Gene-Environment Interactions, Metabolomics, and Racial Disparities in CardioMetabolic Diseases

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• Racial Disparity in Diseases
• Gene-Environment Interactions
• Metabolomics
• Personalized Prevention
The Change of US Population

Modified from US Census Bureau
Percentage Surviving by Race and Sex, U.S. 2008

![Graph showing percentage surviving by race and sex in the U.S. 2008](image)

**SOURCES:** CDC/NCHS, National Vital Statistics System and Centers for Medicare & Medicaid Services, Medicare data.
Prevalence of Diseases across Races

Data source: Heart Disease and Stroke Statistics—2011 AHA Update
Why racial disparity on complex disease?
Genetic vs. Non Genetic on Complex Disease

- **Type 2 Diabetes**
  - Genetic: 26%
  - Non-Genetic: 74%

- **Coronary artery disease**
  - Genetic: 49%
  - Non-Genetic: 51%

- **Hypertension**
  - Genetic: 30-84%
  - Non-Genetic: 16-70%

- **Body Mass Index**
  - Genetic: 50-90%
  - Non-Genetic: 10-50%
T2D and related complications

Murea et al. Rev Diabet Stud, 2012
Genetic effects
Published Genome-wide Associations
(~June 2013)

http://www.ebi.ac.uk/fgpt/gwas/#
Consistent Association of Type 2 Diabetes Risk Variants Found in Europeans in Diverse Racial and Ethnic Groups

19 loci were tested
5 ethnic groups were compared

Waters et al. PLoS Genet. 2010
### Direction in association (null=50%)

All ethnic groups >63%; 100% in Japanese

### Heterogeneity in ORs

5 of the 19 risk variants showed nominal evidence for heterogeneity; Only one remained significant after correction of multiple comparison; CDKAL1

### Combined genetic effect, per allele of genetic risk score

- **European Americans**, 1.11, 1.06–1.17
- African Americans: 1.09, 1.05–1.12
- Native Hawaiians, 1.10, 1.06–1.15
- Latinos, 1.12, 1.09–1.14
- Japanese, 1.20, 1.17–1.24
Difference among African origin populations

Age-adjusted prevalence of disease

- Rural Cameroon
- Urban Cameroon
- Jamaica
- Caribbean migrants to Britain

Cruickshank et al. 2001
Environmental factors on racial disparity

- Life style
- Socioeconomic status
- Education, income, Residential segregation
- Health practices
- Racial discrimination
Prevalence of regular leisure-time physical activity among adults by race/ethnicity and sex (NHIS: 2009)

Source: CDC/NCHS, Health Data Interactive. All percentages are age-adjusted. NH indicates non-Hispanic. * Includes both Hispanics and non-Hispanics.

Roger VL et al. Circulation. 2010
Prevalence of current smoking for adults by race/ethnicity and sex (NHIS: 2006-2008)

Source: CDC/NCHS, Health Data Interactive. All percentages are age-adjusted. NH indicates non-Hispanic. * Includes both Hispanics and non-Hispanics.

Roger VL et al. Circulation. 2010
Education Effects on Hypertension by Races

Anderson et al. 2004
Racial difference in drug response
(the same environmental effect)
Causes of Human Disease

Environmental

Genetic

Who took my piece of pizza?
• Disparity in Diabetes

• Gene-Environment Interactions

• Metabolomics

• Personalized medicine
Missing Heritability of Complex Disease

Finding the missing heritability of complex diseases

Manolio et al. 2009

Sabatti et al. 2009
Sources of missing heritability

1. Other genetic determinants, such as common copy number variations, and rare variants;

2. Interplay of different factors, such as epistasis, and gene-environment interaction
An illustration of gene-diet interaction
A Classic GXE Example

Phenylketonuria

Protein from food
Protein from muscles

Amino Acids
Other amino acids

Phenylalanine (Phe)

Phenylalanine Hydroxylase

Tyrosine

Build up of Phe
Health Problems
Sugar-Sweetened Beverages and Genetic Risk of Obesity


Sugar-Sweetened Beverages and Genetic Obesity Risk
September 21, 2012 | Q. Qi and Others
(DOI: 10.1056/NEJMoa1203039)

