Pathogenic mechanism of neurodegenerative disease. commonalities end progress towards treatment

John Hardy
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DRI at UCL

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Conflicts of Interest
SAB for Ceracuity (Biotech start up)
Recent Consulting for Eil Lilly, Merck, Eisai and Roche

Very interested in collaboration with Palestinian groups
j.hardy@ucl.ac.uk

- Eg. collect blood samples from neurodegenerative disease cohorts
- Send student to UCL to be trained to do the analysis

Overproduction of deposited proteins leads to mendelian disease

α-Synuclein Locus Triplication Causes Parkinson's Disease

A. B. Singleton,[1*†] M. Farrer,[4†] J. Johnson,[1] A. Singleton,[2] S. Hague,[1] J. Kachergus,[4] M. Hulihan,[4] T. Peuralinna,[1] A. Dutra,[3] R. Nussbaum,[2] S. Lincoln,[4] A. Crawley,[2] M. Hanson,[1] D. Maraganore,[5] C. Adler,[6] M. R. Cookson,[1] M. Muenter,[6] M. Baptista,[1] D. Miller,[1] J. Blancato,[7] J. Hardy,[1] K. Gwinn-Hardy[2]

APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy

Anne Rovelet-Lecrux[1], Didier Hannequin[1,2], Gregory Raux[1], Nathalie Le Meur[3], Annie Laquerrière[4], Anne Vital[5], Cécile Dumanchin[1], Sébastien Feuillette[1], Alexis Brice[6], Martine Vercelletto[7], Frédéric Dubas[8], Thierry Frebourg[1] & Dominique Campion[1,9]

Journal of Alzheimer's Disease 21 (2010) 897–902
DOI 10.3233/JAD-2010-100441
IOS Press

Frontotemporal Dementia Phenotype Associated with *MAPT* Gene Duplication

Anne Rovelet-Lecrux[a], Didier Hannequin[a,b], Olivier Guillin[c], Solenn Legallic[a], Snejana Jurici[a,b], David Wallon[a,b], Thierry Frebourg[a] and Dominique Campion[a,c,*]
[a]*Inserm U614, Faculty Medicine, University of Rouen, Rouen, France*
[b]*Department of Neurology, University Hospital, Rouen, France*

RESEARCH ARTICLE

NEUROSCIENCE

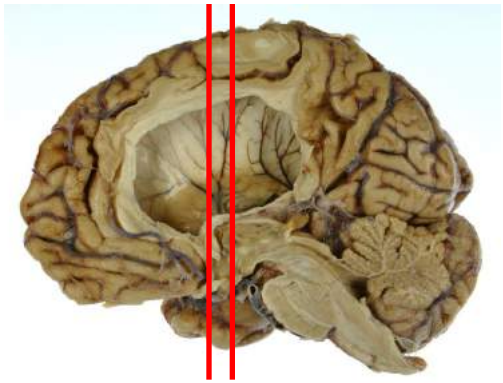
A protein homeostasis signature in healthy brains recapitulates tissue vulnerability to Alzheimer's disease

10.1126/sciadv.1600947

Rosie Freer,[1] Pietro Sormanni,[1] Giulia Vecchi,[1] Prajwal Ciryam,[1,2] Christopher M. Dobson,[1] Michele Vendruscolo[1]*

In Alzheimer's disease, aggregates of Aβ and tau in amyloid plaques and neurofibrillary tangles spread progressively across brain tissues following a characteristic pattern, implying a tissue-specific vulnerability to the disease. We report a transcriptional analysis of healthy brains and identify an expression signature that predicts—at ages well before the typical onset—the tissue-specific progression of the disease. We obtain this result by finding a quantitative correlation between the histopathological staging of the disease and the expression patterns of the proteins that coaggregate in amyloid plaques and neurofibrillary tangles, together with those of the protein homeostasis components that regulate Aβ and tau. Because this expression signature is evident in healthy brains, our analysis provides an explanatory link between a tissue-specific environmental risk of protein aggregation and a corresponding vulnerability to Alzheimer's disease.

Alzheimer's Disease



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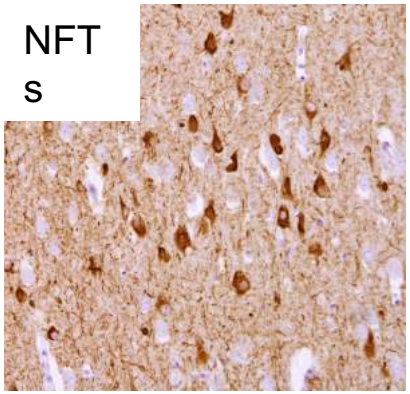
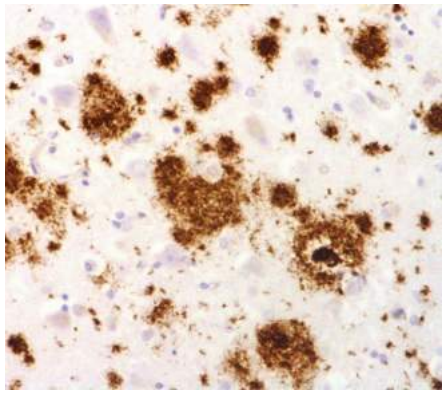
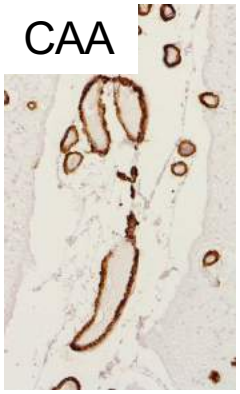
NFTs





CAA



Original Amyloid Hypotheses (1984/5).

Vol. 122, No. 3, 1984 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
August 16, 1984 Pages 1131-1135

ALZHEIMER'S DISEASE AND DOWN'S SYNDROME: SHARING OF A UNIQUE CEREBROVASCULAR AMYLOID FIBRIL PROTEIN

George G. GLENNER, M.D. and Caine W. WONG

University of California, San Diego (M-012), La Jolla, CA 92093

Received June 26, 1984

SUMMARY: The cerebrovascular amyloid protein from a case of adult Down's syndrome was isolated and purified. Amino acid sequence analysis showed it to be homologous to that of the β protein of Alzheimer's disease. This is the first chemical evidence of a relationship between Down's syndrome and Alzheimer's disease. It suggests that Down's syndrome may be a predictable model for Alzheimer's disease. Assuming the β protein is a human gene product, it also suggests that the genetic defect in Alzheimer's disease is localized on chromosome 21.

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 4245–4249, June 1985
Medical Sciences

Amyloid plaque core protein in Alzheimer disease and Down syndrome

(protein sequence/HPLC/congophilic angiopathy/unconventional virus infection/scrapie)

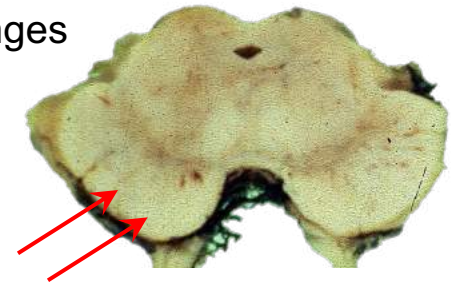
COLIN L. MASTERS*†, GAIL SIMMS*, NICOLA A. WEINMAN*, GERD MULTHAUP‡, BRIAN L. MCDONALD*, AND KONRAD BEYREUTHER‡

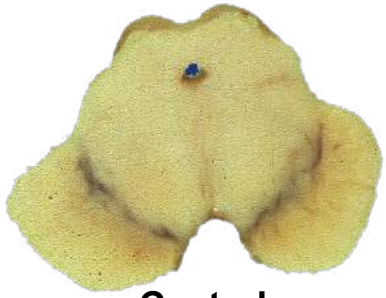
*Laboratory of Molecular and Applied Neuropathology, Neuromuscular Research Institute, Department of Pathology, University of Western Australia, Nedlands, Western Australia, 6009; †Department of Neuropathology, Royal Perth Hospital, Perth, Western Australia, 6001; and ‡Institute of Genetics, University of Cologne, Cologne, Federal Republic of Germany

Communicated by D. Carleton Gajdusek, January 30, 1985

Parkinson's Disease

Macroscopic changes





Control

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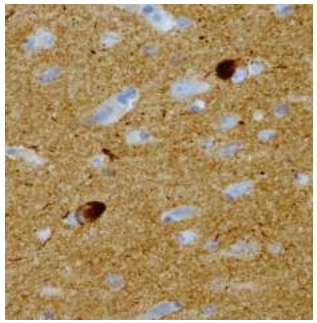
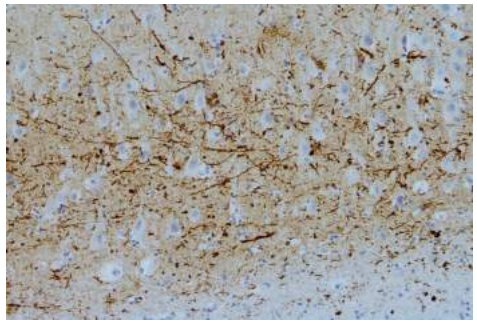
Microscopic changes

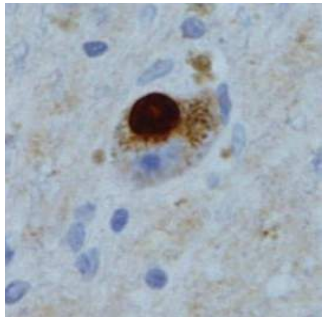
Parkinson's disease



Lewy bodies in cingulate cortex



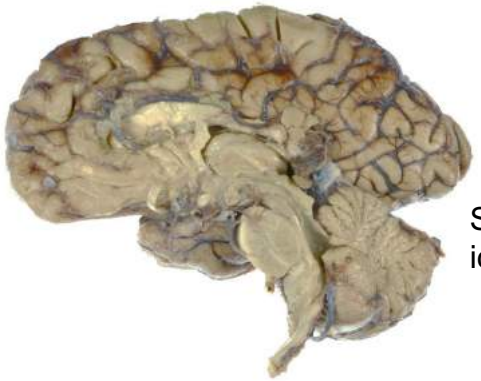
Lewy neurites in hippocampus

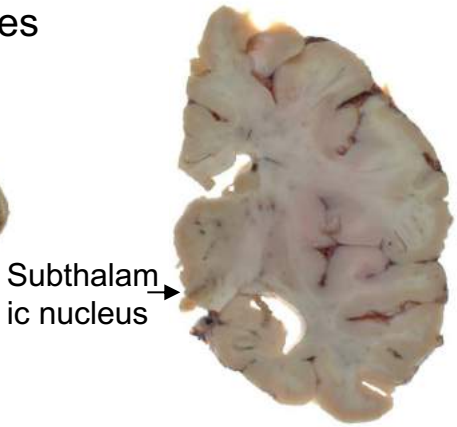


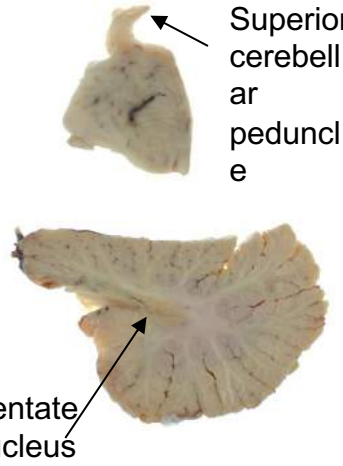
Lewy body in substantia nigra

Tangle Diseases (eg PSP)

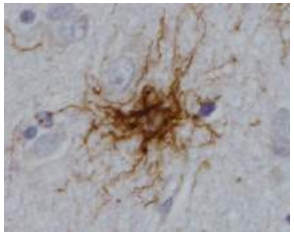
Macroscopic changes

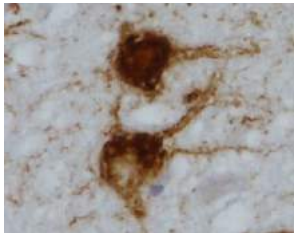


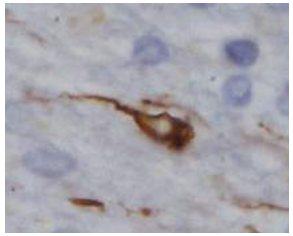




Microscopic changes







UCL QUEEN SQUARE INSTITUTE OF NEUROLOGY BRAIN BANK

Overproduction of deposited proteins leads to mendelian disease

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APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy

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Frontotemporal Dementia Phenotype Associated with *MAPT* Gene Duplication

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[a]*Inserm U614, Faculty Medicine, University of Rouen, Rouen, France*
[b]*Department of Neurology, University Hospital, Rouen, France*

RESEARCH ARTICLE

NEUROSCIENCE

A protein homeostasis signature in healthy brains recapitulates tissue vulnerability to Alzheimer's disease

10.1126/sciadv.1600947

Rosie Freer,[1] Pietro Sormanni,[1] Giulia Vecchi,[1] Prajwal Ciryam,[1,2] Christopher M. Dobson,[1] Michele Vendruscolo[1]*

