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Familial Alzheimer’s Disease as a research model for Alzheimer’s: A pathological perspective

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Alzheimer’s Disease

Auguste D

β Amyloid Plaques

Neurofibrillary Tangles

Brain Atrophy in Advanced Alzheimer’s Disease

Normal

AD

http://static.ow.ly/photos/original/3XGIP.jpg
FAD vs SAD

pTau in FAD

A

SAD

FAD

FC

TC

PC

OC

CB

B

C

AT8 immunosignal (μm² x 1000)

AT8 immunosignal (μm² x 1000)

FC

TC

PC

OC

CB

%
TDP43 in FAD

Phospho TDP 43

SAD

FAD

- TDP-43
- GAPDH
- pTDP-43
- GAPDH
- FUS
- GAPDH

Control (Ctrl), SAD, FAD
de novo generation of Aβ in PS1E280A brain tissue

Cerebellar dysfunction in PS1E280A FAD

Mitochondrial dysfunction in PS1 mutations

B. % of Abnormal Mitochondria in Hippocampus

C. % of Abnormal Mitochondria in Cortex

E. ETS Capacity

F. Proton Leak
### Differences between Sporadic and Familial Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SAD</th>
<th>PS1-FAD</th>
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<tbody>
<tr>
<td>Beta Amyloid Pathology</td>
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<tr>
<td>Increased Beta Amyloid 1-42</td>
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<td>Cerebellar Beta Amyloid pathology</td>
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<tr>
<td>Cerebellar symptoms</td>
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<td>Increased IDE in plaques</td>
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<td>Neprylisin in plaques</td>
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<tr>
<td>Hyperphosphorylated Tau Pathology</td>
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<tr>
<td>Cerebellar pTau pathology</td>
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<tr>
<td>Elevated BACE1 levels</td>
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<td>Increased beta APP-CTF levels</td>
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<tr>
<td>Increased Purkinje cells loss</td>
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<td>Cerebellar abnormal mitochondria</td>
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<td>Dysregulation of Ca2+ channels</td>
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<td>γ-secretase dysfunction</td>
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<tr>
<td>Increased Beta Amyloid 1-38 (IHC)</td>
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<td>Increased 38/42 ratio (IHC)</td>
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<td>Increased 40/43 ratio (IHC)</td>
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<td>Increased 42/40 ratio (IHC)</td>
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<tr>
<td>TDP43 Pathology (IHC)</td>
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<td>Increased insoluble pTDP43</td>
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</table>
Aβ pathology according to age of onset in PS1E280A FAD

A

6E10 Immunohistochemistry

B

6E10 Immunosignal

C

Small Oligomers

Monomers

D

Aβ Peptides

E

Aβ Peptides de Novo
pTau pathology according to age of onset in PS1E280A FAD

AT8 Immunohistochemistry

SAD | EOFAD | AOFAD | LOFAD
---|------|------|------
Frontal Cortex | Temporal Cortex | Parietal Cortex | Occipital Cortex

B

AT8 Immunosignal

D

Soluble

Insoluble

[Graphs and images of immunohistochemical and Western blot analyses]

Total Tau

pTau-S400 / Tau

A.U. | Ratio

SAD | EOFAD | AOFAD | LOFAD
---|------|------|------

** | ***

[Additional statistical analyses and data visualization]
1. Are SAD and FAD the same disease?

2. Have all FAD (or even all PS1 FAD) the same pathology?

3. At least are all E280A cases the same from a pathological point of view?
Primary → APP Processing Dysfunction → Metabolic Dysfunction → Inflammation / Immunity → Homeostasis / Turnover → Environment → pTau Pathology → Aβ Pathology → Endpoint Pathology

Birth → Cognitive impairment → Death
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