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HLA haplotypes in primary sclerosing cholangitis patients of admixed and non-European ancestry

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SUPPORTING INFORMATION

The following supporting information is available for this article:

CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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Abstract

Primary sclerosing cholangitis (PSC) is strongly associated with several human leukocyte antigen (HLA) haplotypes. Due to extensive linkage disequilibrium and multiple polymorphic candidate genes in the HLA complex, identifying the alleles responsible for these associations has proven difficult. We aimed to evaluate whether studying populations of admixed or non-European descent could help in defining the causative HLA alleles. When assessing haplotypes carrying HLA-DRB1*13:01 (hypothesized to specifically increase the susceptibility to chronic cholangitis), we observed that every haplotype in the Scandinavian PSC population carried HLA-DQB1*06:03. In contrast, only 65% of HLA-DRB1*13:01 haplotypes in an admixed/non-European PSC population carried this allele, suggesting that further assessments of the PSC-associated haplotype HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03 in admixed or multi-ethnic populations could aid in identifying the causative allele.

Keywords

Causative; Human leukocyte antigen; Multi-ethnic; PSC; Trans-ancestry

MAIN TEXT

Primary sclerosing cholangitis (PSC) is a rare disease characterized by chronic inflammation of intra- and extrahepatic bile ducts, ultimately leading to liver cirrhosis and liver failure. The prevalence of PSC in populations of Northern European descent is approximately 1 in 10 000, while in Southern European and Asian populations the prevalence seems to be 10 to 100-fold lower.¹ The etiology of PSC is unknown, however siblings of PSC patients have a 9–39 fold increased risk of disease,² suggesting that genetic components are involved in PSC pathogenesis. PSC is strongly associated with the human leukocyte antigen (HLA) complex, an association that was first described in the early 1980s.^{3,4} The two most prominent risk HLA haplotypes are the HLA-A*01:01-C*07:01-B*08:01-DRB3*01:01-DRB1*03:01-DQA1*05:01-DQB1*02:01 haplotype (also known as the 8.1 ancestral haplotype [AH8.1]), and the HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03 haplotype.⁵ The most consistently observed protective association with PSC has been with the HLA-

DRB1*04-DQA1*03-DQB1*03 haplotype.^{6–11} Due to the extensive linkage disequilibrium (LD) in the HLA complex, the causative alleles on these associated haplotypes have remained unknown.

Large-scale trans-ancestry studies have identified new risk loci in complex diseases such as inflammatory bowel disease (IBD) and rheumatoid arthritis, and further reported that the majority of associated risk loci were shared across ethnicities.^{12,13} Since allele frequencies and LD patterns differ between populations from different geographical origins, studying populations of admixed ancestry or multiple ethnicities could aid in fine mapping causative HLA alleles. This was previously demonstrated in multiple sclerosis (MS): to better localize the HLA gene responsible for the association between MS and the HLA-DRB1*15:01-DQB1*06:02 haplotype, the *HLA-DRB1* and *HLA-DQB1* genes of African American MS patients and controls were assessed, showing a selective association between MS and the HLA-DRB1*15:01 allele.¹⁴ In PSC, it is challenging to establish the necessary admixed or multi-ethnic sample size due to the low prevalence of disease in populations of non-Northern European ancestry.¹ Nevertheless, in this descriptive study, we aimed to explore to what extent studying populations of admixed and non-European descent might aid in pinpointing the causative HLA alleles in PSC.

We included 92 PSC patients of admixed or non-European ancestry and 150 PSC patients of Scandinavian ancestry. The diagnosis of PSC was based on accepted criteria with typical findings of bile duct irregularities on cholangiography.¹⁵ The study was performed in accordance with the Declaration of Helsinki. Ethics committees or institutional review boards of all participating centres approved patient recruitment, and written informed consent was obtained from all patients prior to participation. Among the patients in the admixed/non-European study population, 67 had previously been characterized as ‘ancestry outliers’ due to non-European ancestry and were therefore excluded from the final analysis of the Immunochip-based PSC study.¹⁶ They had originally been recruited in Finland, the United Kingdom, the Netherlands, France, Germany, Italy, the United States of America (USA) and Canada. The remaining patients that were included in the admixed/non-European study population comprised 21 self-reported African American PSC patients sampled in the USA and four PSC patients of admixed or non-European ancestry sampled in Canada (one Iranian, one Pakistani/Indian, one admixed Canadian Caucasian/Iranian and one admixed Canadian Caucasian/African Canadian). The 150 Scandinavian patients were selected from a previously described Scandinavian PSC population.^{17,18} The 135 Norwegians and 15 Swedes were randomly selected among patients carrying *HLA-DRB1* alleles found on PSC-associated haplotypes, *i.e.* HLA-DRB1*01:01, HLA-DRB1*03:01, HLA-DRB1*04:01, HLA-DRB1*07:01, HLA-DRB1*11:01, HLA-DRB1*13:01 and HLA-DRB1*15:01.⁵ Notably, we selected only a limited number of Scandinavian patients who were homozygous for both HLA-B*08 and HLA-DRB1*03:01 (n=10). Using a multidimensional scaling analysis, we assessed the genetic ancestry of the patients for which Immunochip data was available,¹⁶ *i.e.* the 67 ‘ancestry outliers’ and 150 Scandinavians (Figure 1).

