MAYO CLINIC

@DrNErtekinTaner

Alzheimer's Disease and Related Disorders (ADRD): Towards Precision Medicine Therapies and Biomarkers

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Precision Medicine in Neuroscience: Tools, Translation, and Implementation: A Workshop

NATIONAL ACADEMIES Sciences Engineering Medicine

March 5th, 2026

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NATIONAL INSTITUTE ON AGING
National Institutes of Health

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

alzheimer's association

BrightFocus™ Foundation
Cure in Mind. Cure in Sight.

curePSP
Foundation for PSP | CBD and Related Brain Diseases
because hope matters

Florida HEALTH

CENTER FOR INDIVIDUALIZED MEDICINE

AMP-AD

CLEAR-AD
Centrally-linked Longitudinal pEripheral biomARkers of AD in multi-ethnic populations

M²OVE-AD
Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease

Alzheimer's Disease

Epidemiology

Most common cause of dementia

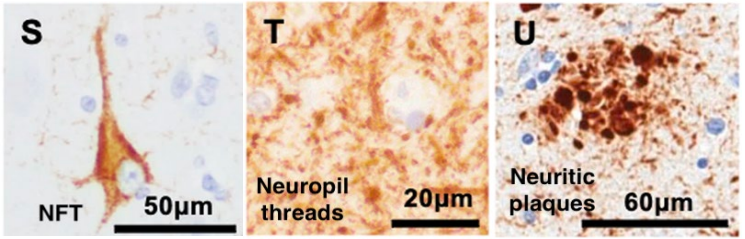
- Estimate of 6.7 million Americans aged ≥ 65 with AD in 2023.
- >40 million with AD globally.

Impact

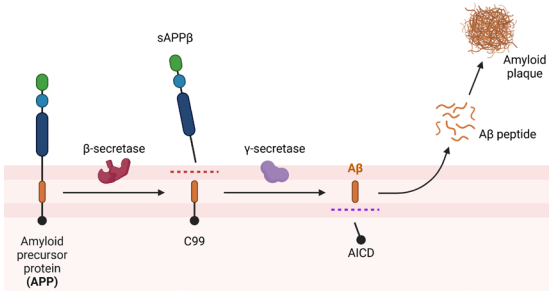
No disease-modifying therapy (DMT)-until recently

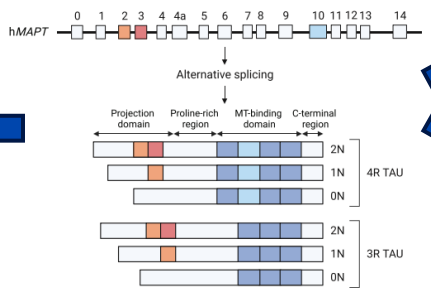
- By 2060 Americans living with AD are projected to increase to 13.8 million.
- Deaths from AD increased by 145%, in 2000-2019.

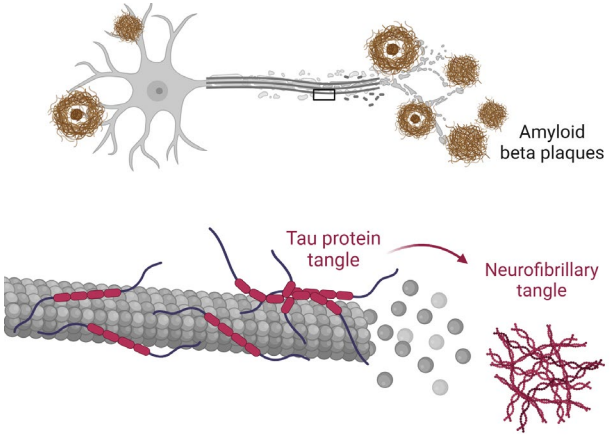
Amyloid and Tau Neuropathology in AD



Chung et al., *Mol Neurodegeneration*, 2021



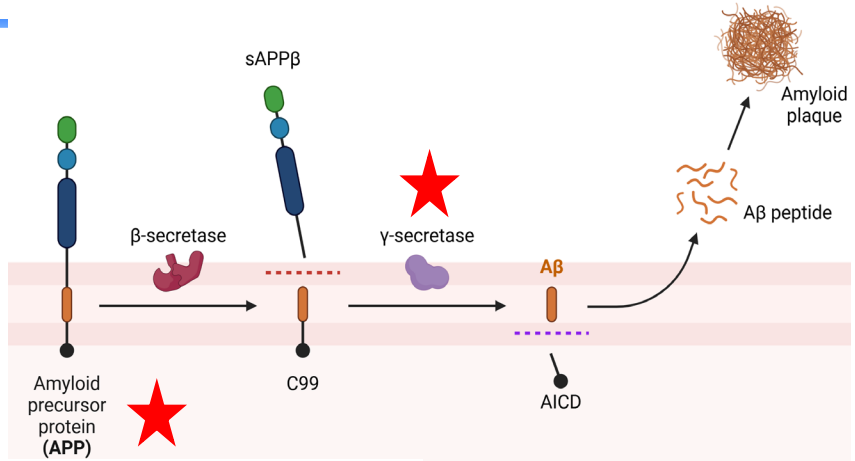




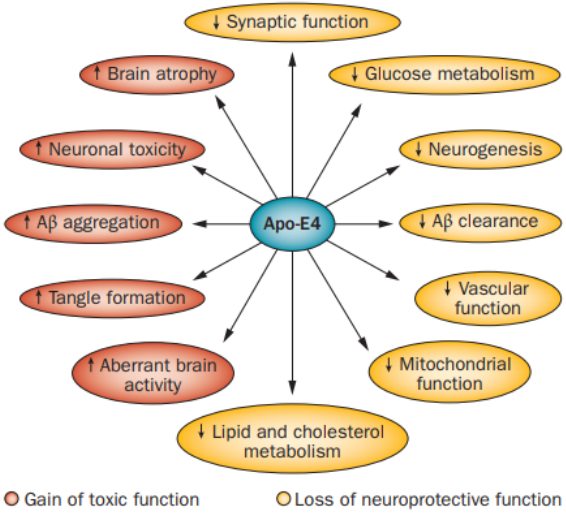
1. *2023 Alzheimer's disease facts and figures.* Alzheimers Dement, 2023. **19**(4): p. 1598-1695
2. Sachdev, P. S. et al. *Nature Reviews Neurology*, 2023, *10*(11), 634-642.

AD – Genetics (1980s – 2009):

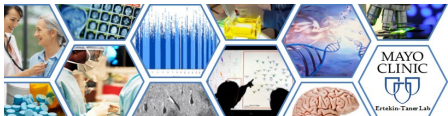
- **Early-onset familial AD mutations in *APP, PSEN1/2*:**
  - Constitute <1% of all AD
  - Fully penetrant
  - Influence amyloid production/processing



- **Apolipoprotein E ε4 genotype:**
  - Increase risk for AD, dose- and ancestry-dependent
  - Constitute about 20% population risk
  - Influences multiple processes



1. Ertekin-Taner N., *Neurol Clin*, 2007
2. Ertekin-Taner N., *Alz Res & Ther*, 2010
3. Ertekin-Taner N., *Mol Neurodeg*, 2011
4. Liu et al., *Nat Rev Neurol*, 2013
5. Iş Ö, *Glia*, 2025



Clinical Impact of AD Genetics: 1980s-2009

Plasma Aβ levels are influenced by genes.

