Sex-Specific Genetic Drivers of Alzheimer's Disease

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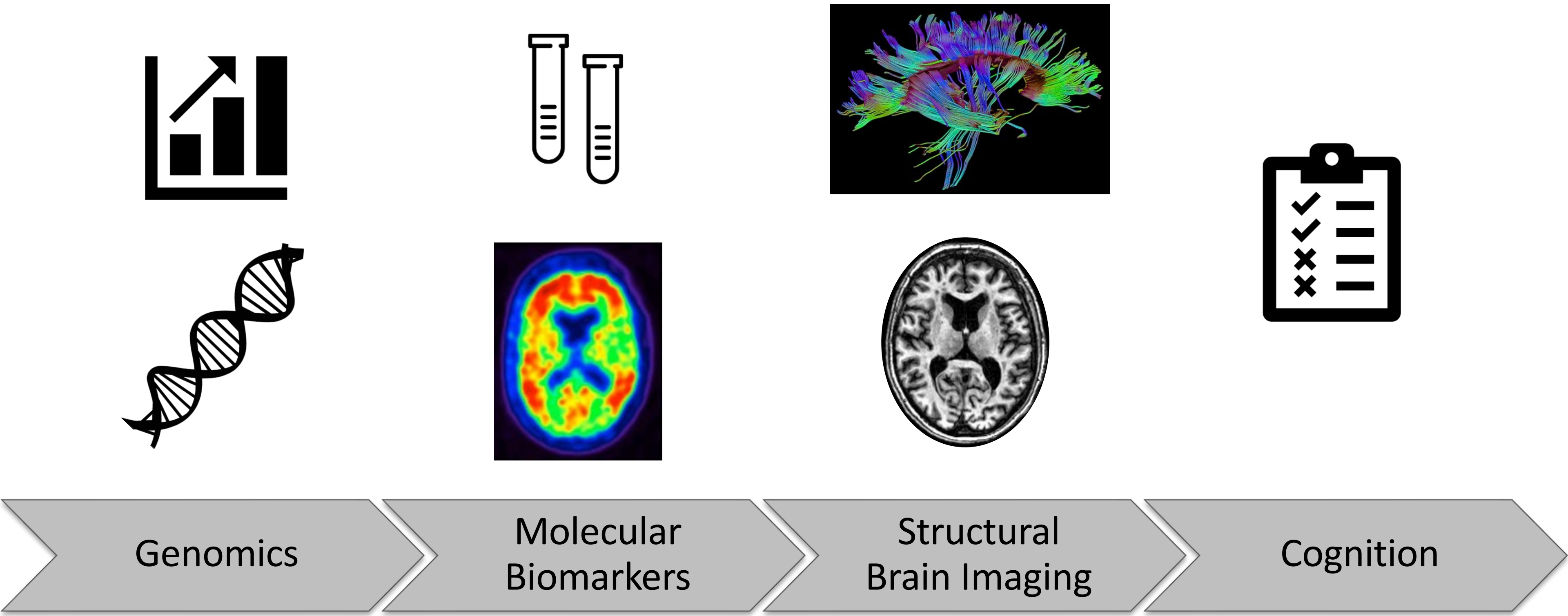
Associate Professor of Neurology
Vanderbilt University Medical Center

August 25, 2023

Disclosures

- Scientific Advisory Board for Vivid Genomics

Explosion of Big Data in Alzheimer’s Disease



Failed Clinical Trials Targeting Amyloid

TARGET TYPE | THERAPY TYPE

Target Types	Timeline	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Phase 4	Approved	Inactive	Discontinued	Not Regulated	Total

The New York Times

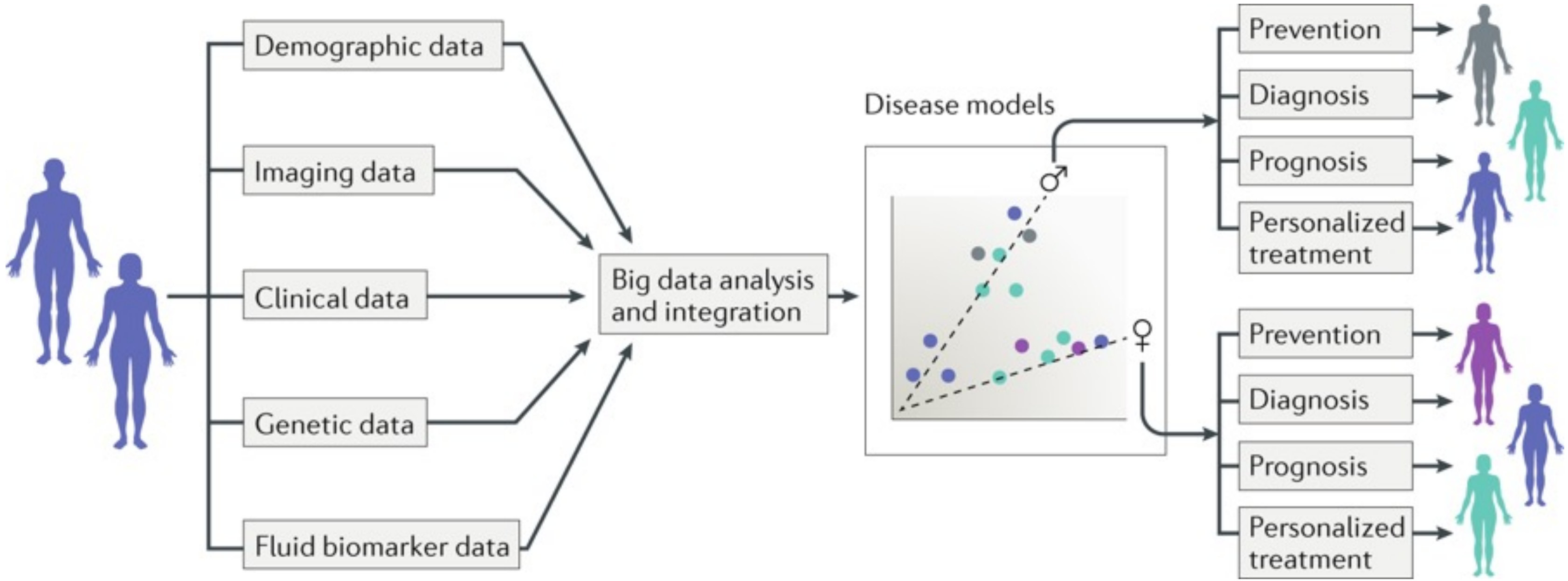
BUSINESS | TECH | ECON | MEDIA | MONEY | DEALBOOK

Amgen, Novartis And Banner Alzheimer's Institute Discontinue Clinical Research Program With BACE Inhibitor CNP520 For Alzheimer's Prevention

THOUSAND OAKS, Calif., July 11, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN), Novartis and Banner Alzheimer's Institute today

