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ABSTRACTS

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022: Zebrafish behavioral genetics of nicotine dependency

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On a worldwide basis, lung cancer is the most common and most deadly of all malignant diseases. Cigarette smoking accounts for 90% of lung cancer cases. At current smoking rates, over 1 billion people are expected to die in the twenty-first century from tobacco-induced health effects. Nicotine is the substance in tobacco that drives dependence. A major genetic component is now known to play an important role in the ability of nicotine to lead to tobacco dependence in some individuals and not others. However, many questions remain concerning the pathways and processes that underlie these genetic differences. We have established the zebrafish (*Danio rerio*) as a model for drug dependency, including establishing nicotine response and sensitization rapid behavioral assays. Using our gene-breaking insertional mutagenesis approach in a forward genetic screen, we identified two new nicotine response loci, *Bette Davis* and *Humphrey Bogart*. We have cloned these two loci in zebrafish and determined their mammalian orthologs. These genes are abundantly expressed in the nervous system of rodents with no prior known functional roles in the nicotine response. The combination of insertional mutagenesis with the nicotine response assays in zebrafish opens the door to a systematic approach to the genetics of vertebrate behavior.

023: A common genetic variation in inositol polyphosphate 4 phosphatase A (INPP4A) enhances susceptibility to atopic asthma

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Introduction: Atopic asthma is a chronic, inflammatory lung disorder characterized by recurrent breathing problems in response to various environmental stimuli. Many asthma associated genes have been identified nevertheless; more remain to be discovered. Objectives: To identify novel genes associated with atopic asthma taking leads from existing microarray datasets.
Methodology: We performed genetic association analyses on selected markers within or in proximity of 21 human homologous genes, short-listed from GEO database of NCBI, in 171 trios. Family-based ($N = 277$) and case ($N = 288$)–control ($N = 293$) studies were undertaken for fine mapping and functional variation analysis of inositol polyphosphate 4 phosphatase type I (INPP4A). INPP4A expression was determined by real time PCR, immunohistochemistry and western blot analyses.
Results: Using comparative analysis of the three GEO datasets, we identified 69 differentially expressed genes present in regions that were linked with asthma/atopy and related phenotypes. Based on novelty and presence of potential polymorphic repeat in/around the gene, we included 21 genes (human homologs) in our study. Our trio-based genetic studies on simple repeats in these genes (171 triads) suggested the association of INPP4A with atopic asthma ($P = 0.009$). INPP4A is a magnesium independent phosphatase, which is expressed in human brain, platelets, megakaryocytes and Jurkat T cells and suggested to negatively regulate PI3 K pathway. Further, using additional three SNPs and two microsatellite markers, we found significant genetic associations with loci +92031A/T ($P = 0.0012$) and +92344C/T ($P = 0.004$). Additionally, a non-synonymous A + 110832GThr/Ala polymorphism, present within a PEST sequence showed significant association with atopic asthma using two different study designs ($P = 0.0006$ and 0.004 in trio and case-control studies, respectively). We further demonstrated that the threonine to alanine substitution reduces the susceptibility of INPP4A-alpha 3 to calpain proteases, as protein from platelets of individuals with AA genotype was found to be more susceptible to degradation as compared to individuals with GG genotype. Further, expression analysis of INPP4A protein using immunohistochemistry in murine asthma model demonstrated its protective role.
Conclusion: We have successfully utilized high throughput microarray data in the identification of genes associated with atopic asthma. This is the first report of the INPP4 gene being associated with atopic asthma.

024: Common variants influencing type 2 diabetes, body mass index and fasting glucose

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Ongoing efforts to define common variants influencing traits of biomedical importance are motivated by the biological insights that follow identification of robust causal relationships between sequence variation and phenotypes of interest. Once the 'low hanging fruit' have been picked, further success depends on improving power through combined analysis of multiple GWA and replication data sets: a growing number of global consortia have emerged to manage such efforts. For type 2 diabetes (T2D), the Diabetes Genetics Replication And Meta-analysis (DIAGRAM) consortium has concentrated on T2D signals in European-descent populations. Formal meta-analysis of the WTCCC, DGI and FUSION data sets (4,500 cases, 5,500 controls) followed by replication in over 50,000 samples, identified six novel loci involved in T2D predisposition, bringing the total of confirmed association signals close to 20. The DIAGRAM + effort is extending this meta-analysis to additional GWA datasets. The Genomic Investigation of Anthropometric Traits (GIANT) consortium, concentrates on identification of signals influencing BMI, risk of obesity, height and central adiposity. The most recent meta-analysis (32,000 GWA scans, 58,000 replication samples) has identified six additional loci influencing BMI and risk of obesity. Several of these genes are highly expressed in the CNS emphasising the role of central mechanisms in regulation of energy balance. Finally, the Meta-Analysis of Glucose- and Insulin-related traits Consortium (MAGIC) focuses on variants influencing glucose homeostasis in healthy populations. MAGIC has combined GWA data from over 45,000 individuals informative for fasting glucose and related traits. As well as confirming previously reported signals in *GCK* and *G6PC2*, several novel loci have been identified, including a signal in *MTNR1B*, encoding one of the melatonin receptors, which influences both fasting glucose levels and individual risk of T2D. We expect these efforts to deliver additional susceptibility loci and to stimulate translational benefits through improved understanding of key biological processes. Despite their size, the studies so far address only a small component of global sequence variation: that is, common variants represented on or tagged by the SNPs on commodity genotyping arrays, and their relationships to these traits in European-descent populations. Future efforts will need to encompass a wider range of structural and sequence polymorphisms, and a broader coverage of human populations.