WILL I GET IT?

GENETIC TESTING AND ALZHEIMER DISEASE

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Wesley Medical Center
Participants will learn:

■ Modes of inheritance of genetic conditions

■ Genes associated with Alzheimer disease (AD)

■ Diagnostic algorithms for AD, and the role of genetics in an AD diagnosis

■ How to incorporate current genetics knowledge in AD prediction and prevention

■ Available clinical genetic testing for AD
GENETICS 101
Cells

-- the building blocks of an organism
Chromosome to Gene to Protein

Cell

Chromosomes

Gene

Protein

- Adenine
- Thymine
- Guanine
- Cytosine
The Human Genome

- **Cells in the human body**
  - approx. 37 trillion

- **Human genome**
  - 23 chromosome pairs (46 chromosomes)
  - Approx. 20,000 genes
    - Approx. 3 trillion base pairs
    - We have 2 copies of all genes

- **1 Chromosome**
  - 2,000 – 5,000 genes
    - Only about 2-3 percent of the genome is coding DNA
INSIDE THE CELL

Cell  Nucleus  Chromosome  DNA  Gene
(Segment of DNA)
The Human Genome

Source: Ars technica
Types of Genetic Disorders

- Chromosomal
- Single-gene (or Mendelian)
- Multifactorial
- Other
  - Mitochondrial disorders
  - Epigenetic disorders
  - Teratogenic disorders
Chromosomal Disorders

- Example: Down syndrome
Single-gene disorders

Autosomal dominant

- Marfan syndrome / FBN1 (Chr. 15)
- Hereditary breast and ovarian cancer (HBOC)
  - BRCA1 (Chr. 17)
  - BRCA2 (Chr. 13)
- Achondroplasia / FGFR3 (Chr. 4)
- Hemochromatosis / HFE (Chr. 6)
al·lele  /əˈlel/  

noun

one of two or more alternative forms of a gene that arise by mutation and are found at the same place on a chromosome.
Autosomal dominant disorders

U.S. National Library of Medicine
Single-gene disorders

Autosomal recessive

- PKU / PAH (Chr. 12)
- Cystic fibrosis / CFTR (Chr. 7)
- Albinism / OA1 (Chr. 15)
- Sickle cell anemia / HBB (Chr. 11)
Autosomal recessive disorders
Single-gene disorders

X-linked dominant
- *Fragile X syndrome*
  - Both males and females affected
  - Females generally more mildly affected

X-linked recessive
- *Hemophilia*
  - Males overwhelmingly affected
  - Females rarely express symptoms

Y-linked
- *Infertility (low sperm count)*
  - ONLY males affected
X-linked inheritance

- All daughters affected
- No male-to-male transmission
- All daughters carriers
- All sons affected
multi-factorial /mŭl'te-fŏk-tôr'ēəl/

adj.
1. Involving, dependent on, or controlled by several factors.

2. Of, relating to, or caused by a pattern of familial inheritance resulting from multiple genetic or environmental factors or from a combination of both.
Examples of Multifactorial (or Complex) Disorders

- Obesity
- Heart disease
- Alzheimer disease *(most common form)*
- Cancer
- Diabetes
- Mental illness
Multifactorial conditions

- Often “run in families”
- May be due to:
  - Shared genetics
  - Shared environmental risk factors
  - Shared lifestyle factors
  - Any combination of these factors
- Genetic variations within a number of genes may combine to confer a predisposition to a particular condition
  - E.g. cleft lip, cleft palate / MTHFR gene
GENETICS OF ALZHEIMER DISEASE
Alzheimer disease

1. Clinical description
2. Incidence / Genetics
3. Pathophysiology
4. Treatment / therapies
Alzheimer disease – clinical description

Early stage:

- People may have trouble remembering recent events, activities, or the names of familiar people or things.

- They may not be able to solve simple math problems.

- They may begin to repeat themselves in conversation.
Alzheimer disease – clinical description

Middle stage:

- Individuals may forget how to do simple tasks, e.g. brushing teeth or combing hair.
- They can no longer think clearly; may act impulsively.
- They begin to have problems speaking, understanding, reading, or writing.
Alzheimer disease – clinical description

Late stage:

- Patients may become anxious, aggressive, disoriented
- They may wander away from home.
- Eventually, patients need total care.
Alzheimer disease incidence

- Alzheimer disease is the most common degenerative brain disease
  - (~ 5 million USA, 46 million globally)

- Most important risk factor
  - Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>65-74</th>
<th>75</th>
<th>80</th>
<th>&gt;85</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>~5%</td>
<td>~10%</td>
<td>~20%</td>
<td>~50%</td>
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</tbody>
</table>
Alzheimer disease incidence (cont.)

