**FUNCTIONAL MEDICINE UPDATE**
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**Identifying Functional Genetic Variants**

Advances in molecular genetic technology now make large-scale resequencing efforts increasingly viable, and these efforts are revealing extensive variation in genes of potential interest to biomedical researchers. With access to new information, some of the assumptions that underpinned earlier efforts at gene mapping have begun to be challenged. For most of the past decade, a generally accepted assumption was that variations observed in complex phenotypes were the result of common genetic variants with fairly substantial effects, and whereas that does seem to be the case in some instances, it is not a universal pattern. It is now being recognized that several single nucleotide polymorphisms (SNPs) within a gene may show effects, even when each SNP on its own appears to have little effect. What this means from a practical standpoint is that identification of the state of one SNP does not offer any information about the state of the others. REF #1

**Single-Nucleotide Polymorphism Markers in the Diagnosis of Wilson's Disease**

Wilson's disease (WD) represents a monogenic disease resulting in copper accumulation within tissues. Symptoms include acute and chronic liver disease, hemolysis, and neurodegenerative and psychiatric symptoms. Effective treatment for WD such as copper chelating drugs and zinc is available, which usually prevents disease progression. Therefore, a simple diagnostic screening test is needed for WD, ideally to identify patients before symptoms appear. WD is caused by various mutations within the *ATP7B* gene. An article recently published in *Clinical Chemistry* details the identification of 4 SNPs as markers for genetic testing. REF #2

**Modern Genotyping and Coronary Artery Disease Risk**

A large group of authors recently collaborated on a joint analysis of two genome-wide association studies of coronary artery disease and reported their findings in the *New England Journal of Medicine*. This group identified chromosomal loci that were strongly associated with coronary artery disease in the Wellcome Trust Case Control Consortium (WTCCC) study and looked for replication in the German MI (Myocardial Infarction) Family Study. This analysis identified several genetic loci that, individually and in aggregate, substantially affect the risk of development of coronary artery disease. REF #4

**Metabolic Syndrome and Implications for Nonalcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease (NAFLD) affects 70 million adults in the United States (30% of the adult population). An estimated 20% of these individuals have the most severe form of NAFLD—nonalcoholic steatohepatitis (NASH). Many NAFLD patients have multiple components of metabolic syndrome, whether they are overweight or not. The *American Journal of Clinical Nutrition* recently published a comprehensive article that reviews the implications of current dietary approaches, including national guidelines and popular weight-loss diets, with a focus on determining the optimal diet to prescribe

for NAFLD and NASH patients. The premises, effects, barriers, and issues related to current dietary guidelines and specific diets are discussed. REF #5

**Sugary Drinks Linked to Insulin Resistance**

One component of the Framingham Offspring Study examined the effects of sugar-sweetened drinks, diet soda, and fruit juice consumption on insulin sensitivity in 2500 subjects. This study found that people who consumed no sugar-sweetened drinks had a fasting insulin of 188 pmol/L compared to 206 pmol/L for those drinking at least 2 servings of sugar-sweetened drinks per day. Sugar-sweetened drink consumption was not associated with a change in fasting glucose or the insulin sensitivity index. Yoshida, the study author, concludes, "…in these healthy adults, sugar-sweetened drink consumption appears to be unfavorably associated with surrogate measures reflecting hepatic more than peripheral insulin sensitivity." REF #6

**Carbohydrate Restriction and Metabolism**

Dr. Bland discusses a thematic review of carbohydrate restriction recently published in the *American Journal of Clinical Nutrition*, which concludes:

- The persistence of an epidemic of obesity and type 2 diabetes suggests that new nutritional strategies are needed if the epidemic is to be overcome.
- Recent studies show that, under conditions of carbohydrate restriction, fuel sources shift from glucose and fatty acids to fatty acids and ketones.
- Ad libitum-fed carbohydrate-restricted diets lead to appetite reduction, weight loss, and improvement in surrogate markers of cardiovascular disease.

However, Dr. Bland points out that the authors of the review do not, in the course of presenting their data, differentiate between types of carbohydrates, a point he feels is very important when addressing information of this nature. REF #7

**Different Lipid Measures and the Prediction of Coronary Heart Disease**

The *Journal of the American Medical Association* recently published and article addressing the performance of apolipoproteins versus traditional lipids for predicting coronary heart disease (CHD) risk. In this large, population-based cohort, the overall performance of apo B:apo A-I ratio for the prediction of CHD was comparable with that of traditional lipid ratios but did not offer incremental utility over total cholesterol:HDL-C. The authors state that their data do not support measurement of apo B or apo A-I in clinical practice when total cholesterol and HDL-C measurements are available. REF #8

Dr. Bland acknowledges the article conclusions are valid when the all patients are being considered, but he encourages listeners to consider the predictive value and higher diagnostic specificity that the apo B;apo A-I ratio could provide when dealing with a subset of individuals.

**References**

1. Cole SA, Comuzzie AG. The end of the beginning. *Am J Clin Nutr*. 2007;86:274-275.

2. Schmidt HHJ. Introducing single-nucleotide polymorphism markers in the diagnosis of Wilson disease. *Clin Chem*. 2007;53(9):1568-1569.
3. Vakili S, Caudill MA. Personalized nutrition: nutritional genomics as a potential tool for targeted medical nutrition therapy. *Nutr Rev*. 2007;65(7):301-315.
4. Samani NJ, Erdmann J, Hall AS, Henstenberg C, Mangino M, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357(5):443—453.
5. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. *Am J Clin Nutr*. 2007;86:285-300.
6. Yoshida M, McKeown NM, Rogers G, Meigs JB, Saltzman E, et al. Surrogate markers of insulin resistance are associated with consumption of sugar-sweetened drinks and fruit juice in middle and older-aged adults. J Nutr. 2007;137(19):2121-2127.
7. Westman EC, Feinman RD, Mavropoulos JC, Vernon MC, Volek JS, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007;86:276-284.
8. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298(7):776-785.