Genomic Med. (2008) 2:189–191
DOI 10.1007/s11568-009-9123-4

ABSTRACTS

Pharmacogenomics and toxicogenomics

052: An acute antidepressant pharmacogenomic study and association of *ADM*, a paroxetine-regulated gene, with antidepressant response

[1]**Dylan M. Glubb**, [2]Peter R. Joyce, [1]Martin A. Kennedy

[1]Department of Pathology, University of Otago, Christchurch, P.O. Box 4345, Christchurch, New Zealand, [2]Department of Psychological Medicine, University of Otago, Christchurch, P.O. Box 4345, Christchurch, New Zealand

Aim Genes which are regulated by antidepressants may associate with antidepressant response or be susceptibility factors for mood disorders. We decided to explore acute antidepressant-induced gene expression changes in a serotonergic cell line to find candidate genes for association studies.
Methods Differentiated RN46A cells were exposed to the antidepressant paroxetine for 36 h. RNA was taken for microarray analysis using Affymetrix rat 230 2.0 GeneChips and quantitative PCR (Q-PCR) assays were developed to validate transcriptional changes. From the gene expression study, the human homologue of *Adm* was screened for genetic variation and a single nucleotide polymorphism (SNP) was identified. Reporter gene assays examined expression of the two alleles and association studies were carried out in a family study of depression.
Results 253 genes were found to be differentially expressed after paroxetine treatment. The expression of two genes (*Id2* and *Ucn2*) were validated by Q-PCR methods and the transcriptional changes of a further three genes (*Adm*, *Bnip3* and *Ankrd37*) approached conventional statistical significance ($p < 0.1$). *ADM* was chosen as a candidate gene for association studies because of its relatively large paroxetine-induced expression change and the previous association of ADM levels with bipolar and other psychiatric disorders. Screening of the upstream and 5′ region of *ADM* identified-1923 C>A SNP (rs11042725). The C allele of this SNP had less expression than the A allele in reporter gene assays in RN46A cells and the C/C genotype was associated with less likelihood of response to paroxetine in depressed individuals.
Conclusions This study needs to be replicated in an independent cohort before the association of *ADM*-1923 C/C with response to paroxetine can be confirmed. However, this work has shown that the pharmacogenomic approach can be successfully used to identify genes which may associate with antidepressant response.

053: Pharmacogenomic study of drug transporter ABCB1 and CYP3A4*1B, CYP3A5*3 polymorphisms associated with daily dose requirement of cyclosporine A to prevent renal allograft rejection in North India

Rama Devi Mittal, Ranjana Singh, Aneesh Srivastava, Anant Kumar, Rakesh Kapoor

Department of Urology and Renal Transplantation, Sanjay Gandhi Post Graduate Institute of Medical Sciences, India

Introduction Cyclosporine A (CsA) is a substrate of cytochrome P-450 3A (CYP3A) and ATP binding cassette subfamily B member 1 (ABCB1). Inter-individual heterogeneity in the expression of CYP3A4, CYP3A5 and ABCB1 genes has been suspected to be one of the factors resulting in CsA pharmacokinetic variation.
Objective The present study explored the association of CYP3A4, CYP3A5 and ABCB1 SNPs on CsA dose requirements and dose-adjusted C2 levels (CsA level/daily dose requirement) in renal allograft recipients.
Methods Daily doses (mg/kg/day) and dose-adjusted C2 levels (μg/ml per mg/kg/day) at 1 and 3 months post transplantation for 155 recipients on CsA immunosuppression based therapy were compared with frequency distribution of CYP3A4*1B-290A>G, CYP3A5*3 c.6986A>G, and ABCB1 c.1236C>T, c.2677G>T, c.3435C>T. C2 levels (μg/ml) in whole blood was measured by EMIT assay.
Result The *1/*1 genotype of CYP3A4*1B exhibited lower dose-adjusted C2 levels as compared to *1/*1B or *1B/*1B genotypes at 1 and 3 months post transplantation (Mann–Whitney U test; $p = 0.025$ and $p = 0.009$). The dose-adjusted C2 levels were also lower in ABCB1 c.2677G>T GG genotype (1 month, $p = 0.009$; 3 months, $p = 0.043$). The GG genotype was further associated with lower allograft survival as indicated by Kaplan–Meier analysis ($p = 0.021$). The CYP3A5*3 polymorphism was not linked with CsA dose requirement in the present study cohort.
Conclusion The identification of patients with *1/*1 genotype of CYP3A4*1B and GG genotype of ABCB1 c.2677G>T may have a significant impact on allograft outcome clinically and may be helpful in providing pre-transplant pharmacogenetic information to individualise cyclosporine A dosing to prevent allograft rejection.
Acknowledgement Grant support received from DBT and CSIR (India).

