Epigenetics and the Aging Brain
Epigenetics and the Aging Brain

- The human brain - anatomy and function
- The aging brain
- The Alzheimer’s brain
- Epigenetics
- Nutrition and Brain Health
Alzheimer’s Disease

• **Age** is the greatest **risk factor** for Alzheimer’s
• Over 96% of all cases are sporadic and there is no indication of any genetic association
• Initial degeneration of neuronal morphology and connectivity progressing to a loss of neurons
• Progressive neurodegeneration accompanied by severe inflammatory and oxidative stress
• 6\textsuperscript{th} leading cause of death in the US
A Cure for Alzheimer’s

- Most animal research is not successful in promising drug leads
- Most drug trials target plaques
- Plaques do not cause cognitive decline associated with Alzheimer’s
- 4 approved drugs
- 99% of new drug trials fail
- Federal research funds $100/AD patient
• More than **196,000 people die and 2.2 million are injured each year by adverse reactions to prescription drugs**

• **Fatalities in Motor Vehicle Accidents (US) 2008 = 39,000**
The Prevalence of Diseases

- Diphtheria, 40.3
- Senility, 50.2
- Cancer, 64.0
- Accidents, 72.3
- Nephropathies, 88.6
- Cerebrovascular disease, 106.9
- Heart disease, 137.4
- Gastrointestinal infections, 142.7
- Tuberculosis, 194.4
- Pneumonia or influenza, 202.2
- Cancer, 185.9
- Heart disease, 192.9
- Suicide, 12.2
- Pneumonia or influenza, 16.2
- Nephropathies, 16.3
- Diabetes, 22.3
- Alzheimer’s disease, 27.0
- Accidents, 38.2
- Cerebrovascular disease, 41.8
- Noninfectious airways diseases, 44.6
Diseases and Society

Mental Illness in America
More than a quarter of adults are afflicted

In any given year 26 percent of American adults suffer from mental disorders, based on guidelines in the official handbook for diagnosing mental illness, the DSM-IV. Only about a fifth of the cases are serious enough to cause a major disruption of everyday life, however, which has prompted some experts to call for more stringent diagnostic criteria. Others counter that tracking mild symptoms is important for preventing their escalation into more severe illness. The chart below lists many of the most prevalent mental illnesses in Americans older than 18 years, according to a 2005 survey by the National Institute of Mental Health. Nearly half of all people who have one illness also suffer from at least one more.

—Peter Sergo
Figure 2. County-Level Mortality From Cardiovascular Diseases

A. Age-standardized mortality rate from cardiovascular diseases, both sexes, 2014

Deaths per 100,000 population

76 to 158 | 213 | 269 | 324 | 380 | 435 to 546
Figure 4. County-Level Mortality From Neurological Disorders

A. Age-standardized mortality rate from neurological disorders, both sexes, 2014

Deaths per 100,000 population

30 to 47 | 67 | 88 | 108 | 129 | 149 to 199
Figure 5. County-Level Mortality From Self-harm and Interpersonal Violence

A Age-standardized mortality rate from self-harm and interpersonal violence, both sexes, 2014

Deaths per 100,000 population

- 7 to 11
- 18
- 24
- 31
- 37
- 44 to 118
Disease Management

US spending $2.5 trillion in 2009 (17.3% of GDP) and $4.3 trillion in 2018 (20.3% of GDP).

Preventable Deaths (< 75 years of age): heart disease, stroke, certain cancers, obesity, diabetes, certain bacterial infections, influenza, ulcers, pneumonia, NUTRITION.

1. France: 65
2. Japan: 71
3. Australia: 71
4. Spain: 74
5. Italy: 74
6. Canada: 77
7. Norway: 80
8. Netherlands: 82
9. Sweden: 82
10. Greece: 84
11. Austria: 84
12. Germany: 90
13. Finland: 93
14. New Zealand: 96
15. Denmark: 101
16. UK: 103
17. Ireland: 103
18. Portugal: 104
19. US: 110

Prevention:
Effective and Affordable Form of Care and Cure

• Nutrition and Exercise
• proven health benefits for cognition, heart, blood pressure, glucose absorption and more
• no side effects
Epigenetics and the Aging Brain

- The human brain - anatomy and function
- The aging brain
- The Alzheimer’s brain
- Epigenetics
- Nutrition and Brain Health
What is Epigenetics?