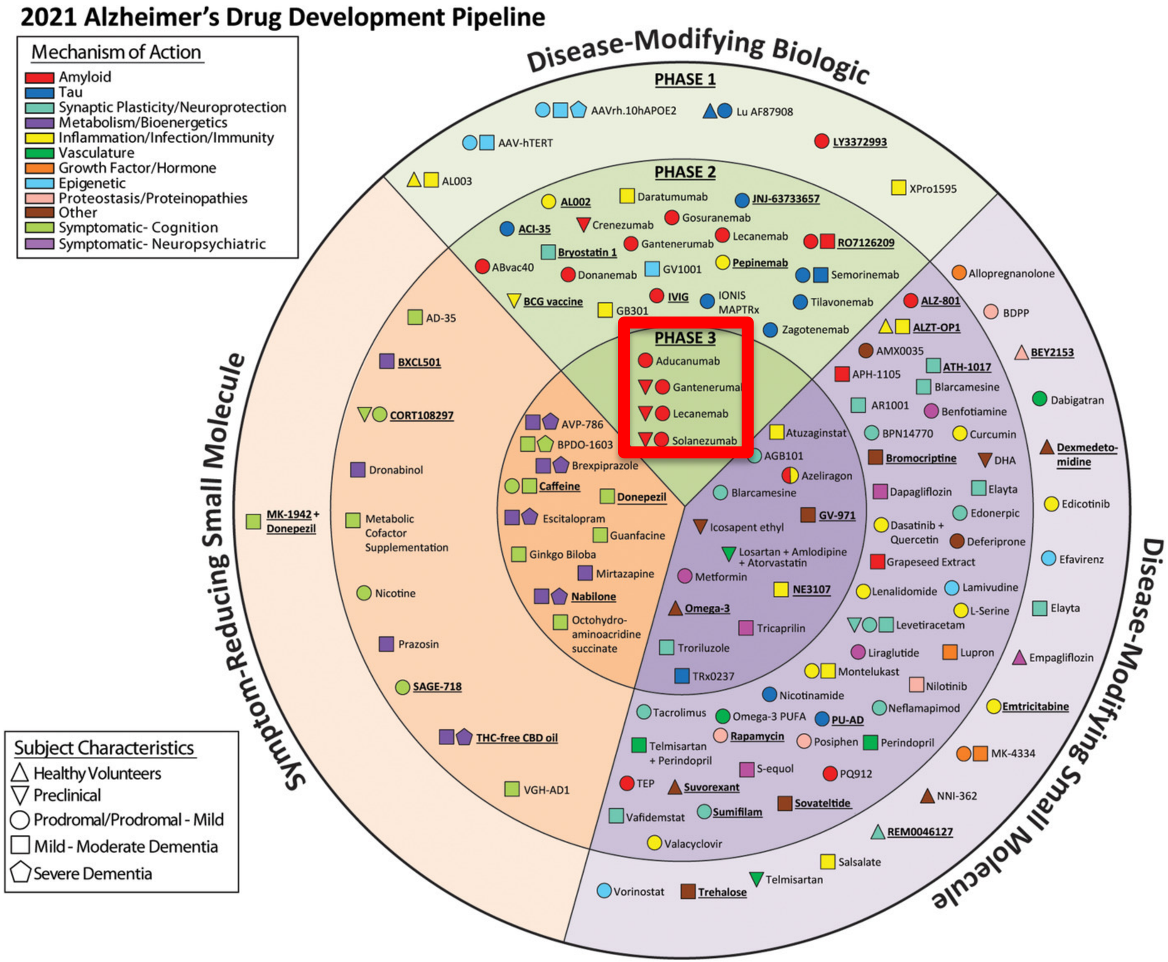
Published: July 12, 2019

Precision Medicine in AD



Ferretti et al., Nature Reviews Neurology, 2018

2021– 2022: Excitement and Controversy



2021– 2022: Excitement and Controversy

NEWS | 08 June 2021

Landmark Alzheime
approval confounds
community

Many scientists say there is not enough evidence t effective therapy for the disease.

The New York Times April 7, 2022

Medicare Officially
Aduhelm to Patients

Officials cited data showing the ne
safety risks and may not help pati

The New York Times

Alzheimer's Drug Slows Cognitive Decline in Key Study

Biogen and Eisai reported the finding from a large late-stage clinical trial of lecanemab, a drug they are developing.

Give this article 70

Lecanemab reduced cognitive decline by 27 percent in a clinical trial with 1,800 participants, Biogen and Eisai said. Steven Senne/Associated Press

By Rebecca Robbins and Pam Belluck
Sept. 27, 2022

herapy gantenerumab
improve Alzheimer's
n clinical trials

22

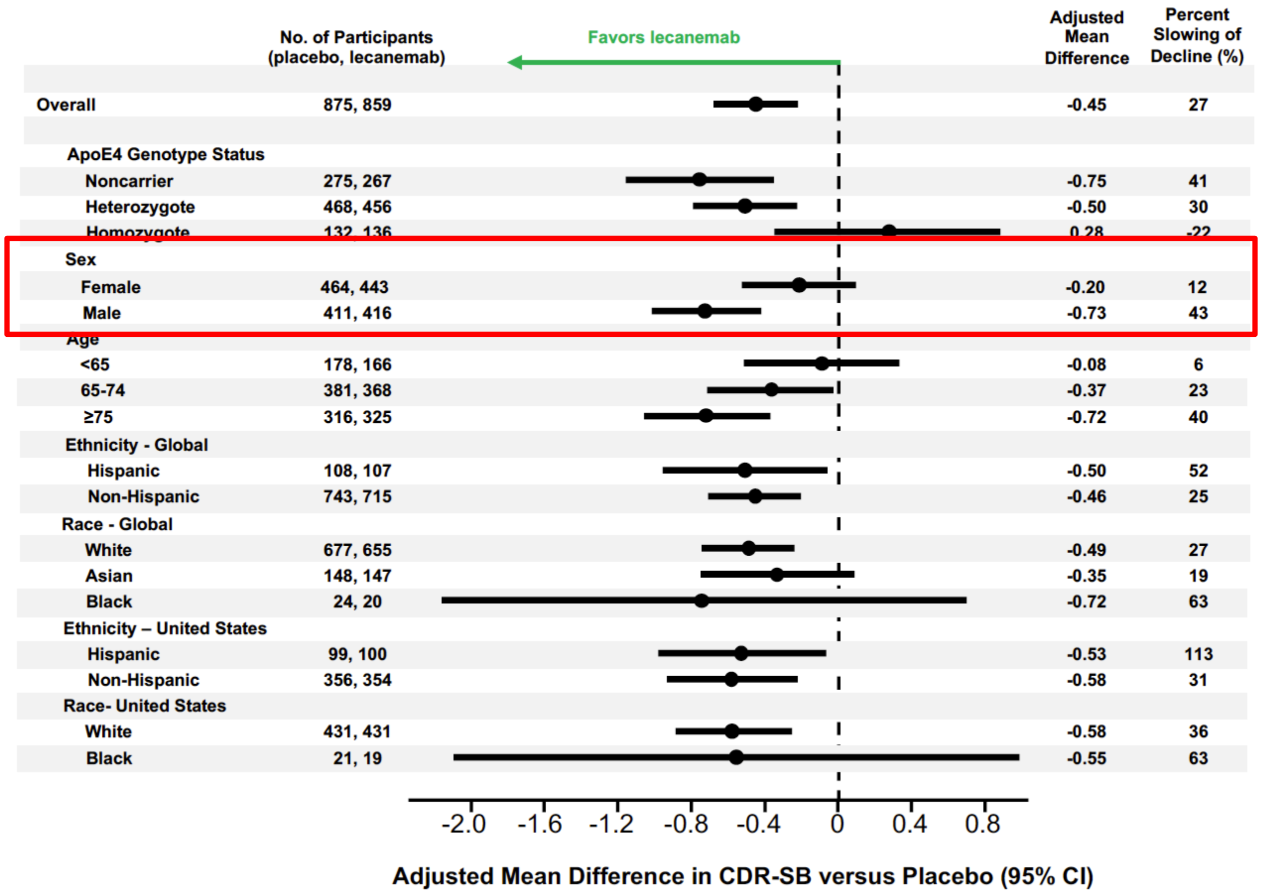
SCIENCEINSIDER | BRAIN & BEHAVIOR

Second death linked to potential antibody treatment for Alzheimer's disease

Woman's brain hemorrhage while receiving Eisai's widely heralded lecanemab heightens concerns overs its safety

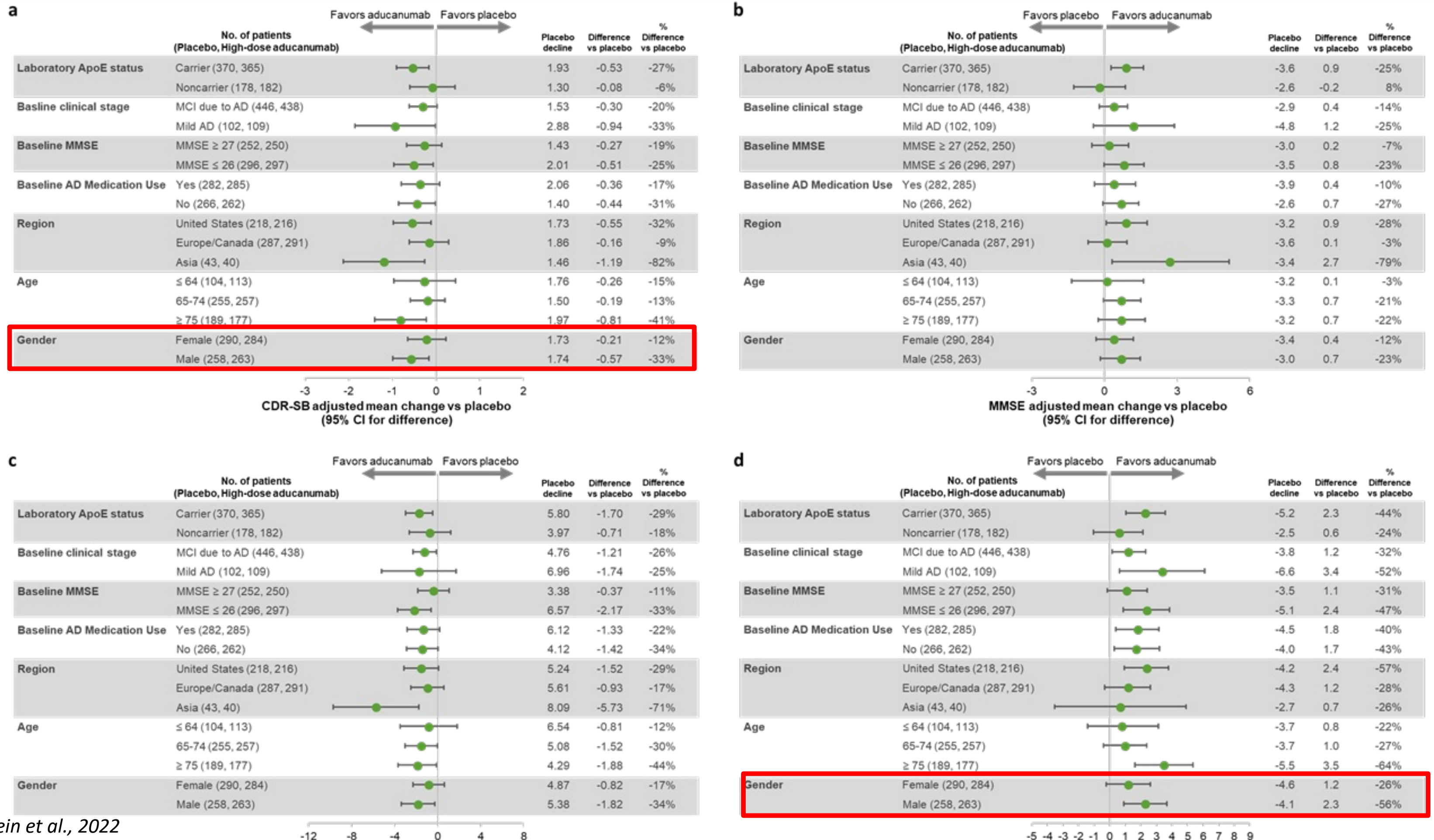
27 NOV 2022 • 8:00 PM • BY CHARLES PILLER