We performed HLA typing on the admixed/non-European and Scandinavian study populations using genomic DNA and a high-throughput sequencing method.¹⁹ RNA baits were used for the targeted enrichment of *HLA-A*, *HLA-B* and *HLA-C* (HLA class I), and

HLA-DPA1, *HLA-DPB1*, *HLA-DRB3*, *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1* (HLA class II). Following library preparation, sequencing was carried out on a HiSeq instrument (Illumina, San Diego, CA, USA) with 100 base pair paired-end runs, and the alleles were assigned using the HLAAssign software.¹⁹ Genotyping success rate was 98.9% for all HLA genes. In subsequent analyses, the HLA alleles were at a four-digit resolution. LD measurements and estimation of allele frequencies were performed in Unphased v.3.0.10.²⁰ Haplotypes were estimated using 1000 iterations in PHASE v2.1.1.^{21,22} We focused our further assessments on the three PSC-associated haplotypes carrying the risk alleles HLA-DRB1*13:01 and HLA-DRB1*03:01 and the protective HLA-DRB1*04 alleles.⁵ The frequencies for alleles comprising these haplotypes are listed for the admixed/non-European study population in Table S1 (Supporting information).

The HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03 haplotype was observed with a frequency of 8.7% in the admixed/non-European study population. Approximately one third of all HLA-DRB1*13:01 haplotypes in the admixed/non-European study population did not carry the HLA-DQB1*06:03 allele (Figure 2A). In comparison, every HLA-DRB1*13:01 haplotype in the Scandinavian study population carried the HLA-DQB1*06:03 allele (Figure 2B). The admixed/non-European study population displayed reduced LD between HLA-DRB1*13:01 and HLA-DQB1*06:03 compared to the previously described Scandinavian PSC population¹⁸ ($r^2=0.50$ in the admixed/non-European study population, $r^2=0.87$ in Scandinavians). The nine PSC patients carrying non-DQB1*06:03 alleles on the HLA-DRB1*13:01 haplotype were of African or admixed African/Caucasian ancestry (Figure S1). Three of these nine patients carried the HLA-DQB1*05:01 allele on the HLA-DRB1*13:01 haplotype (Table S2), which is not unexpected since both HLA-DRB1*13:01-DQB1*06:03 and HLA-DRB1*13:01-DQB1*05:01 are common haplotypes in African Americans.²³ The HLA-DRB1*13:01 haplotype was recently hypothesized to specifically increase the susceptibility of inflammatory bile duct diseases, as it is associated with both large and small duct PSC, irrespective of IBD status.²⁴ Association analyses to define a causative allele were inappropriate in the present study due to the sample size and further the selection process of the patients in the admixed/non-European study population, which rendered it impossible to recruit an adequate healthy control population. Nevertheless, findings from this descriptive study suggest that assessing further the HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03 haplotype in admixed or multi-ethnic populations of PSC patients and ethnicity-matched healthy controls could aid in fine mapping the causative HLA allele, assuming the same causative allele across ethnicities.

In the admixed/non-European study population, 36% of HLA-DRB1*03:01 haplotypes carried the HLA-B*08:01 allele (Figure 3A) and 56% of HLA-B*08:01 haplotypes carried the HLA-DRB1*03:01 allele (Figure 3B), whereas in the previously described Scandinavian PSC population¹⁷, 86% of HLA-DRB1*03:01 haplotypes carried the HLA-B*08 allele and 89% of HLA-B*08 haplotypes carried the HLA-DRB1*03:01 allele. The LD between HLA-B*08:01 and HLA-DRB1*03:01 was weak in the admixed/non-European study population ($r^2=0.17$) compared to the previously described Scandinavian PSC population¹⁷ ($r^2=0.65$). On the other hand, every HLA-DRB1*03:01 haplotype carried the HLA-DQB1*02:01 allele, irrespective of ethnic origin (Figure 3A). This observation was supported by LD measurements between HLA-DRB1*03:01 and HLA-DQB1*02:01 ($r^2=0.93$ in the admixed/

