

Aging, memory, dementia and heredity

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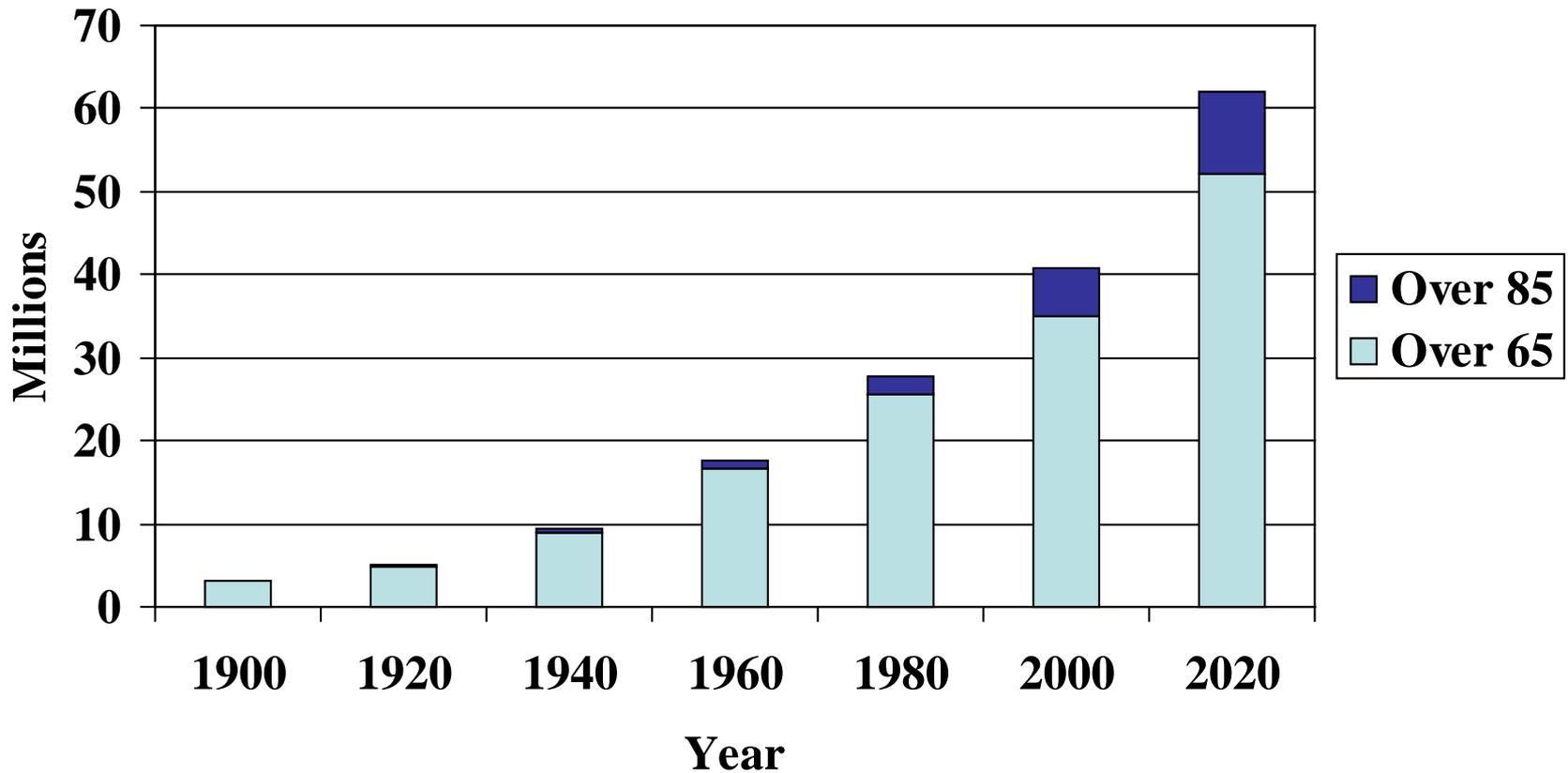
Aging Well:

The older the violin, the sweeter the music



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Number of persons over 65 in US



“The great secret that all old people share is that you really haven’t changed in 70 or 80 years. Your body changes, but you don’t. And that, of course, causes great confusion”

Doris Lessing



Aging and the memory process

- Working memory (short term): small bits of information held for about 20 seconds
 - Recently processed sensory input
 - Recently retrieved memory from long term storage
 - Recent mental processing
- Long term memory:
 - Indefinite storage of seemingly unlimited amount
 - Affected by retrievals, repetition and depth of processing
 - Involves theory of potentiation (change in neurons)



Memory Decline in Normal Aging

- Ability to encode new memories of events from working memory shows decline
- Episodic memory is especially impaired
- Impairments in ability to refresh recently processed information



Areas of Memory Spared With Aging

- Implicit or procedural memory
 - Playing musical instrument, riding bicycle
- Semantic knowledge such as vocabulary improves somewhat
- Enhancement of memory for emotional events is maintained



Does Aging Affect How We Remember?

- Functional brain studies show older adults use both brain hemispheres more often than younger adults when completing memory tasks.
- Older adults show a *positivity effect*: that is they are more likely to pay attention to positive stimuli than negative stimuli.



What is dementia?

- “Insanity with loss of intellectual power due to brain disease or injury”
 - Oxford Dictionary
- A disease of the brain that causes a loss of cognitive function and functional decline
 - The medical definition



Early History

- Dementia (Latin: Demens)
 - Without Mind
- 2000 BC (Egypt): Memory Loss Related to Aging
- 200 AD: Galen wrote about cerebral dysfunction
- Middle Ages: Not focused upon much
- 1700s: Philippe Pinel likely coined “dementia”
- 1700s: Jean Esquirol - **Des Maladies Mentales**
 - Causes: Age, syphilis, mercury, wine, masturbation, and menstrual disorders.



