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GENOTYPE-PHENOTYPE ASSOCIATIONS: MODULATION BY DIET AND OBESITY

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Abstract

Changes in diet are likely to reduce chronic disorders, but after decades of active research and heated discussion the question still remains: what is the optimal diet to achieve this elusive goal? Is a low fat, as traditionally recommended by multiple medical societies? Or a high monounsaturated fat as predicated by the Mediterranean diet? Perhaps a high polyunsaturated fat based on the cholesterol lowering effects? The right answer may be all of the above but not for everybody. A well-known phenomenon in nutrition research and practice is the dramatic variability in interindividual response to any type of dietary intervention. There are many other factors influencing response, and they include, among many others, age, sex, physical activity, alcohol, and smoking as well as genetic factors that will help to identify vulnerable populations/individuals that will benefit from a variety of more personalized and mechanistic based dietary recommendations. This potential could and needs to be developed within the context of nutritional genomics that in conjunction with systems biology may provide the tools to achieve the holy grail of dietary prevention and therapy of cardiovascular diseases. This approach will break with the traditional public health approach of “one size fits all.” The current evidence based on nutrigenetics has begun to identify subgroups of individuals who benefit more from a low fat diet, whereas others appear to benefit more from a high monounsaturated or polyunsaturated fat (PUFA) diets. The continuous progress in Nutrigenomics will allow some time in the future to provide targeted gene-based dietary advice.

INTRODUCTION

The promises of the genomic revolution have attracted this area a large number of other scientific disciplines including nutritional sciences. The potential benefits of harnessing the power of genomics for dietary prevention of disease are enormous and impossible to ignore and this new approach is considered the future of nutritional research (1-6).

The major practical translation of nutrition research to public health consists of defining optimal dietary recommendations aimed to prevent disease and to promote health for everybody and for each stage of human life. For this purpose, several dietary guidelines have been implemented in the US for over 90 years to improve the health of the general population and of those at high risk for specific diseases [i.e., cardiovascular disease (CVD), cancer, hypertension, and diabetes]. However, past and current dietary guidelines have not been able to properly address and integrate the dramatic differences on the individual’s physiological response to changes in nutrient intake. These differences in response may greatly affect the efficacy of these recommendations at the individual level.

The mechanisms responsible for the inter individual differences in dietary response are very complex and poorly understood. A role of genetic factors contributing to those differences in response to nutrients has been proposed for several decades (7) and successfully demonstrated for rare inborn errors of metabolism. More recently researchers began to comprehensively examine these nutrient-gene interactions at the molecular level for metabolic alterations that affect the general population (4). The current hypothesis is that these diseases are triggered

because of interactions between genes and environmental factors (8). These interactions are dynamic, beginning at conception and continuing through adulthood (9,10). Moreover, the concept of “environment” is complex and broad and it has been frequently associated with tobacco smoking, drug consumption, exposures to pollutants, education, and socioeconomic status (11). However, food intake is the environmental factor to which we are all exposed necessarily and permanently from conception to death and it has been a major driving force through species’ evolution. Therefore, dietary habits may be the most important environmental factor modulating gene expression during one’s life span, but, certainly, is not the only one.

The concept of gene-diet interaction describes the modulation of the effect of a dietary component on a specific phenotype (i.e., plasma lipid concentrations, glucemia, and obesity) by a genetic variant. Alternatively, this notion refers to the dietary modification of the effect of a genetic variant on a phenotypic trait. The potential benefits of harnessing the power of genomics for dietary prevention of disease are evident and this notion is already changing the landscape of nutritional research (2,12,13). Moreover, the genomic revolution has fostered the development of several complementary technologies that will greatly benefit nutritional sciences (14). In addition to genomics, techniques such as proteomics, metabolomics, and bioinformatics are already providing insights about gene-nutrient interactions at the cell, individual, and population level (1,15,16). All these techniques can and should be combined to understand both the influence of specific nutrients and whole dietary patterns on the metabolic behavior of cells, organs, and the whole organism (17,18).

