Epigenetics and the Aging Brain

University of Alaska Fairbanks
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Cereon Biotechnology LLC
www.cereonbiotech.com
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

• Progressive neurodegeneration accompanied by severe inflammatory and oxidative stress
• Initial degeneration of neuronal morphology and connectivity progressing to a loss of neurons
• 6th leading cause of death in the US
• 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
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
The Prevalence of Diseases

Percent of All Deaths

- Heart Disease (26.6%)
- Cancer (20.1%)
- Chronic Lower Resp. Dis. (6.5%)
- Stroke (4.2%)
- Accidents (3.1%)
- Alzheimer’s (5.1%)
- Diabetes Mellitus (3.7%)
- Kidney Disease (2.3%)
- Pneumonia/Influenza (2.0%)
- Suicide (1.4%)
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 Sero

<table>
<thead>
<tr>
<th>Mental Illness in America</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than a quarter of adults are afflicted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Illness Type</th>
<th>Number of Adults</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All anxiety disorders</td>
<td>20.9 million</td>
<td>9.5%</td>
</tr>
<tr>
<td>All mood disorders</td>
<td>19.2 million</td>
<td>8.7%</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>15 million</td>
<td>6.8%</td>
</tr>
<tr>
<td>Social phobia</td>
<td>14.8 million</td>
<td>6.7%</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention-deficit hyperactivity disorder (ADHD)</td>
<td>9 million (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic stress disorder (PTSD)</td>
<td>7.7 million</td>
<td>3.5%</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>6.8 million</td>
<td>3.1%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>6 million</td>
<td>2.7%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>5.7 million</td>
<td>2.6%</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>4.5 million</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dysthmic disorder</td>
<td>3.3 million</td>
<td>1.5%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2.4 million</td>
<td>1.1%</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>2.2 million</td>
<td>1%</td>
</tr>
<tr>
<td>Agoraphobia (fear of crowded spaces)</td>
<td>1.8 million</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

- Anxiety disorders
- Mood disorders
- Other
A Cure for Alzheimer’s

A Common Tale of Science
To make a long story short
The cause for most Alzheimer’s cases is still essentially unknown

- Most cases of early-onset AD are caused by changes in one of three known genes and represents less than 5% of all AD patients.

- The vast majority of AD cases are late-onset or sporadic and are not genetically inherited. Some genes may act as risk factors.

- The more researchers learn about Alzheimer’s disease, the more they realize that genes play an important role in its development.

Many studies linked ApoE gene to late-onset AD, and local geno...
But wait........

• Mice are the **most prevalent animal model** in Alzheimer’s research
• **However**, mice do not develop Alzheimer’s
• consequently, scientists developed **“humanized” mice!!**
• Most clinical trials resting on genetically modified mice failed when tested in human trials.

• **Primates** also do not develop Alzheimer’s
• **More inexplicable**, chimpanzee and other non-human primate brains develop plaques
Alzheimer’s Disease: 30 years - 4 drugs!

FDA Approved Alzheimer’s Drugs (2010)

- **Donepezil** (Aricept, Pfizer, 1996)
- **Galantamine** (Razadyne, 2001) - natural extract from Daffodil bulbs and Red spider lily described 3,000 years ago and rediscovered in 1950
- **Rivastigmine** (Exelon, 2000)
- **Memantine**

- All 4 drugs show **modest benefits** to cognition and become **ineffective** within 1 year of application

- more than 90 drugs are in clinical trials for Alzheimer’s
Clinical Trial targeting Alzheimer’s Disease

• A multinational, late-stage study by Pfizer showed that Dimebon had no effect.... Dimebon, a FDA approved cold medicine, showed promise in treating AD (small trial in Russia). Currently, Pfizer is running 4 other trials of Dimebon including one involving Huntington's disease.