Throughout Literature

...Last scene of all that ends this strange eventful history, is second childishness and mere oblivion; Sans teeth, sans eyes, sans taste, sans everything

Shakespeare. **As You Like It**. 1600



The 3 requirements for dementia diagnosis

- Cognitive impairment involving two or more cognitive areas (memory, language, visual spatial skills, executive function)
- Functional decline from a previous higher functional level.
- Impairments not due to delirium



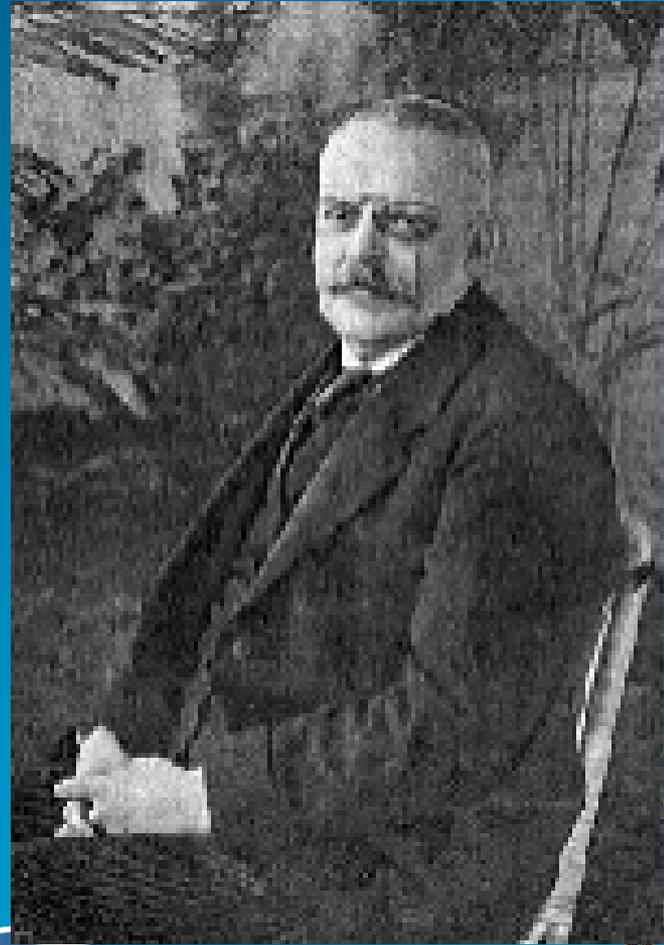
Ten warning signs of dementia

- Memory problems that affect job
- Difficulty with familiar tasks
- Language problems
- Disorientation to time and place
- Judgment problems
- Problems with abstract thinking
- Misplacing things
- Changes in mood or behavior
- Changes in personality
- Loss of initiative



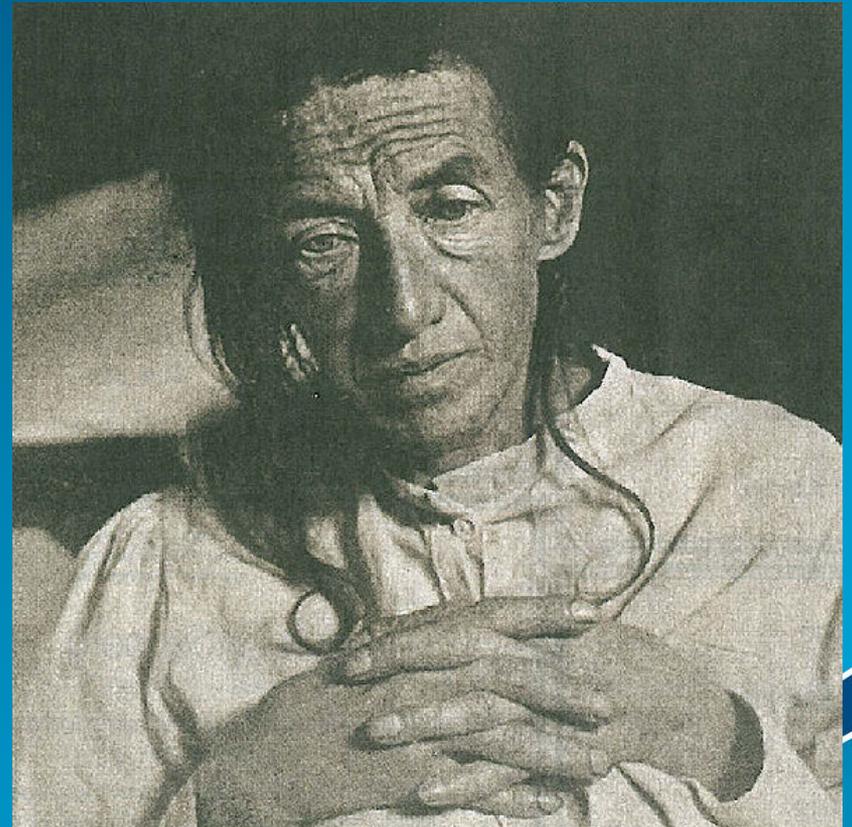
Alzheimer's Disease

- First described in 1906 by Dr. Alois Alzheimer
- Initial case report was a 51 year old woman with a progressive dementia
- She died at age 56 and at autopsy he described the plaques and tangles that are the hallmark of AD



