# Supplemental data

**Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and class II alleles**

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**Supplemental Materials and Methods**

Genome-wide association study QC

QC was conducted at both single marker and subject levels. Any marker that did not pass the following criteria was excluded from analysis: (i) genotype call rate in the batch of subjects greater than 95%, (ii) minor allele frequency greater than 1%, (iii) p-value for Hardy-Weinberg equilibrium greater than $10^{-7}$ in controls (if applicable). After applying these criteria, 249,893 markers (including SNPs and CNV probes) were discarded and 822,927 SNPs were left for downstream analysis.

Any subject that did not pass the following criteria was excluded from analysis: (i) missing genotype rate < 0.1 among the SNPs that passed QC; (ii) not a sample duplicate or closely related based on estimated identity-by-descent (IBD) using PLINK v 1.05.[22] In total, 10 cases were discarded on this basis.

HLA genotyping

Typing was performed by sequencing PCR products for exons 2 and 3 for *HLA-A* and *B* and exon 2 for *DRB1*, *DQA1* and *DQB1* on both strands using cycle sequencing with BigDye V3.1 (Applied Biosystems, Foster City, CA) chemistry. For *HLA-A* and *B*, typing, generic PCR amplifications were carried out for each locus.[1] *HLA-A* had additional group-specific amplifications using an A2-specific site in intron 1. The A2-group contains the most common alleles among the *HLA-A* alleles and this additional allele sequencing separated A2-carrying heterozygotes and reduced ambiguous allele combinations. For *HLA-B*, six subgroup amplifications, TA, CG (Di-allelic sites in intron 1)[2], B7, B15, B13, and Bw4 groups, were performed.

HLA class II sequencing was carried out on amplicons produced by group-specific amplifications. A total of 17 gene- and group-specific DRB1 amplifications were performed using exon-based

amplification primers: *DRB1*01*, *DRB1*15/16*, *DRB1*03/11/13/14, DRB1*03/11/13/14-86V, DRB1*11, DRB1*04, DRB1*04-86V, DRB1*07, DRB1*08/12, DRB1*09, DRB1*10.*

In addition to exon-based group-specific sequencing, intron based group-specific sequencing was used for *DRB1*01*-In, *DRB1*15*-In, *DRB1*03/11/13/14*-In, *DRB1*04*-In, *DRB1*08*-In, and *DRB1*10*-In. These newly added intron-based amplifications not only improved the resolution but also the accuracy of the typing by capturing variations at the beginning of exon 2 sequences which were missing in the exon-based group-specific amplicons. Sorting DRB1 sub-groups was accomplished by DRB generic typing. DRB generic typing was carried out by a hybridization-based sequence-specific oligonucleotide probe (SSO) method using AP-conjugated oligo probes. These SSO results were used for sorting *DRB1* subgroups and also for quality assurance purposes.

*DQA1* high resolution typing was achieved by sequencing amplicons generated by *DQA1* generic PCR products. *DQB1* high resolution typing was achieved by sequencing amplicons generated by *DQB1* generic, and three other *DQB1* subgroups. Sequencing data files were analyzed using Histogenetics' proprietary analysis programs Histomatcher and HistoMagic for HLA typing assignment of each sample. Allele assignments are based on IMGT/HLA Database release version 2.21.0 and Release date April 2008 (http://www.ebi.ac.uk/imgt/hla/).

**References**


1. Cereb N, Maye P, Lee S, Kong Y, Yang SY. Locus-specific amplification of HLA class I genes from genomic DNA: locus-specific sequences in the first and third introns of HLA-A, -B, and -C alleles. Tissue Antigens 1995;45:1-11.
2. Cereb N, Yang SY. Dimorphic primers derived from intron 1 for use in the molecular typing of HLA-B alleles. Tissue Antigens 1997;50:74-6.

