The role of nutritional genomics and epigenetics in the IFMNT RDN’s toolbox

Diana Noland, MPH RD CCN LD
Leigh Wagner, MS RDN LD (PhD Cand)
Integrative & Functional Medical Nutrition Therapy
University of Kansas Medical Center
Dietetics & Nutrition & KU Integrative Medicine

©2015 copyright Diana Noland, MPH RD CCN LD
University of Kansas Medical Center
Dietetics & Nutrition and KU Integrative Medicine

Diana Noland, MPH, RD, CCN, LD
Adjunct faculty, KUMC
Integrative Medical Nutrition Therapy
diana@diananoland.com

Leigh Wagner, MS, RD, LD (PhD Cand.)
KUMC Internship Preceptor
Integrative & Functional Nutritionist
lwagner@kumc.edu

©2015 copyright Diana Noland, MPH RD CCN LD
IFMNT

Integrative & Functional Medical Nutrition Therapy

How do we train and apply nutrigenomics in IFMNT?
KEY MESSAGE

Dietitian-nutritionists trained in nutrigenomics within the practice of IFMNT can provide guidance to match diet and lifestyle with a client’s genotype and biochemical individuality.

©2015 copyright Diana Noland, MPH RD CCN LD
OBJECTIVES

1. Review the evidence-based *nutri-epigenetics* tool box for the advanced dietetics specialty IFMNT

2. Identify two key evidenced-based gene marker sets useful in IFMNT clinical practice

3. Identify physiological biomarkers influenced by an individual’s gene markers that are useful in monitoring nutrition status and metabolic response to targeted nutritional therapy

4. Understand the role of functional foods and dietary supplements in the practice of IFMNT *nutriepigenetics*
...reviews the evidence from randomized, controlled trials; cohort and case-controlled studies; and observational studies, which can also provide valuable evidence, and takes into account the number of studies that have provided consistent outcomes of support...
“At this time, the best "genetic test" for most disorders and traits is the family history; dietitians need to be able to gather and interpret family history to incorporate into the nutrition care process.”
“Nutri-epigenetics”

“...the influence of dietary components on mechanisms influencing the epigenome - has emerged as an exciting new field in current epigenetic research.”

Nutritional Epigenetics

**Epigenetic effects of nutrition**
- **Methyl donors**
  - Vitamin B12
  - Folate
  - Choline
  - Betaine
  - Methionine
  - Serine
  - Glycine
- **Fatty acids**
  - Butyrate
  - Arachidonic acid
  - Docosahexaenoic acid
  - Eicosapentaenoic acid
- **Vitamins**
  - Retinol
  - Tocopherols
  - Vitamin C
- **Phytochemicals**
  - Genistein
  - Soy isoflavones
  - Curcumin
  - Resveratrol
  - Sulforaphane
  - Polyphenols

**Epigenetic control gene expression**
- **Epimutations - EpiSNPs**
  - Disease
  - Specific
  - Genes:
    - involved in
    - Metabolic
    - Syndrome &
    - Inflammaging
  - ADME Genes:
    - Phase I enzymes
    - Phase II
    - Transporters
    - Metabolisation
    - DNA repair
    - For example
      - PITX2, BRCA1, GPX3,
      - MGMT, PLK2, TFAP2E,
      - OSCP1, SFRP5, RASSF1A
      - MPO, CFTR, ...
    - For example
      - LEP, NPY, POMC,
      - MC4R, IRS1, INS,
      - ADIPOQ, UCP1, TNF
      - FTO, GLUT4, IGF2,
      - CEBP1, FASN, MHTF
      - HIF1A, SOD2, SOD3,
      - IFNG, PPARA, NR3C1
    - Disease risk
    - Diagnosis
    - Prognosis

**Personalized Nutrition**

*Figure 4 Overview of the mechanisms and consequences of epigenetic regulation by nutritional compounds.* Modulation of different classes of chromatin writers-erasers by phytochemicals (left panel). Genes encoding absorption, distribution, metabolism, and excretion (ADME) proteins can be epigenetically regulated and thereby determine individual nutritional responses. Epigenetic modification of disease-related genes can contribute to diagnosis (biomarker) as well as disease prevention or progression (right panel).

vel Szic et al. From inflamming to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition? Clinical Epigenetics (2015) 7:33
Figure 4 Overview of the mechanisms and consequences of epigenetic regulation by nutritional compounds. Modulation of different classes of chromatin writers-erasers by phytochemicals (left panel). Genes encoding absorption, distribution, metabolism, and excretion (ADME) proteins can be epigenetically regulated and thereby determine individual nutritional responses. Epigenetic modification of disease-related genes can contribute to diagnosis (biomarker) as well as disease prevention or progression (right panel).