Linkage of Plasma Aβ42 to a Quantitative Locus on Chromosome 10 in Late-Onset Alzheimer's Disease Pedigrees

Nilufer Ertekin-Taner,[1] Neill Graff-Radford,[1] Linda H. Younkin,[1] Christopher Eckman,[1] Matthew Baker,[1] Jennifer Adamson,[1] James Ronald,[1] John Blangero,[2] Michael Hutton,[1]* Steven G. Younkin[1]

SCIENCE VOL 290 22 DECEMBER 2000

Changes in plasma Aβ levels can be detected in LOAD family members

Ertekin-Taner, et al. *Neurology*® 2008;70:596-606

Plasma amyloid β protein is elevated in late-onset Alzheimer disease families

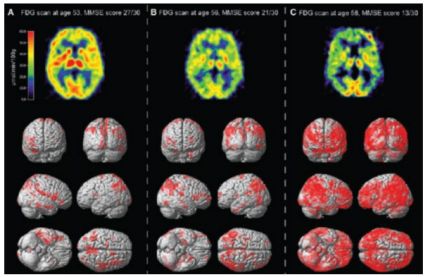
Changes in plasma Aß levels can predict AD progression

Association of Low Plasma Aβ42/Aβ40 Ratios With Increased Imminent Risk for Mild Cognitive Impairment and Alzheimer Disease

Neill R. Graff-Radford, MBBCh, FRCP; Julia E. Crook, PhD; John Lucas, PhD; Bradley F. Boeve, MD; David S. Knopman, MD; Robert J. Ivnik, PhD; Glenn E. Smith, PhD; Linda H. Younkin, PhD; Ronald C. Petersen, MD, PhD; Steven G. Younkin, MD, PhD

ARCH NEUROL/VOL 64, MAR 2007 WWW.ARCHNEUROL.COM

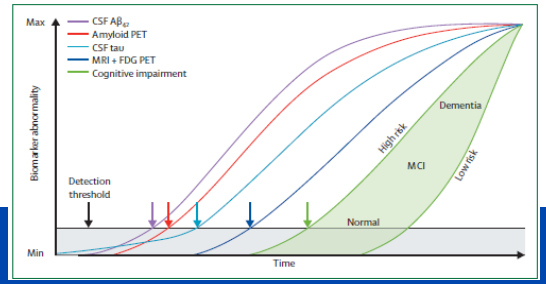
Brain Aß imaging correlates with functiona decline in AD.



(Klunk et al., 2004, Kadir et al., 2011)

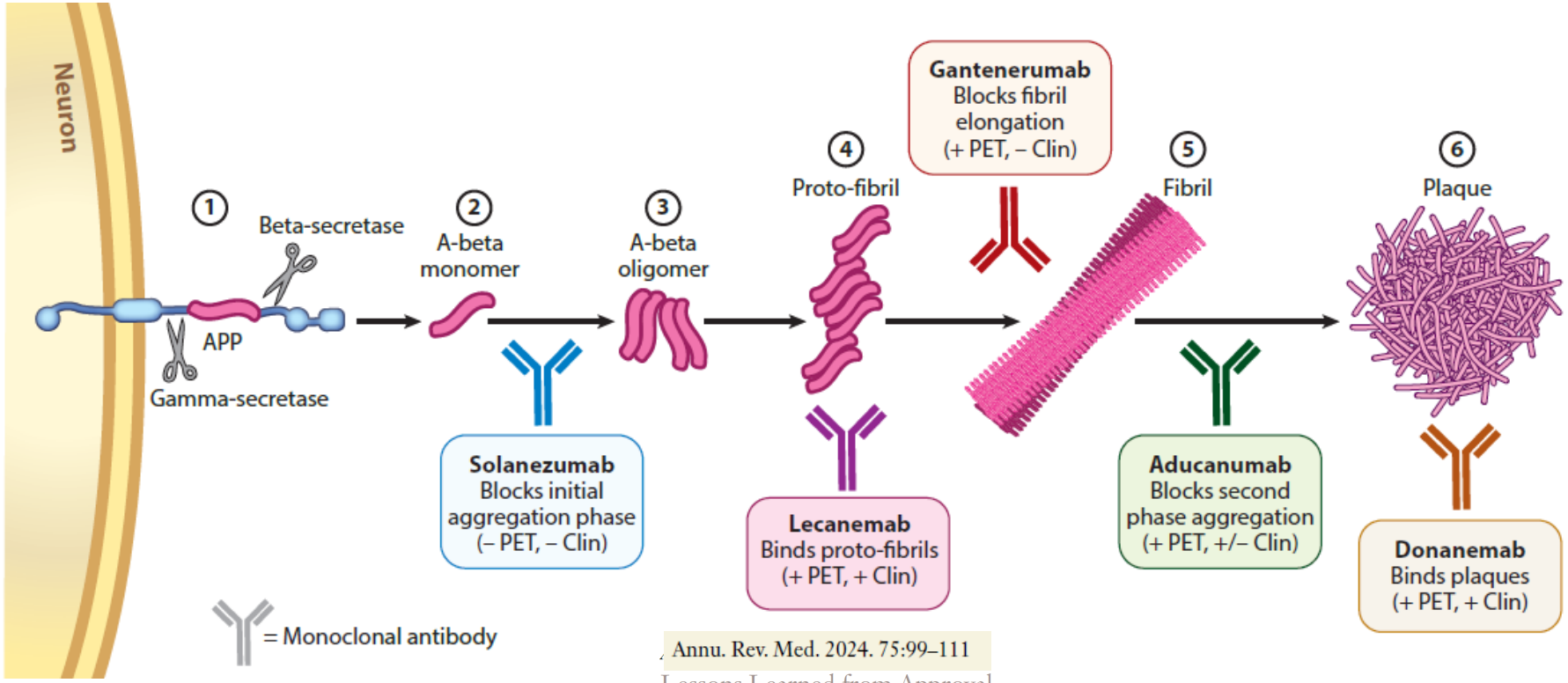
Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski



- **Pathophysiology:**
  - Amyloid cascade hypothesis.
  - Model systems of EOFAD mutations/*APOE*.
- **Prediction:**
  - EOFAD mutation testing
  - Aβ as a biomarker (CSF, plasma, imaging)
  - *APOE* ε4 carriers
- **Prevention/Cure:**
  - Amyloid pathway as a drug target
  - Therapeutic trials in EOFAD mutation and *APOE* ε4 carriers (API, DIAN, A4)

Alzheimer's disease – Monoclonal Anti-Amyloid Antibody Therapies



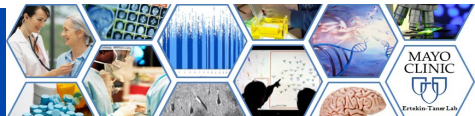
Annu. Rev. Med. 2024. 75:99–111

Lessons Learned from Approval of Aducanumab for Alzheimer's Disease

Judith L. Heidebrink[1,2] and Henry L. Paulson[1,2,3]

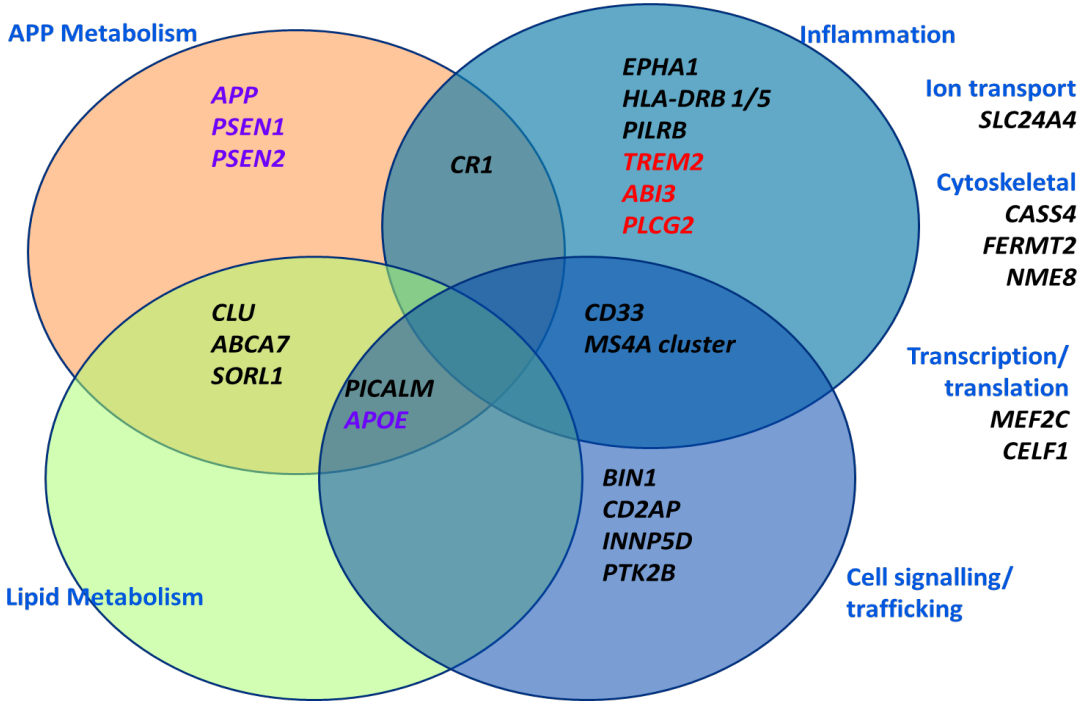
AD Genetic Studies (1980s-2009): Lessons Learned

- Pathology and biochemistry studies in relevant tissue (brain) can pinpoint disease molecules (Aß, tau, APOE).
- Studying rare forms of disease (Down's syndrome, EOFAD) can uncover pathologic proteins and deterministic genetic risk factors.
- Rare genetic forms of disease can yield useful model systems.
- Pathologic proteins can be measured in blood and CSF and can serve as disease biomarkers (CSF and plasma Aß and tau) and endophenotypes in genomic studies.
- Pathologic proteins can become therapeutic targets (anti-amyloid therapies).



Alzheimer's Disease GWAS era: 2009-

- Discovered >80 AD risk loci.
- Candidate genes near GWAS loci are enriched in certain pathways: APP, Tau, Inflammation etc.
- Actual genes/variants/disease mechanisms are not revealed by disease GWAS.
- Most genetic variants are in non-protein coding but transcriptionally active (open chromatin) regions.



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3. Ertekin-Taner N., *Mol Neurodeg*, 2011
4. Liu et al., *Nat Rev Neurol*, 2013
5. İş Ö, *Glia*, 2025

Despite discoveries of genetic loci or risk variants, curative therapies for neurodegenerative diseases are elusive

Mean cost of developing a new FDA-approved drug: $1.3 billion.

JAMA | Original Investigation

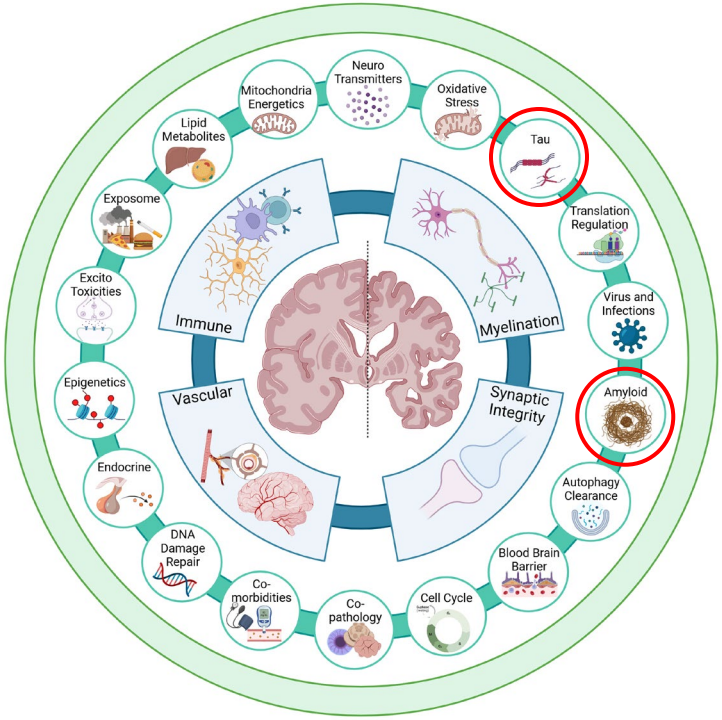
Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018

Olivier J. Wouters, PhD; Martin McKee, MD, DSc; Jeroen Luyten, PhD

Table 4. Mean And Median Expected Research and Development Expenditure on New Therapeutic Agents Approved by the US Food and Drug Administration (2009-2018) by Therapeutic Area

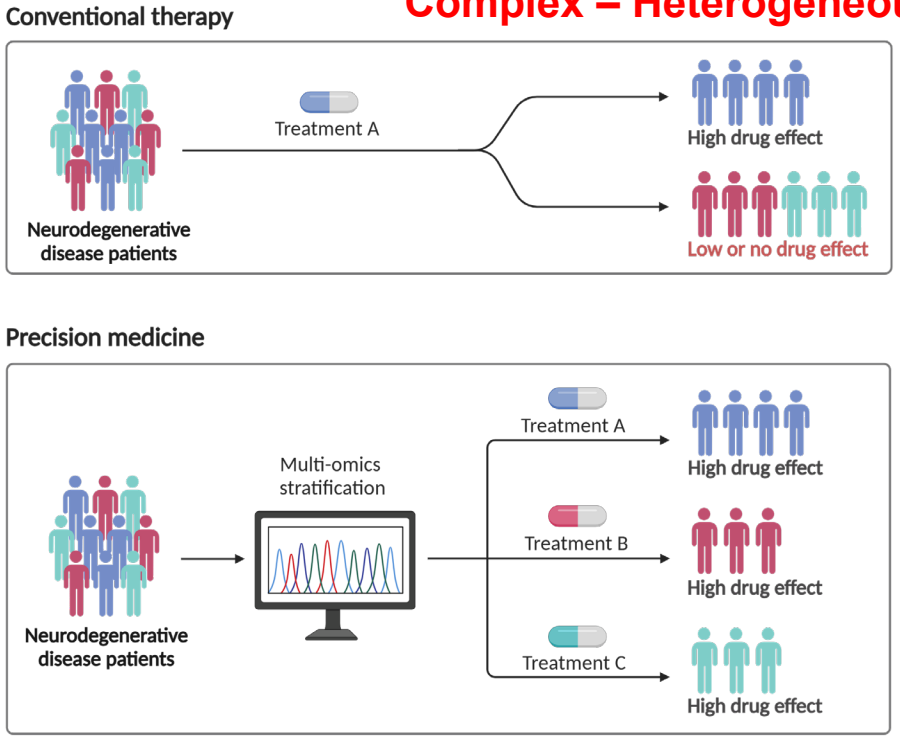
Therapeutic Area[a]	Sample Size	Expenditure in US$, Millions (95% CI)[b]	
		Median	Mean
Antineoplastic and immunomodulating agents	20	2771.6 (2051.8-5366.2)	4461.2 (3114.0-6001.3)
Alimentary tract and metabolism	15	1217.6 (613.9-1792.4)	1430.3 (920.8-2078.7)
Nervous system	8	765.9 (323.0-1473.5)	1076.9 (508.7-1847.1)
Antiinfectives for systemic use	5	1259.9 (265.9-2128.3)	1297.2 (672.5-1858.5)
Dermatologicals	4	747.4	1998.3
Cardiovascular system	3	339.4	1152.4
Musculoskeletal system	3	1052.6	937.3
Blood and blood-forming organs	2	793.0	793.0
Sensory organs	2	1302.8	1302.8
Other[c]	1	1121.0	1121.0

Biological Complexity of ND



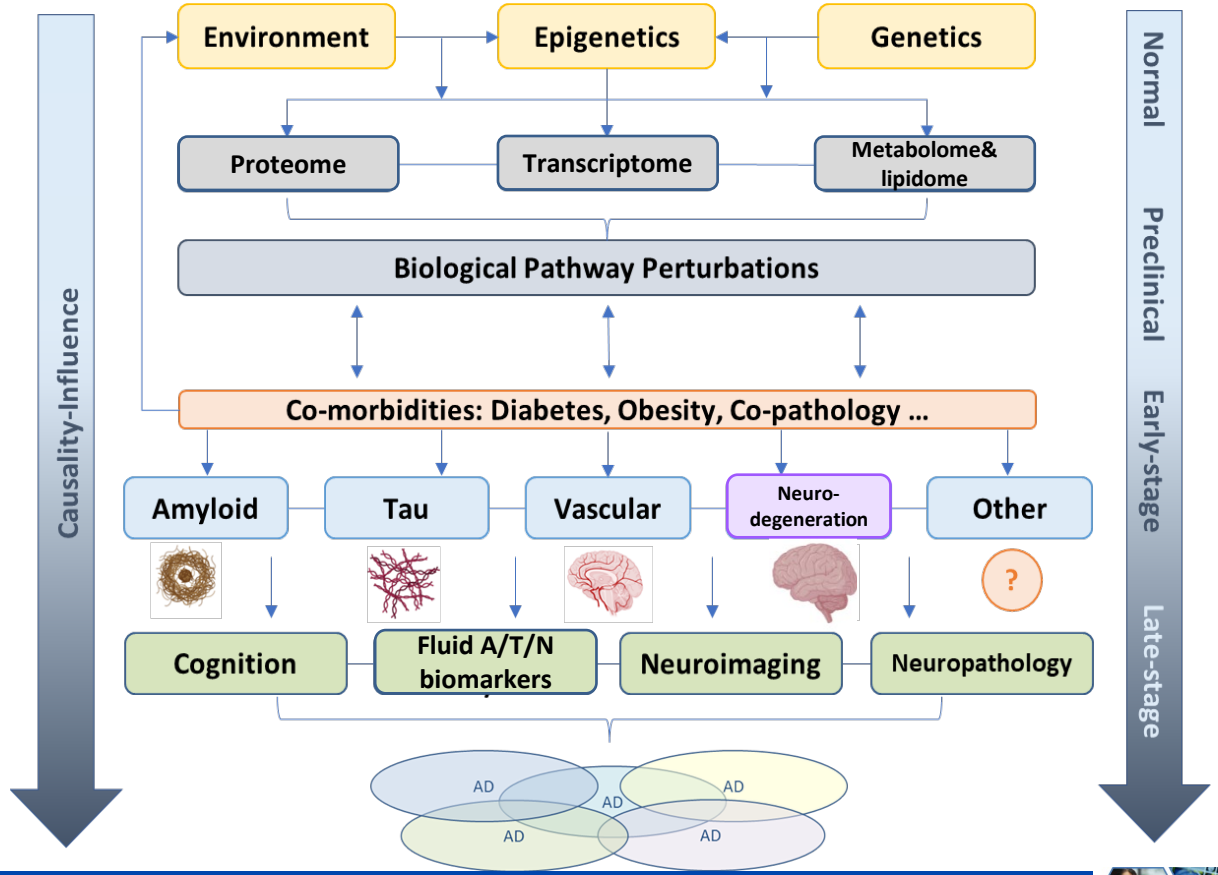
Why do we need precision medicine approaches for neurodegenerative diseases (ND)?

Complex – Heterogeneous - Long prodrome



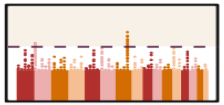
We need to diagnose and treat the right patient, with the right therapy at the right time.

A framework for precision medicine in ND:



Big omics data guide the journey to precision medicine

Genome

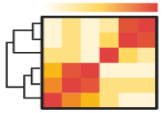


- DNA variation
- Genotyping array, whole exome, whole genome sequencing.
- GWAS

Epigenome

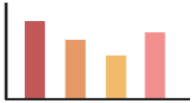
- Modifications to DNA, histones or chromatin.
- Results in gene expression changes

Transcriptome



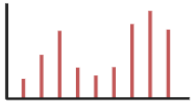
- Gene expression levels.
- Expression array, RNA sequencing.
- eQTL, expression regulation, DEG

Proteome



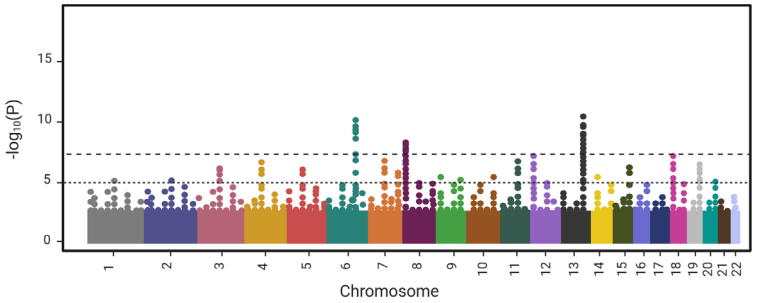
- Protein levels.
- Mass spectrometry.
- pQTL, protein regulation, DEP

Metabolome

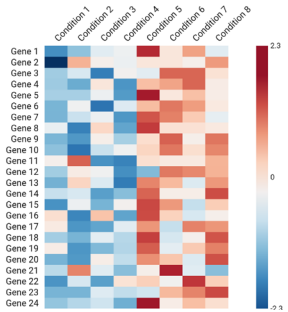


- Metabolite lipidome levels.
- Differential levels.
- QTL analysis.

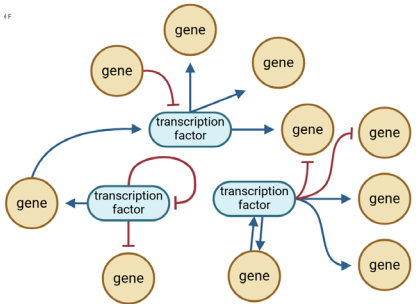
Genotype + Phenotype (disease risk, endophenotypes, expression etc.) -> Loci/Candidate gene

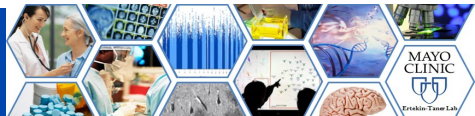


Compare groups for differential expression (DEGs, DEPs etc.)



Network analysis for groups of molecules, pathways, cell types



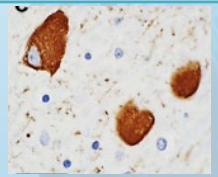


Data

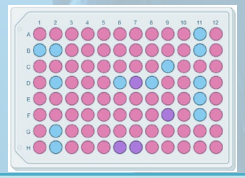
Generation, Curation, Analysis

Clinical:

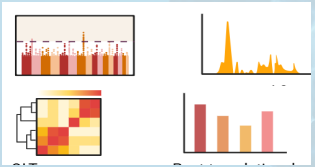
Neuropath:



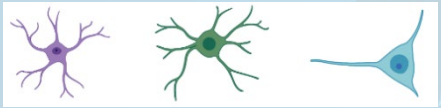
Biochemical:



Molecular:



Cellular:



Knowledge

Data Integration, Harmonization, Sharing

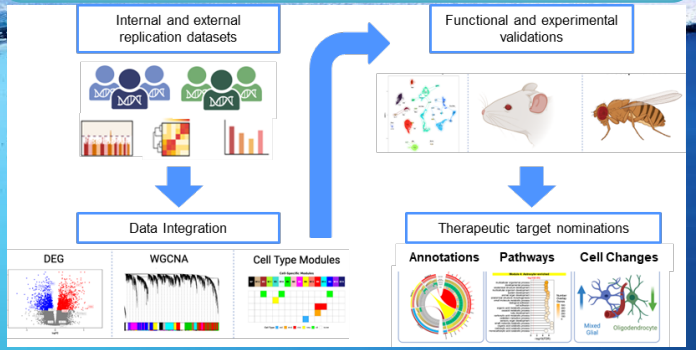
1. Widespread molecular perturbations

2. Disease genes and variants

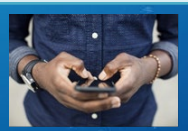
3. Cell-specific molecular disease pathways

Cures and Diagnostics

Therapeutic Target and Biomarker Prioritization

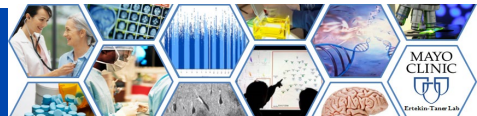


Towards Precision Therapies and Biomarkers

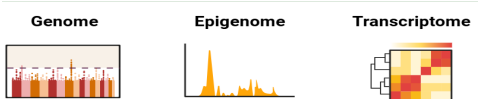


ADRD Precision Medicine Studies (2010s-ongoing): Lessons Learned

1. Neurodegenerative diseases are characterized by widespread multi–omics molecular perturbations in the brain.
2. Integrative –omics can uncover novel disease genes, functional variants and their therapeutic (vs. detrimental) direction of effect.
3. Brain and peripheral multi-omics perturbations in neurodegenerative diseases pinpoint cell-specific dysfunction that strongly correlate with disease risk and endophenotypes.
4. Integrative multi-omics and deep phenotyping in neurodegenerative diseases identify novel molecular targets and pathways that lay the groundwork for precision medicine in these common, complex disorders.



1. ADRD have widespread brain molecular perturbations:



Brain tau neuropathology and biochemical levels associate with gene expression and methylation perturbations in oligodendrocyte/myelin genes.

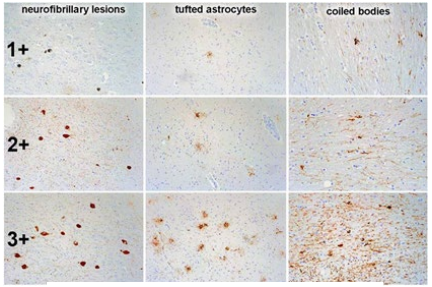
Acta Neuropathol (2016) 132:197–211
DOI 10.1007/s00401-016-1576-7

ORIGINAL PAPER

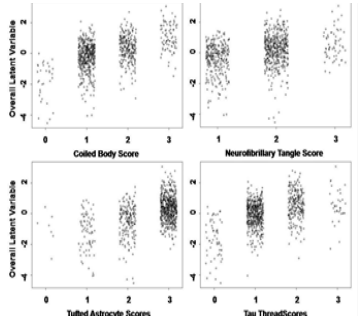
Gene expression, methylation and neuropathology correlations at progressive supranuclear palsy risk loci

Mariet Allen[1] · Jeremy D. Burgess[1] · Travis Ballard[1] · Daniel Serie[2] · Xue Wang[2] · Curtis S. Younkin[1] · Zhifu Sun[3] · Naomi Kouri[1] · Saurabh Baheti[3] · Chen Wang[3] · Minerva M. Carrasquillo[1] · Thuy Nguyen[1] · Sarah Lincoln[1] · Kimberly Malphrus[1] · Melissa Murray[1] · Todd E. Golde[4] · Nathan D. Price[5] · Steven G. Younkin[1] · Gerard D. Schellenberg[6] · Yan Asmann[2] · Tamas Ordog[7] · Julia Crook[2] · Dennis Dickson[1] · Nilüfer Ertekin-Taner[1,8]

Semi-quantitative PSP neuropathology



Quantitative PSP neuropathology



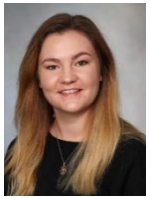
From Dennis Dickson

nature communications

Article

https://doi.org/10.1038/s41467-026-68864-9

Integrative epigenomic landscape of Alzheimer's Disease brains reveals oligodendrocyte molecular perturbations associated with tau



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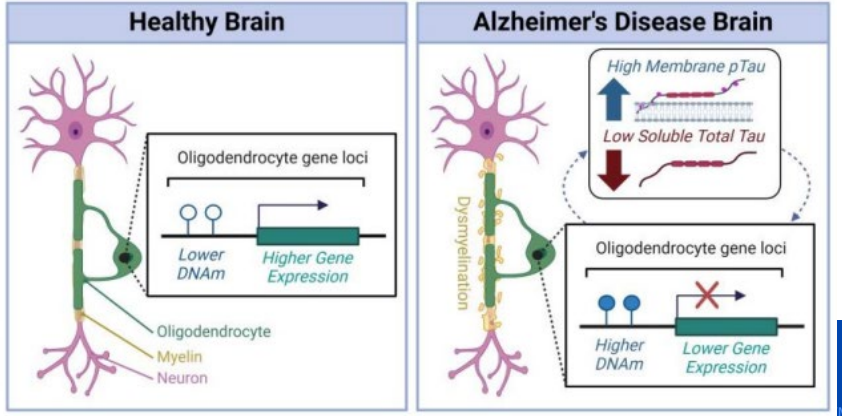
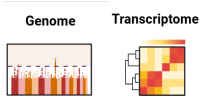
Stephanie R. Oatman[1], Joseph S. Reddy[2], Amin Atashgaran[1], Xue Wang[2], Yuhao Min[1], Zachary Quicksall[2], Floor Vanelderen[1], Minerva M. Carrasquillo[1], Chia-Chen Liu[1], Yu Yamazaki[1], Thuy T. Nguyen[1], Michael Heckman[2], Na Zhao[1], Michael DeTure[1], Melissa E. Murray[1], Guojun Bu[1], Takahisa Kanekiyo[1], Dennis W. Dickson[1], Mariet Allen[1], Nilüfer Ertekin-Taner[1,3]



2. Integrative omics uncover genes-variants-pathways in ADRD:



PLoS Genet. 2012;8(6):e1002707. doi: 10.1371/journal.pgen.1002707. Epub 2012 Jun 7.

Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants.

Zou F[1], Chai HS, Younkin CS, Allen M, Crook J, Pankratz VS, Carrasquillo MM, Rowley CN, Nair AA, Middha S, Maharjan S, Nguyen T, Ma L, Malphrus KG, Palusak R, Lincoln S, Bisceglio G, Georgescu C, Kouri N, Kolbert CP, Jen J, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD; Alzheimer's Disease Genetics Consortium, Petersen RC, Graff-Radford NR, Dickson DW, Younkin SG, Ertekin-Taner N.

Neurology. 2012 Jul 17;79(3):221-8. doi: 10.1212/WNL.0b013e3182605801. Epub 2012 Jun 20.

Novel late-onset Alzheimer disease loci variants associate with brain gene expression.

Allen M[1], Zou F, Chai HS, Younkin CS, Crook J, Pankratz VS, Carrasquillo MM, Rowley CN, Nair AA, Middha S, Maharjan S, Nguyen T, Ma L, Malphrus KG, Palusak R, Lincoln S, Bisceglio G, Georgescu C, Schultz D, Rakhshan F, Kolbert CP, Jen J, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD, Petersen RC, Graff-Radford NR, Dickson DW, Younkin SG, Ertekin-Taner N; Alzheimer's Disease Genetics Consortium (ADGC), Apostolova LG, Arnold

Alzheimers Res Ther. 2014 Jul 1;6(4):39. doi: 10.1186/alzrt268. eCollection 2014.

Association of MAPT haplotypes with Alzheimer's disease risk and MAPT brain gene expression levels.

Allen M[1], Kachadoorian M[1], Quicksall Z[1], Zou F[1], Chai HS[2], Younkin C[1], Crook JE[3], Pankratz VS[2], Carrasquillo MM[1], Krishnan S[1], Nguyen T[1], Ma L[1], Malphrus K[1], Lincoln S[1], Bisceglio G[1], Kolbert CP[4], Jen J[4], Mukherjee S[5], Kauwe JK[6], Crane PK[5], Haines JL[7], Mayeux R[8], Pericak-Vance MA[9], Farrer LA[10], Schellenberg GD[11], Parisi JE[12], Petersen RC[13], Graff-Radford NR[14], Dickson DW[1], Younkin SG[1], Ertekin-Taner N[15].

Neurol Genet. 2015 Jul 23;1(2):e15. doi: 10.1212/NXG.0000000000000012. eCollection 2015 Aug.

Late-onset Alzheimer disease risk variants mark brain regulatory loci.

Allen M[1], Kachadoorian M[1], Carrasquillo MM[1], Karhade A[1], Manly L[1], Burgess JD[1], Wang C[1], Serie D[1], Wang X[1], Siuda J[1], Zou F[1], Chai HS[1], Younkin C[1], Crook J[1], Medway C[1], Nguyen T[1], Ma L[1], Malphrus K[1], Lincoln S[1], Petersen RC[1], Graff-Radford NR[1], Asmann YW[1], Dickson DW[1], Younkin SG[1], Ertekin-Taner N[1].

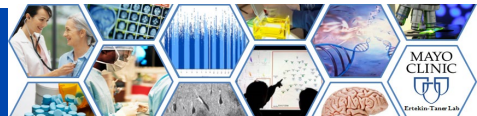
Neurol Genet. 2017 Jan 5;3(1):e126. doi: 10.1212/NXG.0000000000000126. eCollection 2017 Feb.

***ABCA7* loss-of-function variants, expression, and neurologic disease risk.**

Allen M[1], Lincoln SJ[1], Corda M[1], Watzlawik JO[1], Carrasquillo MM[1], Reddy JS[1], Burgess JD[1], Nguyen T[1], Malphrus K[1], Petersen RC[1], Graff-Radford NR[1], Dickson DW[1], Ertekin-Taner N[1].

Combined use of brain gene expression levels and disease risk can:

- Identify actual disease gene at the GWAS loci.
- Discover additional risk candidate genes/variants.
- Nominate gene expression regulation as a disease mechanism.
- Uncover therapeutic vs. detrimental direction of effect.



3. ADRD have brain cell-type specific molecular perturbations that reveal potential disease pathways:

Transcriptome

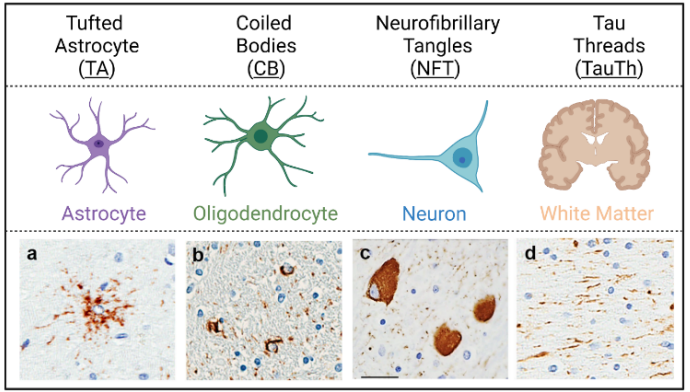
Acta Neuropathologica (2018) 136:709–727
https://doi.org/10.1007/s00401-018-1900-5

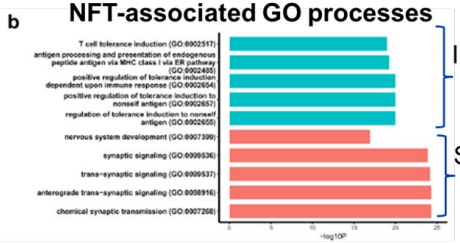
ORIGINAL PAPER

Divergent brain gene expression patterns associate with distinct cell-specific tau neuropathology traits in progressive supranuclear palsy

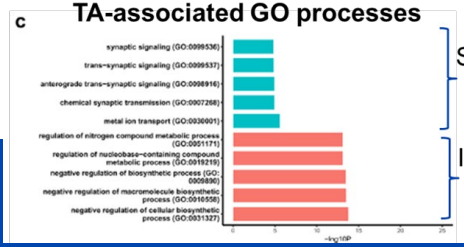
Mariet Allen[1] · Xue Wang[2] · Daniel J. Serie[2] · Samantha L. Strickland[1] · Jeremy D. Burgess[1] · Shunsuke Koga[1] · Curtis S. Younkin[3] · Thuy T. Nguyen[1] · Kimberly G. Malphrus[1] · Sarah J. Lincoln[1] · Melissa Alamprese[4] · Kuixi Zhu[5] · Rui Chang[5,6] · Minerva M. Carrasquillo[1] · Naomi Kouri[1] · Melissa E. Murray[1] · Joseph S. Reddy[2] · Cory Funk[7] · Nathan D. Price[7] · Todd E. Golde[8] · Steven G. Younkin[1] · Yan W. Asmann[2] · Julia E. Crook[2] · Dennis W. Dickson[1] · Nilüfer Ertekin-Taner[1,9]

Cell-Type-Specific Tau Neuropathology in PSP



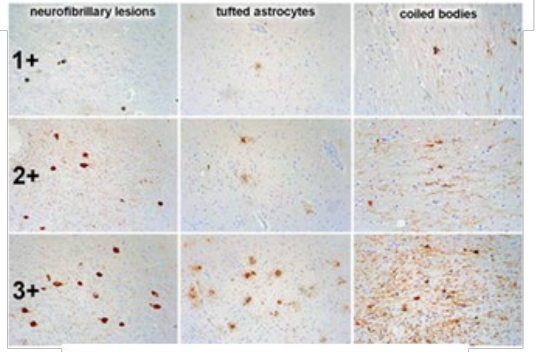


Synaptic genes/networks: Positive correlations with neuronal tau (negative or none with astrocytic).



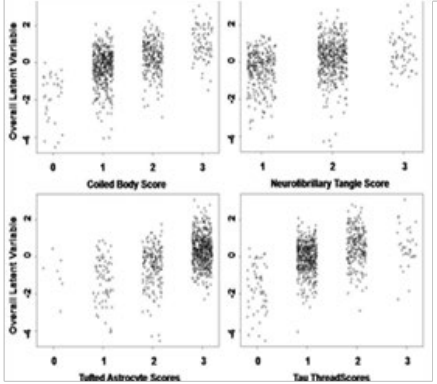
Immune genes/networks: Positive correlations with astrocytic tau pathology (negative or none with neuronal).

Semi-quantitative PSP neuropathology



From Dennis Dickson

Quantitative PSP neuropathology



4. Towards precision medicine therapies in ADRD:

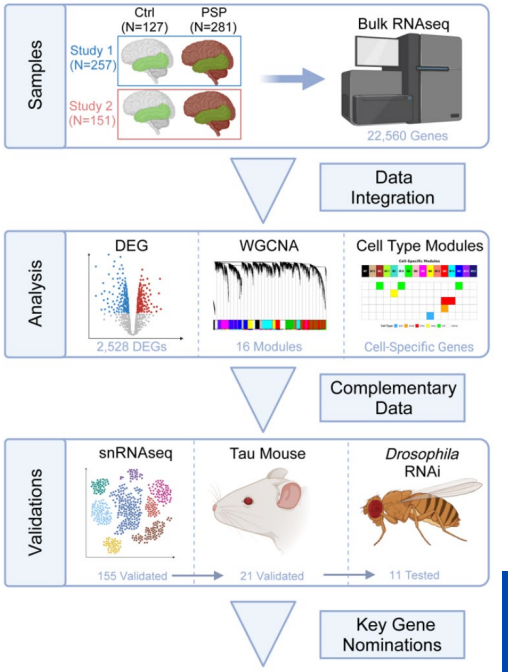
nature communications

Article

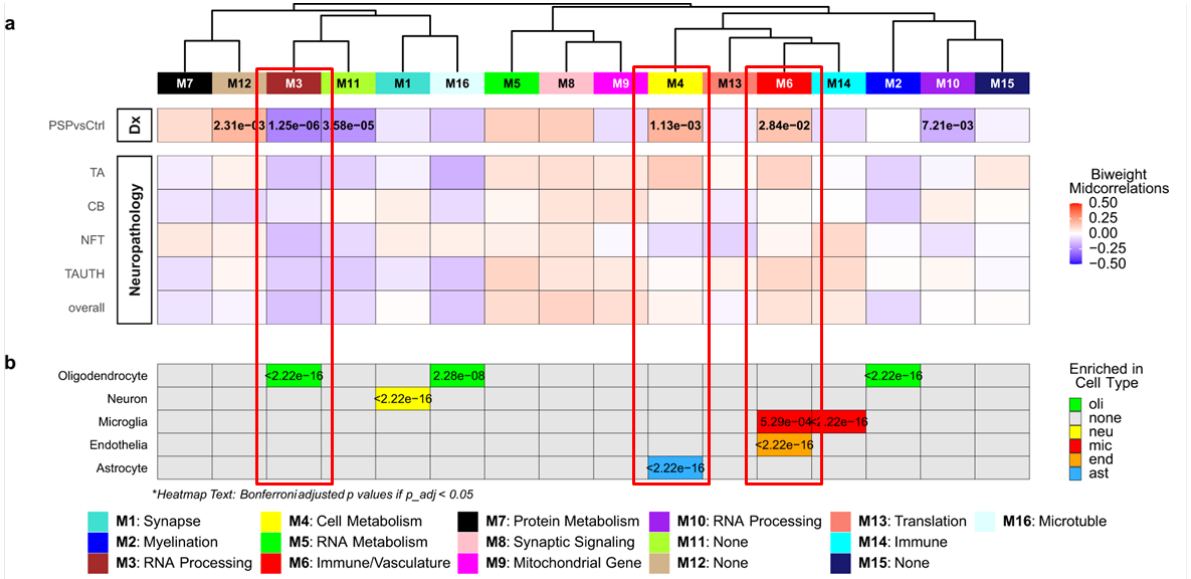
https://doi.org/10.1038/s41467-023-42626-3

Cross species systems biology discovers glial *DDR2, STOM,* and *KANK2* as therapeutic targets in progressive supranuclear palsy

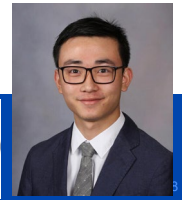
Yuhao Min [1 2 3], Xue Wang [4], Özkan İş [1], Tulsi A Patel [1], Junli Gao [1], Joseph S Reddy [4], Zachary S Quicksall [4], Thuy Nguyen [1], Shu Lin [1], Frederick Q Tutor-New [1], Jessica L Chalk [1], Adriana O Mitchell [1], Julia E Crook [2], Peter T Nelson [5 6], Linda J Van Eldik [5 7], Todd E Golde [8], Minerva M Carrasquillo [1], Dennis W Dickson [1], Ke Zhang [1], Mariet Allen [1], Nilüfer Ertekin-Taner [9 10]



- There are robust glial gene expression perturbations in PSP brains.
- We built an interactive data sharing platform.

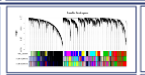
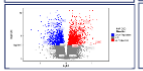
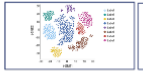


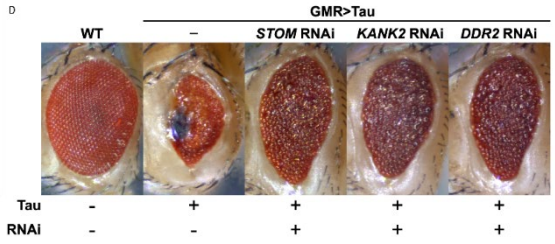
PSP RNAseq Atlas (https://rtools.mayo.edu/PSP_RNAseq_Atlas/)

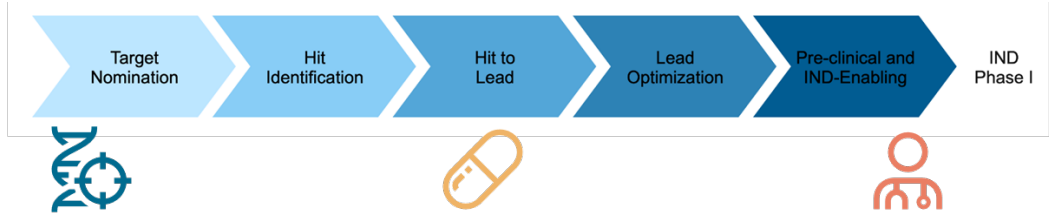


4. Towards precision medicine therapies in ADRD:

- We established a cross-species platform and prioritized *DDR2*, *STOM*, and *KANK2* as candidate therapeutic targets for PSP.

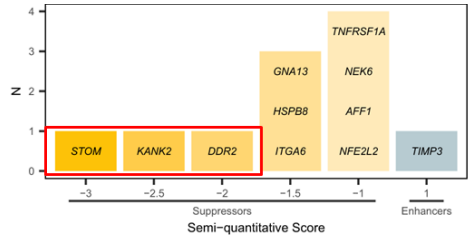
Stage	Datasets & Models		M3	M4	M6	Total
Discovery		Module Genes	1,998	1,636	1,335	4,969
		Hub Genes	372	493	340	1205
		Bulk RNAseq	222	234	94	550
Validations		snRNAseq	56	59	40	155
		Mouse Model (rTG4510)	1	7	13	21
		*Drosophila melanogaster*	0	3	8	11

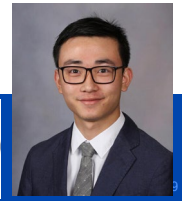




Done

Planned





MAYO CLINIC

curePSP UNLOCKING THE SECRETS OF BRAIN DISEASE

CLEAR-AD Centrally-linked Longitudinal pEripheral biomARkers of AD in multi-ethnic populations

AMP-AD

Towards Precision Medicine in ADRD:

1. Widespread multi–omics molecular perturbations in the brain.

Myelination, immunity, synaptic dysfunction many others.

