Genome Medicine

MEETING REPORT

Pharmacogenetics and pharmacogenomics: practical applications in routine medical practice

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Abstract

A report of the 3rd joint European Science Foundation and University of Barcelona Conference in Biomedicine, San Feliu de Guixols, Catalonia, Spain, 6-11 June 2010.

This was the third meeting on pharmacogenetics and pharmacogenomics organized by the European Science Foundation and University of Barcelona. The meeting was chaired by Laurent Becquemont (Université Paris-Sud, France), with Ann Daly (University of Newcastle, UK) as co-chair. It was attended by more than 100 people and covered a wide range of topics, including genome variability, pharmacogenomics of adverse drug reactions, cardiovascular diseases, transplantation and personalized cancer treatment. In addition, informative sessions on current knowledge of technology, methodology, application of pharmacogenetics in drug companies and regulatory agencies complemented the interesting and varied program of the conference. There was a strong emphasis on the application of pharmacogenetics in routine clinical practice, which was discussed in length at the end of each plenary session with good contributions from all participants. A friendly atmosphere encouraged even the youngest researchers to express their opinions in formal discussion as well as in informal after-session conversation.

Patrice Jaillon (Hôpital Saint Antoine, Paris, France) provided an overview of the contribution of pharmacogenetics to clinical pharmacology. He emphasized that the personalized medicine era is already upon us and, in some clinical specialties, such as cancer medicine, pre-treatment genetic testing is required in order to prescribe effective and safe drugs. A list of drugs for which genetic testing is required is available from several websites (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm; http://www.ema.europa.eu/).

Becquemont discussed an important issue of study design in clinical pharmacogenetics. Most of the findings so far have been based on candidate gene approaches and only a few randomized controlled trials have been conducted. One example is the PREDICT1 study conducted in Australia to establish the effectiveness of prospective screening for the human leukocyte antigen variant *HLA-B*5701* to prevent the hypersensitivity reaction to abacavir, which is used to treat HIV infection.

The recent expansion of genome-wide association studies (GWASs) was discussed by Matt Nelson (GlaxoSmithKline, Research Triangle Park, NC, USA). Study design, quality control of genotype and individual sample data, together with full reporting of ethnicity, are crucial components for correct interpretation of genome-wide analyses. Conducting both appropriate follow-up and replication in an independent cohort is necessary to validate associations found through an unbiased GWAS approach.

Pharmacogenetics of adverse drug reactions

The importance of GWASs was stressed throughout several talks in the Pharmacogenomics of Adverse Drug Reactions session. Daly provided an overview of drug-induced liver injury (DILI) and presented two genome-wide studies on penicillin-induced DILI. Flucloxacillin (an antibiotic) has been found to be associated with the *HLA-B*5701* allele (with a high odds ratio of 80), whereas *DRB1*1501* (*HLA class II, beta chain*) seems to be the most important marker for DILI induced by co-amoxiclav (an antibiotic). It is apparent that the associations between different HLA alleles and DILI are drug-specific. A further example confirms this hypothesis; hepatotoxicity induced by lumiracoxib, a selective COX-2 inhibitor (non-steroidal anti-inflammatory drug), has recently been associated with the *DQA1*0102(HLA class II, alpha chain)* allele. Despite these striking associations in terms of statistical significance (P-values < 3.5×10^{-35}), the clinical utility of genetic markers for predicting liver toxicity is very limited. The negative predictive value of

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*HLA-B*5701* for flucloxacillin-induced toxicity approaches 1, but given the low prevalence of DILI (7×10^{-5}), its positive predictive value is low (0.0009), therefore preventing its use as a predictive marker for DILI. The use of genetic testing as a diagnostic tool, rather than as a predictive marker, was also discussed.

Ana Alfirevic (University of Liverpool, UK) discussed drug-induced hypersensitivity reactions and HLA associations. Considerable progress has been made in determining the genetic factors responsible for carbamazepine (a drug to treat epilepsy)-induced maculopapular exanthema (a skin reaction) and drug-induced hypersensitivity reactions with systemic symptoms, but clinical application of HLA typing in Caucasian populations is not ready to be translated into routine medical practice. Further effort to standardize phenotype and identify affected individuals through international collaboration has been initiated recently with the help of the Serious Adverse Events Consortium (http://www.saeconsortium.org/). The International Consortium on Drug Hypersensitivity and the SAE Phenotype Standardization Program are two initiatives that will undoubtedly help researchers to achieve better results through the collection of diverse patient cohorts and integrated genomic support.

Several other adverse drug reactions, including statin-induced myopathy, were discussed at the meeting. Mikko Niemi (University of Helsinki, Finland) discussed statin-induced myopathy in relation to polymorphisms in transporter genes. All statins are substrates for the organic anion-transporting polypeptide 1B1 (OATP1B1), but the effects of the *SLCO1B1* (*Solute carrier organic anion transporter family member 1B1*) gene polymorphisms differ greatly depending on which statin has been used. Most statins are also substrates for efflux transporters and it has been proposed that *ABCG2* (ATP-binding cassette sub-family G member 2) may have potential clinical value to guide and increase the safety of statin therapy.

Personalized cancer treatment

Pierre Laurent-Puig (INSERM, Université Paris V, France) discussed the individualization of epidermal growth factor receptor (EGFR)-targeted therapy in patients with colorectal cancer. *KRAS* (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) mutations are the major determinant of response to anti-EGFR antibody therapy; however, in the population of cancer patients with wild-type *KRAS* tumors, other mutations have a significant role, including the Val600Phe mutation in BRAF, a principal downstream effector of KRAS. Interestingly, tumors with wild-type *KRAS* and *BRAF* and increased *EGFR* gene copy number have a high response rate (80%). These findings could help clinicians in selecting which colorectal cancer patients should be treated surgically.