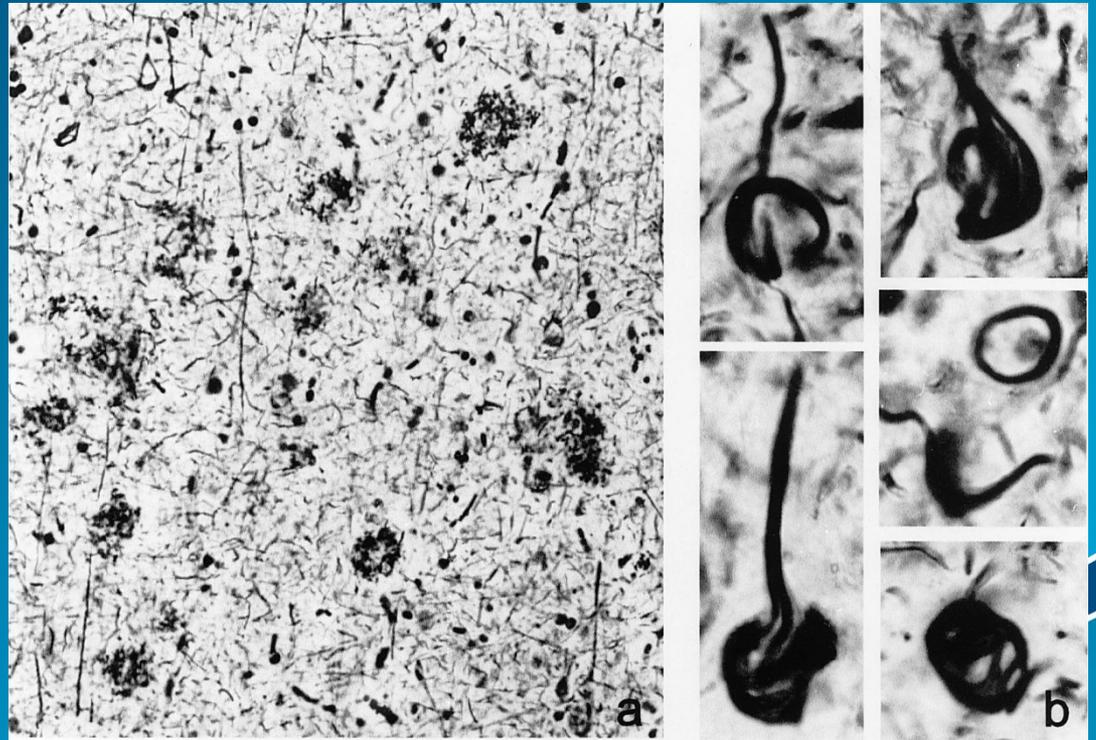
Auguste Deter (1901)

- Interested Alzheimer because she was young
- Progressively worsened
- Died of sepsis 4.5 years later (decubitus ulcer)
- Genetics:
 - ApoE3 homozygote
 - No APP mutations
 - Suspect she had a Presenilin 2 mutation



Alzheimer's Most Famous Case

- Kept records of her hospital course
- Performed an Autopsy
- Sections from frontal, parietal and occipital cortex



Yu, et al. Arch Neurol 2010

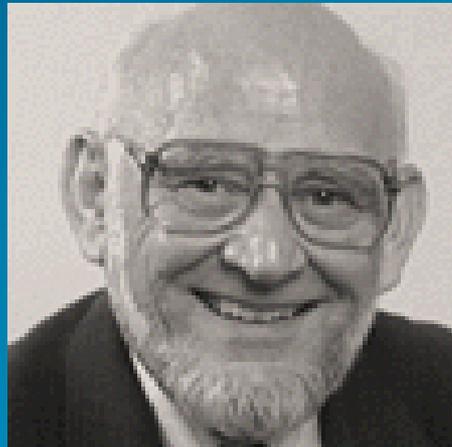
Classification of Dementia 1906-1976

- Prior to 1976, dementia was classified as either senile or “pre-senile” dementia
- Senile dementia was considered to be an expected consequence of aging
- “Pre-senile” dementia was attributed to Alzheimer’s disease, which was believed to be a relatively rare condition causing dementia in younger people



Senile Dementia and Alzheimer's Disease

In his landmark article in 1976, Dr. Robert Katzman demonstrated that the majority of senile dementia was, in fact, Alzheimer's disease



