The Genetics in Alzheimer’s disease

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First Polish Alzheimer’s disease case (1913)....
Dementia

- AD – Alzheimer’s disease
- VaD – Vascular Dementia
- FTD – Fronto temporal Dementia
- DLB – Lewy Body Dementia
- MCI – Mild Cognitive Impairment

Alzheimer’s disease, dementia rising worldwide

The worldwide prevalence of Alzheimer’s disease and other dementias is predicted to more than triple over the next four decades, mostly due to increasing longevity in low- and middle-income countries.

The global cost of the disease was estimated at $815 billion in 2015, and the cost of care in low- and middle-income countries is rising as the quality of health care improves and access increases.

For each person with Alzheimer’s disease, the Alzheimer's Association says there are one or two people acting as caregivers, exponentially multiplying the impact of the illness. The emotional toll for these caregivers is also high. In the United States, more than 60 percent of caregivers report the strain of taking care of a loved one with Alzheimer’s is as high or very high. Studies of low- and middle-income countries reveal the strain is much as high for caregivers, despite larger extended family networks.

About 35.5 million people worldwide are living with Alzheimer’s disease and other dementias in 2016, and that is projected to rise to 115.4 million by 2050, according to recent report by Alzheimer’s Disease International. In Ohio, there are currently about 220,000 people with Alzheimer’s disease. The Alzheimer’s Association predicts that this number will rise to about 350,000 by 2050.

The map below shows the total population older than age 60 for each region (in millions) in the year 2019, 2050 and 2050.

SOURCES: Alzheimer's Association, Alzheimer's Disease International

**Worldwide dementia cases**

<table>
<thead>
<tr>
<th>Region</th>
<th>Year 2019</th>
<th>Year 2050</th>
<th>Year 2050</th>
<th>Year 2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2 million</td>
<td>4 million</td>
<td>9 million</td>
<td>10 million</td>
</tr>
<tr>
<td>Americas</td>
<td>23 million</td>
<td>65.7 million</td>
<td>115.6 million</td>
<td>20 million</td>
</tr>
<tr>
<td>Europe</td>
<td>180 million</td>
<td>65.7 million</td>
<td>115.6 million</td>
<td>20 million</td>
</tr>
<tr>
<td>Asia</td>
<td>457 million</td>
<td>65.7 million</td>
<td>115.6 million</td>
<td>20 million</td>
</tr>
</tbody>
</table>
Abnormal Protein Aggregates

Neurofibrillary tangles

Senile plaques

Lewy Bodies

Pick Bodies

Nuclear polyglutamine inclusions

Neurodegeneration
Multifactorial Diseases

Broekhoven, 2007

Number of patients

molecular genetics  

Genetic Environment

Early-onset Late-onset

Genetic  

Environment

Early-onset Late-onset
Asymptomatic Alzheimer’s disease:

- Genetic testing
- CSF biomarkers (Aβ, tau and ptau)
- Neuroimaging
Why it is so important to diagnose dementia in preclinical stage?

- Recognizing dementia in its preclinical phase is of great importance for patients and their relatives. Pharmacoeconomics!
- New causative (!?) drugs.... (vaccination, inhibitors of: β- and γ-secretases, GSK3β inhibitors, β-amyloid and tau breakers)....
Alzheimer disease
“causative” treatment

Ongoing trials:
- PBT2 (hydroxyquinoline, FDA-III)
- Rember (metylen blue)- FDA-III

Problems....
Prevention

- Treatment of blood pressure and diabetes
- Lowering of cholesterol and homocysteine levels in serum
- High education
- High physical activity in any period of life (walk!)
- Great and successful social life
New criteria 2010....


Alzheimer’s disease

A clinical phenotype typically with progressive dementia that includes episodic memory impairment
Sood i wsp. 2010, Aralasmak i wsp. 2010, Schuff i wsp. 2010, ADNI, Descripa
Preliminary results of 77 cases MCI

- $\alpha_\beta 42 : 73\%$
- t-TAU : 54%  P-TAU: 42%
- A$\beta$ 42 lub t-TAU : 85%

Wallin i wsp 2010, Koric i wsp. 2010, Jack i wsp 2010  Filipek et al.2010
Genetics of Alzheimer’s disease

1. Familial autosomal dominant Alzheimer disease - FAD 10%

2. Sporadic Alzheimer’s disease - SAD, 90 %
Revising the definition of Alzheimer’s disease

1. Monogenic AD: individuals with known autosomal dominant single gene mutation
2. Multigenic AD: GWAS
3. Non-genetic familial aggregation of the disease (x2)

Dubois et al. 2010
Genetics of AD

- Early-onset AD: ~1%
- Positive family history in 60%, of which 10% with autosomal dominant inheritance
- Mutations in APP, PS1 and PS2

- APOE ε4 increases risk for AD, and decreases onset age
Sporadic Alzheimer's disease

## Results

<table>
<thead>
<tr>
<th></th>
<th>Allele frequency</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APOE ε2 ε3 ε4</td>
<td>AD</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.003</td>
<td>0.645</td>
<td>0.325*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.045</td>
<td>0.845</td>
<td>0.11</td>
</tr>
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</table>

*p < 0.005

Not recommended - EFNS, McKhann, criteria!

