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# The Potential For Nutrigenomics in Prevention of Metabolic Syndrome

**Keywords**

Nutrigenomics, Metabolic Syndrome

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# The Potential For Nutrigenomics in Prevention of Metabolic Syndrome

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The relationship between diet and health has been recognized for millennia, but precisely “how” diet interacts with human physiology to elicit health or disease is only now beginning to be understood. The sequencing of the human genome as well as the development of new and innovative technologies in systems biology has allowed scientists to ask more probing questions into the relationship between diet and health at the most fundamental levels of biology. From this the “science of nutrigenomics” has emerged and it is now clear that certain dietary nutrients have the ability to interact with the human genome regulating gene function in positive and negative ways. Most importantly, the identification of specific nutrient chemicals that regulate genes is rapidly unfolding and the use of naturally occurring nutrient chemicals as pharmacological agents is becoming a reality. The net result is the development of new and innovative nutritional products for wellness and disease prevention.

## Introduction

Dietary components provide the nutrient resources and energy needed for growth and repair of tissue throughout our lives. In adults, energy balance or homeostasis occurs when energy intake equals energy expenditure. Maintenance of this balance is required for a stable body weight. A chronic positive energy balance results in excess fat and obesity, which is linked to a constellation of health maladies, and is referred to as “metabolic syndrome”. This syndrome is associated with an increased risk of chronic diseases, including diabetes, cardiovascular disease, and stroke. Two hallmarks of metabolic syndrome are insulin resistance and increased markers of chronic inflammation.

Metabolic syndrome is characterized by a group of metabolic risk factors in a single person<sup>1</sup>. They include:

- Central obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol — that foster plaque buildups in artery walls)
- Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- Raised blood pressure (130/85 mmHg or higher)
- Proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood)

The underlying causes of this syndrome are overweight/obesity, physical inactivity and genetic factors. People with the metabolic syndrome are at increased risk of coronary heart disease, other diseases related to plaque buildups in artery walls

(e.g., stroke and peripheral vascular disease) and type 2 diabetes.

South Carolina has the dubious distinction of having one of the highest metabolic disease prevalence rates in the country<sup>2</sup>. The occurrence of diseases related to this syndrome has resulted in a significant health-care burden and has prompted scientists from Clemson University, The University of SC and The Medical University of SC to join forces to seek solutions. In this regard an effort is now underway to form the SC Center of Economic Excellence in Molecular Nutrition where faculty from each university will collaborate to combine their individual strengths in plant breeding, nutrition, genomics, and gene regulation and function to develop prevention strategies. Motivation for this Center comes from long-held beliefs that chronic disease syndrome may one day be prevented through a better understanding and the mechanism through which specific nutrients are able to affect gene expression for human health.

## Molecular Nutrition and Wellness

Molecular nutrition examines the interactions between nutrients and intracellular and extracellular molecules and is beginning to unravel the way nutrients affect cellular processes. This emerging field has been identified as one of the most exciting new frontiers in biomedical technology with the potential to dramatically improve human health and wellness worldwide<sup>3</sup>.

A component of molecular nutrition, nutrigenomics, or nutritional genomics, is a multidisciplinary science that combines information from genetics, nutrition, physiology, pathology, and molecular biology. The diet - nutrient interactions which occur in different individuals is complex and scientists are focusing on the polymorphisms which affect these interactions to help alleviate health disparities.

Dietary chemicals have been shown to alter gene expression in a number of ways<sup>4</sup>. For example, they may:

- act as ligands for transcription factor receptors
- be metabolized by primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates or
- alter signal transduction pathways

genes not believed to be associated with nutrient utilization. While more complex than yeast, the constellation of genes that make up the human genome respond in a similar fashion to dietary inputs<sup>5</sup>.

The science of nutrigenomics is multifaceted, but primarily looks at the molecular relationships between dietary intake and the response of genes, with the aim of extrapolating how gene expression affects human health<sup>3,4</sup>. Nutrigenomics focuses on of the molecular relationships between dietary intake the effect of diet on the genome, epigenome, proteome, and metabolome. In understanding these effects, nutrigenomics attempts to define the relationship between specific nutrients and specific nutrient regimes (diets) on human health. Nutritional genomics, or nutrigenomics, is the study of how foods affect our genes and how individual genetic differences can affect the way we respond to nutrients (and other naturally occurring compounds) in the foods we eat.

