HLA Associations with Infliximab-Induced Liver Injury

Christopher D. Bruno, BA[1]; Brandon Fremd, BS[1]; Rachel J. Church, PhD[2]; Ann K. Daly, PhD[3]; Guruprasad P. Aithal, MD, PhD[4]; Einar S. Björnsson, MD[5,6]; Dominique Larrey, MD, PhD[7]; Paul B. Watkins, MD[2]; and Christina R. Chow, PhD[1]

[1]Emerald Lake Safety, Newport Beach, CA; [2]Eshelman School of Pharmacy, University of North Carolina Institute for Drug Safety Sciences, Chapel Hill, NC; [3]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; [4]National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK; [5]Department of Internal Medicine, Landspitali University Hospital, Reykjavik, Iceland; [6]Faculty of Medicine, University of Iceland, Reykjavik Iceland; [7]Liver Unit, CHU St Eloi Hospital, Montpellier, France.

Corresponding author:
Christina R. Chow, PhD
Emerald Lake Safety
23 Corporate Plaza Drive, Suite 150
Newport Beach, CA 92660 USA
christina@elsafety.com
(630) 698-0484

ABSTRACT:

Biomarkers that are able to identify patients at risk of drug-induced liver injury (DILI) after treatment with infliximab could be important in increasing the safety of infliximab use. We performed a genetic analysis to identify possible human leukocyte antigen (HLA) associations with drug-induced liver injury in European Caucasian users of infliximab in a retrospective study of 16 infliximab-DILI patients and 60 matched controls. In infliximab-associated liver injury, multiple potentially causal individual HLA associations were observed, as well as possible haplotypes. The strongest associated HLA allele was *HLA-B*39:01* (P=0.001; odds ratio [OR] 43.6; 95% confidence interval [CI] 2.8-infinity), which always appeared with another associated allele *C*12:03* (P=0.032; OR 6.1; 95% CI 0.9-47.4). Other associations were observed with HLAs *DQB1*02:01* (P=0.007; OR 5.7; 95% CI 1.4-24.8), *DRB1*03:01* (P=0.012; OR 4.9; 95% CI 1.2-20.5), and *B*08:01* (P=0.048; OR 3.4; 95% CI 0.9-13.2), which also appeared together whenever present in cases. Additional associations were found with *HLA-DPB1*10:01* (P=0.042; OR 20.9; 95% CI 0.7-infinity) and *HLA-DRB1*04:04* (P=0.042; OR 20.9; 95% CI 0.7-infinity). A strong association with *HLA-B*39:01* was identified as a potentially causal risk factor for infliximab-induced DILI. Future work should aim to validate this finding and explore possible mechanisms through which the biologic interacts with this particular allele.

BACKGROUND:

Infliximab (brand names Inflectra®/Ixifi®/Remicade®/Renflexis®) is a mouse-human chimeric monoclonal antibody (mAb) to tumor necrosis factor alpha (TNF-alpha) indicated for use in Crohn's disease, ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), psoriatic arthritis, psoriasis, and several other autoimmune conditions [1]. Since its initial approval for use as a biologic drug in Crohn's disease by the US Food and Drug Administration (FDA) in 1998, infliximab has been widely used to treat patients with autoimmune diseases. However, during clinical trials and in practice, drug-induced liver injury (DILI) has been observed amongst infliximab users, driving the FDA to add a hepatotoxicity warning to the Remicade® label in December of 2004 [1]. There are multiple case reports of drug-induced hepatotoxicity in infliximab users, including reactivation of hepatitis B, leading to outcomes such as liver failure, need for liver transplantation, and occasionally, death [2]. Based on a two-year prospective study in a homogenous Icelandic population, the frequency of infliximab-induced liver injury is reported to be 1 in 148 patients treated [3]. Over a 5-year study period in the same population, infliximab induced liver injury was observed at a higher frequency of 1 out of 120 patients treated [4]. The LiverTox website [5], a collaboration between the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Library of Medicine (NLM), assigned infliximab a DILI likelihood score of "A" to indicate "well established cause of clinically apparent liver injury." Two recent studies have reported a distinct biological, clinical, and histological phenotype of infliximab DILI [4–6].