Sex Difference in Lecanemab results?



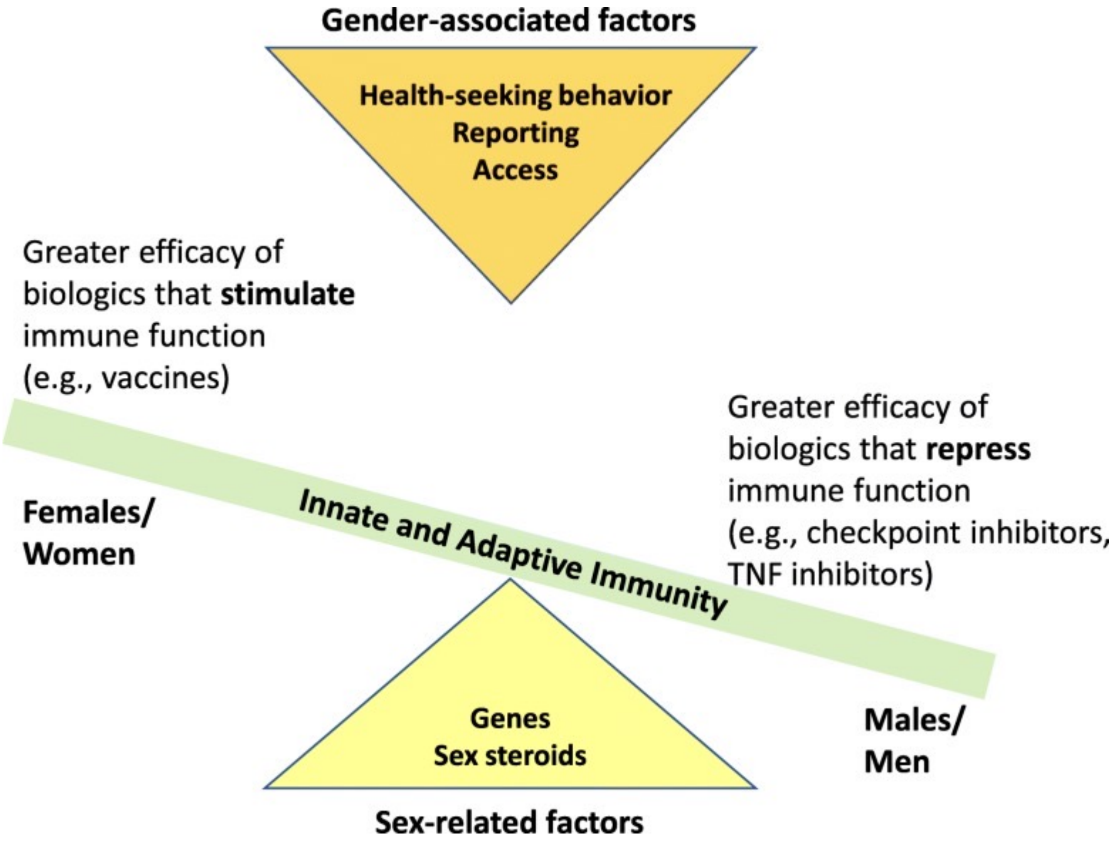
Van Dyck et al., New England Journal of Medicine, 2023

Sex Difference in Aducanumab results?



Haeberlein et al., 2022

Sex Difference in Efficacy of Immunotherapies?



Klein & Morgan, Biology of Sex Differences, 2020

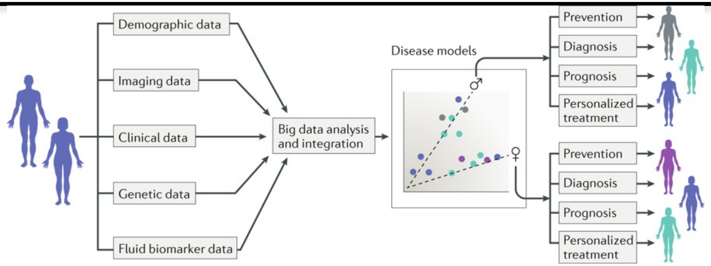
Sex Difference in Pharmacodynamics?

Table 1. Anticancer agents with relevant differences in clearance between men and women

Class/drug, name	Indication	*n* (men)/(women)	Variability on CL (CV%)	Relative change in women versus men	
Angiogenesis inhibitors					
Aflibercept [47]	Advanced solid tumours	767/739	31%	Clfu Vfu	−16% −19%
Bevacizumab [48, 49]	Gastric cancer; solid tumours	1101/949	26%	CL	−14% to −27%
Antineoplastic agents: antimetabolites					
5-Fluorouracil [50, 51] and metabolite	GI malignancies; metastatic colorectal cancer	74/42	22%–40%	CL CLmet	−14% to −27% −18%
Myeloablative agents					
Busulfan [52]	Marrow transplantation	904/689	22%	V	+7%
Antineoplastic agent: alkylating agents					
Temozolomide [53, 54]	Glioma, glioblastoma, melanoma	303/177	5%–10%	CL	−19 to 27%
Mephalan [55]	Advanced malignancies	22/42	45%	CL	−19%
Trabectedin [56]	PD study	232/467	51%	V Keo	−17% +22%
Antineoplastic agents: alkaloids					
Paclitaxel [57, 58]	Solid tumours	159/160		CL Vmax	−30% +14%
Irinotecan (SN38) [59–61]	Solid tumours, glioblastoma	67/58	47%	CL	−30% to 38%
Antineoplastic agent: antibodies					
Rituximab [62]	Lymphoma	16/13	19%	CL	−21%

CL, total clearance; CLfu, clearance of the unbound fraction; *V*, volume of distribution; *V*fu, volume of distribution of the unbound fraction; *V*max, maximal metabolization rate; CLmet, metabolic clearance (i.e. the part of the total clearance corresponding to metabolism); CLren, renal clearance (i.e. the part of the total clearance corresponding to excretion); CL, CLmet+CLren; Keo, equilibration constant between central and effect compartments; CV%, interindividual variability of the total clearance.

Back to Precision Medicine: Who Should Receive this Treatment?