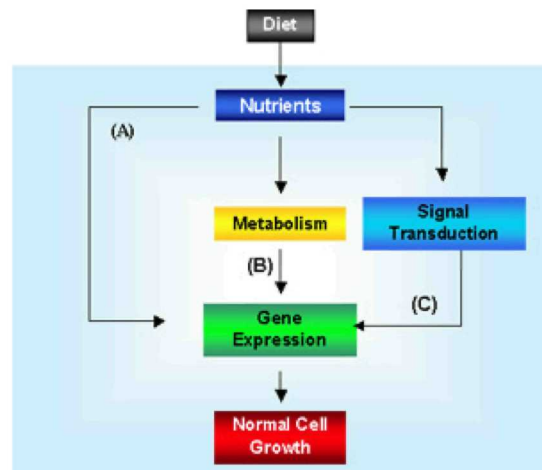
While somewhat controversial, nutrigenomics has been popularized with the idea of personalized nutrition based on genotype. While there is hope that nutrigenomics will ultimately enable such personalized dietary advice, the science is in its infancy and many more fundamental questions must be answered<sup>6</sup>.

### **Nutrigenomics and Disease Prevention**

Throughout the 20th century, nutritional science focused on finding vitamins and minerals, defining their use and preventing the deficiency diseases that they caused. As the nutrition-related health problems of the developed world shifted to overnutrition, obesity and type 2 diabetes, the focus of modern medicine and of nutritional science changed accordingly.

In order to address the increasing incidence of these diet-related-diseases, the role of diet and nutrition has been and continues to be extensively studied. To prevent the development of disease,

nutrition research is investigating how nutrition can optimize and maintain cellular, tissue, organ and whole body homeostasis. This requires understanding how nutrients act at the gene, protein and metabolic levels. As a result, nutrition research has shifted from epidemiology and physiology to molecular biology and genetics<sup>6</sup>.



With this paradigm shift new data has emerged in support of dietary interventions in preventing, mitigating, or treating chronic disease, and certain cancers. The conceptual basis and scientific evidence to support dietary interventions can be found in the following observations:

- Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases.
- Common dietary chemicals can act on the human genome, either directly or indirectly, to alter gene expression or structure.
- The degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup.
- Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.
- Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype, have been used to prevent, mitigate or cure chronic disease.

The emergence and development of nutrigenomics has been possible due to powerful developments in genetic research. With these developments, biochemical disorders with a high nutritional relevance have been linked to a genetic

origin. Such disorders include a polymorphism in the gene for the hormone Leptin which results in gross obesity. While a few other genetic polymorphisms have been described, it is thought that many others result in minor deviations in nutritional biochemistry. The tools to study the physiological impact of these genetic polymorphisms are only now becoming available. Such tools include those that measure the transcriptome - DNA microarray, exon array, single nucleotide polymorphism arrays and genotyping<sup>5,6</sup>.

### The Promise of Nutrigenomics

In nutrigenomics, nutrients are seen as signals that communicate with specific cells in the body. These nutrients may be detected by a sensory system much like those associated with toll-like receptors on cell surfaces. Like the toll receptor, cellular signaling is induced through transcription factors which alter gene expression and protein/metabolite production in accordance with the level of nutrient present in the cell environment. As a result, it is believed that different diets will elicit different patterns of gene and protein expression and metabolite production. Nutrigenomics seeks to describe the patterns of these effects which have been referred to as *dietary signatures*<sup>6</sup>. Such dietary signatures can be examined in specific cells, tissues and organisms and in this way the manner by which nutrition influences homeostasis can be better understood. Genes which are affected by differing levels of nutrients are now being identified and their regulatory pathways are under investigation<sup>3</sup>. Through the identification of these genes and their regulatory pathways, scientists will soon have a better understanding of how nutrition influences metabolic pathways and homeostasis. Such an understanding will be essential in attempts to prevent the development of chronic diet related diseases such as obesity and type 2 diabetes. In this regard, finding markers of the early phase of diet related diseases for intervention with selected nutrients that could reverse or slow the disease process will expand the application of nutrigenomics. Thus, once a marker has been found and measured, the extent to which an individual is susceptible to disease development may be quantified and personalized dietary recommendations prescribed. Progress in this area will lead to the marketing and distribution of "science-based functional foods" that will keep people healthy according to their individual needs.

### Chronic Disease Syndrome in SC

An estimated 79 million American adults (1 in 3) have cardiovascular disease (CVD), and millions more are at risk due to the presence of obesity, hypertension, and hyperlipidemia<sup>1</sup>. CVD

accounts for 36.3% of U.S. mortality, or 1 out of every 2.8 deaths. SC is a leader in heart disease and in stroke among the U.S states; heart disease is the leading cause of death in SC, accounting for 10,000 deaths annually.<sup>2</sup> Further, in 2007, SC had the seventh worst obesity rate in the nation, with over 65% of all SC adults either overweight or obese. When examined across race/ethnicity in SC adults, a larger proportion of African-Americans in the state are overweight or obese (73.6%) as compared to Whites (63%)<sup>7</sup>. Recent research has established that inflammation plays a key role in the atherosclerotic process<sup>8,9</sup>. Endothelial injury and plaque rupture are inflammatory processes that lead to thrombosis, myocardial infarction and stroke. Several proteins participate in the inflammatory processes that are useful for measurement. The most common and clinically useful measure is highly sensitive C-reactive protein (hsCRP), but several other markers have been investigated<sup>9,10</sup>.