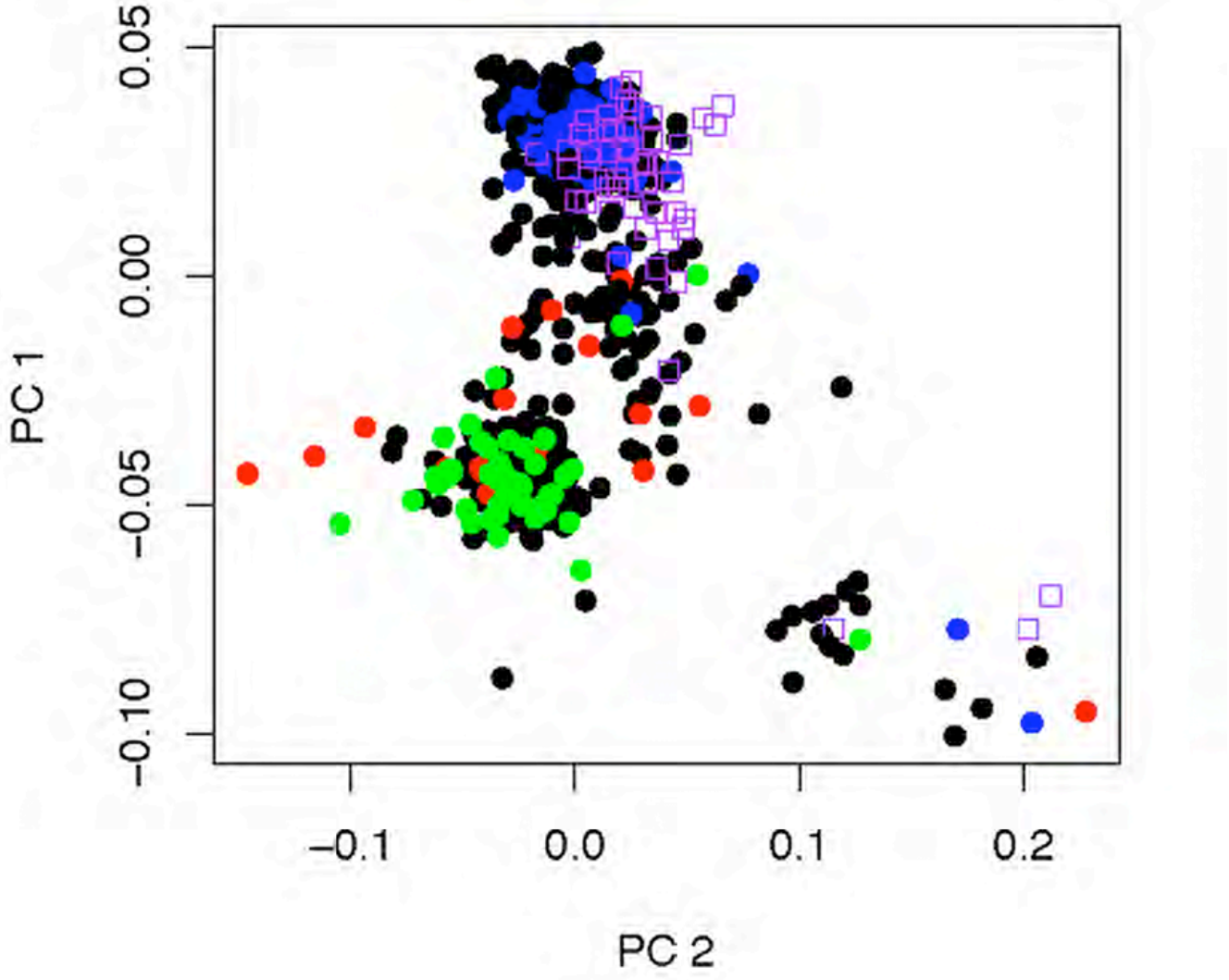
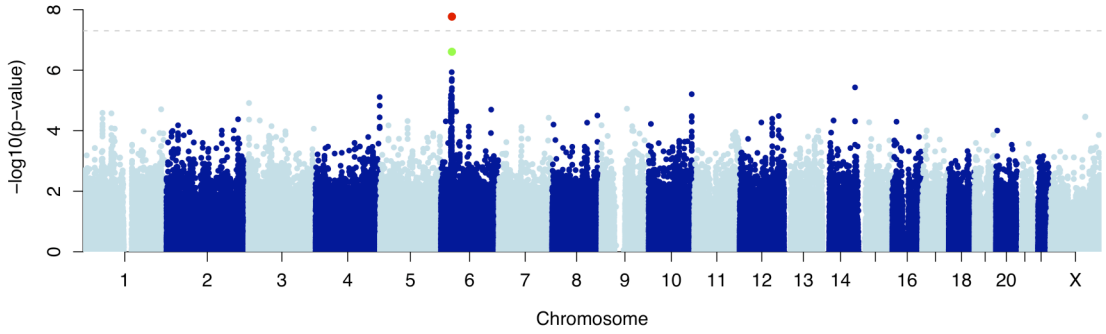
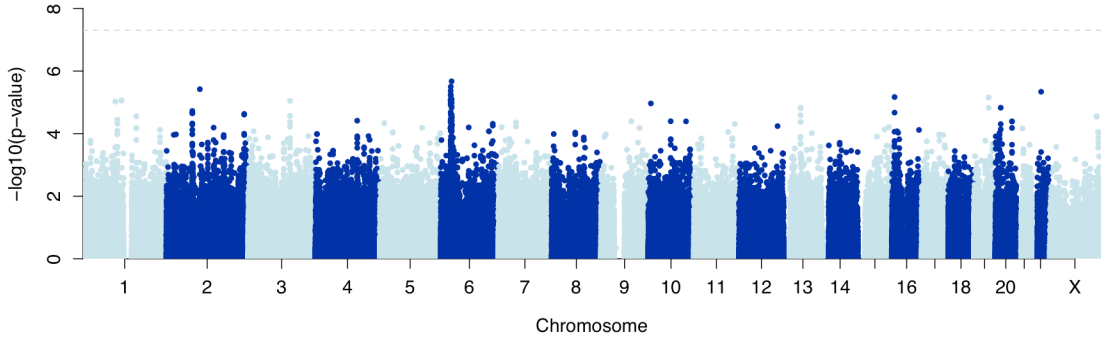