Biochemical individuality

Individualized Nutrition

Everyone is a unique individual, biochemistry, person...
Personalized Nutrition

Figure 4 Overview of the mechanisms and consequences of epigenetic regulation by nutritional compounds. Modulation of different classes of chromatin writers-erasers by phytochemicals (left panel). Genes encoding absorption, distribution, metabolism, and excretion (ADME) proteins can be epigenetically regulated and thereby determine individual nutritional responses. Epigenetic modification of disease-related genes can contribute to diagnosis (biomarker) as well as disease prevention or progression (right panel).

Mechanisms

ENVIRONMENTAL REGULATION BY NUTRITIONAL COMPOUNDS AND LIFESTYLE INFLUENCES
Methylation Status Biomarkers:

**BLOOD:**
- Hgb/Hct
- MCV/MCH (optimum 90/30)
- Homocysteine (optimum 5-6)
  (optimum/adequate=mid-range reference)
- Methylmalonic Acid (functional B12)
- Folate
- Vitamin B6

**Nutrition-focused Physical Exam:**
- Tongue
- Mouth

**MSQ/Signs & Symptoms:**
- Fatigue
- Pain
- Insomnia
- Developmental disorders, neurological, mood disorders

**Genomic / Family History:**
- MTHFR homozygous or heterozygous & others
- COMT
- FHx: Downs, Cleft Palate, Spinabifia, Marfans, Autism/Austistic Spectrum, tongue-tie

**Fatty Acid Status Biomarkers:**

**BLOOD:**
- Lipid Panel (Total Chol, HDL, LDL, Triglycerides)
- Lipoprotein Particle Panel
- CK / Creatine Kinase
- RBC Fatty Acid Analysis
- Plasma Fatty Acid Analysis
- CRP-hs/ inflammation R/T EFA imbalances
- Autoimmune testing
- Infection-related testing

**STOOL:**
- SCFA – Butyrate, Propionate, Acetate

**Nutrition-focused Physical Exam:**
- Skin aberrations, Dry skin
- Inflammation

**MSQ/Signs & Symptoms:**
- Skin rashes, redness
- Pain, Insomnia, mood disorders, neurological

**Genomic / Family History:**
- FADS homozygous or heterozygous & others
- FHx: neurological, mood disorders, inflammation

---

**Oxidative Stress Status Biomarkers:**

**BLOOD:**
- Lipid Panel (Total Chol, HDL, LDL, Triglycerides)
- Lipoprotein Particle Panel
- CRP-hs/ inflammation R/T EFA imbalances
- Sed Rate
- Inflammatory specific Dx Testing
- Infection-related testing

**STOOL:**
- SCFA – Butyrate, Propionate, Acetate

**Nutrition-focused Physical Exam:**
- Skin integrity
- Inflammation

**MSQ/Signs & Symptoms:**
- Infection, inflammation-related symptoms, chronic diseases (cancer, etc.)

**Genomic / Family History:**
- ____ homozygous or heterozygous & others
- FHx: inflammation, cancer
Review Article

Theme: Natural Products Drug Discovery in Cancer Prevention
Guest Editors: Ah-Ng Tony Kong and Chi Chen

Plant Phytochemicals as Epigenetic Modulators: Role in Cancer Chemoprevention

Vijay S. Thakur,¹ Gauri Deb,¹,² Melissa A. Babcock,¹,³ and Sanjay Gupta¹,³,⁴,⁵

Received 7 June 2013; accepted 18 November 2013; published online 5 December 2013

Abstract. In recent years, “nutri-epigenetics,” which focuses on the influence of dietary agents on epigenetic mechanism(s), has emerged as an exciting novel area in epigenetics research. Targeting of aberrant epigenetic modifications has gained considerable attention in cancer chemoprevention research because, unlike genetic changes, epigenetic alterations are reversible and occur during early carcinogenesis. Aberrant epigenetic mechanisms, such as promoter DNA methylation, histone modifications, and miRNA-mediated post-transcriptional alterations, can silence critical tumor suppressor genes, such as transcription factors, cell cycle regulators, nuclear receptors, signal transducers, and apoptosis-inducing and DNA repair gene products, and ultimately contribute to carcinogenesis. In an effort to identify and develop anticancer agents which cause minimal harm to normal cells while effectively killing cancer cells, a number of naturally occurring phytochemicals in food and medicinal plants have been investigated. This review highlights the potential role of plant-derived phytochemicals in targeting epigenetic alterations that occur during carcinogenesis, by modulating the activity or expression of DNA methyltransferases, histone modifying enzymes, and miRNAs. We present in detail the epigenetic mode of action of various phytochemicals and discuss their potential as safe and clinically useful chemopreventive strategies.

