Epigenetics – What Your Patients are Asking, What You Need to Know

Robert A Saul, MD, FACMG, FAAP
Robert O Wright, MD, MPH, FAAP

Thursday, December 20
12:00 – 12:30pm Central

Time Out for Genetics Webinar Series
Presented by the Genetics in Primary Care Institute
Faculty

• Robert A Saul, MD, FACMG, FAAP
  – Director of Clinical Services at the Greenwood Genetic Center

• Robert O Wright, MD, MPH, FAAP
  – Professor, Departments of Pediatrics and Preventive Medicine, Mount Sinai School of Medicine
Drs Saul and Wright have no financial relationships or conflicts of interest to disclose relevant to this presentation.
Acknowledgements

Funding for the GPCI is provided by the Health Resources & Services Administration/Maternal & Child Health Bureau, Genetic Services Branch
Learning Objectives

1. State the scientific basis of epigenetics and its relation to environmental health factors and genetics/genomics.

2. Review relevant historical examples of epigenetics and their potential relevance in today’s health care.

3. Demonstrate the clinical relevance of epigenetics in primary health care and its applicability to the prevention, diagnosis and treatment of health and disease for the PCP.
Why learn Epigenetics?

• “Epigenetic diseases are rare”
  – It is far more common than you think
  – It plays a major role in development

• “It’s like genetics, we can’t change it anyway.”
  – By definition, epigenetics is modifiable, prospects for treatment are far greater than for genetic engineering.
From Genes to Proteins-
Traditional View
So if every cell in the body has all the same genetic information, why do some cells become brain cells, others cardiac muscles, etc...
Epigenetics

“The study of changes in gene function that occur without a change in DNA sequence”
Overview of Talk

• Epigenetic mechanisms and modifications
  DNA Methylation
  Histone modifications
  microRNA

• Clinical applicability
Epigenetics

1942: “The branch of biology which studies the interactions of genes and their environment that bring the phenotype into being.”

Histone modifications

- Chromatin = histone proteins wrapped with DNA
  - Nucleosome, subunits of chromatin
- Histone modifications
  - change how the DNA is wrapped
  - influence binding of other proteins
  - Can profoundly influence transcriptional activity
- Methylation of histone or of DNA usually turns a gene off.
- Acetylation of histone usually turns a gene on.
- Phosphorylation – function is Amino acid specific
- Ubiquitination: increases transcription (turns on)
DNA methylation

Only occurs at cytosine which are found next to guanines (CpG repeats)
DNA methylation and Life stage

• Methylation patterns change during life.
  – Changes appear to related to both constitutive factors and environment
    • Identical twins have greater concordance of methylation than fraternal twins
    • Correlation in methylation patterns among identical twins decreases with age
Diet can change DNA methylation patterns: Epigenetically labile phenotype in genetically identical animal twins

Less methylated

More methylated

PS1A gene codes for Fur color

Folic acid, B12, choline, betaine

Genistein - major phytoestrogen in soy

Dolinoy et al., 2006 Env Health Persp 114:567-572

Waterland et al., 2003 Mol Cell Biol 23:5293-5300
Other Epigenetic factors

• MicroRNA
  – Part of a larger family of RNA called siRNA (silencing RNA)
  – are evolutionarily conserved, small noncoding RNA molecules which regulate gene expression at the level of translation.
MicroRNA complex.