**Figure S1. Population structure of the cases and genetically-matched controls**. Principal component analysis plot for 201 cases and their 532 genetically matched controls. Blue dots: UK cases; Purple squares: DILIN cases; Green dots: Malaga; Red dots: Eudragene; Black: POPRES controls

(a)




(b)




(c)

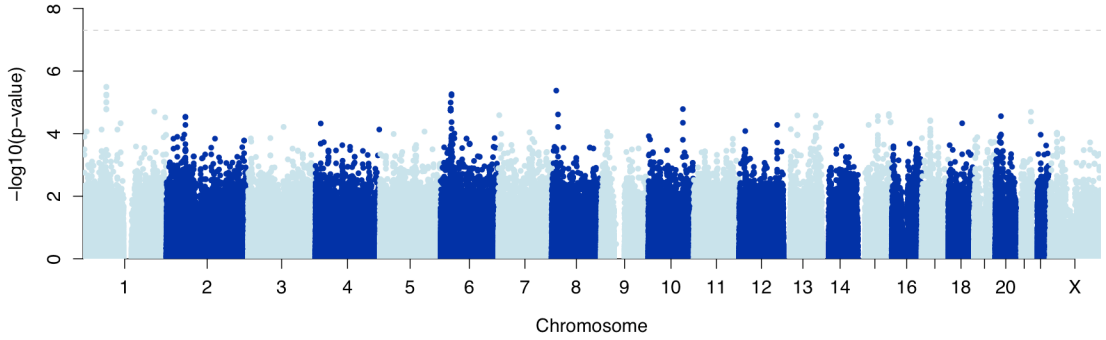
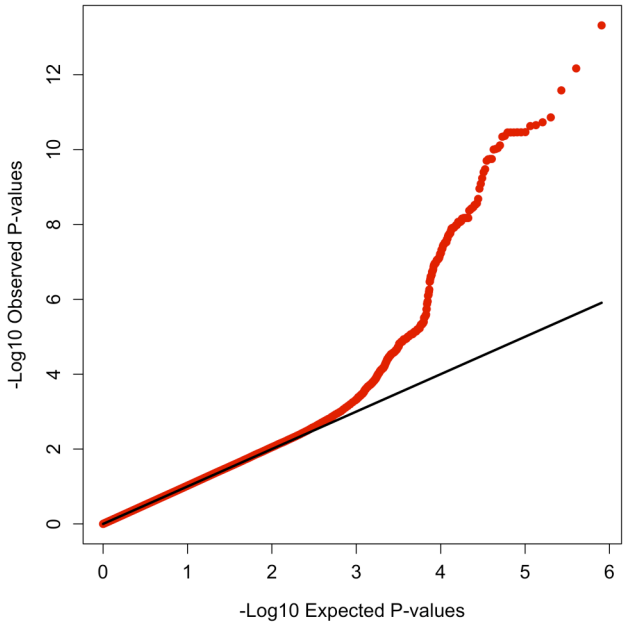