Insight into genetic predispositions and the mechanisms underlying infliximab-induced hepatotoxicity could identify a susceptible subset of patients who might require closer monitoring or may consider alternative therapies. There is evidence that specific human leukocyte antigen (HLA) polymorphisms are associated with DILI across a number of unrelated drugs [7], although to date, these associations have only been reported with small molecule drugs. Using the Vanderbilt University Medical Center (VUMC) BioVU biorepository [8,9] to

retrospectively identify cases of infliximab-induced hepatotoxicity, this pharmacogenetic study aimed to identify the first known association between HLA variants and DILI caused by a biologic drug.

METHODS:

***Patient Identification and Characteristics*:**

BioVU Samples:

Eleven self-reported Caucasian cases for this retrospective study were identified using de-identified clinical data extracted from BioVU by Nashville Biosciences, a subsidiary of VUMC established to support translational research. Clinical and genotype data were provided from BioVU in accordance with BioVU's data use policies; subjects provided informed consent prior to their inclusion in BioVU [8,9]. Since infliximab is administered via infusion, high-confidence doses were found in the BioVU's structured clinical data by comparing infliximab prescription code dates with infusion Current Procedural Terminology (CPT) code dates, which were later confirmed via manual review of the de-identified clinical notes to provide true infliximab exposure timeframes and dosing intervals. Serial liver chemistry values for alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum total bilirubin (BILI) were converted to multiples of upper limit of normal (ULN) by dividing by the BioVU assay-specific ULN values. Possible cases were identified by selecting for infliximab-exposed patients who experienced serum ALT greater than 3x the ULN, serum ALP greater than 2x the ULN, or serum BILI values greater than 2x the ULN during infliximab treatment. Additionally, cases were only considered if there was evidence of baseline ALT, ALP, and BILI values within normal limits prior to infliximab exposure. Clinical information related to subjects meeting these criteria were further manually reviewed to exclude competing causes of liver injury via underlying condition (e.g. fatty liver disease) or concomitant medications known to elevate liver enzymes (e.g. 6-mercaptopurine) during the course of therapy.

Potential cases meeting the above criteria were then evaluated for likelihood of infliximab-induced liver injury by a DILI expert (PBW) [10]. Along with structured data describing clinical lab values, dosing intervals, and relevant International Classification of Diseases (ICD, 9^{th} and 10^{th} revisions) codes with dates, infliximab-induced liver injury was confirmed using de-identified clinical notes from relevant specialists, including hepatologists. Only cases deemed "Possible," "Probable," or "Definite" were included in this study.

iDILIC Samples:

An additional seven Caucasian cases for this study were provided by the International Drug-Induced Liver Injury Consortium (iDILIC). The cases were adjudicated according to criteria previously described [11] and were recruited from centers in Newcastle, UK, Reykjavik, Iceland and Montpellier, France as described in more detail elsewhere [7]. All patients from iDILIC experienced ALT greater than 5x the ULN.

Controls:

In order to achieve sufficient power (80%) to detect meaningful HLA associations in this study, we sought to include at least three matched controls per DILI case [12]. The 60 Caucasian controls for this study were gathered from BioVU's de-identified structured clinical data and notes. Control candidates were identified as patients who (1) were exposed to infliximab for at least 12 months, (2) had multiple lab values with no record of ALT or ALP > 1.5x ULN or BILI

> 1x ULN within 6 months pre- or post-infliximab exposure, and (3) had no record of DILI-related ICD codes. Wherever possible, controls were matched for self-reported ethnicity, indication of use, age, sex, and BMI. Cases with unknown indication of infliximab use were primarily matched to controls with Crohn's disease, as this is the most common disease among infliximab users available in BioVU. De-identified medical records were then manually reviewed to confirm these patients had prolonged infliximab exposure consistent with the structured data.

Genome-wide SNP and HLA analysis:

Genotyping for genome-wide genotyping association studies (GWAS) of cases and controls was performed by Vanderbilt Technologies for Advanced Genomics (VANTAGE, Nashville, Tennessee) using the Illumina Human MEGA Ex Vanderbilt platform (N=18 cases, N=60 controls). A total of 528,683 single nucleotide polymorphisms (SNPs) passed quality control (QC). One control sample was found to have insufficient DNA for accurate genotyping; no other samples were excluded for quality issues. Principal components analysis (PCA) was used to assess population structure and verify self-reported ethnicities of 18 cases and 59 controls prior to inclusion in the study.