This challenge can be accomplished by using bioinformatics that provide tools for managing the large and complex datasets provided by genomics, transcriptomics, proteomics, and metabolomics, and constitute what we know as functional genomics, also referred to as systems biology (19) (5,13,18). The development of systems biology transformed the concept of gene-nutrient interaction from the traditional reductionism approach of studying the effect of a nutrient over a specific metabolic event into a global one, in which a significant fraction of all regulated genes and metabolites can be queried simultaneously (20).

Driven by these technologies and paradigms, nutrition science has embraced “nutritional genomics” (1-5,18,19,21-24), promoting an increased understanding of (a) how nutrition influences metabolic pathways and homeostatic control, (b) how this regulation is altered in the early phase of a diet-related disease, and (c) to what extent individual sensitizing genotypes contribute to such disease.

Nutritional genomics has already raised high interest and expectations and some researchers (25) warn that genomic profiling and its interaction with environmental factors such as diet is not ready for prime time. It is true that evidence supporting health outcome benefits based on such testing is lacking, and that before this approach becomes valid and clinically useful, well designed epidemiologic studies and clinical evaluations of recommended interventions based on genotype are required.

This work describes some of the advances in nutritional genomics primarily in relation to variables related with the metabolic syndrome. This work is not intended by any means to be comprehensive as several such revisions have recently been published (4,26-28). Rather, the focus will be on presenting a window of evidence as well as the challenges ahead.

Environment as a modulator of the effect of genetic variants. The example of Apolipoprotein E (APOE)

Given the above mentioned goal, it is quite safe to say that the apolipoprotein E (*APOE*) gene is the “poster boy” of complex gene environment interactions. *APOE* has been one of the loci most intensively examined in terms of its potential use as a marker of disease risk. Initially the

interest was relegated to cardiovascular disease (CVD) risk, but this interest soon expanded quite dramatically to neurological disorders (29-34), osteoporosis,(35,36) cancer(37), vision (38) as well as inflammatory processes and overall longevity (39)

APOE in serum is associated with chylomicrons, very low density lipoproteins (VLDL), and high density lipoproteins (HDL), and serves as a ligand for multiple lipoprotein receptors. The best studied genetic variation at the *APOE* locus results from three common alleles in the population, E4, E3, and E2, with frequencies in Caucasian populations of approximately 0.15, 0.77, and 0.08, respectively (40). Population studies show that plasma cholesterol, LDL cholesterol (LDL-C), and APOB levels are highest in subjects carrying the E4, intermediate in those with the E3, and lowest in those with the E2 alleles(40). However, these studies also pointed to the possibility that the higher LDL-C levels observed in subjects carrying the E4 allele were manifested primarily in the presence of an atherogenic diet and brought up the notion that the response to dietary saturated fat and cholesterol could differ among individuals carrying different *APOE* alleles. Such hypothesis has been tested numerous times under different experimental conditions and those findings have been extensively reviewed (4,28,41,42).

Overall, there is considerable inconsistency regarding the magnitude and significance of the reported associations (42-44). This heterogeneity is expected on the basis of the multifactorial characteristics of the phenotypes examined and underscores the need for more comprehensive genetic panels combined with better assessment of the environmental factors. In general, a significant diet by *APOE* gene interaction has been shown primarily in studies with men alone, with carriers of the E4 allele being associated with increased response to dietary changes. In those studies including men and women, significant effects were noted only in men, suggesting a significant gene-sex interaction. Another difference between the negative studies and those reporting significant *APOE* gene-diet interactions related to the baseline lipid levels of the subjects. Positive findings were frequently observed in those studies reporting significant associations included subjects who were moderately hypercholesterolemic and/or had significant differences in base TC and LDL-C among the *APOE* genotype groups, suggesting that the significant gene by diet interaction is apparent only in subjects who are susceptible to hypercholesterolemia. Concerning differences in dietary interventions, significant interactions were more commonly observed among studies in which total dietary fat and cholesterol was modified. It is possible that dietary cholesterol will play a significant effect in this gene-diet interaction. It should also be noted that some reports have shown that cholesterol absorption is related to *APOE* genotype (45-47).