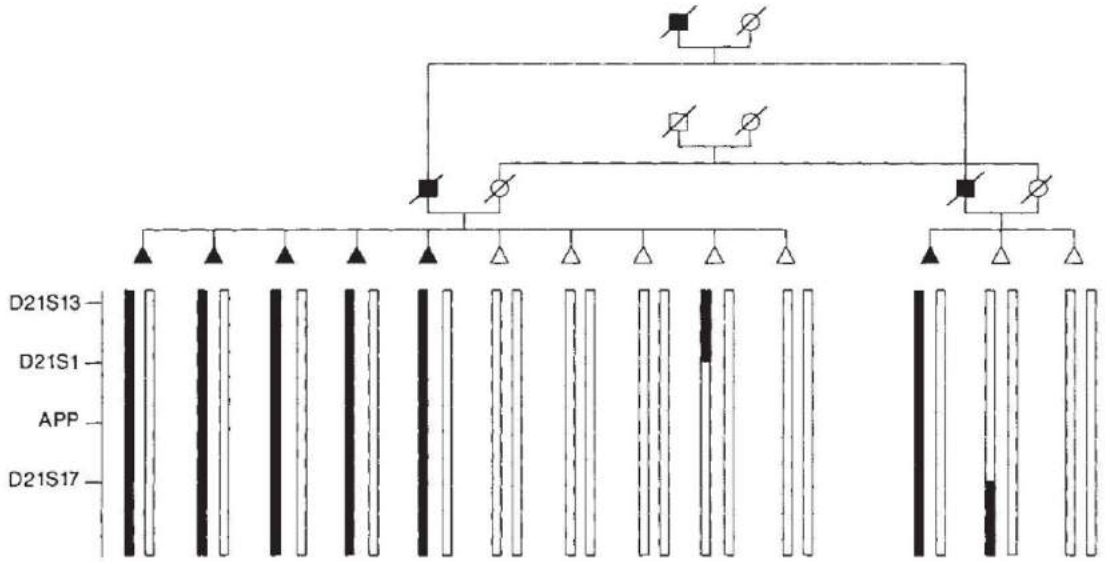
In Alzheimer's disease, aggregates of Aβ and tau in amyloid plaques and neurofibrillary tangles spread progressively across brain tissues following a characteristic pattern, implying a tissue-specific vulnerability to the disease. We report a transcriptional analysis of healthy brains and identify an expression signature that predicts—at ages well before the typical onset—the tissue-specific progression of the disease. We obtain this result by finding a quantitative correlation between the histopathological staging of the disease and the expression patterns of the proteins that coaggregate in amyloid plaques and neurofibrillary tangles, together with those of the protein homeostasis components that regulate Aβ and tau. Because this expression signature is evident in healthy brains, our analysis provides an explanatory link between a tissue-specific environmental risk of protein aggregation and a corresponding vulnerability to Alzheimer's disease.

Amyloid Gene Identification

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant||, Phillippa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance§, Allen Roses§, Robert Williamson*, Martin Rossor*, Mike Owen|| & John Hardy*¶

* Alzheimer's Disease Research Group, Departments of Biochemistry and Neurology, St Mary's Hospital Medical School, London W2 1PG, UK
† Department of Human Genetics, Yale University Medical School, 333 Cedar Street, New Haven, Connecticut 06150, USA
§ Duke University Medical Center, Durham, North Carolina NC 27710, USA
|| Departments of Psychological Medicine and Medical Genetics, University of Wales College of Medicine, Cardiff CF4 4XN, UK



The FEBS Journal

FEBS PRESS science publishing by scientists

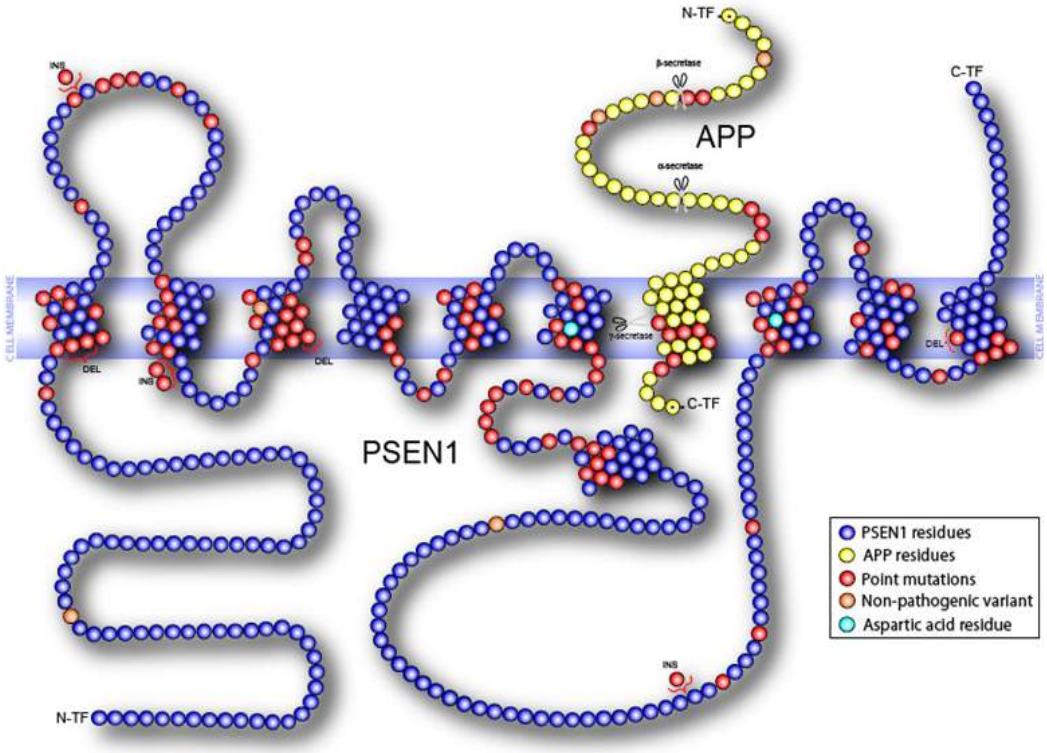
DISCOVERY-IN-CONTEXT REVIEW

The discovery of Alzheimer-causing mutations in the APP gene and the formulation of the "amyloid cascade hypothesis"

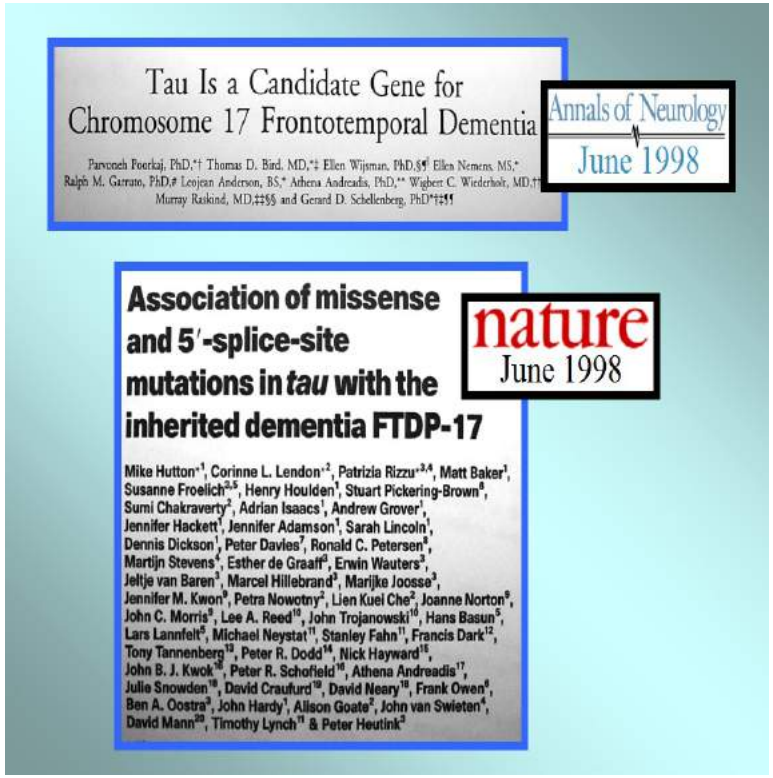
John Hardy

Reta Lila Weston Research Laboratories and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

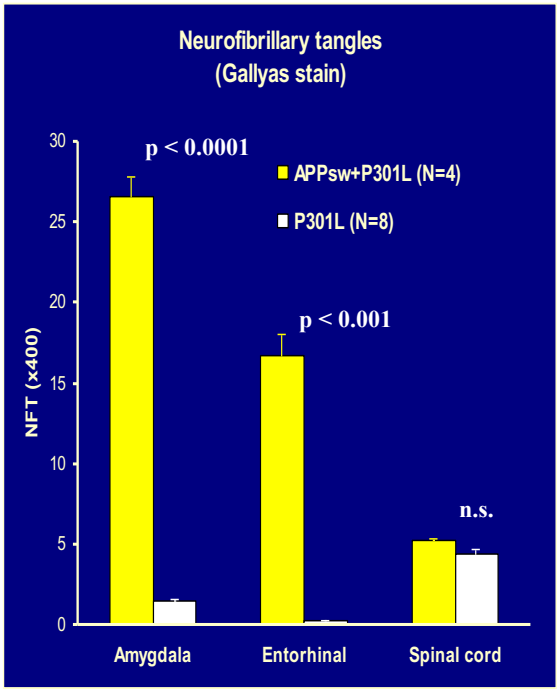
Presenilin with APP in the Active Site



The Tauopathies



Old data: Amyloid Drives Tau Pathology



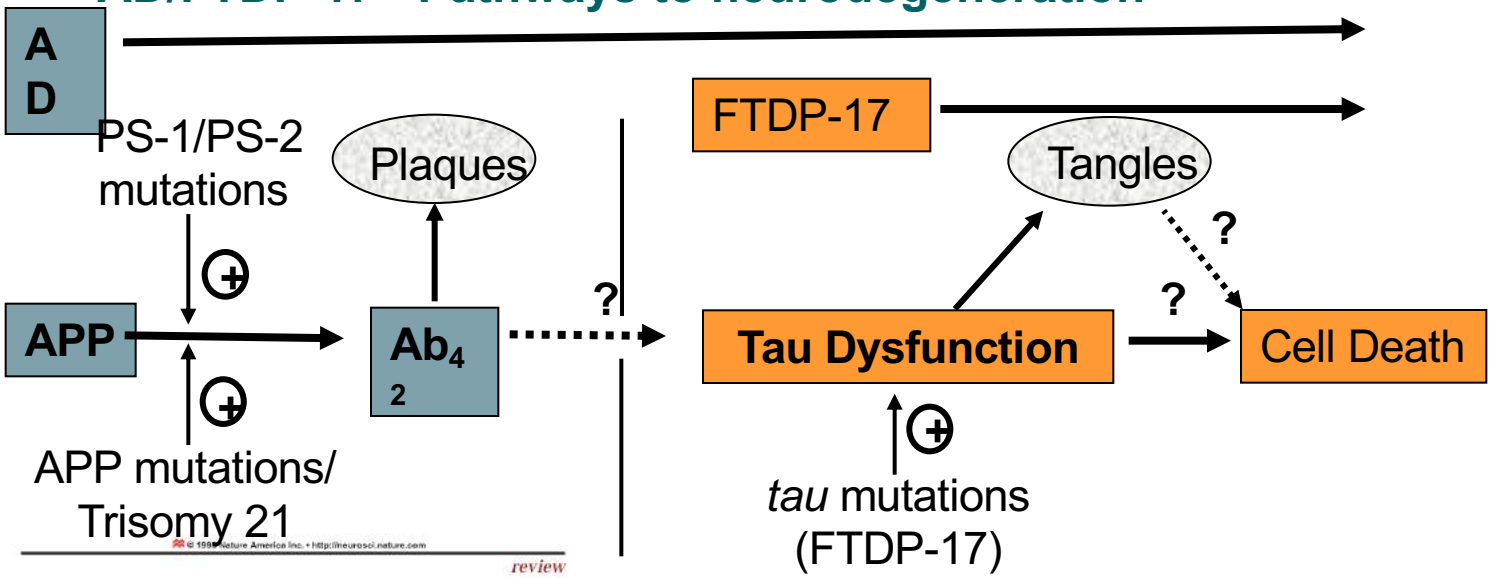
Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP

Jada Lewis,* Dennis W. Dickson,* Wen-Lang Lin, Louise Chisholm, Anthony Corral, Graham Jones, Shu-Hui Yen, Naruhiko Sahara, Lisa Skipper, Debra Yager, Chris Eckman, John Hardy, Mike Hutton,† Eileen McGowan

JNPL3 transgenic mice expressing a mutant tau protein, which develop neurofibrillary tangles and progressive motor disturbance, were crossed with Tg2576 transgenic mice expressing mutant β-amyloid precursor protein (APP), thus modulating the APP-Aβ (β-amyloid peptide) environment. The resulting double mutant (tau/APP) progeny and the Tg2576 parental strain developed Aβ deposits at the same age; however, relative to JNPL3 mice, the double mutants exhibited neurofibrillary tangle pathology that was substantially enhanced in the limbic system and olfactory cortex. These results indicate that either APP or Aβ influences the formation of neurofibrillary tangles. The interaction between Aβ and tau pathologies in these mice supports the hypothesis that a similar interaction occurs in Alzheimer's disease.

Science
Aug. 2001

AD/FTDP-17 - Pathways to neurodegeneration



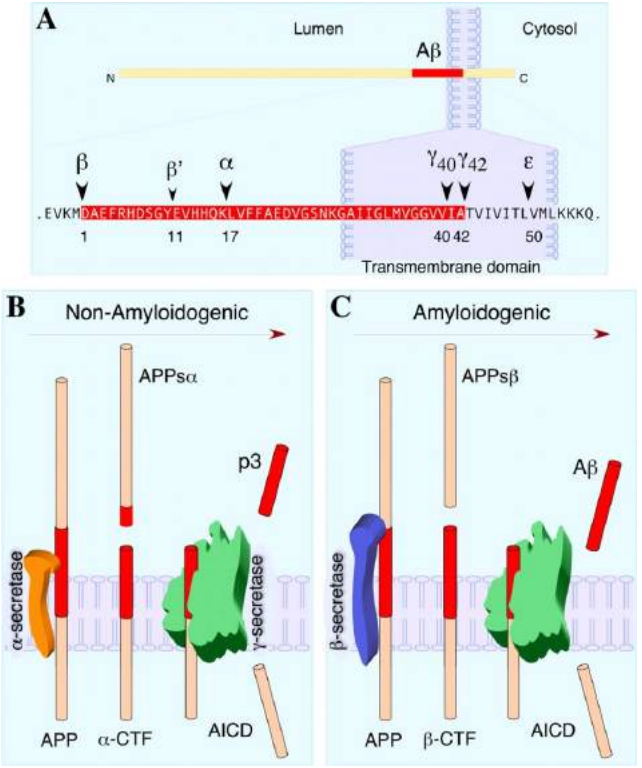
review

Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau

John Hardy, Karen Duff, Katrina Gwinn Hardy, Jordi Perez-Tur and Mike Hutton

nature neuroscience
Sept.

