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

≥150 mg/dL

(1.7 mmol/L)

- Reduced HDL-C

<40 mg/dL males

<50 mg/dL females

- Elevated Blood Pressure

≥ 130/ ≥ 85 mmHg

- Elevated fasting blood sugar or Type 2 diabetes

≥ 100 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 hypercholesterolemia
- ↑ 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 ≥ 126 mg/dl and/or a HbA1C > 6.5% (Chakkera et al., 2010)
- Diabetes more prevalent among specific ethnic/racial groups → 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 ≥ 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 → *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)

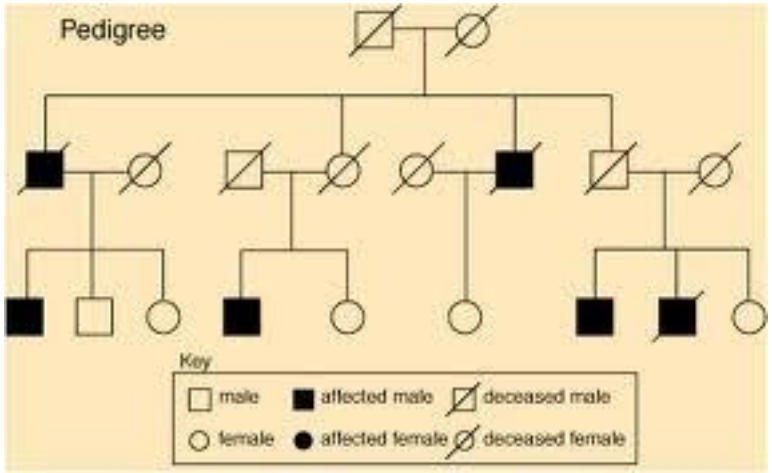
Implications for Practice and Research

CLINICAL PRACTICE

- 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

CLINICAL PRACTICE

- 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

RESEARCH
PRACTICE

- 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

www.ncbi.nlm.nih/gov/sites/GeneTests

Genetic Testing Registry

www.ncbi.nlm.nih.gov/gtr

Genetic/Genomic Competency Center for Education (G2C2)

http://www.g-2-c-2.org

Online Mendelian Inheritance in Man

www.ncbi.nlm.nih.gov/omim

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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