- Significant effects were observed in men
- No statistically significant effect in women
- Adverse events not reported by gender

Caveats

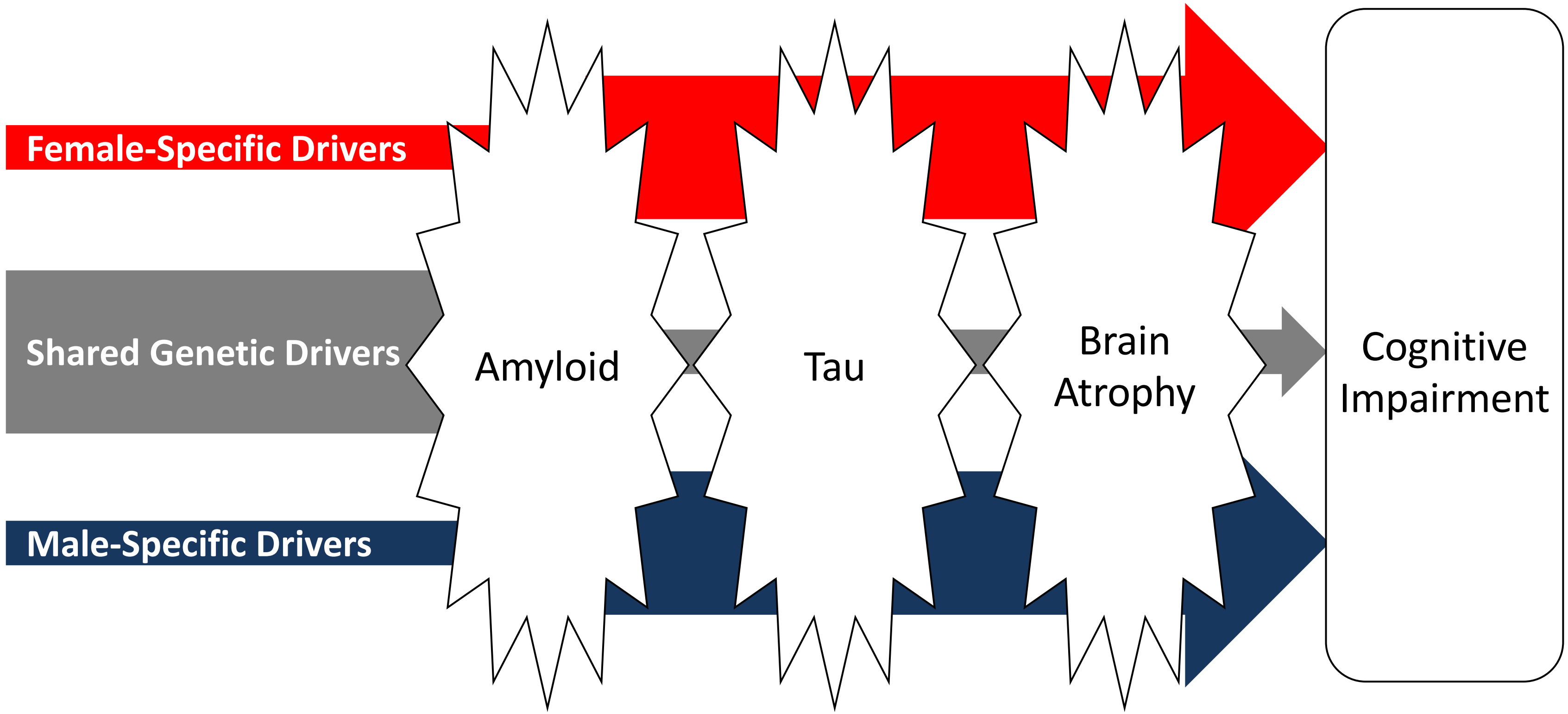
- Trial not designed to test for sex interaction or sex-stratified effects
- No statistical evidence of a sex difference

Opportunities

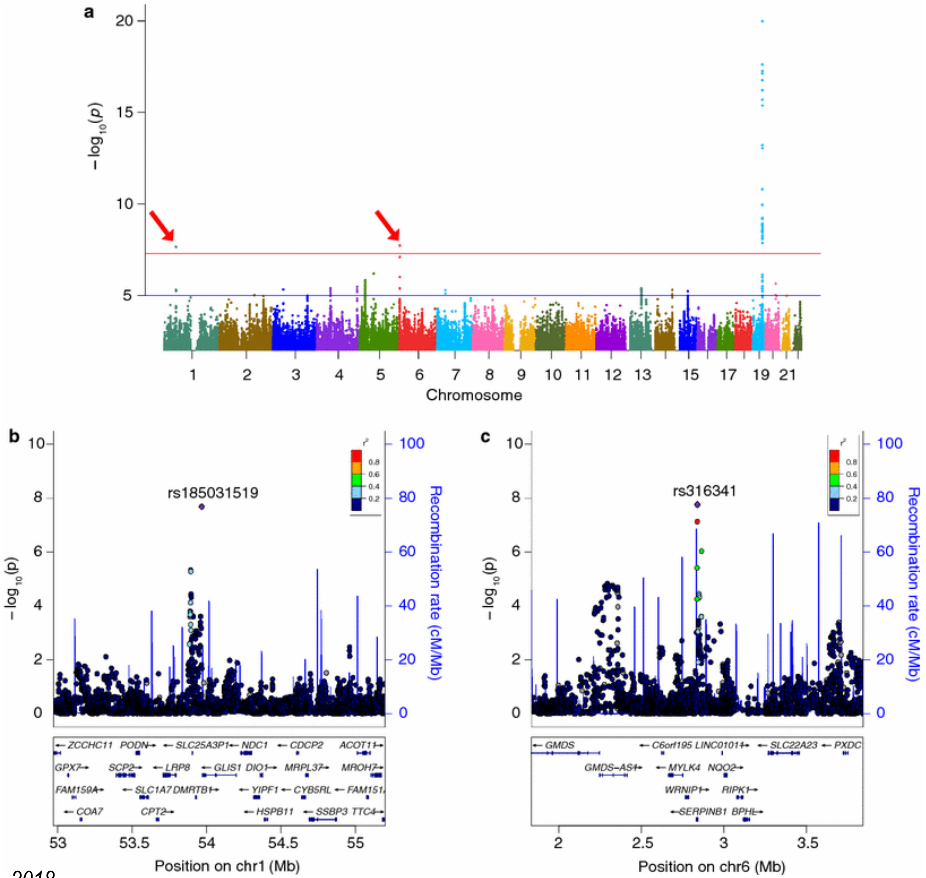
- Report sex differences in the preclinical testing for drug
  - Should we have expected a difference in efficacy, drug delivery, brain infiltration, or clearance?
- Evaluate and recommend based on intersectional effects of age, sex, race/ethnicity, *APOE*