Styczynska et al. Neuroscience Letters 2003, Small et al. 2010, REVEAL study, Christensen et al., 2008
- APP mutations in EOAD
- Presenilin 1 and 2 mutations
- MAPT, progranuline
- APO E polymorphism, only in symptomatic AD

- 4912 DNA samples (Controls, MCI, AD, FTD, DLB, VaD cases)
## Mutations identified in the studied group

<table>
<thead>
<tr>
<th>gene</th>
<th>mutation</th>
<th>codon</th>
<th>location</th>
<th>domain</th>
<th>age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN2</td>
<td>Q228L*</td>
<td>CAG → CTG</td>
<td>E7</td>
<td>TM-V</td>
<td>60</td>
</tr>
<tr>
<td>APP</td>
<td>T714A</td>
<td>ACA → GCA</td>
<td>E17</td>
<td>TM-I</td>
<td>44</td>
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<tr>
<td>APP</td>
<td>V715A</td>
<td>GTG → GCC</td>
<td>E17</td>
<td>TM-I</td>
<td>42</td>
</tr>
<tr>
<td>APP</td>
<td>V717L</td>
<td>GTC → CTC</td>
<td>E17</td>
<td>TM-I</td>
<td>46</td>
</tr>
</tbody>
</table>

* - novel mutations
## Mutations identified in the studied group

<table>
<thead>
<tr>
<th>gene</th>
<th>mutation</th>
<th>codon</th>
<th>location</th>
<th>domain</th>
<th>age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN1</td>
<td>P117R</td>
<td>CCA → CGA</td>
<td>E5</td>
<td>HL-I</td>
<td>36</td>
</tr>
<tr>
<td>PSEN1</td>
<td>M139V</td>
<td>ATG → GTG</td>
<td>E5</td>
<td>TM-II</td>
<td>40</td>
</tr>
<tr>
<td>PSEN1</td>
<td>H163R</td>
<td>CAT → CGT</td>
<td>E6</td>
<td>HL-II</td>
<td>50</td>
</tr>
<tr>
<td>PSEN1</td>
<td>S170F**</td>
<td>TCT → TTT</td>
<td>E6</td>
<td>TM-III</td>
<td>29</td>
</tr>
<tr>
<td>PSEN1</td>
<td>F177L</td>
<td>TTT → CTT</td>
<td>E6</td>
<td>TM-III</td>
<td>37</td>
</tr>
<tr>
<td>PSEN1</td>
<td>I213F*</td>
<td>ATT → TTT</td>
<td>E7</td>
<td>TM-IV</td>
<td>33</td>
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<tr>
<td>PSEN1</td>
<td>L226F*</td>
<td>CTC → TTC</td>
<td>E7</td>
<td>TM-V</td>
<td>33</td>
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<tr>
<td>PSEN1</td>
<td>P264L</td>
<td>CCG → CTG</td>
<td>E8</td>
<td>HL-VIa</td>
<td>49</td>
</tr>
<tr>
<td>PSEN1</td>
<td>A360T*</td>
<td>GCT → ACT</td>
<td>E10</td>
<td>HL-VIb</td>
<td>57</td>
</tr>
<tr>
<td>PSEN1</td>
<td>L424H*</td>
<td>CTC → CAC</td>
<td>E12</td>
<td>TM-VIII</td>
<td>39</td>
</tr>
<tr>
<td>PSEN1</td>
<td>L424R</td>
<td>CTC → CGC</td>
<td>E12</td>
<td>TM-VIII</td>
<td>34</td>
</tr>
</tbody>
</table>

* - novel mutations  
** - de novo mutation
Schematic representation of PS1 and a part of APP

C. Żekanowski, according to A. Tandon, 2002
GWAS: Genome – Wide Scan

LOAD:

chromosomes: 1, 2, 3, 6, 8, 9, 10, 12

(PICALM, CLU)

Ferrer-Alcon i wsp 2009, Heizen i wsp 2010, Stein et al. 2010 Seshadri i wsp. 2010
Recomendations for practice
APP and presenilins mutations

- Individuals with a family history of early onset AD
- A positive test result is highly informative.(95-100%)
- A negative test result is often uninformative
- Genetic testing should be done with informed consent adhere
to strict confidentiality and provide genetic consuelling before
and after test (in Huntington’s protocol)

*Evidence-based Dementia Practice  2004*
The decision to participate in genetic testing is a personal one.

Genetic counseling for people with non-familial AD and their family members must be empiric and relatively nonspecific.

Predictive screening in otherwise healthy people will be useful when effective ways to treat or prevent AD are available.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given banking DNA of affected individuals.
Clinicians:

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M. Golan
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KBN GRANTS: 6PO5B05820, 2 PO5B 13227
Our pub med publications 2010-211

**Ultrafiltrate of Blood Plasma Modulates Amyloid-β Aggregation.**
Nowicka A, Szczepankiewicz AA, Jakiewicz A, Filipak A, Barcikowska M, Elbaum D.

**Intra-Familial Clinical Heterogeneity due to FTLD-U with TDP-43 Proteinopathy Caused by a Novel Deletion in Progranulin Gene (PGRN).**
Gabryelewicz T, Masellis M, Berdyski M, Bilbao JM, Rogaeova E, St George-Hyslop P, Barczak A, Czyzewski K, Barcikowska M, Wszolek Z, Black SE, Zekanowski C.

**Cell cycle regulation distinguishes lymphocytes from sporadic and familial Alzheimer's disease patients.**

**Association of pyridoxal kinase and Parkinson disease.**

**Increased CD44 gene expression in lymphocytes derived from Alzheimer disease patients.**
Uberti D, Cenini G, Bonini SA, Barcikowska M, Styczynska M, Szymbinska A, Memo M.

**Mitochondrial transcription factor A variants and the risk of Parkinson's disease.**

**Calbindin-1 association and Parkinson's disease.**

**GRN 3'UTR+78 C>T is not associated with risk for Parkinson's disease.**