Although the obvious dietary factors implicated in gene-diet interactions affecting plasma lipid levels are dietary fats and cholesterol, other dietary components have revealed significant interactions. This is the case for alcohol intake. Although the raising effect of alcohol consumption on high-density lipoprotein (HDL)-cholesterol levels is well established, the effect on LDL-C is still unclear. It is possible that the reported variability will be due to interactions between genetic factors and alcohol consumption. Our analyses in the Framingham Study (48) showed that in male nondrinkers, LDL-C levels were not different across *APOE* groups; however, in male drinkers, there were differences in LDL-C, with E2 subjects displaying the lowest levels. When LDL-C levels were compared among the *APOE* subgroups by drinking status, LDL-C levels in E2 male drinkers were lower than in E2 nondrinkers. Conversely, in E4 males, LDL-C was higher in drinkers than in nondrinkers. In women, the expected effect of *APOE* alleles on LDL-C levels was present in both drinkers and nondrinkers. These data suggest that in men variability at this locus modulates the effects of consuming alcoholic beverages on LDL-C levels.

Smoking has also shown to be a potentially important modulator of the effect of *APOE* on CVD risk (49). Based on the evidence we analyzed the data from the Framingham Offspring

Study, specifically examining APOE:smoking interactions modulating CVD (50). No such interactions were found in women, but in men the overall hazard ratio (HR) for smoking was 1.95 compared to non-smokers. Using *E3E3* as the group of reference, in non-smokers, HRs for *E2* carriers (1.04) and *E4* carriers (1.04) showed no major risk increase. In smokers, HRs were 1.96 in *E3E3* men, 3.46 in *E2* and 3.81 in *E4*, with a significant interaction between daily cigarette consumption and APOE genotype on risk. Overall, the data suggest significant interactions between the APOE gene and behavioral factors; however, the fact that several of these factors have the potential to interact and that these may be differently distributed among populations, may result in one of the factors (i.e., alcohol drinking, smoking) having more weight in some populations and less in others. Taken together, these data highlight the complexity of these interactions and the gender and context dependency of the influence of alcohol on lipid metabolism and of smoking in CVD risk.

Physical activity is another factor that has been receiving increased and well-deserved attention. Usually, it is difficult to obtain reliable information about this variable in large population studies, especially when they have not been specifically designed to have physical activity as one of the main outcomes of the study. Despite those limitations, at least two independent studies have reported a consistent interaction between APOE genotype and the effect of physical activity on plasma lipid concentrations. The first one reported in a Spanish population that the association between HDL-C concentrations and physical activity (energy expenditure) is APOE dependent (51). This interaction was confirmed and examined in more detail by Berstein et al.(52). These authors investigated this interaction in population-based cross-sectional surveys. As described for alcohol, smoking and BMI, the findings were gender dependent. For men, increased physical activity had a greater protective effect in *E4* carriers as compared with *E3* homozygotes and *E2* carriers in terms of HDL-C increases and TG decreases. In women, the protective effect of exercise on *E4* carriers was limited to HDL-C and it was significant only for the difference versus carriers of the *E2* allele. Along the same lines, there appears to be a significant interaction between exercise training and APOE genotype (53).

Obesity as a modulating phenotype of the effect of the genetic variants

In this section, we will focus on obesity; but rather than using it as a main outcome, we will examine its effect as an effect modifier. The working hypothesis is that obesity modulates genotype-phenotype associations for a variety of candidate genes making necessary the stratification for this phenotype. So far the best described effects are those affecting traits related with the metabolic syndrome. We have previously summarized over thirty reports investigating the modulating effect of obesity on the other features of this syndrome (hypertension, dyslipidemia, and glucose intolerance) published before 2004 (54). One of the limitations observed when comparing the outcomes was the lack of standardization in the definition of obesity. The majority of studies focus on BMI; however, BMI is only an incomplete surrogate of body fat mass. In addition, this heterogeneity persisted in the criteria for defining obesity between the WHO and the ATP III. The rationale for the use of waist criteria arises from data showing that measures of BMI are relatively insensitive indicators for CVD risk as compared with measures of abdominal obesity. However, more investigation is needed and the incorporation of the novel anthropometric and biochemical measures of adipose mass and function into large epidemiological studies is required. Another subject of debate is the different cut-off point to define obesity depending on the ethnicity. Such is the case of Asian populations for which the WHO universal cut-off point of 30 kg/m² for obesity and 25 kg/m² for overweight have been considered very high and a reduction of 3 points have been proposed (55). Finally, a methodological issue appears as another difficulty for replication, this is the treatment of the obesity variable in the statistical analysis: as a continuous variable, as categorical based on international criteria or based on the characteristics of the population.