In addition to GWAS genotyping, direct HLA typing was possible for a total of 71 samples (N=11 cases, N=60 controls) by the Institute for Immunology & Infectious Diseases (iiiD, Perth, Australia). Using Illumina next generation sequencing (NGS) of exons 2 and/or 3, iiiD was able to resolve the HLA alleles at 4-digit resolution for Class I HLAs A, B and C, as well as Class II HLAs DPB1, DQA1, DQB1, and DRB1 for further evaluation. For cases with inadequate DNA for direct HLA typing (N=7), HLA profiles at these loci were imputed from GWAS data using HIBAG [13] (version 1.4) with the European Illumina Infinium MEGA BeadChip prediction model.

Statistical Methods:

Power calculations were performed using Quanto [14] (version 1.2.4). Population structure and outlier identification were determined through PCA using the smartPCA program from the EIGENSTRAT [15] package (version 3.0). Reported ethnicities were assessed by combining the study population with Thousand Genomes Project [16] (1KG) data and demonstrating clustering as expected based on principal components. Identity by descent calculations and filtering were run using PLINK [17] (version 1.90b6.9) to confirm that samples were unrelated. To evaluate HLA variant association with case-control status, R [18] (version 3.4.0) was used to calculate two-sided p-values, odds ratios (ORs) and confidence intervals (CIs) using Fisher's Exact Test. Given the fairly low number of alleles tested for causal associations (N=76), as well as known HLA haplotype associations within homogenous ethnicities [13,19,20], no corrections for multiple comparisons were employed in this study and p-values below 0.05 were considered significant. Secondary to HLA associations, GWAS associations were also explored using PLINK and a genotypic Fisher's Exact Test with a genome-wide significance threshold of 5.0×10^{-8}. Differences in clinical characteristics between cases and controls were tested in R using Fisher's Exact Test for discrete variables and the Wilcoxon-Mann-Whitney test with normal approximation for continuous variables. Population impact measures (e.g., sensitivity, specificity, population attributable fraction) were calculated according to Tonk et al. [21].

RESULTS:

Patient Population:

A total of 18 European Caucasian patients with infliximab-DILI were gathered for our study. Eleven of these cases were found retrospectively in VUMC's BioVU, while the other seven were recruited through European recruitment centers participating in the iDILIC study. Following a principal components analysis, two cases were removed as "outliers" (see Supplementary Figure 1). The lone control with insufficient DNA for GWAS genotyping was deemed Caucasian based on the directly-typed HLA profile. As shown in Table 1, the majority of DILI cases were female (69%). Primary indications for infliximab use among cases included Crohn's disease (44%), psoriatic arthritis (13%), ulcerative colitis (6%), ankylosing spondylitis (6%), erythroderma (6%), sarcoidosis (6%), juvenile idiopathic arthritis (6%), or unknown (13%). The majority of cases presented with a hepatocellular DILI pattern, and the median time-to-DILI was approximately 150 days (range: 48-690 days). Mean maximums for ALT, ALP, and BILI were 8.89, 1.49, and 9.27 x ULN, respectively. A summary of latency and liver enzyme values among cases can be found in Table 2.

A total of 60 European Caucasian controls found retrospectively in BioVU were used in this study. Average body mass index (BMI) was 27.1 (range: 17-41) for cases and 24.6 (range: 17.2-48.7) for controls, while the average age at the initiation of treatment for cases was 37 years (range: 12-60) in cases and 34 years (range: 11-70) in controls. There were significantly more controls with underlying Crohn's disease (P=0.02), and significantly more cases with unknown indication of use (P=0.04), which was due to matching unknown indications in cases with Crohn's disease controls.

Genetic Association:

GWAS was performed on 16 cases and 59 controls. The results of the GWAS scan did not yield any significant SNPs or genomic regions with infliximab-DILI following correction for multiple testing (see Supplementary Figure 2).