Sugar-free Drinks in Normal-Weight Children
September 21, 2012 | J.C. de Ruyter and Others | (DOI: 10.1056/NEJMoa1203034)

EDITORIAL
Calories from Soft Drinks — Do They Matter?
September 21, 2012 | S. Caprio
(DOI: 10.1056/NEJMe1209884)

Sugar-Sweetened Beverages and Adolescent Weight
September 21, 2012 | C.B. Ebbeling and Others | (DOI: 10.1056/NEJMoa1203388)
Sugar-Sweetened Beverages & Genetic Effect

Sugar-sweetened Beverage consumption

-<1 serving/mo
-1-4 servings/mo
-2-6 servings/wk
-≥1 servings/day

$P$ for interaction = 0.008
$P$ for interaction = 0.02
$P$ for interaction = 0.001
$P$ for interaction < 0.001

Sugar-Sweetened Beverages & Genetic Effect


(n=6,934)
(n=4,423)
(n=21,740)

Pooled
The Effects of SSB Intake (1 serving/day) on BMI According to quartiles of genetic risk score

Quartiles of Obesity Genetic Risk Score

Beta=-0.07
P=0.36

Beta=0.44
P=0.003

Beta=-0.07
P=0.36

P for interaction <0.001

P for interaction =0.003

P for interaction =0.09

Genetic predisposition score quartile
Q1  Q2  Q3  Q4

P for interaction <0.001
Physical Activity, Television Watching and Genetic Predisposition in relation to Body Mass Index in Women and Men
Genetic Predisposition Score and BMI by Physical Activity

Quintile of physical activity

- Q1
- Q2
- Q3
- Q4
- Q5

Differences in BMI per risk allele (kg/m²)

Women

- Q1: 0.21
- Q2: 0.17
- Q3: 0.16
- Q4: 0.13
- Q5: 0.13

Men

- Q1: 0.15
- Q2: 0.07
- Q3: 0.08
- Q4: 0.10
- Q5: 0.05

Pooled

- Q1: 0.18
- Q2: 0.12
- Q3: 0.12
- Q4: 0.11
- Q5: 0.08

P for interaction = 0.001

P for interaction = 0.03

P for interaction < 0.001
Genetic Predisposition Score and BMI by TV Watching

Hours of TV watching per week

- 0-1
- 2-5
- 6-20
- 21-40
- ≥ 41

$P$ for interaction = 0.05

$P$ for interaction = 0.04

$P$ for interaction = 0.001

Differences in BMI per risk allele (kg/m²)

- Women: 0.11, 0.13, 0.17, 0.16
- Men: 0.07, 0.07, 0.10, 0.13
- Pooled: 0.08, 0.08, 0.14, 0.15

0.34
GENETICS & METABOTYPES

the Human Metabolome

IP: Intermediate Phenotype

• Disparity in Diabetes
• Gene-environment interactions
• Metabolomics
• Personalized medicine
• **Metabolome**: the complete set of small-molecule metabolites to be found within a biological sample (cell, tissue, or organism).

• **Metabolomics**: the systematic study of small-molecule metabolites in a biological sample under a given set of conditions.
**ARTICLES**

Metabolite profiles and the risk of developing diabetes

Thomas J Wang\(^1\,^3\), Martin G Larson\(^3\,^4\), Ramachandran S Vasan\(^3\,^5\), Susan Cheng\(^2\,^3\,^6\), Eugene P Rhee\(^1\,^7\,^8\), Elizabeth McCabe\(^2\,^3\), Gregory D Lewis\(^1\,^2\,^8\), Caroline S Fox\(^3\,^9\,^{10}\), Paul F Jacques\(^1\,^11\), Céline Fernandez\(^1\,^12\), Christopher J O’Donnell\(^2\,^3\,^8\), Stephen A Carr\(^8\), Vamsi K Mootha\(^8\,^{13}\,^{14}\), Jose C Florez\(^8\,^{13}\), Amanda Souza\(^8\), Olle Melander\(^1\,^15\), Clary B Clish\(^8\) & Robert E Gerszten\(^1\,^2\,^8\)

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**Table 2** Relation of baseline amino acid concentrations to risk of future diabetes (Framingham Offspring Study)