KEY WORDS: cancer chemoprevention; dietary agents; DNA methylation; epigenetics; histone modification; microRNA.
<table>
<thead>
<tr>
<th>Phytochemical/Dietary agent (source)</th>
<th>Epigenetic modification(s)</th>
<th>Mechanism(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green tea polyphenol—epigallocatechin-3-gallate (EGCG)</td>
<td>DNA methylation</td>
<td>DNMT inhibitor</td>
<td>(21-32)</td>
</tr>
<tr>
<td>(green tea)</td>
<td></td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAM, 5mC ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDAC activity ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAT exp ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ac-H3, H3K9Ac, Ac-H4 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMT inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI-1, SUZ12, EZH2, EED, H3K27me3 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>miR-16 ↑, miR-21, miR-27 ↓, miR-330 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeCP2 binding ↑</td>
<td></td>
</tr>
<tr>
<td>Curcumin (turmeric)</td>
<td>DNA methylation</td>
<td>DNM2 inhibitor</td>
<td>(34-50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mC ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDAC1, HDAC3, HDAC-8 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>p300 (HAT) ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ac-H3, Ac-H4 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Differential miRNA modulations</td>
<td>miR-16, miR-186 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>miR-15a ↑</td>
<td></td>
</tr>
<tr>
<td>kneesoraphane (Broccoli)</td>
<td>DNA methylation</td>
<td>DNM2 expression ↓</td>
<td>(52-58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>HDAC inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ac-H3 and Ac-H4 ↑</td>
<td></td>
</tr>
<tr>
<td>Diindolylmethane (DIM) and Indole-3-carbinol (I3C;</td>
<td>Histone modifications</td>
<td>Class 1 HDACs degradation ↑</td>
<td>(60-63)</td>
</tr>
<tr>
<td>Cruciferous vegetables—Brassica genus)</td>
<td></td>
<td>HDAC1,2,3 expression ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Differential miRNA modulations</td>
<td>miR-let-7b, miR-146, miR-let-7c,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>miR-200b, and miR-200c,miR-21 ↑</td>
<td></td>
</tr>
<tr>
<td>Genistein (soy beans)</td>
<td>DNA methylation</td>
<td>DNM2 inhibitor</td>
<td>(61,65-78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>HDAC exp ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAT exp ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Differential miRNA modulations</td>
<td>Ac-H3, Ac-H4, Ac-H3K9 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>H3K9me2 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>miR-200 ↓, miR1296 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>miR-27a ↓</td>
<td></td>
</tr>
<tr>
<td>Phenthel Isothiocyanate (cruciferous vegetables)</td>
<td>DNA methylation</td>
<td>GSTP1 Promoter methylation ↓</td>
<td>(80-85)</td>
</tr>
<tr>
<td>(cruciferous vegetables)</td>
<td></td>
<td>H3 and H4 acetylation ↑</td>
<td></td>
</tr>
<tr>
<td>Resveratrol (Grapes)</td>
<td>DNA methylation</td>
<td>DNM2 inhibitor</td>
<td>(87-90)</td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>MBD2 recruitment ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td>Organosulfur Compounds (Allium vegetables such as garlic)</td>
<td>Histone modifications</td>
<td>MTA1/NuRD corepressor complex ↓</td>
<td>(81,92,93)</td>
</tr>
<tr>
<td>(Allium vegetables such as garlic)</td>
<td></td>
<td>H3 and H4 acetylation ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA methylation</td>
<td>HDAC ↓</td>
<td></td>
</tr>
<tr>
<td>Lycopene (Tomatoes)</td>
<td></td>
<td>Promoter methylation ↓</td>
<td>(66)</td>
</tr>
<tr>
<td>Quercetin (Citrus fruits and Buck wheat)</td>
<td>DNA methylation</td>
<td>DNM2 inhibitor</td>
<td>(96-99)</td>
</tr>
<tr>
<td></td>
<td>Histone modifications</td>
<td>Promoter methylation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ac-H3 ↑</td>
<td></td>
</tr>
<tr>
<td>Ellagitannins (Berries)</td>
<td>Differential miRNA modulations</td>
<td>miR-let-7e, miR-370, miR-373* and miR-526b ↑</td>
<td>(101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>let-7a, let-7c, let-7d ↓</td>
<td></td>
</tr>
</tbody>
</table>
Nutri-epigenetics Ameliorates Blood–Brain Barrier Damage and Neurodegeneration in Hyperhomocysteinemia: Role of Folic Acid

Anuradha Kalani,
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Pradip K. Kamat,
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Srikant Gavimani,
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Kasey Brown,
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Naira Metreveli,
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Suresh C. Tyagi, and
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Neele Tyagi
Department of Physiology and Biophysics, School of Medicine, University of Louisville, 500 South Preston Street, Louisville, KY 40202, USA

Neele Tyagi neettyagi01@louisville.edu

Abstract

Epigenetic mechanisms underlying nutrition (nutrition epigenetics) are important in understanding human health. Nutritional supplements, for example folic acid, a cofactor in one-carbon metabolism, regulate epigenetic alterations and may play an important role in the maintenance of neuronal integrity. Folic acid also ameliorates hyperhomocysteinemia, which is a consequence of elevated levels of homocysteine. Hyperhomocysteinemia induces oxidative stress that may epigenetically mediate cerebrovascular remodeling and leads to neurodegeneration, however, the mechanisms behind such alterations remain unclear. Therefore, the present study was designed to observe the protective effects of folic acid against hyperhomocysteinemia-induced epigenetic and molecular alterations leading to neurotoxic cascades. To test this hypothesis, we employed 8-weeks-old male wild-type (WT) cystathionine-beta-synthase heterozygote knockout methionine-fed (CBS−/−Met), WT, and CBS−/−Met mice supplemented with folic acid (FA) (WT+FA and
Interventions using supplementation with folic acid or methyl donors during pregnancy, or folic acid after weaning, alter the phenotype and epigenotype induced by maternal dietary constraint during gestation.