- About 25% of all Alzheimer disease is familial
  - (i.e., 2 or more people in a kindred are affected)

- Most common cause of dementia in N. America and Europe
  - Incidence is somewhat lower in other parts of the world, lowest in sub-Saharan Africa
Alzheimer disease diagnostic criteria

- Latest version 2011

  - The only way to definitively diagnose Alzheimer disease is at autopsy
    - Characteristic “plaques” and “tangles”

  - Mild cognitive impairment is often the first sign
    - Biomarkers are continually being developed to discern Alzheimer disease preclinically

  - Emphasize distinction between “mild cognitive impairment” in early stage
    - There must be loss of skills in two or more aspects of cognition / behavior in order to be considered dementia

  - Characteristic findings on brain imaging in later stage Alzheimer disease
Brain Atrophy in Advanced Alzheimer’s Disease

Normal

AD
More on those “biomarkers”

- Decreased amyloid beta in cerebrospinal fluid
- Elevated CSF measurement of tau
- PET imaging to find early plaque deposits
- MRI to assess brain atrophy in early stage Alzheimer disease

- Conspicuously missing:
  - DNA testing
There are two forms of Alzheimer disease

Late-onset

- Most common form
- Approx. 95% of all Alzheimer cases
- Can run in families, but no obvious inheritance pattern
- Several genes are thought to contribute
- Certain alleles of the *APOE* gene are known to alter individual risk
- *APOE* is a **susceptibility** gene

Early-onset

- Rare
- Onset of symptoms by ~60
- **Autosomal dominant** transmission
- Single-gene disorder – three known genes:
  - *PSEN1* (up to 70%)
  - *PSEN2* (<5%)
  - *APP* (up to 15%)
- Chromosomal etiology – Down syndrome (<1%)
HETEROZYGOATS
Just allele uneven.
GENETIC TESTING FOR ALZHEIMER DISEASE

Benefits and Limitations
Early-onset familial Alzheimer disease (EOFAD)

- **Autosomal dominant**
  - *Children of an affected parent have a 50% chance of being affected*

- Clinical genetic testing is possible for all three EOFAD genes
  - *Sensitivity ~80%*

- Can be ordered by a physician / GC
<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of EOFAD Attributed to Pathogenic Variants in This Gene</th>
<th>Test Method</th>
<th>Pathogenic Variants Detected</th>
<th>Variant Detection Frequency by Gene and Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN1</td>
<td>30%-70% ⁴</td>
<td>Targeted analysis for pathogenic variants</td>
<td>4555-bp deletion of exon9 (Finnish founder variant) ⁵</td>
<td>100% for the targeted variant</td>
</tr>
<tr>
<td></td>
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<td>Sequence analysis ⁶</td>
<td>Sequence variants</td>
<td>~98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis ⁷</td>
<td>Partial- and whole-gene deletions, including exon9 Finnish founder deletion</td>
<td>100% for deletions, which are rare</td>
</tr>
<tr>
<td>APP</td>
<td>10%-15%</td>
<td>Sequence analysis ⁶ / scanning ⁸ of exons 16 and 17 for pathogenic variants</td>
<td>Sequence variants in exons 16 and 17</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis ⁷</td>
<td>Partial- and whole-gene duplications</td>
<td>100% for the targeted duplication</td>
</tr>
<tr>
<td>PSEN2</td>
<td>&lt;5%</td>
<td>Sequence analysis ⁶</td>
<td>Sequence variants</td>
<td>~100%</td>
</tr>
</tbody>
</table>
Genetic Testing for EOFAD

- Commercial labs performing EOFAD testing in the US:
Late onset Alzheimer disease (LOAD)

- The APOE gene is most strongly associated with LOAD
- APOE
  - Apolipoprotein E
  - Chromosome 19
  - The APOE protein is part of a system that helps carry necessary fats (lipids) through the body. (E.g., cholesterol)
  - APOE protein that doesn’t work properly allows for accumulation of these lipids in other places in the body where they don’t belong.
APOE Alleles

- There are three variants of APOE
  - The differences in the genetic code of APOE lead to slightly different versions of the APOE protein
- These different forms are called isoforms
  - \( E_2 \) ~ may have a protective role
  - \( E_3 \)
  - \( E_4 \) ~ increased risk
## APOE Alleles

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>Normal Controls (n=304)</th>
<th>All Individuals with AD (n=233)</th>
<th>Individuals with AD and Positive Family History of Dementia (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e2/e2</td>
<td>1.3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>e2/e3</td>
<td>12.5%</td>
<td>3.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>e2/e4</td>
<td>4.9%</td>
<td>4.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>e3/e3</td>
<td>59.9%</td>
<td>38.2%</td>
<td>23.5%</td>
</tr>
<tr>
<td>e3/e4</td>
<td>20.7%</td>
<td>41.2%</td>
<td>45.9%</td>
</tr>
<tr>
<td>e4/e4</td>
<td>0.7%</td>
<td>12.9%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>
Genetic Testing for APOE