<table>
<thead>
<tr>
<th>Model</th>
<th>Isoleucine</th>
<th>Leucine</th>
<th>Valine</th>
<th>Tyrosine</th>
<th>Phenylalanine</th>
<th>Isoleucine, tyrosine and phenylalanine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models adjusting for age, sex, BMI and fasting glucose (n = 378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite as continuous variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per s.d.</td>
<td>1.70 (1.27–2.28)</td>
<td>1.62 (1.20–2.17)</td>
<td>1.57 (1.17–2.09)</td>
<td>1.85 (1.35–2.55)</td>
<td>2.02 (1.40–2.92)</td>
<td>2.42 (1.66–3.54)</td>
</tr>
<tr>
<td>P</td>
<td>0.0004</td>
<td>0.001</td>
<td>0.002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolite as categorical variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Second quartile</td>
<td>1.11 (0.58–2.10)</td>
<td>2.40 (1.24–4.68)</td>
<td>1.49 (0.75–2.94)</td>
<td>1.89 (0.94–3.81)</td>
<td>1.39 (0.74–2.59)</td>
<td>3.48 (1.68–7.23)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>2.14 (1.07–4.27)</td>
<td>3.15 (1.46–6.84)</td>
<td>2.15 (1.05–4.42)</td>
<td>3.26 (1.56–6.84)</td>
<td>2.12 (1.04–4.32)</td>
<td>2.82 (1.25–6.34)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>3.14 (1.51–6.55)</td>
<td>3.66 (1.61–8.29)</td>
<td>3.14 (1.43–6.86)</td>
<td>2.82 (1.25–6.34)</td>
<td>2.28 (1.00–5.20)</td>
<td>5.99 (2.34–15.34)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.001</td>
<td>0.004</td>
<td>0.003</td>
<td>0.010</td>
<td>0.035</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*Among 2,422 normoglycemic individuals followed for 12 years, 201 developed diabetes.*

Dietary BCAA intake and plasma BCAA levels

Age-adjusted

Age- and BMI-adjusted

Qi et al. unpublished data
Metabolomics in African Americans

- The Atherosclerosis Risk in Communities (ARIC) Study is a population-based prospective biracial cohort study to investigate the causes of atherosclerosis and its clinical outcomes.

Metabolomic profiles were measured in ~2000 African-Americans at baseline examination.

Characteristics of study population at baseline examination in 1987-89.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population (N=1977)</th>
<th>Females (N=1275)</th>
<th>Males (N=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.9 ± 5.7</td>
<td>52.8 ± 5.7</td>
<td>53.0 ± 5.8</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>498 (28.8)</td>
<td>308 (24.2)</td>
<td>261 (37.2)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>6.6 ± 1.4</td>
<td>6.4 ± 1.5</td>
<td>6.6 ± 1.4</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>29.5 ± 6.0</td>
<td>30.8 ± 6.4</td>
<td>27.6 ± 4.5</td>
</tr>
<tr>
<td>Prevalent hypertension, n (%)</td>
<td>1050 (53.1)</td>
<td>694 (54.4)</td>
<td>356 (50.7)</td>
</tr>
<tr>
<td>Prevalent diabetes, n (%)</td>
<td>319 (16.2)</td>
<td>218 (17.1)</td>
<td>101 (14.4)</td>
</tr>
<tr>
<td>Prevalent heart failure, n (%)</td>
<td>97 (4.9)</td>
<td>76 (6.0)</td>
<td>21 (3.0)</td>
</tr>
</tbody>
</table>
GWAS Metabolomics

Cofactors and vitamins

- bilirubin (E,E) UGT1A
- biliverdin UGT1A
- [H]HWESAS LLR[OH] ACE
- acetyl carnitine SIAE
- deoxy carnitine SLC6A13
- 3-hydroxy decanoate THEM4
- aspartyl phenyl alanine ACE
- threonyl phenyl alanine ACE
- hexade canedioate ADH4
- creatine GATM
- glycine CPS1
- phenyl acetate ACSM2B
- N-acetyl phenyl alanine ACY3
- N-acetyl ornithine NAT8
- trehalose TREH

Peptide

- Leu-Phe KLKB1
- HXGXA KLKB1
- LEU-PHE KLKB1
- N-acetyl phenyl alanine ACY3
- N-acetyl ornithine NAT8