Guide strand base pairs with complementary sequence of mRNA & induces cleavage

 MiRNA complex
 Chews up mRNA Specifically based on the mRNA sequence
Micro RNA

- miRNAs have been reported to be:
  - critical in the development of organisms
  - differentially expressed in tissues
  - involved in viral infection processes
  - associated with oncogenesis
Imprinting

- If a certain region of one chromosome (maternal or paternal) is differentially methylated as compared to the corresponding region of the other chromosome – the region is “turned off”
- Most likely to be silent
- Imprinting can lead to expression of specific disease states
- Certain diseases can differ depending on methylation status of maternal or paternal chromosome
Prader-Willi vs. Angelman Syndrome

Prader-Willi Syndrome

Angelman Syndrome
Disorders with Known or Putative Epigenetic Etiology

- Angelman Syndrome*
- Autism Spectrum Disorders
- Beckwith-Wiedemann syndrome*
- CHARGE association
- Fragile X Syndrome
- Maternal duplication 15q11-13
- Metabolic syndrome
- Prader-Willi Syndrome*
- Rett Syndrome
- Russell-Silver syndrome*

*Presumed due to imprinting
Artificial Reproductive Technologies (ART)

• Evidence suggests that ART can be associated with early methylation changes of zygotes around fertilization and implantation

• Condition with epigenetic factors that are possibly associated with ART:
  – Beckwith-Wiedemann syndrome
  – Russell-Silver syndrome
  – Retinoblastoma
  – Maternal hypomethylation syndrome
  – Angelman syndrome
Epigenetic Influences Across Generations

- Epigenetic changes can occur in utero
- Changes affect postnatal development of infant/child and occur in germ cells (sperm or ovum)
- Changes can be secondary to environmental influence and passed on to subsequent generations
- Trans-generational effects may emerge in 1-2 generations
Historical Evidence

• Retrospective data from national famines reveal presumed effects from intrauterine nutritional deficiency

• Data from Dutch famine in World War II and Chinese famine in 20th century show connection between mental illness and maternal intrauterine environment

• Children conceived had a 2-fold risk of schizophrenia
Gambia and Dutch Famine

- Developmental establishment of DNA methylation is sensitive to the maternal environment

Swedish Harvest

- Developmental establishment of hereditary material is sensitive to the paternal environment
Key Factors Leading to Epigenetic Changes

- Asthma
- Chemical Exposures
- Diet during SGP
- Endocrine disrupting compounds (BPA)
- Hypoxia
- Maternal Diabetes
- Maternal habitus, maternal age, placenta size
- Maternal smoking
- Psychosocial stress
- Psychological trauma
What’s Next for Epigenetics?

**Epigenetics**
- Epigenetic marks can be modified
- Potential to target specific marks in specific cells for modification
- Current treatments may work via this method (AZT and HIV)

**Genetics**
- DNA sequence static
- Risk may be inferred from presence of DNA mutations or variants
- Interventions to change DNA sequence not likely
Prevention

- Opportunity to impact disease prevention!
  - Multiple factors early in life affect the onset of adult diseases and degree of severity
  - Known factors can be expected to grow as influences on DNA methylation, histone modification, and micro-RNA are delineated

- Track factors occurring in prenatal, perinatal, or early infancy period over the health care trajectory
Diagnosis

• Applicability is dependent on our ability to use associated tools in diagnosis

• Benefits of diagnosis
  – PCP and subspecialist provide appropriate care
  – Provide anticipatory guidance
  – Offer reproductive counseling
Treatment

• Treatments based on epigenetic changes have not yet been established
• Dietary intervention studies have not shown significant results
• Future treatments possible:
  – Altering epigenetic marks: gene expression, subsequent protein expression, and phenotype
  – Delineate more precisely epigenetic mechanisms that affect DNA: methylation, histone modification and microRNAs
Summary

- Epigenetics represents an exciting yet perplexing look into the further complexities of hereditary material.
- Our understanding of epigenetic marks will provide some significant clues into the interaction between genetic material and the environment.
- Epigenetic changes will likely provide clues into various health conditions, particularly common diseases in the population.
Summary

• PCPs will need to *understand* epigenetic changes in order to translate the practical implications to primary care

• Our ability to translate epigenetic discoveries will require an ability to coordinate care over the *lifetime* of patients
Questions
Thank you for your participation!

For more information, please contact
Lindsay Wilson
lwilson@aap.org
847/434-7612

www.medicalhomeinfo.org/gpci.aspx