It really matters what we do Choices?
The Science of Epigenetics

A Nova Video

An Introduction to the underlying science
Epigenetics    ------    Genetics

WHAT IS THE DIFFERENCE
Genetics

- Gregor Johann Mendel (1822, Hynčice)
- Studied philosophy and physics
- 1843 – joined Augustinian Abbey of St Thomas in Brno
- Founder of genetics
- Significance not recognized early 1900

- Genetics is the science of genes, heredity, and variation in living organisms
- Genes correspond to regions within DNA
- Mutations are chemical changes in DNA
Human Genome Organization

- 23 chromosomes
- 25 - 30,000 genes
- Total length about 2 m
- 10,000 fold compaction
- Chromatin, a DNA/protein complex

Dark bands = inactive
Light band = active
Puffs = very active
Human Genome Organization

- 23 chromosomes
- 25 - 30,000 genes
- Total length about 2 m
- 10,000 fold compaction
- Chromatin, a DNA/protein complex
- Below is a schematic organization of a gene

[Diagram showing gene organization with labels for Regulatory region, Exon, and Intron]
Consequence of Compaction

- Accessible information: euchromatin
- Restricted information: heterochromatin
Epigenetics

• Changes in gene expression through chromatin modulation only
• No changes in DNA sequence
• Responsive to extrinsic stimuli
• Chromatin remodeling as an organizing principal of genetic information
• Significant expansion of the genetic code
• Dynamic changes in chromatin organization is inheritable

Accessibility of our genetic information is flexible
Genetics vs Epigenetics

Genetics:
- DNA
- Stored information
- Organized information
- Epigenomes

Epigenetics:
- GENETICS
- Mutations
- Inherited germ line
- Species
- Stable?
- Soma
- Variability

Epigenomes:
- 1 genome
Maternal diet and aging alter the epigenetic control of a promoter–enhancer interaction at the Hnf4a gene in rat pancreatic islets

Ionel Sandovic\textsuperscript{a,b,1}, Noel H. Smith\textsuperscript{c1}, Marloes Dekker Nitert\textsuperscript{d}, Matthew Ackers-Johnson\textsuperscript{e}, Santiago Uribe-Lewis\textsuperscript{e}, Yoko Ito\textsuperscript{e}, R. Huw Jones\textsuperscript{e}, Victor E. Marquez\textsuperscript{f}, William Cairns\textsuperscript{g}, Mohammed Tadayyon\textsuperscript{h}, Laura P. O’Neill\textsuperscript{i}, Adele Murrell\textsuperscript{a}, Charlotte Ling\textsuperscript{d}, Miguel Constância\textsuperscript{a,b,1,2}, and Susan E. Ozanne\textsuperscript{c1,2}

Environmental factors interact with the genome throughout life to determine gene expression and, consequently, tissue function and disease risk. One such factor that is known to play an important role in determining long-term metabolic health is diet during critical periods of development. Epigenetic regulation of gene expression has been implicated in mediating these programming effects of early diet. The precise epigenetic mechanisms that underlie these effects remain largely unknown. Here, we show that the transcription factor Hnf4a, which has been implicated in the etiology of type 2 diabetes (T2D), is epigenetically regulated by maternal diet and aging in rat islets. Transcriptional activity of Hnf4a in islets is restricted to the distal P2 promoter through its open chromatin configuration and an islet-specific interaction between the P2 promoter and a downstream enhancer. Exposure to suboptimal nutrition during early development leads to epigenetic silencing at the enhancer region, which weakens the P2 promoter–enhancer interaction and results in a permanent reduction in Hnf4a expression. Aging leads to progressive epigenetic silencing of the entire Hnf4a locus in islets, an effect that is more pronounced in rats exposed to a poor maternal diet. Our findings provide evidence for environmentally
Epigenetics - Histones

**Signals**

- Active
- Repressed

**ON**
- HAT activator
- UAS

**OFF**
- HDAC repressor
- URS

**Histone H3**

- ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVKKPH
Epigenetics - DNA

- Methylation at the 5’-position of cytosine
- CH3-Cyt restricted to thos 5’ of guanosine
- CpG islands
- Methyl group protrudes into major groove
- DNA methylation has gene repressive effects
- CpG islands unevenly distributed
Consequences

- epigenetic code?
- epigenetic inheritance?
- nature of cellular memory?
- germ line imprint?
- non-coding RNAs?
- stem cells?
- regeneration?
- cell type identity?
- aging?
- epigenetic dysfunction?
NEUROLOGICAL PROGRESS

Epigenetics and the Nervous System

Mark F. Mehler, MD

We are in the midst of a revolution in the genomic sciences that will forever change the way we view biology and medicine, particularly with respect to brain form, function, development, evolution, plasticity, neurological disease pathogenesis and neural regenerative potential. The application of epigenetic principles has already begun to identify and characterize previously unrecognized molecular signatures of disease latency, onset and progression, mechanisms underlying disease pathogenesis, and responses to new and evolving therapeutic modalities. Moreover, epigenomic medicine promises to usher in a new era of neurological therapeutics designed to promote disease prevention and recovery of seemingly lost neurological function via reprogramming of stem cells, redirecting cell fate decisions and dynamically modulating neural network plasticity and connectivity.

Ann Neurol 2008;64:602–617