Carbohydrate

- trehalose TREH

Lipid

- 3-hydroxy decanoate THEM4
- deoxy carnitine SLC6A13
- palmitoleate (16:1n7) PKD2L1

Amino acid

- glycine CPS1
- phenyl acetate ACSM2B
- N-acetyl phenyl alanine ACY3
- N-acetyl ornithine NAT8

Common variants with p-value < 1.6 × 10^{-10}

GWAS Metabolomics

Cofactors and vitamins

- Bilirubin (E,E) UGT1A
- Biliverdin UGT1A
- [H]HWESAS LLR[OH] ACE
- Acetyl carnitine SIAE
- Deoxy carnitine SLC6A13
- 3-hydroxy decanoate THEM4
- Aspartyl phenyl alanine ACE
- Threonylp henyl alanine ACE
- Rehydration HXGXA KLKB1
- LEU-PHE KLKB1
- Acetyl carnitine SILAE
- Deoxy carnitine SLC6A13
- Hexade canedioate ADH4
- Palmitoleate (16:1n7) PKD2L1
- Creatine GATM
- Trehalose TREH
- N-acetyl phenyl alanine ACY3
- N-acetyl ornithine NAT8
- Glycine CPS1

Lipid

- Palmitoleate (16:1n7) PKD2L1

Amino acid

- Palmitoleate (16:1n7) PKD2L1

Common variants with p-value < $1.6 \times 10^{-10}$

Gene-Metabolite-Disease Pathway

Nutritional Metabolomics

Super pathway of metabolites
- cofactors and vitamins
- carbohydrate
- xenobiotics
- energy
- peptide
- lipid
- amino acid

Metabolomics in incident heart failure

Reliability of human metabolome

Metabolomics in incident hypertension

Oxidative break-down of benzenoid substances in guts

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang¹,², Elizabeth Klipfell¹,², Brian J. Bennett³, Robert Koeth¹, Bruce S. Levison¹,², Brandon DuGar¹, Ariel E. Feldstein¹,², Earl B. Britt¹,², Xiaoming Fu¹,², Yoon-Mi Chung¹,², Yuping Wu⁴, Phil Schauer⁵, Jonathan D. Smith¹,⁶, Hooman Allayee⁷, W. H. Wilson Tang¹,²,⁶, Joseph A. DiDonato¹,², Aldons J. Lusis³ & Stanley L. Hazen¹,²,⁶

Figure 6 | Gut-flora-dependent metabolism of dietary PC and atherosclerosis. Schematic summary illustrating newly discovered pathway for gut-flora-mediated generation of pro-atherosclerotic metabolite from dietary PC.
Meta-analysis of red meat intake and T2 diabetes

Pan et al., AJCN 2011
Three major pathways via which intestinal microbiota can alter human cardio-metabolism.

Vinjé S et al. Eur Heart J 2013;eurheartj.eht467
Gut Microbiota Metabolites of Dietary Lignans and Risk of Type 2 Diabetes: A Prospective Investigation in Two Cohorts of U.S. Women
Gut Microbiota as a Cardiometabolic Target

• Gut bacteria play a critical role in metabolism of nutritional factors in the pathogenesis of diabetes:
  – Components in red meat
  – Plant-based foods: soluble fiber, polyphenols from fruits, vegetables, coffee, etc.

• Emerging evidence indicates that gut flora metabolites in development of complex metabolic phenotypes including obesity, diabetes, and CVD.

• This research can provide novel prevention and therapeutic strategies for metabolic diseases (including diet/lifestyle, probiotic, and prebiotic approaches).
Figure 1—The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.
• Racial Disparity in diseases
• Gene-environment interactions
• Metabolomics
• Personalized medicine
Personalized prevention and racial disparity

• NOT racialized BUT personalized medicine

• Race and Pharmacogenetics

• Advance in GXE research and systems epidemiology approach

• Application of Metabolomics in clinical setting
Acknowledgement

• Yan Zheng
• Qibin Qi
• Lu Qi
• Marilyn Cornelis
• Peter Kraft
• Brian Wolpert
• Mike Pan
• Rob van Dam
• Qi Sun