Speaker 3: Sachio Matsushita, Japan

Title: Genetic variations of alcohol metabolizing enzymes and phenotypes of alcohol related disorders

Abstract

Alcohol dehydrogenase (ADH1B) and aldehyde dehydrogenase-2 (ALDH2) play central roles in the metabolism of alcohol and its metabolite, acetaldehyde. In Asian populations, genetic variant forms of ADH1B and ALDH2 exist and genotypes of these genes explain individual differences in elimination of alcohol and acetaldehyde in the blood after drinking. These differences could be used as models to elucidate the contribution of alcohol and acetaldehyde to the development of alcohol dependence and various types of organ damage.

We have examined the influence of genetic variations of alcohol metabolizing enzymes on sensitivity to alcohol and alcohol-related disorders in the Japanese. Our main results include that the less active allele of the ADH1B gene (ADH1B*1, rs1229984) was associated with an increased risk for alcohol dependence, alcohol-induced persistent amnestic disorder and alcohol withdrawal syndrome. The inactive allele of the ALDH2 gene (ALDH2*2, rs671) was associated with a decreased risk for alcohol dependence and an increased risk for alcoholic polyneuropathy and cancer in the upper GI tract.

These genetic variations also modify clinical features of alcohol dependence. Comparing time course of development of alcohol dependence and clinical features between alcoholic patients with active ALDH2 and inactive ALDH2 revealed that male patients with inactive ALDH2 developed alcohol dependence more slowly than those with active ALDH2. However, female patients with inactive ALDH2 had earlier onset age and more comorbid psychiatric disorders than those with active ALDH2.

We also examined the relationship between the genetic variation of ADH1B and ALDH2 and level of response to alcohol as well as the association between the level of response to alcohol and alcohol use disorder risk in healthy Japanese young adults prospectively. We found stronger subjective responses to alcohol in subjects with inactive ALDH2 than those with active ALDH2 as well as an association between less active ADH1B and weaker responses to alcohol compared with active ADH1B. Moreover, our prospective study revealed that stronger stimulant effect and weaker sedative effect of alcohol were associated with problem drinking. These studies suggest that: 1) acetaldehyde has a strong sedative effect; 2) ADH1B*1 is associated with alcohol use disorders through low level of response to alcohol; and 3) strong subjective stimulant effect and weak sedative effect of alcohol predict later alcohol related problems among healthy young Japanese adults.

Speaker 4: Joel Gelernter, USA

Title: Genes Influencing Cannabis Dependence Risk from GWAS

Richard Sherva, Qian Wang, Henry Kranzler, Hongyu Zhao, Ryan Koesterer, Aryeh Herman, Lindsay A. Farrer, Joel Gelernter

Abstract

The prevalence of cannabis dependence (CaD) is increasing in the United States, where action to legalize use of the substance is worsening an existing public health problem.

Although genetic factors contribute substantially to CaD risk, there are at present no well-established specific genetic risk factors for CaD. Over a 15-year period, we collected a sample of >10,000 subjects, ascertained for opioid, cocaine, or alcohol dependence, or because they were controls; and completed a series of genomewide association studies (GWAS) for these substance dependence traits, as well as nicotine dependence. In light of its biological and medical interest and because cannabis use and dependence are prevalent in our sample, we performed a GWAS for DSM-IV cannabis dependence criterion count. We also included in our GWAS publicly-available data, e.g. from the SAGE consortium. This resulted in a subject sample including 6,063 African-American and 8,866 European-American subjects, including some small families. We identified three distinct regions with genome-wide significant SNP associations with variants mapped to genes encoding antisense transcript RP11-206M11.7; solute carrier family 3, member G1 (SLC35G1); and cub and sushi multiple domains 1 (CSMD1). We also found evidence for genome-level pleiotropy between CaD and major depressive disorder, and for association with SNPs in genes associated with schizophrenia risk. Several of the genes implicated have functions related to neuronal calcium homeostasis or central nervous system development.

This is, to our knowledge, the first study to identify specific CaD risk alleles and identify potential genetic factors contributing to the co-morbidity of CaD with major depression and schizophrenia.

Presidential Symposium: Toward Innovation in CNS Drug Development - The Role of Public-Private Partnerships

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