Therefore, a higher standardization for defining and analyzing obesity in the metabolic syndrome is needed in order to obtain valid results.

Beyond those concerns, the *APOE* locus can be used also as a model to illustrate the effect of obesity on genotype-phenotype associations. We examined the interaction between obesity and *APOE* genotype in determining fasting insulin and glucose levels in about 3000 participants in the Framingham Offspring Study (56). In men, we observed a statistically significant interaction between obesity and *APOE* genotype on insulin and glucose level. Obese men with the *APOE4* genotype presented with higher levels of insulin and glucose than obese men in the other genotype groups. No association between genotype and insulin or glucose in no obese men was observed. In women, the effect of interaction between *APOE* genotype and obesity on fasting insulin and glucose was not statistically significant. Therefore, obesity modulates the association between the *APOE* genotype and fasting insulin and glucose levels in men. Although weight control is important in all people, it may be especially important in *APOE4* men to modify potentially elevated fasting insulin and glucose levels.

In addition to *APOE*, genetic variants at other candidate genes have reported similar modulating effects by BMI or obesity (54). One of them is endothelin-1 (*EDN1*) Lys198Asn polymorphism and blood pressure. Several studies in Caucasians and Japanese have shown that obesity increases the effect of the 198 Asn allele on blood pressure and hypertension (57-60). A significant and repeated role for obesity on the phenotypic expression of the *LPL* gene has been reported by several investigators (60-65). All those studies consistently showed evidence supporting that the effect of *LPL* polymorphisms on plasma lipids is strongly modulated by obesity, BMI or adiposity. In brief, *LPL* polymorphisms are associated with a more atherogenic profile only in combination with elevated adiposity or BMI.

The evidence is not relegated only to *APOE*, *EDN1* and *LPL*, and more recently, several other loci including adiponectin(66), Angiotensin I-converting enzyme(67), Apolipoprotein A5 (68), Cholesteryl ester-transfer protein(69), linkage signal on chromosome 1(70), Selectin-E (71), G-protein beta-3(72-74), interleukin-6(75), hepatic lipase(76) and Peroxisome proliferator-activated receptor-gamma(77) have been showing similar interactions and the findings are summarized in Table 1. A common theme is observed by which those SNPs that have been associated with an increased risk phenotype, they do so primarily in the context of obesity. Conversely, alleles that are deemed to be protective, may lose their protection in the presence of obesity.

Most of the current evidence supporting the modulating effect of diet and obesity on genotype-phenotype associations relates to cardiovascular risk factors. Less information exists related to cancer risk. However, there are enough indications from the literature to support that similar interactions exist for cancer as reviewed by Gunter and Weitzman (78). These authors focus primarily on the association between dysregulation of energy homeostasis and colorectal carcinogenesis. It is interesting to point out how Obesity-induced insulin resistance leads to elevated levels of plasma insulin, glucose and fatty acids, which may induce a mitogenic effect on the colonocyte. Inflammation is another rising CVD risk factor it is also related to obesity and may also impact colorectal carcinogenesis. Investigators are beginning to study genetic variants within these pathways in relation to colorectal neoplasia, but the information is still sparse.

CONCLUSIONS

Nutrition is probably the most important environmental factor that modulates the action of genes and the phenotypes being considered. This has been known for decades(79) but somehow ignored. Therefore, it is of paramount importance that genes are considered in the context of

nutrition and that nutrition is considered within the context of genes. This paradigm constitutes the basis for nutritional genomics, a fast-developing research area with tremendous potential to yield results that could change the way dietary guidelines and personal recommendations are established and carried out in the future. The hope is that nutrigenetics will provide the basis for personalized dietary recommendations based on the individual's genetic make up and information from other factors such as gender and obesity, the latter being the focus of this review. To bring all this potential to reality will probably require individual ascertainment of all informative SNPs or, as forecast by others, complete sequencing of an individual's genome. Health professionals will use this data to forecast future genetic predisposition for disease, and it will guide them to the implementation of the proper preventive measures. Nutrigenetics needs to move forward with nutrigenomics to translate observational findings into molecular mechanisms. To achieve these ambitious goals, it will be necessary to move toward strategies that will yield findings that are more robust. Whether this will be feasible for the population at large any time soon remains to be seen.