Hiltrud Brauch (Margarete Fischer-Bosch Institut für Klinische Pharmacologie (IKP), Stuttgart, Germany) showed new developments in the pharmacogenetics of cytochrome P450 2D6 (CYP2D6) and tamoxifen outcome in early breast cancer and confirmed a strong relationship between a patient's capacity to metabolize tamoxifen and treatment outcome. A stratification of endocrine treatment based on *CYP2D6* genotype has the potential to reduce breast cancer recurrence and mortality. Mathias Schwab (University of Tübingen and IKP, Stuttgart, Germany) discussed the individualization of thiopurine methyltransferase therapy (used to treat cancer) and stressed the need for integrative approaches that will include microarrays, genome-wide association data, systems biology and regulatory epigenetics.

Pharmacogenetics of cardiovascular diseases

In the Cardiovascular Disease session, Celine Verstuyft (Université Bicêtre, Le Kremlin-Bicêtre, France) presented the pharmacogenetics of clopidogrel (an antithrombotic drug). In the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study it was shown that patients on clopidogrel carrying the *CYP2C19* loss-of-function allele had an increased risk of cardiovascular events when undergoing percutaneous coronary intervention. Prasugrel could be considered as an alternative as it did not show these deleterious effects, but it was more toxic. Therefore, the clinical implications of these findings are still very much the subject of debate.

Mia Wadelius (Uppsala University, Uppsala, Sweden) and one of us (AH-M-vdZ) discussed pharmacogenetic interactions between coumarins (anticoagulant drugs) and *VKORC1* (Vitamin K epoxide reductase complex subunit 1) and the cytochrome P450 gene *CYP2C9*. These genes have been shown to be important in both candidate gene studies and in GWASs. In Europe, the clinical utility of genotyping before starting therapy with a coumarin (warfarin, acenocoumarol or phenprocoumon) will be studied in the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial. Martin Fromm (University of Erlangen, Germany) showed that drug transporters (such as *SLCO1B1* (*Solute carrier organic anion transporter family member 1B1*)) and organic cation transporters (for example *SLC22A1/A2* (*Solute carrier family 22 member 1/member 2*)) might have a role in the efficacy of oral hypoglycemic agents.

Felix Frueh (Medco Health Solutions, Bethesda, MD, USA) explained the implementation of pharmacogenetics by Medco Health Solutions. If patients are prescribed a certain drug (for example, warfarin) their general practitioner will be contacted by telephone. If the general practitioner agrees with performing a pharmacogenetic test (67%) the patient will be contacted to be informed

about the possibility of using a genetic test to find out whether the medication should be adjusted. If the patient agrees to use the test (82%), the test will be sent to the patient. Finally, the test will be sent to the Medco laboratory, and, if necessary, the general practitioner can be advised to recommend changes to the medication.

Pharmacogenomics of organ transplantation

In the session on pharmacogenomics of organ transplantation, Eric Thervet (Université Paris Descartes, France) presented the Tacrolimus in Renal Transplantation Individualization Through Pharmacogenetic (TacTic) study. In this study tacrolimus, an immunosuppressive drug used to prevent rejection in organ transplantation, was dosed according to *CYP3A5* genotype in one arm of the study, and in the usual daily dose in the second arm. The primary outcome of the study (fewer dose modifications) was significantly different between the two arms. However, there was no difference in clinically relevant endpoints. Ron van Schaik (Erasmus University, Rotterdam, the Netherlands) presented the pharmacogenetics of mycophenolic acid, an immunosuppressive drug used to prevent rejection in organ transplantation. Two genes, *UGT1A9* (*UDP-glucuronosyltransferase 1 family polypeptide A9*) and *SLCO1B3* (*Solute carrier organic anion transporter family member 1B3*), have been suggested to influence the efficacy of organ rejection prevention. However, there is not enough evidence for clinical implementation. Evelyne Jacqz-Aigrain (INSERM, Hôpital Robert Debré, Paris, France) talked about the pharmacogenetics of immunosuppressants in pediatric organ transplantation. She emphasized the importance of specific research in children; 28% of the world's population is under 18 years of age. Given the differences in pharmacokinetics in children compared with the adult population, it is important to conduct pharmacogenetic studies in children, and these studies should be performed in different age groups.

Pharmacogenetics: hope or hype?

Ingolf Cascorbi (Christian Albrechts University, Kiel, Germany) delivered the final talk of the conference in which he discussed whether pharmacogenetics was a 'hype or hope'. He presented an overview of examples of pharmacogenetic utility that were considered during the conference. He added that the US Food and Drug Administration now requires genetic testing before starting therapy with abacavir and carbamazepine (in patients of Han Chinese or Thai origin) and also recommends testing before starting warfarin, irinotecan (a drug used in cancer) and azathioprine (an immunosuppressive drug) therapy. Furthermore, there is a long list of drugs used in cancer therapy for which a pharmacogenetic test is required (for example, imatinib, nilotinib, dasatinib, trastuzumab, cetuximab, erlotinib and gefitinib). These examples show that pharmacogenetics is becoming more common in clinical practice. New developments in genotyping technologies, including next generation sequencing and the role of epigenetics, will move the field of pharmacogenetics forward.

We can conclude that pharmacogenetics is not hype. Pharmacogenetics already has a role in clinical practice and we believe that it will have an even more prominent role in personalizing pharmacotherapy in the future.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Both authors have been involved in drafting the manuscript and revising it critically and have given final approval of the version to be published.

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