Incorporating Sex Differences into Genomic Discovery

Summary of Sex Differences



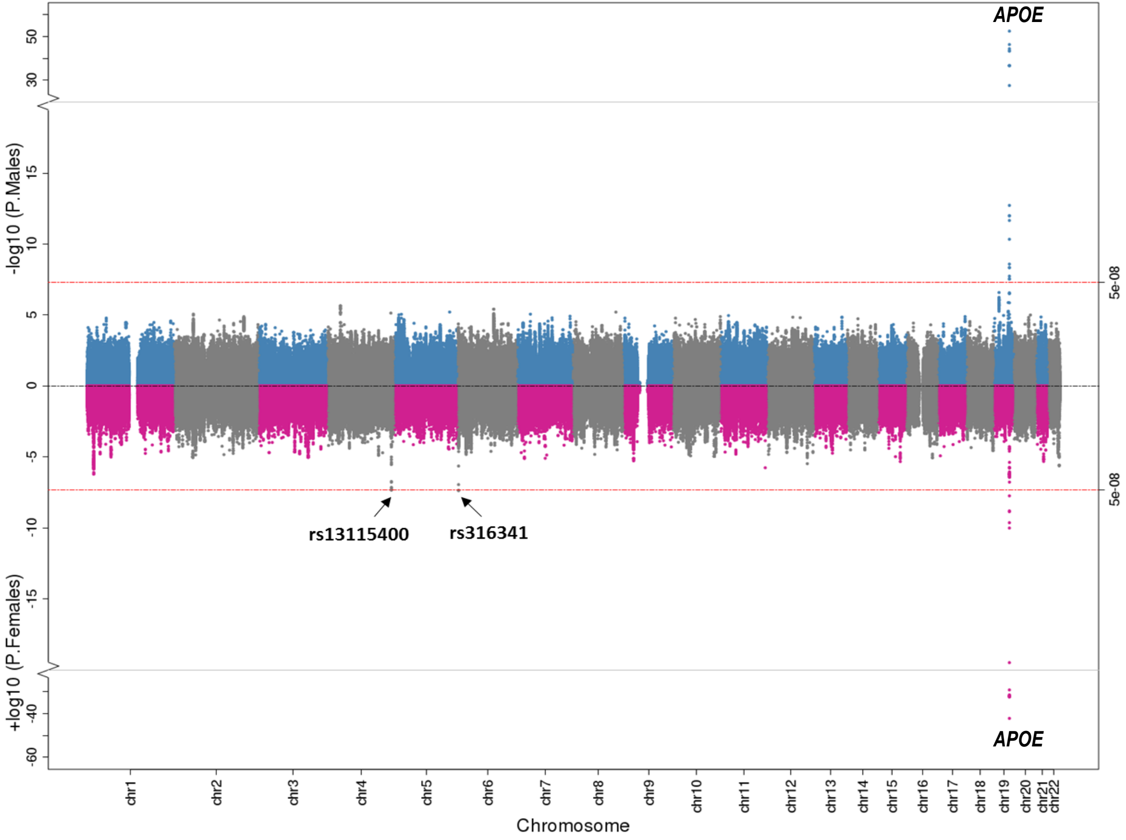
GWAS of CSF Aβ-42



Deming, Dumitrescu … Hohman, Acta Neuropathologica, 2018

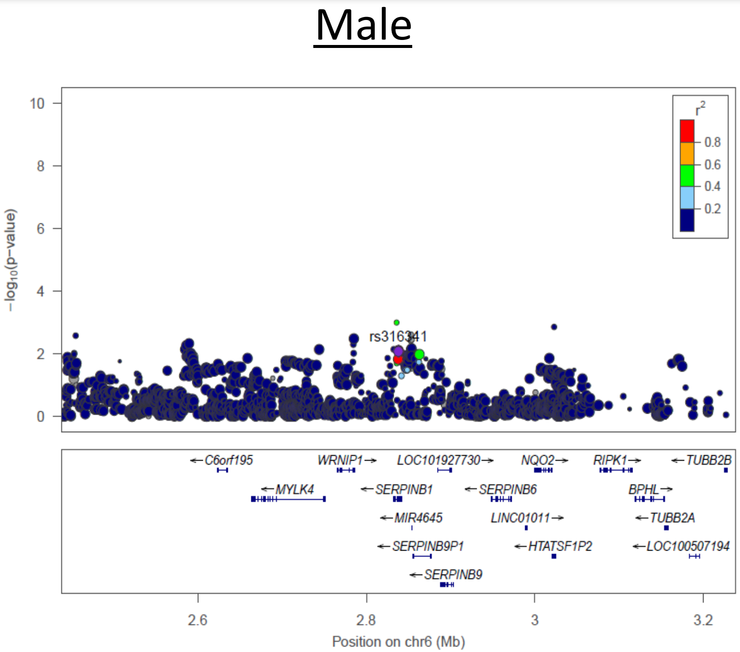
GWAS of CSF Aβ-42

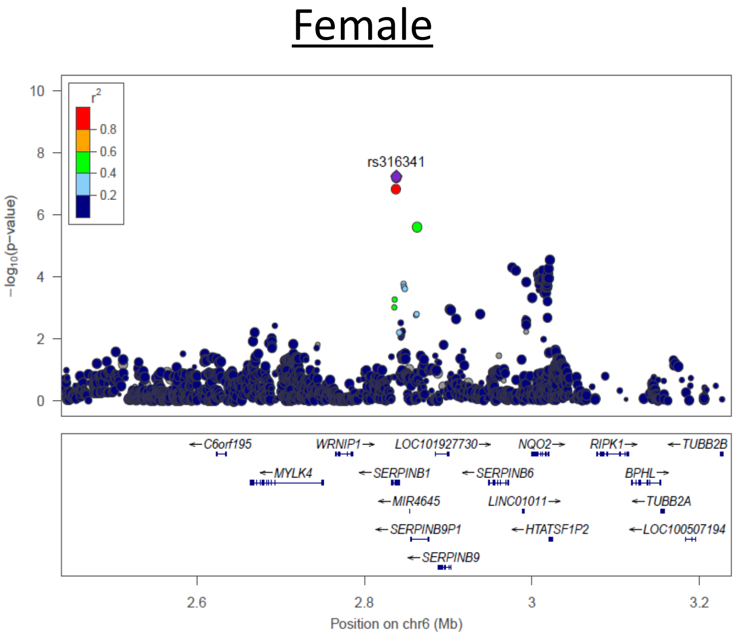
Logan Dumitrescu, PhD



Deming, Dumitrescu … Hohman, Acta Neuropathologica, 2018

Locus Zoom



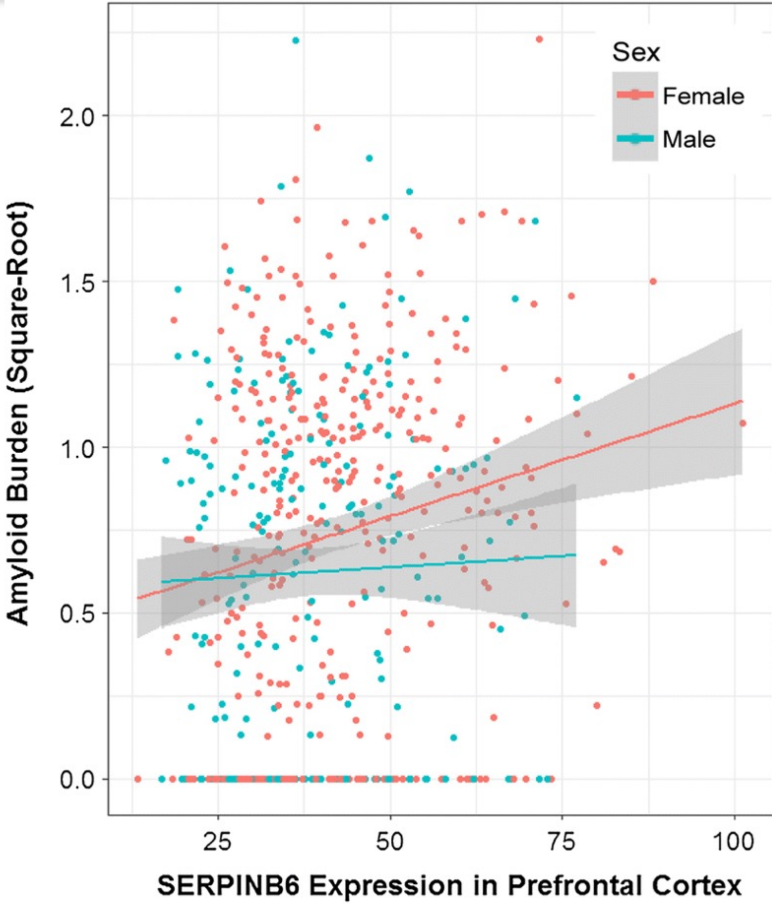


rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex

Deming, Dumitrescu … Hohman, Acta Neuropathologica, 2018

SERPINB1 Functional Evidence

- Female-specific association between prefrontal cortex expression of *SERPINB1* (p=0.02) and *SERPINB6* (p=0.00007) and amyloid levels in brain tissue