Proteolytic processing of APP always drawn with “soluble”Aβ



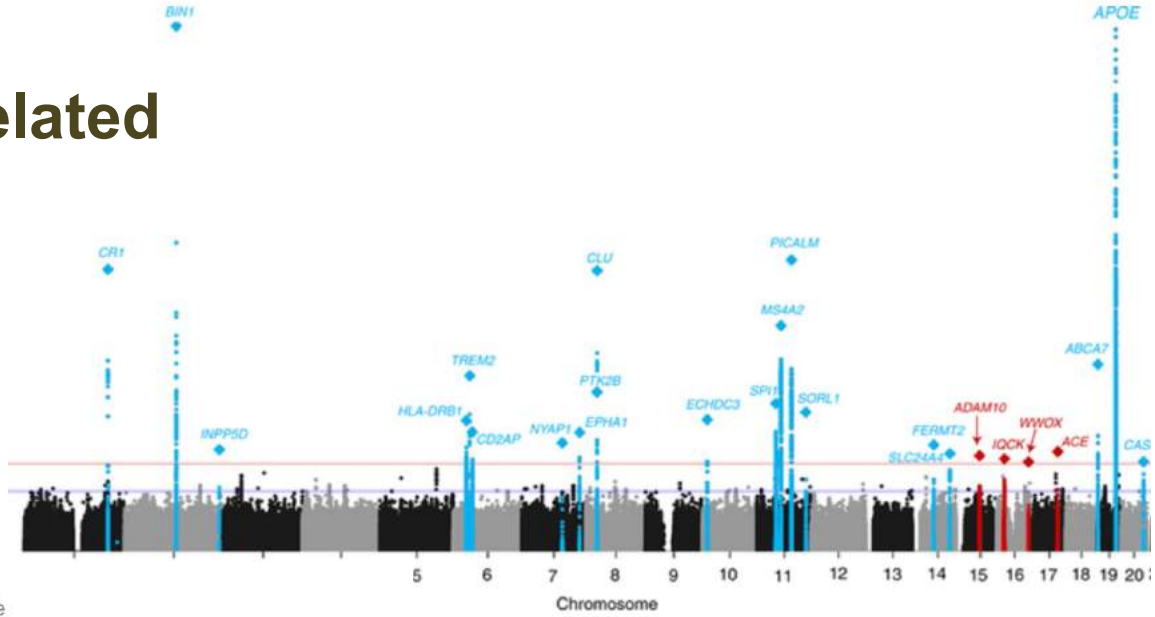
Gopal Thinakaran, and Edward H. Koo J. Biol. Chem. 2008;283:29615-29619

Alzheimers Dement (Amst). 2018; 10: 311–321.
Published online 2018 Mar 22. doi: 10.1016/j.dadm.2018.02.005
PMCID: PMC5956932
PMID: 29780875

Amyloid β peptides are differentially vulnerable to preanalytical surface exposure, an effect incompletely mitigated by the use of ratios

Jamie Toombs,[a,*] Martha S. Foiani,[a] Henrietta Wellington,[a] Ross W. Paterson,[b] Charles Arber,[c] Amanda Heslegrave,[a] Michael P. Lunn,[d] Jonathan M. Schott,[c] Selina Wray,[b] and Henrik Zetterberg[e,f,g,h]

GWAS… largely not *obviously* amyloid related



OPEN ACCESS Freely available online

PLoS one

Genetic Evidence Implicates the Immune System and Cholesterol Metabolism in the Aetiology of Alzheimer's Disease

Lesley Jones[1,9], Peter A. Holmans[1,9], Marian L. Hamshere[1], Denise Harold[1], Valentina Moskvina[1], Dobril Ivanov[1], Andrew Pocklington[1], Richard Abraham[1], Paul Hollingworth[1], Rebecca Sims[1], Amy Gerrish[1], Jaspreet Singh Pahwa[1], Nicola Jones[1], Alexandra Stretton[1], Angharad R. Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K. Lupton[3], Carol Brayne[4], David C. Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S. Brown[7], Peter A. Passmore[8], David Craig[8], Bernadette McG[illegible], Patrick G. Keho[illegible], Frank Jessen[15], Johannes Kornh[illegible], Michael Hüll[24], Nowotny[25], Joh[illegible], Andrew McQuil[illegible], Andrew B. Sing[illegible], Moebus[33], Karl[illegible], Minerva M. Car[illegible], O'Donovan[1], M[illegible]

Abstract

Background: Late Onset Alzheimer's disease (LOAD) is the leading cause of dementia. Recent large genome-wide association studies (GWAS) identified the first strongly supported LOAD susceptibility genes since the discovery of the involvement of *APOE* in the early 1990s. We have now exploited these GWAS datasets to uncover key LOAD pathophysiological processes.

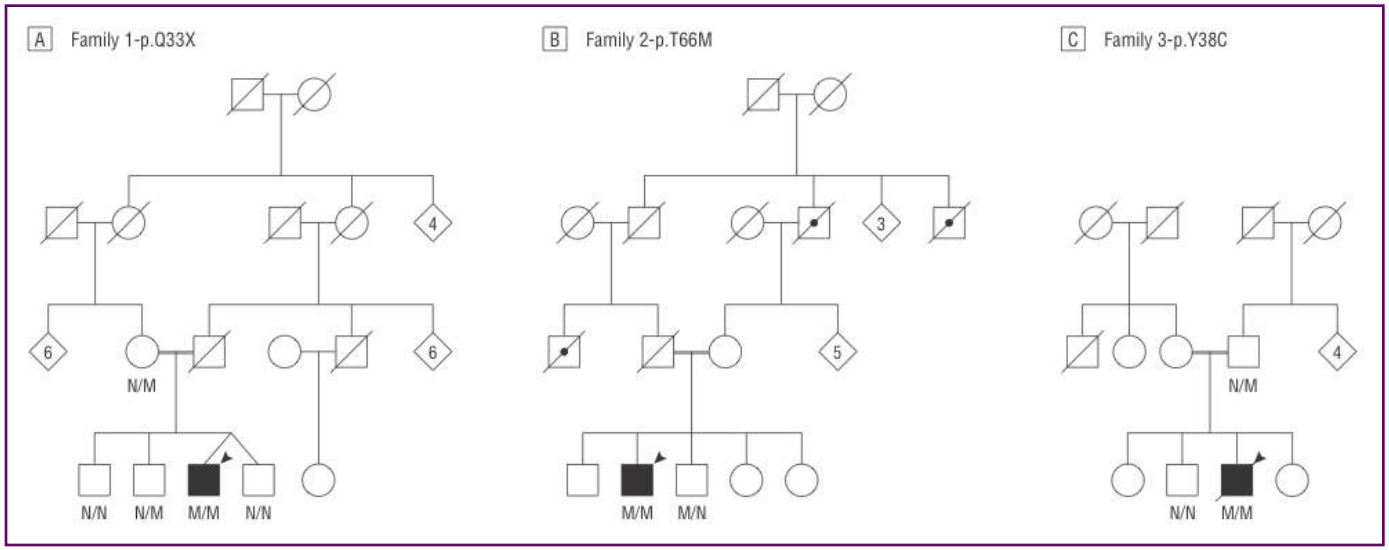
Methodology: We applied a recently developed tool for mining GWAS data for biologically meaningful information to a LOAD GWAS dataset. The principal findings were then tested in an independent GWAS dataset.

Principal Findings: We found a significant overrepresentation of association signals in pathways related to cholesterol metabolism and the immune response in both of the two largest genome-wide association studies for LOAD.

Significance: Processes related to cholesterol metabolism and the innate immune response have previously been implicated by pathological and epidemiological studies of Alzheimer's disease, but it has been unclear whether those findings reflected primary aetiological events or consequences of the disease process. Our independent evidence from two large studies now demonstrates that these processes are aetiologically relevant, and suggests that they may be suitable targets for novel and existing therapeutic approaches.

Using Exome Sequencing to Reveal Mutations in *TREM2* Presenting as a Frontotemporal Dementia–like Syndrome Without Bone Involvement

Rita João Guerreiro, PhD; Ebba Lohmann, MD; José Miguel Brás, PhD; Jesse Raphael Gibbs, MS; Jonathan D. Rohrer, MRCP; Nicole Gurunlian, MS; Burcu Dursun, MD; Basar Bilgic, MD; Hasmet Hanagasi, MD; Hakan Gurvit, MD; Murat Emre, MD; Andrew Singleton, PhD; John Hardy, PhD



Guerreiro R, et al. JAMA Neurol. 2013 Jan;70(1):78-84.

TREM2 in Alzheimer's disease

Table 2. Coding Variants Found in TREM2 through DNA Sequencing in Patients with Alzheimer's Disease and in Controls.*

Variant	SNP Number	Position†	Minor Alleles	Patients with Alzheimer's Disease		Controls		Reference Allele	P Value‡	Odds Ratio (95% CI)	PolyPhen-2§
				No. of Nonreference Alleles	No. of Cases	No. of Nonreference Alleles	No. of Controls				
All variants				60		38			0.02¶		
L211P	rs2234256	41126655	G	0	281	3	503	A	0.56	0	Benign (0.001)
H157Y	rs2234255	41127543	A	1	281	0	504	G	0.36	NA	Possibly damaging (0.7)
R136Q	rs149622783	41127605	T	1	281	1	501	C	1.00	1.8 (0.1–28.6)	Benign (0.0)
R98W	rs147564421	41129100	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
T96K	rs2234253	41129105	T	4	1091	3	1105	G	0.72	1.4 (0.3–6.0)	Probably damaging (1.0)
D87N	rs142232675	41129133	T	6	1091	0	1105	C	0.02	NA	Probably damaging (1.0)
N68K	NA	41129188	C	0	1090	1	1105	G	1.00	0	Benign (0.05)
T66M	rs201258663	41129195	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
R62H	rs143332484	41129207	T	25	1090	31	1104	C	0.50	0.8 (0.5–1.4)	Benign (0.02)
R47H	rs75932628	41129252	T	22	1091	5	1105	C	<0.001	4.5 (1.7–11.9)	Probably damaging (1.0)
Y38C	NA	41129279	G	3	1091	0	1107	A	0.12	NA	Probably damaging (1.0)
Q33X	rs104894002	41129295	A	2	1084	0	1103	G	0.25	NA	NA
Nasu–Hakola mutations	Q33X, Y38C, T66M			6		0			0.01	NA	Known damaging

Guerreiro R, et al. N Engl J Med. 2013 Jan 10;368(2):117-27.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D., Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D., Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D., Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D., Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D., Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D., Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D., Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D., for the Alzheimer Genetic Analysis Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg Ph.D., Ingileif Jonsdottir, Ph.D., Palmi V. Jonsson, M.D., Jon Snaedal, M.D., Sigurbjorn Bjornsson, M.D., Johanna Huttenlocher, B.S., Allan I. Levey, M.D., Ph.D., James J. Lah, M.D., Ph.D., Dan Rujescu, M.D., Harald Hampel, M.D., Ina Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Knut Engedal, M.D., Ph.D., Ingun Ulstein, M.D., Ph.D., Srdjan Djurovic, Ph.D., Carla Ibrahim-Verbaas, M.D., Albert Hofman, M.D., Ph.D., M. Arfan Ikram, M.D., Ph.D., Cornelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D., Augustine Kong, Ph.D., and Kari Stefansson, M.D., Ph.D.

Article abstract—Progressive presenile dementia with lipomembranous polycystic osteodysplasia was first described by Jarvi and Hakola in an isolated region of Finland. We report the occurrence of this disorder in 4 of 10 siblings in an American family of Czechoslovakian ancestry. Characteristics of the disease include multiple bone cysts with pathologic fractures, progressive dementia with seizures and abnormal EEG, calcification of basal ganglia, and death in the fourth to sixth decades. Autosomal-recessive inheritance is likely. Electronmicroscopy of fat cells reveals peculiar membrane convolutions. Limited neuropathologic material has shown gliosis and demyelination of white matter, senile plaques, and neurofibrillary tangles. Leukemia and a disorder of intestinal motility may be associated findings. Prevalence of the disorder is unknown, partly because it may be confused with Alzheimer disease and fibrous dysplasia of bone. Radiographs of hands and feet should be part of the evaluation of patients with unexplained presenile dementia.