054: Polymorphisms in statin metabolism pathway genes predict statin mediated LDL cholesterol lowering in coronary artery disease patients

[1]**A. Poduri**, [2]A. Bahl, [2]Y. P. Sharma, [2]K. K. Talwar, [1]M. Khullar

[1]Dept. of Exp Medicine and Biotechnology, PGIMER, Sector-12, Chandigarh 160012, India, [2]Dept. of Cardiology, Sector-12, Chandigarh 160012, India

Statins can substantially lower plasma LDL cholesterol (LDLC) and reduce risk for coronary heart disease, but their efficacy varies among individuals. Prior studies have reported various genes, often singly for association with drug response, with contradictory results. Few studies have systematically tested for interactions between single nucleotide polymorphisms (SNPs) between genes. To test whether this variation is related to cumulative effects of gene–gene interactions, we examined the genotypic variations and haplotype associations in several candidate genes of statin metabolism pathway as the potential determinants of drug responsiveness in coronary artery disease (CAD). 265 newly diagnosed CAD patients, with an LDLC (mean 131 mg/dl) were treated with 20 mg/day Atorvastatin for 6 weeks. We genotyped 11 SNPs of four genes involved in statin, cholesterol, and lipoprotein metabolism CETP-C629A, TaqIB, I405V, ApoAI-PstI, G75A, C2500T, ABCB1-G2677T/A, C3435T, A41G and CYP7A1-A-278C, A-204C by PCR–RFLP assays. Patients were grouped as responders (LDLC < 100 mg/dl) and non-responders (LDLC > 100 mg/dl) to atorvastatin according to the National Cholesterol Education Program and Adult Treatment Panel III guidelines. Genotypic and haplotypic interactions were studied using multifactor dimensionality reduction MDR method and PHASE 2.1, respectively. The frequency of genotypes ApoAI-2500CC,PstIP1P1, CETP TaqIB1B2, 629CC and ABCB1 3435CC were significantly higher in responders ($p < 0.05$), and frequency of ApoAI-PstI P1P2, CETP-TaqI B2B2, 405IV,629AA and ABCB13435TT genotypes were significantly higher in non-responders. Frequency of haplotypes CETP: B1VA, ApoA1-P1TA, P2CA, ABCB1: CGT were found to be significantly higher in responders ($p < 0.05$). The linkage disequilibrium was significantly low across the studied SNPs ranging from $D = 0.04$ to $D = 0.20$. MDR analysis showed three loci SNP combination (TaqIB1B2-629CC-3435CT) to be the best genotype combination model predicting LDLC lowering response (OR: 5.5078,95% CI: 2.64–11.48). This study is the first to comprehensively investigate variation in multiple statin metabolism genes and LDL lowering by statins. SNPs in ABCB1, APOAI, and CETP predict response to Atorvastatin. This study highlights the use of a multigene strategy in pharmacogenetic studies.

055: Arsenic induced premature senescence: a biomarker study in exposed population from West Bengal, India

Sujata De Chaudhuri, Manjari Kundu, Susanta Roychoudhury, Ashok K. Giri

Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata 700 032, India

Arsenic is an environmental contaminant that causes cancer, developmental retardation and other degenerative diseases and thus is a serious health concern worldwide. In India, West Bengal, 9 out of 18 districts are contaminated with ground water arsenic at a concentration much above the threshold limit recommended by WHO (10 μg/l). Although, arsenic is a well-known carcinogen, limited knowledge exists about its potential to induce stress-induced premature senescence. Normally, somatic cells enter a state of irreversibly arrested growth after a finite number of divisions, termed as replicative senescence, characterised by gradual shortening of telomeres. On the contrary, premature senescence is caused by external or internal stresses, resulting into altered physiological, biochemical and structural changes such as increased beta-galactosidase activity (histochemically detectable at pH 6), rapid shortening of telomeres and altered telomere behaviour. In this study, we wanted to find out whether arsenic can induce these characteristic changes of premature senescence in peripheral blood lymphocytes. As exposed area, we selected Murshidabad district with heavy contamination of groundwater arsenic; as arsenic-unexposed area, we selected Midnapore district where arsenic contamination has not yet been reported. As study subjects, we recruited 21 arsenic exposed individuals (cases) and 21 age–sex matched control individuals who were completely unexposed to arsenic. We measured the expression of senescence-associated beta-galactosidase (SA-beta-Gal) in peripheral blood lymphocytes. We also measured telomere length by Telomere Restriction Fragment (TRF) analysis through genomic DNA isolation, digestion with restriction enzyme, electrophoresis, Southern transfer and detection by chemiluminescence method. We also analysed chromosomal aberrations to find out specific aberrations at telomere region. In our results, SA-beta-gal positive cells were found to be significantly higher (p value less than 0.05) in exposed individuals than control individuals. Mean TRF length were found to be significantly lower (p value less than 0.001) in cases than controls. Cytogenetic analysis revealed that arsenic exposed individuals exhibit several aberrations at telomeric region. Thus, this study indicates that arsenic induces premature senescence that is reflected by drastic telomere shortening and abnormal changes in the telomeric regions of the chromosomes.

