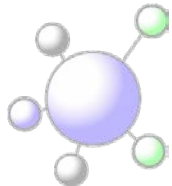




Global Health Conference FIU Miami May 7-9, 2019

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

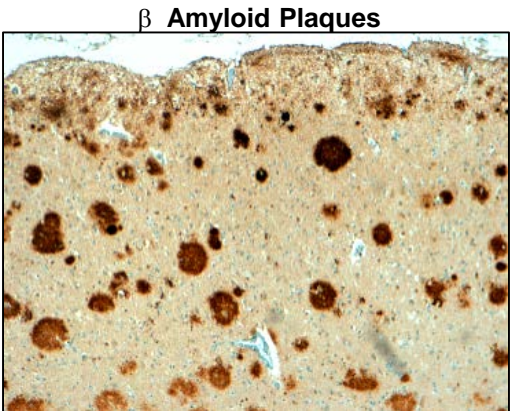


Dr. Med. Diego Sepulveda-Falla
MoNeA - Gruppenleiter

Alzheimer's Disease

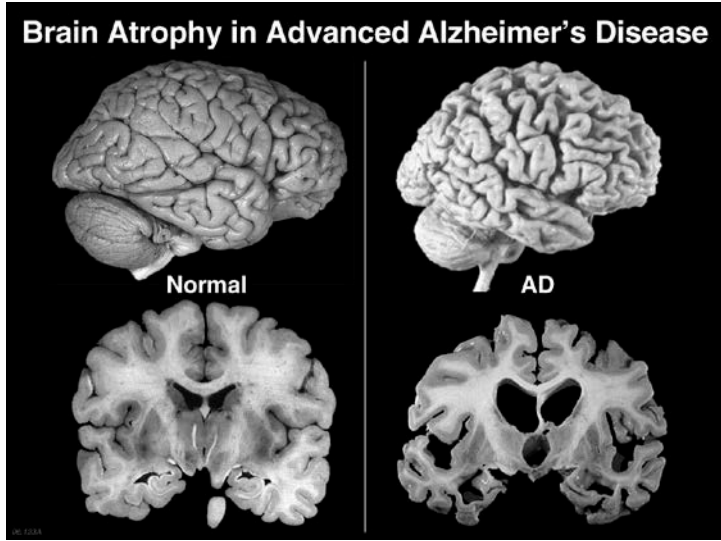
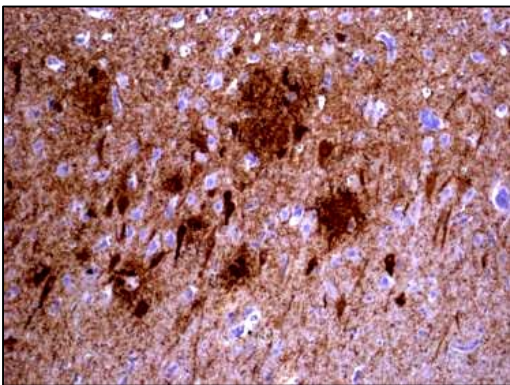


Auguste D



β Amyloid Plaques

Neurofibrillary Tangles



Brain Atrophy in Advanced Alzheimer's Disease

Normal

AD

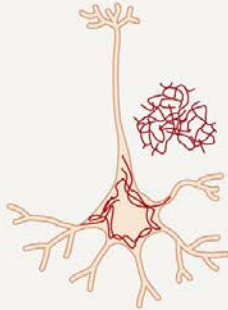
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Biochemical phase

Abnormal A β

Quantitative, but mainly qualitative changes

- A β -conformational changes
- A β -oligomers
- A β -spreading
- A β -membrane interactions
- A β -receptor/protein interactions
- A β -oxidative stress



Abnormal tau

- Phosphorylation
- Tau-conformational changes
- Tau-oligomers
- Tau-spreading
- Tau-membrane interactions
- Tau-protein interactions
- Tau-mislocalisation

Aggregate/proteopathic stress
Clearance problems
Proteostasis failure because of aging

Cellular phase

Neurovascular unit

- Vascular blood brain barrier
- CSF barrier
- G-lymphatic system
- Clearance dysfunction
- APP metabolism

Pericyte
Endothelium



Microglia

- Beneficial and destructive inflammation
- Clearance dysfunction
- Immune responses

Glioneuronal unit

Astroglia



Oligodendrocyte

- Myelin breakdown
- Lipid metabolism

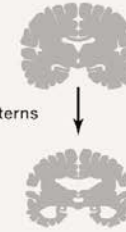
Neuron

Neuron

Chronic inflammation
Chronic circuitry imbalances
Cell failure and cell death

Clinical phase

- MRI changes
- Hippocampal shrinkage
- CSF alterations



Neuron
Excitatory / inhibitory
Short term and long term plasticity
Homeostatic scaling

- Alterations in connective patterns
- Default pathway
- Functional compensation
- Alterations in refined cognitive tests

Astroglia

- Astrogliosis
- Atrophy
- Neuronal plasticity
- Clearance dysfunction
- Lipid metabolism
- Immune responses



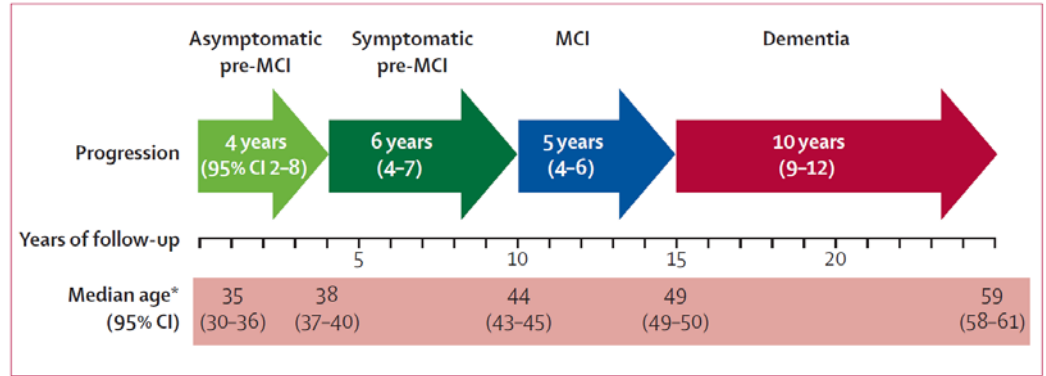
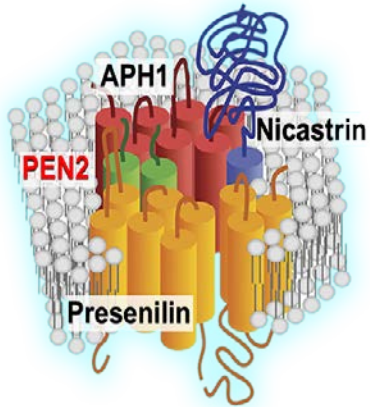
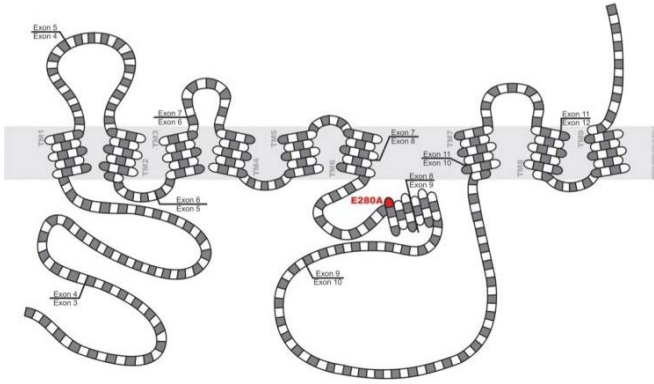
- Spatial memory
- Helplessness dysfunction
- Dementia