Alzheimer's Disease

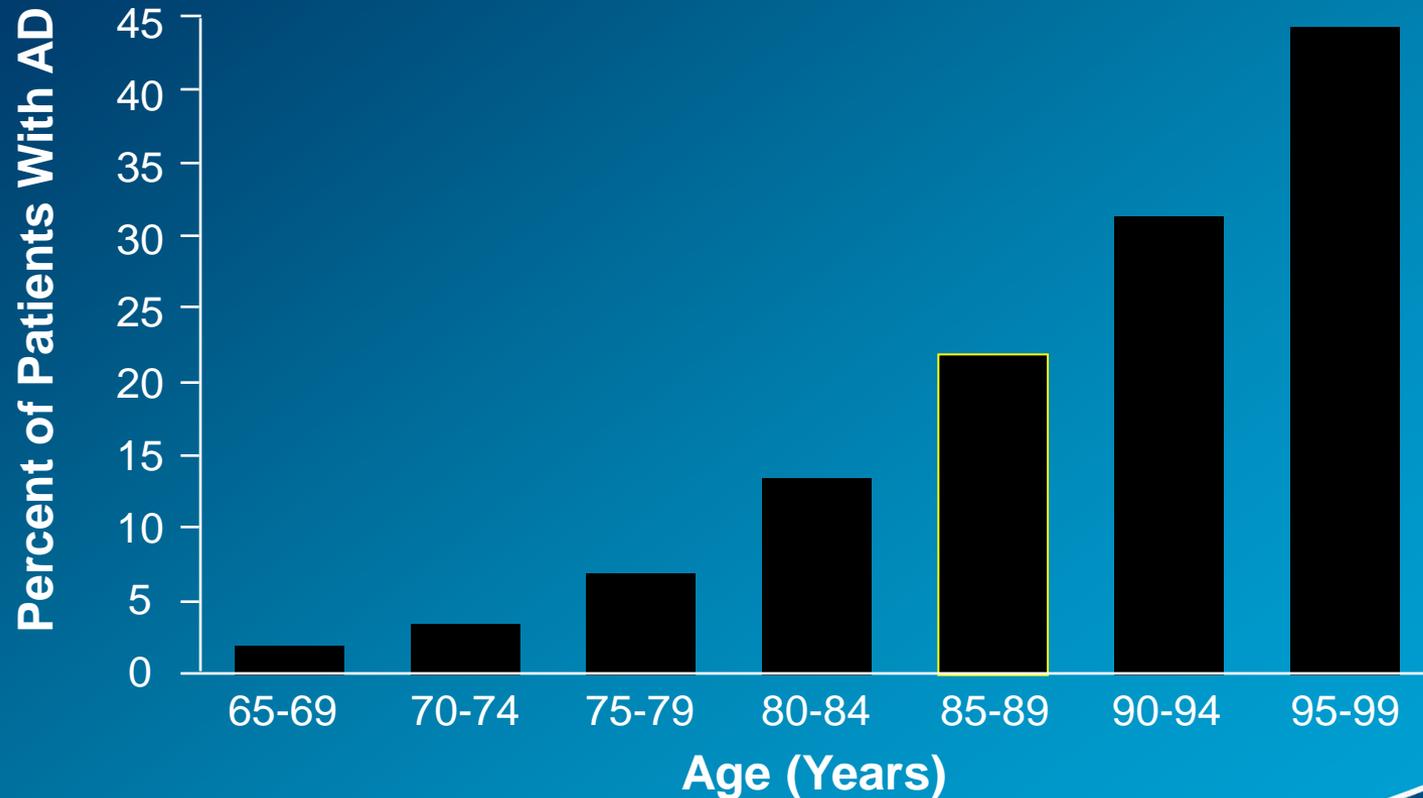
- Is a progressive degenerative disease of the brain
- The hallmark pathology is plaques (amyloid) and tangles (tau)
- It is not fully understood what causes Alzheimer's disease, but age is a major factor and genes play an important role.



Epidemiology of Alzheimer's Disease (AD)



Prevalence of Alzheimer's Disease with Increasing Age



Adapted from Ritchie K, Kildea D. *Lancet*. 1995;346:931-934.



Risk factors for AD

- Age
- Genetics
- Co-morbid illness
 - Diabetes
 - Hypertension: especially in middle aged males
 - Stroke
 - Head trauma/ brain injury



Potentially protective factors

- Education: higher educational level associated with decreased risk for AD and later onset
 - HARMONY study in Swedish Twins
- Exercise: aerobic exercise associated with decreased risk in epidemiologic studies
- As for dietary factors: Fish oil, Omega-3 fatty acids, antioxidants, red wine?

THE JURY IS STILL OUT



Cognitive reserve

- There does not appear to be a direct relationship between the degree of brain pathology and clinical evidence of disease
- Individuals with higher levels of education and intellectual development seem to develop cognitive symptoms later in the disease.



Possible mechanisms cognitive reserve

- **Passive:**
 - Greater initial cognitive capacity makes a reduction in capacity less noticeable
- **Active:**
 - Reserve systems and compensation
 - Using brain networks that are less sensitive to disruption
 - Using structures and networks not usually used for memory or other cognitive task



Genes and Alzheimer's Disease

- Familial Autosomal Dominant Alzheimer's Disease
- Risk Factor Genes
- Epigenetics



But first a brief review of basic genetics

- The nucleus of each human cell contains 23 paired chromosomes consisting of DNA and proteins
- The sequence of base pairs in DNA is the “blueprint” of the genetic code
- Through the processes of transcription and translation the DNA base pair sequence becomes the structural and functional proteins the make up a human being