**Figure S2. Manhattan plots for the three groups separately**. (a) UK cases (n=74) versus Northwestern European controls (n=306) (b) DILIN cases (n=51) versus Northwestern European controls (n=306) (c)Spanish DILI Registry cases (n=46) versus Spanish controls (n=160)

A.




B.

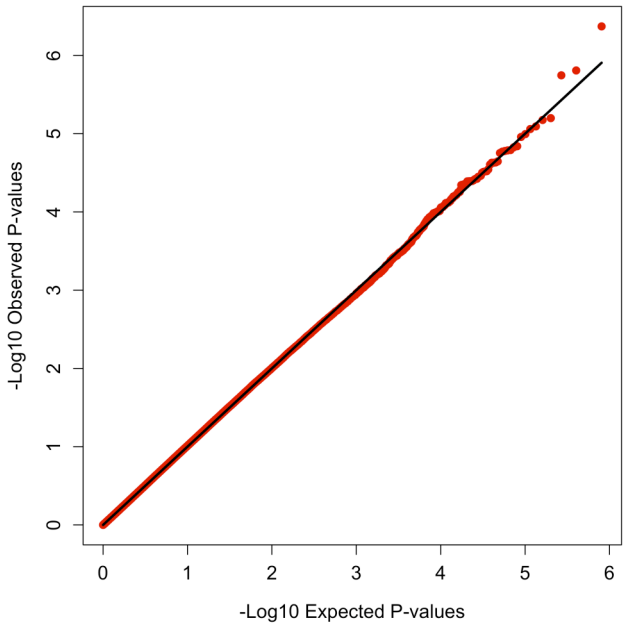
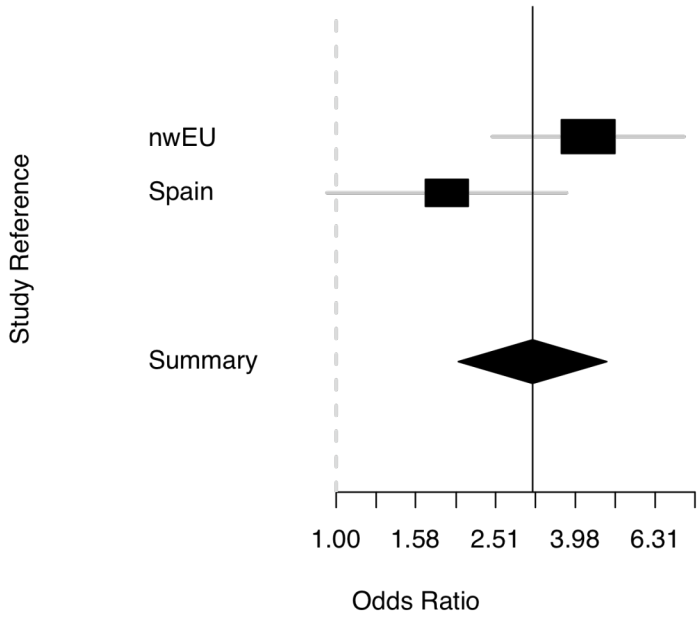



**Figure S3 Quantile-quantile plot of p-values from case-control analyses.** A. The comparison of empirical p-value quantiles from the genome-wide analysis to the expected quantiles under the uniform distribution (null hypothesis). The black solid line represents the null model where observed p-values

match the expected values. The red dots represent observed p-values versus the expected values. B The same as in A, after conditioning on the top class I and II SNPs as in Figure 1D.




p = 0.071.