This suggests a possible means for reducing risk of induced noncommunicable disease.
Dietary Manipulation of Histone Structure and Function

Barbara Delage and Roderick H. Dashwood
Linus Pauling Institute, Oregon State University, Corvallis, Oregon 97331-6512
Barbara Delage; Roderick H. Dashwood: rod.dashwood@oregonstate.edu

Abstract

Post-translational modifications of histones are the subject of intensive investigations with the aim of decoding how they regulate, alone or in combination, chromatin structure, genomic stability, and gene expression. Major epigenetic programming events take place during gametogenesis and fetal development and are thought to have long-lasting consequences on adult health. Epidemiological and experimental studies have pointed toward maternal nutrition as a major player during prenatal development in influencing disease susceptibility later in life. Although the mechanisms underlying such observations are not well elucidated, epigenetic alterations of histones by particular maternal diets might be of central importance. Moreover, as much as dietary sources can influence epigenetic programming during pregnancy, they have started to be implicated in cancer chemoprevention, via the targeting of reversible epigenetic deregulations at the level of the histones.
Figure 4.
Overview of the methionine-homocysteine-folate-B12 cycle, which provides methyl donors for methyltransferases. Nutritional regulations of the cycle by phytochemicals and metals are shown in red. BHMT, betaine homocysteine; CS, cystathionine synthase; DNMT, DNA methyltransferase; EGCG, epigallocatechin-3-gallate; MAT, methionine adenosyl transferase; MS, methionine synthase; SAAH, S-adenosyl-L-homocysteine hydrolase; SAH, S-adenosyl-L-homocysteine; SAM, S-adenosyl-L-methionine; THF, tetrahydrofolate. Delage and Dashwood Page 24 Annu Rev

©2015 copyright Diana Noland, MPH RD CCN LD
...the epigenetic actions of dietary components, including phytochemicals, and macro- and micronutrients as well as metabolites, that can attenuate inflammaging.
...what are the **challenges** facing personalized nutrition to translate highly variable inter-individual epigenetic diet responses to potential individual health benefits/risks related to aging disease.

Challenges:
1. Individuals display **different responses** to pharmacological nutritional interventions, respectively, that result in variable benefits to particular treatments.
2. **Heterogeneity**, or variety, in responsiveness can obscure associations between dietary intakes and health outcomes.
3. Dosing has to be personalized.
4. **Several genetic variants exist** for genes encoding glutathione S-transferases (GSTs), which play major roles in the metabolism of glucosinolates and bioavailability of isothiocyanates that are present in cruciferous vegetables (broccoli).
Nutri-epigenomics: lifelong remodeling of our epigenomes by nutritional, phytochemical, and metabolic factors. Phytochemicals from plants appear to be crucial to achieve the correct relationship between man and nature - between dietary balance and health.

...food is now also a conditioning environment that shapes the activity of the (epi)genome and determines stress adaptive responses, energy metabolism, immune homeostasis, and the physiology of the body.

**Food is information to our genes**

Video Dr. Church, geneticist
Harvard University
Practice-based evidence promotes the value of the knowledge and evidence gained from the practitioner’s clinical experiences and observations.
Individual-based evidence
“n of 1”
the patient’s story and genotype
MTHFR 677 -/- \textit{WILD/NORMAL}

100% efficiency

- DRI Folate adult 320 μg/d
- DRI Folate preg 520 μg/d
- DRI B12 adult ND
- DRI B6 adult 1.0-1.3 mg/d
- DRI B6 preg 1.6 mg/d
- DRI B6 lactation 1.7 mg/d

(2004 NAS)

MTHFR 677 +/- \textit{Optimum Requirements}

Folate-B6-B12

DRI Estimated
Requirements

DRI Estimated
Requirements

Optimum
Methylation

Optimum
Methylation

Optimum
Health

Optimum
Health

Health not easily found at +/- 2 Standard Deviation

DRI Folate adult 640 μg/d
DRI Folate preg 1000 μg/d
DRI B12 adult ND
DRI B6 adult 2.0 mg/d
DRI B6 preg 3.0 mg/d
DRI B6 lactation 3.0 mg/d

(2004 NAS)

©2015 copyright Diana Noland, MPH RD CCN LD
Examples practice based nutri-epigenetics MNT

55 yo male Depression, OCD

23andme.com MTHFR C677T -/+ and MTHFR 1298C +/- MTR +/- COMT +/- SNPs

Diet Low vegetable intake / almost no green/color vegetables
Diet no egg yolk – only egg whites
High processed food diet
No nutritional supplements

