Multiple HLA B*57 alleles, sharing the amino acid residue Valine^{97}, are associated with drug-induced liver injury (DILI) due to flucloxacillin in a European population.

National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK

Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, USA

Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

UGC Digestivo, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd);

Division of Gastroenterology and Hepatology, Department of Internal Medicine, The National University Hospital of Iceland, Reykjavík, Iceland

Medical Research Institute, University of Dundee, Ninewells Hospital, Dundee, UK;

Department of Medical Sciences and Science for Life Laboratory, Uppsala University, Uppsala, Sweden;

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, Netherlands;

School of Medicine and Public Health, University of Newcastle, New South Wales, Australia;

Department of Primary Care and Public Health Sciences, King's College, London, UK;

Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK;

The Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA

Department of Biomedical Informatics, Columbia University, New York, USA

UNC Eshelman School of Pharmacy, Chapel Hill, NC, USA

Target Sciences, GSK, King of Prussia, PA, USA

for the International Drug-induced Liver Injury consortium (iDILIC) and DILIN
Flucloxacillin and Drug-induced Liver Injury (DILI)

- Beta-lactamase resistant penicillin with isoxazolyl ring; effective in the treatment of staphylococcal infections
- Used widely especially in UK, Australia and Sweden
- DILI in 6.1 – 8.5 per 100,000 people
  - Presentation within 45 days of 1\textsuperscript{st} exposure
  - 2\textsuperscript{nd} most important cause of DILI in the UK
  - Rash and fever described
  - Fatality and vanishing bile duct syndrome

Genome-Wide Association Study (GWAS): Flucloxacillin DILI

Strongest signal with SNP in HCP5 gene which tags HLA-B*57:01

Genetic studies on DILI susceptibility

- **DILIGEN (UK-based)**
  - DILI due to co-amoxiclav, flucloxacillin, anti-TB agents, diclofenac
  - Now complete

- **iDILIC (worldwide)**
  - Any licensed drug
  - Data analysis ongoing
Patients and Methods

- GWAS: 197 Flucloxacillin DILI cases (2005-2013)
  - All of European ethnicity
  - 51 of these reported previously (DILIGEN)
- 6835 matched population controls
- Used Illumina HC and 1M chips for genotyping
- Performed imputation to increase data coverage
  - Four digit HLA alleles and amino acid changes were inferred using SNP2HLA
# Patients and DILI characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Gender (F/M)</td>
<td>133/64 (68% female)</td>
</tr>
<tr>
<td>Mean Age (years) (±SD)</td>
<td>62 ± 13</td>
</tr>
<tr>
<td>Mean Time to onset from first exposure (days) (±SD)</td>
<td>24 ± 18</td>
</tr>
<tr>
<td>Total days on drug (±SD)</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>74 (38%)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>39 (20%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>84 (43%)</td>
</tr>
<tr>
<td>RUCAM scores</td>
<td></td>
</tr>
<tr>
<td>3-5 (possible)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>6-8 (probable)</td>
<td>90 (46%)</td>
</tr>
<tr>
<td>&gt;8 (highly probable)</td>
<td>85 (43%)</td>
</tr>
</tbody>
</table>
New GWAS: Results

-\log_{10}(p\text{-value})

Chromosome

MHC region
Results

- *HLA-B*57:01 major Risk factor; allelic OR=36.6; 95% CI 26.14-51.29, p=2.67x10^-97)
- Protective effect from *HLA-B*07:02, *C*07:02 and *DQB1*03:01
- *HLA-B*57:03 is also a risk factor; OR=79.21; 95% CI 13.57-462.2, p=1.2X10^-6)
  - Shown by conditioning on B*57:01
- HLA-B alleles positive for valine-97 had largest effect size; OR 38.1 (27.1-53.6) p = 9.7x10^-97)
  - Different to abacavir hypersensitivity where there is strong specificity for HLA-B*57:01 only
Residues 97, 114 and 116 appear crucial
- Abacavir: B*57:01 only
- Flucloxacinillin: B*57:01 and B*57:03 only
- Neither associates with B*58:01
HLA-B*5701

- Serine 116 essential for binding of abacavir purine group
- Position 97 sits at the bottom of the peptide-binding cleft and is critical for HLA protein conformation and folding

Results

- Arg97 and Ser97 have significant protective effects (OR= 0.43, P=5.13x10^{-14} and OR= 0.53, P=9.82x10^{-7})

- Approx. 20% of flucloxacillin DILI cases not positive for B*57
  - HLA-A*02:02 enriched in these cases (OR 16.57, (2.05-133.8) p = 0.008)
  - Two other class I alleles, A*30:01 and B*13:02, also show significant associations (P=0.009 and 0.017)

- Amoxicillin and other isoxazolyl penicillin DILI cases don’t share HLA alleles seen in either the B*57 positive or negative flucloxacillin DILI cases
  - Suggests that there isn’t a common genetic risk factor relating to T cell response to the beta lactam structure
Summary

- Strong association of Flucloxacillin DILI with HLA B*57:01 confirmed in an enlarged cohort
- Novel association with B*57:03 detected
- No evidence for non-HLA genetic risk factors
- Abacavir hypersensitivity is associated only with B*57:01 and appears to have a different mechanism from flucloxacillin DILI
- 83% of DILI patients and 6% normal with HLA-B*5701/03; Genetic factors can support the diagnosis of DILI in specific scenarios