**Figure S4.** Test of heterogeneity on *A*0201* between Northwestern European and Spanish subjects.

**Table S1. Comparison of clinical characteristics between cohorts**

| **Clinical characteristics** | Test | UK | EUDRAGENE | Spanish DILI Registry | DILIN | Note |
|---|---|---|---|---|---|---|
| Gender | Fisher's exact | 0.24 | 1 | 0.87 | 0.16 | |
| Age | Two sample t-test | 0.75 | 0.054 | 0.66 | 0.24 | |
| Total days on drug | Two sample t-test | 0.0035 | 0.042 | 0.19 | 0.021 | UK vs DILIN: 0.0028 |
| Time to onset | Two sample t-test | 0.00065 | 0.0042 | 0.016 | $1.6x10^{-8}$ | DILIN vs UK: $8.7x10^{-8}$ |
| Pattern of injury | Chi-square | 0.20 | 0.20 | 0.22 | 0.20 | Combining cholestatic and mixed yields similar result |
| Causality (CIOMS) | Two sample t-test | 0.08 | 0.94 | 0.19 | 0.00091 | DILIN contains more probable cases |
| Peak Bilirubin | Two sample t-test | 0.34 | 0.29 | 0.46 | 0.017 | In log scale |
| Peal ALT | Two sample t-test | 0.60 | 0.26 | 0.70 | 0.45 | In log scale |
| Peak ALP | Two sample t-test | 0.31 | 0.59 | 0.14 | 0.79 | In log scale |

Each cell is the p-value from cohort vs all other cohorts.

**Table S2. Top SNPs among reported GWAS hits of autoimmune diseases**

| Top SNPs | Overall | | UK (74 cases vs 306 controls) | | US (51 cases vs 306 controls) | | Spain (46 cases vs 160 controls) | | MAF in nwEU | MAF in Spanish |
|---|---|---|---|---|---|---|---|---|---|---|
| | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | | |
| rs2476601 (chr: 1p13) | $1.3x10^{-4}$ | 2.1 (1.5 – 3.2) | 0.025 | 2.0 (1.1-3.6) | $8.7x10^{-6}$ | 3.9 (2.2-7.0) | 0.48 | 1.4 (0.50 - 3.4) | 0.16 vs. 0.065 | 0.087 vs. 0.063 |
| rs6679677 (chr: 1p13) | $2.3x10^{-4}$ | 2.1 (1.4 – 3.1) | 0.025 | 2.0 (1.1-3.6) | $8.7x10^{-6}$ | 3.9 (2.2-7.0) | 0.64 | 1.2 (0.50 - 3.0) | 0.16 vs. 0.065 | 0.076 vs. 0.063 |

**Table S3. Pair-wise $r^2$ between top SNPs and HLA alleles**

| allele 1 | allele 2 | Northwestern European | | Spanish | |
|---|---|---|---|---|---|
| | | cases | controls | cases | controls |
| rs9274407/Minor | *DQB1*0602* | 0.8 | 0.93 | 0.88 | 0.64 |
| rs9274407/Minor | rs3135388/T | 0.76 | 0.77 | 0.82 | 0.59 |
| rs9274407/Minor + rs3135388/C | *DQB1*0402* | 0.89 | 1 | 0.65 | 0.85 |
| rs3135388/T | *DQB1*0602* | 0.94 | 1 | 0.88 | 0.9 |
| rs3135388/T | *DRB1*1501* | 0.98 | 1 | 0.94 | 1 |
| rs2523822/C | *A*0201* | 0.96 | 0.91 | 0.64 | 0.87 |
| *DRB1*1501* | *DQB1*0602* | 0.91 | 1 | 0.94 | 0.90 |