A total of 76 unique 4-digit HLA alleles were tested for association with infliximab-induced liver injury in this study. The strongest association was found among cases with *HLA-B*39:01* (P=0.0014, Odds Ratio [OR] 43.6, 95% Confidence Interval [CI] 2.82-Infinity). Other HLA alleles yielding strong signals include *DQB1*02:01*, *DRB1*03:01*, *C*12:03*, *DPB1*10:01*, *DRB1*04:04*, and *B*08:01*; the statistics for all significant ($P < 0.05$) alleles are shown in Table 3. Further inspection revealed that cases carrying *HLA-B*39:01* and *HLA-C*12:03* were identical, as were cases carrying *HLAs DQB1*02:01*, *DRB1*03:01*, and *B*08:01* suggesting possible causal HLA haplotypes. In the case of the latter haplotype, we also found that cases with these alleles also carried *HLAs C*07:01* and *DQA1*05:01*, which were not significant when tested for individual presence (see Supplementary Table 1). The seven significant alleles were also reviewed among cases with the most significant liver injury (ALT > 5x ULN, N = 10), and all but HLAs *DRB1*03:01* and *B*08:01* remained significant at $P < 0.05$ (see Supplementary Table 2).

The population-level carriage frequencies of each of the top HLA alleles according to reference studies in the Allele Frequency Net Database [22,23] (AFND) are reported in Table 4. Wherever possible we used the USA National Marrow Donor Program (NMDP) European Caucasian cohort as a reference population, as the sample size of 1,242,890 subjects is among the largest in AFND and we would expect the USA European Caucasian ethnic makeup to best match the population structure of our study samples. For alleles or haplotypes where the USA

NMDP reference was not available, we substituted other "Caucasoid" study populations (e.g. Italian) from AFND. Per AFND, *HLA-B*39:01* is present in approximately 2% of Caucasian individuals. Additionally, the *HLA-B*39:01-C*12:03* haplotype carriage frequency is 1.3% in Caucasoid populations.

DISCUSSION:

This study, to our knowledge, is the first report of MHC class I and class II alleles associated with DILI due to a biologic drug. In a cohort of 16 European ancestry patients who developed DILI while being treated with infliximab, the strongest association was observed for *HLA-B*39:01*, which appeared in 25% of our DILI cases but was absent in controls and has a carriage frequency of about 2% in Caucasian populations. Among cases with ALT greater than 5x ULN, *HLA-B*39:01* had an even stronger association with a carriage frequency of 30% and OR of 56.5. Assuming a population-wide carriage frequency of 2.3% for *HLA-B*39:01* among Caucasians, an adverse event frequency of 1 in 120 patients, and an odds ratio similar to that observed in this study (43.6), we estimate that as few as 6 patients carrying the *HLA-B*39:01* allele would need to avoid treatment with infliximab to prevent one DILI case. If patients were screened for this HLA prior to infliximab therapy, we would expect to avoid one DILI case for every 267 patients tested. A summary of population impact measures and benefits of pharmacogenomics testing can be found in Table 5.

Beyond individual HLA allele associations, this study also identified multiple possible haplotypes associated with infliximab DILI. Interestingly, we observed that all DILI cases carrying *HLA-B*39:01* also carried *HLA-C*12:03*, each of which on its own was found to be significantly enriched compared to controls. While *HLA-C*12:03* was present in controls, no controls with *HLA-C*12:03* also carried *HLA-B*39:01*. In Caucasian populations, the *HLA-B*39:01-C*12:03* haplotype is reported to appear at a frequency of 1.3%, but was observed at a rate of 25% in infliximab DILI cases (see Table 4).

Another possible haplotype association was observed among the five HLA alleles *B*08:01*, *C*07:01*, *DRB1*03:01*, *DQA1*05:01* and *DQB1*02:01*, three of which were found to be significantly enriched in infliximab DILI cases on an individual level (see Table 3). This 5-allele haplotype was observed in 7/16 (44%) cases, but was present in only 7/60 (12%) matched controls. Although this particular haplotype is not reported explicitly in the AFND database, subsets of these alleles consistently appear at a rate of 13-16% (see Supplementary Table 3). There are previous reports of HLA haplotypes conferring risk for DILI [24–26], so the haplotypes observed in this study should continue to be considered in future work.

While preliminary and limited by a small number of infliximab-induced DILI cases, there appears to be a strong association between carriers of *HLA-B*39:01* and developing DILI. Since *HLA-B*39:01* appears across multiple indications (CD, erythroderma, NA) and is totally absent among matched controls, there is little reason to believe that this finding is an artifact of a genetic link to underlying indications.

We are continuing to collect information on infliximab-induced DILI patients in order to build a replication cohort in which to validate these findings. Additionally, we are interrogating the molecular mechanisms by which HLA alleles may interact with infliximab and thus cause hepatotoxicity. Validation of these findings in a replication cohort and elucidation of the mechanisms behind this phenomenon could allow for the identification of patients at risk of

developing infliximab-induced DILI and proactive alteration of their treatment regimens to avoid this adverse event.