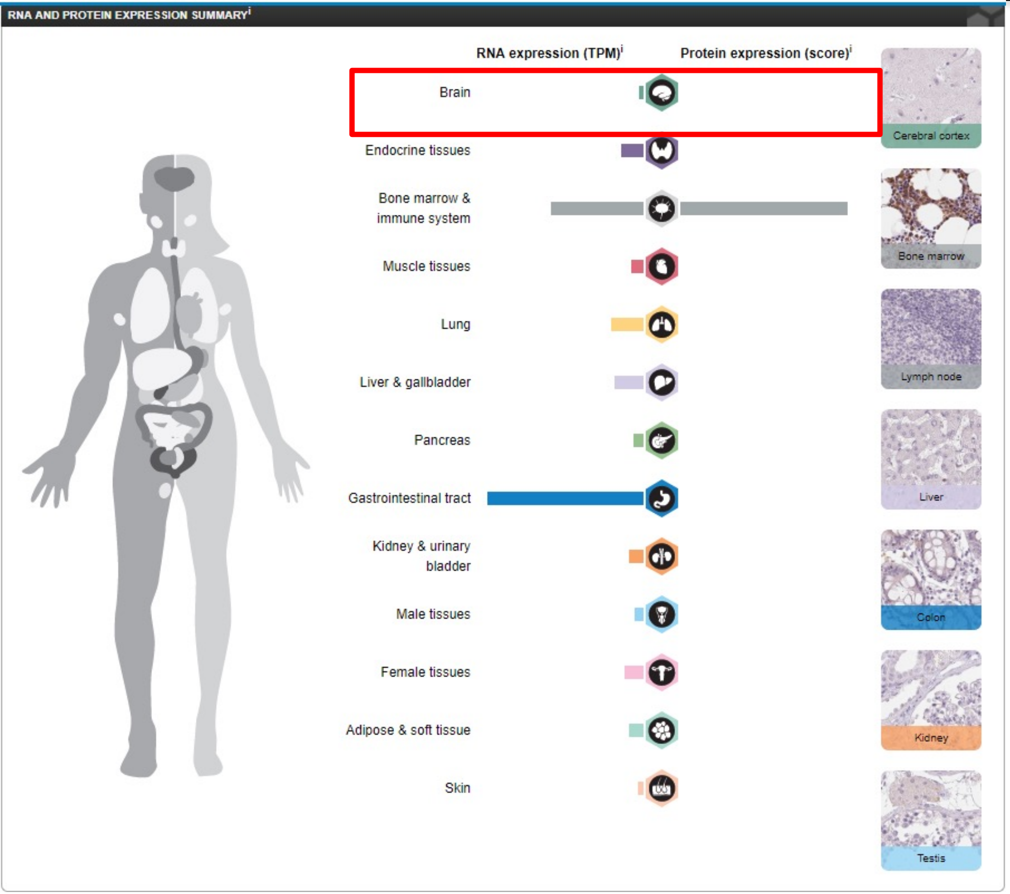


Deming, Dumitrescu … Hohman, Acta Neuropathologica, 2018

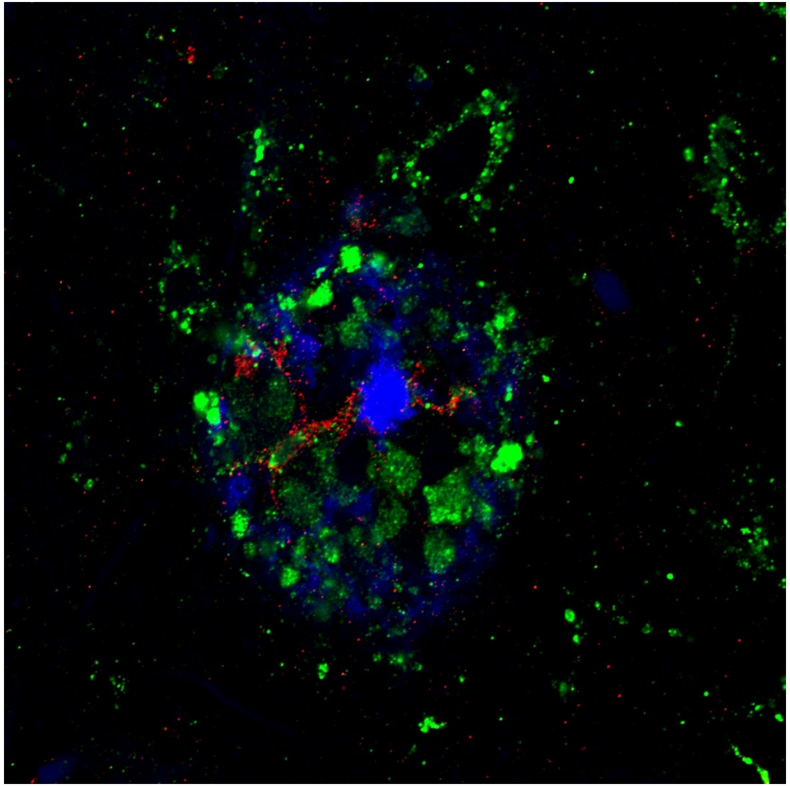
Serpin Signaling and Amyloidosis

- Serpins are Protease Inhibitors
  - Serpin-B1 Regulates Neutrophil Infiltration
- Serpins have been shown to inhibit Aβ toxicity *Schubert, 1997*
  - Likely through regulation of neutrophils *Zenaro et al., 2015*
- Some evidence of sex difference in neutrophil infiltration and clearance
  - Female mice show more activated neutrophils than male mice following stroke
  - Estradiol modulates neutrophil infiltration and clearance

SERPINB1 in Brain Tissue



SERPINB1 Staining in AD Cortex



Sex-Specific Drivers of Resilience

Jackie Eissman
PhD Candidate

Original Research | Published: 03 February 2016

Sex differences in the association between AD biomarkers

Mary Ellen I. Koran, M

Initiative

Brain Imaging and Be

2071 Accesses | 11

Original Investigation

August 201

Sex-Sp

Cereb

Timothy J. Hoh

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JAMA Neurol. 2

Sex differences in the genetic predictors of Alzheimer's pathology FREE

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John Q Trojanowski, E

Alison M Goate, Nancy

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for the Alzheimer's Dis

Neuroimaging Initiativ

David A Bennett, Julie

Author Notes

Brain, Volume 142, Iss

https://doi.org/10.109

Published: 20 July 2019 **Article history** ▾

ACCEPTED MANUSCRIPT

Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease

Jaclyn M. Eissman, Logan Dumitrescu, Emily R. Mahoney, Alexandra N. Smith, Shubhabrata Mukherjee, Michael L. Lee, Phoebe Scollard, Seo-Eun Choi, William S. Bush, Corinne D. Engelman ... Show more

Brain, awac177, https://doi.org/10.1093/brain/awac177

Published: 13 May 2022 **Article history** ▾

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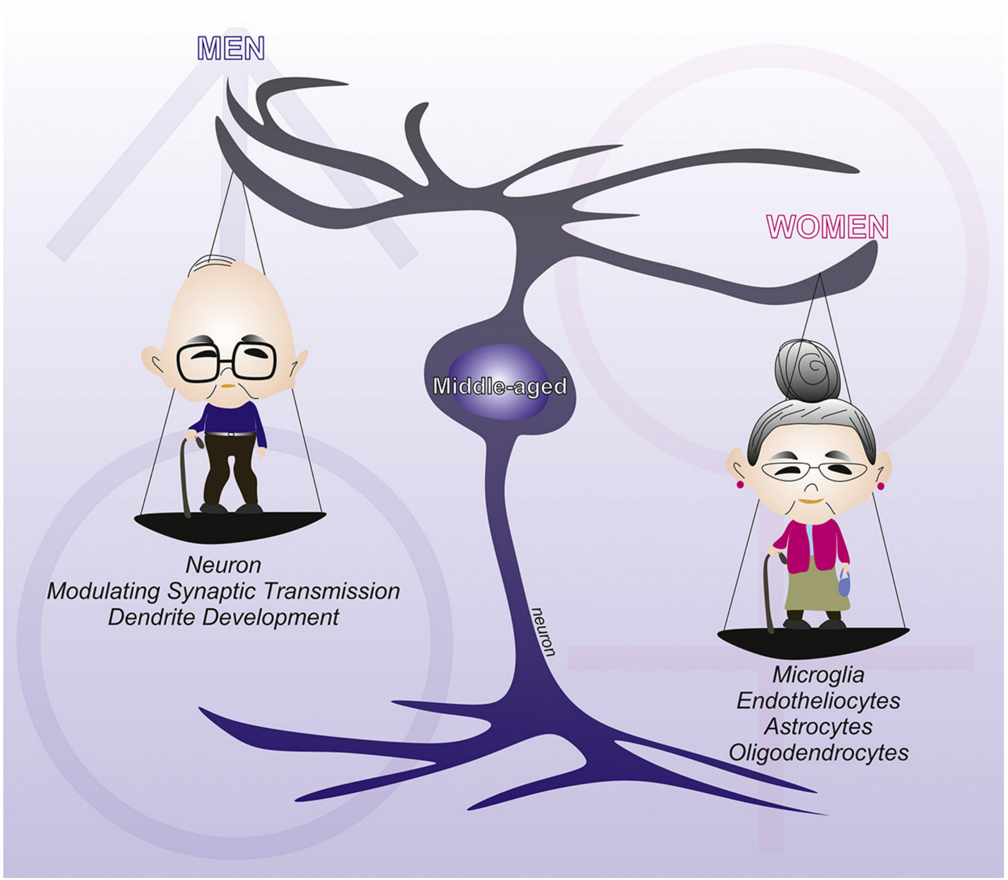
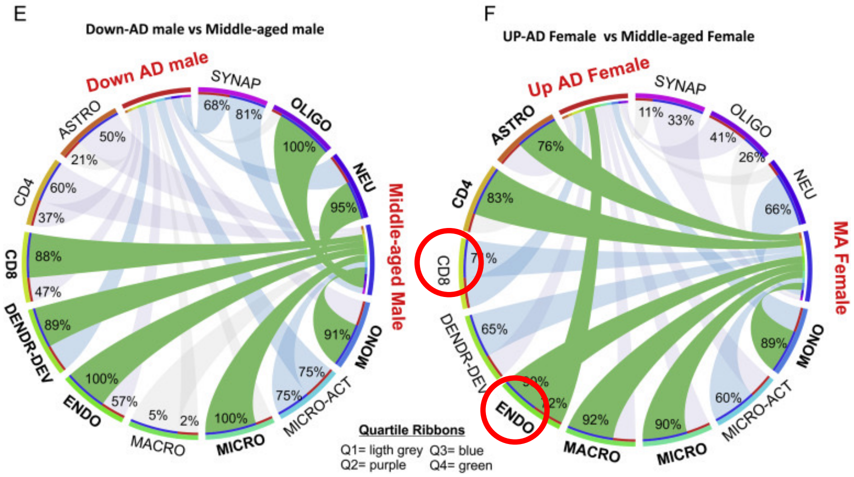
Incorporating Sex Differences into Transcriptomic Discovery