- Clinical testing for carrier status APOE alleles is available

- NOT A DIAGNOSTIC TEST!
  - Can elucidate one (of many) risk factors

- US labs doing testing for APOE:
  - Fulgent (CA)
  - Athena (MA)
  - U of KY

- Testing can be ordered through a physician and/or genetic counselor
Genetic Counseling for Alzheimer Disease

Factors to think about when considering genetic testing:

- *In the US, lifetime risk for developing Alzheimer disease is 10-12%*
  - Biggest risk factor = age

We know that genetics plays a considerable role in the development of Alzheimer disease:

- *Risk of developing Alzheimer disease approx. doubles if one has a first-degree relative with it*
  - ~25%
Genetic Counseling for Alzheimer Disease

- Early Onset Alzheimer Disease (Presymptomatic) testing
  - Testing is best performed first on an affected family member
    - HOWEVER ....
    - There are complicating factors in testing affected individuals:
      - Is the subject able to give informed consent for testing
      - Testing should be explained/performed in the presence of a trusted family member / legal guardian
  - Normal testing in an unaffected person = lower confidence
    - Is that person off the hook?
    - Or did we test for the wrong thing?
Genetic Counseling

- Pre-test genetic counseling is highly recommended
  - Exploration of why testing is desired (does not (yet) affect treatment)
  - Effect of testing on personal life decisions, implications for family members
    - IMPORTANT: disease onset / symptoms may look very different between families and within families
  - Testing of minors is NEVER recommended
    - Adult onset, no preventative treatment, no cure
Genetic Counseling

- Pre-test genetic counseling is **highly recommended**
  - *Exploration of why testing is desired (does not (yet) affect treatment)*
  - *Effect of testing on personal life, life decisions, implications for family members*
    - Pros of testing: relief from anxiety, financial and family planning
    - Cons of testing: negative psychological reaction to a positive test
  - *Testing of minors is NEVER recommended*
    - Adult onset, no preventative treatment, no cure
Symptomatic Testing

Full neurological/neuropsychological evaluation

Genetic counseling and risk evaluation

Autosomal dominant family history or very early onset

Genetic testing offered (PSEN1, PSEN2, APP)

Testing performed

Post-test results counseling

Follow up
Discuss availability of predictive testing for relatives if causative mutation is identified

Sporadic or non-autosomal dominant family clustering

Discuss availability of genetic research and/or DNA banking

Testing not performed

Predictive Testing

Known family mutation in PSEN1, PSEN2 or APP

Genetic counseling and risk evaluation

Neurological, neuropsychological, and psychiatric evaluation

Genetic testing for known familial mutation

Post-test results counseling

Follow-up
Genetic Counseling for Alzheimer Disease

■ Late onset Alzheimer disease: APOE susceptibility testing

■ NOT ROUTINELY OFFERED. Why??

  o The presence of the e4 allele is neither necessary nor sufficient to cause Alzheimer disease

  o Studies still vary widely on the quantitative effect of the e4 allele on development of Alzheimer disease in any given individual

  o Our ability to predict onset, symptomology based on APOE results is still speculative
Genetic Counseling for Alzheimer Disease

- NOT ROUTINELY OFFERED. Why?? (continued)
  - There are SO MANY other risk factors to take into consideration (many of which are also poorly or NOT quantified) that an evidence-based prediction is not yet possible
  - Existing studies based of APOE testing and development of Alzheimer disease only in populations of European and African American descent.
  - Studies in which APOE testing and genetic counseling on Alzheimer risk had widely varying results, which reflects on the complexity of the information, and the methods of communication of results.
In Conclusion…

Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors

Jill S. Goldman, MS, MPhil, Susan E. Hahn, MS, Jennifer Williamson Catania, MS, MPH, Susan LaRusse-Eckert, MS, Melissa Barber Butson, ScM, Malla Rumbaugh, MS, Michelle N. Strecker, MS, J. Scott Roberts, PhD, Wylie Burke, MD, PhD, Richard Mayeux, MD, MSc, and Thomas Bird, MD
Guidelines Summary

- Pediatric testing for AD should not occur.
- Genetic testing for AD should only occur in the context of genetic counseling.
- Genetic counseling for symptomatic patients should be performed in the presence of the individual’s legal guardian or family member.
- Asymptomatic patients: pre-test counseling, similar to the protocol used for Huntington disease, is recommended.
- APOE testing is not advised.
- A ≥3-generation family history should be obtained, with risk assessment as to the most likely etiology of AD in the family (i.e., dominant, familial, sporadic).
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
  - The lifetime risk of AD in the general population is approximately 10–12% in a 75–80-year lifespan.
QUESTIONS?

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