Conflict of Interest:

CDB, BF, and CRC are employees of Emerald Lake Safety. GPA is supported by the NIHR Nottingham Biomedical Research Centre. AKD has received funding from the International Serious Adverse Events Consortium for iDILIC recruitment. RJC, ESB, DL, and PBW have no conflicts to declare.

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Table Legends:

Table 1: * Presented as mean and standard deviation. ** Significant at $P < 0.05$. Abbreviations: BMI, body mass index; CD, Crohn's disease; UC, ulcerative colitis; AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis.

Table 2: * Time to DILI reported as median (range); ** One cholestatic case experienced DILI after dose increase; Time to DILI: length of time from taking the first infliximab dose until the first DILI-qualifying lab value; R-Value: calculated by dividing max ALT (xULN) by max ALP (xULN).

Table 3: * Calculated using Fisher's Exact Test. Calculations for OR involving a 0 were recalculated after adding 0.5 to each cell in the contingency matrix.

Table 4: * Carriage frequency calculated from allele frequency assuming Hardy-Weinberg Equilibrium. Abbreviations: AFND, Allele Frequency Net Database; NMDP, National Marrow Donor Program.

Table 5: Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PAF, population attributable fraction; NNT, number needed to treat; NNG, number needed to genotype.

Table 1: Clinical Characteristics of Cases and Controls

		Cases (N=16)		Controls (N=60)			
Characteristic:		**N**	**%**	**N**	**%**	**P-Value**	**Test**
Sex	Female	11	69%	46	77%	0.53	Fisher's Exact Test
	Male	5	31%	14	23%		
BMI*		27.1	7.1	24.6	6	0.16	Wilcoxon test
Age*		37	17	34	16	0.61	Wilcoxon test
Indication	CD**	7	44%	46	77%	0.02	Fisher's Exact Test
	Psoriatic Arthritis	2	13%	4	7%	0.60	
	UC	1	6%	6	10%	1.00	
	AS	1	6%	2	3%	0.51	
	Erythroderma	1	6%	0	0%	0.21	
	Sarcoidosis	1	6%	1	2%	0.38	
	JIA	1	6%	1	2%	0.38	
	Not Available**	2	13%	0	0%	0.04	

Table 2: Mean (standard deviation) of DILI Latency and Clinically Relevant Lab Values

DILI Pattern	N	Time to DILI (days)*	Max ALT (xULN)	Max ALP (xULN)	Max BILI (xULN)	R-Value
All cases	16	150 (48-690)	8.89 (7.97)	1.49 (1.69)	9.27 (11.35)	9.44 (7.66)
Hepatocellular	12	140 (48-605)	10.64 (8.41)	0.91 (0.69)	10.09 (11.52)	12.02 (7.07)
Cholestatic	3	180 (141-690)**	3.57 (3.74)	4 (2.66)	8.8 (14.03)	0.76 (0.32)
Mixed	1	225	3.83	0.85	0.80	4.51

Table 3: Significant HLA Allele Associations

Allele	Cases (N=16)		Controls (N = 60)		P-Value*	Odds Ratio (95% Confidence Interval)*
	Present	Absent	Present	Absent		
*HLA-B*39:01*	4	12	0	60	0.001	43.6 (2.8 - Inf)
*HLA-DQB1*02:01*	7	9	7	53	0.007	5.7 (1.4 - 24.8)
*HLA-DRB1*03:01*	7	9	8	52	0.012	4.9 (1.2 - 20.5)
*HLA-C*12:03*	4	12	3	57	0.032	6.1 (0.9 - 47.4)
*HLA-DPB1*10:01*	2	14	0	60	0.042	20.9 (0.7 - Inf)
*HLA-DRB1*04:04*	2	14	0	60	0.042	20.9 (0.7 - Inf)
*HLA-B*08:01*	7	9	11	49	0.048	3.4 (0.9 - 13.1)

