Designing cohorts to study genetics of drug safety: ADRs

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Why study the genetic basis of ADRs?

• Identifying genes which influence susceptibility to ADRs would contribute to

Understanding the molecular basis of ADRs
-design of safer drugs-examine drug targets for disease syndromes that occur both as ADRs and spontaneously

Development of tests to predict susceptibility
– Warfarin dosing with CYP2C9 & 19
Research on genetics of ADR susceptibility

• most drugs need degradation before excretion in urine or bile
  – cytochrome P-450-2D6 (oxidative)
  – N-acetylation pathway (synthesis of a new molecule)

2 main types of reaction

• Dose-dependent (Type A) reactions: can study genetic effects on drug metabolism and excretion

• Idiosyncratic (Type B) reactions: not generally dose dependent
In the news
GWAS Manhattan plot Flucloxacillin DILI

*HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin*  
Ann K Daly, Peter T Donaldson, Pallav Bhatnagar, Yufeng Shen, Itsik Pe’er, Aris Floratos, Mark J Daly, David B Goldstein, Sally John, Matthew R Nelson, et al.  
*Nature Genetics* 41, 816-819 (31 May 2009) doi:10.1038/ng.379 Letter
Flucloxacillin DILI

- Association peak rs2395029G mis-sense polymorphism in HCP5 gene (liver inflammation) in complete LD with HLA-B*5701 (MHC) OR 80.6, p=9 x 10^{-19} 51 cases; 282 controls
- Replicated in cohort of 23 cases
- In HLA-B*5701 cases, rs10937275 in ST6GA1 csome 3 showed genome wide significance OR 4.1 p=1.4 x 10^{-8}
- No structural similarity with abacavir
- However low PAF 0.64; allele freq rarer in non European populations than Europeans (6%)
ADR monitoring

• In the UK through Committee on Safety of Medicines and Medicines and Healthcare products Regulatory Agency (MHRA, formerly MCA) launched 1964

• Yellow card system for physicians, dentists, pharmacists & other healthcare professionals to report ADRs

• Patients can also now make reports

• FDA MEDWATCH & European PV similar

• Key problem is underreporting
The challenge: Why an international collaboration is necessary

• Few serious type B ADRs: ~5 reports annually per 10 million population (but true rate probably \( >10 \times \) higher)
• Many fragmented case collections
• Case ascertainment requires large populations
• Complex phenotypes
Why a case-control design is appropriate

• Serious Type B ADRs are rare: prescription event cohorts will not yield enough cases
• Exposure (genotype) can be determined retrospectively
• Linkage studies not feasible because families with multiple affected members are not available
Case definitions

- Strict case definition for each class of ADR based on review of:
  - clinical data
  - laboratory evidence where available (e.g. Liver Function Tests)
  - temporal sequence from drug exposure to ADR (± outcome of re-challenge)
  - can restrict collection to definite cases
Proposed sampling frame for controls

Population-based controls (later stage)
- age, ethnicity and sex matched
  - statistical methods can deal with hidden stratification and selection bias in the analysis of genetic associations (genomic inflation factor; EIGENSTRAT)
  - matched by drug in some controls to avoid confounding by indication in some ADRs
  - Possible use of controls from genotype banks e.g. GSK POPRES; WTCC; 1000genomes project
Questionnaire

- Medical and drug history including dosage-checked with medical records/yellow card data
- Demographic data
- Data on environmental exposures associated with condition
- Ethnicity
- Alcohol use
- Specific additional questions for each class of ADR
Information flows: case ascertainment

Reports of ADRs

Hospital/GP records

Patient responds to study co-ordinator

Study co-ordinator excludes ineligible cases and contacts reporting dr to forward patient invitation using report ID

Study co-ordinator passes patient details to researcher (RA)

Reporting Dr replies
RA invites pt Qu, consent + DNA

RA retrieves med records,

Data Q, medical records

lab: DNA

database

Case review
Feedback of results

- Patient will be asked to consent to
  - release of clinical and laboratory data to investigators
  - use of anonymized sample for genetic studies of ADR susceptibility
- Because sample are irreversibly anonymized, patients cannot be informed of their results
- Longer term: discoveries of tests that predict susceptibility can be fed back via pharmacovigilance agencies
- Genetic testing of individuals should be undertaken by licensed laboratories (UK Genetic Testing Network advises NHS)
What classes of adverse reaction should be studied?
Liver injury (NSAIDS) commonest cause of withdrawals (CTs PM); ~130 cases collected via EUDRAGENE

- Symptoms of liver disorder (vomitting, abdominal pain, jaundice)
- And elevated ALT alanine aminotransferase to > x 2 upper limit normal
- Or elevated AST aspartate transaminase and ALK P alkaline phosphatase AND total bilirubin to > x 2 upper limit normal
- Exclusions previous liver disease, viral hepatitis, malignancy, HIV, gallbladder or pancreas disease, rheumatoid, sarcoidosis
The problem: Drug Induced Liver Injury DILI

- Multiple drugs
- Overlapping phenotypes
- Establishing causality WHO algorithm; ICC RUCAM (Roussel Uclaf Causality Assessment Method) score for hepatotoxicity
- Missing data
Classification scoring using RUCAM data

<table>
<thead>
<tr>
<th>Classification</th>
<th>Question (if no. of days is required, enter 'N' for not applicable, and 'U' for unknown)</th>
<th>Answer</th>
<th>Units</th>
<th>Specify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Enzymes</td>
<td>ALT level?</td>
<td>SI</td>
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<tr>
<td></td>
<td>ALP level?</td>
<td>SI</td>
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<tr>
<td></td>
<td>ALT:ALP ratio</td>
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<td>Time to onset</td>
<td>Known is it a slowly metabolized drug?</td>
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<td>Days</td>
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<td></td>
<td>After how many days did the reaction occur after the subsequent drug intake? (second exposure)?</td>
<td>Days</td>
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<td>After how many days did the reaction occur after discontinuation of the drug? (first exposure)?</td>
<td>Days</td>
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<td></td>
<td>After how many days did the reaction occur after discontinuation of the drug? (second exposure)?</td>
<td>Days</td>
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<td></td>
<td>Has ALT, ALP or total bilirubin decreased by more than 50% of the excess over the upper limit normal after discontinuation? (first exposure)</td>
<td>Days</td>
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<tr>
<td></td>
<td>No of days from discontinuation of drug to the decrease in ALT, ALP or total bilirubin by 50% or more of the excess over upper limit of normal?</td>
<td>Days</td>
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<tr>
<td></td>
<td>Has ALT or ALP or total bilirubin decreased by less than 50% of excess over upper limit normal after discontinuation? (first exposure)</td>
<td>Days</td>
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<tr>
<td></td>
<td>No of days from discontinuation of drug to the decrease in ALT, ALP or total bilirubin by less than 50% of the excess over upper limit of normal?</td>
<td>Days</td>
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<td>Was there recurrent increase in ALT after the drug was discontinued?</td>
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<td>Was there a persistence or an increase in APH, after the drug was discontinued, or is this information unavailable?</td>
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<td>Risk-Factors</td>
<td>Was alcohol taken at the time of reaction?</td>
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<td>Concomitant Drugs</td>
<td>Was patient taking any other drugs before or at the time of the onset of the reaction?</td>
<td>Days</td>
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<td></td>
<td>If yes,</td>
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<td>After how many days did the reaction occur after initial exposure to the concomitant drug? (choose minimum)</td>
<td>Days</td>
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<td>After how many days did the reaction occur after secondary exposure to the concomitant drug?</td>
<td>Days</td>
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<td>Are any of the concomitant drugs known to cause hepatotoxicity? (within six months preceding initial reaction)</td>
<td>Days</td>
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<td>Has the concomitant drug been proven to be the causes of hepatotoxicity in this case (by positive re-challenge, validated test or toxic levels)?</td>
<td>Days</td>
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<td>Search for nondrug causes</td>
<td>Acute recent hypotension history ?</td>
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<td></td>
<td>Recent viral infection shown by HAV serology, + and specify type / - not done</td>
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<td></td>
<td>Recent viral infection shown by HBV serology, + and specify type / - not done</td>
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<td></td>
<td>Recent viral infection shown by HCV serology (also circumstantial arguments for non A, non B hepatitis), + and specify type / - not done</td>
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<td></td>
<td>Evidence of biliary obstruction on ultrasound, + / - / not done</td>
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<td>Alcoholism and (AST ALT 1:2)</td>
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<td>Complications of underlying disease(s): clinical and/or biological context suggesting CMV, EBV or herpes infection</td>
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<td>Response to readministration</td>
<td>Has the patient been re-exposed to the causative drug?</td>
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<tr>
<td></td>
<td>If yes,</td>
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<tr>
<td></td>
<td>Has a doubling of ALT or ALP or Total Bilirubin occurred when re-exposure to the causative drug alone?</td>
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<tr>
<td></td>
<td>Has a doubling of ALT or ALP or Total Bilirubin occurred with the drugs already given at the time of the first reaction?</td>
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<td></td>
<td>Has an increase in ALT or ALP or Total Bilirubin occurred, but less than ULN in the same conditions for the first administration?</td>
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<td></td>
<td>Are the liver enzyme results for re-exposure not available nor interpretable?</td>
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Myopathy/rhabdomyolysis (statins, fibrates)

- Muscle pain tenderness or weakness
- Elevated creatinine kinase (x 5-10 normal)
- Exposure to drug within last 3 months
- Exclusions recent steroid use, inflammatory muscle disease, hyperthermia, seizures, acute trauma, dehydration, burns, HIV, salmonella, influenza, herpes
Steven Johnsons Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Inclusion criteria:
• => 18 years; hospitalised
• widespread exanthema with ≥1% detachment epidermis, ≥ 1 blister, with or without mucous membrane erosions

Exclusion Criteria:
• Medically or mentally unfit
• HIV positive
• bone marrow transplant recipient
• Immunocompromised
Case ascertainment UK: Primary Care Databases

- THIN and AIS (information division) have helped us identify 18 cases statin associated myopathy with elevated CK measurements of which 9 (50%) have been recruited
- 330 practices 2.4 million active pts
- 98% patients registered with a GP
- Other initiatives using EHR in US underway with SAEC
Pharmacovigilance networks in Europe

- Identified PVA reports across a number of ADR classes (Europe)
- In many PV centres these can be electronically searched
- A number of cases have also been recruited in the UK using MHRA yellow card ascertainment across DILI SJS and myopathy
UK MHRA case ascertainment

DILI 2000-2008

- 219 possible cases
- 34 excluded due to illness/self reports
- 185 letters 1st mailing; 131 reminders sent
- 30 refused/pt or dr not identified
- 4 pt declined
- 9 dr agreed and in progress
- 10 patients recruited w DNA

- Other European networks show case ascertainment rates of around 20%
Methodological challenges

- Sample size
- Heterogenous drug effects and multiplicity of drugs
- Confounding by indication: risk false positive results
- Control selection
- Phenotype misclassification
- Exploring use of Bayesian hierarchical modeling for SNPs and drugs (methods for accounting for LD between markers and simultaneously analysing all SNP data in GWAS)
Next steps

- GWAS of DILI underway with SAEC
- Further analyses planned for SJS/TEN and other ADRs
- Collaborators for Phenotype Standardisation Project SJS; DILI; LQT
- Extending ADR collections and sites
Recent initiatives in UK

- Role of primary care
- NIHR Clinical Research Network
- Scan GP electronic medical and prescribing records
- Involves recruiting practices/hospitals
- DB search based on queries with READ/ICD medical and BNF drug codes
- Augment with collaborator clinical networks e.g. dermatology etc.
Proposed methods of case ascertainment: CRN using primary care EHR

- Several practices have completed initial searches
- We have developed detailed search strategies for DILI, SJS and myopathy
- Several patients already recruited
- Opportunities to share experience and feedback
Recruitment in EUDRAGENE UK

- So far, we have 98 practices across 9 Clinical Local Research Networks CLRNs in the UK recruited to scan their databases for DILI, Myopathy and SJS.
- 56 practices are piloting searches

<table>
<thead>
<tr>
<th>Cheshire and Merseyside</th>
<th>Kent and Medway</th>
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<tbody>
<tr>
<td>Cumbria and Lancashire</td>
<td>N&amp;E Yorkshire and N Lincolnshire</td>
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<tr>
<td>Greater Manchester</td>
<td>Northumberland, Tyne and Wear</td>
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<tr>
<td>County Durham and Tees Valley</td>
<td>London (S)</td>
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<td>London (NW)</td>
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Recruitment update EUDRAGENE UK

• EUDRAGENE UK has research governance approval in 125 of 164 Primary Care Trusts, across the UK (others pending)

• We intend to access a further 15 CLRN’s (each yielding between 15-40 practices), depending on the outcome of the current action

• There is also the possibility to further expand (Scotland, Northern Ireland and Wales)
Scotland to be included as part of phase 2, but will recruit via their centralised EHR resource. This is to be coordinated with SPCRN.

Potential to expand EUDRAGENE into Wales after July 2010, if required.
Data/Project Management

A central database system is used to control all aspects of the project, from PCRN communication, PCT research governance approval status, practice expression of interest and patient recruitment. We are requesting patient/doctor action via a system of mail merges.
Data/Project Management

Regarding management of the questionnaire data, we have a secure website hosted at LSHTM, www.eudragene.org, where data is uploaded to be combined with the data retrieved
Acknowledgements

- All EUDRAGENE collaborators
- Funding support NIHR, SAEC
- Arthur Holden, Matt Nelson, Yufeng Shen, Itsik Pe’er Aris Floratos, Ann Daly, Munir Pirmohamed, Julian Arbuckle, Guruprasad Aithal & SAEC (Serious Adverse Events Consortium) and collaborators
- John Whittaker Richard Jackson
- All Practice Managers, Nurses, GPs and practice staff involved
- THIN and AIS
- MHRA
- EU-ADR FP7 www.alert-project.org
- www.eudragene.org
- www.saeconsortium.org