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ABSTRACTS

Genomics of complex disorders I

039: Genome-wide association study with blood pressure traits

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Hypertension is a common disease affecting 25% of the adult population. Different studies have suggested that approximately 33–66% of the inter-individual variance in BP level is heritable. In order to search for novel genetic variants associated with BP levels, we conducted a genome-wide association study (GWAS) for three blood pressure traits (SBP, DBP and HYP) in the KORA (Kooperative Gesundheitsforschung in der Region Augsburg) S3/F3 epidemiological cohort ($n = 1{,}644$) recruited from a general population in Southern-Germany. Using a three stage study design, we identified two new loci (at 16q23 and 17p13) associated with BP traits and replicated these associations in two European populations (Germans, Estonians). In a third population (British) we obtained consistent effect signs but borderline p-values. The minor variants of these SNPs reduce BP and therefore, protect from the development of hypertension (joint analysis, $n = 1{,}900$ hypertensives/4365 normotensives: $P = 5.41 \times 10^{-8}$, $OR = 0.73$ and $P = 7.42 \times 10^{-7}$, $OR = 0.65$, respectively). The identification of two novel loci encourages further research to clarify the functional basis of the identified associations.

040: Physiological effect of human angiotensinogen haplotypes on blood pressure in transgenic mice

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Hypertension is a serious risk factor for myocardial infarction, heart failure, vascular disease, stroke, and renal failure. The incidence of hypertension and complications due to hypertension are even greater in the African-American population. Angiotensinogen (AGT) gene locus is associated with human essential hypertension and overexpression of the AGT gene increases blood pressure in transgenic mice. There are five polymorphic sites (A/G at -6, A/G at -217, T/C at -532, A/G at -793, and T/G at -1074) in 1.2 kb promoter of the human AGT gene. Variant -217A almost always occurs with -532T, -793A, and -1074T and variant -217G almost always occurs with -532C, -793G, and -1074G. Since allele -6A is the predominant allele (frequency 0.85) in African-Americans, this population can be subdivided into two major haplotypes -6A:-217A (AA); -6A:-217G (AG. The frequency of AA haplotype is significantly increased in African–American hypertensive patients as compared to the AG haplotype. AGT gene is primarily expressed in the liver and reporter constructs containing AA haplotype of the AGT gene promoter have increased promoter activity on transient transfection in human liver cells as compared to the AG haplotype. In order to understand the role of AA and AG haplotypes on human AGT expression in an in vivo situation, we have generated double transgenic mice containing either haplotype AA or AG of the human AGT gene using knock-in strategy at the HPRT locus and human renin gene. Our quantitative RT-PCR analysis has shown that transgenic mice containing AA haplotype have 1.6-fold increase in the AGT mRNA level in the liver as compared to the transgenic mice containing AG haplotype. In addition, Western blot analysis has shown that transgenic mice containing AA haplotype have 30% increase in the AGT protein level in the liver as compared to transgenic mice containing AG haplotype. In addition we show that blood pressure of 3-months-old male transgenic mice containing AA haplotype is increased by 7 mmHg during the day time and 11 mMHg during the night time ($n = 4$ for 4 days) as compared to the transgenic mice containing AG haplotype. To our knowledge, this is the first report where polymorphisms in the

promoter of a human gene have been shown to have physiological affect in an in vivo situation.

041: Genome wide study of tuberculosis susceptibility in West Africans reveal novel associations

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Tuberculosis continues to cause substantial morbidity and mortality throughput the world, especially in developing countries where infrastructure and access to treatment is limited. Host genetics play an important role in tuberculosis disease as demonstrated by twin studies. Although many tuberculosis candidate gene studies have been published many fail to replicate. We performed a genome wide association study of tuberculosis susceptibility in a Gambian population to determine genetic loci associated with tuberculosis disease process. DNA was collected and genotyped for 1,498 pulmonary tuberculosis cases and 1,496 population controls from The Gambia. In total 429,403 SNPs were analysed to find 38 independent loci associated with tuberculosis disease with P less than 10^{-4} and seven loci with P less than 10^{-5}. The analysis revealed that several of the associated genes are all related to NCAM1, suggesting a role of this gene family in the development of pulmonary tuberculosis. Replication studies are currently underway to attempt to confirm these findings. Functional analysis of two of the loci associated with tuberculosis has revealed differential TNF production based upon genotype, suggesting a mechanism of protection against tuberculosis.