Table 4: Population Frequencies of Significant HLA Alleles

Allele	Carriage Frequency (%)			AFND Reference	
	DILI Case	Control	AFND Reference	Reference Population	Population Size
*HLA-B*39:01*	25.0	0.0	2.3*	USA NMDP European Caucasian	1,242,890
*HLA-DQB1*02:01*	43.8	11.7	31.6	Italy Central	380
*HLA-DRB1*03:01*	43.8	13.3	22.8*	USA NMDP European Caucasian	1,242,890
*HLA-C*12:03*	25.0	5.0	9.5*	USA NMDP European Caucasian	1,242,890
*HLA-DPB1*10:01*	12.5	0.0	2.6*	USA Caucasian pop 5	268
*HLA-DRB1*04:04*	12.5	0.0	7.6*	USA NMDP European Caucasian	1,242,890
*HLA-B*08:01*	43.8	18.3	21.6*	USA NMDP European Caucasian	1,242,890
*HLA-B*39:01 + HLA-C*12:03*	25.0	0.0	1.3	Italy pop 5	975

Table 5: Population Impact Measures for Top HLA Associations

Allele	Odds Ratio (95% CI)	Sensitivity	Specificity	PPV	NPV	PAF	NNT	NNG
*HLA-B*39:01*	43.6 (2.8 - Inf)	46.2%	98.1%	16.7%	99.5%	45%	6	267
*HLA-DQB1*02:01*	5.7 (1.4 - 24.8)	72.2%	68.7%	1.9%	99.7%	59%	64	202
*HLA-DRB1*03:01*	4.9 (1.2 - 20.5)	58.8%	77.5%	2.1%	99.6%	47%	59	257
*HLA-C*12:03*	6.1 (0.9 - 47.4)	38.4%	90.7%	3.4%	99.4%	32%	36	375
*HLA-DPB1*10:01*	20.9 (0.7 - Inf)	33.3%	97.7%	10.7%	99.4%	32%	10	380
*HLA-DRB1*04:04*	20.9 (0.7 - Inf)	61.6%	92.9%	6.8%	99.7%	58%	16	205
*HLA-B*08:01*	3.4 (0.9 - 13.1)	48.0%	78.6%	1.9%	99.4%	34%	77	356

Figure Legends:

Supplementary Figure 1: Plot of principal component 1 vs. principal component 2 for 18 cases and 59 controls gathered for the study as calculated by smartPCA program of EIGENSTRAT package. Two cases were removed as outliers.

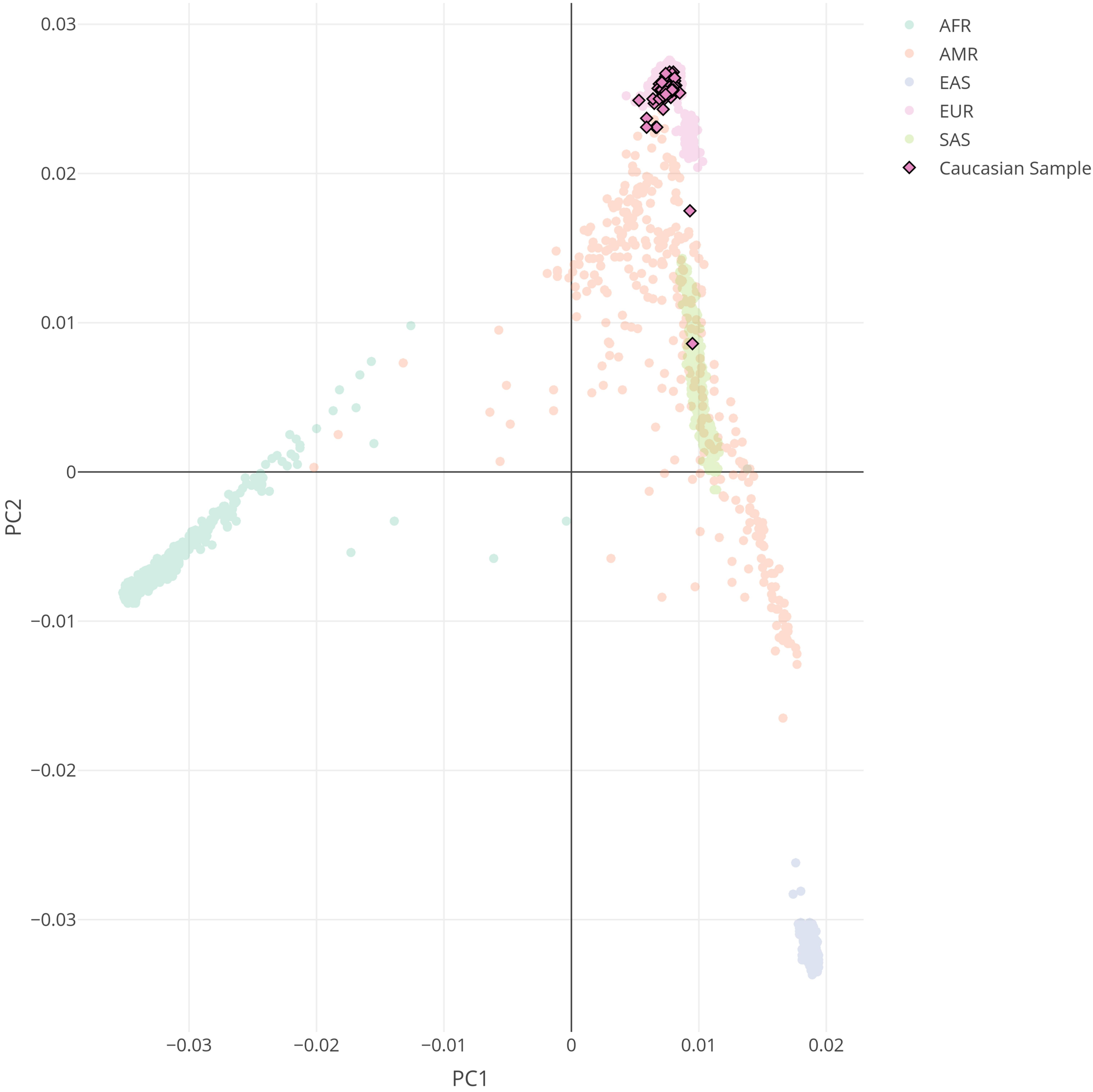
Supplementary Figure 2: Manhattan plot displaying the association results of infliximab-DILI cases (n = 16) vs. matched controls (n = 59). No SNPs are significant at 5×10^{-8}.

