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Faculty of Medicine and Pharmacy Casablanca
Laboratory of Medical Genetics and Molecular Pathology

Proteomics aspects of Morrocan cases with Alzheimer's Disease.

Nadia El Kadmiri

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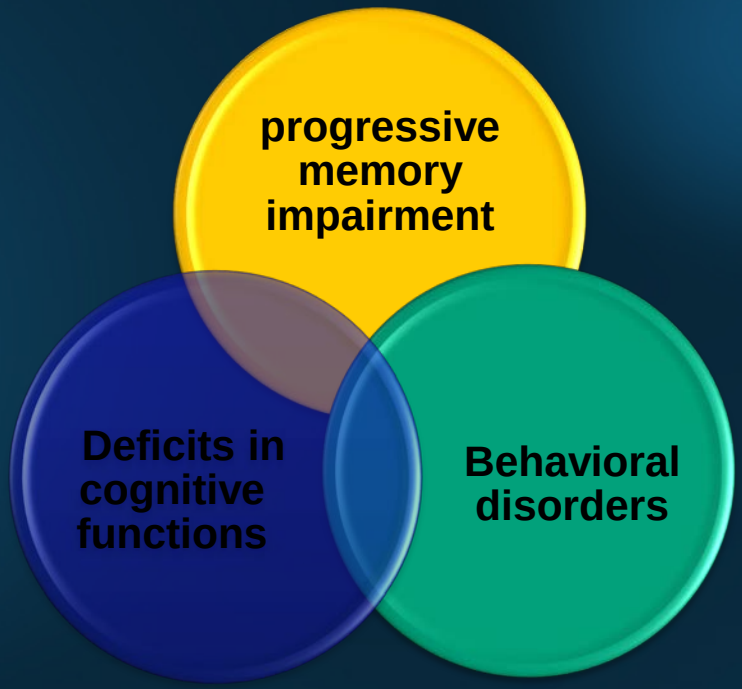
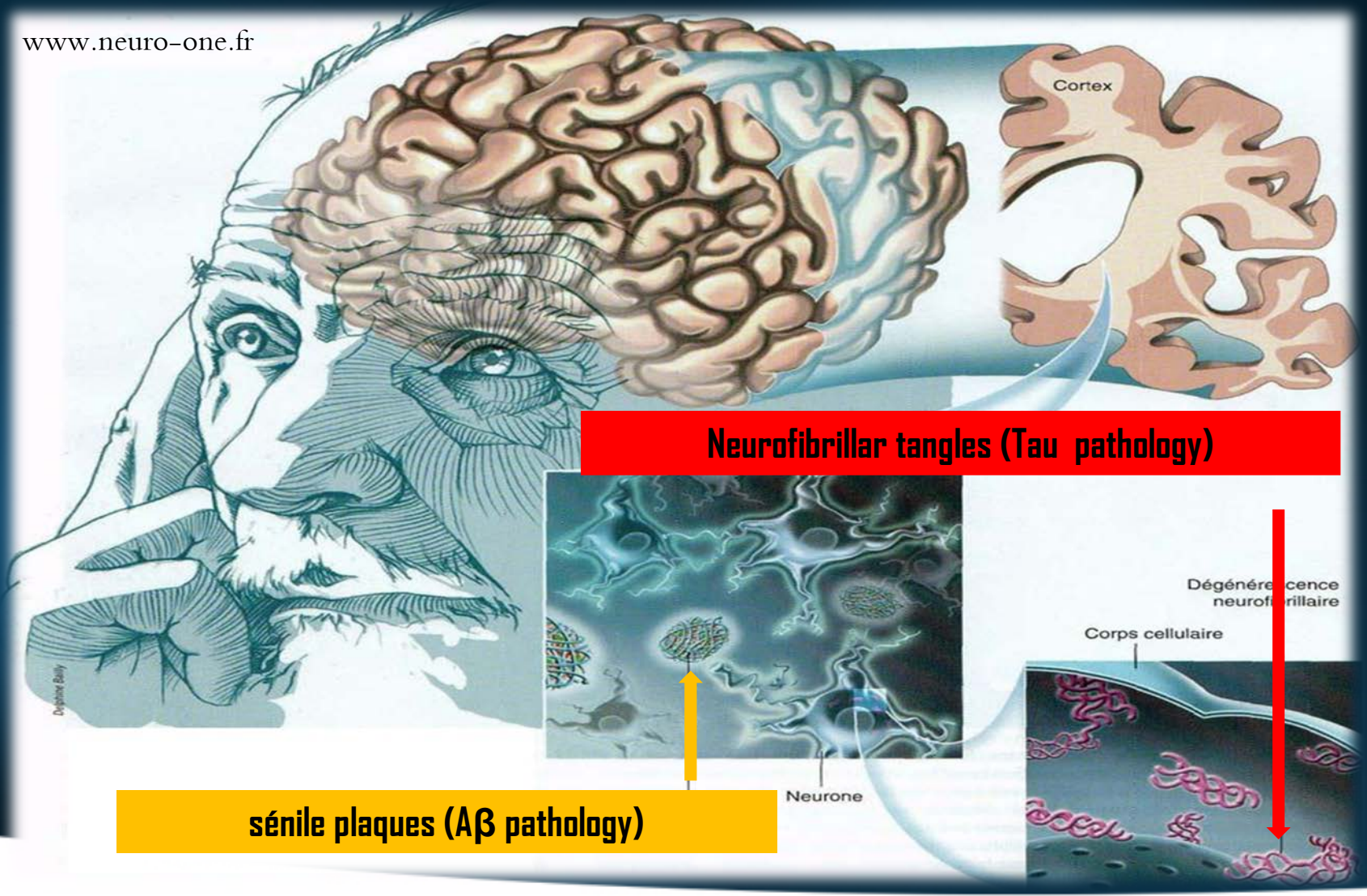
Intoduction

- Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Clinically characterized by :



(Julien CHAPUIS,2008)

Introduction



Introduction

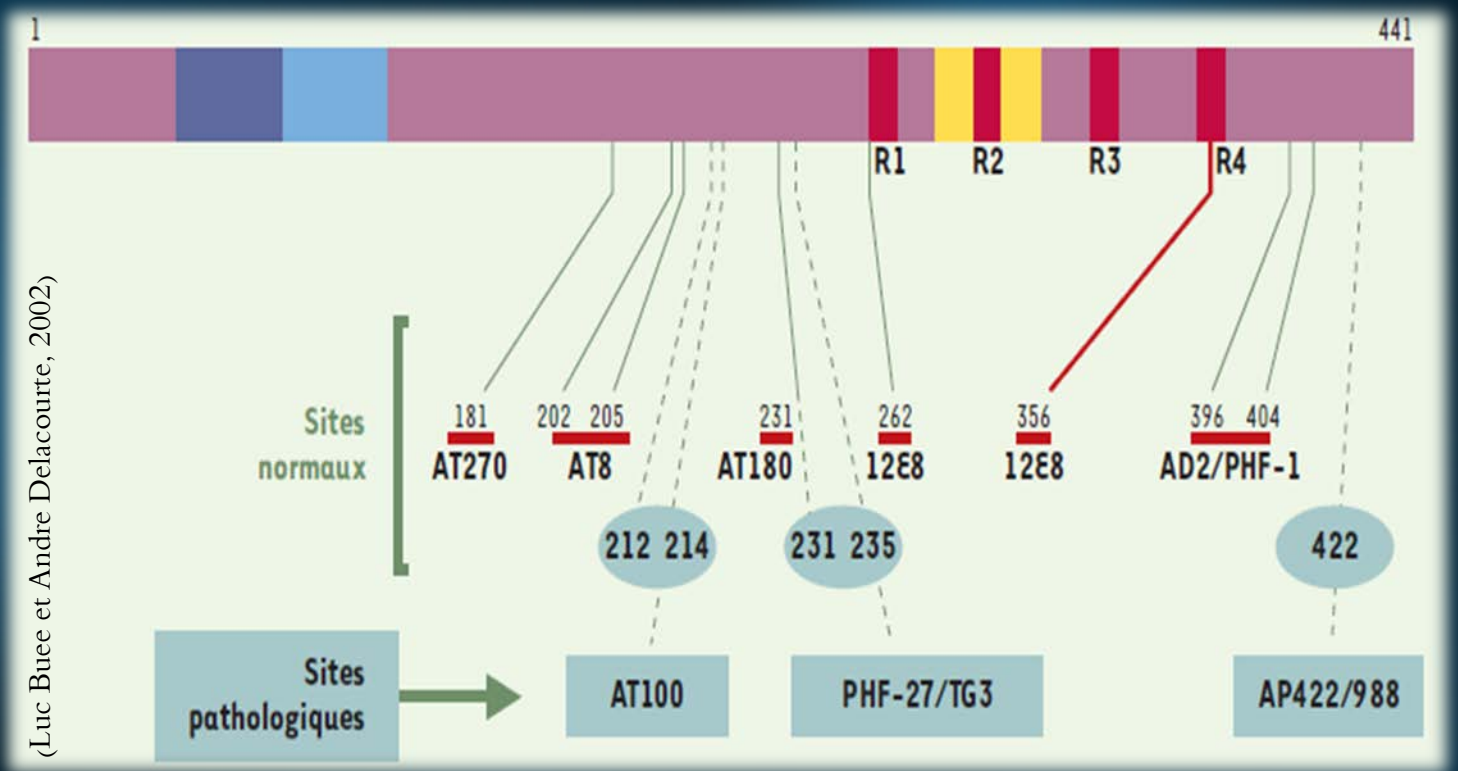
Table 1 : Genetic factors

Chromosome	gene	% due to mutation	Age of Onset	Form of AD
21	APP	0,4%	45–60	Early–Onset Familial AD (EOAD) /autosomal dominant inheritance)
14	PS1	5,6%	35–60	