10

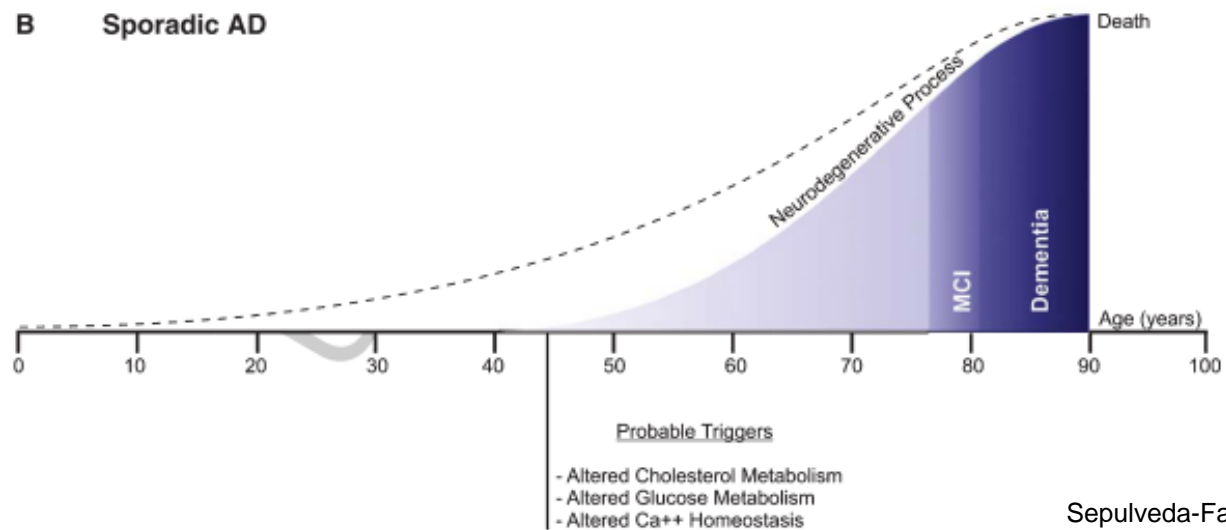
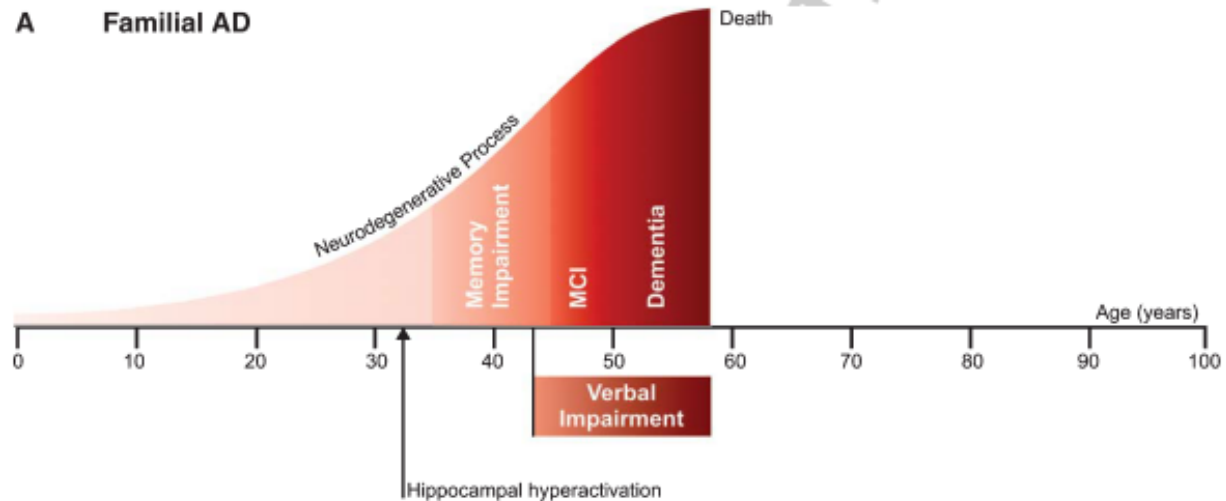
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Years