**Table S4. Frequencies of HLA alleles and haplotypes.**

HLA haplotypes inferred from unphased single gene alleles using Beagle

Five gene haplotype (Class I and Class II)

| | | | NW-EU Controls (n=107) | | | NW-EU Cases (n=134) | | | Spanish controls(n=121) | | | Spanish cases (n=48) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haplotype | count | Overall frequency | alleles | carriers | freq (%carriers) | alleles | carriers | freq (%carriers) | alleles | carriers | freq (%carriers) | alleles | carriers | freq (%carriers) |
| A*0101-B*0801-DRB1*0301-DQA1*0501-DQB1*0201 | 49 | 0.0598 | 18 | 18 | 8.41% (16.82%) | 20 | 17 | 7.46% (12.69%) | 10 | 10 | 4.13% (8.26%) | 1 | 1 | 1.04% (2.08%) |
| A*0201-B*0702-DRB1*1501-DQA1*0102-DQB1*0602 | 38 | 0.0463 | 2 | 2 | 0.93% (1.87%) | 30 | 30 | 11.19% (22.39%) | 1 | 1 | 0.41% (0.83%) | 5 | 5 | 5.21% (10.42%) |
| A*0301-B*0702-DRB1*1501-DQA1*0102-DQB1*0602 | 22 | 0.0268 | 9 | 8 | 4.21% (7.48%) | 6 | 6 | 2.24% (4.48%) | 3 | 3 | 1.24% (2.48%) | 4 | 4 | 4.17% (8.33%) |
| A*0201-B*4402-DRB1*0401-DQA1*0301-DQB1*0301 | 17 | 0.0207 | 5 | 5 | 2.34% (4.67%) | 10 | 10 | 3.73% (7.46%) | 2 | 2 | 0.83% (1.65%) | 0 | 0 | 0.0% (0.0%) |
| A*2902-B*4403-DRB1*0701-DQA1*0201-DQB1*0201 | 17 | 0.0207 | 4 | 4 | 1.87% (3.74%) | 2 | 2 | 0.75% (1.49%) | 8 | 7 | 3.31% (5.79%) | 3 | 3 | 3.13% (6.25%) |
| A*0201-B*5701-DRB1*0701- | 8 | 0.0098 | 2 | 2 | 0.93% (1.87%) | 5 | 5 | 1.87% (3.73%) | 0 | 0 | 0.0% (0.0%) | 1 | 1 | 1.04% (2.08%) |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DQA1*0201-DQB1*0303 | | | | | | | | | | | | | | |
| A*2501-B*1801-DRB1*1501-DQA1*0102-DQB1*0602 | 8 | 0.0098 | 2 | 2 | 0.93% (1.87%) | 5 | 5 | 1.87% (3.73%) | 0 | 0 | 0.0% (0.0%) | 1 | 1 | 1.04% (2.08%) |
| A*0101-B*5701-DRB1*0701-DQA1*0201-DQB1*0303 | 7 | 0.0085 | 3 | 3 | 1.4% (2.8%) | 1 | 1 | 0.37% (0.75%) | 2 | 2 | 0.83% (1.65%) | 1 | 1 | 1.04% (2.08%) |
| A*3201-B*1401-DRB1*0701-DQA1*0201-DQB1*0201 | 7 | 0.0085 | 3 | 3 | 1.4% (2.8%) | 0 | 0 | 0.0% (0.0%) | 3 | 3 | 1.24% (2.48%) | 1 | 1 | 1.04% (2.08%) |
| A*0101-B*0702-DRB1*1501-DQA1*0102-DQB1*0602 | 6 | 0.0073 | 1 | 1 | 0.47% (0.93%) | 5 | 5 | 1.87% (3.73%) | 0 | 0 | 0.0% (0.0%) | 0 | 0 | 0.0% (0.0%) |