Hi Stress – job, mother just died, severe insomnia

RECOMMENDATIONS:
• Referral to psychologist or psychiatrist
• Multi supplement with all bioactive forms B-Complex at 2x DRI
• DIET: Whole clean foods, 6-9 servings hi-folate vegetables daily, beneficial balanced fats/oils, 2 eggs daily boiled or poached(egg yolk = folate, PC)
• SLEEP: Sleep hygiene education, magnesium 400 mg hs, herbal sleep aid
• Rx: SSRI, Deplin (7.5 mg 5MTHF) x 1 month

OUTCOME x 6 weeks: Normal mood and normal function QOL
Nutrigenetics

Nutrigenetics explores interactions of our inherited genome and nutrition.

Nutrigenomics

Describes a broader scope than nutrigenetics including nutritional interactions of our genome. 

*Nutrigenomics* refers to **all regulatory processes** that involve our genome that includes a new field of study called *nutriepigenetics.*

• *Nutrigenetics:* applying the science of personal nutrition. Martian Kohlmeir Elsevier (2013)
Polymorphisms

- Single Nucleotide Polymorphisms
- Deletions
- Copy Number

Clinical Application

©2015 copyright Diana Noland, MPH RD CCN LD
Introduction to Translational Nutrigenomics

“Genes influence everything, And determine nothing.”

©2015 copyright Diana Noland, MPH RD CCN LD
FUNCTIONAL MEDICINE MATRIX

Retelling the Patient’s Story

Antecedents

Triggering Events

Mediators/Perpetuators

Physiology and Function: Organizing the Patient’s Clinical Imbalances

Assimilation

Defense & Repair

Structural Integrity

Mental

Emotional

Energy

Spiritual

Communication

Biotransformation & Elimination

Transport

Modifiable Personal Lifestyle Factors

Sleep & Relaxation

Exercise & Movement

Nutrition

Stress

Relationships

©2015 copyright Diana Noland, MPH RD
...including nutritional approaches from a systems biology perspective, nutrigenomics, and biochemistry as the core knowledge to understand the root cause of a chronic disorder and to choose appropriate nutritional tools for interventions.

INTRODUCTION

The global burden of disease is unsustainable, and changes in health care and education are required; the public policy, dietary changes [6–15]. But if nutritional interventions are to address the chronic disease epidemic, a well-trained workforce is mandatory [5,16–19].
key evidenced-based gene markers

METHYLATION
METHYLATION

Nutrigenomic Medical Nutrition Therapy

KEY Methylation genes

MTHFR C677T

MTHFR A1298C

©2015 copyright Diana Noland, MPH RD CCN LD
METHYLATION

Nutrigenomic Medical Nutrition Therapy

KEY Methyl Donor Supplements

MTHFR C677T
MTHFR A1298C

INTERVENTION:
Recommend bioactive form of folate - “5MTHF”
and co-factors of B-Complex
+ Dietary folate rich foods
Methylation: Cardiometabolic Syndrome
Methylation: Mood Disorders

©2015 copyright Diana Noland, MPH RD CCN LD
DNA Methylation - two center cytosines
DNA methylation also plays a crucial role in the development of nearly all types of cancer.

Experimental Cell Research, Volume 314, Issue 6, 1 April 2008, Pages 1193–1201
In neuronal systems, extensive studies have revealed **important regulatory roles of DNA methylation in brain function**, from the embryonic stage through the process of aging.

The **dynamics of DNA methylation** involved in aging, learning and memory, and neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and CGG repeat-induced neurodegenerative disorders.

**Epigenetic changes in neurology: DNA methylation in multiple sclerosis.**

*Neurologia.* 2015 May 11. doi: 10.1016/j.nrl.2015.03.011. [Epub ahead of print]
In *Systemic lupus erythematosus (SLE)* ... Epigenetic factors have significant effects on T-cell functions by modulating its DNA methylation pattern.


Defective maintenance of DNA methylation ...during mitosis, resulting in the development of a lupus-like disease or perhaps other autoimmune disorders.

key evidenced-based gene markers
Celiac Disease

Statistical frequency of CD race-related

Developing Symptoms & Diagnosis Celiac

- **Genetics:** HLA-DQ2+/HLA-DQ8+
- GI Barrier compromised infection or trigger
- pieces of gluten (called α-gliadins) absorb into blood
- a complicated immune response which actually damages the small intestine.
Celiac Disease

Untreated, celiac disease can cause:

- **Malnutrition.** The damage to your small intestine means it can't absorb enough nutrients. Malnutrition can lead to anemia and weight loss. In children, malnutrition can cause stunted growth and delayed development.

- **Loss of calcium and bone density.** Malabsorption of calcium and vitamin D may lead to a softening of the bone (osteomalacia or rickets) in children and a loss of bone density (osteoporosis) in adults.

- **Infertility and miscarriage.** Malabsorption of calcium and vitamin D can contribute to reproductive issues.