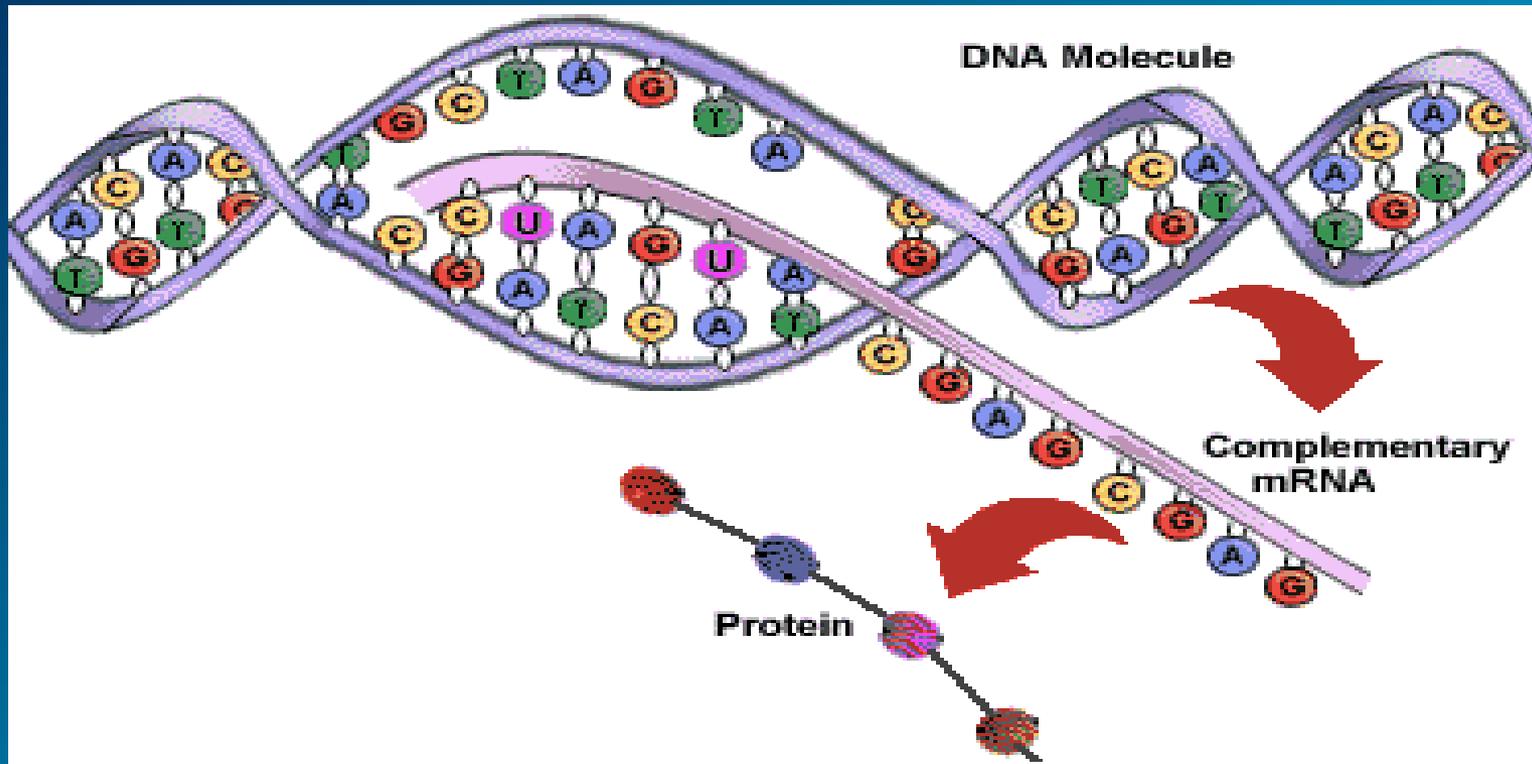


DNA Transcription

- A portion of the DNA double helix is “unwound” exposing the base sequence
- This sequence serves as a template to form a complementary strand on messenger RNA
- This mRNA leaves the cell nucleus and travels to a ribosome on the cell endoplasmic reticulum
- A base pair sequence that codes for a specific protein product is called a gene