Presenilin 1

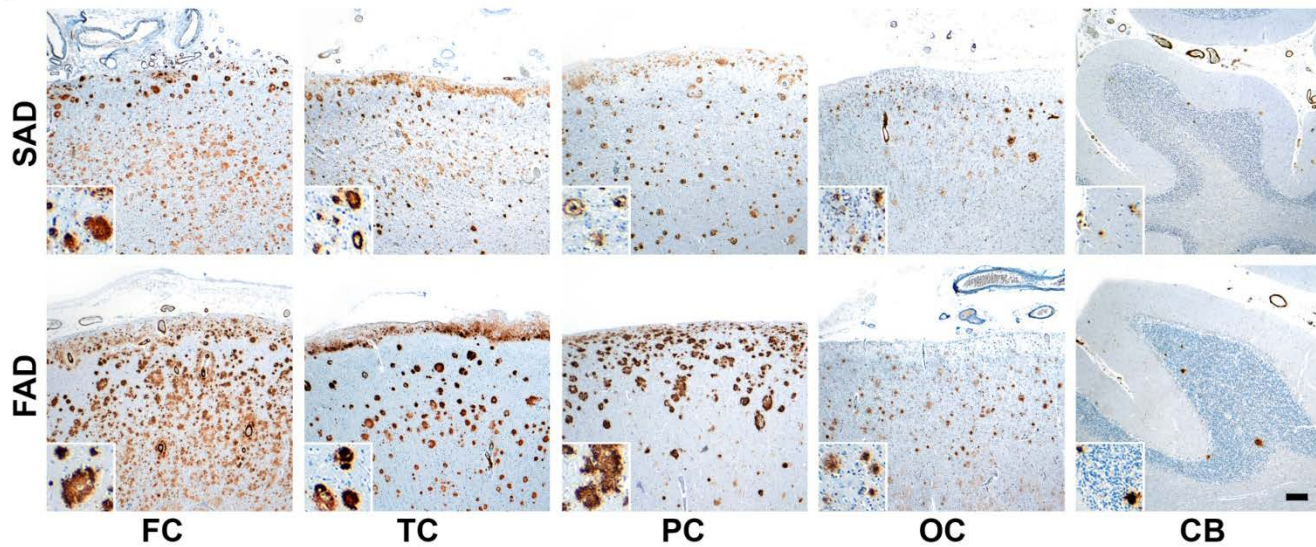


FAD vs SAD

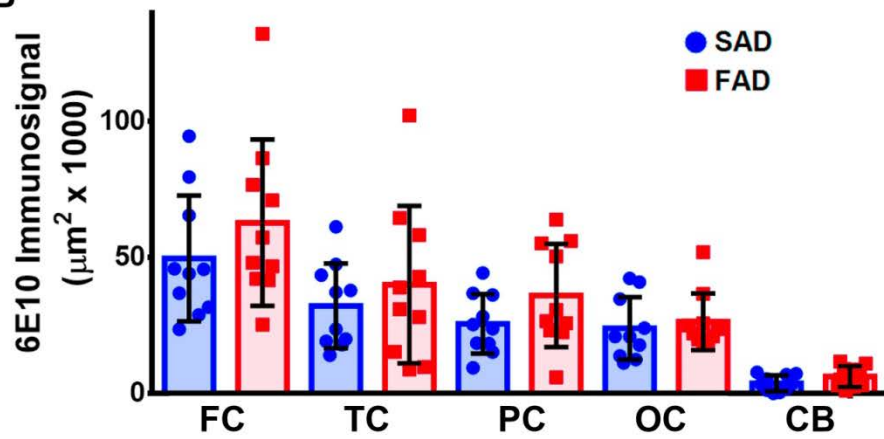


Aβ in FAD

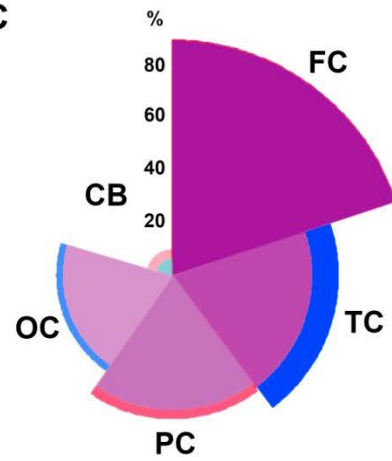
A



B

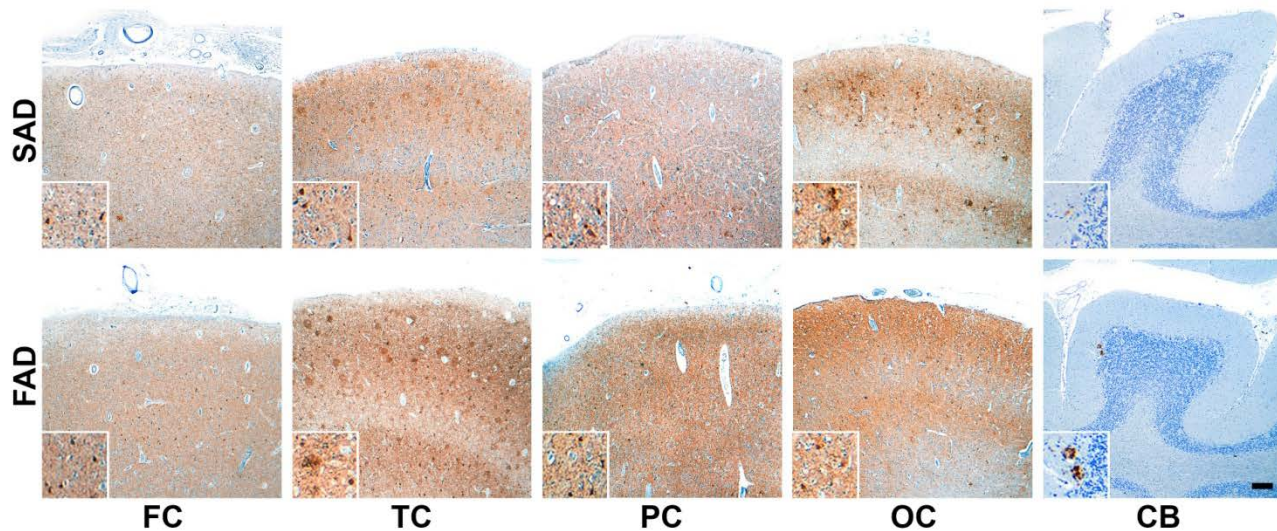


C

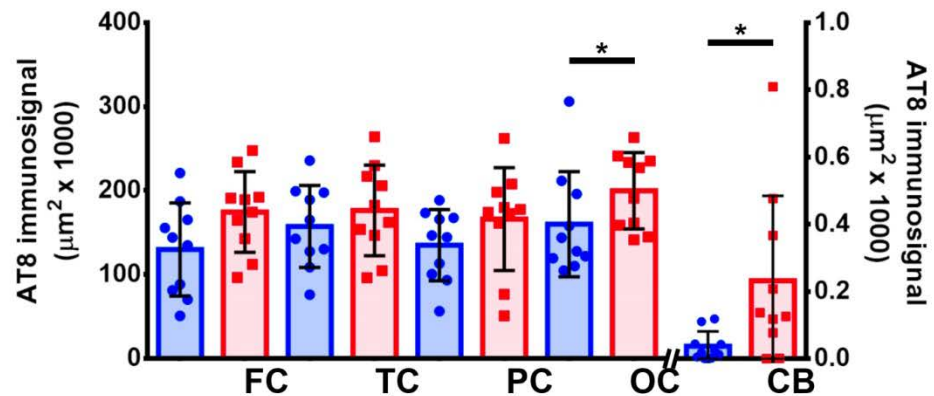


pTau in FAD

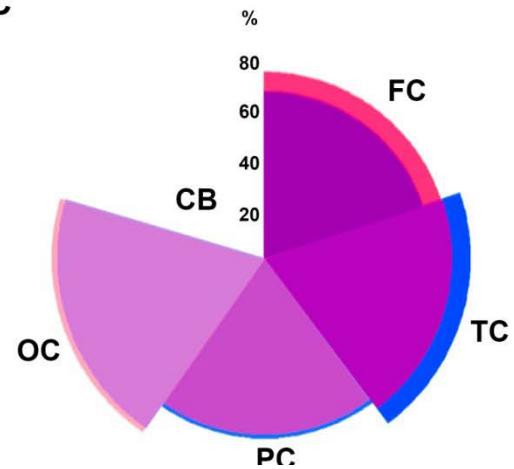
A



B

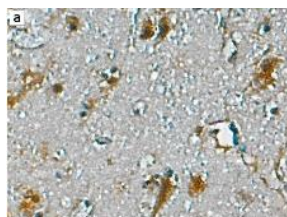
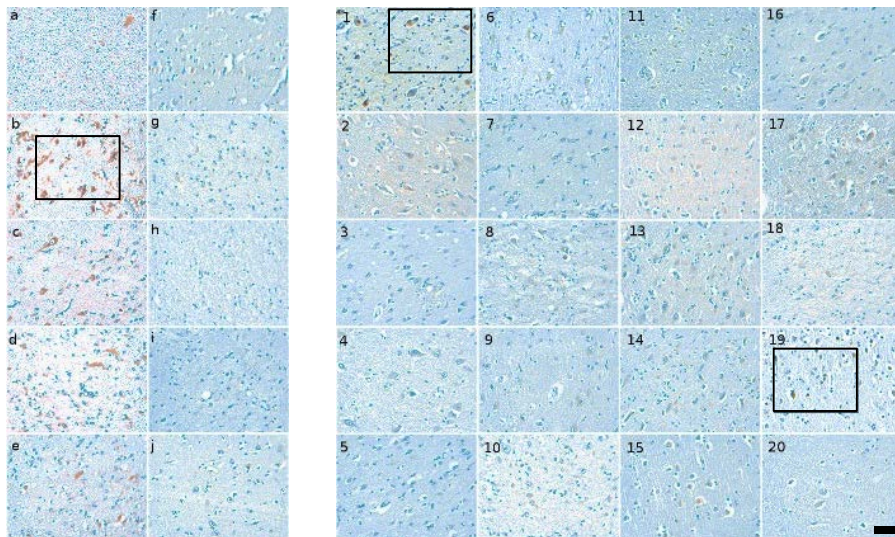


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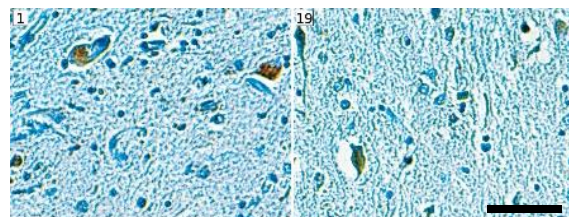


TDP43 in FAD

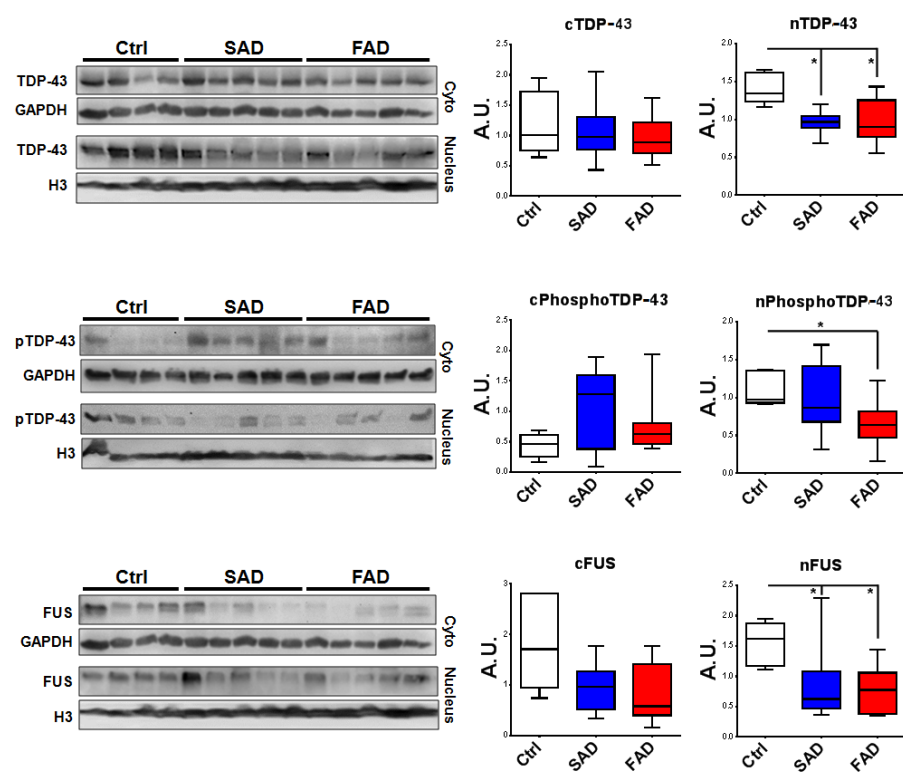
Phospho TDP 43



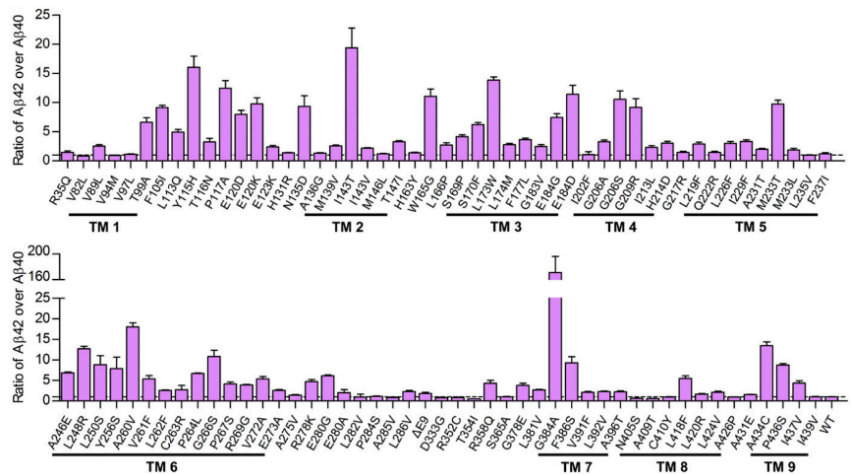
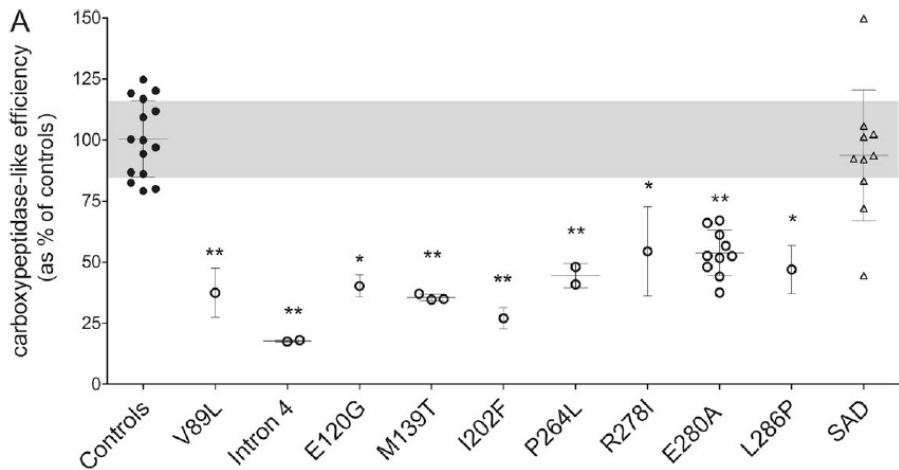
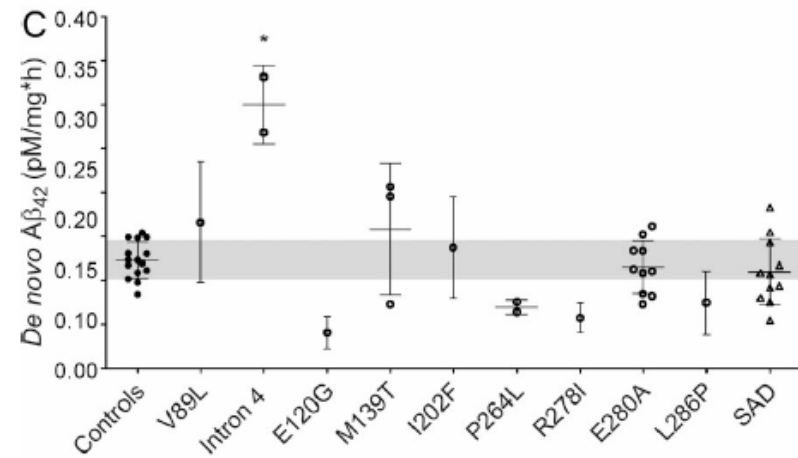
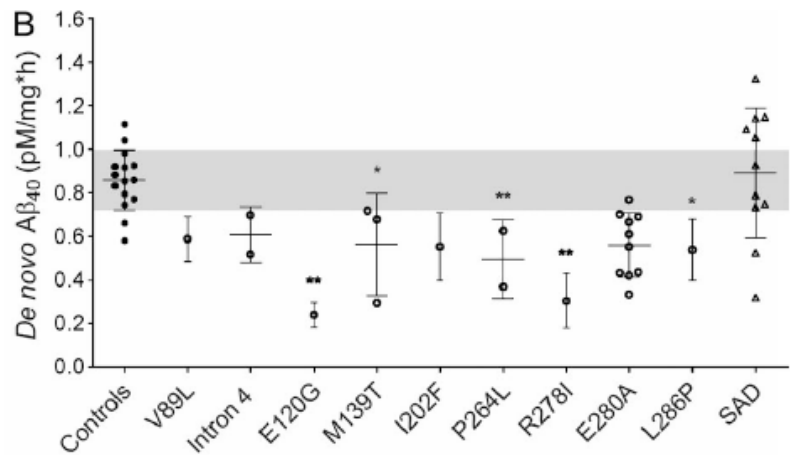
SAD



