PS 1607 GENETIC VARIANTS IN HLA GENES ARE ASSOCIATED WITH DIISOCYANATE-INDUCED ASTHMA IN EXPOSED WORKERS.

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Diisocyanates, low-molecular weight reactive chemicals extensively used in a variety of industrial processes, are one of the most common causes of occupational asthma. Both immunological and inflammatory mechanisms have been implicated in the development of diisocyanate-induced asthma (DA). A case-control study was conducted to investigate whether genetic variations in genes located within the major histocompatibility complex play a role in susceptibility to DA using a high density SNP map. The study population consisted of 140 workers exposed to diisocyanates (hexamethylene diisocyanate (HDI), methylene diphenyl diisocyanate, and toluene diisocyanate) of which 73 were diagnosed with DA based on a positive specific inhalation challenge and 67 were asymptomatic workers exposed to HDI. Genotype analysis was performed on genomic DNA, using Illumina GoldenGate Genotyping technology. The microarray platform consisted of 2,360 loci with an average spacing of 2 kb. After adjusting for potential confounders, single nucleotide polymorphisms in HLA-E (rs1573294), HLA-B (rs1811157), HLA-DOA (rs3128935), HLA-DQA2 (rs7773955), and HLA-DPB1 (rs928976) showed associations with altered risk of developing DA. Since HLA genes play a key role in the regulation of the immune response, variations in these genes may represent important disease modifiers that contribute to DA susceptibility.
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PS 1608 IS WHOLE GENOME AMPLIFIED (WGA) DNA SUITABLE FOR ACCURATE GENOTYPING?

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Advances in genomic technologies have created novel molecular genetic methods with applications in the understanding, diagnosis, and management of genetic diseases and cancer. One of the challenges is acquiring sufficient DNA from clinical samples for analysis. WGA methods have been developed to overcome this problem. The most commonly used WGA approach is the multiple displacement amplification (MDA) method because of its high processivity and low error rate. However, the uniformity of amplification across the genome has not been well-characterized. Here, we compared two MDA kits: GenomiPhi (GE Healthcare) and Repli-G (Qiagen) using array-based comparative genomic hybridization (CGH) to evaluate DNA copy number variations (CNVs) in amplified DNA. Amplified and unamplified DNA samples from a normal individual and two patients with cystic fibrosis were evaluated by Agilent Human 1 million feature CGH arrays. Analyses of Komogorov distances and Phi correlations showed high consistency within each amplified sample group. Both REPLI-g and GenomiPhi generated very similar amplified DNA samples. Less than 2% of the genome showed more than 2-fold CNV after amplification. The majority of the CNVs were under-amplified regions located in the telomeric regions. No CNVs or mutations were detected in the CFTR gene region due to WGA. This was confirmed by quantitative PCR copy number assays at 10 locations within the CFTR gene and sequencing of a 2-kb region within the CFTR gene. These results indicate that WGA DNA is generally suitable for accurate genotyping. However, because there are consistent differences between the WGA DNA and the native DNA, characterization of the genomic region of interest would be necessary to ensure the reliability of genotyping results from WGA DNA.

PS 1609 POLYMORPHISMS IN DNA METABOLIZING AND REPAIR GENES GSTM1, GSTT1, GSTP1, AND OGG1 AND TYPE 2 DIABETES MELLITUS RISK: A CASE-CONTROL STUDY IN A TURKISH POPULATION.

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We investigated impact of polymorphisms in GSTs (GSTM1, GSTT1 and GSTP1) which are very important protective mechanism against oxidative stress and in OGG1 gene which has importance in DNA repair, to risk of Type 2 Diabetes Mellitus (T2DM) with obesity and hypertension in our study. We examined 127 T2DM and 127 control subjects. DNA was extracted from whole blood. Analysis of GSTM1 and GSTT1 gene polymorphisms was performed by allele specific PCR and GSTP1 Ile105Val and OGG1 Ser326Cys by PCR- RFLP. Our data showed that GSTM1 null genotype frequency had 2-6 times statistically significant increase in patient group (OR 3.841 [95% CI 2.280-6.469], p<0.001) but not observed any significance with GSTT1 null/positive and GSTP1Ile105Val genotypes. When T2DM patients with OGG1 Ser326Cys polymorphism was compared with patients with wild genotype, statistically 2-3 times increase has been observed (OR 1.858 [95% CI 1.099-3.141], p)=0.021. The joint effect of GSTM1 null and OGG1 variant genotype frequencies have shown statistically significant. Similarly, the risk of T2DM was statistically increased with GSTM1 null (OR 3.841 [95% CI 2.28-6.469], GSTT1 null+GSTP1 (H+M) (OR 4.118 [95% CI 1.327-12.778]) and GSTM1 null+OGG1 Ser326Cys (H+M) (OR 3.322 [95% CI 1.898-5.816]) and GSTT1 null+OGG1 Ser326Cys (H+M) (OR 2.179 [95% CI 1.083-4.386]) compared to control. However, when patients with T2 diabetic hypertension and obesity are compared with the control group, no significance relationship was observed.According to our study results, it has been seen that combined evaluation of especially GSTM1-GSTT1-GSTP1 and OGG1 Ser326Cys gene polymorphisms can be used as candidate gene in etiology of T2DM, especially in development of T2DM.

PS 1610 EVALUATION OF THELIN USING A MOUSE DIVERSITY PANEL DEMONSTRATES GENETIC DIFFERENCES IN LIVER RESPONSE.

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Sitaxsentan sodium (Thelin) is an endothelin receptor antagonist developed for the treatment of pulmonary arterial hypertension. In clinical studies, Thelin was associated with liver injury. Previous studies have shown that genetically diverse inbred mouse strains comprising a mouse diversity panel (MDP) have utility for identifying genetic markers associated with drug toxicity. In this study, female mice from 34 inbred strains were treated orally by gavage once daily for 7 consecutive days with 300 mg/kg Thelin or vehicle (water; N=4/strain). At necropsy, a significant increase in the liver to body weight ratio in all strains treated with Thelin was observed (two-way ANOVA, p<0.05), ranging from a 28.7% increase in KK/HIJ mice to a 154% increase in P/J mice. Preliminary clinical chemistry analysis revealed large inter-strain variations in serum cholesterol levels ranging from a 19% decrease in MrL/MpJ mice to an 86% increase in C57BLKS/J mice in Thelin versus vehicle-treated groups. Plasma concentration of Thelin was determined 2 hours after the last dose administered, and despite large variations in concentration observed across strains, there was no statistical correlation between Thelin plasma concentration and the changes in liver to body weight ratio or cholesterol levels (Pearson correlation, p>0.05). Taken together, these data suggest that genetically diverse mouse strains differ in hepatic response to Thelin, and this response is not attributable to variable drug exposure in these strains. Thus, the MDP can be used to investigate the biochemical pathways and genetic markers associated with the variable hepatic response.

PS 1611 P-GLYCOPROTEIN TRANSPORT OF PESTICIDES ASSOCIATED WITH PARKINSON'S DISEASE.

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P-glycoprotein (P-gp), encoded by the *ABCB1* gene, is an efflux transporter expressed in many tissues important in xenobiotic disposition. P-gp is highly expressed at the blood-brain-barrier (BBB) and protects the brain from substances circulating in the blood; as a result P-gp substrates do not accumulate in the brain.

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