Sex-Specific Changes in Transcription during Aging

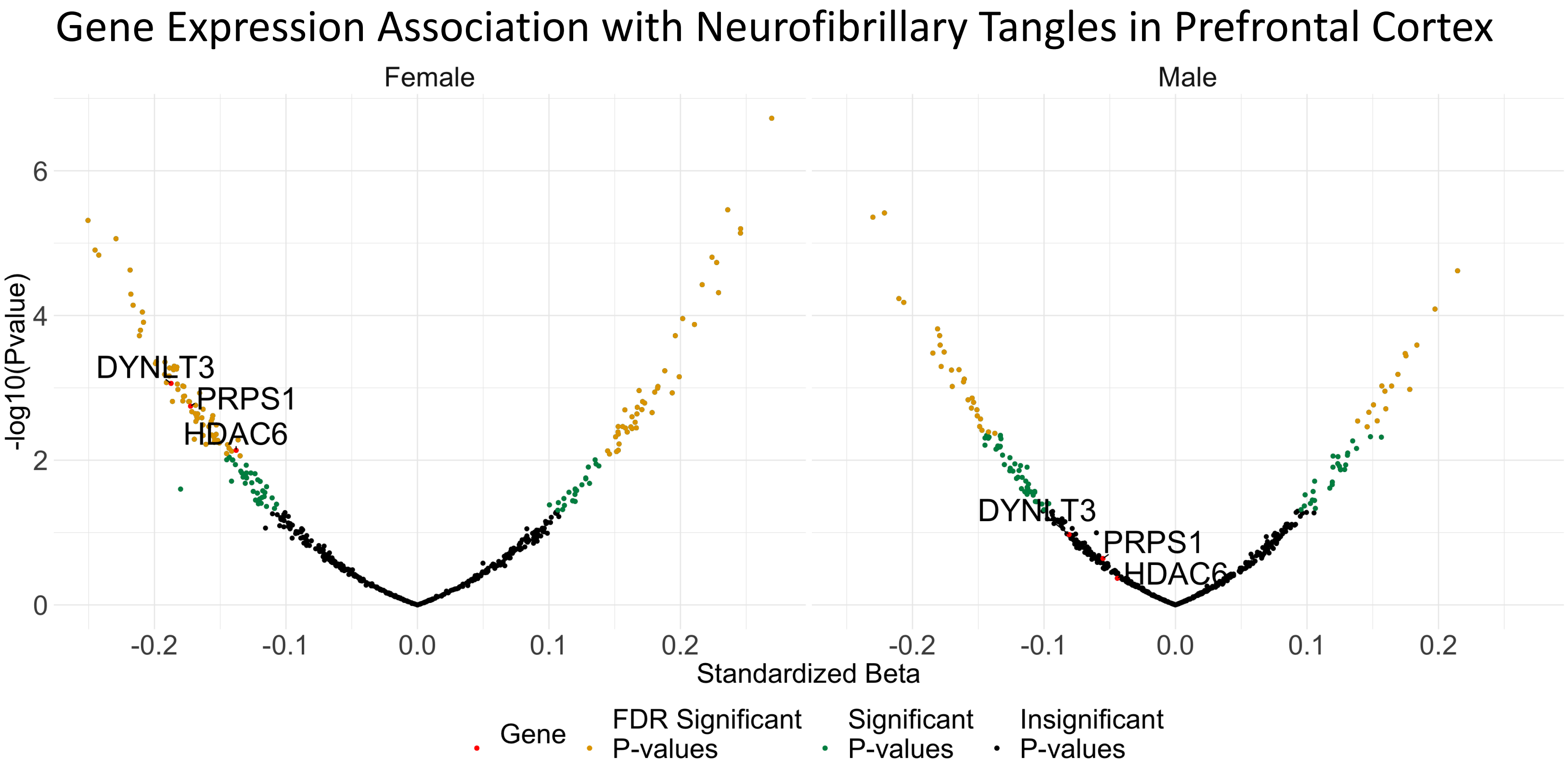




Sanfilippo et al., Neuroscience, 2019

Sex-Specific Drivers of Tangle Pathology

Michelle Clifton, MA

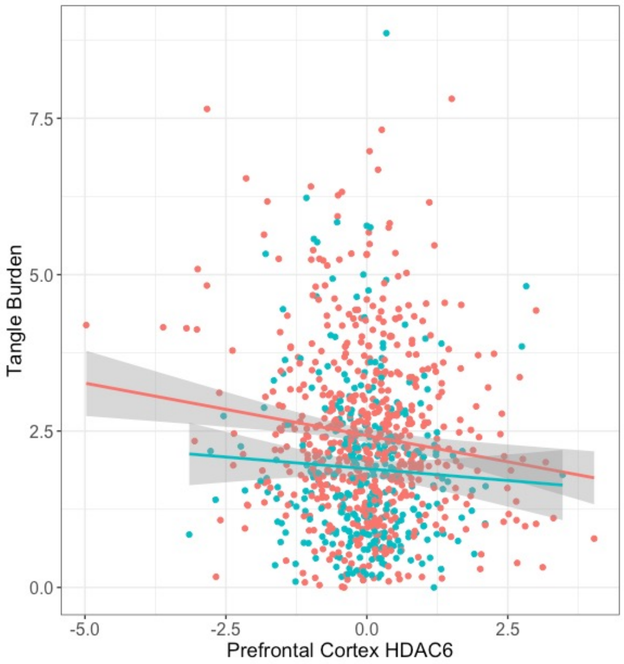


Clifton et al., In Preparation

Sex-Specific Drivers of Tangle Pathology

Michelle Clifton, MA

HDAC6 is implicated in Tau Pathogenesis and Regulated by Estrogen



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-19317-4 OPEN

Check for updates

An HDAC6-dependent surveillance mechanism suppresses tau-mediated neurodegeneration and cognitive decline

Hanna Trzeciakiewicz[1], Deepa Ajit[2], Jui-Heng Tseng[2], Youjun Chen[2], Aditi Ajit[2], Zarin Tabassum[2], Rebecca Lobrovich[3], Claire Peterson[3], Natallia V. Riddick[4], Michelle S. Itano[5], Ashutosh Tripathy[1], Sheryl S. Moy[6], Virginia M. Y. Lee[7], John Q. Trojanowski[7], David J. Irwin[3] & Todd J. Cohen[1,2]

Oncogene (2005) 24, 4531–4539

www.nature.com/onc

Significance of HDAC6 regulation via estrogen signaling for cell motility and prognosis in estrogen receptor-positive breast cancer

Shigehira Saji*,[1], Masayo Kawakami[1], Shin-ichi Hayashi[2], Nobuyuki Yoshida[3], Makiko Hirose[1], Shin-ichiro Horiguchi[4], Akihiro Itoh[5], Nobuaki Funata[4], Stuart L Schreiber[6], Minoru Yoshida[5] and Masakazu Toi[1]