| A*0201-B*4001-DRB1*1302-DQA1*0102-DQB1*0604 | 6 | 0.0073 | 1 | 1 | 0.47% (0.93%) | 5 | 5 | 1.87% (3.73%) | 0 | 0 | 0.0% (0.0%) | 0 | 0 | 0.0% (0.0%) |
| A*1101-B*2705-DRB1*0101-DQA1*0101-DQB1*0501 | 6 | 0.0073 | 4 | 4 | 1.87% (3.74%) | 0 | 0 | 0.0% (0.0%) | 2 | 2 | 0.83% (1.65%) | 0 | 0 | 0.0% (0.0%) |
| A*2301-B*4403-DRB1*0701-DQA1*0201-DQB1*0201 | 6 | 0.0073 | 3 | 3 | 1.4% (2.8%) | 1 | 1 | 0.37% (0.75%) | 2 | 2 | 0.83% (1.65%) | 0 | 0 | 0.0% (0.0%) |
| A*3301-B*1402-DRB1*0102- | 6 | 0.0073 | 0 | 0 | 0.0% (0.0%) | 0 | 0 | 0.0% (0.0%) | 6 | 6 | 2.48% (4.96%) | 0 | 0 | 0.0% (0.0%) |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DQA1*0101-DQB1*0501 | | | | | | | | | | | | | | |
| A*0101-B*0801-DRB1*0101-DQA1*0101-DQB1*0501 | 5 | 0.0061 | 3 | 3 | 1.4% (2.8%) | 2 | 2 | 0.75% (1.49%) | 0 | 0 | 0.0% (0.0%) | 0 | 0 | 0.0% (0.0%) |
| A*0201-B*0801-DRB1*0301-DQA1*0501-DQB1*0201 | 5 | 0.0061 | 0 | 0 | 0.0% (0.0%) | 4 | 4 | 1.49% (2.99%) | 1 | 1 | 0.41% (0.83%) | 0 | 0 | 0.0% (0.0%) |
| A*0201-B*1501-DRB1*0101-DQA1*0101-DQB1*0501 | 5 | 0.0061 | 0 | 0 | 0.0% (0.0%) | 4 | 4 | 1.49% (2.99%) | 0 | 0 | 0.0% (0.0%) | 1 | 1 | 1.04% (2.08%) |
| A*0201-B*4001-DRB1*0404-DQA1*0301-DQB1*0302 | 5 | 0.0061 | 3 | 3 | 1.4% (2.8%) | 2 | 2 | 0.75% (1.49%) | 0 | 0 | 0.0% (0.0%) | 0 | 0 | 0.0% (0.0%) |
| A*0201-B*4402-DRB1*1301-DQA1*0103-DQB1*0603 | 5 | 0.0061 | 1 | 1 | 0.47% (0.93%) | 2 | 2 | 0.75% (1.49%) | 1 | 1 | 0.41% (0.83%) | 1 | 1 | 1.04% (2.08%) |
| A*0201-B*4403-DRB1*0701-DQA1*0201-DQB1*0201 | 5 | 0.0061 | 1 | 1 | 0.47% (0.93%) | 2 | 2 | 0.75% (1.49%) | 2 | 2 | 0.83% (1.65%) | 0 | 0 | 0.0% (0.0%) |
| A*2402-B*3502-DRB1*1104-DQA1*0501-DQB1*0301 | 5 | 0.0061 | 0 | 0 | 0.0% (0.0%) | 1 | 1 | 0.37% (0.75%) | 2 | 2 | 0.83% (1.65%) | 2 | 2 | 2.08% (4.17%) |
| A*2902-B*4403-DRB1*1501- | 5 | 0.0061 | 0 | 0 | 0.0% (0.0%) | 2 | 2 | 0.75% (1.49%) | 0 | 0 | 0.0% (0.0%) | 3 | 3 | 3.13% (6.25%) |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DQA1*0102-DQB1*0602 A*3002-B*1801-DRB1*0301-DQA1*0501-DQB1*0201 | 5 | 0.0061 | 0 | 0 | 0.0% (0.0%) | 1 | 1 | 0.37% (0.75%) | 2 | 2 | 0.83% (1.65%) | 2 | 2 | 2.08% (4.17%) |
| Other | 572 | 0.697560976 | 149 | | 0.696261682 | 158 | | 0.589552239 | 195 | | 0.805785124 | 70 | | 0.729166667 |

