Genomics of Metabolic Syndrome

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What is Metabolic Syndrome (MetS)?

• Clustering of risk factors:
  Hypertension, insulin resistance, & obesity

• ↑ risk for diabetes and cardiovascular disease (Ford, Li, & Zhau, 2010)

• Affects 34% of United States population
  - 3-fold ↑ in cardiovascular-related deaths (Ford, et al., 2010)

• Lack of consensus establishing diagnostic criteria of MetS = uncertain clinical utility of diagnosis
Harmonizing Definition of MetS

- Obesity
  Increased waist circumference by population + country specific definitions

- Elevated Triglycerides
  $\geq 150 \text{ mg/dL}$
  (1.7 mmol/L)

- Reduced HDL-C
  $< 40 \text{ mg/dL}$ females
  $< 50 \text{ mg/dL}$ males

- Elevated Blood Pressure
  $\geq 130/\geq 85 \text{ mmHg}$

- Elevated fasting blood sugar or Type 2 diabetes
  $\geq 100 \text{ mg/dL}$

This definition includes components of MetS definitions from ATPIII, WHO, AACE
Risk Factors Associated with Development of MetS

- Similar to those associated with hypertension, diabetes, renal disease, and obesity
- Lifestyle, gender, ethnicity, and genomic precursors= important role in development of MetS
- Genetic studies: GWAS, epigenetics, proteomics
- MetS→ polygenetic condition with varying influence of multiple environmental factors
Cardiovascular Factors in MetS

DYSLIPIDEMIA

• Alterations in circulating blood lipid levels- predisposition to development of MetS
  (Alberti, et al., 2009)

• Familial hypercholesterolemaia

• ↑ Triglyceride and HDL levels
  – Mutations in the LPL and APOE genes (lipoprotein metabolism)
  (Gungor et al., 2010)
Cardiovascular Factors in MetS

HYPERTENSION

• > 50 genes associated with blood pressure and/or hypertension (Basson, Simino, Rao, 2012)

• Familial hypertension = ↑ risk compared to secondary types of hypertension
  – Mendelian inheritance patterns
  – High penetrance

• Genes responsible create proteins → affect renal electrolyte and water handling (Lifton, Gharavi, & Geller, 2001)
  – Altering expression of adrenal/mineralocorticoid hormones
  – Impacting function of renal sodium transporters (Lifton, et al., 2001)
Diabetes in MetS

- Type 2 diabetes: overnight fasting glucose of $\geq 126$ mg/dl and/or a HbA1C $> 6.5\%$ (Chakkera et al., 2010)
- Diabetes more prevalent among specific ethnic/racial groups $\rightarrow$ genetic predisposition

United States:
- 15.7 million non-Hispanic Whites (10.2%)
- 4.9 million non-Hispanic Blacks (18.7%)
- 7.6% for Cubans, Central and South American Hispanics
- 13.3% to 13.8% for Mexican Americans and Puerto Ricans aged $\geq 20$ have diabetes

(National Center for Chronic Disease and Prevention and Health Promotion, 2011)
Type 2 Diabetes Risk Alleles

• Variants of the TCF7L2 gene = increased risk of T2D and MetS (Kho et al., 2012)
  - May cause: excess fat and glucogen deposition in the liver, hyperlipidemia, glucose intolerance, and type 2 diabetes

• Effects of individual SNPs $\rightarrow$ small
  - Interactive synergistic effect of SNPs contribute to risk and development of MetS and type 2 diabetes (Delgado-Lista et al., 2011)
Obesity in MetS

• BMI as a classification for obesity (≥ 25 overweight; ≥ 30 obese)
  – BMI ≥ 25 increases risk 5-6 fold; BMI ≥ 30 = 32 times as likely to develop MetS (Ervin, 2009)
  – “Genetic trigger” (Ordovas & Corella, 2008)

• Not all obese patients at risk
  - Central fat distribution obesity → greater risk (Cheung et al., 2001; Glickman, Marn, Supiano, & Dengel, 2004)
  - Women’s protective gynoid fat distribution versus ↑ risk with accumulation of visceral fat tissue in a central pattern (Wiklund et al., 2008)
Obesity Risk Alleles

- Two main genes implicated:
  - MC4R associated with fat accumulation
  - FTO associated with development of MetS
- MC4R gene most commonly associated with monogenic forms of obesity, possibly also involved in polygenic forms of common central obesity (SNP rs17782313)
- FTO gene (SNP rs9939609)
Implications for Practice and Research

• Genomic based applications
• Complexity of clinical management
  - Address each component separately using established guidelines
• Nursing
  - Promote lifestyle strategies → target Prevention and Management of the individual
  - Obtain a minimum three generation

(http://www.hhs.gov/familyhistory/)
Implications for Practice and Research

- Personalized health care
- Example: use an individual’s genetic test results to identify specific biologic mechanisms; tailoring management to the individual’s specific needs
- Evidence-based practice and best practice
- Direct-to-consumer genetic testing = CAUTION
Implications for Practice and Research

- Genome wide association studies
  - Small percentage (2%) of the variance in heritable disorders for many MetS related traits are explained by genetic markers (Zhang, Ma, Brismar, Efendic, Gu, 2009)
  - Effect size
  - Genotyping platforms
  - Ethnic ancestry and admixture mapping
Common Methodologies Used in Studies on Genomics of MetS

- Linkage analysis
- Genome wide association studies
- Epigenetic studies
- Proteomics
Future of Genomics and MetS

• Systems-based approaches
  - Expression arrays
  - Mass spectrometry
  - Bioinformatics
• Direct sequencing
• Clinical practice goal of genomic healthcare → the integration of clinical and biological data for improving patient outcomes
Clinical Resources

Evaluation of Genomic Applications in Practice and Prevention
www.egappreviews.org

Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indications
www.genome.gov/pages/careers/healthprofessionaleducation/geneticscompetency.pdf

Gene tests

Genetic Testing Registry

Genetic/Genomic Competency Center for Education (G2C2)
http://www.g-2-c-2.org

Online Mendelian Inheritance in Man

Surgeon General’s Family Health History Initiative
www.hhs.gov/familyhistory
Next Webinar

- **Tuesday, March 20, 2013, 3:30-4:00 p.m. EST**
- **Presenters:** Jane DeLuca, Alex Kemper
- **Implications of Newborn Screening for Nurses** Dr. Jane DeLuca, Clemson University and Dr. Alex Kemper, Duke University School of Medicine, provide an overview of current newborn screening activities with details about controversies and ethical considerations. A summary of future developments in newborn screening (i.e., genome sequencing) with implications for policy, practice, education, and research is also presented.

- **Tuesday, March 20, 2013, 4:00-4:30 p.m. EST**
- **Presenter:** Martha Turner
- **Ethical, Legal and Social issues in the Translation of Genomics into Healthcare** Dr Martha Turner from American Nurses Association provides a review of ethical and legal foundations and highlights issues confronting nurses today such as confidentiality and privacy of genomic information; informed consent, genetic testing, and biorepositories. Understanding these issues is essential for safe and effective translation of genomic information into practice.

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