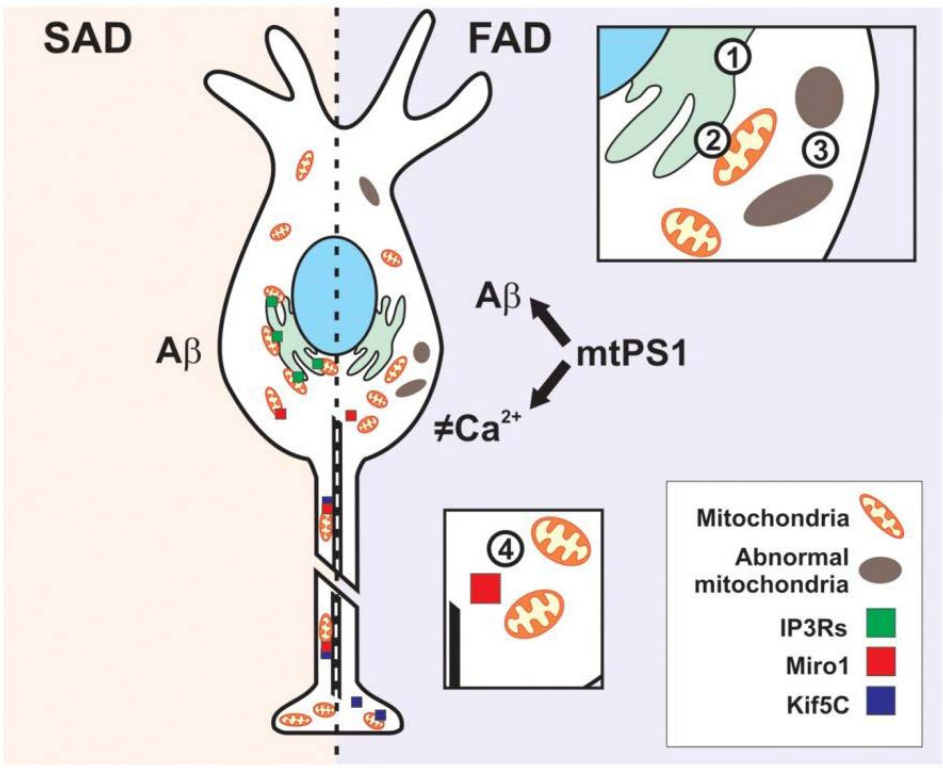
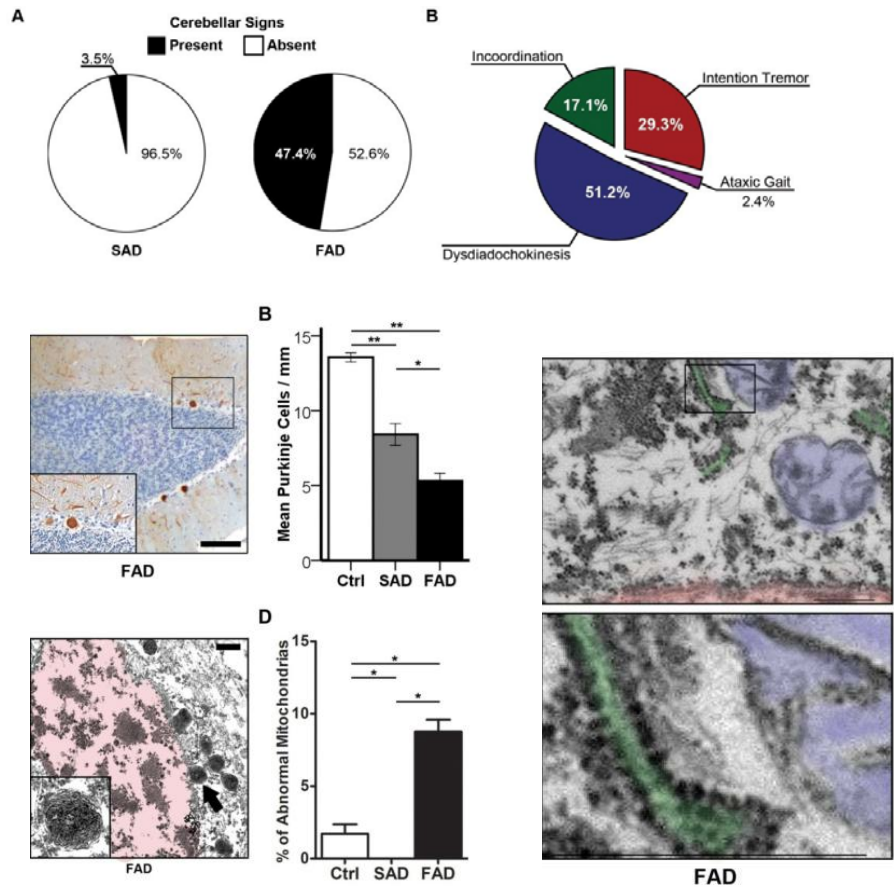
FAD



de novo generation of A β in PS1E280A brain tissue

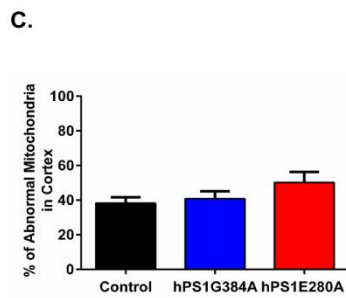
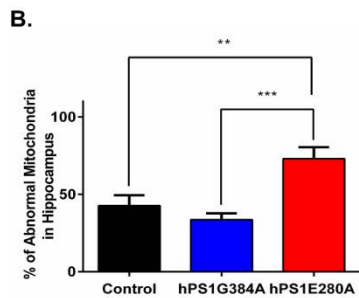
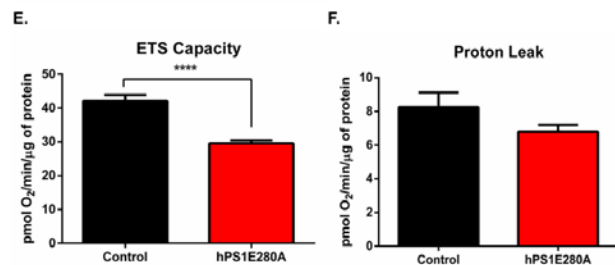
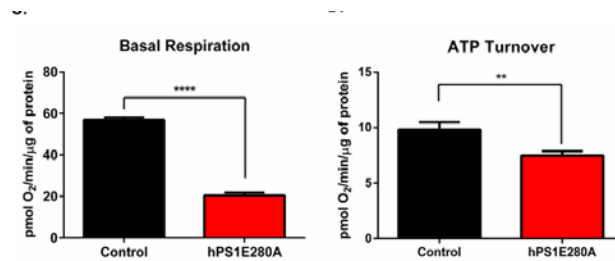
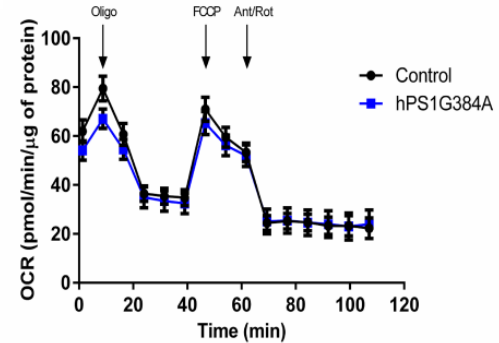
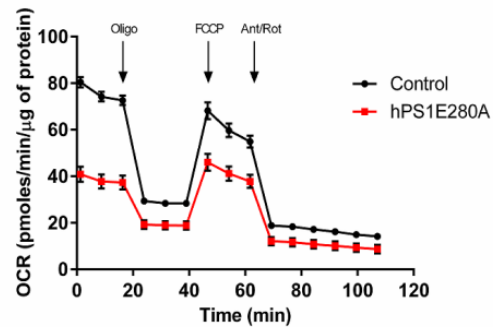
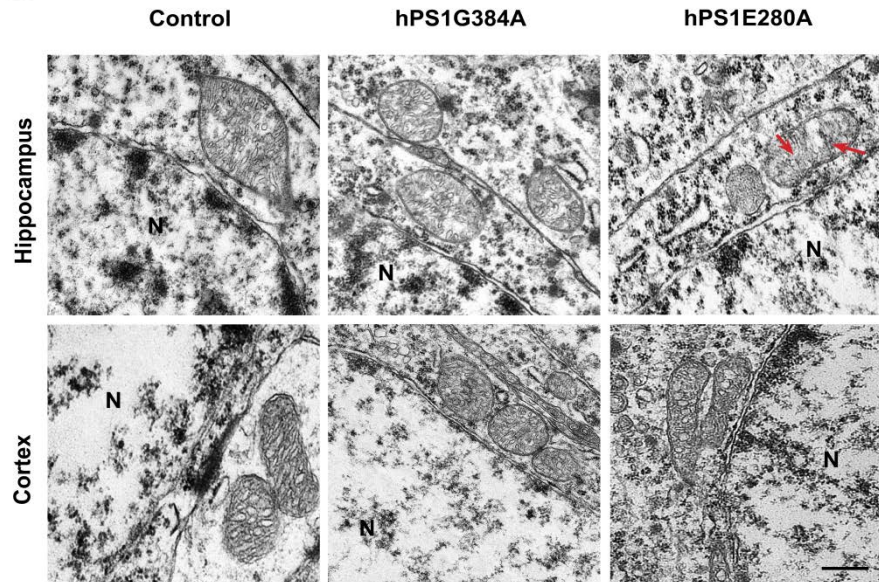


Cerebellar dysfunction in PS1E280A FAD



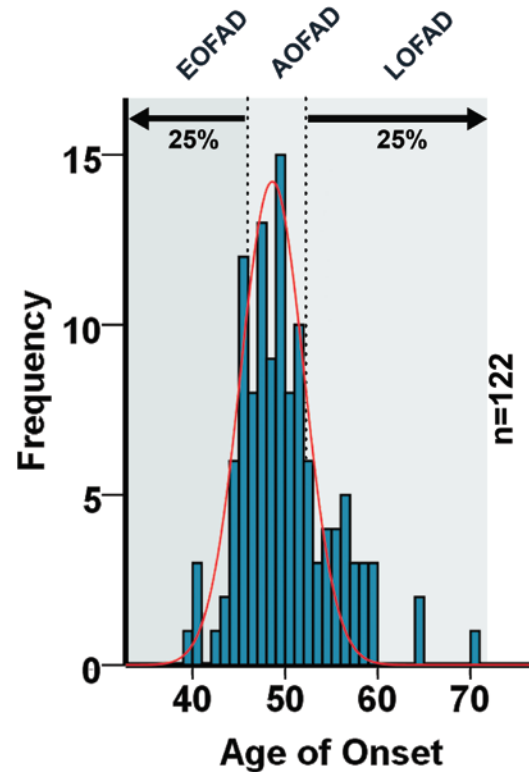
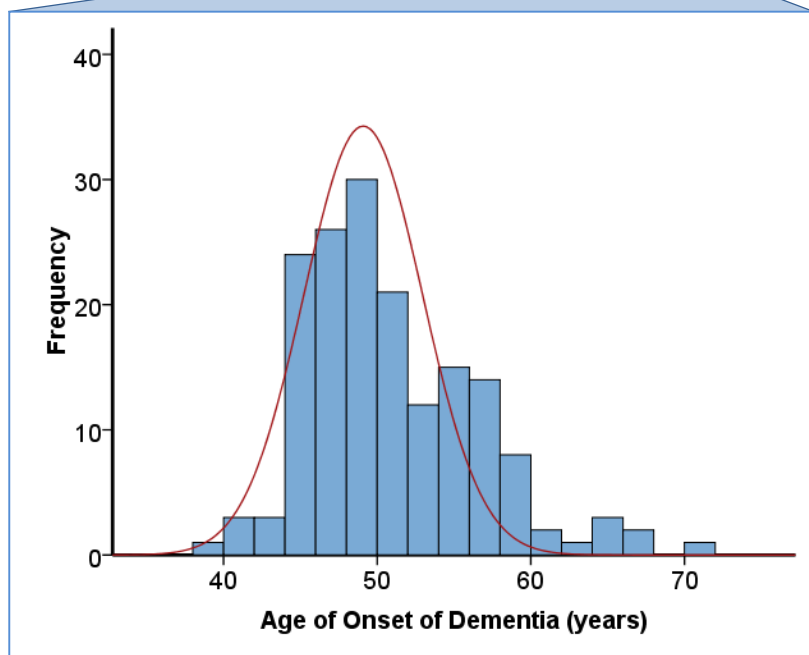
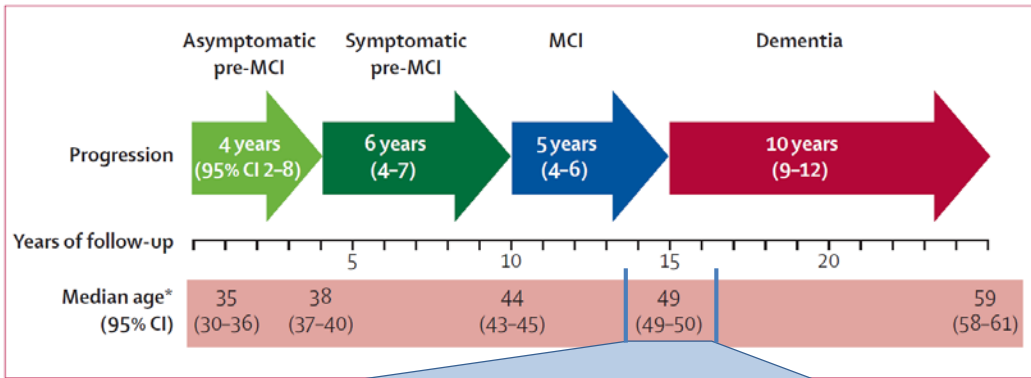
(Modified from Sepulveda-Falla D et al. J Clin Invest, 2014)

Mitochondrial dysfunction in PS1 mutations

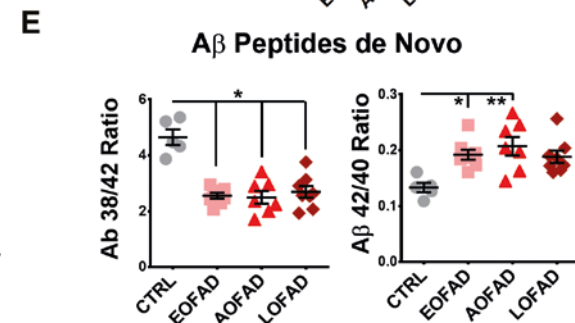
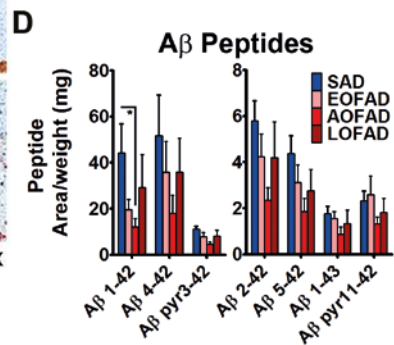
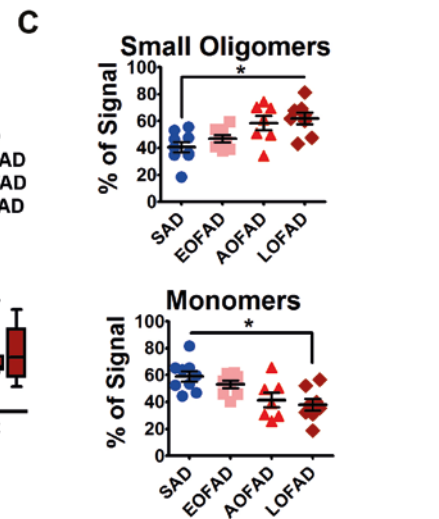
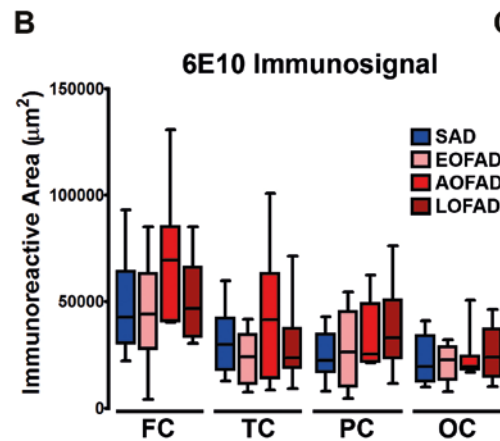
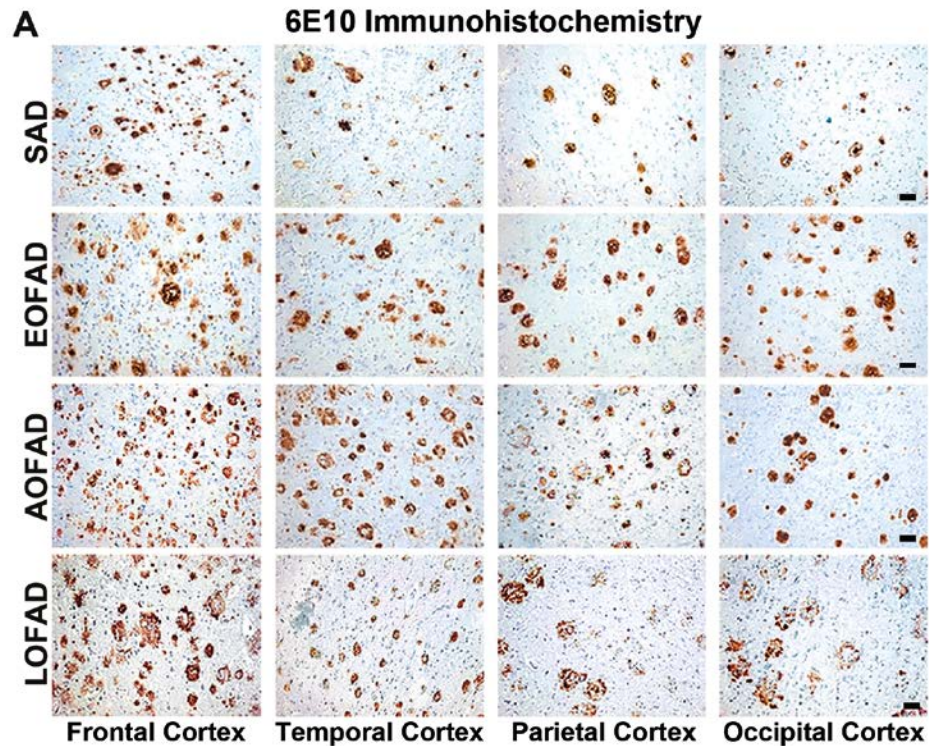


Differences between Sporadic and Familial Alzheimer's Disease

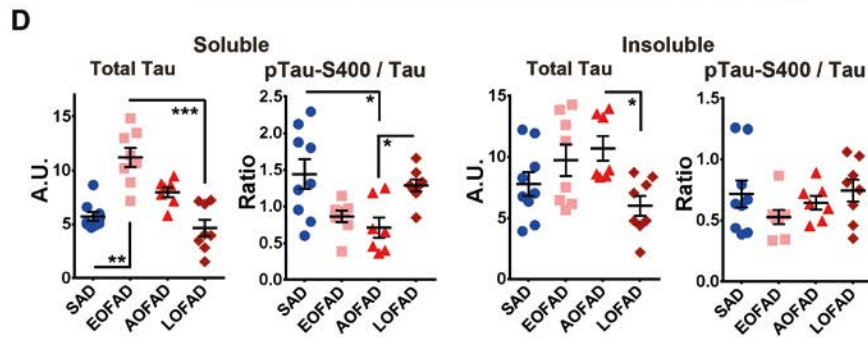
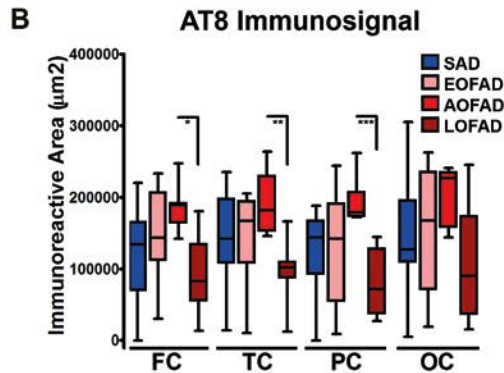
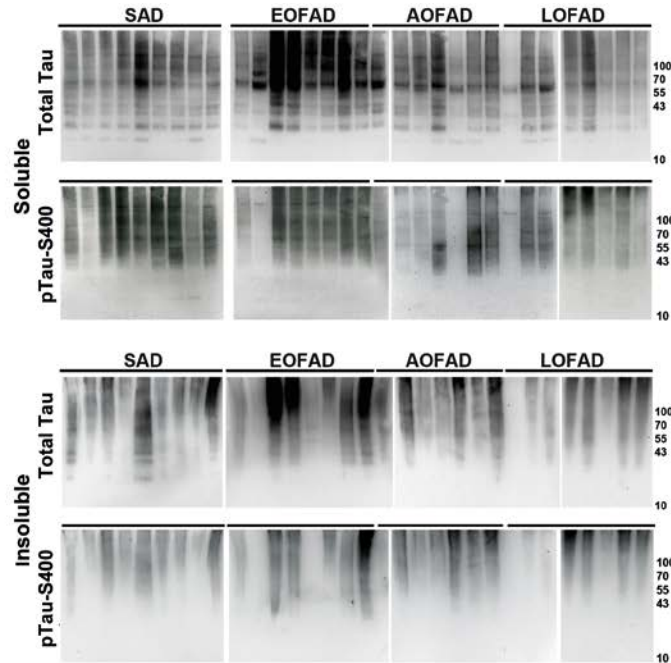
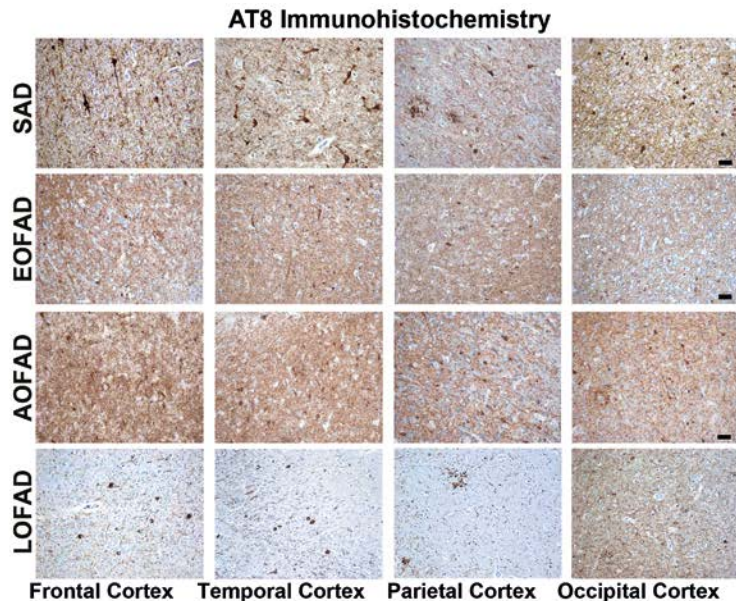
Phenotype	SAD	PS1-FAD
Beta Amyloid Pathology	Blue	Red
Increased Beta Amyloid 1-42	Blue	Red
Cerebellar Beta Amyloid pathology	Blue	Red
Cerebellar symptoms	Blue	Red
Increased IDE in plaques	Blue	White
Neprylisin in plaques	Blue	White
Hyperphosphorylated Tau Pathology	Blue	Red
Cerebellar pTau pathology	Blue	Red
Elevated BACE1 levels	Blue	White
Increased beta APP-CTF levels	Blue	Red
Increased Purkinje cells loss	Blue	Red
Cerebellar abnormal mitochondria	Blue	Red
Dysregulation of Ca ²⁺ channels	Blue	Red
γ-secretase dysfunction	Blue	Red
Increased Beta Amyloid 1-38 (IHC)	Blue	White
Increased 38/42 ratio (IHC)	Blue	White
Increased 40/43 ratio (IHC)	White	Red
Increased 42/40 ratio (IHC)	White	Red
TDP43 Pathology (IHC)	Blue	White
Increased insoluble pTDP43	Blue	White

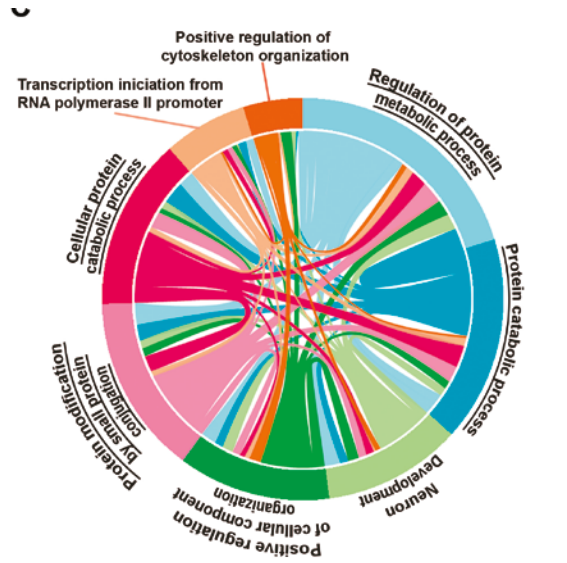
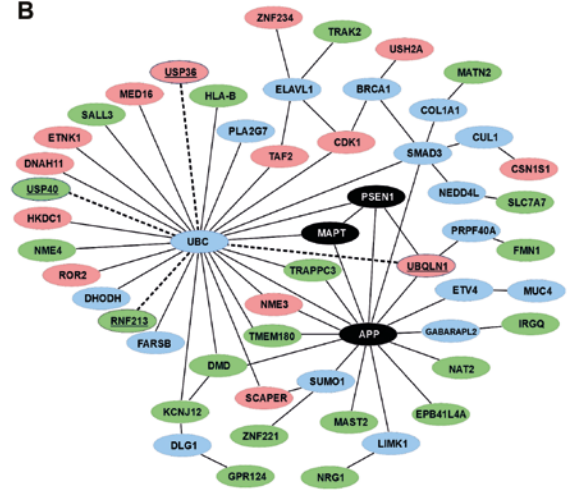
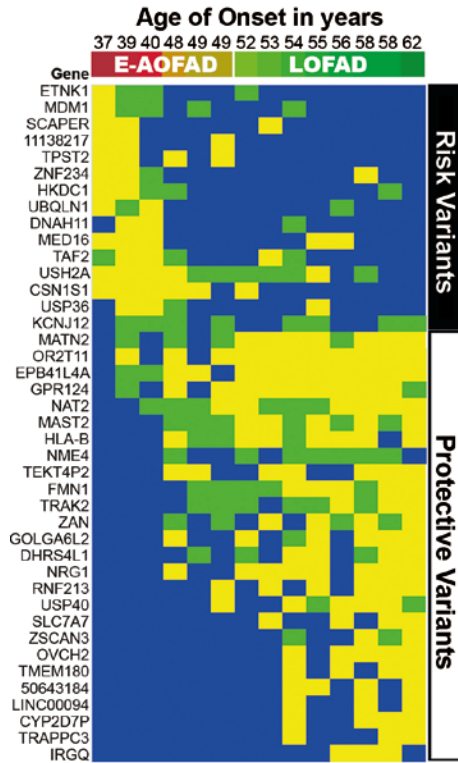
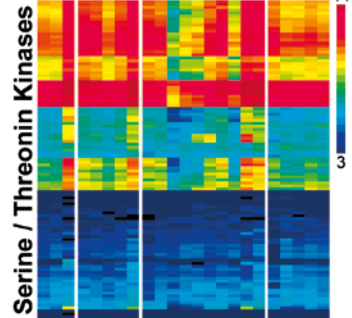
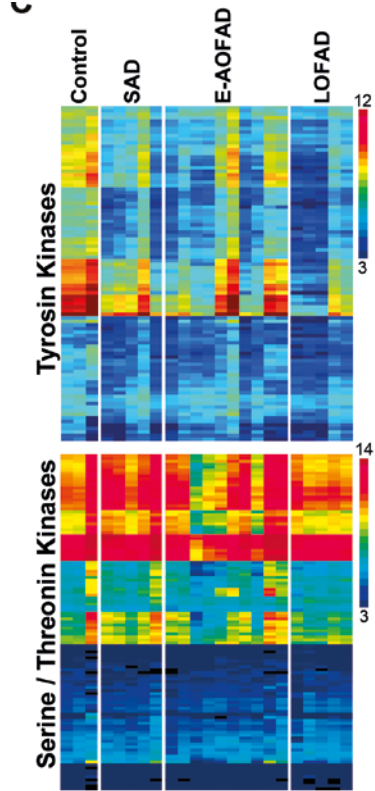
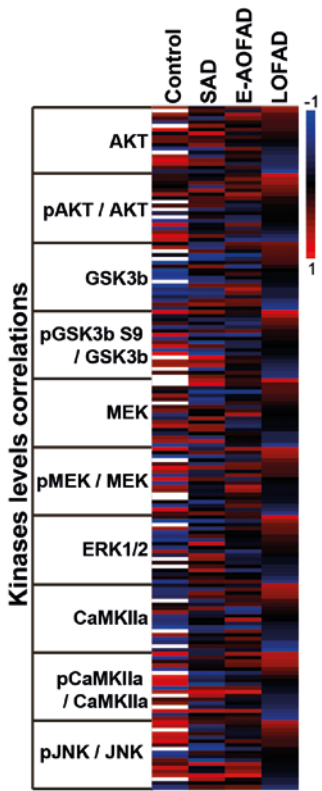


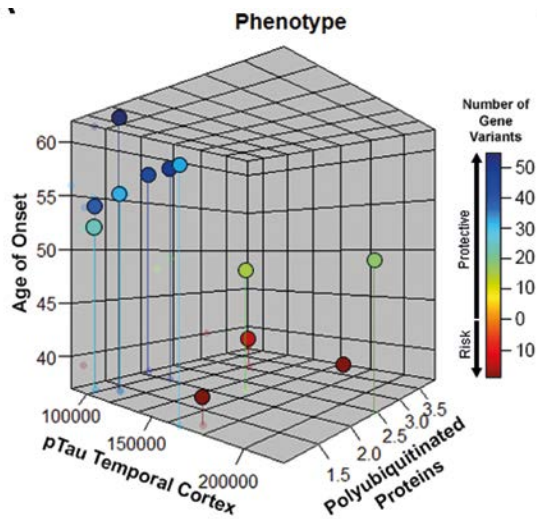
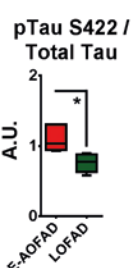
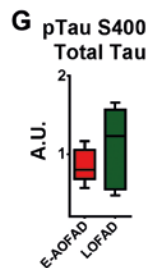
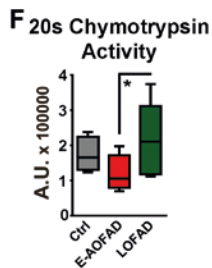
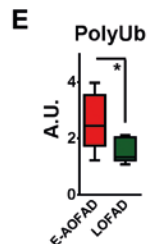
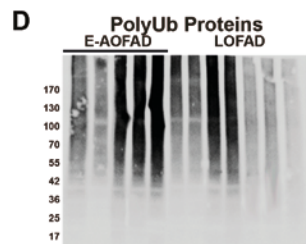
A β pathology according to age of onset in PS1E280A FAD



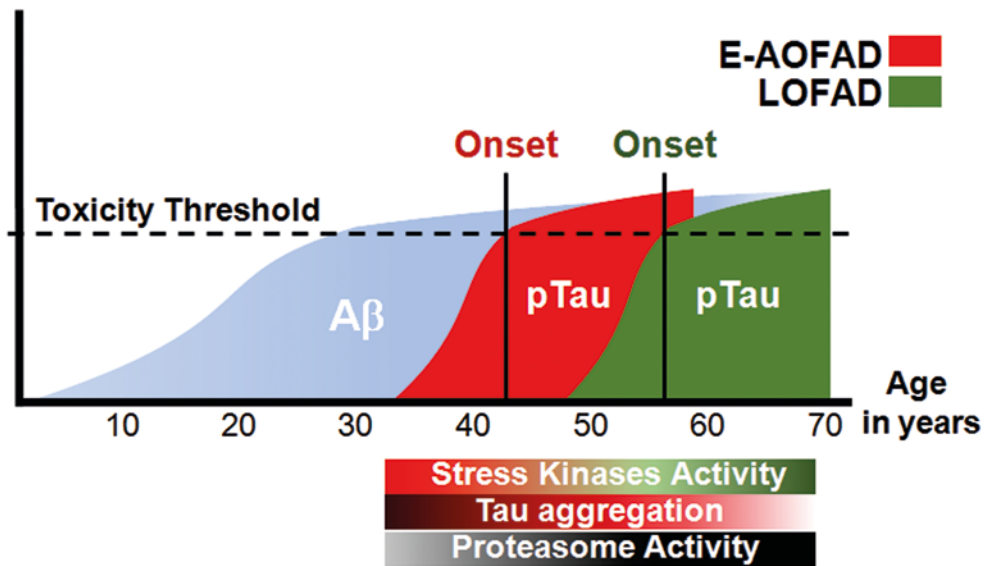
pTau pathology according to age of onset in PS1E280A FAD

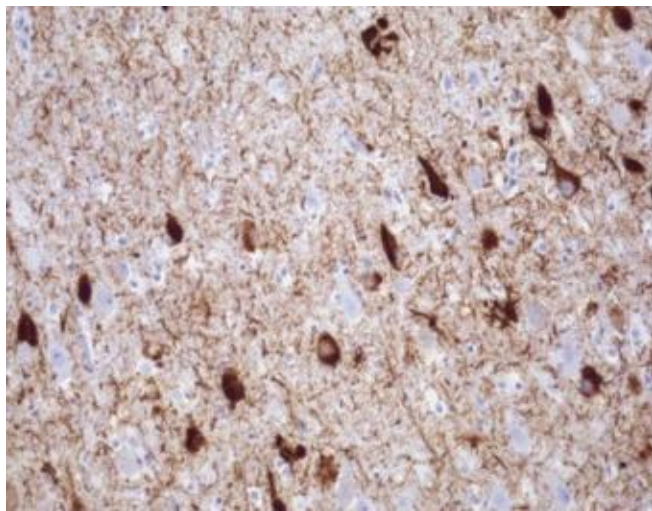
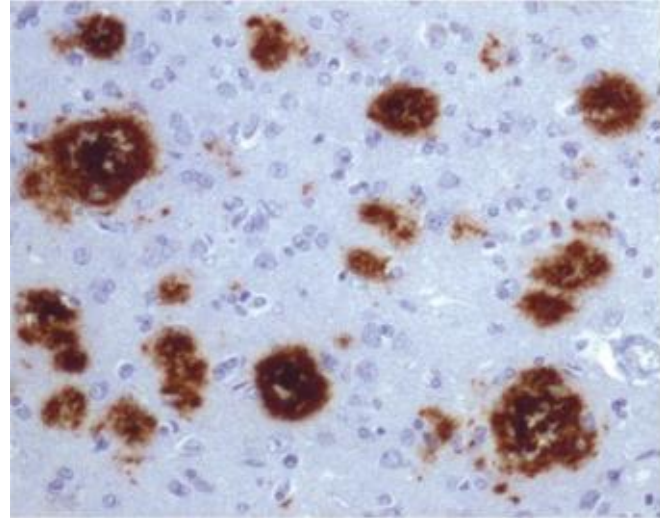