A pharmaceutical approach to prevention of CVD inherently exposes millions of people without disease to the risk of adverse effects and interactions of multiple medications (aspirin—ulcers, bleeding; statins—liver dysfunction/myopathy; fenfluramine and phentermine—valvular heart disease and pulmonary hypertension). A more appealing approach is to identify, test, and use natural phytochemicals with anti-inflammatory and antioxidant activity and few side effects, to not only prevent CVD but promote general wellbeing.

### Dietary Interventions to Reduce Chronic Disease Syndrome in SC

One of the most promising candidates currently under investigation in South Carolina is the common table grape. Animal, laboratory, and epidemiologic data indicate that higher intake of polyphenol-rich grapes have anti-inflammatory and potent antioxidant effects that may reduce the risk of CVD and other chronic disease states such as hypertension. These beneficial effects have been attributed to the bioactive constituents resveratrol and flavonoids such as anthocyanins<sup>11,12</sup>. Recent evidence shows that red wine derived from table grapes (*Vitis vinifera*) may lower the risk of CVD<sup>13-15</sup>. Before proceeding with clinical studies of grape concentrates in clinical populations, the potential bioactive phytochemicals in grapes need to be more fully identified. The molecular mechanisms underlying the effect of grape phytochemicals in CVD prevention are yet to be elucidated, but alterations in cell signaling pathways leading to inflammation are a distinct possibility. Phase I and II trials need to be conducted in a carefully chosen target population with increased inflammation and oxidative stress (overweight/obese but otherwise healthy adults,<sup>16-18</sup> to

determine the maximum tolerable dose, adverse effects and effective dose ranges of grape products.

In contrast to table grapes, research on muscadine (*Vitis rotundifolia*), a native and valuable fruit crop in Southeastern US, including SC and GA, is under-developed. Muscadine is classified under the genus *Vitis* with other grape species, but further classified to a separate subgenus, *Muscadinia*, due to genetic and botanical differences between muscadine and other grapes. Muscadines are well adapted to warm and humid climate in the Southeastern US in which other grapes do not thrive. Muscadines have a higher total phenolic content compared to table grapes and small fruits<sup>19</sup>. Recent evidence shows that photochemical constituents of muscadines are distinct and differ from other grapes by having unique phenolic compounds, such as ellagic acid and other anthocyanins in appreciable amounts<sup>20-22</sup>. Anthocyanins are present as 3,5-diglucosides in the muscadine as opposed to 3-glucosides in other grapes, and glycosylation has been shown to be a major determinant of bioavailability<sup>22,23</sup>. Major phenolics reported in muscadine skins are ellagic acid, myricetin, quercetin, and kaempferol while for the muscadine seeds are gallic acid, catechin, and epicatechin<sup>20</sup>; most of the polyphenols are concentrated in the seed and skin. Therefore, muscadine seed and skin polyphenols may have different bioactivity, as compared to those of other grapes, due to the presence of unique polyphenols. These unique constituents may act as a source of novel compounds for targeted intervention in the inflammatory pathways. Clinical studies now underway at the Medical University of SC will focus on chemically defined constituents from muscadine seed and skin extracts to determine which ones have the greatest impact on inflammatory markers in patients with metabolic syndrome. Once identified, these extracts will be evaluated in larger trials in and out of SC to evaluate the long-term effects on prevention and/or delay in onset of the diseases associated with metabolic syndrome.

While it appears that certain classes of polyphenols, e.g. anthocyanins, in muscadines contain the bioactives needed for reducing inflammation, the cellular mechanism by which these substances impact disease are complex involving a highly evolved cellular circuitry in which gene expression, either directly or indirectly induced, results in physiologic change. With the recent advancements in systems biology (genomics, proteomics, and metabolomics) we may soon be able to dissect and control cellular circuits, which are regulated by polyphenols. Certainly our ability to control expression of nuclear factor-kappaB and inflammatory cytokines such as TNF-alpha and Il-6 appear to be likely candidates for initial investigations.