042: A genome-wide association study identifies a novel sarcoidosis disease gene with potential relevance for related granulomatous inflammatory phenotypes

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Sarcoidosis is a complex chronic inflammatory disorder with predominant manifestation in the lung. In the first genome-wide association study (>440,000 SNPs) of this disease, comprising 499 German sarcoidosis patients and 490 controls, we detected a series of genetic associations, the most prominent being with the "SARC2"* gene on chromosome ten. Validation in an independent sample (1,649 cases, 1,832 controls) confirmed the association (SNP rs00*: $P = 3.0 \times 10^{13}$, rs01*: $P = 1.0 \times 10^{-5}$, allele-based test). Extensive fine mapping located the association signal to a region between exon 5 and 14 of SARC2. A common non-synonymous SNP (rs02*, T > C, p.Arg00*Cys) was found to be strongly associated with sarcoidosis. The GWAS lead SNP and additional risk variants in the region (rs03*, rs04*, rs05*) were in strong linkage disequilibrium with rs02*. The SARC2 protein has complex and essential functions in several biological pathways, including apoptosis and proliferation. We also examined the association of SARC2 with other granulomatous diseases (e.g., Crohn disease, rheumatoid arthritis). Data suggest a potential relevance of SARC2 as a risk gene for phenotypic related disorders and indicate it as a susceptibility locus of general importance.

043: The cancer genome: A-ray of hope

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Solid tumors can be broadly classified into two categories. Clinically homogeneous aggressive cancers such as those of the pancreas, biliary tract, liver, etc., exhibit low survival rates and patients succumb to recurrent metastatic tumors following surgery, necessitating development of efficient treatment strategies. On the other hand, clinically heterogeneous cancers including those of the breast, colon, prostate, etc., exhibit variable survival rates and tumor classification is essential for better patient management. It is widely believed that cancer occurs due to genetic instability leading to multiple molecular perturbations in the genome, resulting in activation of oncogenes and inactivation of tumor suppressor genes. In order to understand the molecular basis for the highly aggressive pancreatic cancer, we employed array-based Comparative Genomic Hybridization to identify recurrent copy number alterations (CNAs) that harbor important oncogenes and tumor suppressor genes. We used genome-wide expression profiling and real time RT-PCR to determine the subset of genes located within the CNAs that exhibited comparably altered expression levels. Our results revealed novel candidate oncogenes and tumor suppressor genes involved in diverse pathways including cell motility, apoptosis, mitochondrial oxidative phosphorylation and chromatin remodeling. Studies are underway to characterize the role of these genes in pancreatic cancer. In addition, we have commenced a large scale multi-pronged molecular analysis of esophagous cancer including characterization of known aberrations such as microsatellite instability, Wnt signaling, and determination of p53 and EGFR status and identification of novel aberrations using genomic approaches. Results indicate important molecular differences between adenocarcinoma (common in western countries) and squamous cell carcinoma (the second most common cancer in several population-based cancer registries of the ICMR in India) of the esophagous (ESCC). Genomic microarray studies have identified a novel recurrent amplicon at 10q21 in ESCC. Efforts are underway to identify the 'driver' oncogene(s) resident within this amplicon.

Recently, we have initiated a comprehensive characterization of sporadic and familial colorectal cancer occurring in the young, an important problem in India. Results have revealed molecular features in tumors occurring in young patients that are distinct from those occurring in older patients.

044: Somatic DNA amplification as a phenotype in cancer

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Cancer is known to have a complex etiology, with both inherited and somatic components. Recent studies have yielded promising results using SNPs as markers in associations studies, detecting associations between certain SNP alleles and susceptibility to a variety of cancer types. However, bearing in mind that somatic copy number changes are a hallmark of cancer, we have conducted a study treating somatic copy number lesions (representing the cancer genome) at each gene as an phenotype, with inhertied SNP alleles (representing the germline genome) as predictors. We have analyzed 474 lung and breast cancer samples. For each of these samples, we posess Affymetrix 250K SNP array data for both tumor DNA and matched normal DNA. Our analysis reveals abundant cis associations between inherited variants and somatic amplification of certain genes, including well-known oncogenes. We also report some evidence for trans associations. This study demonstrates that somatic amplification may be treated as an intermediary molecular phenotype in cancer, and that the germline genome and tumor genome may be simultaneously interrogated in the patient to gain additional insight into inherited cancer susceptibility.