn younger than European American patients. Although there was a predominance of males listed among African American patients (56.0%), this was significantly lower compared to the percentage of males for the European American (69.0%) and Hispanic (64.6%) patient populations. There were no differences in the percentage of Model of End Stage Liver Disease (MELD) exceptions between the groups. However, African Americans were listed at a significantly higher MELD score than European American and Hispanic patients. Regional differences in the ethnic distribution of listings for PSC were noted with higher proportions of African Americans listed along the East Coast and in the Southern States (data not shown).

Including the PSC diagnosis code of “other bowel disease” as IBD along with the UC and CD codes, the proportions of patients with PSC and IBD for European Americans, African Americans and Hispanics were 71.6%, 60.7% and 64.2%, respectively. The lower frequency of IBD in African Americans and Hispanics was accounted for by a significantly lower frequency of UC. There was no difference between groups in CD prevalence.

Multiple logistic regression was used to determine if socioeconomic factors could account for ethnic differences in transplant listing for PSC (Table 3). After accounting for age at

listing, gender, household ownership and urbanicity, African origin remained significantly associated with PSC listing with an OR of 1.32 (95% CI 1.22 – 1.44).

HLA Associations with PSC Liver Transplantation Listings

1834 European American and 116 African American PSC patients had HLA typing available. Within each group, there were no differences in age, gender or frequency of IBD between those with and without HLA typing. Those listed with HLA typing did have a significantly greater MELD score at listing in both European American and African American groups. Similar to previous studies, we found strong associations with the A1, B8, DR3 and DR13 antigens in the European American PSC population compared to the ALD population (Table 4 and Supplementary Table 1). The A1, DR3, and DR13 associations were significantly weaker (OR=1.61, 95% C.I. [1.46 – 1.77], 1.46, 95% C.I. [1.25 – 1.71], and 1.54, 95% C.I. [1.38 – 1.71], respectively) than the B8 (OR=2.77, 95% C.I. [2.51 – 3.07]) association in European Americans. In Hispanics, the B8, DR3 and DR13 associations were replicated but it was not possible to determine their relative importance, and an A1 association could not be established. Importantly, in African American PSC patients, replication of the B8 and DR13 associations in PSC achieved statistical significance (OR=3.91, 95% CI [1.22 – 12.51] and OR=1.98, 95% CI [1.31 – 3.00]), respectively, whereas DR3 was not significantly associated (OR=0.66, 95% CI [0.31 – 1.44]). On the contrary, the negative association with DR4 was detected in European Americans (OR=0.51, 95% C.I. [0.45 – 0.58]), Hispanics (OR=0.17, 95% C.I. [0.17 – 0.54]) and African Americans (OR=0.28, 95% C.I. [0.12 – 0.64]) with PSC.

Investigation of extended HLA-B and DR haplotypes in African Americans (Table 5) showed that the associated alleles HLA-B8, DR13 or DR4 occurred on several, separate haplotypes suggesting that HLA-B and HLA-DR associations observed are likely to represent independent phenomena not arising by linkage disequilibrium. Importantly, in European Americans A1, B8 and DR3 are known to occur together on one extended haplotype, and hence the association of each individual allele is highly correlated. However, in African Americans the correlation between DR3 and B8 is very low (r^2=0.0004), and hence it is possible to distinguish the individual effects.

Discussion

By investigating a large US population listed for LT, we were able to demonstrate that the risk of being listed for LT with a PSC diagnosis is significantly associated with ancestral origin and that phenotype differences in PSC exist across ethnicities. Furthermore, the large study population provided refinement and an unprecedented replication of the HLA association in PSC by pointing toward HLA-B8, DR13 and DR4 as disease associated variants in the European American, Hispanics and African American populations.

We are careful to note that our findings may not be applicable to the total PSC patient population and may only reflect those with the most aggressive disease and with access to transplant care. Differences in the incidence of cholangiocarcinoma, a contraindication for liver transplantation in most cases, may also biased our results. However, we did not find any difference in the frequency of incidental cholangiocarcinomas in liver explants (data not shown).