DNA transcription

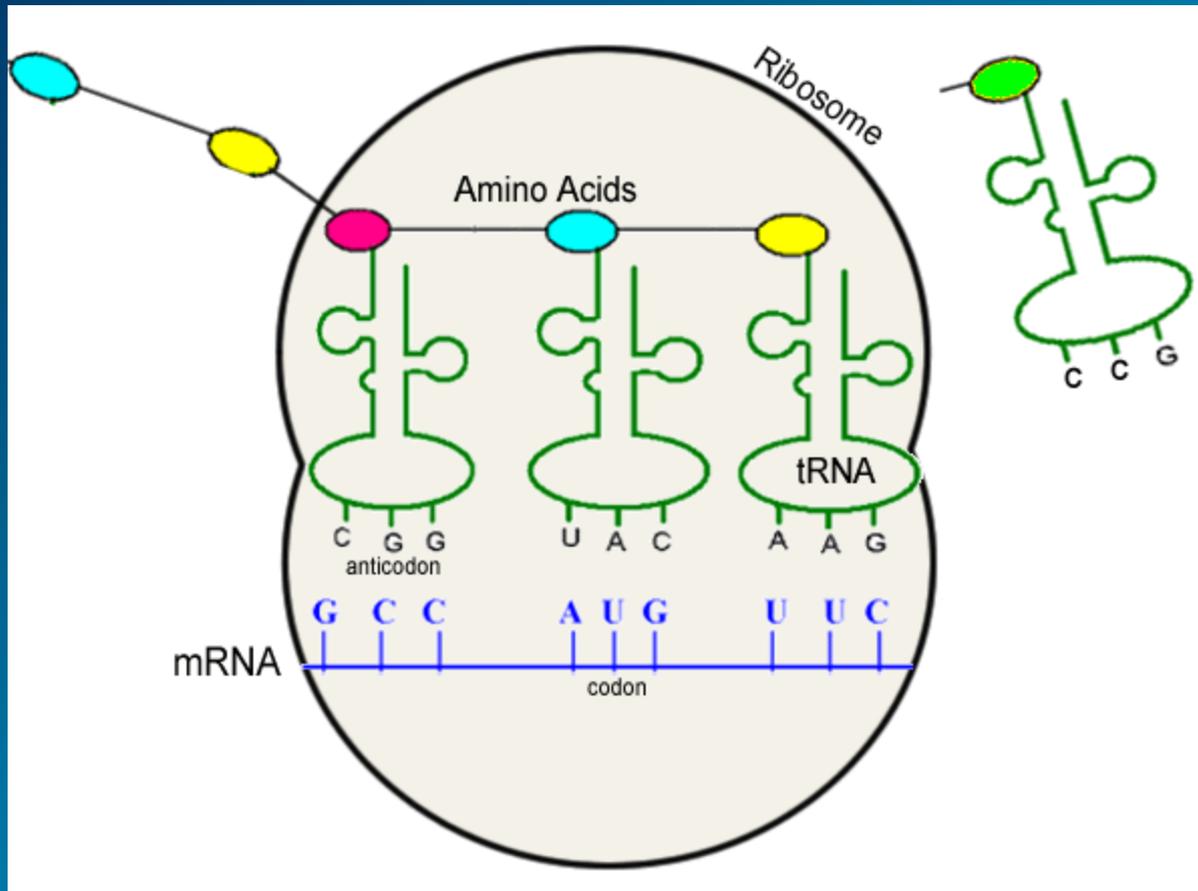


Translation of the Genetic Code

- Each series of three base pairs is called a codon
- A codon sequence corresponds to a single amino acid
- At the cell ribosome the sequence of codons becomes a string of amino acids (a protein) through the interaction of messenger RNA (mRNA) with translational RNA (tRNA)



Translation



Gene alleles, mutations and variations

- An allele is a form of a gene, each individual receives two alleles of each gene on a specific chromosome, one from each parent.
- A gene mutation is a permanent change in a gene that can be transmitted to offspring.
- A gene variation refers to different forms a gene may have (such as APO-E) and these variations may increase or decrease the risk for a disease or trait.



Genetic Disease Inheritance

- Disease determining gene: usually a gene mutation that can be autosomal dominant or recessive. (if on the x chromosome inheritance is sex-linked)
- Genetic risk factor: a gene variation that may increase or decrease the risk of developing a disease



Now Back to Alzheimer's Disease

- Early Onset Alzheimer's Disease
 - Age of onset age 30 to 60
 - Less than 5 % of cases
 - Most cases Familial Alzheimer's Disease (FAD)
- Late Onset Alzheimer's Disease
 - After age 60
 - Cause is not well understood and is likely a combination of genetic, environmental and life style factors

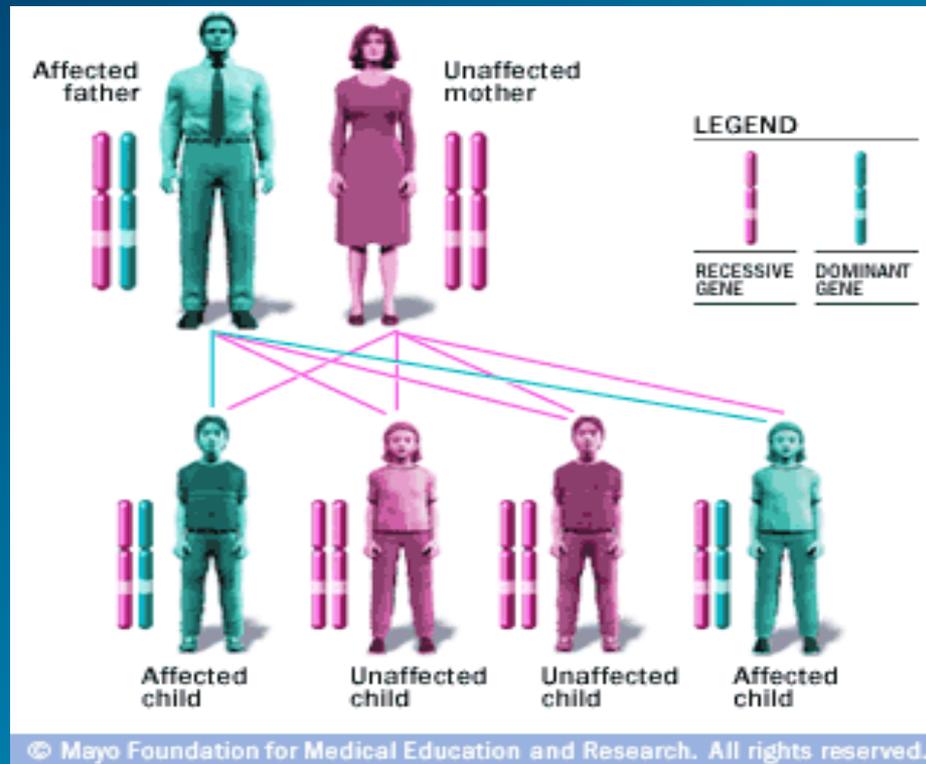


Familial Alzheimer's Disease

- Involves any of a number of single gene mutations on chromosome 1, 14 or 21
 - 21: abnormal amyloid precursor protein (APP)
 - 14: abnormal presenilin 1
 - 1: abnormal presenilin 2
- Each leads to abnormal cleavage of APP
- All are autosomal dominant



Autosomal Dominant inheritance



Late Onset Alzheimer's Disease (the most common form)

- No specific gene mutation has been linked to late onset Alzheimer's Disease
- There is an increased risk for the development of late onset Alzheimer's Disease in individuals with a variant of the apolipoprotein E allele, APOE-4.