## Conclusions

The science of nutrigenomics continue to generate much interest and activity with the expectation that many of the disparities in wellness can be prevented, but much remains to be done, and this science is still in its infancy. The promise of nutritional genomics in personalized medicine and health is based on an understanding of our nutritional needs, nutritional and health status, and our genotype. Nutrigenomics could have significant impacts on society – from medicine to agricultural and dietary practices to social and public policies – and its applications are likely to compare to those arising from the human genome project. Chronic diseases (and some types of cancer) may be preventable, or at least delayed, by balanced, sensible diets. Knowledge gained from comparing diet/gene interactions in different populations may provide information needed to address the larger problem of global malnutrition and disease.

## References

- 1 Rosamond W and the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2007 update. *Circulation* 2007; 115: e69-e171.
- 2 National Vital Statistics Report 2006, National Center for Health Statistics  
[http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56\\_16.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_16.pdf), accessed March 25, 2009.
- 3 Chavez A, Munoz de Chavez M (2003). Nutrigenomics in public health nutrition: short-term perspectives. *European Journal of Clinical Nutrition*. 57(Suppl. 1)97-100.
- 4 Kaput, J. and Rodriguez, RL. 2004. Nutritional genomics: the next frontier in the postgenomic era. *Physiological Genomics* 16, 166 - 177.
- 5 Schuster, GU. (2006) Nutrients and Gene Expression. (In *Nutritional Genomics: Discovering the Path to Personalized Nutrition*). Kaput, J and Rodriguez, R (eds). Wiley and Sons, Inc. NY. 2006. pp 153 – 173.
- 6 Müller M, Kersten S. (2003). Nutrigenomics: Goals and Perspectives, *Nature Reviews Genetics* 4, 315 -322.
- 7 BRFSS 2007, Behavioral Risk Factor Surveillance System, [http://www.cdc.gov/brfss/technical\\_infodata/surveydata/2007.htm](http://www.cdc.gov/brfss/technical_infodata/surveydata/2007.htm), accessed March 22, 2009.
- 8 Ross R. Atherosclerosis: an inflammatory disease. *NEJM* 1999;340:115-126.
- 9 Ridker PM, Rifai N, Rose L. Comparison of c-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl JMed* 2002;347: 1557-1565.
- 10 Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107(3):499-511.
- 11 LaGouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliot P, Geny B, Laakso M, Puigserver P, Auwerx J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 2006;127(6):1109-1122.

- 
- 12 Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 2006; 444(7117):337-342.
- 13 Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339(8808):1523-6.
- 5 14 Leighton F, A Cuevas, and V Guasch. Plasma polyphenols and antioxidants, oxidative DNA damage and endothelial function in a diet and wine intervention study in humans. *Drugs Exp Clin Res.*1999; 25:133-141.
- 10 15 Stein JH, JG Keevil, DA Wiebe, S Aeschlimann, JD Foltz. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. *Circulation.*1999; 100 :10501055.
- 16 Skalicky J, Muzakova V, Kandar R, Meloun M, Rousar T, Palicka V. Evaluation of oxidative stress and inflammation in obese adults with metabolic syndrome. *Clin Chem Lab Med* 2008;46(4):499-505.
- 17 Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. *Nutr Rev* 2007; 65(12 Pt 2):S253-9.
- 20 18 Alexander CM, Landsman PB, Grundy SM. The influence of age and body mass index on the metabolic syndrome and its components. *Diabetes Obes Metab* 2008;10(3):246-50.
- 19 Pastrana-Bonilla E, Akoh CC, Sellappan S, Krewer G. Phenolic content and antioxidant capacity of muscadine grapes. *J Agric Food Chem* 2003;51(18):5497-5503.
- 25 20 Talcott ST, and JH Lee. Ellagic acid and flavonoid antioxidant content of muscadine wine and juice. *J Agric Food Chem.* 2002; 50:3186-3192.
- 30 21 Greenspan P, JD Bauer, SH Pollock, JD Gangemi, EP Mayer, A Ghaffar, JI Hargrove, DK Hartle. Antiinflammatory properties of the muscadine grape (*Vitis rotundifolia*). *J Agric Food Chem.* 2005; 53:8481-8484.
- 22 Karlsen A, Retterstol L, Laake P, Paur I, Kjolsrud-Bohn S, Sandvik L, blomhoff R. Anthocyanins inhibit nuclear factor-kappaB activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults. *J Nutr* 2007;137(8):1951-4.
- 35 23 Bitsch I, Jassen M, Netzel M, Strass G, Frank T. Bioavailability of anthocyanidin-3-glycosides following consumption of elderberry extract and blackcurrant juice. *Int J Clin Pharmacol Ther* 2004; 42(5): 293-300.
- 40
- 45