non-European study population, $r^2=0.99$ in the previously described Scandinavian PSC population¹⁸). The ten Scandinavian PSC patients who were selected for being homozygous for both HLA-B*08:01 and HLA-DRB1*03:01 were also homozygous for the HLA-DRB3*01:01 allele and for HLA-DQA1*05:01-DQB1*02:01 (Table S3). Four of these patients were homozygous for both HLA-A*01:01 and HLA-C*07:01. Of the remaining six patients, four were heterozygous for HLA-A*01:01 and homozygous for HLA-C*07:01, and two were heterozygous for HLA-C*07:01 but did not carry HLA-A*01:01. AH8.1 is a common haplotype in Northern European populations, with a frequency of approximately 10%.^{25,26} Alleles comprising the AH8.1 are strongly associated with a large number of immune-driven diseases.²⁷ For some diseases, the primary association with AH8.1 is confined to the HLA class I region, as seen in myasthenia gravis,²⁸ or to the HLA class II region, as seen in coeliac disease and type 1 diabetes.^{29,30} For other diseases including PSC, associations have been reported for both HLA class I and class II alleles of the AH8.1.⁵ Our data suggest that studying admixed or multi-ethnic populations will likely aid in fine mapping the AH8.1 association in PSC to the HLA class I and/or HLA class II region. This is in agreement with a previous African American PSC study, in which an association with HLA-B8 but not HLA-DR3 was detected.³¹ As we could not dissociate the strong LD between HLA-DRB1*03:01 and HLA-DQB1*02:01, pinpointing the potential causative allele within the HLA class II region (*i.e.* HLA-DRB1*03:01, HLA-DQA1*05:01 or HLA-DQB1*02:01) might remain a challenge.

Every HLA-DRB1*04:01 and HLA-DRB1*04:04 haplotype in the admixed/non-European study population carried HLA-DQB1*03:01 and HLA-DQB1*03:02 alleles, respectively (Table S4). The HLA-DRB1*04:01 and HLA-DRB1*04:04 alleles were each observed in three patients of admixed or non-European ancestry. In the Scandinavian study population, HLA-DRB1*04:01 haplotypes carried either HLA-DQB1*03:01 and HLA-DQB1*03:02, and the HLA-DRB1*04:04 haplotype carried the HLA-DRB1*03:02 allele (Table S5). The HLA-DRB1*04:04 allele was observed only once in the Scandinavian study population due to the selection of Scandinavian PSC patients for the present study: this patient was previously genotyped to have the HLA-DRB1*04:01 allele.¹⁸ Collectively, our data suggest that studying admixed or multi-ethnic populations might not help in identifying the causative allele in the protective HLA-DRB1*04-DQA1*03-DQB1*03 haplotype.

In conclusion, our data suggest that studying admixed or multi-ethnic populations could aid in fine mapping the causative HLA allele in the PSC-associated haplotype HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Multidimensional scaling (MDS) plot of the PSC patients with available Immunochip data¹⁶ together with 1245 samples from 1000 Genomes phase3³². The orange, green and blue points represent 1000 Genomes EUR (European), EAS (East Asian) and AFR (African) super-populations, respectively. The African American ASW (sub-population of AFR) are marked using purple triangles. The larger red dots represent the Scandinavian patients (n=150), overlapping the EUR super-population, while the larger black dots show the PSC patients of admixed or non-European ancestry who were previously characterized as ‘ancestry outliers’ (n=67). Using Plink 1.9³³, a set of 20,226 single nucleotide

polymorphisms (SNPs) with rsids on both the Immunochip and the Illumina Omni2.5 array that was used in the 1000 Genomes Project³² (downloaded from ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/supporting/hd_genotype_chip/ALL.chip.omni_broad_sanger_combined.20140818.snps.genotypes.vcf.gz) were extracted and merged. LD-pruning ($r^2 < 0.1$) and minor allele frequency (MAF)-filtering (MAF > 10%) resulted in 8561 SNPs for use in the MDS analysis. Plots were generated in the statistical software environment R v.3.2.3 (<https://www.r-project.org/>).

Figure 2.

Graphical presentation of the haplotypes carrying HLA-DRB1*13:01 in the (A) admixed/non-European and (B) Scandinavian study population. Each row shows a haplotype, and alleles of the HLA-DRB1*13:01-DQA1*01:03-DQB1*06:03 haplotype are highlighted in blue. Percentages reflect the fraction of HLA-DRB1*13:01 haplotypes carrying the HLA-DQB1*06:03 allele.

Figure 3.

Graphical presentation of the haplotypes carrying (A) HLA-DRB1*03:01 and (B) HLA-B*08:01 in the admixed/non-European study population. Each row shows a haplotype, and alleles of the HLA-A*01:01-C*07:01-B*08:01-DRB3*01:01-DRB1*03:01-DQA1*05:01-DQB1*02:01 haplotype (*i.e.* the AH8.1) are highlighted in blue. Percentages reflect the fraction of (A) HLA-DRB1*03:01 haplotypes and (B) HLA-B*08:01 haplotypes carrying the HLA-B*08:01 and HLA-DRB1*03:01 alleles, respectively.