• Eli Lilly will halt (Phase III Trial) development of semagacestat, a gamma secretase inhibitor, .... studies showed it .... was associated with worsening

• August 9, 2012 - Pfizer and Johnson & Johnson ... the AD drug, bapineuzumab, failed to improve the memory .... mild to moderate AD ... no help for patients that carry a genetic risk factor (dissolve plaques with antibodies most use trial scheme)
Clinical Trial targeting Alzheimer’s Disease

1. Study highlights the relevance of NFT and neuritic plaques and the irrelevance of amyloid plaques to the dementia of AD (Dement Geriatr Cogn Disord 1995;6:21–31)

2. ... genetically engineered mice producing oligomeric Aβ but no plaques .... plaque-free mice did not fare any better (1996-2000)

3. Challenging the Amyloid Cascade Hypothesis: Senile Plaques and Amyloid-β as Protective Adaptations to Alzheimer Disease (Annals of the NY Academy of Sciences 2006)

4. A familial AD form (Japanese) shows no plaque development but severe cognitive failure
# Research Expenditures

<table>
<thead>
<tr>
<th>Disease</th>
<th>Research Costs (2012)</th>
<th>Patients</th>
<th>Research/capita</th>
<th>Research costs 08-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>$498 Million</td>
<td>5 million</td>
<td>$100</td>
<td>$2,421 Million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>$3,075 Million</td>
<td>1.3 Million</td>
<td>$2365</td>
<td>$15,807 Million</td>
</tr>
<tr>
<td>Cancer</td>
<td>$5,570 Million</td>
<td>3 Million</td>
<td>$1,857</td>
<td>$29,844 Million</td>
</tr>
<tr>
<td>DoD</td>
<td>$670,900 Million</td>
<td>316 Million</td>
<td>$2123</td>
<td>$3,420,000 Mil.</td>
</tr>
</tbody>
</table>
US spending $2.5 trillion in 2009 (17.3% of GDP) and $4.3 trillion in 2018 (20.3% of GDP)

<table>
<thead>
<tr>
<th>Country</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>65</td>
</tr>
<tr>
<td>Japan</td>
<td>71</td>
</tr>
<tr>
<td>Australia</td>
<td>71</td>
</tr>
<tr>
<td>Spain</td>
<td>74</td>
</tr>
<tr>
<td>Italy</td>
<td>74</td>
</tr>
<tr>
<td>Canada</td>
<td>77</td>
</tr>
<tr>
<td>Norway</td>
<td>80</td>
</tr>
<tr>
<td>Netherlands</td>
<td>82</td>
</tr>
<tr>
<td>Sweden</td>
<td>82</td>
</tr>
<tr>
<td>Greece</td>
<td>84</td>
</tr>
<tr>
<td>Austria</td>
<td>84</td>
</tr>
<tr>
<td>Germany</td>
<td>90</td>
</tr>
<tr>
<td>Finland</td>
<td>93</td>
</tr>
<tr>
<td>New Zealand</td>
<td>96</td>
</tr>
<tr>
<td>Denmark</td>
<td>101</td>
</tr>
<tr>
<td>UK</td>
<td>103</td>
</tr>
<tr>
<td>Ireland</td>
<td>103</td>
</tr>
<tr>
<td>Portugal</td>
<td>104</td>
</tr>
<tr>
<td>US</td>
<td>110</td>
</tr>
</tbody>
</table>

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

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
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
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
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
Genetics vs Epigenetics

**GENETICS**
- mutations
- inherited
- germ line
- species

**EPIGENETICS**
- alterations
- stable?
- soma
- variability

ncRNAs
mod
remodeler
Maternal diet and aging alter the epigenetic control of a promoter–enhancer interaction at the \textit{Hnf4a} gene in rat pancreatic islets

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

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. \textit{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 \textit{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 \textit{Hnf4a} expression. Aging leads to progressive epigenetic silencing of the entire \textit{Hnf4a} locus in islets, an effect that is more pronounced in rats exposed to a poor maternal diet. Our findings provide evidence for environmentally
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
Consequence of Compaction

- Accessible information: euchromatin
- Restricted information: heterochromatin
Epigenetics - Histones

**Signals**

- Active
- Repressed

- HAT (Histone Acetyltransferase)
- HDAC (Histone Deacetylase)

- UAS
- URS

**Histone H3**

- ARTKQTARKSTGGKAPRKLATKAARKSATGMVKKPH

Spring 2014

OLL
Epigenetics - DNA

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