**Table S5. The relationship between phenotypes and the genotypes of top hits.**

| **Clinical characteristics** | SNP or HLA allele | Nw-EU | Spanish | Overall | Notes |
|---|---|---|---|---|---|
| Bilirubin (log(umol/L)) | rs9274407/Minor | 0.83 | 0.63 | 0.70 | |
| | rs2523822/C | 0.57 | 0.14 | 0.77 | |
| | *DQB1*0602* | 0.92 | 0.55 | 0.82 | |
| | *DQB1*0402* | 0.75 | 0.72 | 0.94 | |
| | *B*1801* | 0.092 | 0.56 | 0.11 | |
| | *B*1801* | 0.30 | 0.31 | 0.27 | hepatocellular cases only |
| Age | rs9274407/Minor | 0.92 | 0.9 | 0.84 | |
| | rs2523822/C | 0.43 | 0.32 | 0.93 | |
| | *DQB1*0602* | 0.83 | 0.61 | 0.62 | |
| | *DQB1*0402* | 0.56 | 0.26 | 0.31 | |
| | *B*1801* | 0.88 | 0.38 | 0.36 | |
| ALT (log(U/L)) | rs9274407/Minor | 0.46 | 0.87 | 0.42 | |
| | rs2523822/C | 0.94 | 0.96 | 0.90 | |
| | *DQB1*0602* | 0.57 | 0.52 | 0.39 | |
| | *DQB1*0402* | 0.62 | 0.24 | 0.36 | |
| | *B*1801* | 0.87 | 0.0056 | 0.029 | ALT is positively correlated with *B*1801* alleles in Spanish cases |
| ALP (log(U/L)) | rs9274407/Minor | 0.050 | 0.43 | 0.049 | ALP is negatively correlated with rs9274407/Minor |
| | rs2523822/C | 0.71 | 0.89 | 0.63 | |
| | *DQB1*0602* | 0.45 | 0.34 | 0.81 | |
| | *DQB1*0402* | 0.050 | 0.43 | 0.049 | |
| | *B*1801* | 0.15 | 0.8 | 0.15 | |

Each cell shows the p-value from linear regression.

**Table S6. Test characteristics based on selected alleles comparing carriers to non-carriers and assuming the probability of AC-DILI to be 0.014%**

| Allele(s) | | nw-EU | Spanish |
|---|---|---|---|
| rs9274407/Minor | specificity | 73.53% | 84.38% |
| | sensitivity | 58.40% | 36.96% |
| | PPV | 0.03% | 0.03% |
| | 1 - NPV | 0.008% | 0.01% |
| rs2523822/C | specificity | 51.63% | 51.25% |
| | sensitivity | 74.40% | 73.91% |
| | PPV | 0.02% | 0.02% |
| | 1 - NPV | 0.007% | 0.007% |
| rs9274407/Minor and rs2523822/C | specificity | 88.24% | 92.50% |
| | sensitivity | 47.20% | 28.26% |
| | PPV | 0.06% | 0.05% |
| | 1 - NPV | 0.008% | 0.01% |
| *DQB1*0602* | specificity | 79.44% | 91.07% |
| | sensitivity | 51.56% | 40.43% |
| | PPV | 0.03% | 0.06% |
| | 1 - NPV | 0.008% | 0.009% |
| *A*0201* | specificity | 59.81% | 56.25% |
| | sensitivity | 74.22% | 59.57% |
| | PPV | 0.03% | 0.02% |
| | 1 - NPV | 0.006% | 0.01% |
| *A*0201* and *DQB1*0602* | specificity | 94.39% | 95.54% |
| | sensitivity | 41.41% | 25.53% |
| | PPV | 0.1% | 0.08% |
| | 1 - NPV | 0.009% | 0.01% |
| *B*1801* | specificity | N/C | 90.18% |
| | sensitivity | N/C | 27.66% |
| | PPV | N/C | 0.04% |
| | 1 - NPV | N/C | 0.01% |
| *B*1801* and *DQB1*0602* | specificity | N/C | 99.11% |
| | sensitivity | N/C | 8.51% |
| | PPV | N/C | 0.13% |
| | 1 - NPV | N/C | 0.01% |