Table Legends:

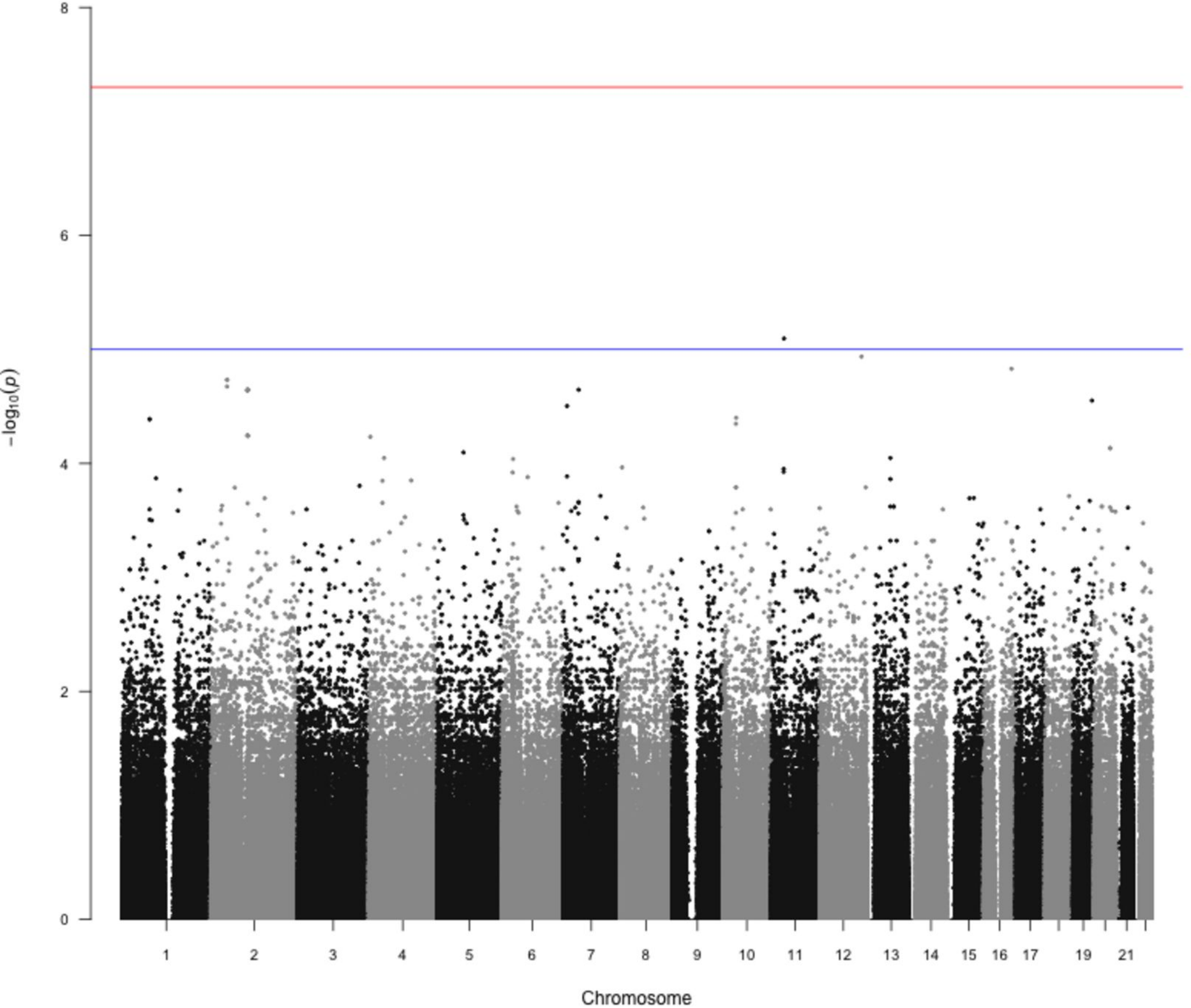
Supplementary Table 2: * Calculated using Fisher's Exact Test. Calculations for OR involving a 0 were recalculated after adding 0.5 to each cell in the contingency matrix.