NEUROLOGY (NY) 1983;33:81-6

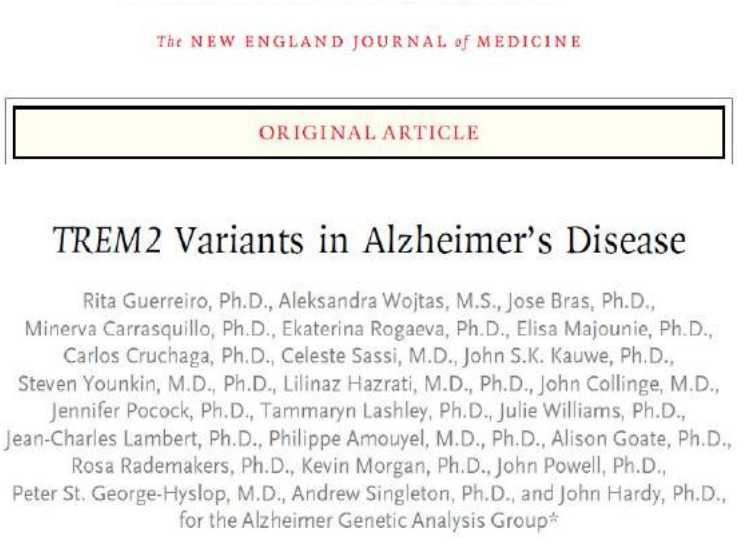
Lipomembranous polycystic osteodysplasia (brain, bone, and fat disease): A genetic cause of presenile dementia

Thomas D. Bird, M.D., Richard M. Koerker, M.D., Ph.D., Brenda J. Leaird, P.A., Brien W. Vlcek, M.D., and David R. Thorning, M.D.

TREM2 is the gene whose expression is most altered during plaque development in transgenic mice

CRND Mice

"Consistent with the results described in a previous study we have shown that the expression of TREM2 rises in parallel with a rise in cortical levels of beta amyloid"

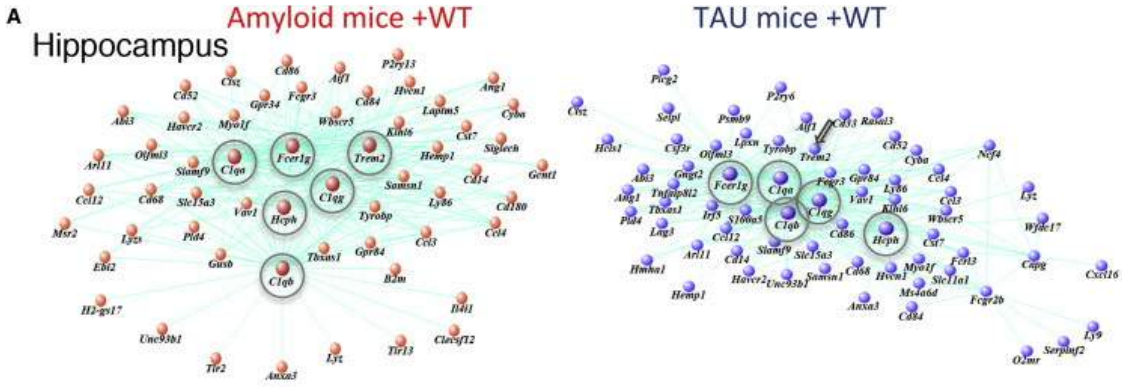


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D., Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D., Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D., Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D., Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D., Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D., Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D., Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D., for the Alzheimer Genetic Analysis Group*



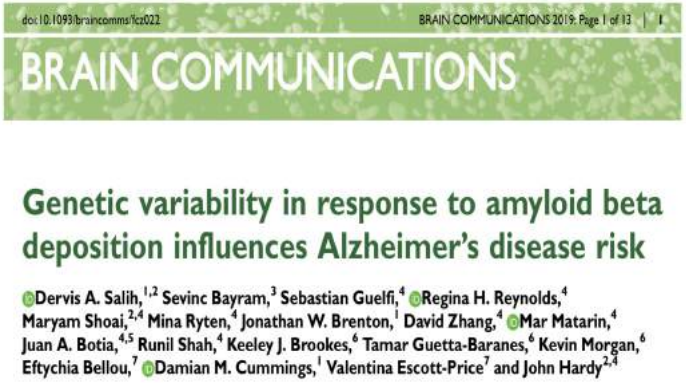
Cell Reports
Resource
OPEN ACCESS
CellPress

A Genome-wide Gene-Expression Analysis and Database in Transgenic Mice during Development of Amyloid or Tau Pathology

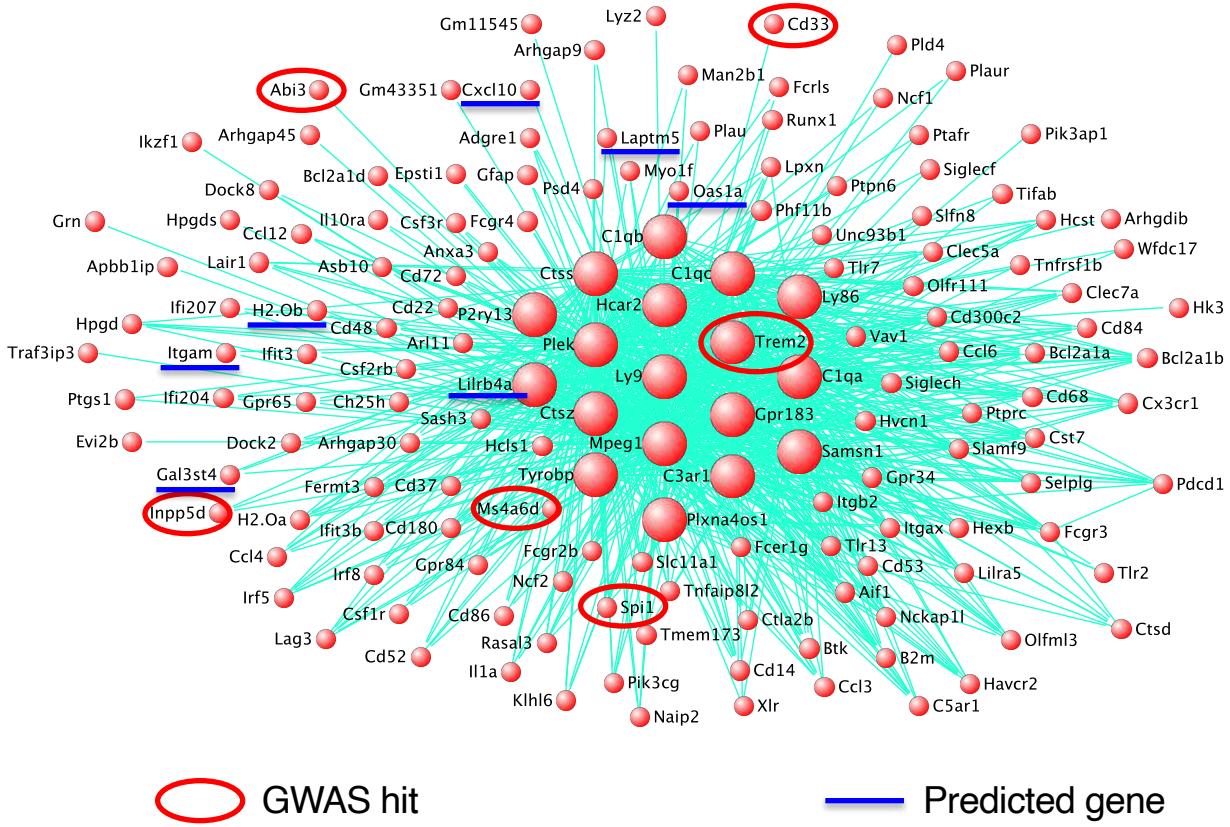
Mar Matarin,[1,3] Dervis A. Salih,[2] Marina Yasvoina,[2] Damian M. Cummings,[2] Sebastian Guelfi,[3] Wenfei Liu,[2] Muzammil A. Nahaboo Solim,[2,6] Thomas G. Moens,[2] Rocio Moreno Paublete,[2] Shabinah S. Ali,[2] Marina Perona,[1] Roshni Desai,[6] Kenneth J. Smith,[6] Judy Latcham,[4] Michael Fulleylove,[4] Jill C. Richardson,[5] John Hardy,[3,*] and Frances A. Edwards[2,*]

Transcriptome sequenced amyloid mouse brains

- Q1: is there an over representation of significant associations with AD in the Aβ response module?
  - Yes: p~10(-41)
- Q2: is there an over representation of significant associations with AD even when we discount declared loci?
  - Yes: p~10(-10)
- So… which genes within the module are contributing to this?



Immune network associated with amyloid plaques



Cell Reports

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Article

Plaque contact and unimpaired *Trem2* is required for the microglial response to amyloid pathology

Jack I. Wood,[1,5] Eugenia Wong,[1] Ridwaan Joghee,[1] Aya Balbaa,[1] Karina S. Vitanova,[1] Katie M. Stringer,[1,5] Alison Vanshoiack,[2] Stefan-Laural J. Phelan,[2] Francesca Launchbury,[3] Sneha Desai,[1] Takshashila Tripathi,[1] Jörg Hanrieder,[3,5] Damian M. Cummings,[1] John Hardy,[4,3] and Frances A. Edwards[1,6,7,*]

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[5]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal Hospital, House V3, 43180 Mölndal, Sweden
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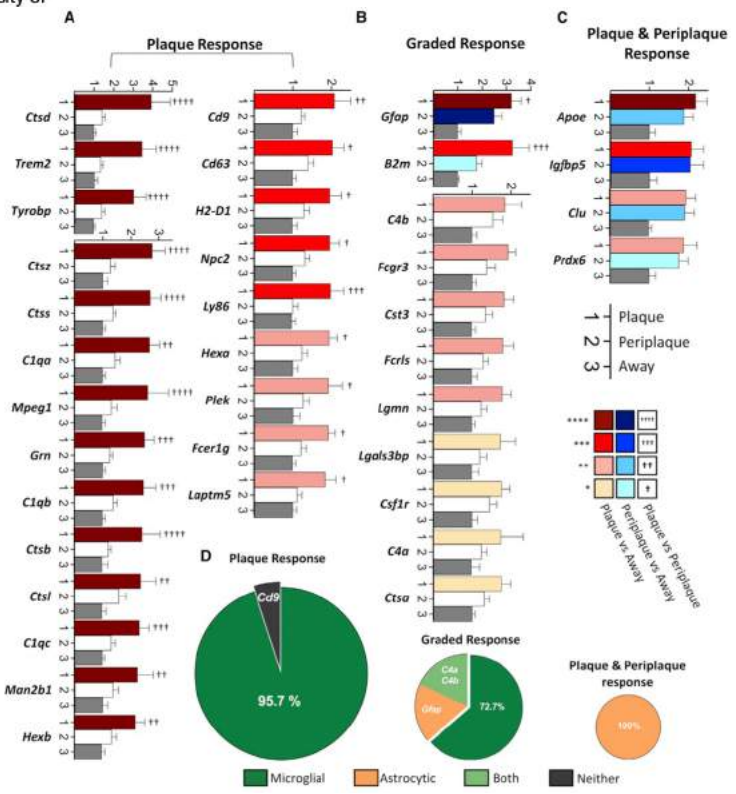
https://doi.org/10.1016/j.celrep.2022.111686

- Many genes are upregulated on plaque contact (dependent on trem2)
- A few are upregulated distant from plaque (presumably by diffusing cytokines)
- Very few genes are neuronal or astroglial



`ABCA7 and TREM2 both involved in microglial phospholipid metabolism

Differential Phospholipid Substrates and Directional Transport by ATP-binding Cassette Proteins ABCA1, ABCA7, and ABCA4 and Disease-causing Mutants*◆

Received for publication, August 8, 2013, and in revised form, September 17, 2013 Published, JBC Papers in Press, October 4, 2013, DOI 10.1074/jbc.M113.508812

Faraz Quazi[1] **and Robert S. Molday**[2]

From the Department of Biochemistry and Molecular Biology, Centre for Macular Research, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada

Article

Cell

TREM2 Lipid Sensing Sustains the Microglial Response in an Alzheimer's Disease Model

Yaming Wang,[1,5] Marina Cella,[1] Kaitlin Mallinson,[2,3,4] Jason D. Ulrich,[2,3,4] Katherine L. Young,[2,3,4] Michelle L. Robinette,[1] Susan Gilfillan,[1] Gokul M. Krishnan,[1] Shwetha Sudhakar,[2,3,4] Bernd H. Zinselmeyer,[1] David M. Holtzman,[2,3,4] John R. Cirrito,[2,3,4] and Marco Colonna[1,*]