Apolipoprotein E

- Gene is located on chromosome 19
- Codes for a protein that is involved in the transport of cholesterol and other types of fat
- APOE exists in three forms that differ from each other by single amino acid substitutions
 - APOE-3: most common, neutral in AD risk
- APOE-4: 25-30%, increase in AD risk
- APOE-2 least common, decrease in AD risk



APOE-4

- Found in 25 to 30 % of general population
- In 40% of all persons with late onset AD
- Persons with APOE-4 tend to develop AD earlier than those without
- It is a risk factor gene
 - Increases risk
 - Does not definitely mean one with gene will develop the disease



Genome-wide Association Study (GWAS)

- Involves the examination of DNA from a large number of individuals who have a disease and a control group that does not
- Looking for common genetic variants to see if there is association with the disease
- Usually looking at single nucleotide polymorphisms (SNPs) or variations at a single nucleotide base pair site
- Can help to identify areas on a chromosome that may be involved in a disease



GWAS in AD

- Has identified a number of genes other than APOE-4 that may increase risk for AD
 - B1N1- a protein associated with heart contraction
 - CLU- clusterin. Involved in apoptosis chromosome 8
 - PICALM- phosphatidylinositol binding clatherin assembly protein chromosome 11
 - CR1- complement receptor 1 chromosome 1
- May help better understand AD and identify possible new treatment or prevention modalities



Genetic Testing in AD

- Early onset FAD
 - In familial AD genetic testing and counseling may be appropriate
- Late onset AD
 - Blood test can identify which APOE allele one has
 - Can't predict if one will get the disease or not
 - It is unlikely any genetic test will be able to predict late onset AD with 100% accuracy due to multiple factors
 - At present only role is in research

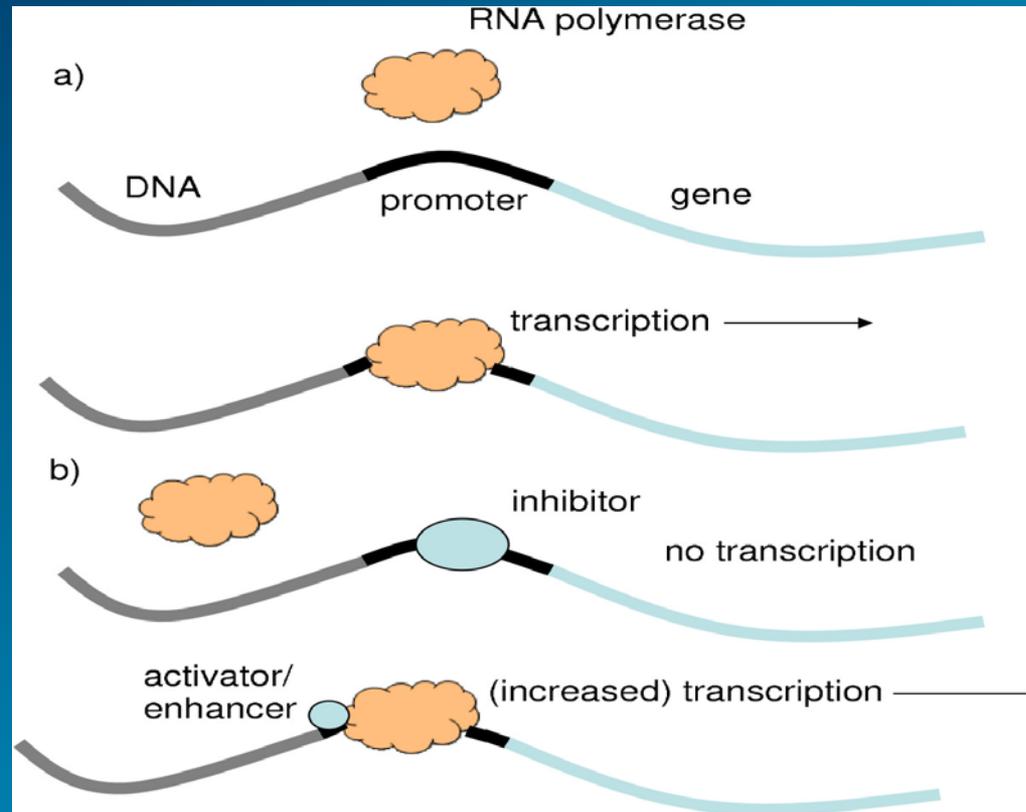


Epigenetics

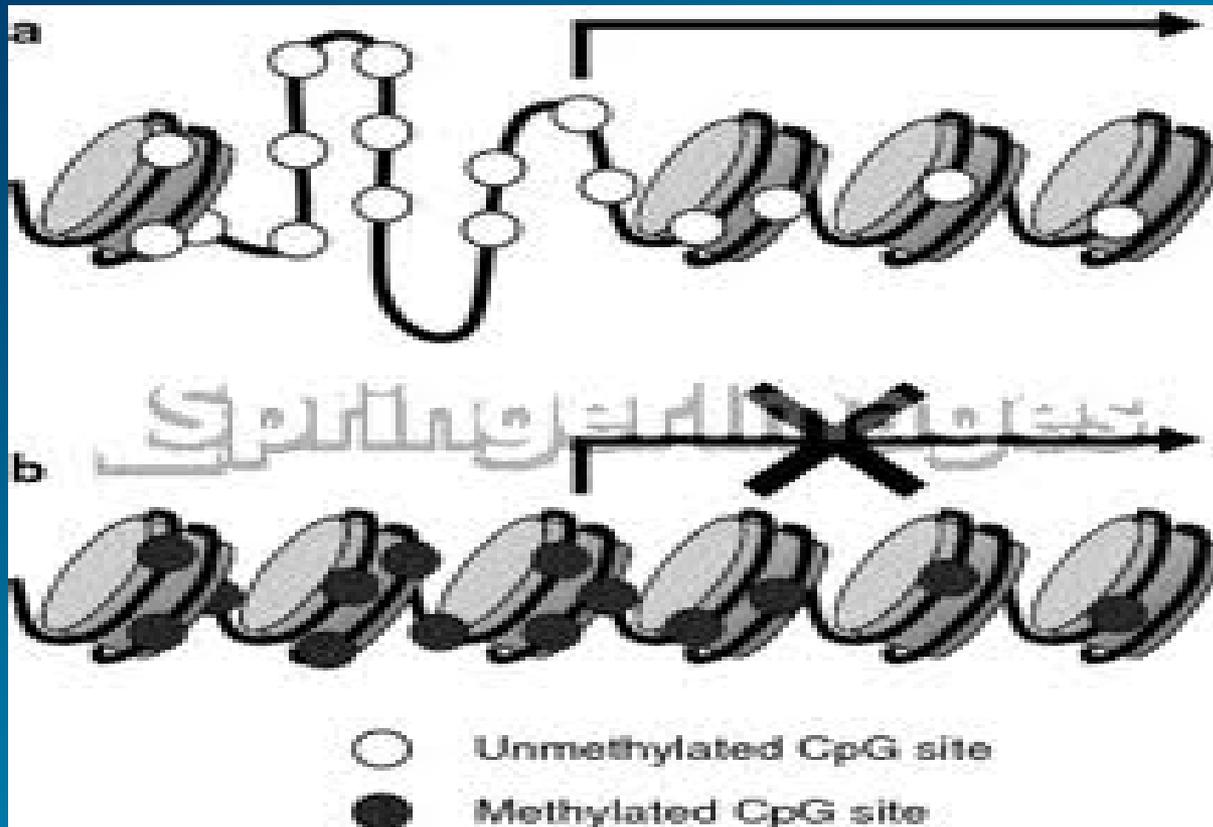
- Biological mechanism by which interaction of environment and genetics can be explained
- The expression of genes may be influenced by environmental factors
- Epigenome can “mark” DNA and play a role in turning specific genes on or off
 - Methyl groups attached to DNA backbone
 - Chemical tags that attach to tails of histones