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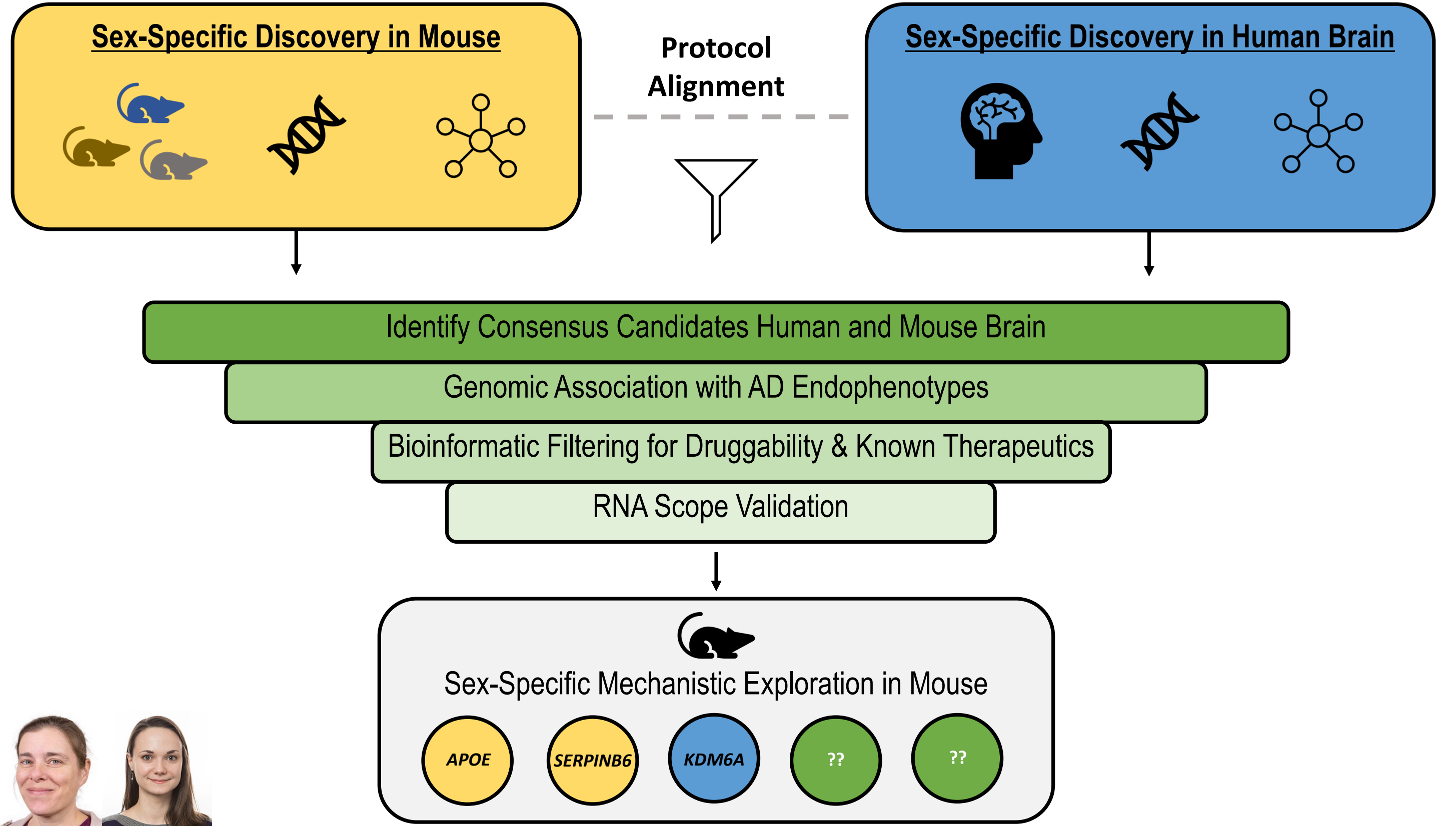
Clifton et al., In Preparation

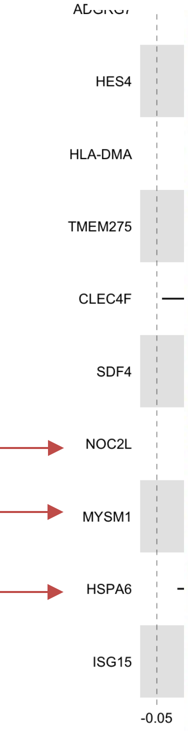
Precision Medicine through Collaboration



Cell + Sex-Specific Drivers of Tangles

Yiyang Wu, MD, PhD

Pathway Enrichment Results



cellular macromolecule metabolic process	2518	342	231.76	1.48	+	3.80E-12	7.46E-09
intracellular transport	1360	211	125.17	1.69	+	4.47E-12	7.79E-09
adaptive immune response	659	16	60.65	.26	-	5.07E-11	7.95E-08
establishment of localization in cell	1752	250	161.25	1.55	+	9.17E-11	1.31E-07
ribonucleoprotein complex biogenesis	449	91	41.33	2.20	+	1.67E-10	2.18E-07
establishment of protein localization	1267	192	116.61	1.65	+	2.61E-10	3.15E-07
protein transport	1179	181	108.51	1.67	+	4.49E-10	5.03E-07
cellular metabolic process	6606	742	608.01	1.22	+	6.54E-10	6.83E-07
cellular localization	2655	340	244.36	1.39	+	2.66E-09	2.61E-06
nitrogen compound transport	1589	223	146.25	1.52	+	3.92E-09	3.61E-06
nitrogen compound metabolic process	6710	742	617.58	1.20	+	9.29E-09	8.09E-06
protein localization	1919	256	176.62	1.45	+	1.87E-08	1.54E-05
ribosome biogenesis	303	64	27.89	2.29	+	2.14E-08	1.67E-05
cellular macromolecule localization	1925	256	177.18	1.44	+	2.47E-08	1.84E-05
organic substance transport	1964	258	180.77	1.43	+	5.14E-08	3.66E-05
cellular component organization or biogenesis	5727	640	527.11	1.21	+	6.13E-08	4.18E-05
G protein-coupled receptor signaling pathway	1223	59	112.56	.52	-	6.22E-08	4.06E-05
immune response	1621	88	149.20	.59	-	8.20E-08	5.15E-05
intracellular protein transport	682	111	62.77	1.77	+	1.06E-07	6.39E-05

Wu et al., In Preparation

ADSP Phenotype Harmonization Consortium

Subject and cohort counts for each domain:

Cohort	Cognition	Biomarker	Neuropath
ACT	1337	0	0
ADNI	1566	1165	0
KGAD	0	64	0
MAP- Rush	639	0	538
MARS	48	0	11
NACC	10488	805	4649
NIA-LOAD	0	2	262
ROS	583	0	532
Total	14661	2036	5992

Neuroimaging
Coming 2023

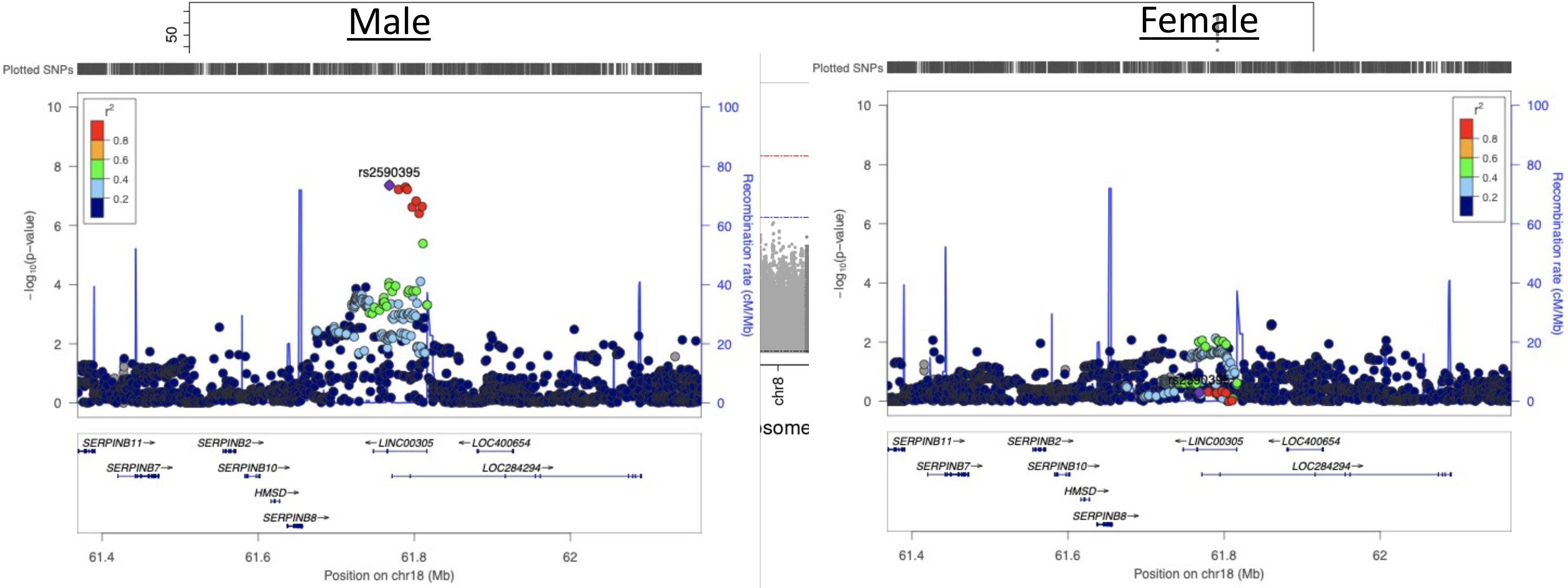
Vascular Risk Factors
Coming 2023

dss NIAGADS

https://dss.niagads.org/

ADSP PHC PHENOTYPE HARMONIZATION CONSORTIUM

Sex-Stratified Memory GWAS



rs2590395 is eQTL for SERPINB2 and SERPINB10 in Blood

Eissman et al., In Preparation

Acknowledgements

@timothyjhohman

- Derek Archer, PhD
- Mary Ellen Koran, MD, PhD
- Annah Moore, PhD
- