what will people say 100 yrs from now?

Chapter 19 - SNCD

what is:
subjective
cognitive
decline?

ALL THE ALZ-D TOPICS THAT ARE FIT TO PRINT

19.1 Astrobiology and Calcium
19.2 Microglia and Neuroinflammation
19.3 Does AlzD = Type 3 Diabetes?
19.4 Molec. Path 1: microRNAs and Cell Physiology
19.5 Molec. Path 2: Genetic Risks and Big Data
19.6 Additional Risk Factors and Preclinical AlzD
19.7 Herpes Brain and Other Infections
19.8 Tau and Amyloid (and PART)
19.9 Prions and Prion-like Proteins: a Role in Alzd?
Treatments and Therapies: NOW CHAPTER 20

You cannot lecture
as you write
or at least
You SHOULD NOT!

HSPH statistics

Chapter 19 Overview

but the real truth behind Chap. 19 is

Preamble to the *AlzD Constitution*

REPRISE: 2 SLIDES FROM **ABO OLIGOMERS**

REVIEW

2015

ABOs

Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis

Kirsten L. Viola · William L. Klein from Northwestern Univ. – the Other NU

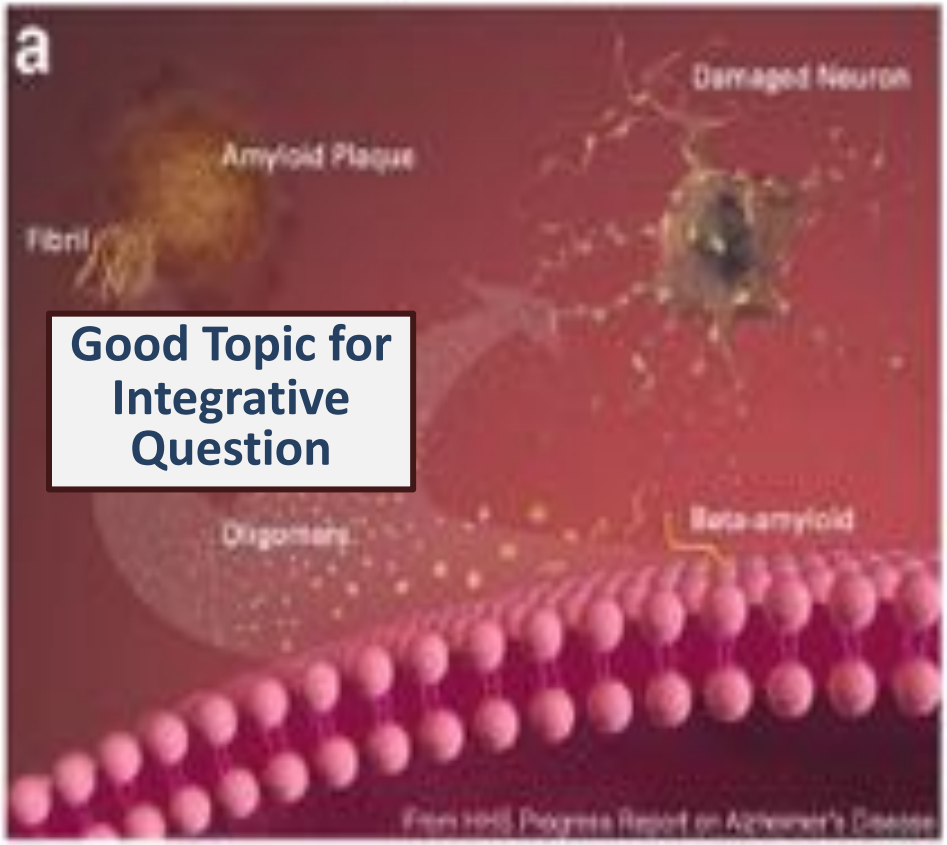
Abstract Protein aggregation is common to dozens of diseases including prionoses, diabetes, Parkinson's and Alzheimer's. Over the past 15 years, there has been a paradigm shift in understanding the structural basis for these proteinopathies. Precedent for this shift has come from investigation of soluble Aβ oligomers (AβOs), toxins now widely regarded as instigating neuron damage leading to Alzheimer's dementia. Toxic AβOs accumulate in AD brain and constitute long-lived alternatives to the disease-defining Aβ fibrils deposited in amyloid plaques. Key experiments using fibril-free AβO solutions demonstrated that while Aβ is essential for memory loss, the fibrillar Aβ in amyloid deposits is not the agent. The AD-like cellular pathologies induced by AβOs suggest their impact provides a unifying mechanism for AD pathogenesis, explaining why early stage disease is specific for memory and accounting for major facets of AD neuropathology. Alternative ideas for triggering mechanisms are being actively investigated. Some research favors insertion of AβOs into membrane, while other evidence supports ligand-like accumulation at

more claims: ABOs

- trigger redistrib. of spine proteins
- ↑'s NMDA, mGluR receptor activity
- cause P-tau, insulin resistance, synapse loss and oxidative stress
- **associated w/ hypercholesterolemia & diabetes (co-morbidities)**
- early presence means ABOs are good for diagnostics and drug-targeting
  [biomarkers & brain imaging now related]
- **failure to target ABOs might explain poor clinical results in AlzD to date**
- rapidly inhibit LTP in brain slices
- kill cells via FYN mechanism
- distinct build-up mech ≠ plaque mech.
- **ABO antibodies rescue memory in transgenic mouse strains**
- an APP mutation reduces Aβ, risk of AlzD

curious: high AB42 in CSF/plasma is "good". "plaque sponges" story weak. ↓↓ clearance?

REPRISED: ABOs are THE BEST (aka the worst) iaw NU's Viola and Klein, Cognitive Neurology Center



Good Topic for Integrative Question

2015

Fig. 1 Aβ oligomers (AβOs) instigate neuron damage in Alzheimer's disease. a Oligomeric Aβ, rather than insoluble amyloid species, instigates neuron damage in AD (adapted from the "2004/2005 Progress Report on Alzheimer's disease" Health and Human Services). b AD-associated changes attributed to AβOs

moreover: ABO's may behave like prions AND may induce tau responses. **BOTH** might contribute to amyloid-tau damage to CNS!

We've moved beyond leeches, phrenology and astrology . . .

ALL Feedback graciously received

Advanced Alzheimeromics

aka: CHAPTER 19 -- A STUDY IN FUTILITY
…um…I mean…the GREAT works of many **practitioners** of the *arts de la dark-ages*!

OR

ALL THE TOPICS THAT ARE FIT TO PRINT
…ala The New York Times…
All the News that's Fit to Print
1897, Adolph S. Ochs, Owner - NYT

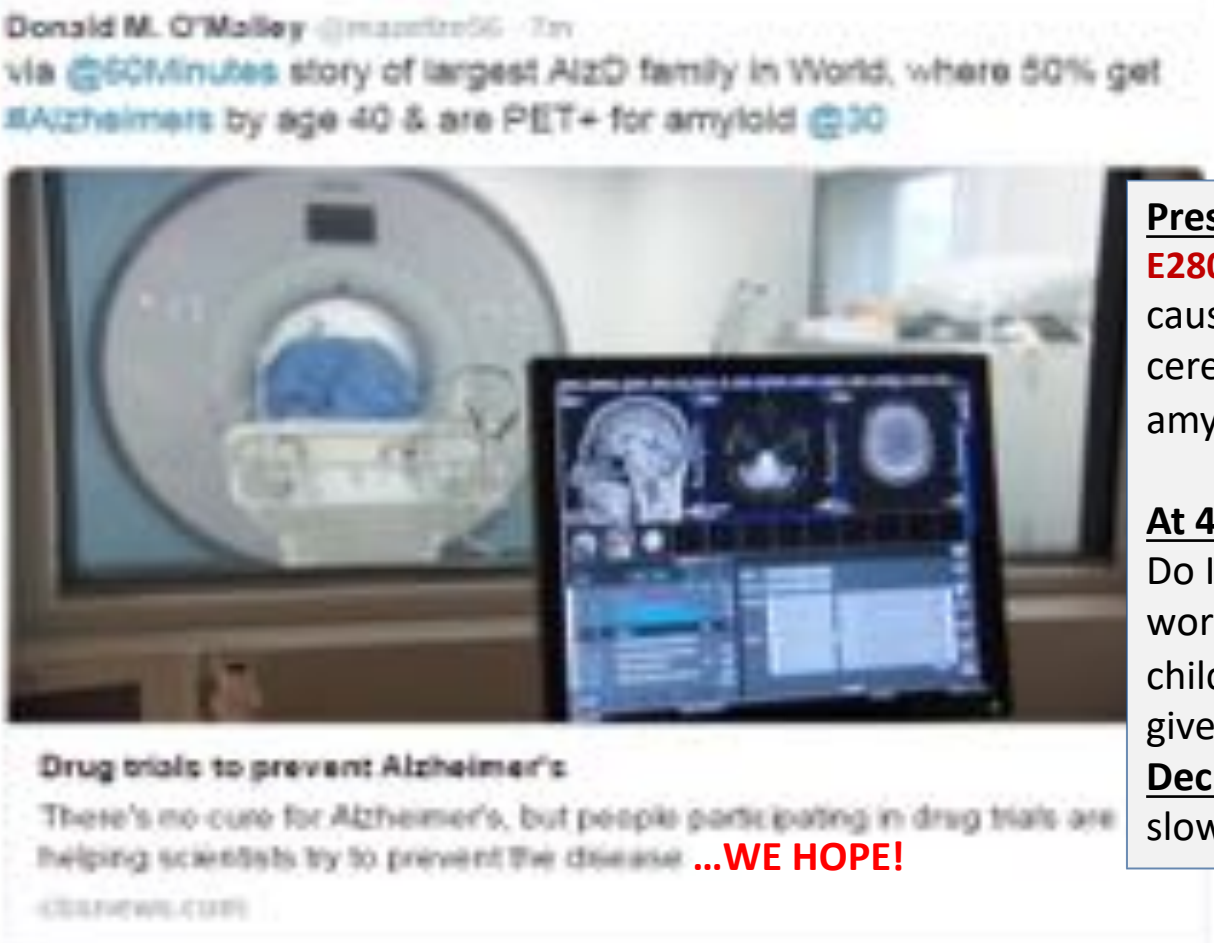
. . . or HAVE we?

The **Alzheimerome** = every bit of info about AlzD
[how much is noise?] spell check thought this should be "**Alzheimer me**"

EOAD – a Deeper Dive ... *in Columbia*

PET positive at 30!

CBS 60 minutes link below = totally awesome story



Presenilin 1 = part of gamma secretase. **E280A = severe EOAD allele in Medellin** causes amyloid deposits and severe cerebellar pathology. PET shows amyloid in presymptomatic, by age 30.

At 45, fellow asks wife what day is it? Do I have to go to work. Later it gets worse– he forgets names of his children. Later becomes confused, given a shirt, puts it on his feet. **Decline over 10 years** (regular AlzD slower by how much?).

Medellin (Antiochia) subject drew poor Reyes figure at age 38 (MCI stage?), worse at 45; accelerating decline at 50, 51.

http://www.cbsnews.com/news/60-minutes-drug-trials-to-prevent-alzheimers-disease/

EOAD is familial, i.e. it is a *genetic defect*: **should we edit EOAD** out of the human genome?

Late-in-life Alzheimer's, by far the most common form of the disease, is not caused by a gene mutation, so there is no test to show definitively if a person will develop it. But there is a test to determine if a person carries a certain form of a gene that indicates greater risk. After watching his mother die from the disease, Scott Stave, a retired physical therapist in Phoenix, opted to take the test.

"I decided I can either continue to live this life of fear, or I can find out," he tells Stahl. "As it turns out, I got the worst possible results."

using routine IVF w/ embryo screen

Sporadic AlzD starts after age 65

CRISPR anyone? an *easier* way?

Norm: age 70. Looks good, confident, gentle manner. Asked "what city are we in now?" he chuckles, says "I cannot answer that right now". Asked who the woman is (in room with them), he says "Betsy". Who is she? She is someone I care about. Is she your sister? [he equivocates] Is she your wife? [he cannot answer; she is his wife of many, many years].

EOAD = Early Onset vs. regular Alzheimer's Disease

Because EOADs can be diagnosed at 30 (or at birth), we can treat earlier (like giving a polio vaccine before contracting the disease). We can treat entire Medellin family. If it works, how many MORE can it treat? **SPORADIC = 1%** incidence at age 60; 40% at age 85! How many PEOPLE should we treat?

60 MINUTES ALL ACCESS

EOAD – the end of the line for most…but not everyone!

EOAD – in Columbia: an unusual case study

A centuries old demon that haunted Medellin villagers in Colombia:

Francisco Lopera cajoled families to donate brains and put this family and EOAD and presenilin on the neurology map like no other. While braving open warfare.

details: A very rare Christchurch mutation in ApoE3! Protection is "recessive": heterozygotes are not spared. key notes below.

locus of action: ApoE3 binds to a glycoprotein necessary for Tau pathology! This crucially "clicks" together a bunch of disparate details in my mind, and refutes a suspicion re: EOAD.

https://www.nytimes.com/2019/11/04/health/alzheimers-treatment-genetics.html

Nature Medicine Article Lead Author: **Yakeel Quiroz-Gaviria, PhD**
Director, Mass General Multicultural Alzheimer's Prevention Program
Clinical Director, Mass General Multicultural Neuropsychology Program, MUNDOS
Assistant Professor, Harvard Medical School. Neuropsychologist.
[no Nobel Prize yet...]

This is a report on a **Nature Medicine article**… Lady CC, next slide had no formal educ / cognitive reserve.

Chapter 19 - SNCD

Much of Chap. 19
overlaps earlier topics

BREAKING NEWS DIVISION:

LADY Christchurch of Medellin

[she was MCI at testing stages]

In which section should she go?

Lady X is referred to here as *Lady Christchurch* for simplicity & to emphasize protective CC mutation in ApoE3 gene

19.2 Microglia and Neuroinflammation
19.3 Does AlzD = Type 3 Diabetes?
19.4 Molec. Path 1: microRNAs and Cell Physiology
19.5 Molec. Path 2: Genetic Risks and Big Data
19.8 Tau and Amyloid – Back to the Future
20: Treatments and Therapies

88 citations as of Dec. 2020; one by Yakeel on ApoE2 others are more random ... **now 123 – 4.6.21**

Nature Medicine: a Brief Communication … ➔

Random Trivia: If you are passing from the Atlantic Ocean to the Pacific Ocean via Panama **are you heading EAST or WEST?**

NOT Random Trivia: How did the Christchurch Mutation (R136S on ApoE3) **get to Medellin?** [The E280A cohort]

re R136S: R-ine and S-ine…that's a pretty key amino acid change!

1000's of Rabbit Holes: *Knowledge Architectures* **are your Cognitive Armor**

nature medicine

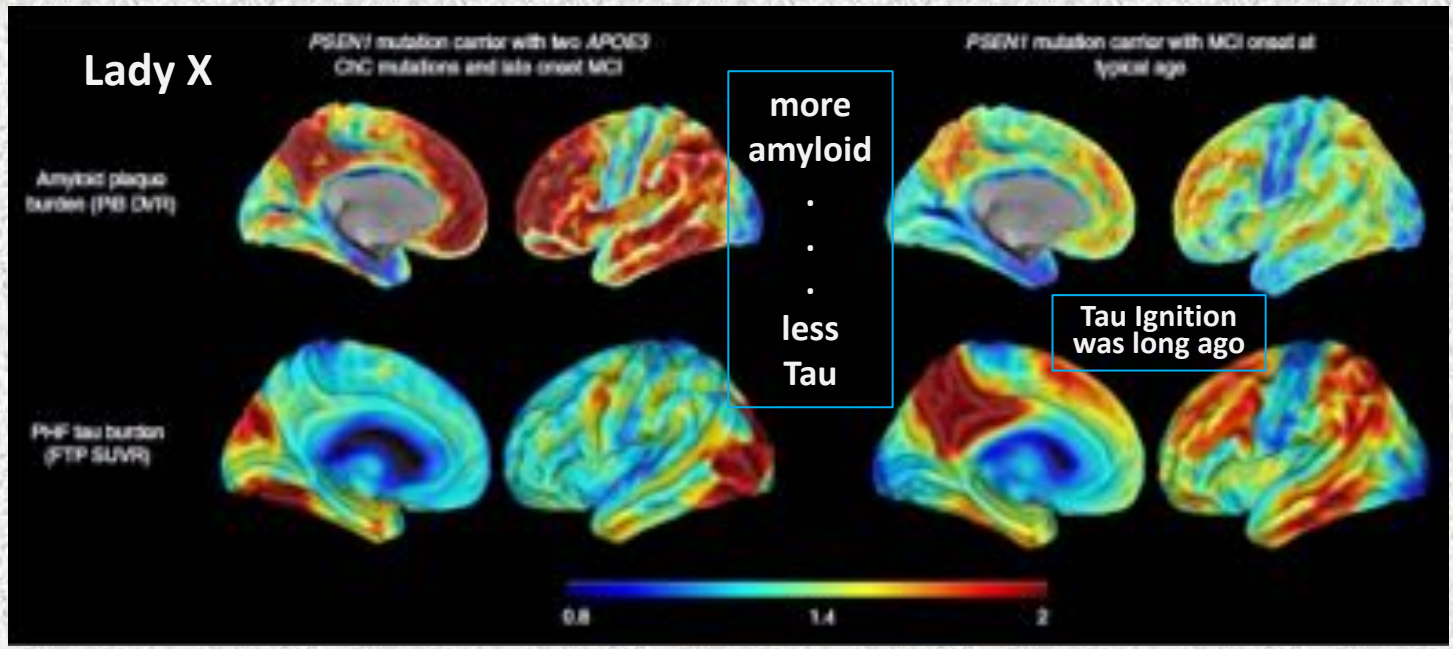
Brief Communication | Published: 04 November 2019

Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report

Joseph F. Arboleda-Velasquez, Francisco Lopera, [...] Yakeel T. Quiroz

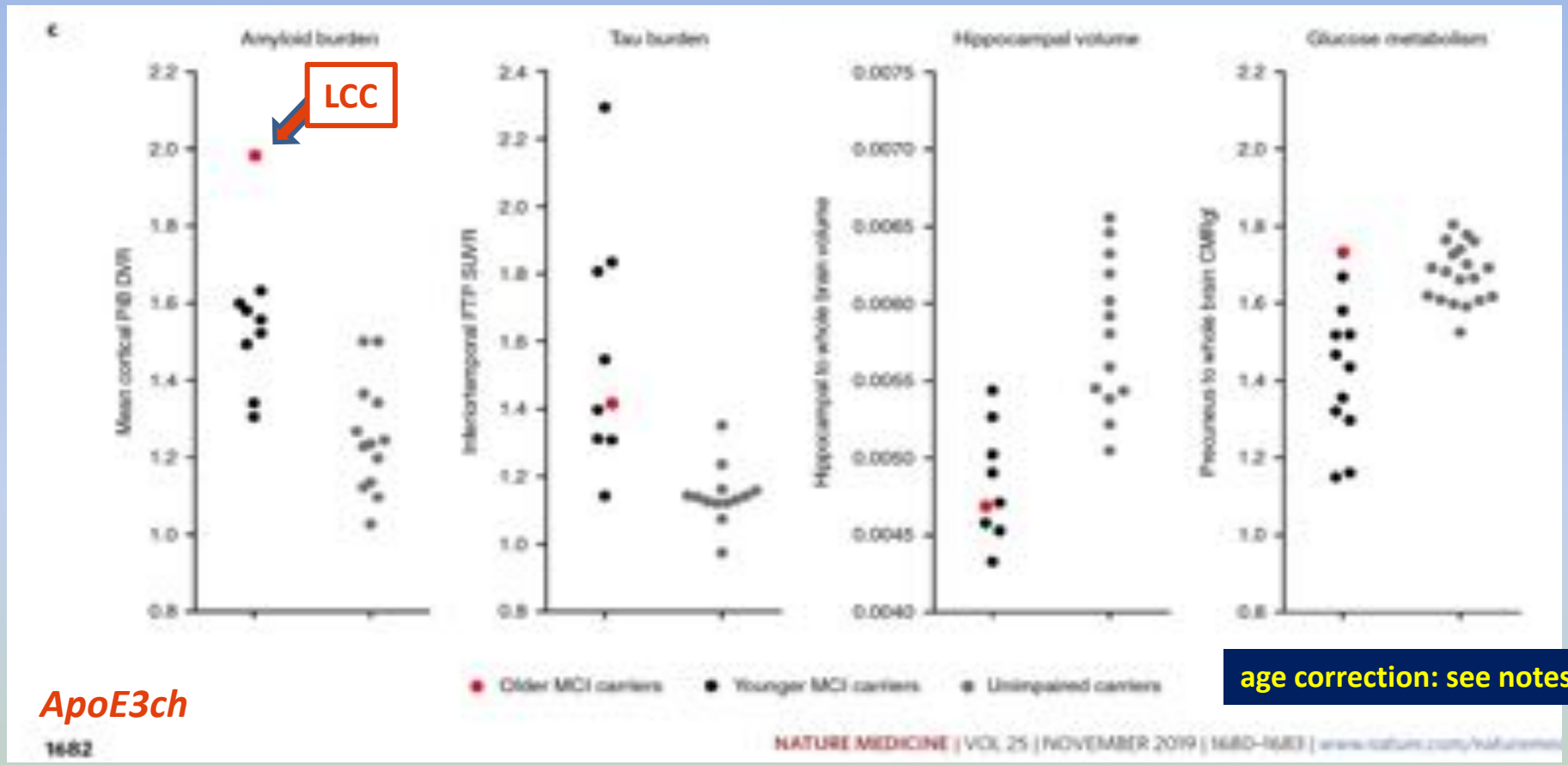
Nature Medicine 25, 1680–1683(2019) | Cite this article

ABSTRACT: We identified a PSEN1 (presenilin 1) mutation carrier from the world's largest autosomal dominant Alzheimer's disease kindred, who did not develop mild cognitive impairment until her seventies, three decades after the expected age of clinical onset. The individual had two copies of the APOE3 Christchurch (R136S) mutation, unusually high brain amyloid levels **and limited tau and** neurodegenerative measurements. Our findings have implications for the role of APOE in the pathogenesis, treatment and prevention of Alzheimer's disease.



MGH, MEEI, HMS, UCSB, BC, Brigham & Women's, ASU, AU, Sweden, London *AND* Universidad de Antioquia

Where Lady Christchurch fits in [presumably due to homozygous R136S]



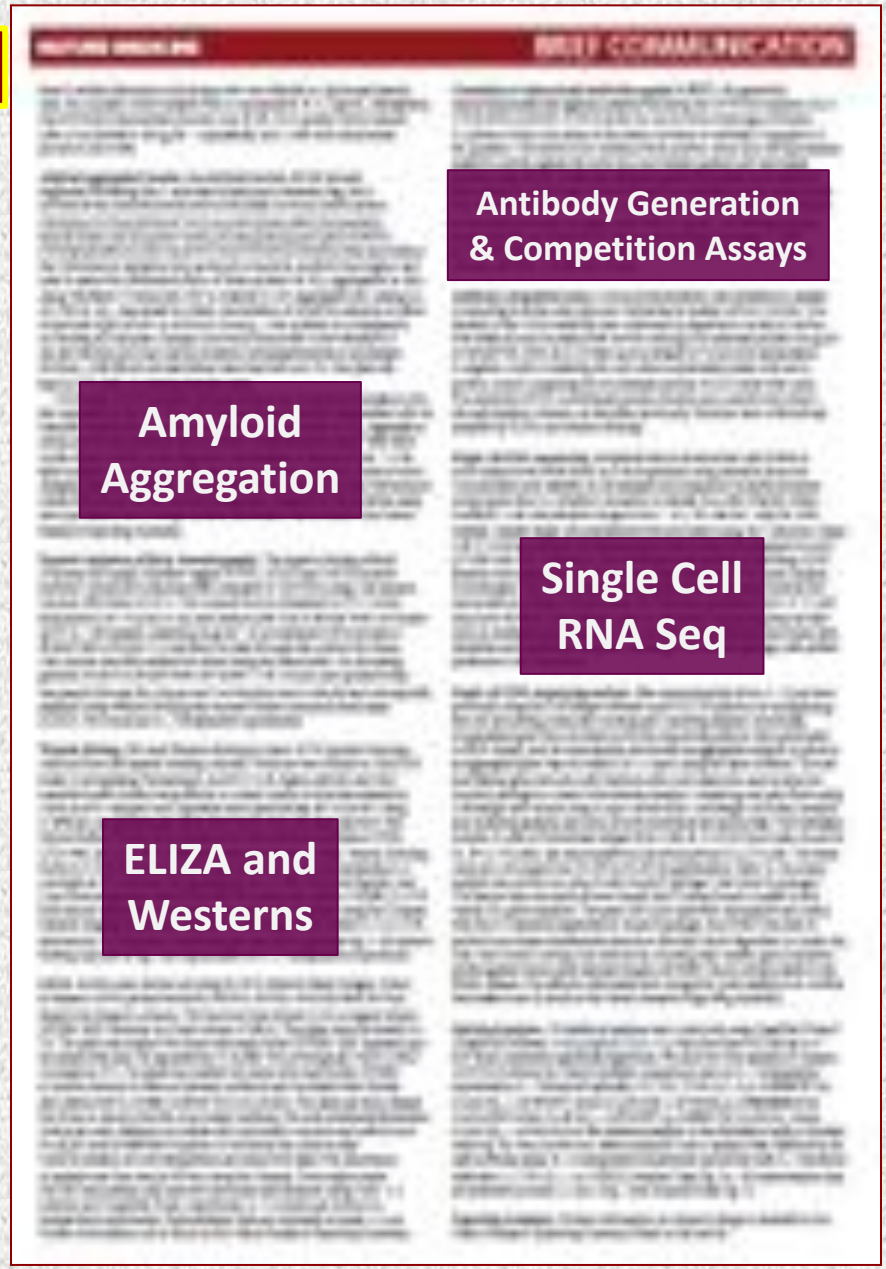
Curious Results: Extremely high amyloid, should have died years or decades earlier and have been severely impaired. Tau burden is *near* normal and mid-lower amongst the *PSEN1* E280A cohort. Her hippo. **atrophy** seems substantial, in **contrast to her most "positive" measure,** glucose (**FDG**) which exceeds all younger cohort members and is near the top of the controls. CC mutation R136S (aRg➔Serine) was found in 1987 research on lipidemia patients (AlzD, neurons not mentioned in paper). Lady CC's double *ApoEch* was discovered via whole-exome sequencing as they sought explanation for her resistance to EOAD. Very limited discussion of CC gene.

HOW brief???

Technology Matters

Tech Know-How Matters

i.e. pages 5 and 6 of 15



Received: 10 Jan 2019; Accepted: 12 Sept 2019: is a Reviewer responsible for all this? NOT BRIEF!

Chapter 19 - SNCD

Implications of Lady Christ Church

Amyloid, by itself, is not seriously toxic
BUT it triggers Tau Pathology
This can be BLOCKED ONLY BY homozygous ApoE3 allele
fits with Amyloid Cascade Hypothesis
fits better with Tau Ignition story?
No WORD yet on the actual protective mechanism
also, still awaiting additional case to confirm (would be rare**)**
Nonetheless, a Game Changer! ... Potentially!

NEW: Could Tau Pathology be an epiphenomenon?

1. **no b/c** its strongly correlated with severity AND the new synaptic-tau study impairing presynaptic function (amongst others).
2. **yes b/c** we still don't have clear understanding of the RESPONSIBLE DAMAGE and it AB/ABOs might be directly driving the damage.
3. **Lady CC story** shows that *something* related to ApoE3 can halt AB-driven neural circuit, which fits with the Cascade & Ignition hypotheses.

Is LCC (Lady ChristChurch) DONE? re: the story, not the person!

2020

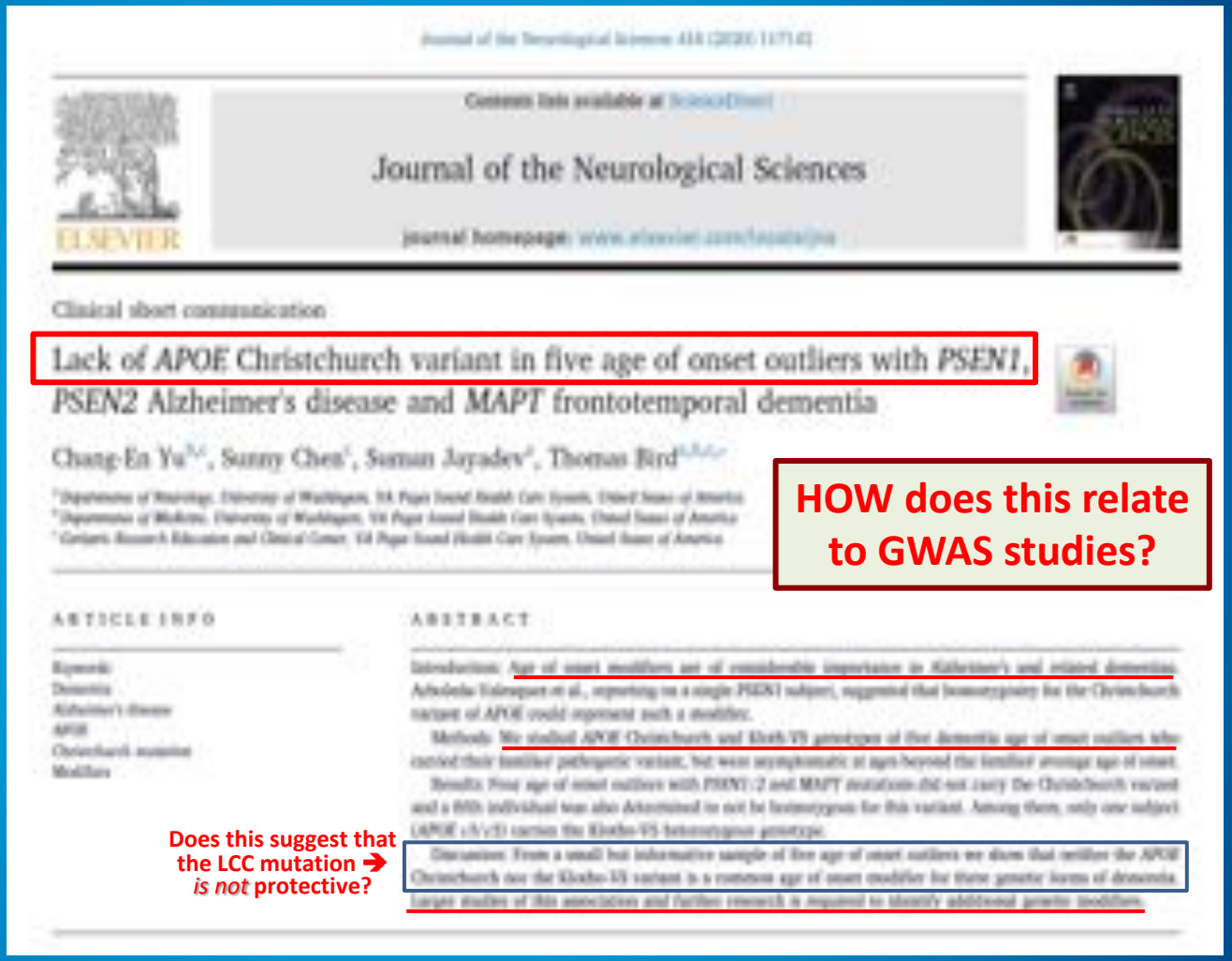
5 patients, one FTD
+ 4 w/ EOAD genes
all showed "late onset"
none had LCC gene

Does this citer of Quiroz eviscerate the LCC story?

Is any of the verbiage MISLEADING?

Where are we Now?

Christchurch *is not* **a "common age of onset modifier"**



Journal of the Neurological Sciences

journal homepage:

Clinical short communication

Lack of *APOE* Christchurch variant in five age of onset outliers with *PSEN1*, *PSEN2* Alzheimer's disease and *MAPT* frontotemporal dementia

Chang-En Yu, Sunny Chen, Suman Jayadev, Thomas Bird

ARTICLE INFO

ABSTRACT

HOW does this relate to GWAS studies?

Does this suggest that the LCC mutation → *is not* protective?

How should we move forward?

Alternative View: citer of Christchurch paper!

2020

THEORETICAL ARTICLE

Alzheimer's & Dementia

Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease ← which is SAD

Amy F. T. Arnsten | Dibyadeep Datta | Kelly Del Tredici | Heiko Braak

FConn Guru

Abstract

The etiology of the common, sporadic form of Alzheimer's disease (sAD) is unknown. We hypothesize that tau pathology within select projection neurons with susceptible interneuronal events can initiate sAD. This postulate rests on extensive data demonstrating that in human brains tau pathology appears about a decade before the formation of Aβ plaques (Aβpl), especially targeting glutamate projection neurons in the association cortex. Data from aging rhesus monkeys show abnormal tau phosphorylation within vulnerable neurons, associated with calcium dysregulation. Abnormally phosphorylated tau (pTau) on microtubules traps APP-containing endosomes, which can increase Aβ production. As Aβ oligomers increase abnormal phosphorylation of tau, this would drive vicious cycles leading to sAD pathology over a long lifespan, with genetic and environmental factors that may accelerate pathological events. This hypothesis could be testable in the aged monkey association cortex that naturally expresses characteristics capable of promoting and sustaining abnormal tau phosphorylation and Aβ production.

an extremely slow vicious ← circle

← monkeys are expensive

HOCs: if 3 things must co-occur, then NONE of them "drives" the pathology. +FB bad.

So WHY is ApoE3 protective? citer of Lady CC paper.

REVIEW Open Access

Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease

in Molecular Neurodegeneration, 2020

Tiantian Guo[†], Denghong Zhang[†], Yuzhe Zeng[2], Timothy Y. Huang[3*], Huaxi Xu[4*] and Yingjun Zhao[1*]

650 references

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder seen in age-dependent dementia. There is currently no effective treatment for AD, which may be attributed in part to lack of a clear underlying mechanism. Studies within the last few decades provide growing evidence for a central role of amyloid β (Aβ) and tau, as well as glial contributions to various molecular and cellular pathways in AD pathogenesis. Herein, we review recent progress with respect to Aβ- and tau-associated mechanisms, and discuss glial dysfunction in AD with emphasis on neuronal and glial receptors that mediate Aβ-induced toxicity. We also discuss other critical factors that may affect AD pathogenesis, including genetics, aging, variables related to environment, lifestyle habits, and describe the potential role of apolipoprotein E (APOE), viral and bacterial infection, sleep, and microbiota. Although we have gained much towards understanding various aspects underlying this devastating neurodegenerative disorder, greater commitment towards research in molecular mechanism, diagnostics and treatment will be needed in future AD research.

Keywords: Alzheimer's disease, Aβ, Tau, Microglia, Astrocyte

****a lot of TUNNELS down this Rabbit Hole!**

So WHY is ApoE3ch protective? **We don't know!**

accumulation [465]. Of note, APOE4 also triggered inflammatory cascades, leading to neurovascular dysfunction, degeneration of the BBB, consequent penetration of toxic proteins from blood into the brain and reduced length of small blood vessels [466]. Thus, APOE4-related cerebrovascular injury may play a key role in AD pathogenesis. Interestingly, a potentially protective mutation in APOE3 (Christchurch, R136S) has been recently identified. One particular case was reported where a woman carrying a fully-penetrant familial early-onset PS1 E280A mutation featured normal cognitive function until seventies despite an abnormally high Aβ load, and showed limited tau pathology which correlated with two copies of the APOE3 R136S allele [467].

APOE also affects tau pathogenesis and tau-mediated neurodegeneration [468]. APOE4 significantly aggravated tau-mediated neurodegeneration in a tauopathy mouse model and induced tau aggregates in brain, while genetic ablation of APOE attenuated tau-induced neurodegeneration [469, 470]. In addition, APOE ε2 is also associated with increased pathological tau levels in the presence of amyloid [471, 472]. Studies have shown that hyperphosphorylated tau species, tau aggregates and behavioral abnormalities were observed in APOE ε2/ε2 mice [471]. However, the association between these findings and AD progression is unclear. Thus, further studies characterizing the pathobiology of APOE in the

to reverse memory deficits in tau transgenic mice, and neuronal BIN1 expression is inversely correlated with pathological tau propagation [478, 479]. However, deletion of BIN1 in microglia reduces tau secretion and spreading in PS19 tau transgenic mice, suggesting BIN1 may act differentially in neurons and microglia. In addition, the SNPs of BIN1, such as rs744373 and rs7561528, may contribute to AD susceptibility by impacting brain structure and function [480, 481].

SORLA

SORLA is encoded by the *SORL1* gene. SNPs in SORLA can either increase or reduce AD risk. For instance, rs668387, rs2070045, rs11218343 and rs3781834 appear to be protective [474, 482], whereas other variants of *SORL1*, such as rs143571823, aggravate AD pathogenesis [483]. SORLA is involved in APP processing, Aβ secretion and Aβ turnover [484]. Overexpression of SORLA in neuronal cells can block amyloidogenic processing and reduce Aβ production [485], whereas loss of SORLA increased extracellular Aβ levels and plaque deposition in several AD mouse models [486, 487]. In addition, we recently reported that SORLA can interact EphA4 and inhibit Aβ-induced EphA4 activation, thereby reducing oAβ-induced synaptotoxicity [488]. Thus, SORLA may protect against AD pathogenesis via multiple mechanisms. As various AD-associated coding mutations in

ApoE – neurovascular dysfunctn, leaky vessels, toxic influx.

ApoE3ch – decreased binding of heparin (??)

also: ApoE effects on Tau, but unclear association w/ AIzD

Other Possible Contributors:
BIN1 and microglia
SORL1 and APP processing
fuzzy stories all!

Unsure if other 650 articles will help; Can You?

VIEW… **Amyloid needs to Trigger Tau**

ELEVATED amyloid triggers Tau across neocortex

[in EOAD] **…to a kill**

in SPORADIC AlzD, Tau is triggered in ERC

[unless Braak is backing off…]

We don't know everything.
Honesty is better than Posturing
[Major Shaver vs. Major Fred]
…at SFN or RISE poster session
…when giving a talk
…during an oral examination

It's OK to say "I don't know"
and far worse to BS an answer…
It's OK to think out loud
It's GOOD to brainstorm together
…
one style
"I don't really know the answer to that but I think maybe xxx or yyy…"

doi:10.1093/brain/awl377

DQ: does EOAD look like Cognitive Aging?

Brain (2007), 130, 720–

The topography of grey matter involvement** in early and late onset Alzheimer's disease

Giovanni B. Frisoni,[1,2] Michela Pievani,[1] Cristina Testa,[1] Francesca Sabattoli,[1] Lorena Bresciani,[1] Matteo Bonetti,[3] Alberto Beltramello,[4] Kiralee M. Hayashi,[5] Arthur W. Toga[5] and Paul M. Thompson[5]

Beyond GM topography, they note **cognitive diffs.** btw sporadic and EOAD. While late-onset (LOAD/sporadic) **shows memory/MTL deficits**, EOADs performed worse on **executive functioning, visuospatial and learning tasks.**

Clinical observations have suggested that the neuropsychological profile of early and late onset forms of Alzheimer's disease (EOAD and LOAD) differ in that neocortical functions are more affected in the former and learning in the latter, suggesting that they might be different diseases. The aim of this study is to assess the brain structural basis of these observations, and test whether neocortical areas are more heavily affected in EOAD and medial temporal areas in LOAD. Fifteen patients with EOAD and 15 with LOAD (onset before and after age 65; Mini Mental State Examination 19.8, SD 4.0 and 20.7, SD 4.2) were assessed with a neuropsychological battery and high-resolution MRI together with 1:1 age- and sex-matched controls. Cortical atrophy was assessed with cortical pattern matching, and hippocampal atrophy with region-of-interest-based analysis. EOAD patients performed more poorly than LOAD on visuospatial, frontal-executive and learning tests. EOAD patients had the largest atrophy in the occipital [25% grey matter (GM) loss in the left and 24% in the right hemisphere] and parietal lobes (23% loss on both sides), while LOAD patients were remarkably atrophic in the hippocampus (21 and 22% loss). Hippocampal GM loss of EOAD (9 and 16% to the left and right) and occipital (12 and 14%) and parietal (13 and 12%) loss of LOAD patients were less marked. In EOAD, GM loss of 25% or more was mapped to large neocortical areas and affected all lobes, with relative sparing of primary sensory, motor, and visual cortex, and anterior cingulate and orbital cortex. In LOAD, GM loss was diffusely milder (below 15%); losses of 15–20% were confined to temporoparietal and retrosplenial cortex, and reached 25% in restricted areas of the medial temporal lobe and right superior temporal gyrus. These findings indicate that EOAD and LOAD differ in their typical topographic patterns of brain atrophy, suggesting different predisposing or aetiological factors.

****NOTE: this article has *nothing* to do with the Grey Matter Networks fantasy.**

Cortical mapping — Frisoni, 2007

Cortical pattern matching analysis showed that in EOAD statistically significant GM reduction was widespread (Fig. 2, left), involving the frontal, temporal, parietal and occipital cortex including the posterior cingulate and the retrosplenial region, and sparing only the somatosensory and primary visual cortex, the anterior cingulate gyrus and the orbitomesial cortex (permutation test: $P = 0.0001$ for both the left and right hemispheres). Conversely, in LOAD patients statistically significant GM reduction was located in

MTL other temporal gyri, T-P junction

Of note in EOAD: fancy name for MRI?

uses "**voxel-based morphometry**"

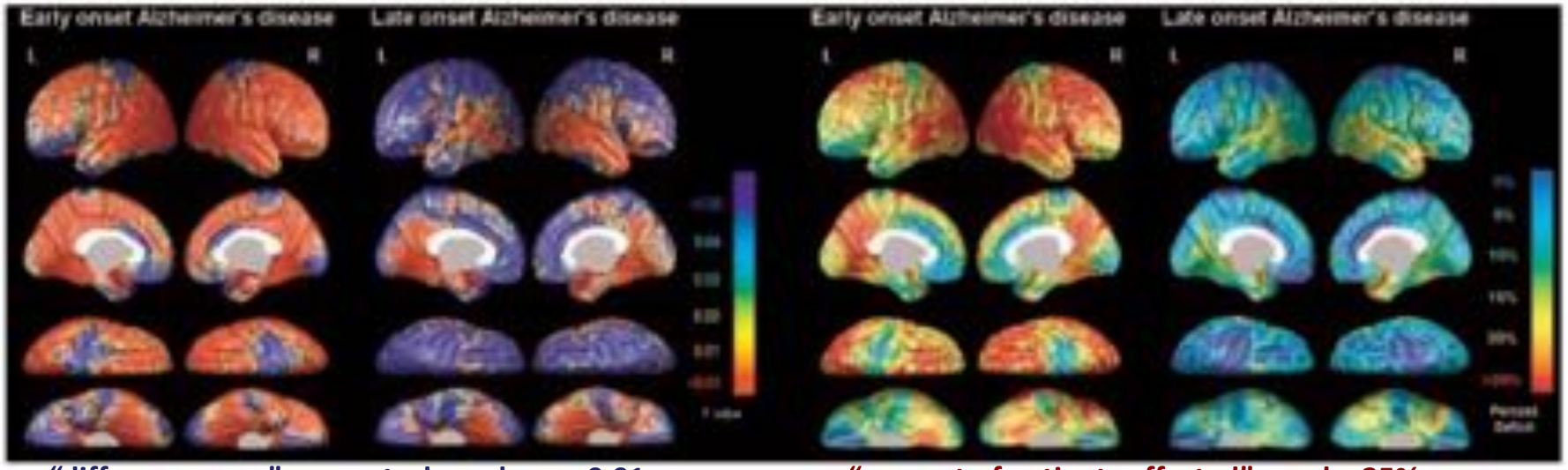
"traditional AlzD" areas are included:
temporal lobe, PCC, parietal lobe

goes to "equivalence" concerns

V1 is spared despite high CAA (S. Greenberg)

intro: 1st Alz case aged 52. EOADs have more language deficits.

Familial **Sporadic** **Familial** **Sporadic**



"difference map" vs. controls: red = p < 0.01

"percent of patients affected" – red > 25%

Fig. 2 Grey matter loss of EOAD and LOAD patients compared with controls. *Left*: significance map, the colour bar denoting significance of GM loss between patients and controls (regions in red correspond to $P < 0.01$). EOAD had significant atrophy of most of the neocortex, sparing only part of the primary sensory, motor, and visual cortex, anterior cingulate and orbital cortex. Atrophy in LOAD patients was confined to the medial temporal and retrosplenial areas, superior and middle temporal gyri, and temporoparietal junction.

2007: no mention of "cortical thinning". Thinning = trendy MRI metric. higher T, better software?

APP, *PSEN1*, and *PSEN2* mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases

2017

Hélène-Marie Lanoiselée[1,2], Gaël Nicolas[3], David Wallon[1], Anne Rovelet-Lecrux[3],

MORE ON EOAD:

sporadic EOAD? …*yes!*

more details on next slide

PLoS Med

OPEN ACCESS

Citation: Lanoiselée H-M, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, et al. (2017) APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med 14(3): e1002270. https://doi.org/10.1371/journal.pmed.1002270

This is "NICHE sporadic": for course purposes, we use **sporadic** ONLY to mean Late-Onset AlzD (often called LOAD, meh). ONLY EXCEPTIONS: THIS SLIDE AND THE NEXT TWO! will explain.

Exam Questions
lurketh…

sporadic EOAD? -- yes

2017

Methods and findings

We report here a novel update (2012–2016) of the genetic screening of the large AD-EOAD series ascertained across 28 French hospitals from 1990 onwards, bringing the total number of families with identified mutations to $n = 170$. Families were included when at least two first-degree relatives suffered from early-onset Alzheimer disease (EOAD) with an age of onset (AOO) ≤ 65 y in two generations. Furthermore, we also screened 129 sporadic cases of Alzheimer disease with an AOO below age 51 (44% males, mean AOO = 45 ± 2 y). *APP*, *PSEN1*, or *PSEN2* mutations were identified in 53 novel AD-EOAD families. Of the 129 sporadic cases screened, 17 carried a *PSEN1* mutation and 1 carried an *APP* duplication (13%). Parental DNA was available for 10 sporadic mutation carriers, allowing us to show that the mutation had occurred de novo in each case. Thirteen mutations (12 in *PSEN1* and 1 in *PSEN2*) identified either in familial or in sporadic cases were previously unreported. Of the 53 mutation carriers with available cerebrospinal fluid (CSF) biomarkers, 46 (87%) had all three CSF biomarkers—total tau protein (Tau), phospho-tau protein (P-Tau), and amyloid β ($A\beta_{42}$)—in abnormal ranges. No mutation carrier had the three biomarkers in normal ranges. One limitation of this study is the absence of functional assessment of the possibly and probably pathogenic variants, which should help their classification.

All FAMILIAL was at some point **SPORADIC**, yes? (Apply *Central Dogma* to Medicine)

describe Central D in 3 words:

Genetic Screening Studies:

170 Families: w/ two or more early-onset, 1st degree relatives across two generations

129 Sporadic Cases: w/ onset by age 51

found: 53 novel families w/ APP or PSEN mutations

of sporadic cases 17 carried a PSEN1 mutation; 1 had an APP mutation

many mutations (13) were novel and all mutation-carriers had abnormal CSF tau

Such events are rare: much less common than late-onset, sporadic AlzD!

DQ: how do we KNOW such events are rare? 95/5 [see notes]

For our/SNCD purposes: sporadic means Late Onset. Such cases lack amyloid mutations.

For every EOAD family: patient 0 (rarely known) was the "sporadic beginning"

MORE sporadic aka *de novo* instances of EOAD

Molecular Psychiatry (2015), 1–11

www.nature.com/mp

2015

IMMEDIATE COMMUNICATION

De novo deleterious genetic variations target a biological network centered on Aβ peptide in early-onset Alzheimer disease

A Rovelet-Lecrux[1,11], C Charbonnier[1,2,11], D Wallon[2,3,11], G Nicolas[1,4,11], MNJ Seaman[5], C Pottier[1], SY Breusegem[5], PP Mathur[6,7],

Most are assoc. w/ AB pathology

We hypothesized that *de novo* variants (DNV) might participate in the genetic determinism of sporadic early-onset Alzheimer disease (EOAD, onset before 65 years). We investigated 14 sporadic EOAD trios first by array-comparative genomic hybridization. Two patients carried a *de novo* copy number variation (CNV). We then performed whole-exome sequencing in the 12 remaining trios and identified 12 non-synonymous DNVs in six patients. The two *de novo* CNVs (an amyloid precursor protein (*APP*) duplication and a *BACE2* intronic deletion) and 3/12 non-synonymous DNVs (in *PSEN1*, *VPS35* and *MARK4*) targeted genes from a biological network centered on the Amyloid beta (Aβ) peptide. We showed that this a priori-defined genetic network was significantly enriched in amino acid-altering DNV, compared with the rest of the exome. The causality of the *APP de novo* duplication (which is the first reported one) was obvious. In addition, we provided evidence of the functional impact of the following three non-synonymous DNVs targeting this network: the novel *PSEN1* variant resulted in exon 9 skipping in patient's RNA, leading to a pathogenic missense at exons 8–10 junction; the *VPS35* missense variant led to partial loss of retromer function, which may impact neuronal APP trafficking and Aβ secretion; and the *MARK4* multiple nucleotide variant resulted into increased Tau phosphorylation, which may trigger enhanced Aβ-induced toxicity. Despite the difficulty to recruit Alzheimer disease (AD) trios owing to age structures of the pedigrees and the genetic heterogeneity of the disease, this strategy allowed us to highlight the role of *de novo* pathogenic events, the putative involvement of new genes in AD genetics and the key role of Aβ network alteration in AD.

Lots of fancy genetic talk but bottom line is these mutations generally involve known EOAD/amyloid genes i.e. APP (a gene duplication in one instance) and BACE (beta-secretase). Exome defined in later slide and genomic hybridization uses microarray technology, also shown later. But some EOAD mutations here ARE NOT AMYLOID!

Chapter 19 - SNCD

MORE on our old friends ApoE & Tau

19.2 Microglia and Neuroinflammation
and Small Vessel Disease (SVD) and
19.5 Genetic Risk Factors & GWAS
19.6 Other Risks: ApoE4, TREM-2, more including Preclinical AlzD

Direct Transcriptional Effects of Apolipoprotein E

2016
J. Neurosci.

Veena Theendakara,[1] Clare A. Peters-Libeu,[1] Patricia Spilman,[1,2] Karen S. Poksay,[1] Dale E. Bredesen,[1,2,3] and Rammohan V. Rao[1,3]

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Gene Regulation is just ONE tidbit from a broad array of ApoE research!

A major unanswered question in biology and medicine is the mechanism by which the product of the apolipoprotein E ε4 allele, the lipid-binding protein apolipoprotein E4 (ApoE4), plays a pivotal role in processes as disparate as Alzheimer's disease (AD; in which it is the single most important genetic risk factor), atherosclerotic cardiovascular disease, Lewy body dementia, hominid evolution, and inflammation. Using a combination of neural cell lines, skin fibroblasts from AD patients, and ApoE targeted replacement mouse brains, we show in the present report that ApoE4 undergoes nuclear translocation, binds double-stranded DNA with high affinity (low nanomolar), and functions as a transcription factor. Using chromatin immunoprecipitation and high-throughput DNA sequencing, our results indicate that the ApoE4 DNA binding sites include ~1700 gene promoter regions. The genes associated with these promoters provide new insight into the mechanism by which AD risk is conferred by ApoE4, because they include genes associated with trophic support, programmed cell death, microtubule disassembly, synaptic function, aging, and insulin resistance, all processes that have been implicated in AD pathogenesis.

ApoE4 is the NUMBER ONE predictor of sporadic AlzD cases

- **did not see direct effect of ApoE on proteins**
- **used Chipping to identify gene-regulatory sites**
- **THM: abnormal transport & gene repression by ApoE4**

"supplemental" slides below

ApoE4 decreases SirT1 expression and causes translocation to cytosol. **SirT1** is neuroprotective and activates the **ADAM10 alpha-secretase gene** (a protective peptide?); it might activate neurotrophic genes and axonal growth (via Ras GTPase)

Table 1 lists Tau Targets and possible drugs of interest

from ApoE to Tau to This?

Don't Memorize Table 1

Table 1. Mechanisms of tau-induced toxicity that are current and potential targets for therapeutic intervention

Mechanism	Potential targets[a]	Drug effort
Tau hyperphosphorylation/misfolding	PAR-1[b] GSK-3β[c] HSPs[b]	Lithium[c] Methylene blue[c] Tideglusib[c] Nicotinamide[b] Valproic acid[c] UMT-X[c] Sodium selenate[c] Compound A[c] Thiamet G[b] SNR-003-556[c]
Tau spread	HSPGs	MC1 antibody[b] PHF1 antibody[b]
Synapse loss	STEP NMDAR Fyn	MEM 1003[c] Nasonexone[c] Saikosaponin[c]
Microtubule destabilization		AL-108[c] Epothilone D[c] TPI-287[c] AL-208[c] Paclitaxel[c]
Impaired axonal transport	JIP1 KLC1/2 DIC	
Actin stabilization	CFL2[b] GSN[b] ACTB[b]	
Mitochondrial dysfunction/oxidative stress	DRP1[c] MFN2[c] OPA1[c] Complex V PRDX2[b] SOD2[b] REST	Lithium[c] ALCAR[c] Idebenone[c] Propentofylline[c] AC-1204[c] α-Tocopherol[c] Resveratrol[c] Curcumin[c] NSAIDs[c]
DNA damage	p53[b] MDM4 ATF	
Heterochromatin relaxation/aberrant gene expression	SIRT1[b] PPAR[b]	
Cell cycle activation	CDK1[b] TSC2[b] RB1[b] Rb	Olomoucine[c] Rapamycin[c]

[a]Proteins selected as potential therapeutic targets are those discussed in the text and/or whose genetic manipulation suppresses aspects of tauopathy and do not represent the entirety of proteins implicated in tauopathy. For proteins that were identified as dysfunctional in animal models of tauopathy, the human homolog is listed in the table. Information about clinical trials was obtained from http://www.clinicaltrials.gov.

Note the broad range of targets / clinical trials and many underlying studies.

Some targets we have heard of like SOD, NMDA, CDK, p53, fyn, HSPs

b = suppressor of tau toxicity. c = dead clinical trial. d= live clinical trial in 2015.

Chapter 19 - SNCD

19.5 Molecular Pathology 2
Genetic Risks and Big Data

GWAS = Genome Wide Association Studies
how many genes?
how many mechanisms?

Trends in Genetics

2018

CONNECTING Risk Genes to Expression Profiles
- gene chips, RNA seq, single-cell seq.
- highlight "allele specific events" and more

Verheijen and Sleegers

Review

Understanding Alzheimer Disease at the Interface between Genetics and Transcriptomics

Alleles are variations of the same gene: **we each carry 2 copies of each gene** many of which have small differences from others in our family or population. ApoE2/E3/E4 are different alleles and **the Christchurch mutation is a rare variant of the E3 allele.**

Over 25 genes are known to affect the risk of developing Alzheimer disease (AD), the most common neurodegenerative dementia. However, mechanistic insights and improved disease management remains limited, due to difficulties in determining the functional consequences of genetic associations. Transcriptomics is increasingly being used to corroborate or enhance interpretation of genetic discoveries. These approaches, which include second and third generation sequencing, single-cell sequencing, and bioinformatics, reveal allele-specific events connecting AD risk genes to expression profiles, and provide converging evidence of pathophysiological pathways underlying AD. Simultaneously, they highlight brain region- and cell-type-specific expression patterns, and alternative splicing events that affect the straightforward relation between a genetic variant and AD, re-emphasizing the need for an integrated approach of genetics and transcriptomics in understanding AD.

take-home messages

Highlights

Alzheimer Disease: Common and Complex

TIGS, 2018

Gene	Primary associated pathway	Primary expressed brain cell type	Differential expression direction in targeted AD risk gene studies	Differential expression direction in microarray meta-analyses [43–46]
ABCA7	Immune response/ Lipid metabolism	Microglia	+/– [36]	+ + ? +
BIN1	Endocytosis/Synaptic transmission	Oligodendrocytes	+ [37]	? + ? ?
CD2AP	Endocytosis	Endothelia		+ ? ? ?
CD33	Immune response	Microglia	+ [37]	+ + ? ?
CLU	Immune response/Lipid metabolism	Astrocyte	+ [36,37]	+ + ? ?
CR1	Immune response	Microglia	+ [37]	? + ? ?
EPHA1	Endocytosis/Synaptic transmission	Endothelia		? + ? ?
HLA-locus	Immune response	Microglia	HLA-DRA: + [36]	HLA-DRA: + ? + ?
MEF2C	Immune response/ Synaptic transmission	Endothelia/Microglia		– – – –
MS4A-cluster	Immune response	Microglia	MS4A4A and MS4A6A: + [37]	MS4A 4A/6A: + + ? ?
PICALM	Endocytosis/Synaptic transmission	Endothelia	– [40] + [40]	? ? + ?
PTK2B	Immune response/ Synaptic transmission	Microglia		? – ? ?
SORL1	Endocytosis	Astrocyte/Neuron	– [41]	? – ? ?
TREM2	Immune response	Microglia	+ [36,42]	+ ? ? ?

Only 1 gene refers to NEURONS!

But all of these are potentially important!

some are mentioned below.

Chapter 19 - SNCD

Research Topic: Could AlzD-neurodegeneration be 1000 different diseases?

One outcome of the foregoing discussion of AlzD, its variants and its genetic risks is that there can be fundamentally different causes, atrophy patterns, molecular contributions and symptoms. 1000 sounds like a lot of variants (which might please "splitters" but would certainly horrify "lumpers") but the deeper issue is whether treatments and prognosis might vary with more finely parsed diagnoses? If there are truly 30 distinct risk loci aka causes/contributors to the emergence of AlzD pathology, and if the different combinations of them can give rise to distinct syndromes, then the number of *possible* syndromes is astronomical (30 factorial, an extremely large number). Even with a more conservative assertion of 10 independent factors, and if every combination was truly different (e.g. requiring a different differential diagnosis and treatment) then AlzD is 3.6 million different diseases. While basic math plus some sketchy assumptions can lead to such hyperbolic conjectures, our genetic risk discussion makes it possible that there are a handful of independent contributors to AlzD and that different combinations of them will present differently, maybe to the point of dozens of distinct variants. Indeed, the foregoing observations on ApoE4 and early/late onset AlzD makes this proposition more possible than the lumpers would like! But the most important point is that everyone is different and at some point down the road personalized genomics and medicine might have something to say and DO about these 1000 (or 2 dozen) different dementias.

19.6 Additional Risk Factors and Preclinical Alzheimers

ApoE and Me: One Particular Genetic Risk. Apolipoprotein E is a lipid-metabolizing protein that transports cholesterol to neurons; most of the ApoE in the CNS is produced by astrocytes. Human ApoE genes have a number of single nucleotide polymorphisms (SNPs) which either predispose one to getting AlzD (ApoE4), are neutral (ApoE3) or confer some neuroprotection (ApoE2); about 50% of AlzD patients are reported by Kaech et al. (2014) to carry the E4 allele. The association of ApoE with vascular damage and neurodegeneration was introduced in Chapter 12. Regarding AlzD, Morris et al. (2010) correlated the ApoE genotype with human amyloid deposition (via PET imaging of PiB). Most cognitively-normal individuals show no PiB binding before age 50, but by age 85, about 30% are PiB positive. Individuals with the ApoE4 allele had more PiB (vs. other individuals) and also a stronger CSF A-beta sign of AlzD which was further increased for homozygous individuals (i.e. those having two E4 alleles). ApoE4 was not predictive of changes in tau levels in the CSF. While PiB binding suggests "preclinical AlzD", and a double-dose of the ApoE4 allele SNP makes the emergence

Chapter 19 - SNCD

GWAS = Genome Wide Association Studies
how many genes?
how many mechanisms?

If each risk-gene combo different, then:
a treatment that works for one might not work for others...
and so: “personalized medicine” **+ METABOLIC HISTORY**

my time is
fading, but you:

Review **Risks**: of polymorphisms analyzed. used GWAS with whole genome and whole exome sequencing. 20 risk-loci have been identified as contributing to increased risk of AlzD.

Alzheimer's Disease Genetics: From the Bench to the Clinic

Neuron, 2014

more in Chapter 19 - SNCD

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http://dx.doi.org/10.1016/j.neuron.2014.05.041

Polymorphism: "the presence of genetic variation within a population, upon which natural selection can operate." Oxford

Alzheimer's disease (AD) is a clinically heterogeneous neurodegenerative disease with a strong genetic component. Several genes have been associated with AD risk for nearly 20 years. However, it was not until the recent technological advances that allow for the analysis of millions of polymorphisms in thousands of subjects that we have been able to advance our understanding of the genetic complexity of AD susceptibility. Genome-wide association studies and whole-exome and whole-genome sequencing have revealed more than 20 loci associated with AD risk. These studies have provided insights into the molecular pathways that are altered in AD pathogenesis, which have, in turn, provided insight into novel therapeutic targets.

Genetics/Transcriptomics PDF above noted issues relating genes to pathology:
Pleiotropy: the production by a single gene of two or more apparently unrelated effects. Multigenic = traits affected by multiple genes.

Neuron, 2014, Karch

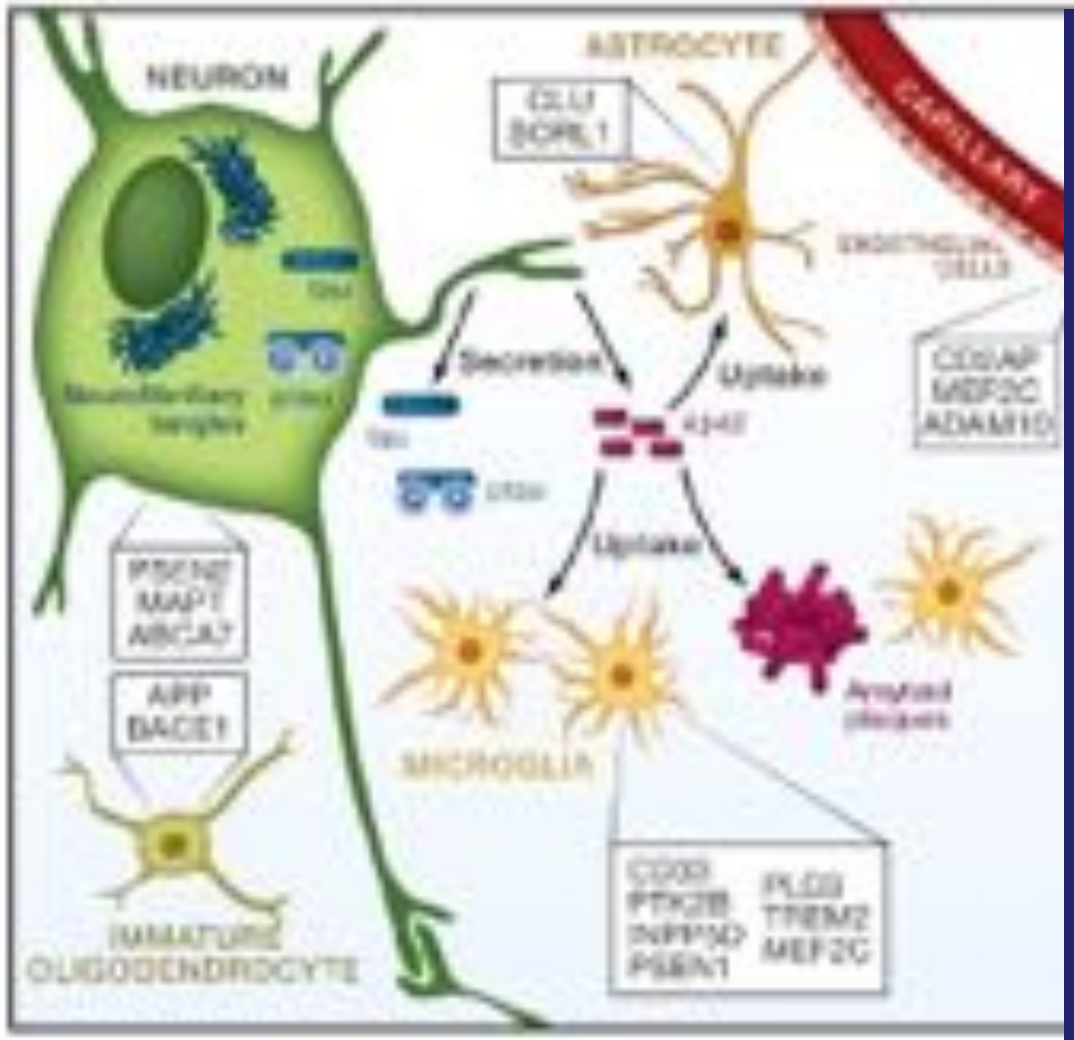


Figure 1. Cell-Type Expression of Alzheimer's Disease Risk Genes May Influence AD Pathogenesis

GWAS = Gene Hunter

Brute sequencing of genomes is not, by itself, sufficient to identify risk genes for AlzD.

Genome-Wide Association Studies enable identification of genes / alleles that are found at higher frequency in AlzD or MCI patients.

While ApoE has been known for decades, **many more factors likely contribute to sporadic, late-onset AlzD.** Identification of risk genes can help us better understand pathology and might benefit clinical trials AND might bring personalized medicine to AlzD.

Term of Endearment: *Genetics Style*

Genome: entire genetic inheritance
Transcriptome: which "proteins" each cell expresses
Exome: (new) all of the proteins encoded BY the genome (much smaller than genome)
GWAS: *Genome Wide Association Studies* look for genetic sequences assoc. w/ disease
Alleles: different versions of a gene found within a population; includes SNPs
SNPs: single-nucleotide polymorphisms i.e. single base changes; might be harmful
QTL: quantitative trait loci = anatomical or physiol. traits assoc. w/ stretch of DNA (locus)
eQTL: expression QTL relates specific loci to a cell's transcriptome, a physiological trait!
RNA Seq: technology allows an entire transcriptome to be sequenced; can be done at **single-cell level**, but tends to be noisy.
microRNAs: small non(protein)-coding RNAs with diverse regulatory roles

Genetic Risk Factors for AlzD

ApoEε: Apo-lipoprotein-Eε is top genetic risk [we drop the **ε** because we eschew Greek symbols]
TREM-2: a receptor found on microglia
HLA-complex: associated with reactive microglia; risk site not precisely id'd
SORL: assoc. w/ APP protein processing-1st late-onset risk associated w/ amyloid
PTK2B: SNP id'd; gene is assoc. w/ LTP, neurotransmission and calcium fluxes.
BIN1: its gene product is associated with tau, RIN3 and SLC24A4
SLC24A4: locus is assoc. w/ hypertension and sodium/potassium/calcium exchange

Note that genetic RISKS do not necessarily cause a disease but increase likelihood of a person getting it— vs. **The EOAD mutations which directly produce** AlzD. Genetic changes/risks above increase likelihood, but other rare alleles at a locus might be protective.

This is copied from SNCD, part of important section on Genetic Risks

p.198 SNCD

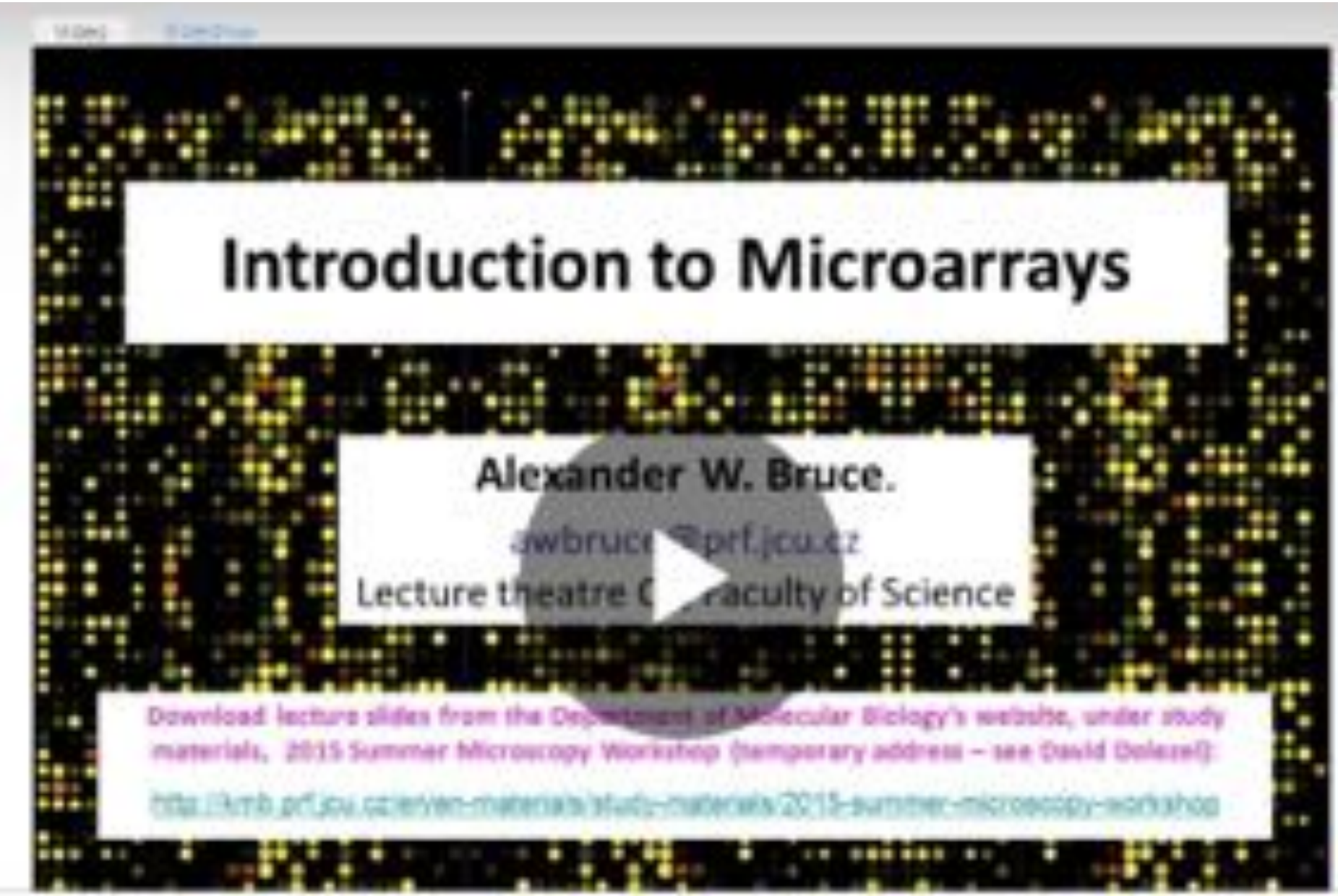
GWAS. While familial / early-onset Alzheimer disease genes have been known for many years, until recently we knew little about what causes the vastly more numerous cases of late-onset aka "sporadic" cases of Alzheimer's dementia. This situation changed profoundly between roughly 2005 to 2015 with the use of Genome Wide Association Studies (GWAS). The GWAS methodology allows us to scan genomes to identify sequences that (in this instance) increase a person's risk of getting AlzD. The first step is to collect many genomes—from controls and AlzD individuals—and determine which DNA sequences occur more frequently in (and thus associate with) the AlzD cases. GWAS identifies short stretches of DNA that contain the variations between individuals, but one wrinkle is that the sequences often contain multiple genes and mutations, along with non-coding stretches of genome so precise identification of risks and mechanisms is not trivial: this is where the hard work begins.

required reading!

editorial note: not so sure about "**changed profoundly**" ... MAYBE?

GWAS in AlzD is enabled by gene-sequencing technologies where individuals with and without AlzD have genomic features compared. This allows us to detect sequences present at higher frequencies in the AlzD population (NHGRI, 2019). The compilation of blood tests from large numbers of individuals proved essential to discovering small, risky sequences within the vast stretches of our genome (Karch et al., 2014). These disease-associated mutations often turn out to be single-nucleotide polymorphisms (SNPs). SNPs refer to instances where a single DNA nucleotide (in a particular gene) differs between two individuals—i.e. those two individuals have different versions of the gene (different alleles), differing only at that one specific base-pair. Note that SNPs (and other mutations) can occur within coding regions, within introns or at genomic locations outside of gene sequences, thus making interpretation difficult. Any genome will have many SNPs and so the presence of those SNPs in an AlzD patient does not affirm a role in AlzD. But if thousands of individuals are genotyped, one can identify SNPs that often sort with the AlzD group (vs. controls) while the sister allele may be neutral or have some minor protective effect. Beyond SNPs, other mutations can lurk in these risky sequences (short genomic stretches) identified by GWAS, including the insertions or deletions of base pairs. For this reason, the "bad" DNA stretches associated with e.g. AlzD are typically referred to as *loci*, and there might be more than one deleterious change within a locus. Still, statistical methods can often identify a particular SNP within a sequence/locus that is likely responsible agent for the associated genetic risk. We provide some exemplar GWAS and transcriptome results to explore applications of this technology in AlzD research.

GWAS requires massive data and computation, but we now have more than 100 candidate sequences of which 42 genomic "risky" loci have been examined in some depth yielding 25 AlzD risk factors/loci as confirmed by "replication" studies. This progress arose in large part through cooperative consortiums and the aggregation of data as more


Introduction to Microarrays
Alexander W. Bruce.
Lecture theatre
Faculty of Science
Download lecture slides from the
's website, under study
materials, 2015 Summer Microscopy Workshop (temporary address – see David Dolezel)

GENOME-WIDE MICROARRAY

Proc Natl Acad Sci U S A. 1997 Nov 25; 94(24): 13057-62

Yeast microarrays for genome wide parallel genetic and gene expression analysis.

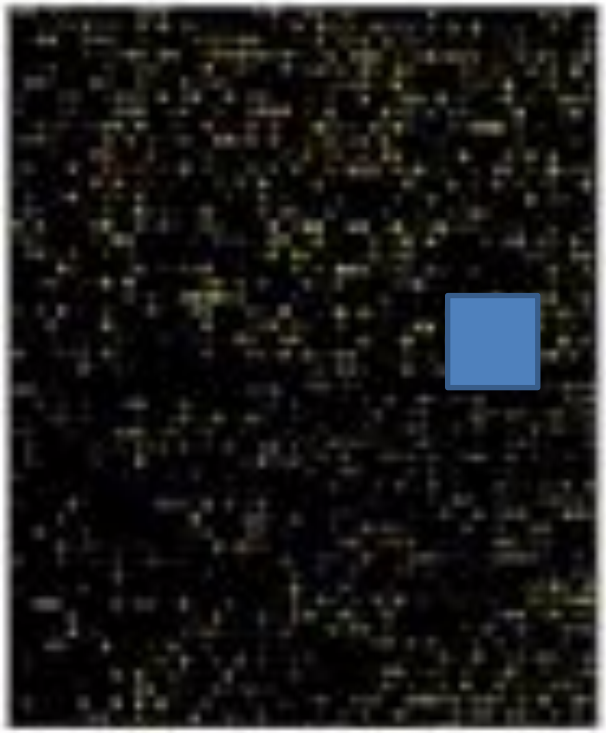
Lashkari DA, DeRisi JL, McCusker JH, Namath AF, Gentile C, Hwang SY, Brown PO, Davis RW
Source
Department of Genetics, Stanford University, CA 94305, USA.

PMID: 9371799

An array of cDNAs from all known ORFs in the yeast genome (yeast genome DNA sequence had been released in April 1996)

Comparison of mRNA expression between yeast growing in either glucose or galactose containing media

See red and green spots for relative expression differences and note most spots are yellow because there is no change in expression between the two samples



Interrogation of the ENTIRE TRANSCRIPTOME in a single experiments

Early application of GWAS methods to AlzD

Naj, 2011 Nature Genetics

Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease

The Alzheimer Disease Genetics Consortium (ADGC) performed a genome-wide association study of late-onset Alzheimer disease using a three-stage design consisting of a discovery stage (stage 1) and two replication stages (stages 2 and 3). Both joint analysis and meta-analysis approaches were used. We obtained genome-wide significant results at *MS4A4A* (rs4938933; stages 1 and 2, meta-analysis P (P_M) = 1.7×10^{-8}, joint analysis P (P_J) = 1.7×10^{-8}; stages 1, 2 and 3, $P_M = 8.2 \times 10^{-11}$), *CD2AP* (rs9349407; stages 1, 2 and 3, $P_M = 8.6 \times 10^{-9}$), *EPHA1* (rs11767557; stages 1, 2 and 3, $P_M = 6.0 \times 10^{-10}$) and *CD33* (rs3865444; stages 1, 2 and 3, $P_M = 1.6 \times 10^{-9}$). We also replicated previous associations at *CR1* (rs6701713; $P_M = 4.6 \times 10^{-10}$, $P_J = 5.2 \times 10^{-11}$), *CLU* (rs1532278; $P_M = 8.1 \times 10^{-9}$, $P_J = 1.9 \times 10^{-8}$), *BIN1* (rs744373; $P_M = 4.0 \times 10^{-14}$, $P_J = 5.2 \times 10^{-14}$) and *PICALM* (rs561655; $P_M = 7.8 \times 10^{-11}$, $P_J = 3.0 \times 10^{-10}$), but not at *EXOC3L2*, in late-onset Alzheimer's disease susceptibility[1–5].

Worst Abstract Ever?

Alzheimer's disease is a neurodegenerative disorder affecting more than 13% of individuals aged 65 years and older and 30–50% of individuals aged 85 years and older[6,7]. Early work identified mutations in *APP*, *PSEN1* and *PSEN2* that cause early-onset autosomal dominant Alzheimer's disease[8–10] and variants in *APOE* that affect late-onset Alzheimer's disease (LOAD) susceptibility[11]. Recent genome-wide association studies (GWAS) identified variants in *CR1*, *CLU*, *PICALM* and *BIN1* as LOAD susceptibility loci[1–5]. However, because LOAD heritability estimates are high (h^2 = 60–80%)[12], much of the genetic contribution to this condition remains unknown.

To identify genetic variants associated with risk for Alzheimer's disease, the ADGC assembled a discovery dataset (stage 1: 8,309 individuals with LOAD (cases) and 7,366 cognitively normal elders (CNEs) as controls) using data from eight cohorts and a ninth newly assem-

from the association analyses of individual datasets and a joint analysis approach in which genotype data from each study were pooled. The latter method has improved power over the meta-analysis in the absence of between-study heterogeneity[13] and has a more direct correction for confounding sampling bias[14]. We were limited to meta-analysis for stage 3 analyses.

HELP!

Because the cohorts were genotyped using different platforms, we used imputation to generate a common set of 2,324,486 SNPs. We applied uniform stringent quality control measures to all datasets to remove low-quality and redundant samples and problematic SNPs (Supplementary Tables 3,4 and Online Methods). We performed an association analysis assuming an additive model on the log-odds ratio scale with adjustment for population substructure using logistic regression for case-control data and generalized estimating equations (GEE) with a logistic model for family data. We combined results from individual datasets in the meta-analysis using the inverse variance method, applying a genomic control to each dataset. We performed the joint analysis using GEE and incorporated terms to adjust for population substructure and site-specific effects (Online Methods). For both approaches, we also examined an extended model of covariate adjustment that adjusted for age (age at onset or death in cases and age at exam or death in controls), sex and number of *APOE* ε4 alleles (0, 1 or 2). Genomic inflation factors (λ) for both the discovery meta-analysis and the joint analysis and extended models were less than 1.03, indicating that there was not substantial inflation of the test statistics (Supplementary Table 3 and Supplementary Fig. 1). Association findings from the meta-analysis and joint analysis were comparable.

In stage 1, the strongest signal was from the *APOE* region (rs440310; $P_M = 1.1 \times 10^{-200}$, $P_J = 1.5 \times 10^{-177}$; Supplementary Table 5). Excluding the *APOE* region, SNPs at nine distinct loci

Anyone speak Molecular? Informed help welcome!

For now: Nevermind this FIGURE!

Genome-Wide Significance is important!

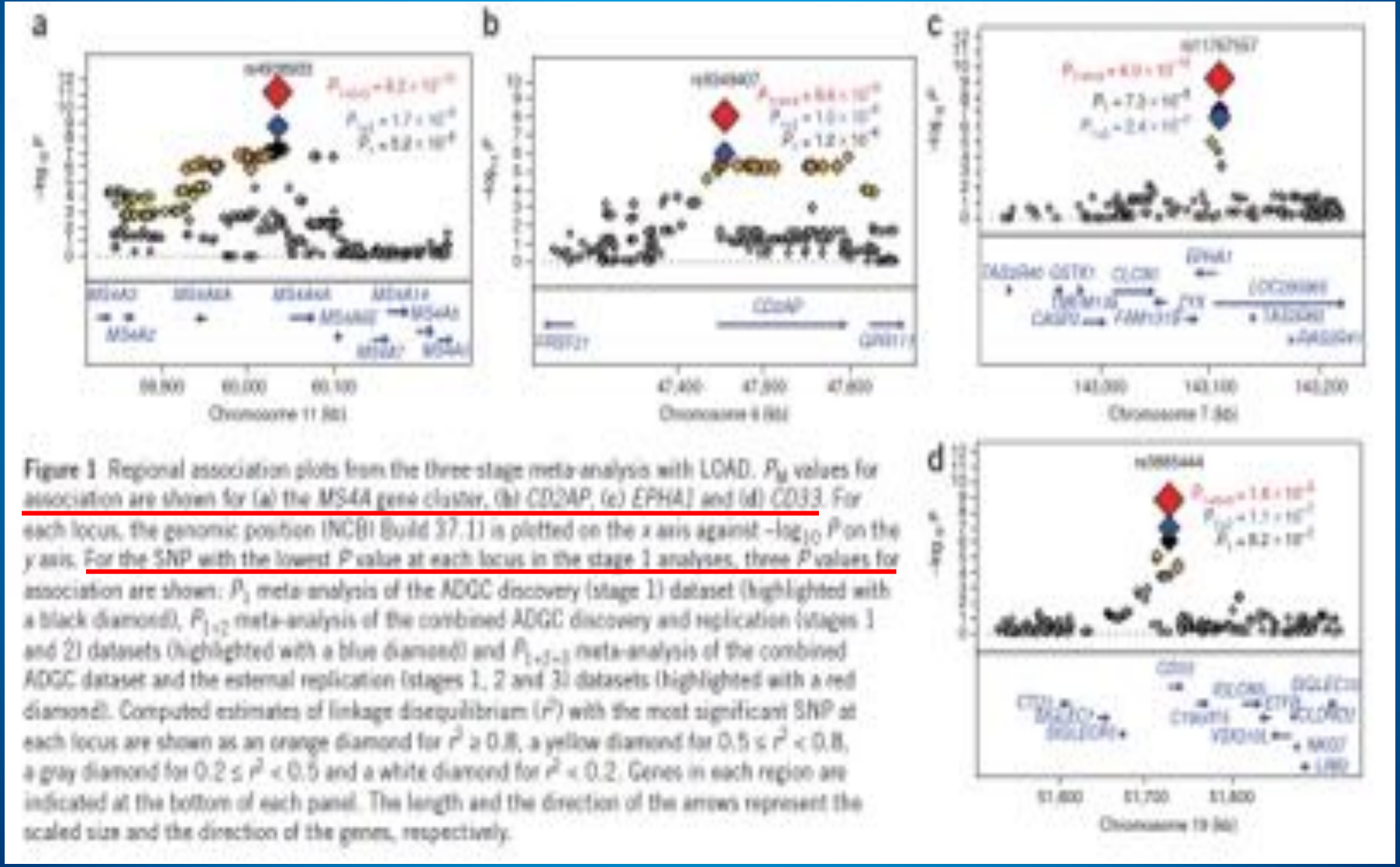


Figure 1 Regional association plots from the three-stage meta-analysis with LOAD. P_M values for association are shown for (a) the *MS4A* gene cluster, (b) *CD2AP*, (c) *EPHA1* and (d) *CD33*. For each locus, the genomic position (NCBI Build 37.1) is plotted on the *x* axis against $-\log_{10} P$ on the *y* axis. For the SNP with the lowest *P* value at each locus in the stage 1 analyses, three *P* values for association are shown: P_1 meta-analysis of the ADGC discovery (stage 1) dataset (highlighted with a black diamond), P_{1+2} meta-analysis of the combined ADGC discovery and replication (stages 1 and 2) datasets (highlighted with a blue diamond) and P_{1+2+3} meta-analysis of the combined ADGC dataset and the external replication (stages 1, 2 and 3) datasets (highlighted with a red diamond). Computed estimates of linkage disequilibrium (r^2) with the most significant SNP at each locus are shown as an orange diamond for $r^2 \geq 0.8$, a yellow diamond for $0.5 \leq r^2 < 0.8$, a gray diamond for $0.2 \leq r^2 < 0.5$ and a white diamond for $r^2 < 0.2$. Genes in each region are indicated at the bottom of each panel. The length and the direction of the arrows represent the scaled size and the direction of the genes, respectively.

aMCI = amnestic
naMCI = non-amnestic
na is assoc. w/ diabetes

Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0030-4

ARTICLE

Twins Study- Vietnam

2018

Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s

Mark W. Logue[1,2,3] · Matthew S. Panizzon[4,5] · Jeremy A. Elman[4,5] · Nathan A. Gillespie[6] · Sean N. Hatton[4,5] · Daniel E. Gustavson[4,5] · Ole A. Andreassen[7,8] · Anders M. Dale[4,5,9,10] · Carol E. Franz[4,5] · Michael J. Lyons[11] ·

Polygenic Risk Score (AD-PRS) was derived by genotyping European-descent twins based upon SNPs and an AlzD haplotype database. Risks independent of ApoE were estimated. **The PRS identified adults in their 50's at greater risk for aMCI**; presence of **diabetes** boosted risk of **naMCI**. Not sure if PRS is an *improvement* over usual cognitive tests; query pending.

Early identification of younger, non-demented adults at elevated risk for Alzheimer's disease (AD) is crucial because the pathological process begins decades before dementia onset. Toward that end, we showed that an AD polygenic risk score (PRS) could identify mild cognitive impairment (MCI) in adults who were only in their 50s. Participants were 1176 white, non-Hispanic community-dwelling men of European ancestry in the Vietnam Era Twin Study of Aging (VETSA); 7% with amnestic MCI (aMCI); 4% with non-amnestic MCI (naMCI). Mean age was 56 years, with 89% <60 years old. Diagnosis was based on the Jak/Bondi actuarial neuropsychological approach. We tested six *P*-value thresholds (0.05–0.30) for single nucleotide polymorphisms included in the AD PRS. After controlling for non-independence of twins and non-MCI factors that can affect cognition, higher PRSs were associated with significantly greater odds of having aMCI than being cognitively normal (odds ratios (ORs) = 1.36–1.43 for thresholds *P* < 0.20–0.30). The highest OR for the upper vs. lower quartile of the AD PRS distribution was 3.22. OR remained significant after accounting for APOE-related SNPs from the AD PRS or directly genotyped APOE. Diabetes was associated with significantly increased odds of having naMCI (ORs = 3.10–3.41 for thresholds *P* < 0.05–0.30), consistent with naMCI having more vascular inflammation components than aMCI. Analysis of sensitivity, specificity, and negative and positive predictive values supported some potential of AD PRSs for selecting participants in clinical trials aimed at early intervention. With participants 15+ years younger than most MCI samples, these findings are promising with regard to efforts to more effectively treat or slow AD progression.

↓ random note on ROCs/AUCs

should
zoom in

19.1 Astrobiology and Calcium

w/$_{out}$ Neil deGrasse Tyson

up next: 19.2 Microglia and Neuroinflammation

Focus in this Section is on Astrocyte Biology & AlzD

- begins with a calcium story concerning *calcineurin* (CN):
  a calcium-activated phosphatase
- but CN is just one of myriad *calcium* stories being touted by researchers in myriad journals
- Our Main Goal is to relate a *broader overview* of astrocyte roles in diseases
- Astrocytes are the *glia most intimately associated* with neuronal physiology and neural circuit function

from CALCIUM . . . to ASTROCYTES . . .

Chapter 19 - SNCD

Calcineurin Triggers Reactive/Inflammatory Processes in Astrocytes and Is Upregulated in Aging and Alzheimer's Models

Journal of Neuroscience, May 4, 2005

Christopher M. Norris,[1] Inga Kadish,[1] Eric M. Blalock,[1] Kuey-Chu Chen,[1] Veronique Thibault,[1] Nada M. Porter,[1] Philip W. Landfield,[1] and Susan D. Kraner[2]

[1]Molecular and Biomedical Pharmacology, University of Kentucky, Lexington, Kentucky 40536, and [2]Cell Biology, University of Alabama, Birmingham, Alabama 35294

Astrocyte reactivity (i.e., activation) and associated neuroinflammation are increasingly thought to contribute to neurodegenerative disease. However, the mechanisms that trigger astrocyte activation are poorly understood. Here, we studied the Ca^{2+}-dependent phosphatase calcineurin, which regulates inflammatory signaling pathways in immune cells, for a role in astrogliosis and brain neuroinflammation. Adenoviral transfer of activated calcineurin to primary rat hippocampal cultures resulted in pronounced thickening of astrocyte somata and processes compared with uninfected or virus-control cultures, closely mimicking the activated hypertrophic phenotype. This effect was blocked by the calcineurin inhibitor cyclosporin A. Parallel microarray studies, validated by extensive statistical analyses, showed that calcineurin overexpression also induced genes and cellular pathways representing most major markers associated with astrocyte activation and recapitulated numerous changes in gene expression found previously in the hippocampus of normally aging rats or in Alzheimer's disease (AD). No genomic or morphologic evidence of apoptosis or damage to neurons was seen, indicating that the calcineurin effect was mediated by direct actions on astrocytes. Moreover, immunocytochemical studies of the hippocampus/neocortex in normal aging and AD model mice revealed intense calcineurin immunostaining that was highly selective for activated astrocytes. Together, these studies show that calcineurin overexpression is sufficient to trigger essentially the full genomic and phenotypic profiles associated with astrocyte activation and that hypertrophic astrocytes in aging and AD models exhibit dramatic upregulation of calcineurin. Thus, the data identify calcineurin upregulation in astrocytes as a novel candidate for an intracellular trigger of astrogliosis, particularly in aging and AD brain.

Authors induce astrogliosis (hypertrophy) by delivering calcineurin (a calcium-activated phosphatase) to cultured astrocytes, using a viral vector. Authors also report induction of many genes associated with AlzD. Using antibodies on mouse brain, they observe increased CN-immunoreactivity in both aged and AlzD-model mice.

This Slide/Story is just an exemplar of *methods* and *images* being used today

Calcineurin Triggers Reactive/Inflammatory Processes in Astrocytes and Is Upregulated in Aging and Alzheimer's Models

J NSci, 2005

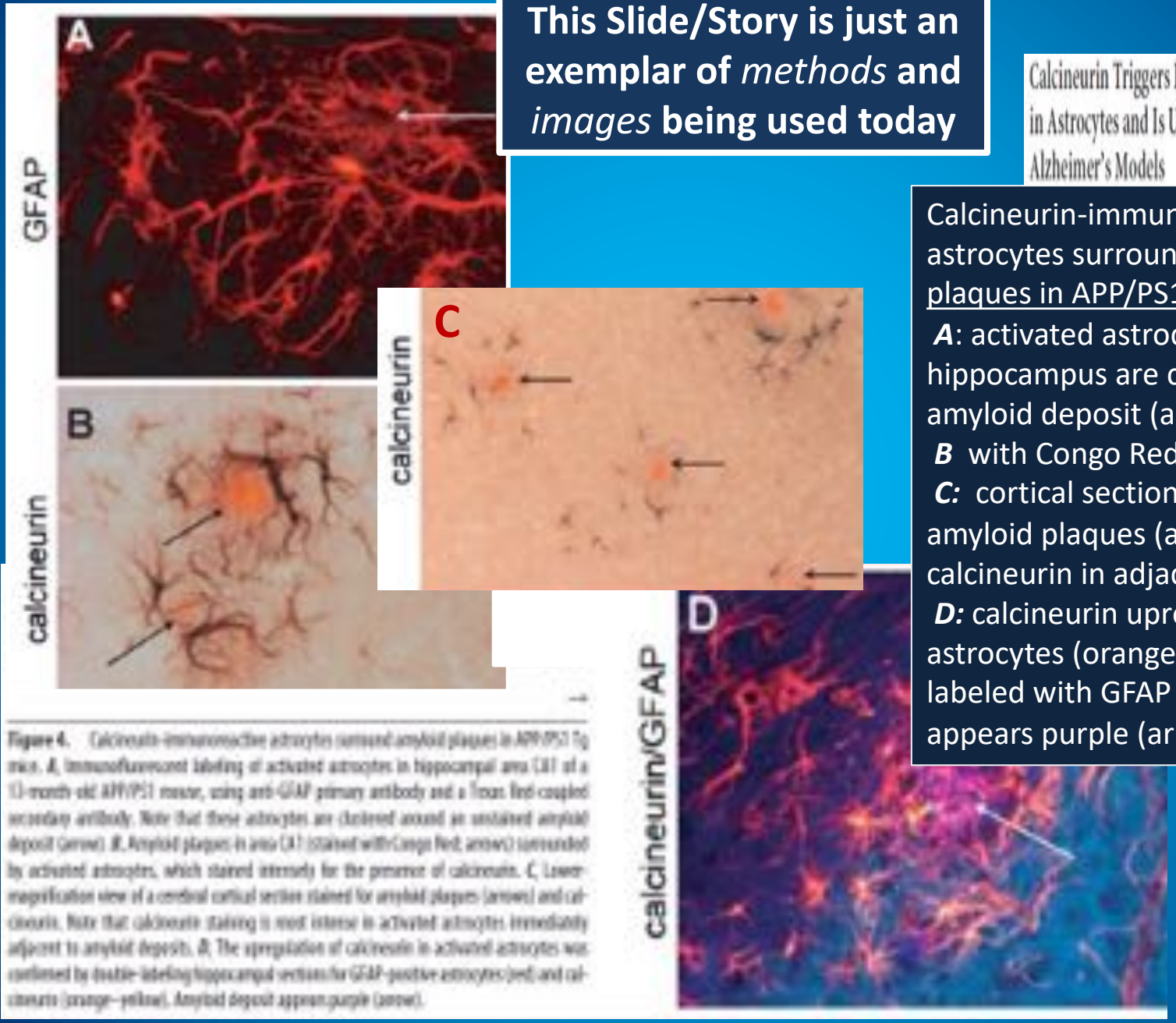


Figure 4. Calcineurin-immunoreactive astrocytes surround amyloid plaques in APP/PS1 Tg mice. *A*, Immunofluorescent labeling of activated astrocytes in hippocampal area CA1 of a 13-month-old APP/PS1 mouse, using anti-GFAP primary antibody and a Texas Red–coupled secondary antibody. Note that these astrocytes are clustered around an unstained amyloid deposit (arrow). *B*, Amyloid plaques in area CA1 (stained with Congo Red, arrows) surrounded by activated astrocytes, which stained intensely for the presence of calcineurin. *C*, Lower-magnification view of a cerebral cortical section stained for amyloid plaques (arrows) and calcineurin. Note that calcineurin staining is most intense in activated astrocytes immediately adjacent to amyloid deposits. *D*, The upregulation of calcineurin in activated astrocytes was confirmed by double-labeling hippocampal sections for GFAP-positive astrocytes (red) and calcineurin (orange–yellow). Amyloid deposit appears purple (arrow).

Calcineurin-immunoreactive astrocytes surround amyloid plaques in APP/PS1 Tg mice.

A: activated astrocytes (GFAP+) in hippocampus are clustered around amyloid deposit (arrow); stained in ***B*** with Congo Red (arrows).

C: cortical section stained for amyloid plaques (arrows) show calcineurin in adjacent astrocytes.

D: calcineurin upregulation in astrocytes (orange–yellow) double-labeled with GFAP (red); amyloid appears purple (arrow).

Neurobiology of Disease

Journal of Neuroscience, 2009, Abdul et al.

Cognitive Decline in Alzheimer's Disease Is Associated with Selective Changes in Calcineurin/NFAT Signaling

ABSTRACT: Calcineurin (CN) signaling appears involved in AlzD pathology. For example, CN activates **NFAT** which **translocates to the nucleus and is associated with severity of dementia**. Also, CN/NFAT changes **correlated to A-beta levels**, while **ABOs reduced astrocytic clearance of glutamate** which could lead to ↑↑ calcium / excitotoxicity.

Calcineurin Update
w/ NFAT = nuclear factor of activated T-cells.

another tenuous link:
AlzD - neuroinflamm

Upon activation by calcineurin, the nuclear factor of activated T-cells (NFAT) translocates to the nucleus and guides the transcription of numerous molecules involved in inflammation and Ca^{2+} dysregulation, both of which are prominent features of Alzheimer's disease (AD). However, NFAT signaling in AD remains relatively uninvestigated. Using isolated cytosolic and nuclear fractions prepared from rapid-autopsy postmortem human brain tissue, we show that NFATs 1 and 3 shifted to nuclear compartments in the hippocampus at different stages of neuropathology and cognitive decline, whereas NFAT2 remained unchanged. NFAT1 exhibited greater association with isolated nuclear fractions in subjects with mild cognitive impairment (MCI), whereas NFAT3 showed a strong nuclear bias in subjects with severe dementia and AD. Similar to NFAT1, calcineurin-Aα also exhibited a nuclear bias in the early stages of cognitive decline. But, unlike NFAT1 and similar to NFAT3, the nuclear bias for calcineurin became more pronounced as cognition worsened. Changes in calcineurin/NFAT3 were directly correlated to soluble amyloid-β ($A\beta_{1-42}$) levels in postmortem hippocampus, and oligomeric Aβ, in particular, robustly stimulated NFAT activation in primary rat astrocyte cultures. Oligomeric Aβ also caused a significant reduction in excitatory amino acid transporter 2 (EAAT2) protein levels in astrocyte cultures, which was blocked by NFAT inhibition. Moreover, inhibition of astrocytic NFAT activity in mixed cultures ameliorated Aβ-dependent elevations in glutamate and neuronal death. The results suggest that NFAT signaling is selectively altered in AD and may play an important role in driving Aβ-mediated

This is not the final word on calcium/calcineurin, but ultimate relevance remains uncertain

Direct involvement of Calcium is suggested by aberrant Ca++ oscillations and waves in astrocytes in the vicinity of senile plaques. ER calcium release **is associated with ERC and PFC pathology** in mouse AlzD models. This fits with THE IDEA of astrocyte dysfunction playing a major role but note "terminal stages".

3 STAGES:

1. neuroprotective
2. pathological features
3. astrodegeneration

Wait, What??? ➔

ERC pathology ➔

Astrocytes are the homeostatic and protective cells of the central nervous system (CNS). In neurological diseases, astrocytes undergo complex changes, which are subclassified into (1) reactive astrogliosis, an evolutionary conserved defensive rearrangement of cellular phenotype aimed at neuroprotection; (2) pathological remodeling, when astrocytes acquire new features driving pathology; and (3) astrodegeneration, which is manifested by astroglial atrophy and loss of homeostatic functions. In aging brains as well as in the brains affected by Alzheimer's disease (AD), astrocytes acquire both atrophic and reactive phenotypes in a region- and disease-stage-dependent manner. Prevalence of atrophy overreactivity, observed in certain brain regions and in terminal stages of the disease, arguably facilitates the development of neurological deficits. Astrocytes exhibit ionic excitability mediated by changes in intracellular concentration of ions, most importantly of Ca^{2+} and Na^{+}, with intracellular ion dynamics triggered by the activity of neural networks. AD astrocytes associated with senile plaques demonstrate Ca^{2+} hyperactivity in the form of aberrant Ca^{2+} oscillations and pathological long-range Ca^{2+} waves. Astroglial Ca^{2+} signaling originating from Ca^{2+} release from the endoplasmic reticulum is a key factor in initiating astrogliotic response. Deficient Ca^{2+} signaling toolkits observed in entorhinal and prefrontal cortices of AD model animals may account for vulnerability of these regions to the pathology.

While overt degeneration of astros occurs very late, dysfunction might occur much earlier

19.1 Part B: Astrobiology
Focus on Reactive Astrocytes

2017

Immunity
Review

GOOD and BAD:

Reactive Astrocytes: Production, Function, and Therapeutic Potential

Shane A. Liddelow[1,*] and Ben A. Barres[1,*]
[1]Department of Neurobiology, Stanford University School of Medi
*Correspondence: liddelow@stanford.edu (S.A.L.), barres@stanford.edu (B.A.B.)
http://dx.doi.org/10.1016/j.immuni.2017.06.006

"We still know very little" re: role of astrocytes in neurodegeneration, but
- two kinds of "reactive astrocytes"
  ~ **Good & Bad**, ensue from injuries
- new markers are being developed
- new therapies are anticipated

Astrocytes constitute approximately 30% of the cells in the mammalian central nervous system (CNS). They are integral to brain and spinal-cord physiology and perform many functions important for normal neuronal development, synapse formation, and proper propagation of action potentials. We still know very little, however, about how these functions change in response to immune attack, chronic neurodegenerative disease, or acute trauma. In this review, we summarize recent studies that demonstrate that different initiating CNS injuries can elicit at least two types of "reactive" astrocytes with strikingly different properties, one type being helpful and the other harmful. We will also discuss new methods for purifying and investigating reactive-astrocyte functions and provide an overview of new markers for delineating these different states of reactive astrocytes. The discovery that astrocytes have different types of reactive states has important implications for the development of new therapies for CNS injury and diseases.

As we seek to understand the connection between **GLIA** and neurodegeneration, the glia most intimately associated with neuronal function is astrocytes and their most prominent response is reactive gliosis**. But in this deep astrogliosis review there is scant mention of neurodegeneration and zero mention of AlzD**. While there is more focus here on acute damage (and scars), I am now questioning the relevance of astrogliosis to dementias. Microglia gliosis is a very different matter and addressed separately.

Molecular dissection of reactive astrogliosis and glial scar formation

Michael V. Sofroniew

Department of Neurobiology, University of California Los Angeles, Los Angeles,

TINS, 2009

Reactive astrogliosis, whereby astrocytes undergo varying molecular and morphological changes, is a ubiquitous but poorly understood hallmark of all central nervous system pathologies. Genetic tools are now enabling the molecular dissection of the functions and mechanisms of reactive astrogliosis in vivo. Recent studies provide compelling evidence that reactive astrogliosis can exert both beneficial and detrimental effects in a context-dependent manner determined by specific molecular signaling cascades. Reactive astrocytes can have both loss of normal functions and gain of abnormal effects that could feature prominently in a variety of disease processes. This article reviews developments in the signaling mechanisms that regulate specific aspects of reactive astrogliosis and highlights the potential to identify novel therapeutic molecular targets for diverse neurological disorders.

Introduction

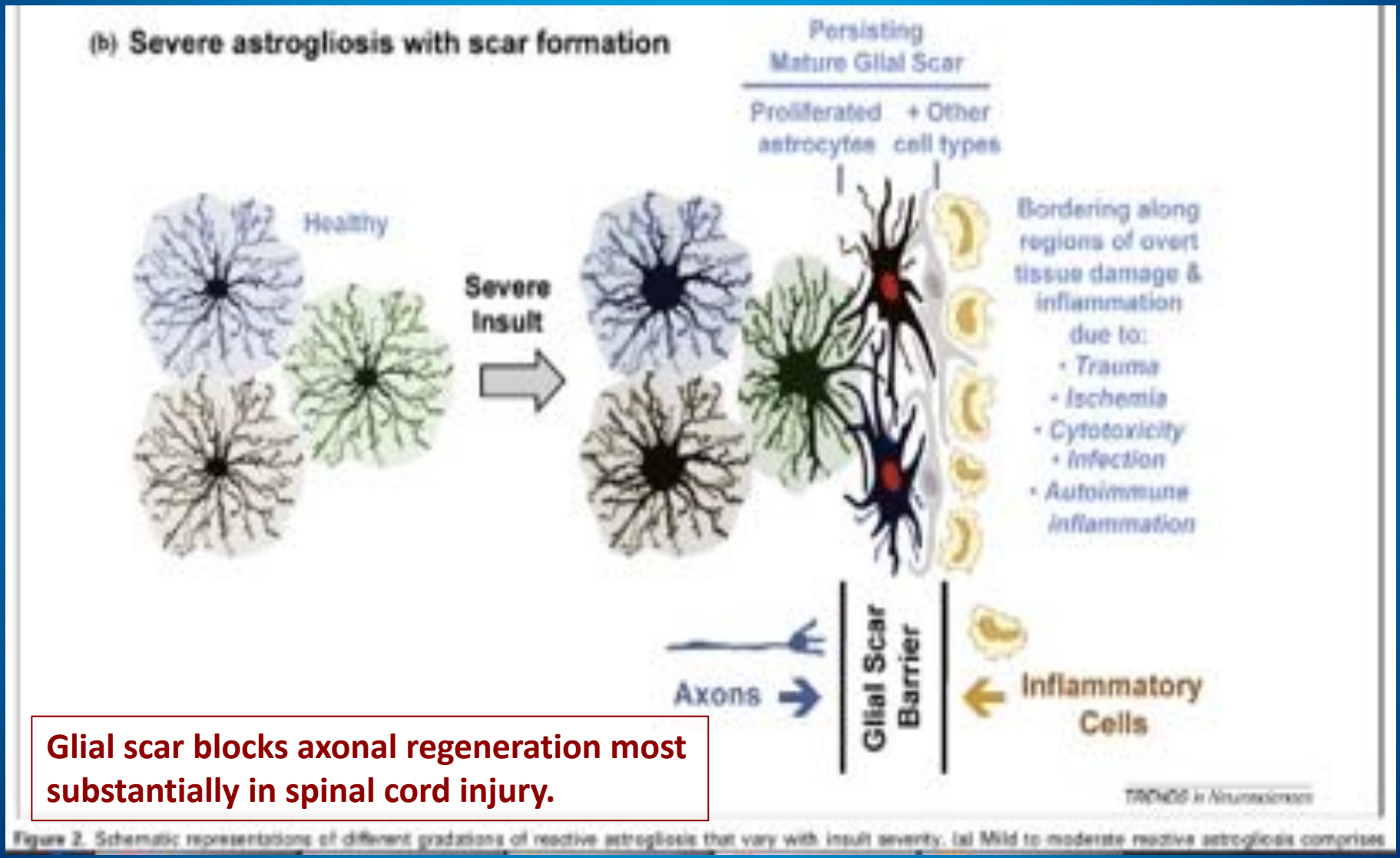
Astrocytes (Figure 1a) are complex, highly differentiated cells that tile the entire central nervous system (CNS) in a contiguous fashion and make numerous essential contri-

subtle, responses to CNS insults, of which scar formation is only one and lies at the extreme end in terms of its severity. This article summarizes recent advances in the molecular dissection of the functions and mechanisms of reactive astrogliosis, with the main focus on deletion experiments using transgenic mouse models that allow either cellular ablation or molecular deletion in combination with different types of injury or disease paradigms in vivo. This article begins with a definition and model of astrogliosis that includes surveys of molecules produced by reactive astrocytes and of triggering mechanisms and signaling pathways that regulate astrogliosis. It concludes with surveys of the functions of astrogliosis, the potential for dysfunction to contribute to disease mechanisms and the identification of novel therapeutic targets. Space constraints prevent exhaustive review of all topics and limit discussion to a cross-section of recent advances.

Defining reactive astrogliosis

What is astrogliosis? What features distinguish a reactive astrocyte from one that is non-reactive? Is astrogliosis an all-or-none process or a graded one? Is it a good thing or

Scarring is important in spinal cord injury and possibly STROKE. But STROKE and SCI are outside our scope this semester.



Glial scar blocks axonal regeneration most substantially in spinal cord injury.

Figure 2. Schematic representations of different gradations of reactive astrogliosis that vary with insult severity. (a) Mild to moderate reactive astrogliosis comprises

BRB, 2018

reviews basic astrocyte functions: metabolic/structural support, neurogenesis, brain wiring and synaptic activity/ plasticity

Review

Human astrocytes in the diseased brain

Elena Dossi [1], Flora Vasile [1], Nathalie Rouach [1]

ASTROCYTES PLAY a role in: depression, epilepsy, tumors, Down's Syndrome AND Alzheimer's Disease…

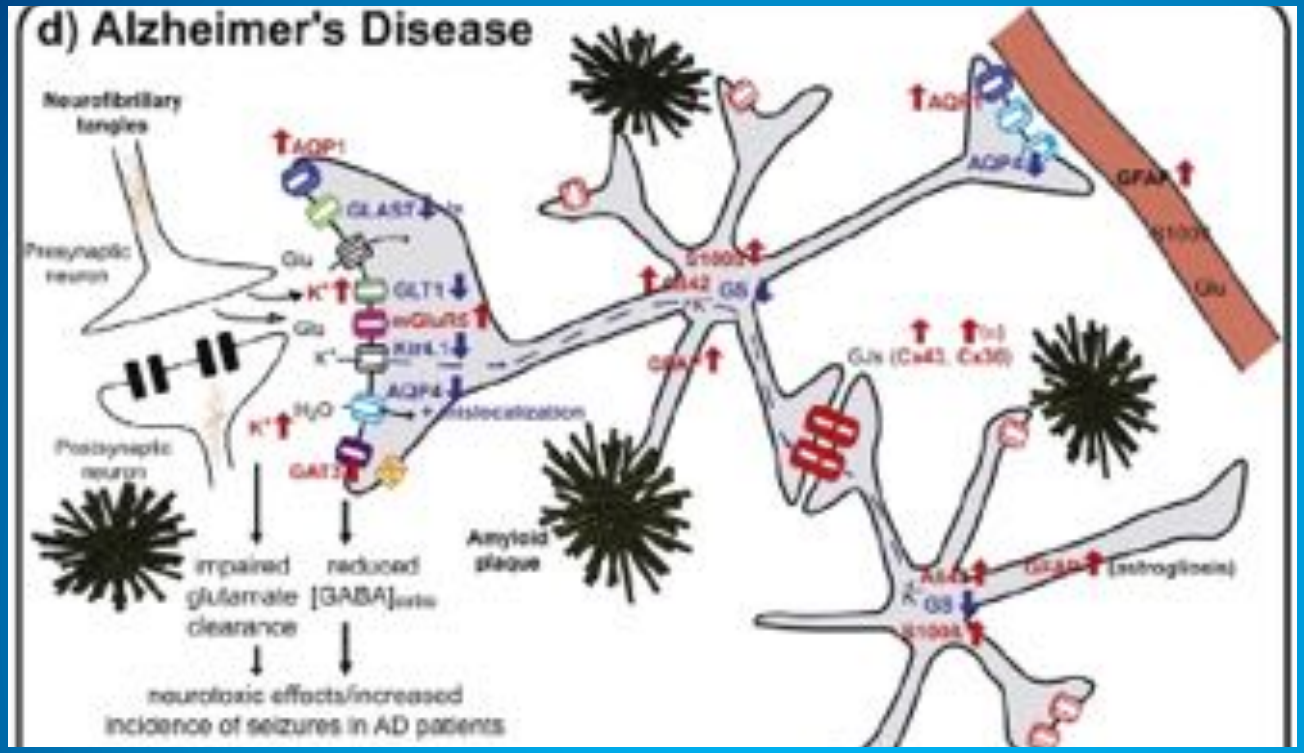
…allegedly…

This article notes differences between rat and human astrocytes AND also asserts role in *many* human neurological conditions

ABSTRACT

Astrocytes are key active elements of the brain that contribute to information processing. They not only provide neurons with metabolic and structural support, but also regulate neurogenesis and brain wiring. Furthermore, astrocytes modulate synaptic activity and plasticity in part by controlling the extracellular space volume, as well as ions and neurotransmitter homeostasis. These findings, together with the discovery that human astrocytes display contrasting characteristics with their rodent counterparts, point to a role for astrocytes in higher cognitive functions. Dysfunction of astrocytes can thereby induce major alterations in neuronal functions, contributing to the pathogenesis of several brain disorders. In this review we summarize the current knowledge on the structural and functional alterations occurring in astrocytes from the human brain in pathological conditions such as epilepsy, primary tumours, Alzheimer's disease, major depressive disorder and Down syndrome. Compelling evidence thus shows that dysregulations of astrocyte functions and interplay with neurons contribute to the development and progression of various neurological diseases. Targeting astrocytes is thus a promising alternative approach that could contribute to the development of novel and effective therapies to treat brain disorders.

general astrocyte biology summary



BRB, 2018

astrocyte interactions: diverse mechanisms

Osmolarity maybe affected by AQPs (aquaporins) and w/ ↓ transport the K+ levels might increase. Excess glutamate and ↓ GABA ➔ over-excitation / excitotoxicity.

Astrocytes interact with pre- and post-synaptic neurons, with other astrocytes and with blood vessels.

This is not the final word on Astrobiology and AlzD-- but relevance remains uncertain!

w/ Holtzman

Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes

PNAS, 2016

Won-Suk Chung[a,1], Philip B. Verghese[b,2], Chandrani Chakraborty[a], Julia Joung[a,3], Bradley T. Hyman[c,d], Jason D. Ulrich[b], David M. Holtzman[b], and Ben A. Barres[a,4]

Contributed by Ben A. Barres, June 20, 2016

The strongest genetic risk factor influencing susceptibility to late-onset Alzheimer's disease (AD) is apolipoprotein E (*APOE*) genotype. APOE has three common isoforms in humans, E2, E3, and E4. The presence of two copies of the *E4* allele increases risk by ~12-fold whereas *E2* allele is associated with an ~twofold decreased risk for AD. These data put APOE central to AD pathophysiology, but it is not yet clear how *APOE* alleles modify AD risk. Recently we found that astrocytes, a major central nervous system cell type that produces APOE, are highly phagocytic and participate in normal synapse pruning and turnover. Here, we report a novel role for APOE in controlling the phagocytic capacity of astrocytes that is highly dependent on APOE isoform. APOE2 enhances the rate of phagocytosis of synapses by astrocytes, whereas APO4 decreases it. We also found that the amount of C1q protein accumulation in hippocampus, which may represent the accumulation of senescent synapses with enhanced vulnerability to complement-mediated degeneration, is highly dependent on *APOE* alleles: C1q accumulation was significantly reduced in *APOE2* knock-in (KI) animals and was significantly increased in *APOE4* KI animals compared with *APOE3* KI animals. These studies reveal a novel allele-dependent role for APOE in regulating the rate of synapse pruning by astrocytes. They also suggest the hypothesis that AD susceptibility of *APOE4* may originate in part from defective phagocytic capacity of astrocytes which accelerates the rate of accumulation of C1q-coated senescent synapses, enhancing synaptic vulnerability to classical-complement-cascade mediated neurodegeneration.

ApoE4 in Astrocytes!

Astrocytes phagocytose synapses [synaptic pruning and turnover]

ApoE2 increases turnover and decreases AlzD risk

ApoE4 reduces turnover and increases complement protein C1q and *risk of AlzD*

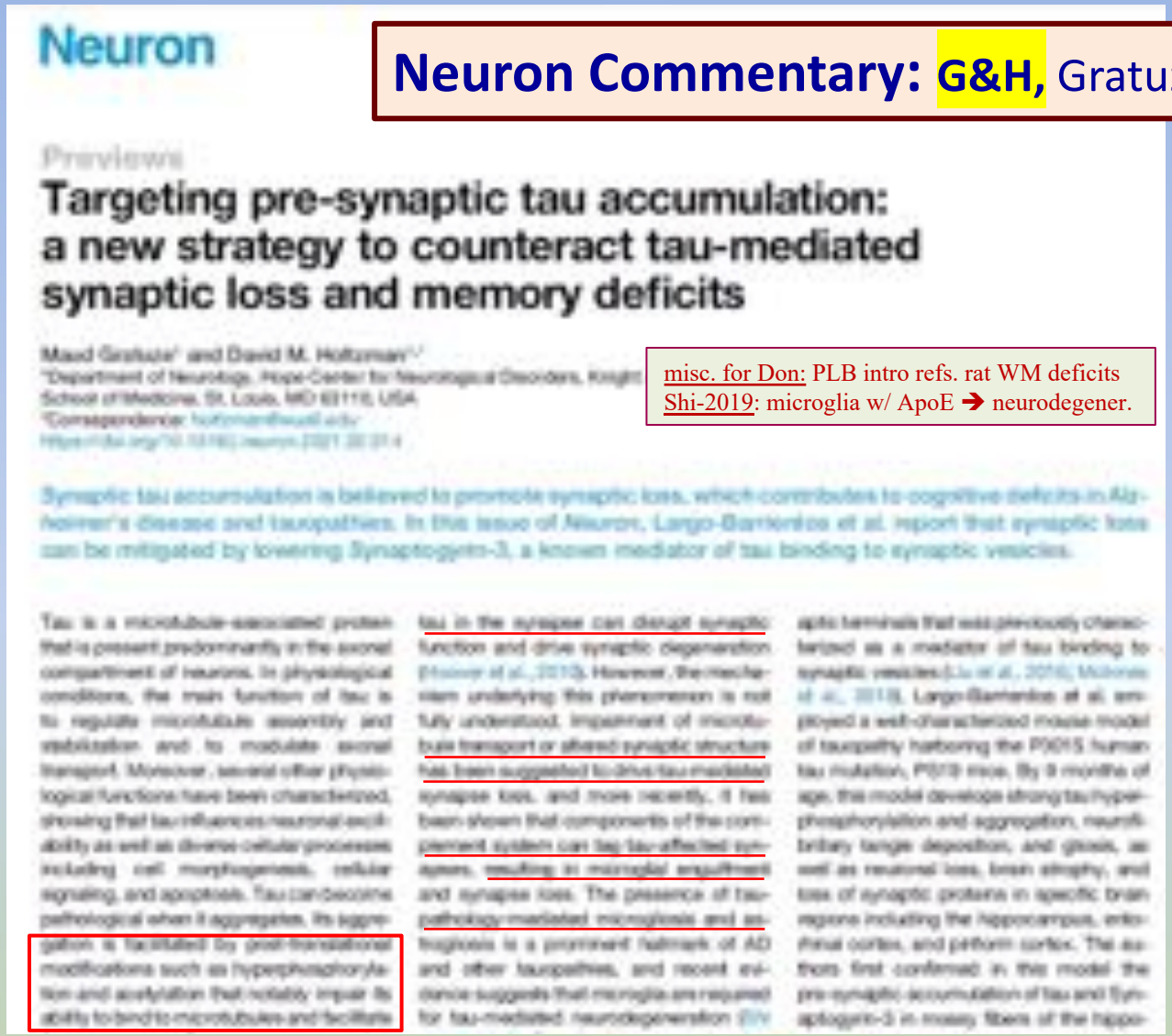
I like this theory b/c its something that:

a. should affect cognitive operations and

b. should gradually worsen with age

next up: MICROGLIA!

Neuron Commentary: G&H, Gratuze & Holtzman, 2021



Neuron

Previews

Targeting pre-synaptic tau accumulation: a new strategy to counteract tau-mediated synaptic loss and memory deficits

misc. for Don: PLB intro refs. rat WM deficits
Shi-2019: microglia w/ ApoE ➔ neurodegener.

Chap. 12-13 slide:
REPRISED:
w/ microglial role
in synaptic pruning

➔ **Tau-mutant line w/ P301 human tau mutation**

Hyperphosphorylation – crucial step in AlzD pathology; always present in tauopathies? [≈ tau-FTLD]
mechanism of tau toxicity inside synapse was uncertain [perhaps altered transport, structure; complement-C1q]
author PLB: mutant-tau binding to synaptogryin-3 ➔ synaptic loss, behavioral deficits
or is it: RNA dyshomeostasis & "PQC" protein quality control ➔ phase separations, stress granules. Mandrioli-2020

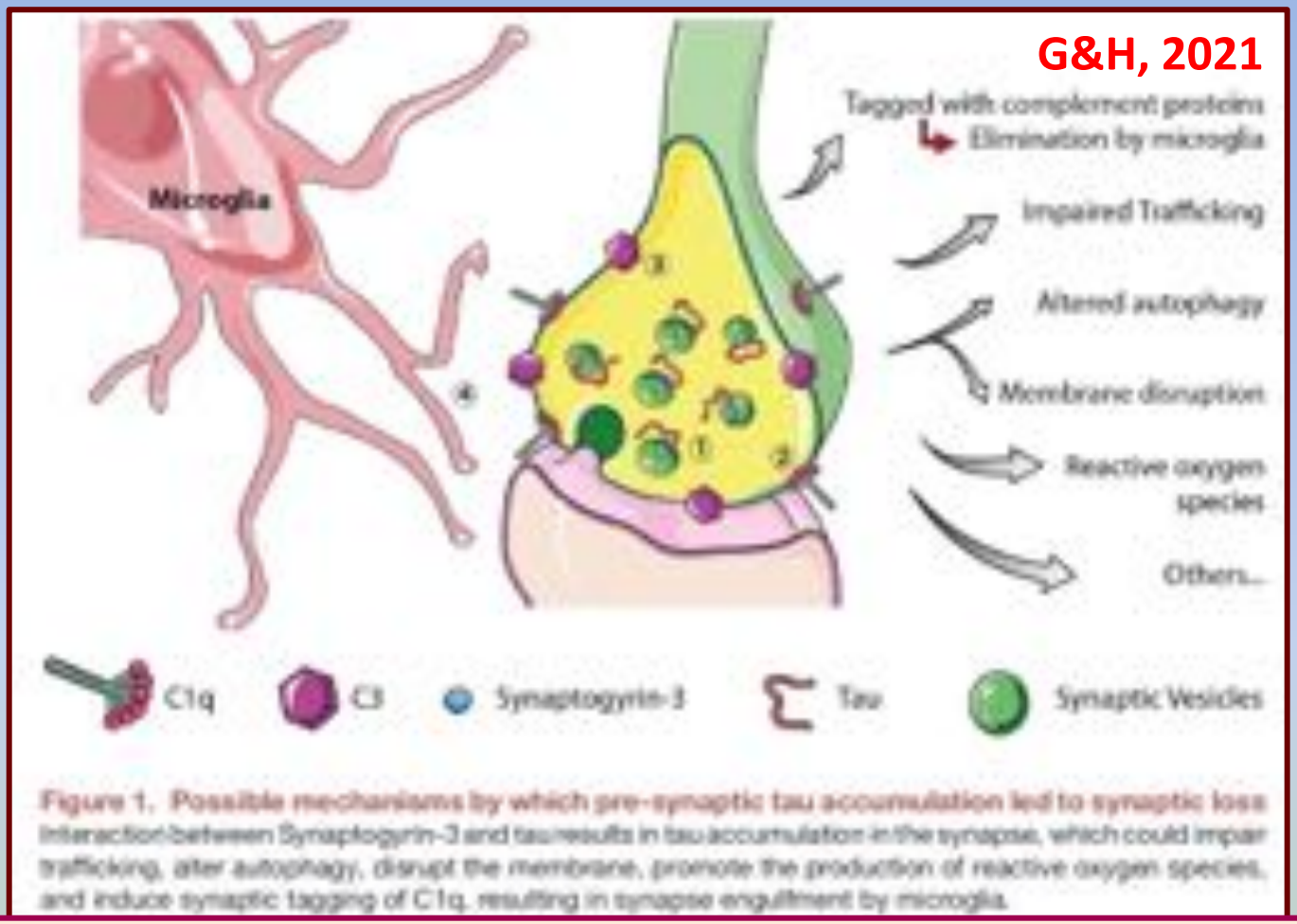


Figure 1. Possible mechanisms by which pre-synaptic tau accumulation led to synaptic loss
Interaction between Synaptogyrin-3 and tau results in tau accumulation in the synapse, which could impair trafficking, alter autophagy, disrupt the membrane, promote the production of reactive oxygen species, and induce synaptic tagging of C1q, resulting in synapse engulfment by microglia.

Oh Where are the Astrocytes?

know this song?

Possible Mechanisms of Tau Pathology: Mutant Tau aggregates impair axonal transport, which impairs autophagy inside the synaptic terminal. This also worsens mitoch. functions, increasing ROS. In addition, tau binds to SG3 vesicle protein, worsening the pathology in the presynaptic terminal (perhaps releasing cytokines or other signal), causing microglia to respond by tagging terminals with C1q (?) which recruits C3 (?) part of "complement" system leading to engulfment of the terminals. There is regular, normal such engulfment (pruning of synapses) but this mechanism takes it to a pathological level leading to loss of synapses and cognitive decline!

Neuron: PLB Pablo Largo-Barrientos et al. 2021

Neuron

Report

Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation

Pablo Largo-Barrientos,[1,2] Nuno Apóstolo,[1,2] Eline Creemers,[1,2] Zsuzsanna Callaerts-Vegh,[1] Jef Swerts,[1,2] Caitlin Davies,[4] Joseph McInnes,[1,2] Kelimpo Wierda,[1,2] Bart De Strooper,[1,4,5] Tara Spires-Jones,[4] Joris de Wit,[1,2] Valerio Uytterhoeven,[1,2,7] and Patrik Verstreken[1,2,6,7]
[1]VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium
[2]KU Leuven, Department of Neurosciences, Leuven Brain Institute, Mission Lucidity, Leuven, Belgium
[3]KU Leuven, mRNT Animal Behavior Facility, Faculty of Psychology, Leuven, Belgium
[4]Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, UK
[5]UK Dementia Research Institute, University College London, London, UK
[6]Lead contact
[7]Correspondence: [redacted] (P.V.)
https://doi.org/10.1016/j.neuron.2020.12.016

SUMMARY

Tau is a major driver of neurodegeneration and is implicated in over 20 diseases. Tauopathies are characterized by synaptic loss and neuroinflammation, but it is unclear if these pathological events are causally linked. Tau binds to Synaptogyrin-3 on synaptic vesicles. Here, we interfered with this function to determine the role of pathogenic Tau at pre-synaptic terminals. We show that heterozygous knockout of synaptogyrin-3 is benign in mice but strongly rescues mutant Tau-induced defects in long-term synaptic plasticity and working memory. It also significantly rescues the pre- and post-synaptic loss caused by mutant Tau. However, Tau-induced neuroinflammation remains clearly upregulated when we remove the expression of one allele of synaptogyrin-3. Hence neuroinflammation is not sufficient to cause synaptic loss, and these processes are separately induced in response to mutant Tau. In addition, the pre-synaptic defects caused by mutant Tau are enough to drive defects in cognitive tasks.

trem2
microRNAs
microbiome
herpes & cognition?
treating astrocytes?

Chapter 19 - SNCD

ALL THE ALZ-D TOPICS THAT ARE FIT TO PRINT

19.1 Astrobiology and Calcium
19.2 Microglia and Neuroinflammation
19.3 Does AlzD = Type 3 Diabetes?
19.4 Molec. Path 1: microRNAs and Cell Physiology
19.5 Molec. Path 2: Genetic Risks and Big Data
19.6 Additional Risk Factors
19.7 Herpes Brain and Other Infections
19.8 Tau and Amyloid – PART
19.9 Prions and Prion-like Proteins
19.10 Treatments and Therapies

Raina microbiome link: gut microbiome + AD: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326209/

…the Storm continues…

STUDENT QUERIES & OTHER UPDATES

MAJOR ARTICLE

JID - 2017

Persistent Herpesvirus Infections and Telomere Attrition Over 3 Years in the Whitehall II Cohort

Jennifer B. Dowd,[1,2] Jos A. Bosch,[3,4] Andrew Steptoe,[5] Bamini Jayabalasingham,[5] Jue Lin,[6] Robert Yolken,[7] and Allison E. Aiello[8]

[1]Department of Global Health and Social Medicine, King's College London, and [2]Department of Epidemiology and Public Health, University College London, United Kingdom; [3]Epidemiology and Biostatistics, CUNY Graduate School of Public Health & Health Policy, New York, New York, [4]Department of Biochemistry and Biophysics, University of California, San Francisco, [5]Johns Hopkins School of Medicine, Baltimore, Maryland, and [6]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill; [7]Department of Psychology, University of Amsterdam, and [8]Academic Medical Centre, Amsterdam, The Netherlands; and [9]Mannheim Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, University of Heidelberg, Germany

(See the editorial commentary by Griffiths, on pages 511–3.)

The determinants of telomere attrition, a potential marker of cellular aging, are not well understood. Persistent herpesvirus infections including cytomegalovirus (CMV) infection may be particularly important for telomere dynamics via mechanisms such as inflammation, oxidative stress, and their impact on peripheral blood lymphocyte composition. This study examined the association of 4 human herpesviruses (CMV, herpes simplex virus type 1, human herpesvirus type 6, and Epstein-Barr virus) with change in leukocyte telomere length (LTL) over 3 years in 400 healthy individuals (aged 53–76 years) from the Whitehall II cohort. CMV, herpes simplex virus type 1, and human herpesvirus 6 infection were independently associated with greater 3-year LTL attrition, with no association found for Epstein-Barr virus. The magnitudes of these associations were large, for example, the equivalent of almost 12 years of chronological age for those CMV seropositive. Seropositivity to more herpesviruses was additively associated with greater LTL attrition (3 herpesviruses vs none, $\beta = -0.07$ and $P = .02$; 4 infections vs none, $\beta = -0.14$ and $P < .001$). Higher immunoglobulin G antibody levels among those seropositive to CMV were also associated with shorter LTL at follow-up. These associations were robust to adjustment for age, sex, employment grade, body mass index, and smoking status. These results suggest that exposure to infectious agents should be an important consideration in future studies of telomere dynamics.

HSV virus associated with telomere shortening
relevant to aging, but NO mention of AlzD, neurodegener. or neurons

[we had screenshared some of Herpes Brain last Friday]

MORE on ApoE

Which is more likely:

ApoE does ALL of these things

or

ApoE does NONE of these things?

APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches

Lancet, 2021

The *APOE* ε4 allele remains the strongest genetic risk factor for sporadic Alzheimer's disease and the *APOE* ε2 allele the strongest genetic protective factor after multiple large-scale genome-wide association studies and genome-wide association meta-analyses. However, no therapies directed at APOE are currently available. Although initial studies causally linked APOE with amyloid-β peptide aggregation and clearance, over the past 5 years our understanding of APOE pathogenesis has expanded beyond amyloid-β peptide-centric mechanisms to tau neurofibrillary degeneration, microglia and astrocyte responses, and blood–brain barrier disruption. Because all these pathological processes can potentially contribute to cognitive impairment, it is important to use this new knowledge to develop therapies directed at APOE. Several therapeutic approaches have been successful in mouse models expressing human *APOE* alleles, including increasing or reducing APOE levels, enhancing its lipidation, blocking the interactions between APOE and amyloid-β peptide, and genetically switching APOE4 to APOE3 or APOE2 isoforms, but translation to human clinical trials has proven challenging.

would deletion of ApoE3cc be bad?

Introduction

Even after multiple large-scale genome-wide association studies (GWAS) and GWAS meta-analyses, the ε4 allele of the *APOE* gene (compared with the most common ε3 allele) continues to be the strongest genetic risk factor associated with sporadic Alzheimer's disease since its discovery in 1993. Moreover, the relatively rare APOE ε2 allele remains by far the strongest genetic protective factor against sporadic Alzheimer's disease (panel 1), emphasising the importance of APOE's role in Alzheimer's disease pathogenesis. Because Alzheimer's disease is defined by the accumulation of two hallmark pathological protein aggregates: amyloid-β peptide (Aβ) plaques and neurofibrillary tangles containing hyperphosphorylated tau, one postulate is that APOE affects these lesions. Although solid evidence supports this view, emerging advances are changing our understanding of APOE involvement in Alzheimer's disease. First, new

to be effective in mouse models and hold promise for translation to human clinical trials. In this Review, we discuss the advances made in genetics, pathophysiology, and therapeutic approaches related to APOE and Alzheimer's disease.

Genetic discoveries related to APOE

Over the past 5 years, human genetic studies have suggested risk modifiers that mitigate or increase APOE ε4-associated Alzheimer's disease risk, and identified haplotypes with heterogeneous effects. Understanding the risk variation in APOE ε4 carriers has the potential to shed further light on APOE pathobiology and mechanisms of resilience and resistance to Alzheimer's disease, which could have therapeutic value.

APOE ε2 homozygosity

In an analysis of a US cohort with approximately

Some nice history and tie-ins here including GWAS, ApoE4 discovery

STUDENT QUERIES & OTHER UPDATES

E3 is most common; found in >50% popul

how many additional copies can YOU have?

Chat Query: how many ApoE alleles can YOU carry (in YOUR genome)?

ARTICLE **2020 – *Nature Communications***

OPEN

Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study

Eric M. Reiman

Univ Ariz.

Does ANYBODY speak English? *or*
My Plaques and Tangles HURT!

Each additional copy of the apolipoprotein E4 (APOE4) allele is associated with a higher risk of Alzheimer's dementia, while the APOE2 allele is associated with a lower risk of Alzheimer's dementia. It is not yet known whether APOE2 homozygotes have a particularly low risk. We generated Alzheimer's dementia odds ratios and other findings in more than 5,000 clinically characterized and neuropathologically characterized Alzheimer's dementia cases and controls. APOE2/2 was associated with a low Alzheimer's dementia odds ratios compared to APOE2/3 and 3/3, and an exceptionally low odds ratio compared to APOE4/4, and the impact of APOE2 and APOE4 gene dose was significantly greater in the neuropathologically confirmed group than in more than 24,000 neuropathologically unconfirmed cases and controls. Finding and targeting the factors by which APOE and its variants influence Alzheimer's disease could have a major impact on the understanding, treatment and prevention of the disease.

How LOW is EXCEPTIONALLY?

Should the <u>ABSTRACT</u> deliver what was PROMISED in the <u>TITLE</u>?

Your Job: is NOT to write things that can be understood.
agree? Your job is to write things that CANNOT be MISUNDERSTOOD

Chapter 19 - SNCD

MORE ALZ-D TOPICS … FIT TO SHARE?

19.4 Molec. Path 1: microRNAs and Cell Physiology and Neuroinflammation

19.6 Additional Risk Factors

19.7 Herpes Brain and Other Infections

The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function

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The innate immune system is strongly implicated in the pathogenesis of Alzheimer's disease (AD). In contrast, the role of adaptive immunity in AD remains largely unknown. However, numerous clinical trials are testing vaccination strategies for AD, suggesting that T and B cells play a pivotal role in this disease. To test the hypothesis that adaptive immunity influences AD pathogenesis, we generated an immune-deficient AD mouse model that lacks T, B, and natural killer (NK) cells. The resulting "Rag-5xfAD" mice exhibit a greater than twofold increase in β-amyloid (Aβ) pathology. Gene expression analysis of the brain implicates altered innate and adaptive immune pathways, including changes in cytokine/chemokine signaling and decreased Ig-mediated processes. Neuroinflammation is also greatly exacerbated in Rag-5xfAD mice as indicated by a shift in microglial phenotype, increased cytokine production, and reduced phagocytic capacity. In contrast, immune-intact 5xfAD mice exhibit elevated levels of nonamyloid reactive IgGs in association with microglia, and treatment of Rag-5xfAD mice or microglial cells with preim-

cytokine and chemokine signaling likely plays an important albeit understudied role in AD. In support of this notion, two recent studies demonstrated profound effects of peripherally derived neutrophils and T-regulatory cells (Tregs) on AD pathogenesis (17, 18). Despite this exciting recent progress, many of the mechanisms and actions of other peripheral immune cell populations in AD remain unknown, and thus a great a deal of additional study is needed.

Here, we show that the adaptive immune system plays an important role in limiting amyloid pathology in AD, by generating and examining a novel immune-deficient transgenic model of AD. The resulting "Rag-5xfAD" mice, which lack an adaptive immune response, exhibit dramatically increased Aβ plaque load, despite already being a very aggressive model of amyloidosis. Gene ontology (GO) analysis revealed significant alterations in cytokine/chemokine signaling and microglial associated pathways that were validated at the protein level. Furthermore, peripherally derived nonamyloid reactive immunoglobulin G (IgG) appears to enter the brain and

A Tale of Two Genes: Microglial *Apoe* and *Trem2*

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Immunity, 2017

Microglial cell function is implicated in the etiology of Alzheimer's disease by human genetics. In this issue of *Immunity*, Krasemann et al. (2017) describe a gene expression signature associated with an APOE- and TREM2-dependent response of microglia to brain tissue damage that accumulates in aging and disease, defining an axis that might be amenable to therapeutic targeting.

Dear Dr. Pimenova,

Before I send this, what am I missing?

I read your nice commentary on Apoe and Trem2 in *Immunity*, 2017. I have drafted a textbook on the *Neurobiology of Aging* and am hoping to improve my coverage of these topics, if I might ask a question. It seems that the transition of microglia to the neurodegenerative phenotype (MGnD) is harmful because "blocking the transition from homeostatic to MGnD microglia" might be therapeutic (iaw Krasemann); also "restoring the homeostatic signature…might be protective against AD". But this seems contrary to a later sentence noting that "promoting the transition to MGnD microglia would delay development and decrease the risk of AD". It seems I am misunderstanding something here—I would welcome any help you might offer. The overview of Trem2 and ApoE is, in any case, very helpful.

I also just came across your 2017 review on "Untangling genetic risk for AD". Your detailed explanations of GWAS, functional genomics and the role of lipid metabolism in AD were quite valuable to my teaching. This is all greatly appreciated! Best Regards, Don

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a diverse array of cellular functions, including trophic support of neurons, immune response to injury and infection, and phagocytic clearance of synapses and other cellular debris in development, homeostasis, aging, and disease (Crotti and Ransohoff, 2016). Microglia respond to alterations in brain tissue homeostasis by changing their gene expression and functional profile, thus providing researchers with a number of transcriptional signatures they can use to define the state of healthy, stressed, or diseased brain tissue. Although several transcriptome-profiling studies have described the microglial gene expression signatures associated with neurodegeneration (Crotti and Ransohoff, 2016), it is unclear which pathways and genes are important for triggering and sustaining these signals. A new study by Krasemann et al. (2017) in this issue of *Immunity* sheds light on the mechanism controlling the acquisition of a neurodegeneration-associated phenotype by microglia; the authors term this MGnD. The transition from homeostatic to MGnD microglia is dependent on apolipoprotein E (APOE) and characteristic of phagocytosing microglia that surround dystrophic neurites around plaques (Figure 1), as well as microglia observed in aging mice and in mouse models of neurodegenerative diseases. Ablation of *Trem2* locks microglia into a homeostatic state, which blocks the formation of MGnD microglia similarly to *Apoe* deficiency (Keren-Shaul et al.,

Tale of Two Genes: 2017

Microglial Functions: trophic support of neurons, respond to infections, clearance of debris including dystrophic neurites.

Depends upon "state"– which depends upon Transcriptional Profile.

"Reactive Microglia" assume the MGnD phenotype (microglia – neurodegenerative) -- this depends upon ApoE.

Ablation of TREM2 locks microglial in resting or homeostatic state.

route for therapeutic intervention in Alzheimer's disease (AD).

Microglia react to brain tissue damage that accumulates in aging and neurodegeneration by acquiring a different morphology and by changing the transcriptome to fulfill their debris-clearance function and restore homeostasis. The authors isolated microglia from aged mice and three mouse models: AD (APP-PS1), multiple sclerosis (experimental autoimmune encephalomyelitis), and amyotrophic lateral sclerosis ($SOD1^{G93A}$). They then analyzed these models' transcriptomes by using a NanoString MG590 chip, which contains microglia-specific genes previously identified by the authors in homeostatic microglia (Butovsky et al., 2014) and additional inflammation- and phagocytosis-related genes. The comparison of gene patterns via K-means clustering of significantly affected genes revealed suppression of homeostatic genes, whereas other genes including *Apoe*, *Axl*, *Clec7a*, *Csf1*, and *Ccl2* were found to be positively correlated with disease progression. Ingenuity pathway analysis identified APOE and transforming growth factor β (TGFβ) as major upstream regulators of the MGnD phenotype, which is consistent with the observed suppression of the TGFβ-dependent homeostatic signature (Butovsky et al., 2014).

Two molecules, P2ry12 and Clec7a, were highly enriched in homeostatic and MGnD microglia, respectively. To

Tale of Two Genes: 2017

Microglial and Aging: in normal aging and dementia they acquire a phagocytotic phenotype in an effort to "restore homeostasis".

MG examined in 3 mouse models: APP/PS1, MS (EAE), ALS (sod1) using a custom gene chip with microglia-specific, inflammatory and other genes.

RESULTS: genes associated with routine homeostasis (non-disease controls?) were suppressed while other genes correlated with disease suppression including ApoE.

ApoE and TGFb appear to be upstream controllers of the MGnD phenotype.

MANY risk genes are associated with microglia
some discussed earlier: 17 genes w/ 9 being microglia specific responses to **complement**, **TREM & AB regulation** are noted

Biological Psychiatry **Review**

2017

Untangling Genetic Risk for Alzheimer's Disease

Anna A. Pimenova, Towfique Raj, and Alison M. Goate

ABSTRACT
Alzheimer's disease (AD) is a genetically heterogeneous neurodegenerative disorder caused by fully penetrant single gene mutations in a minority of cases, while the majority of cases are sporadic or show modest familial clustering. These cases are of late onset and likely result from the interaction of many genes and the environment. More than 30 loci have been implicated in AD by a combination of linkage, genome-wide association, and whole genome/exome sequencing. We have learned from these studies that perturbations in endolysosomal, lipid metabolism, and immune response pathways substantially contribute to sporadic AD pathogenesis. We review here current knowledge about functions of AD susceptibility genes, highlighting cells of the myeloid lineage as drivers of at least part of the genetic component in late-onset AD. Although targeted resequencing utilized for the identification of causal variants has discovered coding mutations in some AD-associated genes, a lot of risk variants lie in noncoding regions. Here we discuss the use of functional genomics approaches that integrate transcriptomic, epigenetic, and endophenotype traits with systems biology to annotate genetic variants, and to facilitate discovery of AD risk genes. Further validation in cell culture and mouse models will be necessary to establish causality for these genes. This knowledge will allow mechanism-based design of novel therapeutic interventions in AD and promises coherent implementation of treatment in a personalized manner.

microglial are very often the locus of AlzD risk genes and pathological events
complement receptor 1 (CR1) is expressed on microglia and activated in AlzD
CD33 seen in GWAS, affects AB uptake & phagocytosis and also TREM2 signaling
Tyro protein on microglia is reqd. for TREM2 signaling and dysregulated in AlzD

nice read – ping me for PDF

Pimenova 2017: for the Gene Jockeys amongst us! *fyi only*

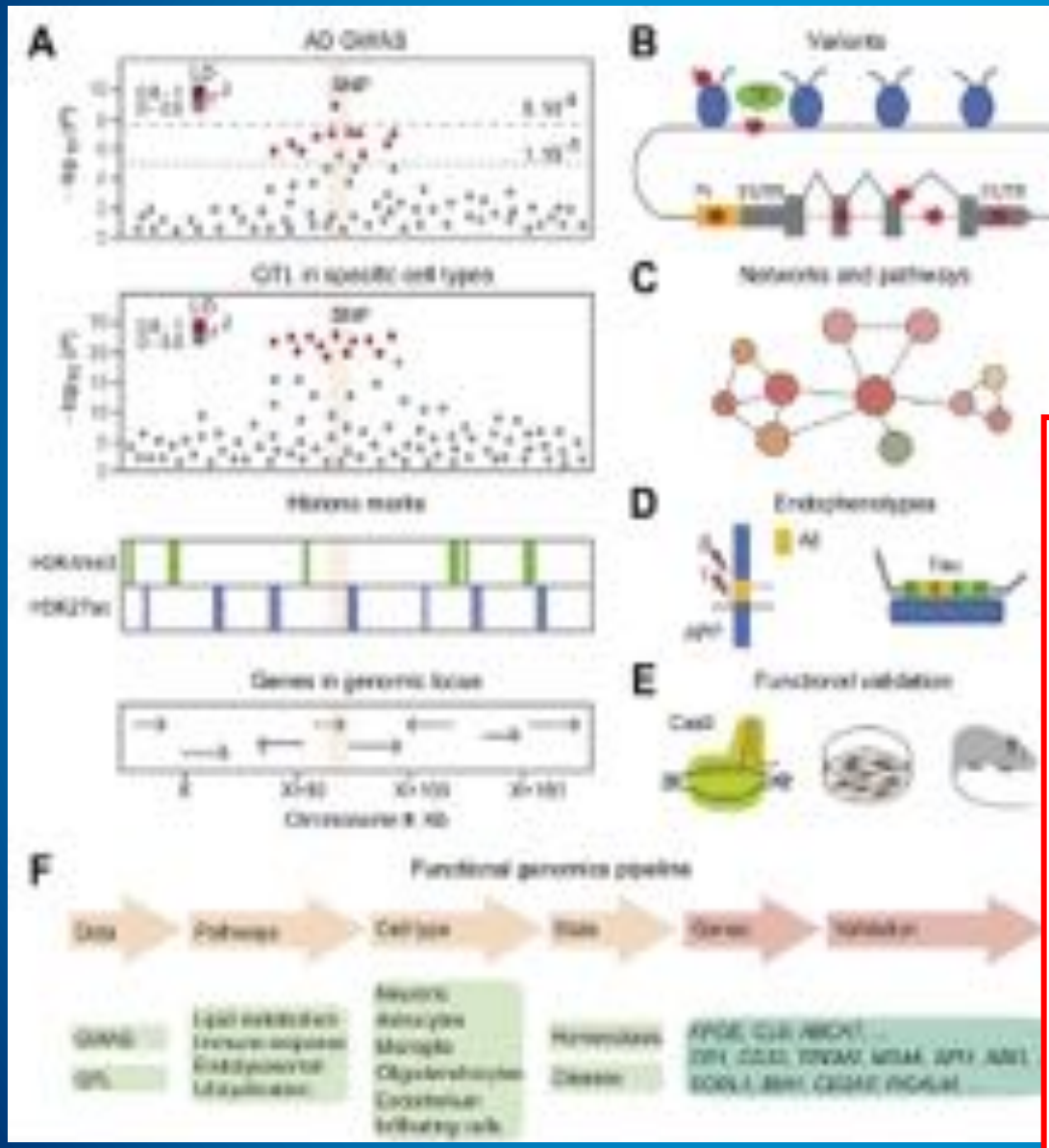

Figure 1. Schematic representation of a multidimensional approach for fine-mapping risk variants in Alzheimer's disease (AD)-associated loci. (**A**) An illustration of a locus-specific association signal from a genome-wide association study (GWAS) of AD, e.g., Manhattan association plot (top panel). Each dot represents a single nucleotide polymorphism (SNP), with the *x* axis showing the chromosomal position and *y* axis showing the association *p* values on the $-\log_{10}$ scale. SNPs are colored (in red) by pairwise [illegible] most strong[illegible]

For folks who want more about EOAD, this is a great summary:

EARLY-ONSET AD: Gruesome Details

The main factors influencing early-onset AD are coding mutations or copy number changes in genes that regulate Aβ production and degradation. Aβ is generated by sequential cleavage of APP by β- and γ-secretases. Overproduction of Aβ is a recognized AD risk factor observed in Down syndrome cases that possess chromosome 21 trisomy encompassing the *APP* locus (8) and *APP* duplication cases because of copy number changes (13,14). Most *APP* pathogenic mutations occur around the Aβ cleavage sites affecting APP processing by secretases, e.g., APP KM670/671NL (15) or APP E682K (16) at the β-secretase cleavage site, which increase Aβ production. Mutations in the Aβ sequence have the potential to affect its biophysical properties, such as hydrophobicity and aggregation rate, while C-terminal Aβ mutations at the γ-secretase site influence the $A\beta_{42}$-to-$A\beta_{40}$ ratio (17). Mutations in *PSEN1* and *PSEN2* that form the active core of γ-secretase complex affect endopeptidase- or carboxypeptidase-like activity, shifting production of $A\beta_{40}$ and $A\beta_{42}$ to longer and more neurotoxic species, e.g., $A\beta_{42}$ in the case of PS1 R278I (18,19) or PS1 L435F (20), which also shows a dramatic reduction in total Aβ production. Thus, the toxic dysfunction mechanism is used to describe AD-related genetic changes in γ-secretase (19). Indeed, evaluation of heterozygous null *PSEN1* mutation in

Analyses of genomic sequence can provide information to categorize functional SNPs if found in regulatory regions (Figure 1), which include any of the elements involved in transcription and translation, such as enhancers, promoters, untranslated regions, introns, and histone marks, and lead to changes in chromatin state causing changes in expression or messenger RNA splicing captured by expression, splicing, and methylation QTLs (46,47). AD-related methylation changes have been detected near known GWAS genes *ABCA7* and *BIN1* and novel genes *ANK1*, *RHBDF2*, *CD2D3*, and *RPL13* (48,49). A study of chromatin state alterations in human samples found an upregulation of immune response genes and regulatory regions that are targeted by *SPI1*, a myeloid-specific transcription factor (50). Furthermore, protein QTLs can be used to map loci that affect protein abundance, which when coupled with GWASs can reveal networks of protein–protein interactions (51). Other epigenomic datasets are being generated by consortia such as PsychENCODE (52), the National Institutes of Health ROADMAP Epigenomics Project (53), BLUEPRINT Epigenome (54), Accelerating Medicines Partnership for AD (55), and CommonMind (56), and will facilitate large-scale integrative functional genomics analyses.

gene

annotations lack context- and cell-specific functions of each gene, thus prohibiting modeling of dynamic processes, such as disease progression. Analyses of networks in samples from patients with AD versus control individuals revealed differentially regulated nodes of immune-related genes, governed by TYRO protein tyrosine kinase binding protein (TYROBP) (57), which is a DNAX-activating protein (DAP12) expressed on microglia and is required for triggering receptor expressed on myeloid cells 2 (TREM2) signaling as an adaptor protein. Whole genome sequencing (WGS) in patients with sporadic early-onset AD has identified rare coding variants in *TYROBP* that perturb expression levels of TREM2 and TYROBP in vitro (58), confirming the significance of this module in AD risk. A proteomic study of cortical tissue from AD patients reported enrichment of AD GWAS candidates in microglial protein networks, supporting a causal role for myeloid cells in AD (59).

While GWASs enable the identification of common variants, usually with small effect size, other approaches are needed to identify rare variants. The most commonly used approaches are whole exome sequencing (WES) and WGS. WGS provides the most comprehensive survey of the genome-including regulatory regions not covered by WES. Like GWASs these studies may be performed in large unrelated cohorts, isolated

Functional Genomics Section: Epigenetics

Genomes reveal ***SNPs which may be found in promoters, introns, histone*** marks. Many risk genes associated with ***methylation state*** [epigenetics] including immune transcription factors.

Epigenomic databases also noted above.

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Gene Networks and Gene Annotations

TYROBP is a binding protein target of tyrosine kinases found on *microglia* and **perturbs TREM2 signaling** in EOAD based on WGS. GWAS reveals common (low-impact) variants but WGS and WES can identify rare variants. **QQ**: what does WES miss that WGS captures? ← look left

LIPID METABOLISM

APOE is the most important genetic AD risk factor influencing prevalence and age at onset. *APOE* association was originally identified from linkage studies and explains 15% to 20% of AD heredity. Two coding SNPs define six *APOE* genotypes—ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4, listed from lowest to highest risk for AD (72,73). Apolipoprotein E (APOE) is the major apolipoprotein expressed in human brain primarily by astrocytes, is involved in cholesterol homeostasis, and has been extensively studied in AD (74). *APOE* influences Aβ plaque load in an isoform-specific manner in APP transgenic mice, with highest Aβ deposition in human knock-in *APOE4* genotype lines compared with *APOE3* and *APOE2* (75). This effect can be explained by decreased Aβ clearance and/or facilitation of Aβ fibrillogenesis that is due to isoform-dependent differences, because APOE4 shows lower binding of Aβ and is degraded more rapidly through lipoprotein receptors (74,76,77). APOE contributes to synapse pruning by astrocytes (78) and together with clusterin (*CLU*) is induced after injury in astrocytes and microglia promoting neuronal survival (74).

CLU is primarily expressed in astrocytes and is involved in lipid transport, apoptosis, and immune response. The minor allele of rs1113600, located in the intron of *CLU*, is associated with reduced AD risk (28,29); however, no eQTL was found in the locus (79). CLU can bind Aβ and influence fibril formation in vitro.

ApoE originally i.d. from Linkage Studies

Two coding SNPS identify six ApoE genotypes! ApoE regulates cholesterol [Ferris Mice: McDonald's is VERY BAD]. **CLU** and ApoE induced by injury in glia. **Clusterin** has immune, apop., lipid transport roles; is assoc. with decr. risk. Can bind A-beta, but not eQTL found at locus.

receptor L (*SORL1*) with AD in case–control studies (92). LOAD GWASs identified rs11218343, a common variant in *SORL1* in European (32) and Asian (35) populations. Rare variants in *SORL1* were also found in several families with autosomal dominant early-onset AD (93). Overexpression of SORL1 in cell lines reduces Aβ production through increased retention of APP in the Golgi (94), while overexpression of the AD associated SORL1-G511R variant results in decreased binding and turnover of Aβ (95). Ablation of *Sorl1* in APP/PS1 mice leads to increased plaque deposition, similar to the effect of *Sorl1* knockout on endogenous murine Aβ production (96).

Bridging integrator 1 (*BIN1*) participates in the endocytic trafficking of synaptic vesicles through membrane remodeling in neurons (97). The index SNP rs6733839 in the *BIN1* locus has been associated with AD risk in different populations (32,98,99). Fine mapping of the *BIN1* locus identified rs59335482, a three-base-pair insertion ~28 kb upstream of *BIN1*, that is associated with higher AD risk, increased transcriptional activity in vitro using a luciferase assay, and higher *BIN1* levels (97). However, contrary evidence demonstrated that knockdown of BIN1 increases tau aggregation in neurons through an enlargement of Ras-related protein Rab-5A–positive vesicles (100), and reduces lysosomal degradation of BACE1, thereby increasing Aβ production (101). Because *BIN1* is largely expressed in mature oligodendrocytes and white matter (102), it is unclear how it could affect AD pathology in neurons.

Sortilin, Bridging Integrator and Endocytosis

SORL1 , protective neuronal vacuole receptor, defects assoc w/ AlzD, plaques in case ctrl/ablation studies.

BiN1-bridging integrator vesicle-remodeler assoc. w/ AlzD risk (fine mapping: i.d. 3 bp insertion 28 kB upstream), incr. Bin1 via luciferase assay. but contrary evidence; Bin1 found in oliogodendrocytes, white matter.

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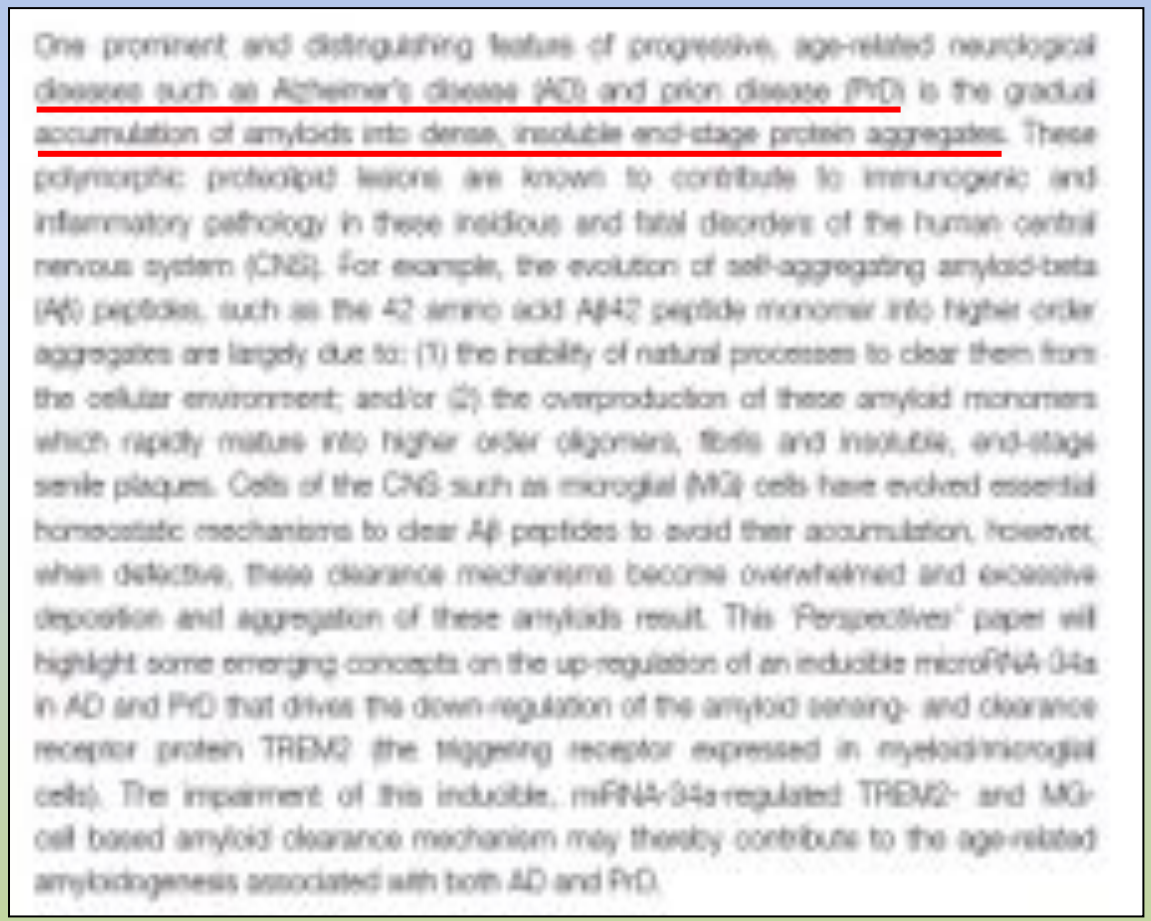
frontiers in Aging Neuroscience

0 mentions of tau in this article

Over-Expressed Pathogenic miRNAs in Alzheimer's Disease (AD) and Prion Disease (PrD) Drive Deficits in TREM2-Mediated Aβ42 Peptide Clearance

prion = proteinaceous infectious agent ala Mad Cow Disease
toxic proteins catalyze native proteins => toxic conformation
can lead to "spread" of infection along nerve fibers/tracts

amyloid issues: (i) poor clearance and (ii) overproduction
➔ insoluble aggregates: immunogenic & inflammatory



One prominent and distinguishing feature of progressive, age-related neurological diseases such as Alzheimer's disease (AD) and prion disease (PrD) is the gradual accumulation of amyloids into dense, insoluble end-stage protein aggregates. These polymorphic proteolipid lesions are known to contribute to immunogenic and inflammatory pathology in these insidious and fatal disorders of the human central nervous system (CNS). For example, the evolution of self-aggregating amyloid-beta (Aβ) peptides, such as the 42 amino acid Aβ42 peptide monomer into higher order aggregates are largely due to: (1) the inability of natural processes to clear them from the cellular environment; and/or (2) the overproduction of these amyloid monomers which rapidly mature into higher order oligomers, fibrils and insoluble, end-stage senile plaques. Cells of the CNS such as microglial (MG) cells have evolved essential homeostatic mechanisms to clear Aβ peptides to avoid their accumulation, however, when defective, these clearance mechanisms become overwhelmed and excessive deposition and aggregation of these amyloids result. This 'Perspectives' paper will highlight some emerging concepts on the up-regulation of an inducible microRNA-34a in AD and PrD that drives the down-regulation of the amyloid sensing- and clearance receptor protein TREM2 (the triggering receptor expressed in myeloid/microglial cells). The impairment of this inducible, miRNA-34a-regulated TREM2- and MG-cell based amyloid clearance mechanism may thereby contribute to the age-related amyloidogenesis associated with both AD and PrD.

*note: 3'-UTR of TREM2 binds to miRNA-34a

failure to clear AB42 leads to:
oligomers, fibrils, senile plaques
via self-aggregation mechanism
microglia normally clean up ECS

TREM2 = triggering receptor
expressed in microglia protein
= amyloid sensing & clearance ptn

↑ miRNA34 ➔ ↓ TREM2* ➔ plaques
[microRNA = noncoding RNA]

WHAT causes ↑ miRNA34? *not stated.*
But, upregulation of inducible, pro-inflammatory miRNAs associated w/ AlzD, PrD, scrapie and AMD-retina.

Depending upon orientation, location, miRNAs might be coordinately regulated w/ surrounding genes. Some balance btw clearance & inflammation is needed.

Alzheimer's & The Immune System

AB plaques and tangles stimulate chronic inflammatory reaction to clear debris

- Inflammation is mediated by pro-inflammatory cytokines and creates a chronic and self sustaining inflammatory interaction between microglia and astrocytes
- Inflammatory mediators may enhance APP production and amyloidogenic processing of APP
- Might also inhibit the formation of soluble APP which can have a neuroprotective effect

Microglia

- Represent first line of defense against brain tissue injury
- Amyloid peptides and APP are potent glial activators
- Chronic activation of glia leads to death of adjacent neurons
  - Releases highly toxic products

Astrocytes

- Important for AB clearance and degradation
  - Form a protective barrier between AB plaques and neurons
- Over express b-secretase in chronic stress conditions

Complement System

- Complex and tightly regulated attack system
- Interact with cell surface receptors to promote local inflammatory response
- Activation causes inflammation and cell damage but is essential for eliminating cell debris and aggregates → large number of research suggesting its activation in AD brain by AB peptides and is therefore present at very early stages
  - Research also suggests the system has a neuroprotective role in inflammation
  - Studies demonstrate inhibition of complement system increases AB plaque formation

Chemokines

- regulators of microglial migration and recruitment of astrocytes
- several chemokines and chemokine receptors have been found to be upregulated in AD brain
  - recruit microglia and astrocytes to AB deposits

Cytokines**

- regulation of t-cell differentiation to helper t cells and regulator t cells
  - Regulatory cells → interferons (IFNs) and tumor necrosis factors (TNFs)
- changes in levels of cytokines in AD brain, blood and CSF
  - INFs, TNFs and other cytokines increased in AD
- interaction between cytokines and AB plaques create vicious circle
  - AB plaques stimulate secretion of certain cytokines (IL-1), cytokines in turn stimulate secretion of other proteins found in plaques
    - IL-1 increases toxicity of AB plaques
  - synergistic effects → interferons synergize with AB to cause release of TNF and reactive nitrogen species toxic to neurons
- a balance between the effects of pro inflammatory and anti inflammatory cytokines is thought to determine the outcome of the disease and some studies have suggested that susceptibility to the disease is genetically determined by the balance or expression of these cytokines

Cytokines also implicated in conversion of TBI cases to PTSD cases, iaw Capstone Speaker Maria.

Results

- dentate gyrus of hippocampus exhibited four fold increase in total plaque volume
- Plaque size also increased
- AB load is not result of increased APP expression or AB production
  - Likely mediated via altered AB clearance
- Disrupted cross talk between adaptive and innate immunity
  - Altered microglial transcripts between immune intact and immune deficient mice
- Loss of B, T and NK cells subtly modulate phenotype of microglia within the brain
  - increased proinflammatory cytokines may play a role in microglial function alteration
  - Decrease in phagocytic efficiency