1	PS2	0,1%	35–60	
19	ApoE ε4	65%	>55	late–onset form of AD(LOAD)/Risk factor
Others : Chrom 11: Sortilin receptor Chrom 8 : Clusterin Chrom 1 : Complement component receptor 1				Risk Factors

(Dominique Campion et Didier Hannequin, 2006)

Introduction

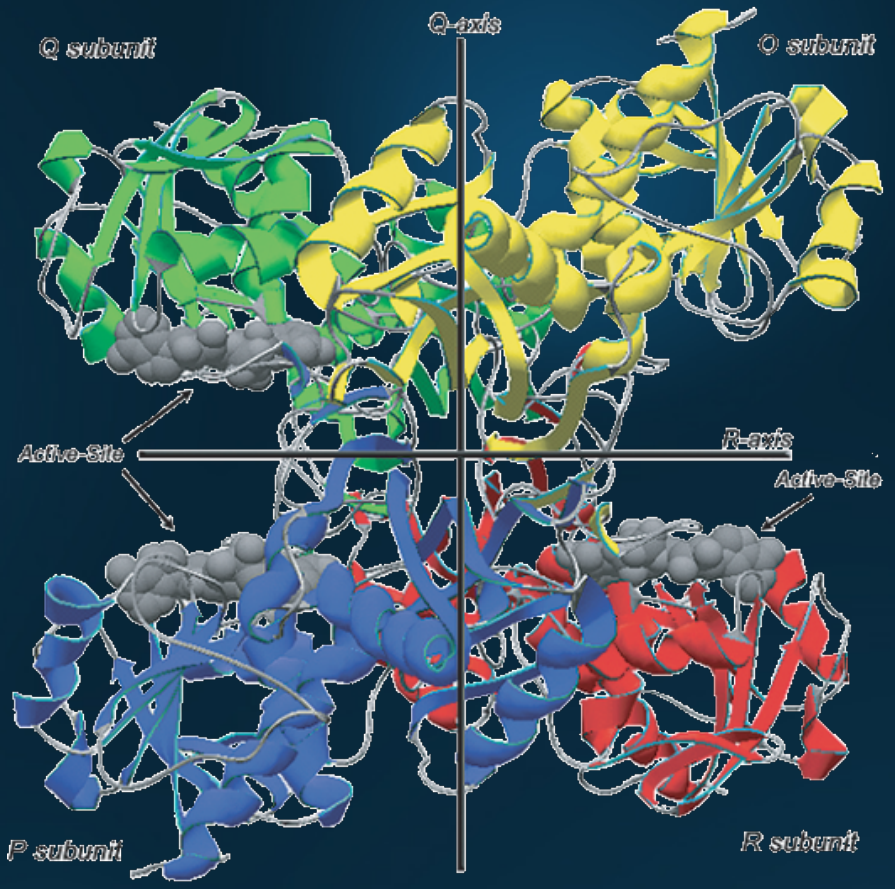
Hyperphosphorylation the microtubule-associated protein tau.



(Luc Buee et Andre Delacourte, 2002)

Introduction

GAPDH enzyme



(GAPDH; EC 1.2.1.12)

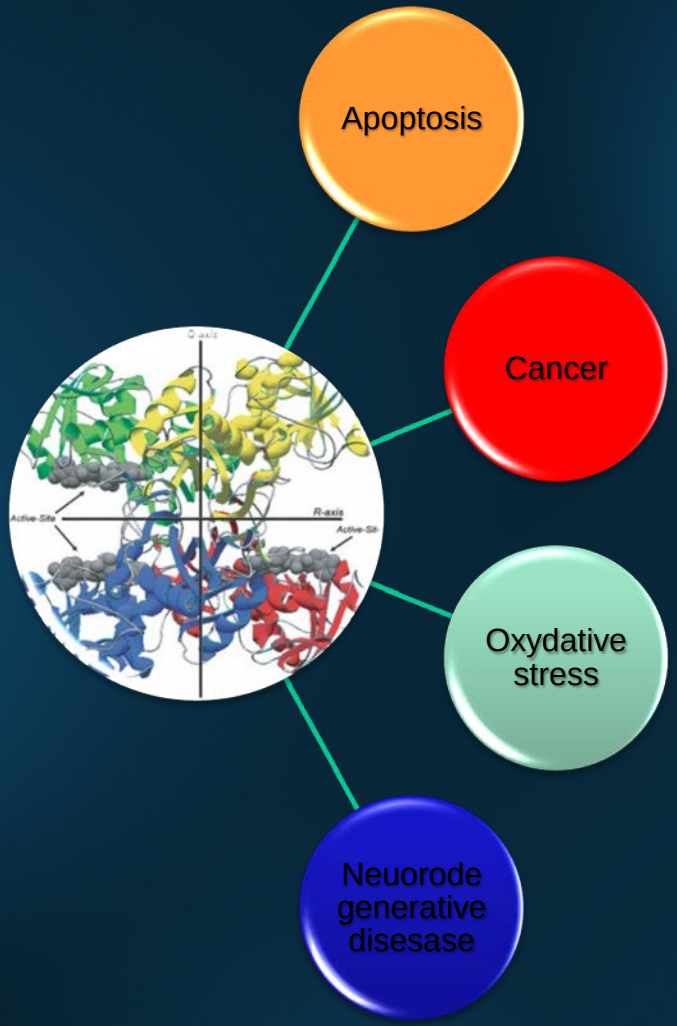
Introduction

Other GAPDH Fonctions

(D. Allan Butterfield et all, 2010)

Introduction

Involvement of GAPDH in cellular pathologies



GAPDH and MA

- The potential involvement of glyceraldehyde-3-phosphate dehydrogenase (GAPDH; EC 1.2.1.12) in neurodegeneration by reporting a non-glycolytic activity of GAPDH specifically in brains of AD cases.

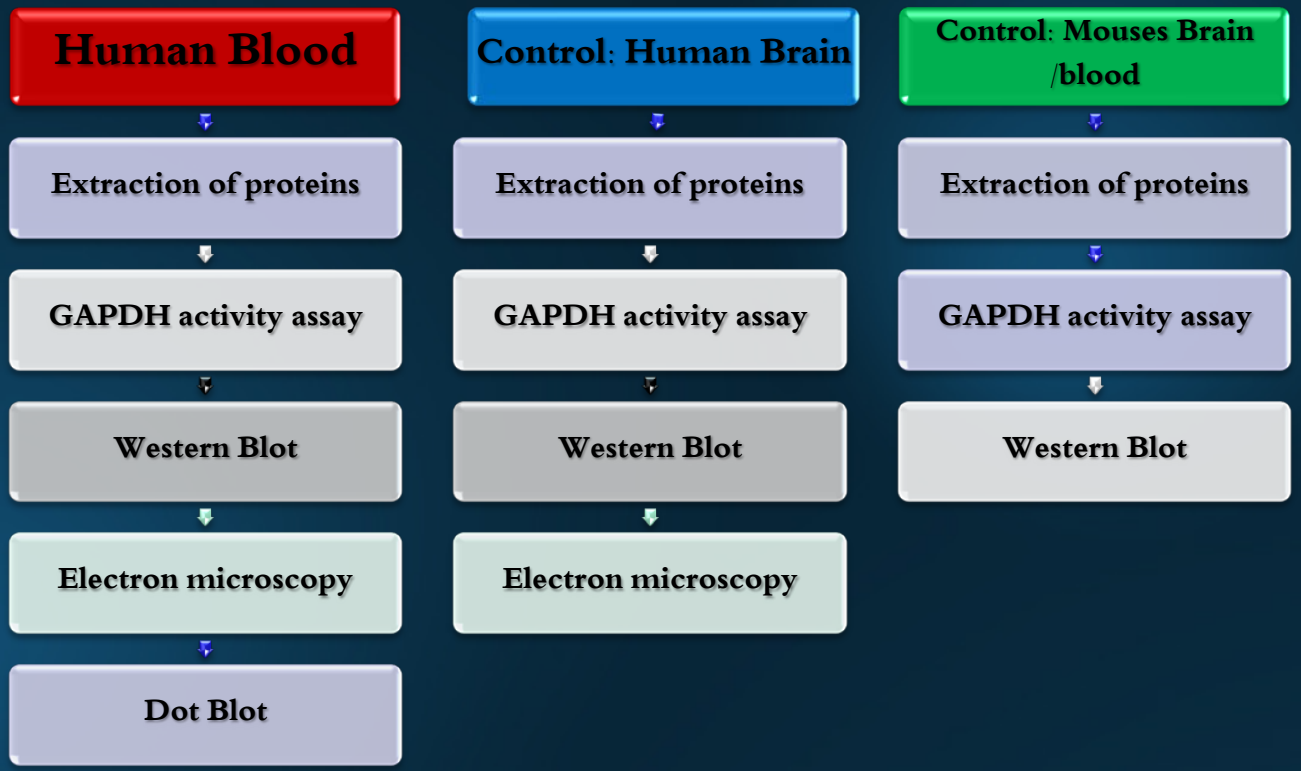
- GAPDH strongly interacts with the β-amyloid precursor protein (β-APP) with high affinity in vitro.

Aim of study

In this study we aimed :

- To probe for the role of GAPDH and its interaction with Aβ amyloid aggregates especially in blood samples from Moroccan patient of FAD cases carrying frameshift mutations in the presenilin genes.

Methods

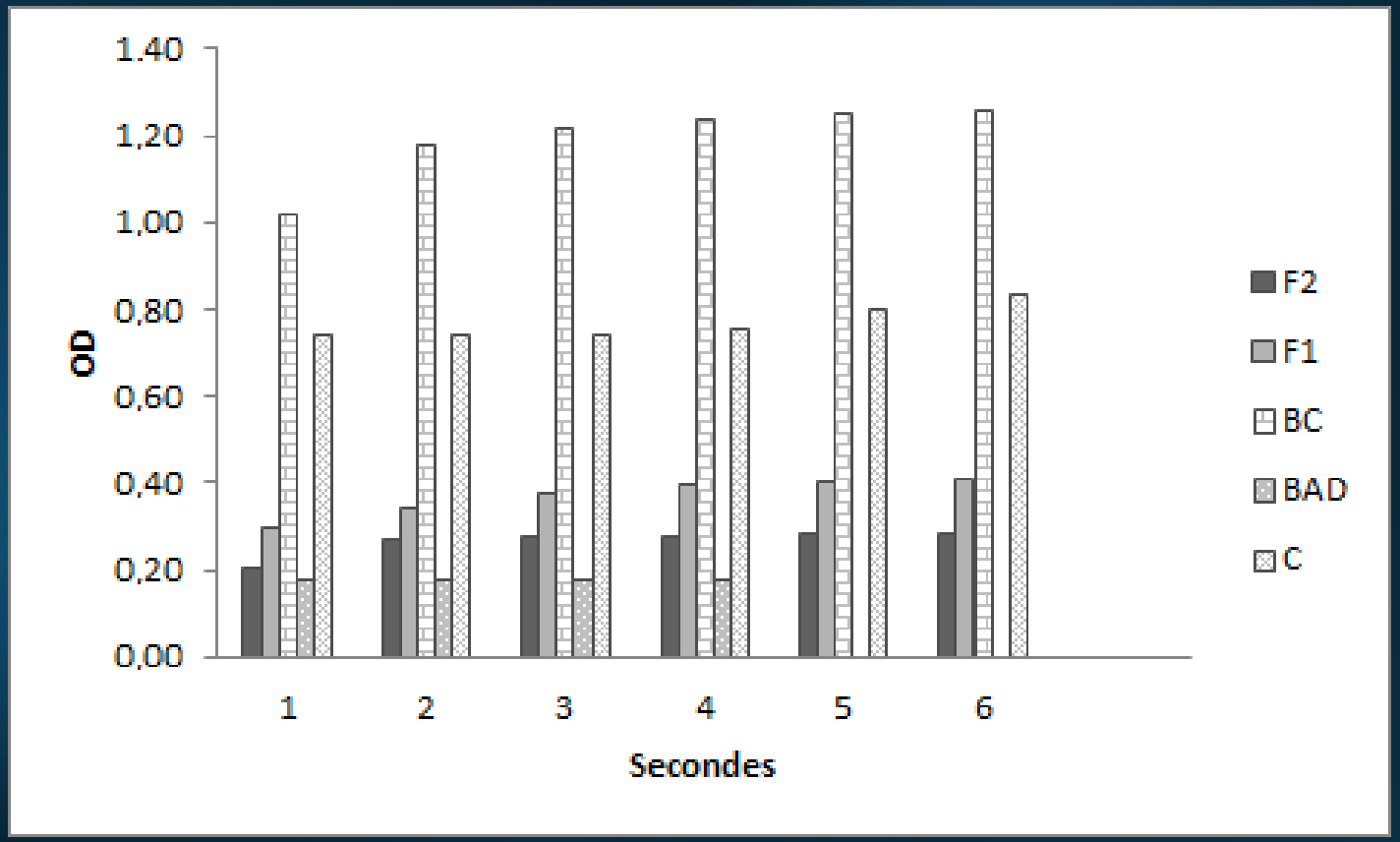

Human Blood
Extraction of proteins
GAPDH activity assay
Western Blot
Electron microscopy
Dot Blot
Control: Human Brain
Extraction of proteins
GAPDH activity assay
Western Blot
Electron microscopy
Control: Mouses Brain /blood
Extraction of proteins
GAPDH activity assay
Western Blot

Results

J Mol Neurosci
DOI 10.1007/s12031-014-0374-8

A Proteomic Approach for the Involvement of the GAPDH in Alzheimer Disease in the Blood of Moroccan FAD Cases

Nadia El Kadmiri · Raquel Cuardos · Bouchra El Moutawakil · Ilham Slassi · Jesus Avila · Sellama Nadifi · Ahmed Hachem · Abdelaziz Soukri



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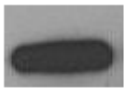
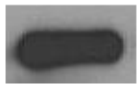
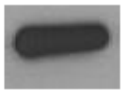
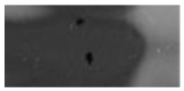
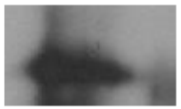
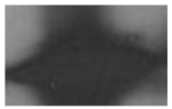
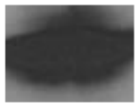
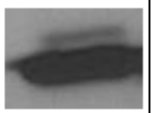
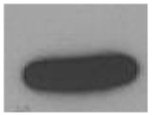
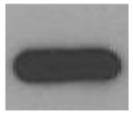
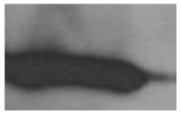
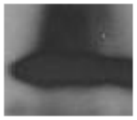
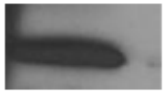
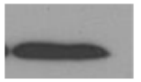
	Brain specimen of AD	Brain specimen of healthy control	Brain specimen of Mutant tau transgenic mice	Brain specimen of Wild type mice	Blood of Mutant tau transgenic mice	Blood of Wild type mice	Blood of healthy subject	Blood of FAD (F3)	Blood of FAD (F2)	Blood of FAD (F1)
β -Actin (Control) (42 kDa)										
GAPDH Expression (37 kDa)										

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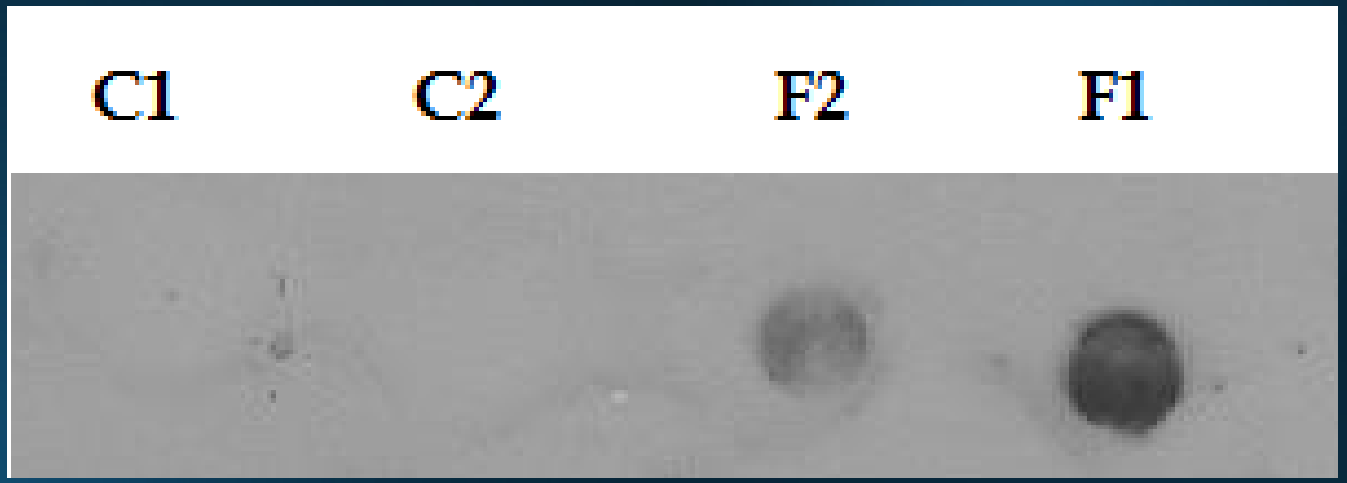

Representative dot blot of formed Aβ aggregates. Protein extracts from peripheral blood from two FAD cases (F1 and F2) and two control individuals (C1 and C2) were incubated with Aβ and then transferred onto nitrocellulose membranes. Membrane were then blotted for Aβ to assess the potential of the protein extracts to induce accumulation of Aβ aggregates.

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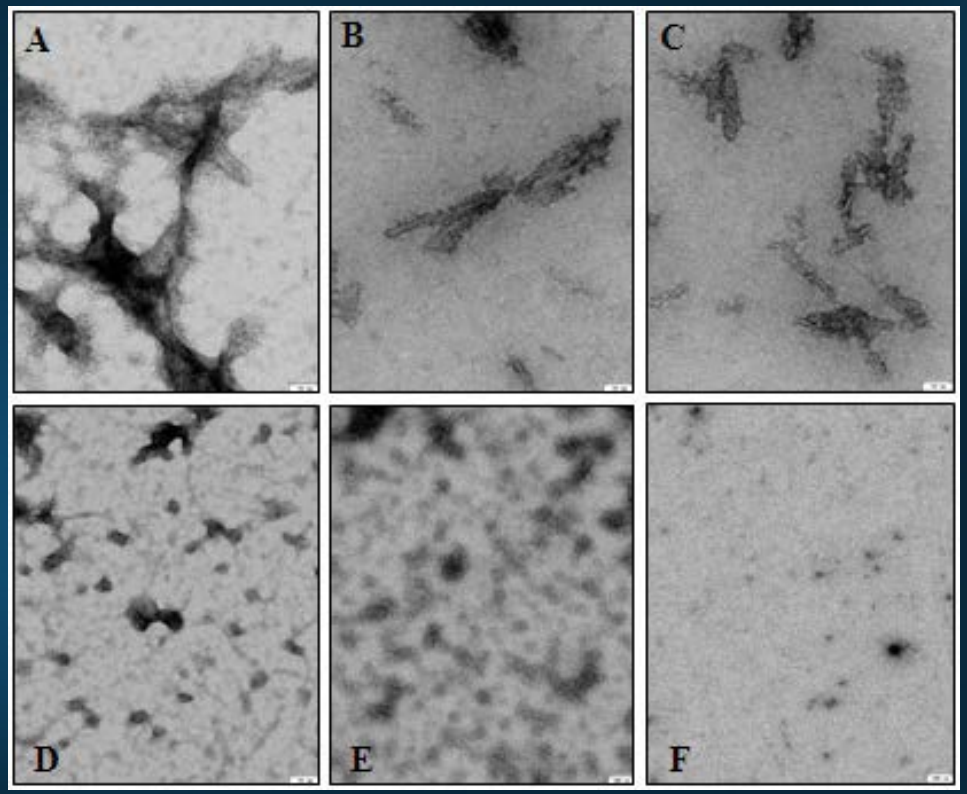

Representative electron microscopy images of formed Aβ aggregates. Protein extracts from (A) protein extracts from brain specimens from a confirmed AD case at autopsy, (B) protein extracts of peripheral blood from a FAD case (ID. F1), (C) protein extracts from peripheral blood from a FAD case (ID.F2), (D) protein extracts from brain specimens from a healthy subject at autopsy, (E) protein extracts from peripheral blood from a healthy subject and (F) PBS as control were incubated with Aβ and then visualized on an electron microscopic to asses amyloid fibril formation. (A), (B) and (C) show significant amyloid fibrils formation, whereas (D), (E) and (F) show no abnormalities. The scale bar for images (A), (B), (C) and (D) represents 70 nm, whereas that for images (E) and (F) represents 100 nm.

Discussion

- Our finding show a significant decrease in GAPDH activity albeit unchanged protein expression in the brain of both mutant tau transgenic mice and FAD case, which may be due to post-translational alterations.

- the expression of GAPDH in the blood of mutant tau transgenic mice and our FAD cases was decreased in comparison to controls, probably due to an alteration at the transcriptional level.

Discussion

- Dot blotting showed increased Aβ accumulation in peripheral blood from our FAD cases but not in healthy controls. EM examination revealed significant amyloid fibrils formation both in brain specimens from confirmed AD case and in peripheral blood from our FAD cases, who carry frameshift mutations located in presenilin genes

Discussion

- We can conclude that there is a link between amyloid aggregation and GAPDH through conversion of the normal conformation of GAPDH to an abnormal one, which leads to a decrease in its activity.

- Our mutational and proteomic analysis report a correlation between genotype and phenotype in our cases of EOAD involving the frameshift presenilin mutations and suggest that these mutations increase the risk of developing neurodegenerative diseases through Aβ-42 accumulation, which is due to modulation in the proteolytic processing of APP.

Perspective

- To clarify this decreased expression of GAPDH observed in the blood compared to brain.

Collaboration

ciberNed
Centro Investigación Biomédica en Red
Enfermedades Neurodegenerativas

PGM

PGM

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Acknowledgments

Staff at the Universita Catholica in Rome, Italy

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