056: Pharmacogenomics and predictive therapy for complex diseases

[1]**Ritushree Kukreti**, [1]Sandeep Grover, [1]Meenal Gupta, [1]Abhay Sharma, [2]Sangeeta Sharma, [2]Kiran Bala, [2]M. Gourie-Devi, [3]Sanjeev Jain, [4]The Indian Genome Variation Consortium, [1]Samir K. Brahmachari

[1]Functional Genomics Unit, Institute of Genomics and Integrative Biology (Council of Scientific and Industrial Research), Mall Road, Delhi 110007, India, [2]Institute of Human Behaviour and Allied Sciences (IHBAS), Dilshad Garden, Delhi 110 095, India, [3]Molecular Genetic Laboratory, Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Hosur Road, Bangalore 560029, India, [4]Nodal Laboratory, Institute of Genomics and Integrative Biology, Mall Road, Delhi 110007, India

Therapeutic efficacies and side effect profiles of drugs differ among individuals. Genetic variations in genes encoding components of drug metabolising enzymes, transporters, primary and secondary targets of metabolites, and downstream pathways are all considered to underlie this difference. Pharmacogenomics of drugs prescribed for common diseases such as epilepsy, mental disorders, etc. is needed for individual specific therapy (personalised medicine) as these diseases have emerged as a major public health problem in recent years. However, personalised medicine is likely to be very expensive and unaffordable in developing world. The pharmacogenomics approach taken here is to make drugs affordable by keeping old and cheap drugs and reviving drugs withdrawn from the market because of their side effects. We have selected 24 Indian populations representing major four groups (Journal of Genetics, Vol. 87, No. 1, April 2008) and genotyped 552 individuals at 488 SNP locus covering 112 genes.

These include 28 genes coding for DMEs of both phase I (oxidation or reduction) and Phase II (conjugation) drug metabolism, 9 drug transporter genes and 75 drug targets. The detailed analysis of these results will be presented.

057: Genetic variations in TCF7L2 influence therapeutic response to sulfonylureas in Indian diabetics

Dipali Dhawan, Harish Padh

B. V. Patel PERD Centre, Thaltej-Gandhinagar Highway, Thaltej, Ahmedabad 380054, Gujarat, India

Type 2 diabetes prevalence is increasing worldwide, expected to reach 333 million diabetics by the year 2025. Sulfonylureas are widely used to treat type 2 diabetes and there is a considerable inter-individual variation in the hypoglycaemic response to sulfonylureas. Genetic variants in the gene encoding for Transcription factor-7-like 2 (TCF7L2) have been associated with type 2 diabetes and impaired β cell function. TCF7L2, also known as Transcription factor-4 (TCF-4), is a nuclear receptor for CTNNB1 (previously known as β-catenin), mediating the canonical Wingless-type MMTV integration site family (WNT) signalling pathway. There are several known mechanisms for the involvement of WNT signalling in both insulin secretion and action, as well as in cell differentiation and maturation. It has been suggested that the WNT/TCF7L2 pathway in enteroendocrine cells may regulate intestinal proglucagon gene expression. Thus TCF7L2 variants may modify type 2 diabetes susceptibility and hypoglycaemic response to sulfonylureas through alterations in glucagon-like peptide-1 (GLP-1) that is linked to physiological insulin secretion. To date, pharmacogenetic studies on the therapeutic response within diabetes have been limited. This study aimed to study the effect of variations in TCF7L2 on therapeutic response to sulfonylureas. The effect of TCF7L2 rs12255372, rs7903146 and rs4506565 genotypes on glycaemic response was observed in 125 diabetic patients treated with sulfonylureas and sulfonylureas along with metformin. Postprandial blood sugar concentrations were used as phenotypic marker. Across the whole cohort 60% of sulfonylurea users did not achieve a target postprandial blood sugar concentrations of <160 mg/dl. Genotype influenced response to sulfonylureas, with more treatment failure in the TT homozygotes in case of rs12255372 and rs4506565. We have seen that GG genotype at rs12255372 favourably influences initial treatment success with sulfonylurea therapy in patients with type 2 diabetes ($p \leq 0.05$). At rs12255372, 70.5% GT or TT genotype failed to achieve therapeutic target, an absolute difference of 19% compared to GG homozygotes. Our preliminary data show that influence of rs4506565 and rs7903146 on therapy was not statistically significant, however, genetic variation at rs12255372 has a direct correlation with therapeutic success with sulfonylureas in type 2 diabetes.