Our data demonstrated that the risk of African Americans to be listed for LT with a diagnosis of PSC was greater than that of European Americans even after adjusting for socioeconomic and other factors. This is even more notable considering that hepatitis C and B infections are more prevalent in African Americans than European Americans and would have been expected to lead to a lower rate of listing for PSC in African Americans relative

to other, more common causes [20]. Several environmental and genetic mechanisms may be involved in the increased risk of PSC in African Americans. Among African Americans listed for LT, higher socioeconomic status reflected by higher home ownership rates was associated with the diagnosis of PSC (data not shown). We also determined that PSC differs phenotypically across ethnic groups with African Americans appearing to have more severe disease as illustrated by their younger age and higher MELD score at listing, as has been observed for African Americans listed for LT regardless of diagnosis [21].

Interestingly, IBD was less common in African Americans and Hispanics with PSC compared to European Americans due to a lower frequency of UC but not of CD. African Americans and Hispanics also had a higher rate of “other” bowel disease, perhaps reflecting a higher frequency of indeterminate colitis. Although we could not confirm that all patients were evaluated for IBD or if there were differences in the rates of investigation between the groups, colonoscopy is a standard part of LT evaluation at most centers in the US. Despite a reported decrease in the frequency of IBD associated with PSC, IBD remains the greatest risk factor for PSC [22]. Several studies have noted that the incidence of IBD has been increasing over time, particularly in Hispanics and African-Americans and the incidence of PSC also appears to be increasing [6,23]. Whether this increase in PSC is a true rise in incidence or an increase in ascertainment with increased physician awareness and the routine use of endoscopic retrograde cholangiography and magnetic resonance cholangiography remains unknown.

Because PSC is specifically associated with pan-colitis and Crohn’s colitis, phenotypic differences in IBD across ethnicities may also be important factors affecting PSC risk. Among African Americans, Hispanics, and European Americans in a large North American IBD cohort, African Americans were more frequently female and those with CD were more likely to have Crohn’s colitis diagnosed compared to European Americans [15]. Our finding of a lower predominance of men and relatively higher frequency of CD among those with IBD in African Americans listed with PSC suggests that differences in IBD phenotype are reflected in those who develop PSC.

An HLA association in PSC was first identified for HLA-B8 (i.e. HLA-B*0801) and DR3 (i.e. DRB1*0301) [24,25] in European Americans. Later studies have verified that PSC associations exist also for the HLA-A1 allele [26], the HLA-C7 allele [27], the major histocompatibility complex class I chain–related A (*MICA*) *008/5.1 allele [28,29], and the *TNFα* promoter -308 A allele [30]. The haplotype defined by these alleles is associated with a wide range of autoimmune diseases [31,32]; however, strong correlation between these variants in European Americans has precluded definition of the causative gene in most of these diseases. In a recent genome-wide association study in PSC [16], the strongest single nucleotide polymorphism (SNP) associations in the HLA complex were detected near HLA-B. Importantly, in the present data, significant replication is obtained for the HLA-B8 variant in European Americans, Hispanics and African Americans, while for DR3 the association was only detectable in European Americans and Hispanics. The lower level of linkage disequilibrium in African Americans in general may explain the dissociation of HLA-B8 and DR3 associations in African American PSC as compared with European Americans [33]. Our data thus strongly support the presence of PSC associated genetic susceptibility near HLA-B and marked by the B8 allele, and point to the prospects of mapping this difficult but important PSC risk region in African Americans [34].

A cross-European study (Norway, Sweden, Great Britain, Italy and Spain) has previously concluded that a consistent, positive HLA class II association in PSC probably exists also for a haplotype that carries the DR13 (i.e. DRB1*1301) variant [35]. Negative associations with HLA class II alleles have been identified for DR4 (no particular subtype) and DR7 (i.e.

DRB1*0701) alleles [35,36]. In the present data, a DR13 association and the protective effect from DR4 was evident in European Americans, Hispanics and African Americans. The lack of high resolution HLA-typing in UNOS data prevented us from concluding whether the DR13 association was due to DRB1*1301, like in Northern Europe, or was caused by other DR13 subtypes, particularly those known to be frequent in African Americans [37,38]. However, a major contribution to the DR13 association from haplotypes carrying HLA-B58 together with previously published high-resolution haplotype data from the African American population [39], makes it likely that the class II association indeed overlaps with the DRB1*1301 – DQB1*0603 haplotype previously detected in European populations. However, in contrast to European data, an almost comparable frequency of a recombinant DRB1*1301 – DQB1*0502 haplotype is found in African Americans [39]. Hence, future high-resolution HLA studies of both DRB1 and DQB1 loci in PSC in African Americans could point to the primary locus, as similar dissociation of DRB1 and DQB1 alleles has previously been exploited in mapping of the HLA class II associated susceptibility in multiple sclerosis [17].

In conclusion, we demonstrated phenotypic differences in patients with PSC listed for LT across ethnic groups. In addition, independent of socioeconomic factors, African Americans have an increased risk of listing for LT with a diagnosis of PSC and are listed at a younger age with more advanced disease. Furthermore, while HLA B8, DR4 and DR13 are associated with PSC in European Americans, Hispanics, and African Americans, the HLA DR3 association is not present in African Americans suggesting that refinement of the B8 locus may be possible in the African American PSC population. These findings illustrate the advantages of studying the genetic basis of disease in different ethnic groups and should be exploited to map the HLA associated susceptibility to PSC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PSC	primary sclerosing cholangitis
LT	liver transplant
UNOS	United Network for Organ Sharing
MELD	Model for End-stage Liver Disease
IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn’s Disease
ALD	alcoholic cirrhosis

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Table 1

PSC and non-PSC Liver Transplant Listings in the UNOS database by Ethnicity (1995–2009)

	Diagnosis at Listing, *n (%)*	
Ethnicity	**PSC**	**Non-PSC**
European American	5,577 (*5.4%*)	98,600 (*94.6%*)
African American	815 (*6.4%*)	11,907 (*93.6%*)
Hispanic	255 (*1.3%*)	19,253 (*98.7%*)
Asian	89 (*1.5%*)	5,949 (*98.5%*)
Native American/Alaskan Native	12 (*1.5%*)	781 (*98.5%*)
Native Hawaiian/Other Pacific Islander	3 (*1.0%*)	302 (*99.0%*)
Multiracial	16 (*2.4%*)	647 (*97.6%*)
Unknown	0	2

Table 2

Clinical characteristics of patients listed for liver transplantation with UNOS with a PSC diagnosis (1995–2009)

	Ethnicity		
	European American (*n = 5,577*)	**African American (*n = 815*)**	**Hispanic (*n =255*)**
Age at listing (*y*)	46.6 ± 13.7	39.7 ± 13.1[a]	42.3 ± 15.9[a,b]
Gender (*% male*)	69.1%	56.0%[c]	64.6%
Inflammatory Bowel Disease, *n (%)*	3,982 (*71.4%*)	493 (*60.5%*)[d]	162 (*63.5*)
Ulcerative colitis	2,683 (*48.5%*)	281 (*34.5%*)[d]	103 (*40.4%*)
Crohn's Disease	924 (*16.6%*)	133 (*16.3%*)	33 (*12.9%*)
No bowel disease	1,595 (*28.6%*)	322 (*39.5%*)[d]	93 (*36.5%*)
Other	375 (6.7%)	79 (9.7%)	26 (10.2%)
MELD/PELD at listing[1], *mean ± SD*	15.2 ± 7.5	18.1 ± 9.3[a,e]	14.9 ± 7.6
MELD/PELD Exception[1], *n (%)*	256 (*10.0%*)	33 (*8.1%*)	14 (*12.7%*)

[1] Includes only cases after February 27, 2002: European American (n = 2560); African American (n = 407); Hispanic (n = 110).

[a] $p < 0.001$ compared to European Americans;

[b] $p = 0.002$ compared to African Americans

[c] $p < 0.05$ compared to European Americans and Hispanics

[d] $p < 0.01$ compared to European Americans and Hispanics

[e] $p = 0.001$ compared to Hispanics

Table 3

Multiple logistic regression of variables associated with listing for liver transplantation with a diagnosis of PSC among all listings in UNOS (1995–2009)

Variable	OR	95% C.I.	*P*-value
Age at listing	0.993	0.991 – 0.994	< 0.001
Gender			
Female	Referent		
Male	1.336	1.267 – 1.410	< 0.001
Ethnicity			
European American	Referent		
African American	1.325	1.221 – 1.438	< 0.001
Other	0.265	0.237 – 0.296	< 0.001
% Household Ownership	2.95	2.48 – 3.51	< 0.001
% Urban	0.945	0.871 – 1.025	0.17

Table 4

Distribution of selected HLA allele frequencies among European American, African American and Hispanic PSC and ALD patients listed for liver transplantation

Allele	European Americans					African Americans					Hispanics				
	PSC (*2n = 3668*)	ALD (*2n = 7220*)	χ^2	*P*-value	OR[1] (95% CI)	PSC (*2n = 390*)	ALD (*2n = 232*)	χ^2	*P*-value	OR[1] (95% CI)	PSC (*2n = 168*)	ALD (*2n = 1116*)	χ^2	*P*-value	OR[1] (95% CI)
HLA-A															
1	0.262	0.181	96.44	9×10^{-23}	1.61 (1.46 – 1.77)	0.000	0.000				0.107	0.067	3.47	0.06	
HLA-B															
8	0.277	0.122	410.23	3×10^{-91}	2.77 (2.51 – 3.07)	0.049	0.013	5.46	0.02	(1.22 – 12.51)	0.119	0.039	19.55	1×10^{-05}	3.29 (1.90 – 5.71)
HLA-DR															
3	0.081	0.057	23.28	1×10^{-06}	1.46 (1.25 – 1.71)	0.036	0.053	1.05	0.31		0.054	0.013	12.82	0.0003	4.16 (1.83 – 9.46)
4	0.095	0.170	110.00	1×10^{-25}	0.51 (0.45 – 0.58)	0.021	0.071	9.66	0.002	0.28 (0.12 – 0.64)	0.077	0.216	17.67	3×10^{-05}	0.31 (0.17 – 0.54)
13	0.182	0.127	60.24	8×10^{-15}	1.54 (1.38 – 1.71)	0.279	0.164	10.61	0.001	1.98 (1.31 – 3.00)	0.202	0.088	20.78	5×10^{-06}	2.64 (1.72 – 4.04)

[1] OR; Odds Ratio, 95% CI; 95% confidence interval

Table 5

Estimated frequencies of HLA-B8, DR13, DR4 and DR3 extended haplotypes in African American patients with PSC and ALD listed for liver transplantation. With the exception of the B8-DR3 haplotype only extended B-DR haplotypes with a frequency ≥1% in PSC patients or ALD controls are shown in detail (others combined at either locus).

HLA-B allele	HLA-DR allele	Frequency in PSC	Frequency in ALD
8	3	0.003	0.0004
8	13	0.011	0.004
8	15	0.010	0.000
8	Other DR combined	0.025	0.009
7	13	0.020	0.016
35	13	0.011	0.004
42	13	0.026	0.022
44	13	0.022	0.011
45	13	0.017	0.006
49	13	0.012	0.014
51	13	0.013	0.000
53	13	0.017	0.020
58	13	0.037	0.002
70	13	0.017	0.007
Other B combined	13	0.076	0.053
44	4	0.005	0.013
51	4	0.000	0.016
Other B combined	4	0.015	0.043
27	3	0.000	0.010
42	3	0.004	0.023
Other B combined	3	0.032	0.021