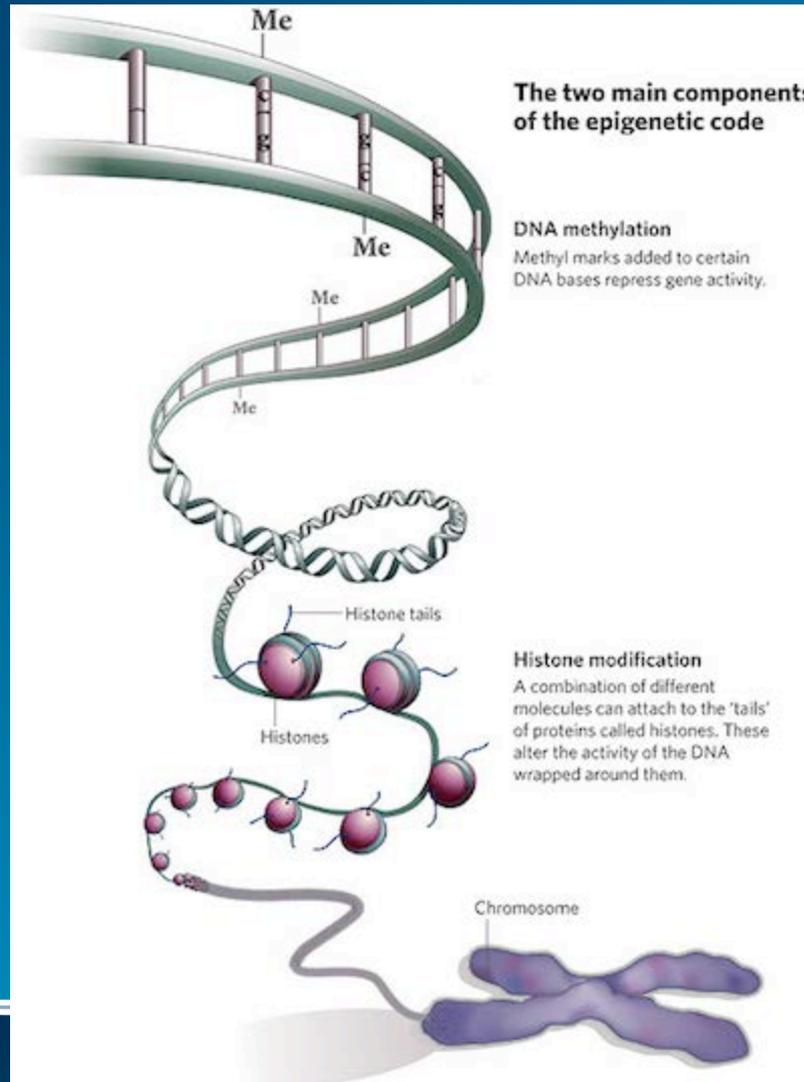
DNA Promotion and Inhibition



DNA methylation



Epigenetic code



Projections for the future

- Number of Alzheimer's patients in US today
 - 5.3 million
- Current cost of Alzheimer's Disease
 - Medicare \$90 billion/year
 - Non-Medicare care costs \$160 billion/year
- Projected number in 2050 given current population and disease trends
 - 16 million
- Projected costs
 - Medicare over \$300 billion/year
 - Non-Medicare care costs over \$500 billion/year





The tip of the iceberg

What will it take to change the future?

- Research
 - Diagnostic modalities
 - Disease modifying treatments
 - Preventative measures
- Clinical Care Delivery
 - Physician training in diagnosis and treatment
 - Public education and disease awareness
 - A national coordinated plan for care delivery





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SOCARE: UCSD California Alzheimer's Disease Centers (CADC) site

- Team provides comprehensive initial evaluation and social assessment
- Referral for: imaging, neuropsychological testing, geriatric psychiatry or neurology as indicated
- A final conference with patient and family to present diagnosis, recommendations and education about community resources



SOCARE Contact Information

Clinic Office

(619) 471-3833



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