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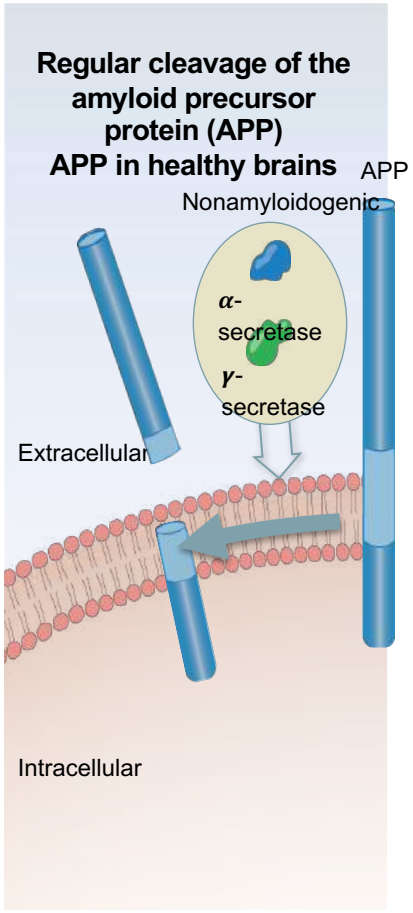
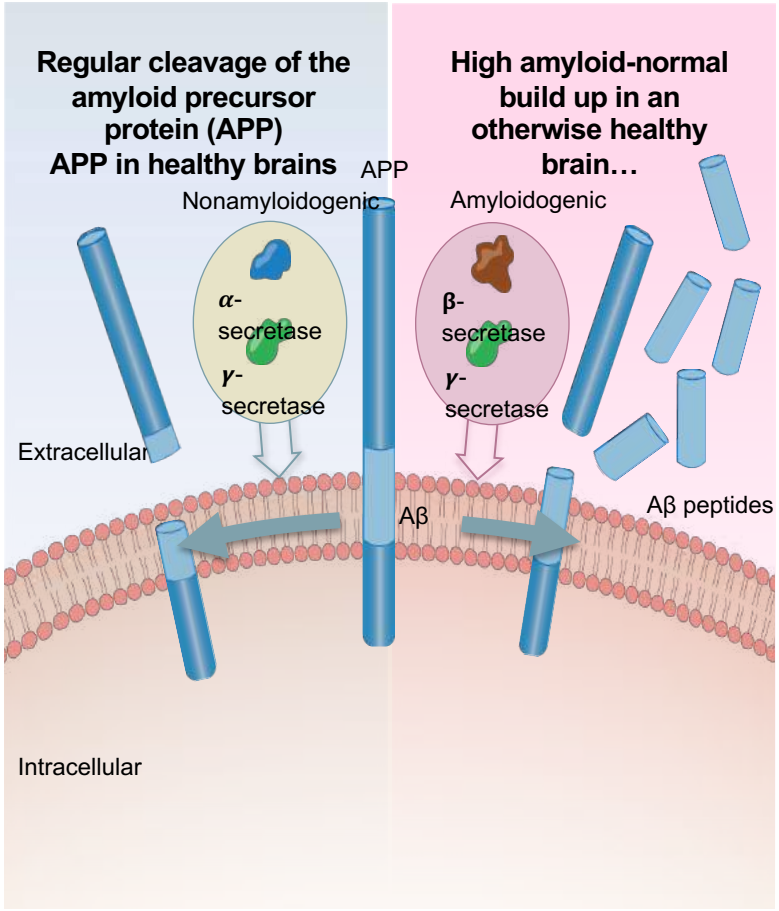
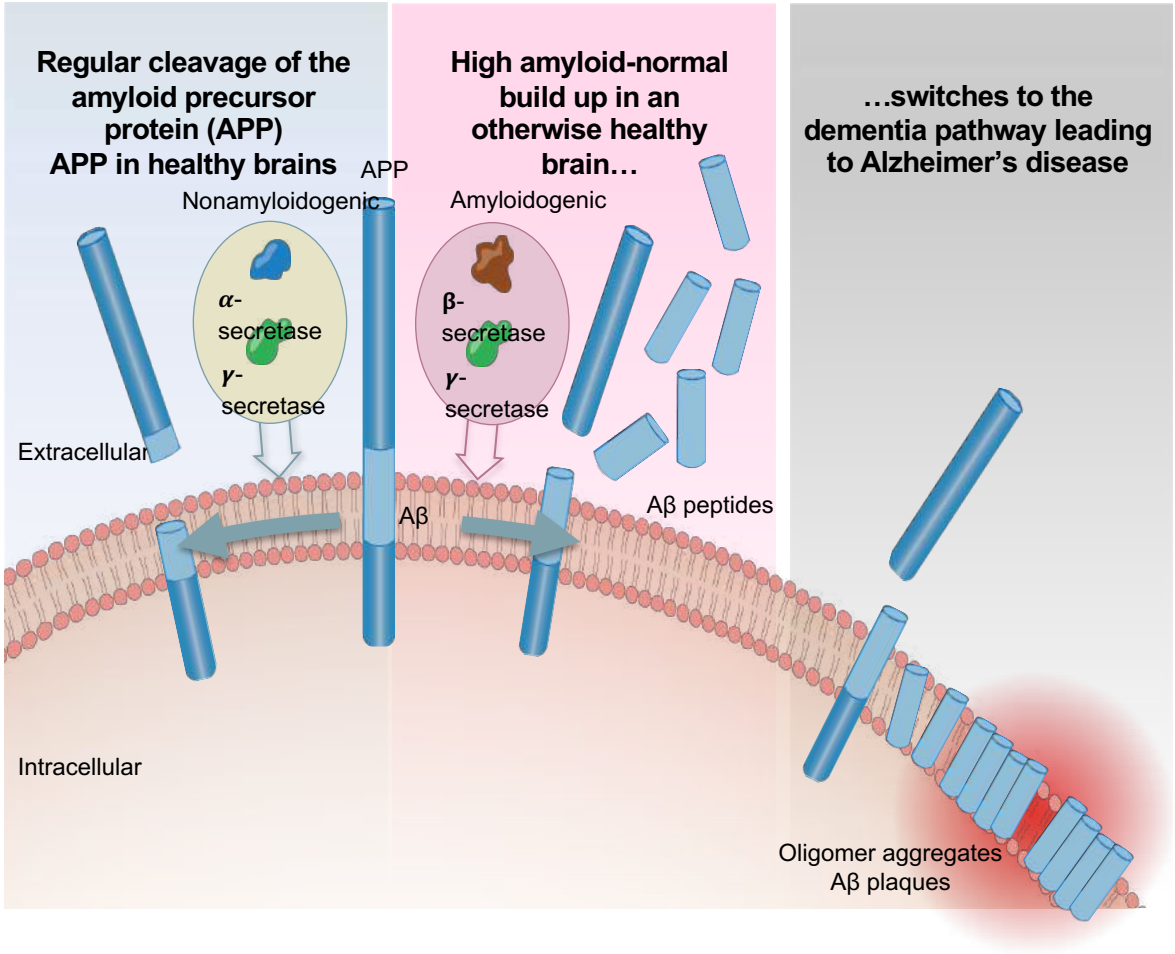
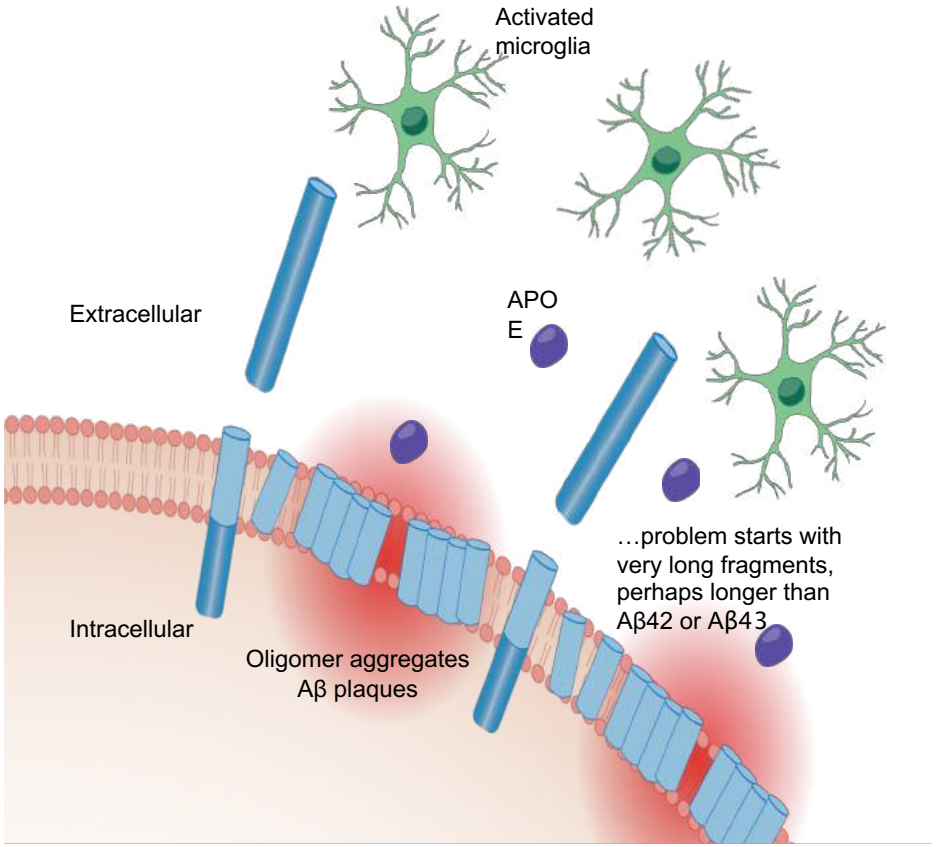
http://dx.doi.org/10.1016/j.cell.2015.01.049


Regular cleavage of the amyloid precursor protein (APP)
APP in healthy brains
APP
Nonamyloidogenic
α-secretase
γ-secretase
Extracellular
Intracellular


Regular cleavage of the amyloid precursor protein (APP)
APP in healthy brains
High amyloid-normal build up in an otherwise healthy brain…
APP
Nonamyloidogenic
Amyloidogenic
α-secretase
γ-secretase
β-secretase
γ-secretase
Extracellular
Aβ
Aβ peptides
Intracellular


Regular cleavage of the amyloid precursor protein (APP)
APP in healthy brains
APP
Nonamyloidogenic
α-secretase
γ-secretase
Extracellular
High amyloid-normal build up in an otherwise healthy brain…
Amyloidogenic
β-secretase
γ-secretase
Aβ
Aβ peptides
…switches to the dementia pathway leading to Alzheimer's disease
Intracellular
Oligomer aggregates
Aβ plaques


Activated
microglia
Extracellular
APO
E
…problem starts with
very long fragments,
perhaps longer than
Aβ42 or Aβ43
Intracellular
Oligomer aggregates
Aβ plaques

What is Downstream of Amyloid Deposition? (1)

- Amyloid deposition is almost entirely apoe dependent
- Dementia depends on PRS (i.e. microglia are key)

RESEARCH ARTICLE

Genetic Risk for Alzheimer Disease Is Distinct from Genetic Risk for Amyloid Deposition

Ganna Leonenko,[1]* Maryam Shoai,[2]* Eftychia Bellou,[1] Rebecca Sims,[1] Julie Williams,[1,3] John Hardy,[2,4] and Valentina Escott-Price,[1,3] the Alzheimer's Disease Neuroimaging Initiative

Objective: Alzheimer disease (AD) is the most common form of dementia and is responsible for a huge and growing health care burden in the developed and developing world. The polygenic risk score (PRS) approach has shown 75 to 84% prediction accuracy of identifying individuals with AD risk.
Methods: In this study, we tested the prediction accuracy of AD, mild cognitive impairment (MCI), and amyloid deposition risks with PRS, including and excluding *APOE* genotypes in a large publicly available dataset with extensive phenotypic data, the Alzheimer's Disease Neuroimaging Initiative cohort. Among MCI individuals with amyloid-positive status, we examined PRS prediction accuracy in those who converted to AD. In addition, we divided polygenic risk score by biological pathways and tested them independently for distinguishing between AD, MCI, and amyloid deposition.
Results: We found that AD and MCI are predicted by both *APOE* genotype and PRS (area under the curve [AUC] = 0.82% and 68%, respectively). Amyloid deposition is predicted by *APOE* only (AUC = 79%). Further progression to AD of individuals with MCI and amyloid-positive status is predicted by PRS over and above *APOE* (AUC = 67%). In pathway-specific PRS analyses, the protein–lipid complex has the strongest association with AD and amyloid deposition even when genes in the *APOE* region were removed ($p = 0.0055$ and $p = 0.0079$, respectively).
Interpretation: The results showed different pattern of *APOE* contribution in PRS risk predictions of AD/MCI and amyloid deposition. Our study suggests that *APOE* mostly contributes to amyloid accumulation and the PRS affects risk of further conversion to AD.

ANN NEUROL 2019;86:427–435

A comprehensive analysis of methods for assessing polygenic burden on Alzheimer's disease pathology and risk beyond *APOE*

Andre Altmann,[1] Marzia A. Scelsi,[1] Maryam Shoai,[2,3] Eric de Silva,[1,4] Leon M. Aksman,[1] David M. Cash,[3,5] John Hardy[2,3] and Jonathan M. Schott[3,5]; for the Alzheimer's Disease Neuroimaging Initiative*

What is Downstream of Amyloid Deposition? (2)

KO-ing TREM2 exacerbated the connection tau pathology indicating the restraining influence of the appropriate microglial response

Neuron

CellPress

Article

Trem2 restrains the enhancement of tau accumulation and neurodegeneration by β-amyloid pathology

Seung-Hye Lee,[1,7] William J. Meilandt,[1,7,8,*] Luke Xie,[2] Vineela D. Gandham,[2] Hai Ngu,[3] Kai H. Barck,[2] Mitchell Rezzonico,[4] Jose Imperio,[1] Guita Lalehzadeh,[1] Melanie A. Huntley,[4] Kimberly L. Stark,[1] Oded Foreman,[3] Richard A.D. Carano,[2] Brad A. Friedman,[4] Morgan Sheng,[1,5] Amy Easton,[1] Christopher J. Bohlen,[1] and David V. Hansen[1,6,*]

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[7]These authors contributed equally
[8]Lead contact
*Correspondence: meilandt.william@gene.com (W.J.M.), dvhansen@chem.byu.edu (D.V.H.)
https://doi.org/10.1016/j.neuron.2021.02.010

Conclusions

- 1) Genetic variability in the response to amyloid deposition is a component of Alzheimer risk: i.e. how well you cope with amyloid deposition is important. Most of this response appears to be microglial
- 2) Two phases of disease (at least): (a) amyloid deposition (b) response to this deposition

Decreased Clearance of CNS β-Amyloid in Alzheimer's Disease

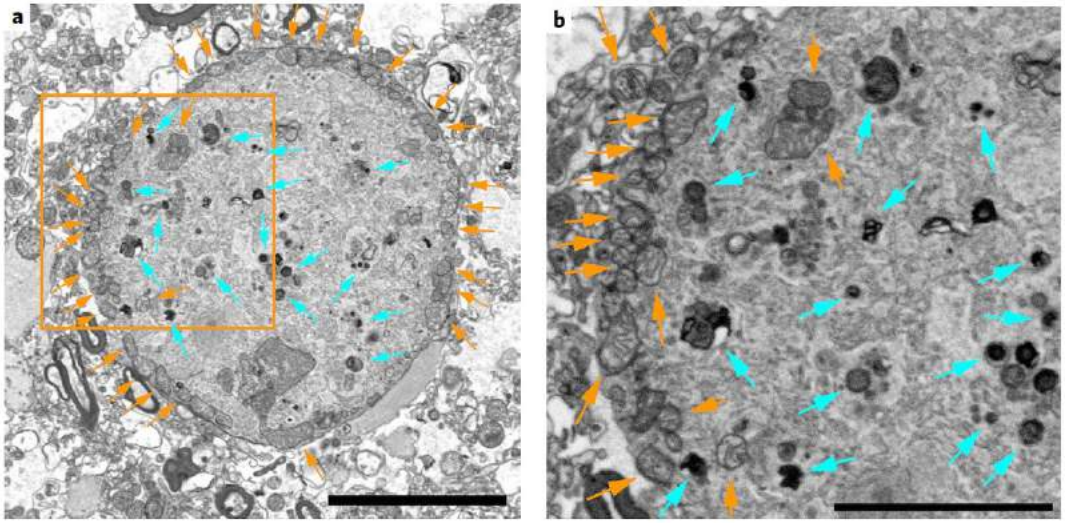
Kwasi G. Mawuenyega,[1] Wendy Sigurdson,[1,2] Vitaliy Ovod,[1] Ling Munsell,[1] Tom Kasten,[1] John C. Morris,[1,2,3] Kevin E. Yarasheski,[4] Randall J. Bateman[1,2,5]*

Summary For Alzheimer's Disease

- 1) Genes involved in early onset mendelian disease are involved in AB production
- 2) Some risk loci also seem to be involved in APP metabolism…. but
- 3)The majority of loci involved in late onset disease are either or both microglial and involved in lipid metabolism
- 4) They are amyloid responsive in mouse transgenic analyses
- 5)….and they are involved in amyloid clearance
- 5) We suggest that APP/AB metabolism disrupts membranes and that this disruption links the two processes.

Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes

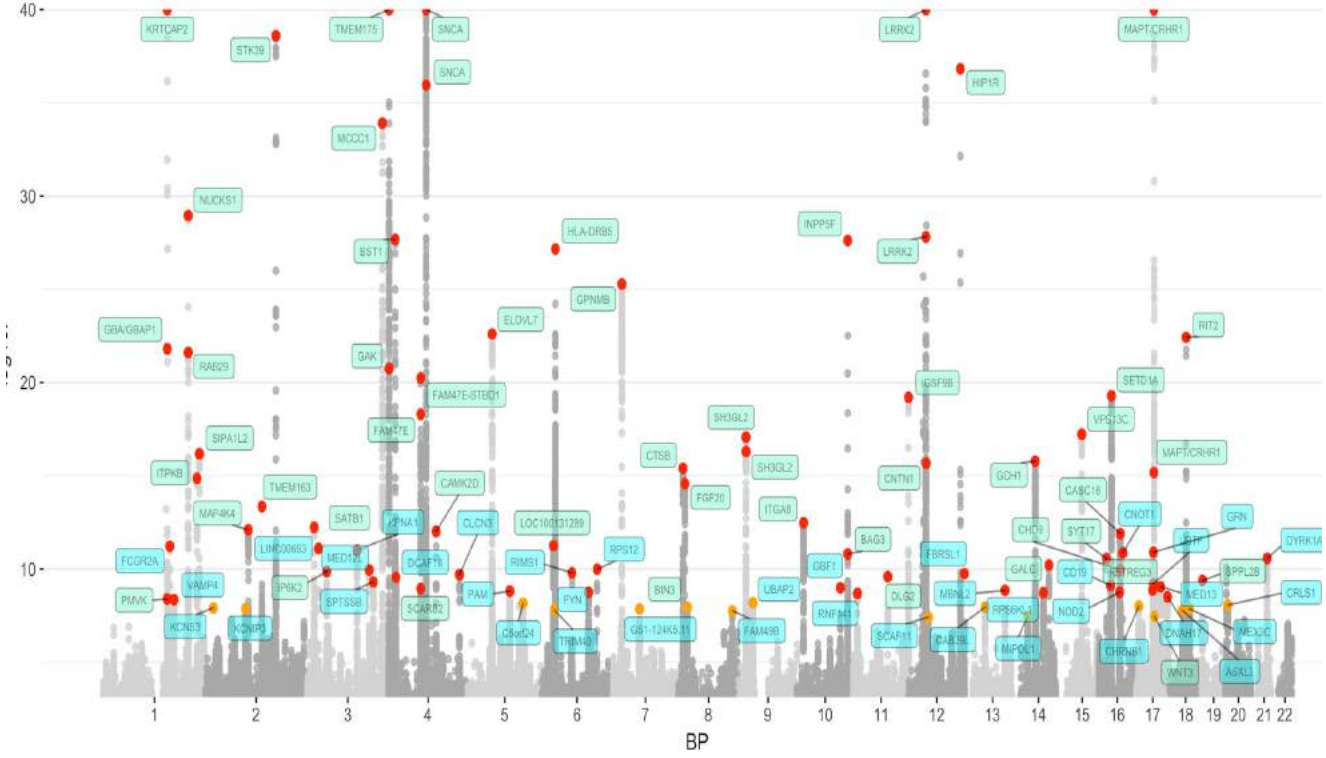
Sarah H. Shahmoradian[1,12], Amanda J. Lewis[1], Christel Genoud[2], Jürgen Hench[3], Tim E. Moors[4], Paula P. Navarro[1], Daniel Castaño-Díez[1], Gabriel Schweighauser[3], Alexandra Graff-Meyer[2], Kenneth N. Goldie[1], Rosmarie Sütterlin[1], Evelien Huisman[4], Angela Ingrassia[4], Yvonne de Gier[4], Annemieke J. M. Rozemuller[5], Jing Wang[1], Anne De Paepe[6], Johannes Erny[7], Andreas Staempfli[7], Joerg Hoernschemeyer[7], Frederik Großerüschkamp[8], Daniel Niedieker[8], Samir F. El-Mashtoly[8], Marialuisa Quadri[9], Wilfred F. J. Van IJcken[10], Vincenzo Bonifati[9], Klaus Gerwert[8], Bernd Bohrmann[11], Stephan Frank[3], Markus Britschgi[11,13], Henning Stahlberg[1,13*], Wilma D. J. Van de Berg[4,13*] and Matthias E. Lauer[6,13*]



Parkinson's disease mendelian loci

Locus	Inheritance	Onset	Gene	Function
PARK1/4	Dominant	30-70	SNCA	Vesicle fusion?
PARK2	Recessive	Teens	PKRN	Mitophagy
PARK6	Recessive	Teens	PINK1	Mitophagy
PARK7	Recessive	Teens	DJ1	Mitophagy
PARK8	Dominant	50-70	LRRK2	Autophagy control?
PARK9	Recessive	Teens	ATP13A2	Lyosomes
PARK14	Recessive	Teens	PLA2G6	Not clear
PARK15	Recessive	Teens	FBXO7	Mitophagy
PARK17	Dominant	50-70	VPS35	Endosomes
PARK19	Recessive	Young	DNAJC6	Endosomes
PARK20	Recessive	Teens	SYNJ1	Endosomes
PARK21	Dominant	30-70	DNAJC13	Endosomes
Unassigned	X linked	30-50	RAB39B	Not clear
Unassigned	High risk	30-70	GBA	Lysosomes

PD GWAS: 40K cases, 1M controls
Many loci are lysosomal or mitochondrial



- **Synuclein metabolised through lysosome**
- **Increased expression of synuclein inhibits GBA**

Gaucher Disease Glucocerebrosidase and α-Synuclein Form a Bidirectional Pathogenic Loop in Synucleinopathies

Joseph R. Mazzulli,[1] You-Hai Xu,[2,3] Ying Sun,[2,3] Adam L. Knight,[4] Pamela J. McLean,[1] Guy A. Caldwell,[4,5] Ellen Sidransky,[6] Gregory A. Grabowski,[2,3] and Dimitri Krainc[1,*]

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DOI 10.1016/j.cell.2011.06.001

Summary for Parkinson's disease

- Too much synuclein
- "Weak" lysosome function….neuronal or glial or both?
- Synuclein is metabolised through the lysosome and too much inhibits lysosome
  - or
- Failure in mitophagy
- Mitophagy is mechanism for removing damaged mitochondria through the lysosome

Sporadic tauopathies: Risk Genes for PSP and CBD

- MAPT
- MOBP — Myelin sheath
- EIF2AK3 — Unfolded protein response
- STX6 — Ubiquitin proteasome pathway?

- TRIM11 — Ubiquitin proteasome

Variation at the *TRIM11* Locus Modifies Progressive Supranuclear Palsy Phenotype

Edwin Jabbari, BSc, MBBS, MRCP,[1] John Woodside, PhD,[1] Manuela M. X. Tan, BPsych,[1] Maryam Shoai, PhD,[2] Alan Pittman, PhD,[2] Raffaele Ferrari, PhD,[2] Kin Y. Mok, PhD, FRCP,[2] David Zhang, MSc,[2] Regina H. Reynolds, MSc,[2] Rohan de Silva, DPhil,[2,3] Max-Joseph Grimm,[4] Gesine Respondek, MD,[4] Ulrich Müller, MD,[5] Safa Al-Sarraj, MBChB, FRCPath,[6] Stephen M. Gentleman, PhD, FRCPath,[7] Andrew J. Lees, MD, FRCP, FMedSci,[3,8] Thomas T. Warner, PhD, FRCP,[3,8] John Hardy, PhD, FMedSci, FRS,[2] Tamas Revesz, MD, FRCPath,[3,8] Günter U. Höglinger, MD,[4] Janice L. Holton, PhD, FRCPath,[3,8] Mina Ryten, MBPhD, MRCP,[2] and Huw R. Morris, PhD, FRCP[1]

38

Tangle Tau is Cleared by the Ubiquitin Proteasome

Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling

Natura Myeku[1], Catherine L Clelland[1], Sheina Emrani[1], Nikolay V Kukushkin[2], Wai Haung Yu[1], Alfred L Goldberg[2] & Karen E Duff[1,3]

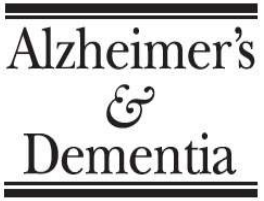
The ubiquitin proteasome system (UPS) degrades misfolded proteins including those implicated in neurodegenerative diseases. We investigated the effects of tau accumulation on proteasome function in a mouse model of tauopathy and in a cross to a UPS reporter mouse (line Ub-G76V-GFP). Accumulation of insoluble tau was associated with a decrease in the peptidase activity of brain 26S proteasomes, higher levels of ubiquitinated proteins and undegraded Ub-G76V-GFP. 26S proteasomes from mice with tauopathy were physically associated with tau and were less active in hydrolyzing ubiquitinated proteins, small peptides and ATP. 26S proteasomes from normal mice incubated with recombinant oligomers or fibrils also showed lower hydrolyzing capacity in the same assays, implicating tau as a proteotoxin. Administration of an agent that activates cAMP–protein kinase A (PKA) signaling led to attenuation of proteasome dysfunction, probably through proteasome subunit phosphorylation. *In vivo*, this led to lower levels of aggregated tau and improvements in cognitive performance.

Overall suggestions

- In all diseases, genetic overproduction of protein leads to autosomal dominant disease
- In all diseases, other genes are involved in protein/damage clearance: Aβ/microglia, SNCA/lysosomes, tau/ubiquitin proteasome.
- Perhaps there is nothing intrinsically distinctive about the proteins… they are “just” the highest expressed proteins of their disposal class.
- Maybe the more important issues, is the age dependent failure of the clearance pathway

Why are there nearly always “co-pathologies”?

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 83-91

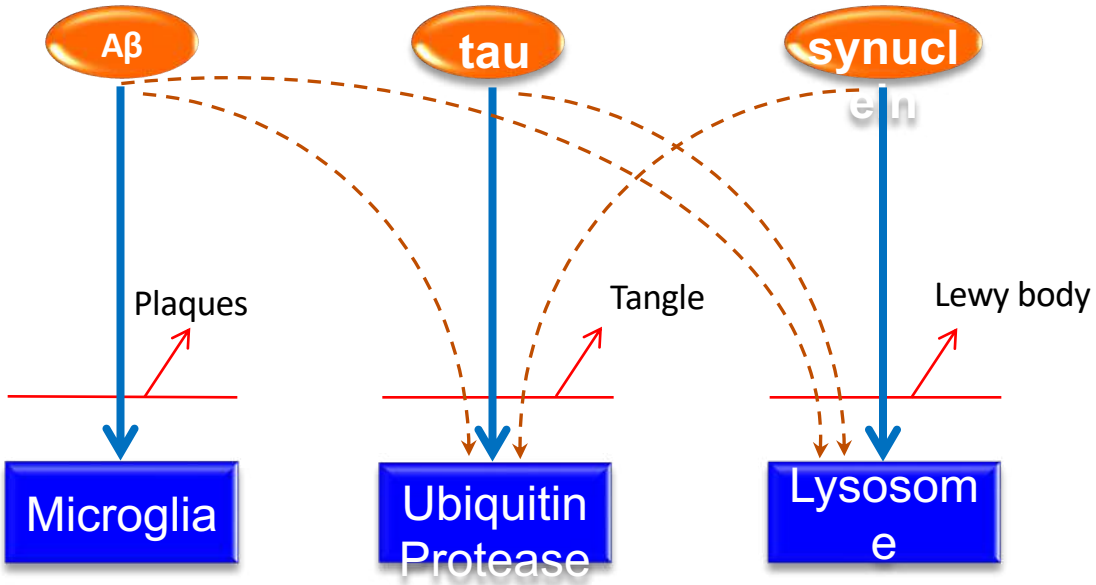


Perspective

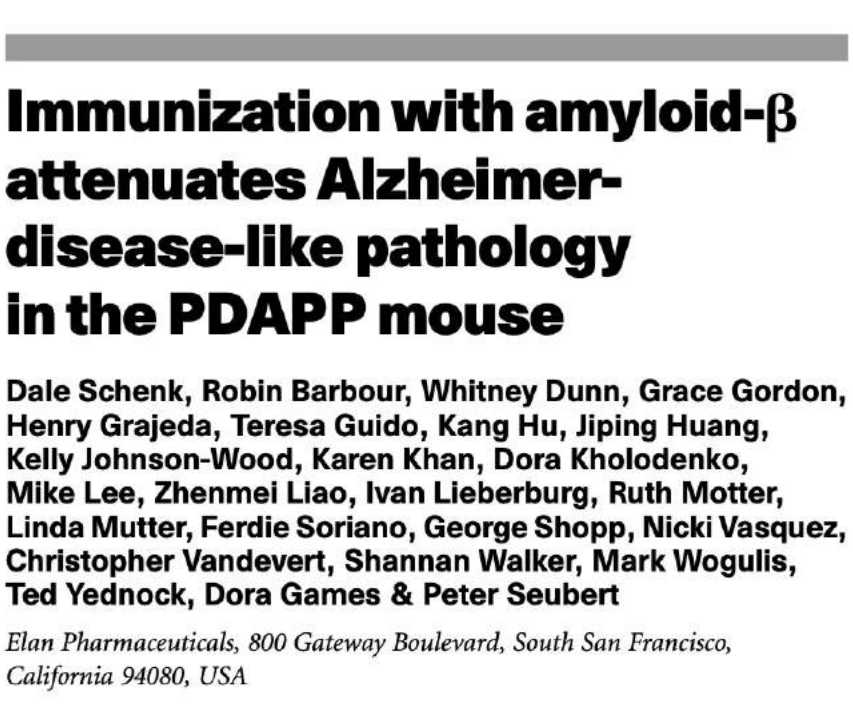
Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development

Gil D. Rabinovici[a], Maria C. Carrillo[b], Mark Forman[c], Susan DeSanti[d], David S. Miller[e], Nicholas Kozauer[f], Ronald C. Petersen[g], Christopher Randolph[h,i], David S. Knopman[g], Eric E. Smith[j], Maria Isaac[k], Niklas Mattsson[l,m], Lisa J. Bain[n], James A. Hendrix[b,*], John R. Sims[o]

…perhaps the connection between pathologies is not direct but relates to overloaded degradative pathways?



Anti amyloid antibodies from 1999



Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

- Early antibodies prevented amyloid build up but did not remove amyloid.
- ….except when there was blood vessel damage (ARIA) which allowed antibody to flood the brain

ARIA = Amyloid Related Imaging Abnormality

LECANEMAB CONFIRMATORY PHASE 3 CLARITY AD STUDY MET PRIMARY ENDPOINT, SHOWING HIGHLY STATISTICALLY SIGNIFICANT REDUCTION OF CLINICAL DECLINE IN LARGE GLOBAL CLINICAL STUDY OF 1,795 PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE

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LR] Roche provides update on Phase III GRADUATE programme evaluating gantenerumab in early Alzheimer's disease

November 14, 2022

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- Phase III GRADUATE studies did not meet their primary endpoints of slowing clinical decline in people with early Alzheimer's
- The level of beta-amyloid removal by gantenerumab was lower than expected
- Topline data will be presented at the Clinical Trials on Alzheimer's Disease (CTAD) Conference
- Roche is committed to the Alzheimer's community and will continue to develop novel diagnostics and potential treatments for Alzheimer's

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Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

S. Budd Haeberlein[1], P.S. Aisen[2], F. Barkhof[3,4], S. Chalkias[1,], T. Chen[1], S. Cohen[5], G. Dent[1], O. Hansson[6,7], K. Harrison[1], C. von Hehn[1,*], T. Iwatsubo[8], C. Mallinckrodt[1,*], C.J. Mummery[9], K.K. Muralidharan[1], I. Nestorov[1], L. Nisenbaum[1,*], R. Rajagovindan[1,*], L. Skordos[1,*], Y. Tian[1], C.H. van Dyck[10], B. Vellas[11], S. Wu[1], Y. Zhu[1], A. Sandrock[1,*]*

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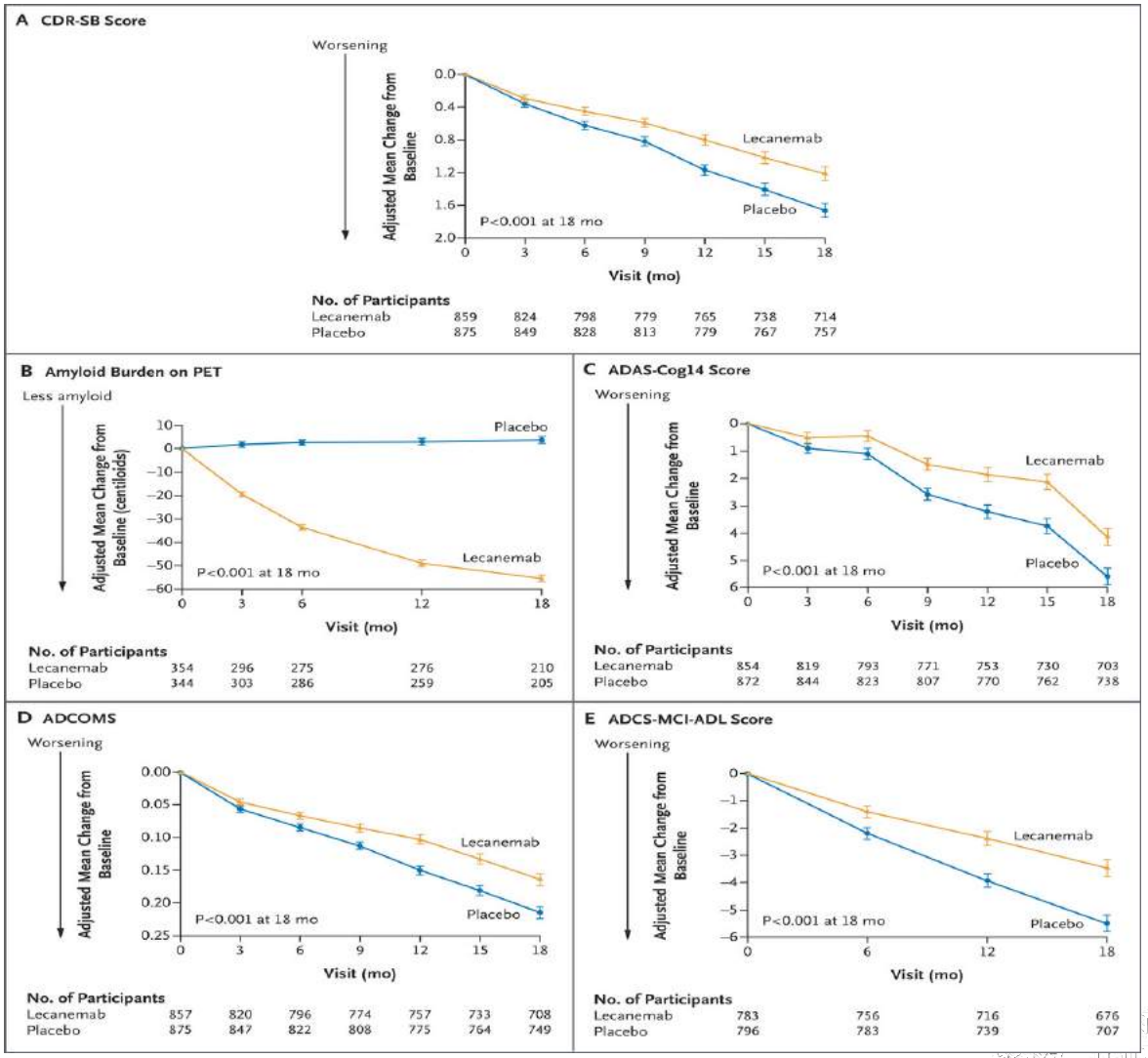
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

ABSTRACT

Lecanemab Primary and Secondary Endpoints (25% slowing at 18 months): still declining though also still diverging from placebo



So……. treatment has a slight benefit but…..

- Recruitment was at early stage of disease and had to be amyloid positive by PET or CSF
  - Diagnostic accuracy of AD is ~70% in specialist centres in US
- Administration was intravenous every two weeks
  - Injection formulation in trial now
- ARIA required monitoring by MRI every 3 months
  - Although most ARIA was asymptomatic (but see next slide)
- Expense of drug? Expense of monitoring?

Amyloid Antibody Review and Predictions (2022)

The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics

Eric Karran and Bart De Strooper

Theoretical slide: when drug drives Ab level below 20, cognitive benefit is seen

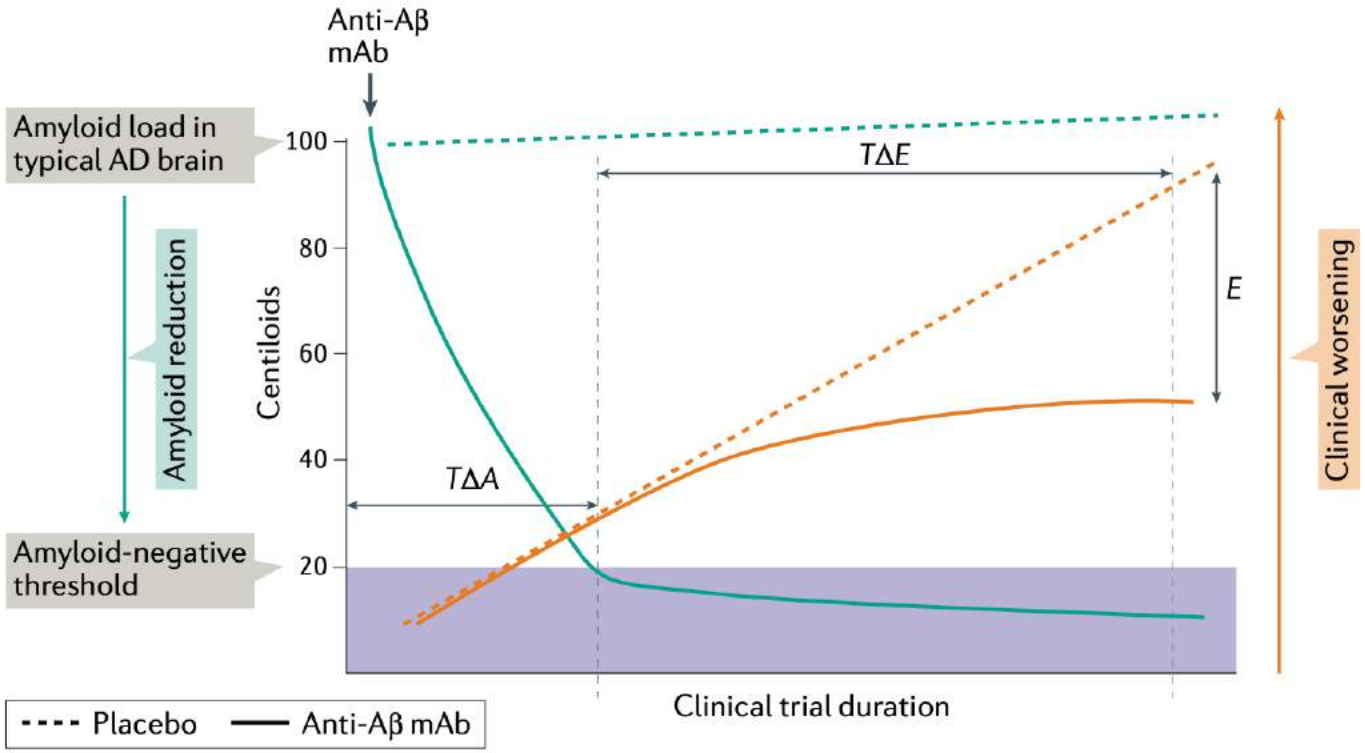
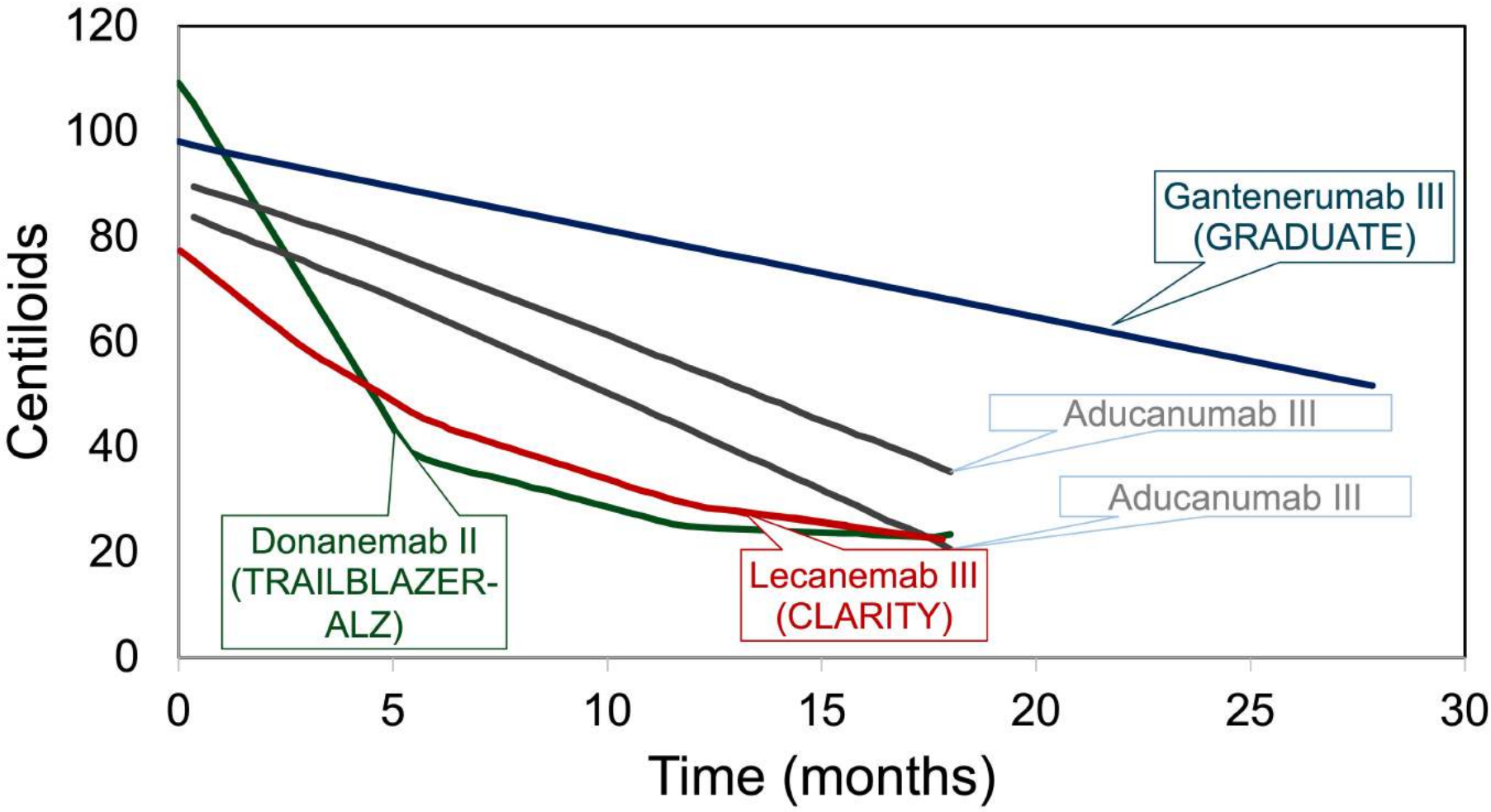


Fig. 3 | **The relationship between amyloid removal and clinical response.** The graph illustrates the


120
100
80
60
40
20
0
Centiloids
0
5
10
15
20
25
30
Time (months)
Gantenerumab III
(GRADUATE)
Aducanumab III
Aducanumab III
Donanemab II
(TRAILBLAZER-
ALZ)
Lecanemab III
(CLARITY)

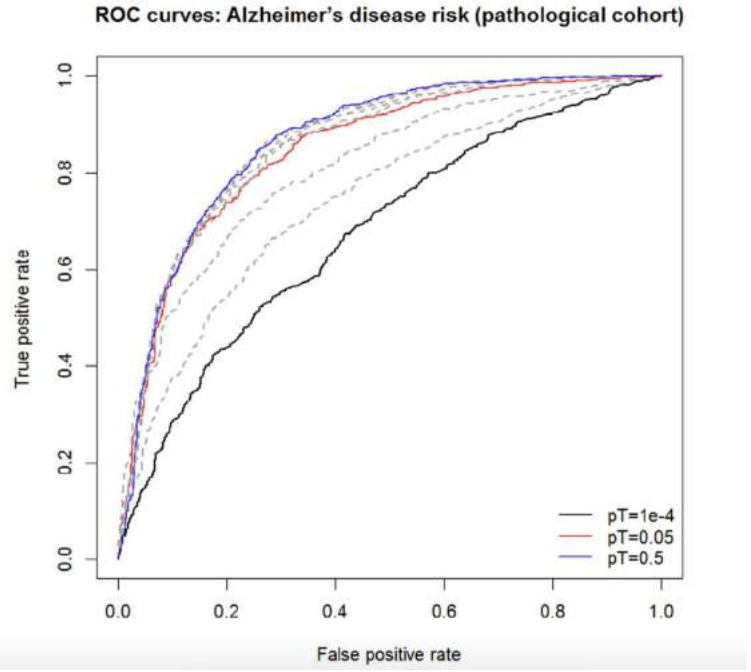
Prediction for 'Sporadic Alzheimer's Disease (AUC ~84%)

Polygenic Risk Score Analysis of Pathologically Confirmed Alzheimer Disease

Valentina, Escott-Price, PhD,[1]
Amanda J., Myers, PhD,[2]
Matt, Huentelman, PhD,[3] and
John, Hardy, PhD[4]

Previous estimates of the utility of polygenic risk score analysis for the prediction of Alzheimer disease have given area under the curve (AUC) estimates of <80%. However, these have been based on the genetic analysis of clinical case–control series. Here, we apply the same analytic approaches to a pathological case–control series and show a predictive AUC of 84%. We suggest that this analysis has clinical utility and that there is limited room for further improvement using genetic data.

ANN NEUROL 2017;82:311–314



Blood-based biomarkers for Alzheimer's disease: towards clinical implementation

Charlotte E Teunissen, Inge M W Verberk, Elisabeth H Thijssen, Lisa Vermunt, Oskar Hansson, Henrik Zetterberg, Wiesje M van der Flier, Michelle M Mielke, Marta del Campo

For many years, blood-based biomarkers for Alzheimer's disease seemed unattainable, but recent results have shown that they could become a reality. Convincing data generated with new high-sensitivity assays have emerged with remarkable consistency across different cohorts, but also independent of the precise analytical method used. Concentrations in blood of amyloid and phosphorylated tau proteins associate with the corresponding concentrations in CSF and with amyloid-PET or tau-PET scans. Moreover, other blood-based biomarkers of neurodegeneration, such as neurofilament light chain and glial fibrillary acidic protein, appear to provide information on disease progression and potential for monitoring treatment effects. Now the question emerges of when and how we can bring these biomarkers to clinical practice. This step would pave the way for blood-based biomarkers to support the diagnosis of, and development of treatments for, Alzheimer's disease and other dementias.

Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease

May 3, 2023

Nearly half (47%) of the participants on donanemab (compared to 29% on placebo) had no clinical progression at 1 year (defined as no decline in CDR-SB)

Phase 3 trial met primary endpoint and all secondary endpoints measuring cognitive and functional decline

Donanemab treatment slowed clinical decline by 35% compared to placebo, and resulted in 40% less decline on the ability to perform activities of daily living

Over half of all participants completed their course of treatment by 12 months

Donanemab also works (as predicted by model): plaque removal is key.

Data seems to suggest earlier treatment has greater beneficial effect

Earler treatment should, perhaps, lead to less ARIA

Two drugs should lead to price competition

Article

https://doi.org/10.1038/s41591-023-02326-3

Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial

Received: 1 September 2022

Accepted: 29 March 2023

Published online: 24 April 2023

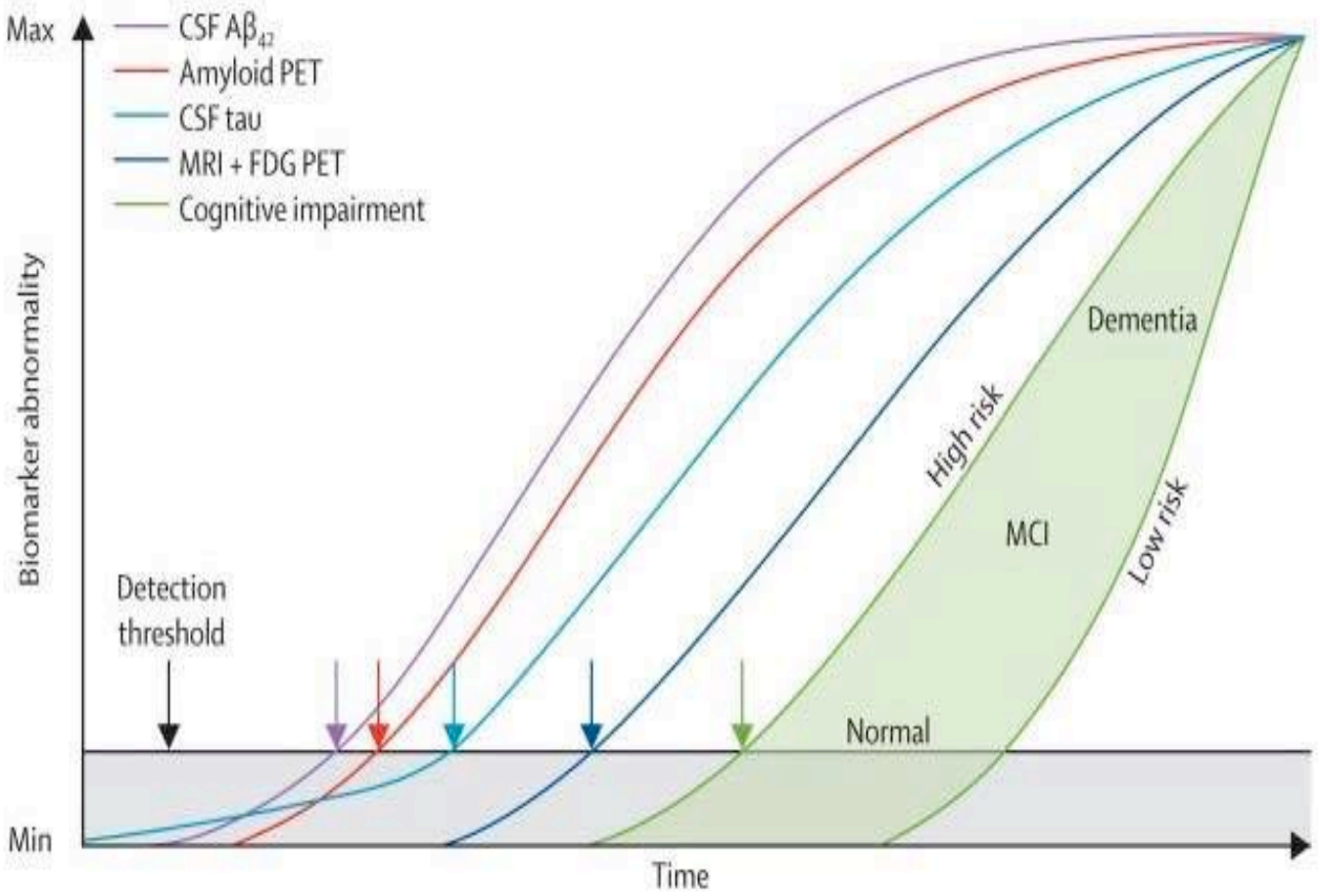
Check for updates

Catherine J. Mummery[1,14], Anne Börjesson-Hanson[2,14], Daniel J. Blackburn[3,14], Everard G. B. Vijverberg[4,14], Peter Paul De Deyn[5,14], Simon Ducharme[6,14], Michael Jonsson[7,14], Anja Schneider[8,14], Juha O. Rinne[9,14], Albert C. Ludolph[10,14], Ralf Bodenschatz[11,14], Holly Kordasiewicz[12,15], Eric E. Swayze[12,15], Bethany Fitzsimmons[12,15], Laurence Mignon[12,14], Katrina M. Moore[12,15], Chris Yun[12,15], Tiffany Baumann[12,15], Dan Li[12,15], Daniel A. Norris[12,15], Rebecca Crean[12,15], Danielle L. Graham[13,15], Ellen Huang[13,15], Elena Ratti[13,15], C. Frank Bennett[12,15], Candice Junge[12,14] & Roger M. Lane[12,14]

Intrathecal antisense to MAPT reduces CSF tau levels

On the “Jack” curves when are treatments attempted?

Jack CR, Holtzman DM. Neuron. 2013 80:1347-58.



My view…now that FDA has approved!!!

- We now “know” what anti-amyloid drugs need to do and this will speed up development of other drugs…. which may be better and which would bring the price down
- Avoiding ARIA would be great and maybe possible
- Blood and genetic analyses are in process to make diagnosis easier and more generally accessible
- This is a wake up call to organize dementia services for this and future Alzheimer therapies.

Future Research Questions…

- Will anti-amyloid therapies halt disease (not in current trials).
  - Perhaps if started earlier?
  - What is the “residual” substrate of pathology (neuropathology investment needed).
- What would be the effect of drug holidays?
- How should we design clinical trials:-
  - Of other anti amyloid therapies
  - Of non amyloid therapies?

Policy and costs

- Present NHS diagnosis at most centres is inadequate
- Present versions of drugs needs intrathecal (doctor's administration) (sub cutaneous versions are on the way)
- Presently drugs require regular MRIs for ARIA reasons (maybe earlier administration will make this less of a worry and maybe more experience will lessen concern; usually a problem in first 6 weeks.
- Cost of antibodies is always high…. ~£25K a year in this case…. But better quality of life and less nursing home care etc. Two drugs means more competition…

My view……

- These are the first successful therapies….
- They. “teach” us what antiamyoid therapies need to do…. both better and safer drugs will follow
- More drug companies will invest

1903 Wright Brothers: First powered flight
1919 London to Paris: First scheduled flight and first transatlantic flight

Topical Press Agency/Hulton Archive/Getty Images