Dementia Onset model in PSEN1 - E280A FAD





2018 Alzheimer's Drug Development Pipeline

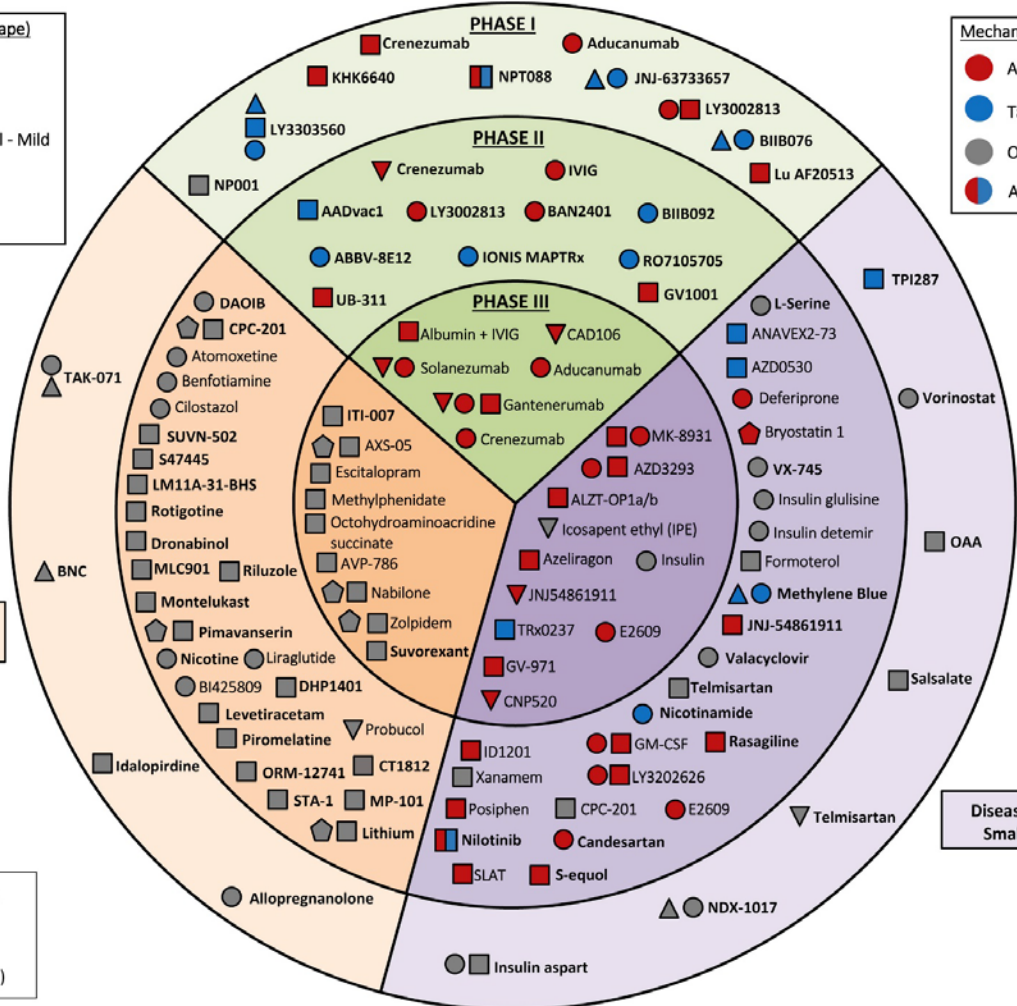
Subject Characteristics (Shape)

- △ Healthy Volunteers
- ▽ Preclinical
- Prodromal/ Prodromal - Mild
- Mild - Moderate
- ⬠ Severe

Disease-Modifying Immunotherapy

Mechanism of Action (Color)

- Amyloid-related
- Tau-related
- Others
- Amyloid & Tau related



Symptom-Reducing Small Molecule

Disease-Modifying Small Molecule

Undisclosed Mechanism

- △ RGN1016 (Phase I)
- BAC (Phase II)
- AGN-242071 (Phase I)

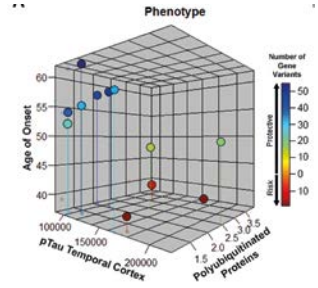
1. Are SAD and FAD the same disease?

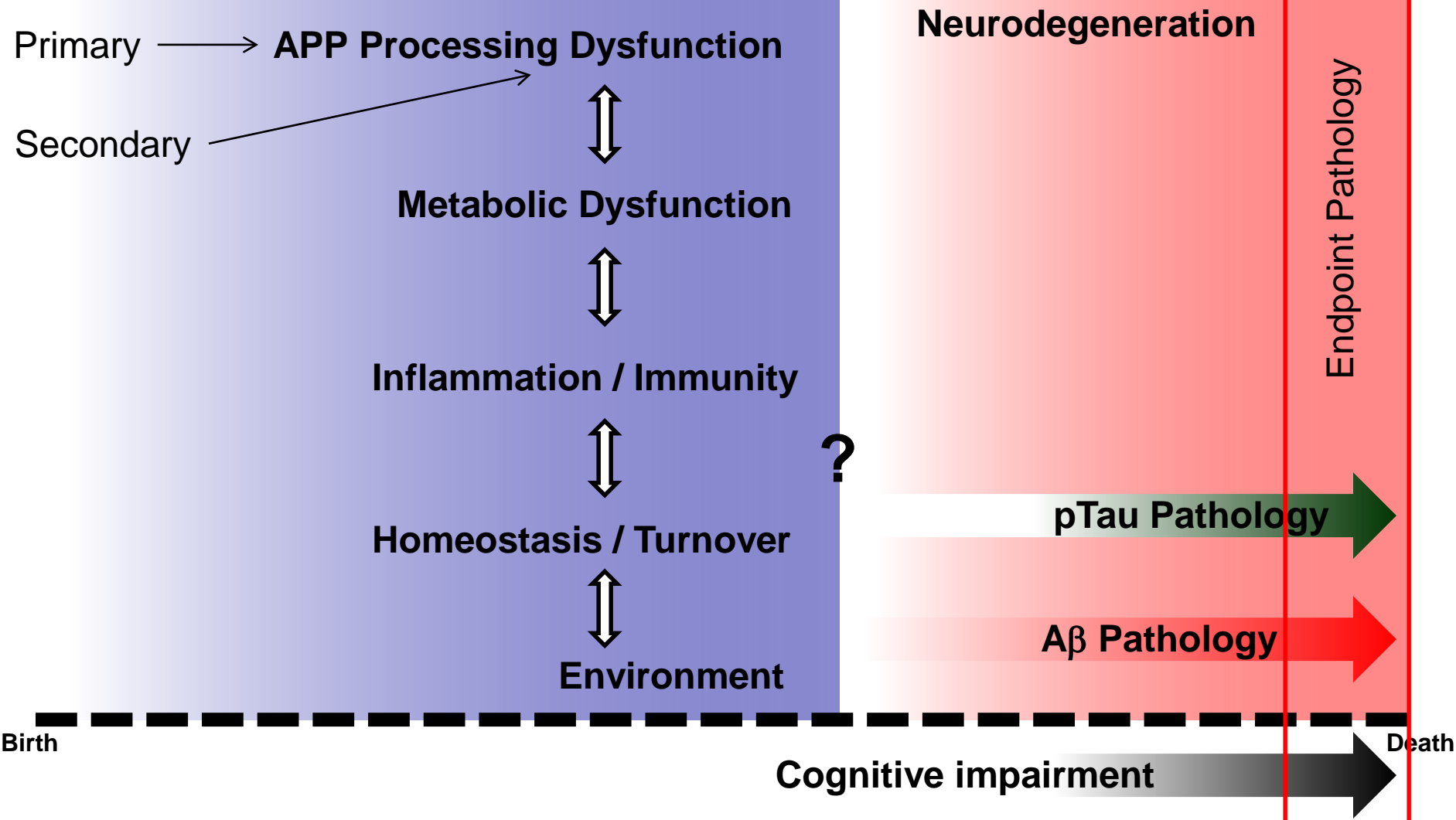
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Nephrin in plaques	Blue	Red
Hyperphosphorylated Tau Pathology	Blue	Red
Cerebellar pTau pathology	Blue	Red
Elevated BACE1 levels	Blue	Red
Increased beta APP-CTF levels	Blue	Red
Increased Purkinje cells loss	Blue	Red
Cerebellar abnormal mitochondria	Blue	Red
Dysregulation of Ca2+ channels	Blue	Red
γ-secretase dysfunction	Blue	Red
Increased Beta Amyloid 1-38 (IHC)	Blue	Red
Increased 38/42 ratio (IHC)	Blue	Red
Increased 40/43 ratio (IHC)	Blue	Red
Increased 42/40 ratio (IHC)	Blue	Red
TDP43 Pathology (IHC)	Blue	Red
Increased insoluble pTDP43	Blue	Red

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?





Acknowledgements

Germany University of Hamburg

*Alvaro Barrera-Ocampo
*Liliana Rojas-Charry
*Sergio Calero-Martinez
*Marcus Broeckmayer
*Tim Versteegen
Berta Puig
*Felix Dinkel
Beata Szalay
Markus Glatzel
Diagnostic team



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Brain Bank team
Andres Villegas
Francisco Lopera
Jorge Ivan Velez
Claudio Mastronardi
Mauricio Arcos-Burgos



Spain University of Barcelona

Isidro Ferrer

Belgium KU Leuven

Lucia Chavez-Gutierrez
Bart de Strooper

Sweden University of Gothenburg

Erik Portelius
Kaj Blennow



National Institute of
Neurological Disorders
and Stroke



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Forschung und Gleichstellung



Bundesministerium
für Bildung
und Forschung



Gracias !