- **Lactose intolerance.** Damage to your small intestine may cause you to experience abdominal pain and diarrhea after eating lactose-containing dairy products, even though they don't contain gluten. Once your intestine has healed, you may be able to tolerate dairy products again. However, some people continue to experience lactose intolerance despite successful management of celiac disease.

- **Cancer.** People with celiac disease who don't maintain a gluten-free diet have a greater risk of developing several forms of cancer, including intestinal lymphoma and small bowel cancer.
Celiac Disease

Iron Deficiency

Oxidative Stress

Osteoporosis

Vitamin D Deficiency

Autoimmune/autoantibodies

Inflammatory genotype

HLA DQ2/DQ8
& functional marker

↑ t-TG IgG, IgA (blood)

Celiac Disease

Inflammatory phenotype

- Blood: Vitamin D25-OH
- Blood: C-Reactive Prot HS
- Blood: Sed Rate/ESR
- Blood: ANA Titer
- Blood: Iron Studies
- Imaging: DEXA Bone Scan

Saliva/blood: HLA-DQ2+/HLA-DQ8+/etc.

DIAGNOSIS/SIGNS&SYMPTOMS – MSQ

NUTRITION-PHYSICAL EXAM

METABOLIC & NUTRITION STATUS?
• Fasting Glucose, fasting insulin, HgA1C
• IgA test for IgA deficiency
• Iron Study: Iron Sat, TIBC, serum iron
• Ferritin Check fingernails – are they flat? Iron deficiency?
• Zinc: Alk Phos 40 (when lower than 75 can suggest low zinc)
• Vitamin D deficiency Vitamin D 25-OH <40 ng/ml / VDR gene
• CRP-hs mg/L (goal <1.0)
• Sed Rate
• Milk/Egg IgG Sensitivity Severe +
• Severe H. Pylori Stool test
• CDSA stool test

BODY COMPOSITION? BMI Body Fat %

TOXINS?
• Toxic Metals: Al, As, Pb, Hg, Cd
• Chemical toxins: petrochemicals, other
Skin

Dermatitis Herpetiformis?
2015 ICD-9-CM Diagnosis Code 694.0

What to do clinically?

- Support client and family education for Gluten-free Diet and Supplements (wheat, barley, rye, kamut, spelt, foods containing these foods)

- Support repair of damaged gut tissue (pre and probiotics, identify and remove inflammatory triggers (antigens, etc.), comprehensive nutritional assessment.

- Monitor and Evaluate effect of intervention (MSQ/signs & symptoms, tissue-Tranglutaminase IgA, IgG blood test)
## Genomic Testing

<table>
<thead>
<tr>
<th>Gene/Marker</th>
<th>Description</th>
<th>rs ID</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTR A2756G</td>
<td>5-methyltetrahydrofolate-homocysteine methyltransferase</td>
<td>MTR rs1805087</td>
<td></td>
</tr>
<tr>
<td>MTRR A66G</td>
<td>Methionine synthase reductase</td>
<td>MTRR rs1801394</td>
<td></td>
</tr>
<tr>
<td>COMT/</td>
<td>catechol-O-methyltransferase</td>
<td>COMT rs731236</td>
<td></td>
</tr>
<tr>
<td>CBS /</td>
<td>cystathionine-beta-synthase</td>
<td>CBS rs844ins68</td>
<td></td>
</tr>
<tr>
<td>GSTM1</td>
<td>Glutathione-S-Transferase Mu 1</td>
<td>GST rs1p13.3</td>
<td></td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D Receptor</td>
<td>VDR rs1695 -↓/+↓/+↓</td>
<td>~50-60% reduced activity</td>
</tr>
</tbody>
</table>

http://www.humgenomics.com/content/7/1/14/table/T4

http://www.genecards.org/cgi-bin/carddisp.pl?gene=GSTM1

©2015 copyright Diana Noland, MPH RD CCN LD
FOOD IS INFORMATION
MESSAGING OUR GENES

http://www.wrfoodsystem.ca/blog/is-it-really-all-about-our-genes
KEY MESSAGE

Dietitian-nutritionists trained in nutrigenomics within the practice of IFMNT can provide guidance to match diet and lifestyle with a client’s genotype and biochemical individuality.
Advanced SPECIALTY training in IFMNT

✅ www.integrativeRD.org
   ▪ “RESOURCES” “Degrees & Training” (several)
   ▪ “Log-in” Members Only “Archived Webinars”
     ▪ Nutritonal Genomics: An Introductory Review and Global Focus
       Colleen Fogarty Draper MS, RD, LDN  Jan. 12, 2012
   ▪ DIFM ListServ (DIFM_Listserv@yahoo.com)
   ▪ Natural Medicines/ Natural Standard Database (DIFM benefit)
     http://integrativerd.org/members-only/nmcd/

✅ University of Kansas Medical Center
   Dietetics & Integrative Medicine Graduate Certificate
   (online in-state tuition 12 hours graduate credit)
   Dietetics & Integrative Medicine Fellowship, Internship/M.S.
Advanced SPECIALTY training in IFMNT

- **www.mthfr.net**  Ben Lynch, ND
- **www.mthfrsupport.com**  Amy Yasko, MD
- **www.functionalmedicine.org**  Institute for Functional Medicine
- **www.23andme.com**  genetic testing
- **www.livewello.com**  genetic testing reporting
- **www.geneticgenie.org**  Neurology and Psychiatry (methylation and detox)
- **http://www.genome.gov/19516567**
- **http://genetics.med.harvard.edu/**
- **http://www.nchpeg.org/nutrition/index.php?option=com_content&view=article&id=395&Itemid=559**  Genetics and Nutrition for Dietitians (funded by NIH)
University of Kansas School of Medicine, Departments of Integrative Medicine and Dietetics and Nutrition

Description: Non-degree Online Graduate Dietetics and Integrative Medicine (DIM) 12 hour Certificate:
Four online graduate classes of 3 CE/semester over one year: Introduction to DIM, Inflammation and Immune Regulation, Dietary and Herbal Supplements, Nutrigenomics and Nutrigenetics in Health and Disease. Prereq: B.S.; Prereq or concurrent: genetics; or by approval of instructor. DIFM members: in-state tuition rates.

Degree: Dietetic Internship Fellowship and MS in Dietetics & Nutrition with Integrative Nutrition emphasis: For candidates having completed a BS including pre-requisites for an Academy of Nutrition and Dietetics approved dietetic internship. The goal is to provide intensive experience in the integrative medicine clinic and create a nutrition professional knowledgeable in integrative and functional nutrition care to function as a skilled practitioner and member of multidisciplinary and integrative patient care teams. KUMC Contact: Rachel Barkley, MS RD LD, Dietetic Internship Director rbarkley@kumc.edu Websites: http://integrativemed.kumc.edu and http://dietetics.kumc.edu/integrative-medicine

University of Medicine and Dentistry (UMDNJ) – School of Health Related Professions

University of Kansas Medical Center:
Dietetics & Nutrition / KU Integrative Med Clinic

• Dietetic Internship/M.S.: Clinical, Integrative Track

• Graduate Certificate in Dietetics & Integrative Medicine (12hrs.)

• Dietetics & Nutrition Fellowship (2-3 Fellows/year)
The University of Kansas Medical Center
Dietetics & Integrative Medicine Graduate Certificate Program
Department of Dietetics & Nutrition

Introduction
The Dietetics and Integrative Medicine graduate certificate program offers an opportunity for graduate students with bachelor’s or master’s degrees in dietetics, nutrition, biological sciences or health professions to acquire knowledge to function as a skilled advisor to the patient and a collaborative member of multidisciplinary health care teams; professionals working effectively with integrative and conventional medical practitioners.

The Institute of Functional Medicine defines dietetics within integrative medicine as personalized medical nutrition therapy for prevention and treatment of chronic disease that embraces conventional and complementary therapies. Dietetics within integrative medicine reaffirms the importance of the therapeutic relationship, a focus on the whole person, lifestyle, biochemical individuality and environmental influences.

Program Director
Rachel Barkley, MS, RD, LD
rbarkley@kumc.edu
913-588-7683

Department Information
Department of Dietetics and Nutrition
Mail Stop 4013
3901 Rainbow Blvd.
Kansas City, KS 66160
www.dietetics.kumc.edu

Certificate Curriculum
A web-based 12 hour program over 4 consecutive semesters:
DN 880 Dietary & herbal supplements (3 hrs.) - summer;
DN 881 Introduction to dietetics & integrative medicine (3 hrs.) - fall;
DN 882 A nutrition approach to inflammation & immune regulation (3 hrs.) - spring; and
DN 980 Nutrigenomics and nutrigenetics in health and disease (3 hrs.) - summer

DN 880 Dietary & herbal supplements
Develop skills to partner with patients in making dietary supplement decisions. Explore the safe, efficacious use of botanicals and supplements in nutritional support of aging, maternal health and wellness. Discussions on supplementation in the prevention and treatment of chronic disease include: arthritis, cancer, cardiovascular, diabetes, digestive, mood and renal disorders.

DN 881 Intro. to dietetics & integrative medicine
Introduction to principles of guiding dietetics and integrative medicine, assessing, diagnosis, intervention, monitoring, and evaluating an individual client to restore function; focusing on the unique nutritional imbalances characteristic of chronic disease pathophysiology; supporting individuals with persistent symptoms; preventing chronic disease.

DN 882 A nutrition approach to inflammation & immune regulation
Inflammation and immune dysregulation are common in chronic disease. The course presents a dietetics and integrative medicine approach to identify underlying causes of inflammatory and immune-related conditions and associated nutritional influences; applies personalized nutritional interventions as powerful modulators of the pathophysiology of inflammatory and immune responses.

DN 980 Nutrigenomics & nutrigenetics in health & disease
A review of nuclear receptors and their mechanisms of action with specific examples of regulation by nutrients, amino acid control of gene expression, lipid sensors, selenoprotein expression, and functional genomic studies (e.g., atherosclerosis, cancer, obesity, metabolic syndrome. Type 2 diabetes mellitus, and inflammation) with relationships to nutrient intake and polymorphisms.

Admission Requirements
Qualified applicants meet one of the following criteria:
1. Completed an accredited dietetic internship program and are enrolled in a graduate program in Dietetics and Nutrition.
2. Enrolled in a graduate health profession major.
3. Registered Dietitian or other health professional seeking post bachelor’s or master’s degree education.

All applicants must:
1. Complete prerequisite courses in Medical Nutrition Therapy and Genetics or obtain consent prior to enrollment to determine if possible to enroll in a course before prerequisite courses are completed.
2. Have a cumulative undergraduate or graduate GPA of 3.0 or greater.
3. Submit application to the program as directed on the department web site including official college transcripts, 3 recommendation letters, resume, and official score report from the Graduate Record Examination. GRE scores are valid for 5 years. Application deadlines: Feb. 1 for summer semester admission or May 15 for fall semester admission.
<table>
<thead>
<tr>
<th>Semester</th>
<th>Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall Semester 2013 – 11 hours</strong></td>
<td><strong>Spring Semester 2014 – 11 hours</strong></td>
</tr>
<tr>
<td>DN 817 Seminar in Dietetics &amp; Nutrition I – 1 hr.</td>
<td>DN 818 Seminar in Dietetics &amp; Nutrition II – 1 hr.</td>
</tr>
<tr>
<td>DN 825 Medical Nutrition Therapy I – 3 hr.</td>
<td>DN 826 Medical Nutrition Therapy II – 3 hr.</td>
</tr>
<tr>
<td>DN 822 Management in Dietetics &amp; Nutrition I – 2 hr.</td>
<td>DN 823 Management in Dietetics &amp; Nutrition II – 2 hr.</td>
</tr>
<tr>
<td>DN 841 International Nutrition – 1 hr.</td>
<td>DN 842 US Public Health Nutrition – 1 hr.</td>
</tr>
<tr>
<td>DN 827 Practicum – 4 hr. (graded S/U) 496 hours supervised practice</td>
<td>DN 827 Practicum – 4 hr. (graded S/U) 496 hours supervised practice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Summer Semester 2014 – 6 hours</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DN 880 Dietary &amp; Herbal Supplements – 3 hr.*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Year 2 – End of year 2 graduate student completes MS degree and DIM certificate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall Semester 2014 – 10 hours</strong></td>
</tr>
<tr>
<td>DN 881 Introduction to Dietetics and Integrative Medicine – 3 hr.*</td>
</tr>
<tr>
<td>DN 895 Macronutrients &amp; Integrative Metabolism – 3 hr.</td>
</tr>
<tr>
<td>DN 834 Methods of Research in Nutrition – 3 hr.</td>
</tr>
<tr>
<td>DN 899 Thesis – 1 hr.**</td>
</tr>
<tr>
<td><strong>Non-thesis replace 3 hr. DN 899 with DN 854 in fall or spring semester</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Spring Semester 2015 – 10 hours</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DN 882 A Nutrition Approach to Inflammation and Immune Regulation – 3 hr.*</td>
</tr>
<tr>
<td>DN 896 Micronutrients &amp; Integrative Metabolism – 3 hr.</td>
</tr>
<tr>
<td>BIOS Principles of Statistics in Public Health – 3 hr.</td>
</tr>
<tr>
<td>DN 899 Thesis – 1 hr.**</td>
</tr>
<tr>
<td><strong>Non-thesis option requires additional 3 hour elective course</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Summer Semester 2015 – 4 hours</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DN 980 Nutrigenomics and Nutrigenetics in Health and Disease – 3 hr.*</td>
</tr>
<tr>
<td><strong>52 graduate hours completed over 2 years for thesis option; 55 hours for non-thesis option</strong></td>
</tr>
</tbody>
</table>

*Required courses for DIM Certificate

Updated May 8, 2013
Know when you are not the expert.

Collaborate with other members of the

www.dietetics.kumc.edu

http://Integrativemed.kumc.edu
Q & A

University of Kansas Medical Center
Dietetics & Nutrition; KU Integrative Med
integrativemed.kumc.edu

Diana Noland, MPH, RD, CCN, LD
Adjunct faculty, KUMC
Integrative Medical Nutrition Therapy
diana@diananoland.com

Leigh Wagner, MS, RD, LD (PhD Cand.)
KUMC DIM Preceptor
Integrative and Functional Nutritionist
lwagner@kumc.edu

©2015 copyright Diana Noland, MPH RD CCN LD


Vel Szic et al. From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition? Clinical Epigenetics (2015) 7:33

Volta U, Villanacci V.

**Celiac disease:** diagnostic criteria in progress