Supplementary Table 3: Key: 1 indicates allele presence in Reference haplotype, 0 indicates absence in haplotype per row.

Supplementary Figure 1: Plot of PC1 vs. PC2 in 1KG Ethnicities and Self-Reported Caucasian infliximab Users



Supplementary Figure 2: GWAS Manhattan Plot



Supplementary Table 1: Statistics for *HLA-C*07:01* and *HLA-DQA1*05:01*

Allele	Cases (N=16)		Controls (N = 60)		P-Value	Odds Ratio (95% Confidence Interval)
	Present	Absent	Present	Absent		
*HLA-C*07:01*	7	9	14	46	0.124	2.5 (0.7 - 9.3)
*HLA-DQA1*05:01*	7	9	27	33	1.00	1 (0.3 - 3.3)

Supplementary Table 2: Significant HLA Allele Associations in Cases with ALT > 5x ULN

Allele	Cases (N=10)		Controls (N = 60)		P-Value*	Odds Ratio (95% Confidence Interval)*
	Present	Absent	Present	Absent		
*HLA-B*39:01*	3	7	0	60	0.002	56.5 (2.8 - Inf)
*HLA-DQB1*02:01*	4	6	7	53	0.044	4.9 (0.8 - 27.5)
*HLA-DRB1*03:01*	4	6	8	52	0.061	4.2 (0.7 - 23)
*HLA-C*12:03*	3	7	3	57	0.034	7.7 (0.9 - 70)
*HLA-DPB1*10:01*	2	8	0	60	0.019	35.6 (1.2 - Inf)
*HLA-DRB1*04:04*	2	8	0	60	0.019	35.6 (1.2 - Inf)
*HLA-B*08:01*	4	6	11	49	0.205	2.9 (0.5 - 14.9)

Supplementary Table 3: Haplotype Frequencies in AFND References

*HLA-B*08:01*	*HLA-C*07:01*	*HLA-DRB1*03:01*	*HLA-DQA1*05:01*	*HLA-DQB1*02:01*	Ref Freq	Ref Sample Size	Reference Pop
1	1	1	0	1	13.7%	250	Ireland South
0	0	1	1	1	13.1%	1,899	USA European American
0	0	1	1	1	14.4%	220	USA San Francisco Caucasian
1	1	0	0	0	16.0%	1,000	Ireland Northern
1	1	0	0	0	10.8%	265	USA Caucasian pop 2
1	1	1	1	1	43.8%	16	INF Cases
1	1	1	1	1	11.7%	60	INF Controls
1	1	1	1	1	18.4%	76	INF Total