In summary, nutritional genomics should be the driving force of future nutritional research, and it has the potential to change dietary disease prevention and therapy and have a major impact on public health. However, the complexity of the goals set for nutritional genomics is tremendous and their accomplishment will require breaking many of the molds of traditional research and seeking integration of multiple disciplines and laboratories working coordinately. Despite the difficulties described, preliminary evidence suggests that the concept will work and that by using behavioral tools founded on nutrition, we will be able to harness the information contained in our genomes to achieve successful and healthy aging.

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Recent evidence showing the modulating effect of BMI on genotype-phenotype associations related with CVD risk or metabolic syndrome

Table 1

Locus/SNP	Population characteristics	Main Outcome	Reference
Adiponectin (APM1 or ADIPOQ)/(-11391G>A, -1377C>G [promoter] and +45T>G[exon 2] and +276G>T[intron 2])	The Prospective Second Northwick Park Heart Study (NPHS) two haplotypes GCTT/GCGG and the II. European population including myocardial infarct survivors and controls	+276G>T SNP increased risk of T2DM in interaction with obesity	66
Angiotensin I-converting enzyme (ACE)/insertion/deletion	2642 healthy middle aged Caucasian (mean age 56 years) followed for 15 years	The ACE D allele may worsen glucose metabolism which could raise the prospective T2DM risk in obese men but not in lean men.	67
Apolipoprotein A5 (APOA5)/(-1131T>C, -3A>G, 56C>G, IVS3+476G>A, and 1259T>C)	2,273 Framingham Offspring Study participants	The rare allele of each of the -1131T>C, -3A>G, IVS3+476G>A, and 1259T>C variants and the haplotype defined by the presence of the rare alleles in these four variants were each significantly associated with CCA IMT only in obese participants	68
Cholesteryl ester-transfer protein (CETP)/TaqIB	237 hospitalized patients (185 males) with a first event of ACS and 237 controls matched by age and sex.	the likelihood of having a first event of ACS is observed only in normal-weight persons. There is a significant genetic response to the adiposity environment in Lp-PLA(2)	69
Chromosome 1 linkage	Subjects from the San Antonio Family Heart Study with measured Lp-PLA(2)	These results suggest a BMI-specific effect of L/F554 polymorphism of the E-selectin gene on blood pressure	70
E-Selectin (SELE)/Leu554Phe	478 men and 546 women were selected from the Stamias cohort	The presence of obesity reveals an association between blood pressure and the GNB3 gene in White females.	71
G-protein beta-3 (GNB3)/(-350A>G, 657A>T, 814G>A, 825C>T and 1429C>T)	282 female Caucasian dizygotic twins aged 21-80 years	These findings suggest that the variation within the GNB3 gene may interact with physical activity level to influence obesity status and, together with obesity and physical activity, this SNP may influence hypertension prevalence in AAs.	72
G-protein beta-3 (GNB3) 825C>T	14,716 African Americans (AAs) and whites from the Atherosclerosis Risk in Communities (ARIC) study	the C825T genotype was predictive of SBP only in individuals with increased body mass index	73
G-protein beta-3 (GNB3) 825C>T	Random Brazilian population (n=1,568)	Among men with the CC genotype, increasing BMI was associated with increased prevalence of diabetes. The IL-6-BMI interaction was not significant in women.	74
Interleukin-6 IL6/-174	1525 Framingham participants	These data suggest that obesity may modify the association between the LIPC C(-514)T polymorphism and CHD risk among diabetic men.	75
Hepatic lipase (LIPC)/-514C/T	Health Professionals Follow-up Study, case control, 220 diabetes men with CHD and 641 diabetes men without CVD	This study reports a significantly increased risk associated with the A12 allele among individuals with a BMI >=25 kg/m2, but not among those <25 kg/m2	76
Peroxisome proliferator-activated receptor-gamma (PPARG)/pro12Ala	Women (Nurses' Health Study) and men (Health Professionals Follow-Up Study) in nested case control settings		77