Gene-Environment Interactions In Complex Human Diseases

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Complex Human Diseases

- Preterm Birth, LBW, FGR
- Obesity, MS
- Food allergy
- Asthma
- Type 2 Diabetes
- Hypertension
- Dyslipidemia
- Osteoporosis
- Mental disorders
- Cancer
Heterogeneous Etiology

Psycho-Socio-Environmental Risk Factors

Intrauterine Infection/Inflammation

Maternal and Fetal HPA Axis Activation

Maternal and Fetal Genes, Gene-Env. interactions

Uteroplacental Vascular pathology

Pathologic uterine Contraction

Preterm Labor, PPROM, Medical Induction

Preterm Birth
Complexity of Gene-Environment Interaction

Exposure → Internal Dose → Biological Effective Dose → Early Biologic Effect → Shorter Gestational Age → Preterm Birth → Increased Infant Mortality

Susceptibility Genes
Complexity of Gene-Environment Interaction

Sufficient Cause I

G1
G2
E1
E2
E3

G1-G3: Genetic Factors
E1-E5: Environmental Factors

Sufficient Cause II

G2
G3
E3
E4
E5
Genetic Dissection of Complex Diseases

DNA

5’

rSNP

ssSNP

iSNP

cSNP

TRANSCRIPTION

3’

pre-mRNA

SPLICING

Intron 1

Intron 2

Intron 3

Mature mRNA

ORF

AUG - B₁…Bₙ - STOP

Protein Sequence

protein 3D structure

Phenotype Change
(e.g. Preterm)
Goal of Gene-Environment Studies

- To estimate how the risk of a given disease changes as a joint function of genetic factors and environmental exposures.
Need Concurrent Data on both Gene and Environment

- **Population level**
  - Broad social, cultural, physical environment

- **Individual level**
  - Exposure to biological, chemical, physical agents
  - Subclinical and clinical manifestation of disease

- **Molecular level**
  - Genetic susceptibility or predisposition to disease
  - Gene-environment interactions
  - Gene-gene interactions
Key Steps to Reliably Identify Gene-Environment Interactions

- **Careful Study Design**
  - Define phenotype, exposure, candidate genes, genotyping methods, sample size, statistical analysis

- **Attention to Measurement Issues**
  - Environmental exposure and genetic assessment

- **Caution about Potential Bias or Confounding**
  - Environmental and genetic source

- **Need for Replication**
Our Team’s Published Work

- Familial Aggregation
  - Wang et al, NEJM, 1995

- Genetic Susceptibility
  - Wang et al, Epidemiology, 1998
  - Wu et al, Epidemiology, 2000
  - Hao et al, Human Molecular Genetics, 2004

- Gene-Environment Interactions
  - Wang et al, AJE, 2000
  - Wang et al, JAMA, 2002

- Statistical and Lab Methods
Familial Aggregation Study (Wang et al, NEJM, 1995).

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**Bars:**
- **White**
- **Black**
**Methods**

- PTD (Gestational Age < 37 wks)
- A multi-ethnic cohort consisting of 300 mothers with PTD and 458 with term deliveries at BMC
- 25 candidate genes were included in the haplotype analysis

**Results**

- F5 gene haplotype was significantly associated with PTD after adjustment for multiple testing

- Pairwise LD ($D'$) decays rapidly with an increasing physical distance
- By fitting the exponential decay model, the decay rate was twice as high in Blacks ($0.038 \pm 0.005$) as in Whites ($0.018 \pm 0.002$) and in Hispanics ($0.018 \pm 0.003$)
Gene-Cigarette Smoking Interaction on Preterm Birth
(Wang et al, JAMA, 2002)
Opportunities

Human Genome Project
- Determine the sequences of the 3 billion base pairs that make up human DNA
- Identify all the approximately 35,000 genes in human DNA
- Identify over 4 million SNPs in human DNA
- Store this information in databases
- Address the ELSI that may arise from the project

International HapMap Project
- A 3-year, 100 million project (Canada, China, Japan, Nigeria, the United Kingdom and the United States)
- To develop a haplotype map of the human genome
- To study 270 DNA samples (90 from US Utah; 90 from Nigeria; 45 Japanese; 45 Han Chinese)
Opportunities

● Biotechnology
  » cDNA/Affymetrix Oligonucleotide Array (1,000 – 20,000 genes)
  » Taqman mRNA Quantitative Analysis (1 – 100 genes)
  » Illumina’s BeadArray Genotyping System (1,536-plex/sample)
  » ABI SNPlex Genotyping System (48-plex/sample)

● Bioinformatics/Statistics
  » Mathematical Modeling and Computational Simulations
  » Development of Data Collection and Management Tools
  » Development and Application of Data Analysis and Visualization Tools
Impact of Gene-Environment Studies on Public Health

- **Predictive Medicine**
  - Gene-environment risk profiling enables individuals to learn their susceptibility to particular disease
  - Develop individual based intervention rather than traditional “shot gun” approach

- **Targeted intervention**
  - Identify high-risk sub-population
  - Targeted intervention likely more cost-effective than general intervention
Impact of Gene-Environment Studies on Clinical Medicine

- Prediction of drug response
  - Degree of effectiveness
  - Optimal dosage
  - Side effects

- Individualize prescription
  - To end the era “one size shoe for all”

- Targets for new drugs development
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All the co-investigators, consultants, field team, laboratory team, data manager and analyst, and administrative staff

Nursing staff of the Department of OB Gyn at the Boston Medical Center

All the participating mothers and their families