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ABSTRACTS

HGM2008 complex disease genomics II symposium abstracts (neuropsychiatric and ocular disorders)

034: Genetic determinants of Parkinson's disease: Insights from multiple gene analysis

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The etiopathology of sporadic Parkinson's disease (PD) remains elusive due to complex interaction between genes and environmental factors. Genes from dopaminergic, xenobiotic metabolism, oxidative stress, apoptosis, and inflammatory and other pathways have been commonly implicated. But results from large number of association studies on these genes have been confounding. On the other hand seven genes namely—alpha-synuclein (SNCA, PARK1), Parkin (PARK2), UCHL1 (PARK5), PINK1 (PARK6), DJ1 (PARK7), LRRK2 (PARK8) and ATP13A2 (PARK9) identified in monogenic forms of PD provide considerable insight into cellular mechanisms underlying the degeneration of nigral dopaminergic neurons. Considering neuronal cell death is the basic pathophysiology underlying all forms of PD, our goals were to investigate the contribution of a) candidate genes from multiple pathways, b) mutations and SNPs/SNP haplotypes in familial PD genes and c) to test epistatic gene interactions, to the etiology of sporadic PD. We examined 72 functional/non-synonymous/commonly investigated polymorphisms in 30 candidate genes from multiple pathways mentioned above using a case control approach in two independent cohorts, one from south India (SI, n = 148 cases, 130 controls) and another from north India (NI, n = 339 cases, 344 controls). Of the several significant associations observed in this study, most promising were allelic/genotypic/haplotypic associations of DRD4, DBH, NAT2 and NQO1 gene variants. DRD4 and NAT2 significance were also retained when the samples were re-grouped based on age of onset of illness. As for the mutations in familial PD genes, there is negligible contribution of alpha-synuclein, UCHL1, and LRRK2 in our population but several novel and known mutations were observed in Parkin, PINK1 and DJ1 genes contributing to different extents to early onset PD. Results of association analysis of 16 SNPs from these three and alpha-synuclein genes suggest their significant contribution to genetics of sporadic PD. Several SNPs/SNP haplotypes were associated but they were distinctly different between early and late onset PD cases. These need to be explored further at a functional level.

035: Integrative approaches to the identification of genes involved in brain structure and function

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The human brain is an enormously complex organ. Variation in brain anatomy and function is now known to play an important role in the determination of risk of many neuropsychiatric diseases. In this talk, I will first provide an integrative paradigm for the joint utilization of genomic and transcriptomic information that allows for the rapid identification of genes involved in complex diseases. As a specific example, the approach will be applied to the search for causal genes involved in human brain structure/function. I will describe a unique data resource, the San Antonio-based "Genetics of Brain Structure and Function Study", for which genome-wide association data and lymphocyte-based transcriptional profiles are being jointly used to identify causal genes influencing brain anatomy and neurocognition. Multiple brain structural phenotypes have been obtained using high resolution magnetic resonance imaging. Similarly, extensive neurocognitive testing has been employed to obtain objective measures of brain function. High-dimensional endophenotype identification using large-scale transcriptional profiling has revealed a large number of genes whose expression levels correlate with various aspects of neurofunction. When combined with genome-wide association data, we use this method to identify novel empirically-justified candidate genes for more exhaustive genetic analysis. Similarly, the approach can be used to identify upstream regulators and downstream targets of known candidate genes whose functions are incompletely understood. As an example of this type of usage, I will provide new data on the DISC1 gene, an important candidate in several psychiatric disorders.

036: Genomic variation and cancer

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Genomic variation, through its effect on gene structure and expression, plays an important role in disease predisposition, biology, and clinical response to therapy. Cancer mutations can be classified as germline (inherited) and somatic (tumoral). I will provide examples of ongoing projects in my laboratory that are pertinent to both classes of cancer mutations. Recent studies of genetic variation across the human genome have led to concepts for a systematic approach to study a large fraction of human genes, using strategies that exploit linkage disequilibrium. In the first part of my talk, I will describe a project called ARCTIC (Assessment of Risk for Colorectal Tumours in Canada) which is designed to identify genetic variants predisposing to colorectal cancer. Employing a multi-stage genome-wide association strategy involving 7480 cases and 7779 controls, we identified several loci associated with colorectal cancer. I will focus on a locus on chromosomes 8q, which has also been implicated in prostate cancer, suggesting the possibility of a role in a broad spectrum of cancers. Current efforts in my laboratory at this and other loci are aimed at narrowing the search for the causal variants, and involve next-generation sequencing of templates generated using array-based selection strategies. In April 2008, representatives from Australia, Canada, China, France, India, Japan, Singapore, the United Kingdom, the United States, and the European Commission announced the launch of the International Cancer Genome Consortium (ICGC) which has been organized to coordinate a large number of projects that have the common aim of elucidating comprehensively the genomic changes present in many forms of cancers that contribute to the burden of disease in people throughout the world. The primary goals of the ICGC are to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal expression of genes, epigenetic modifications) in tumors in 50 different cancer types and/or subtypes and make the data available to the research community as rapidly as possible, and with minimal restrictions, to accelerate research into the causes and control of cancer. In addition to presenting the goals, structure and policies of the consortium, I will describe the design and early results from the pancreatic cancer genome team at the Ontario Institute for Cancer Research.

037: Genetics of Restless legs syndrome

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The Restless legs syndrome (RLS) is a common neurological disorder with an age dependent prevalence up to 10% in the elderly. Since the first description of the symptoms a large genetic contribution in the aetiology was suspected. Up to 40–60% of idiopathic RLS patients have a positive family history. Linkage analysis in large RLS families uncovered five loci based on a recessive (RLS1) or dominant inheritance (RLS2–RLS5). A genome-wide association study with samples from 1600 RLS patients and 2600 controls of the general population (KORA) was conducted. Individuals originated from Germany, Austria and French Canada. Four chromosomal regions have been identified with signals within the genes *MEIS1*, *BTBD9*, *LBXCOR1* and *PRPRD*. The *MEIS1* associated SNPs are located in a region of high interspecies conservation. The attributable risk fraction estimated for the four loci was higher than 50% for the populations studied. A comparison of familial versus sporadic cases demonstrated very similar results. The identified genes *MEIS1* and *LBXCOR1* are known as control factors in embryonic development. *PTPRD* belongs to the family of type IIa receptor-like protein tyrosine phosphatases and functions in axon guidance and termination of mammalian motorneurons during embryonic development.