2. Disease genes/variants and their therapeutic (vs. detrimental) direction of effect.

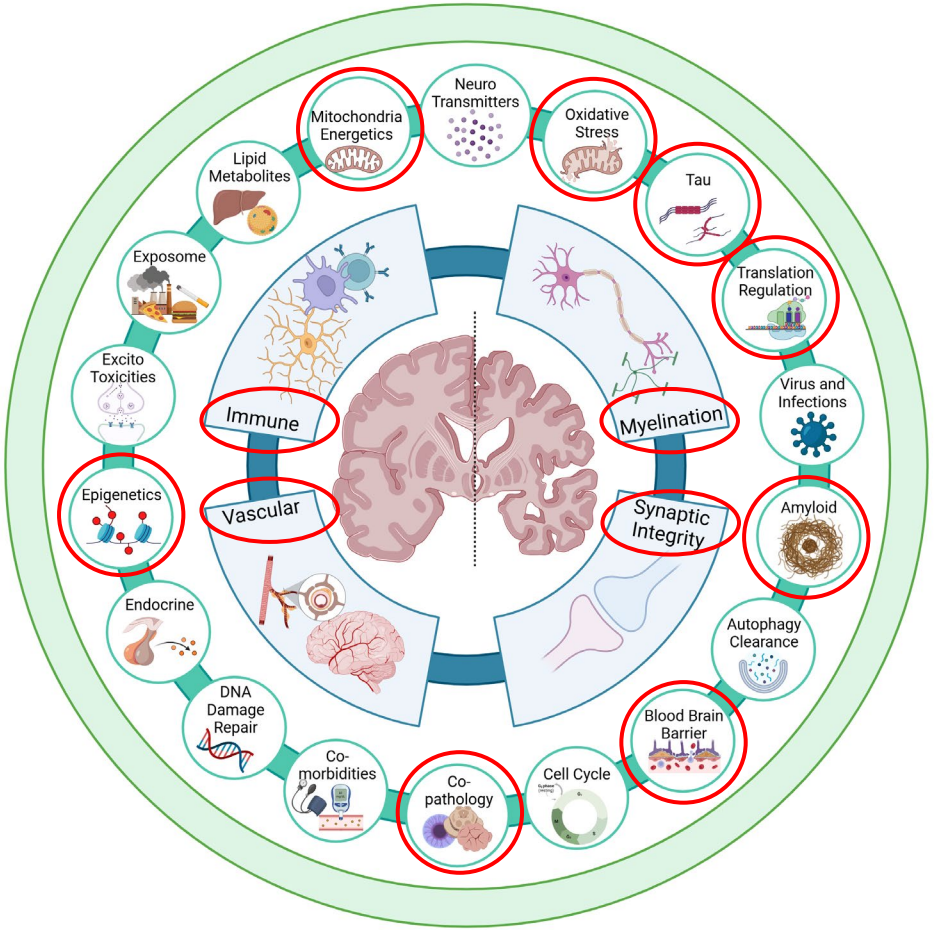
Gene (dys)regulation as disease mechanism and therapeutic target.

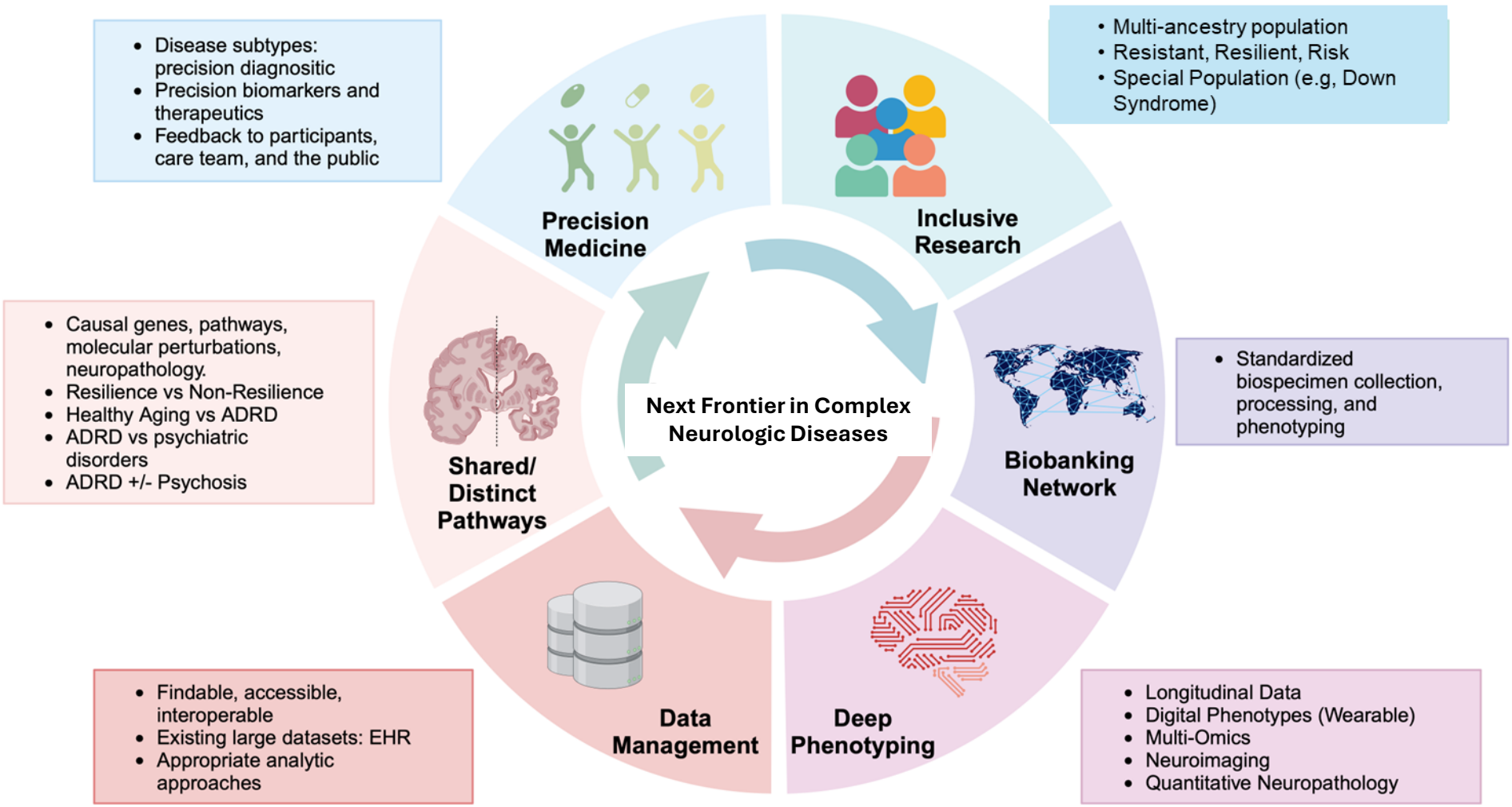
3. Cell-specific dysfunction.

Oligodendrocytes in AD+PSP, divergent pathways in neurons vs. astrocyes.

4. Integrative multi-omics and deep phenotyping identify novel molecular targets and pathways that lay the groundwork for precision medicine.

DDR2, STOM, KANK2 as therapeutic targets in PSP.




Disease subtypes: precision diagnositic
Precision biomarkers and therapeutics
Feedback to participants, care team, and the public
Precision Medicine
Multi-ancestry population
Resistant, Resilient, Risk
Special Population (e.g, Down Syndrome)
Inclusive Research
Causal genes, pathways, molecular perturbations, neuropathology.
Resilience vs Non-Resilience
Healthy Aging vs ADRD
ADRD vs psychiatric disorders
ADRD +/- Psychosis
Shared/ Distinct Pathways
Next Frontier in Complex Neurologic Diseases
Standardized biospecimen collection, processing, and phenotyping
Biobanking Network
Findable, accessible, interoperable
Existing large datasets: EHR
Appropriate analytic approaches
Data Management
Deep Phenotyping
Longitudinal Data
Digital Phenotypes (Wearable)
Multi-Omics
Neuroimaging
Quantitative Neuropathology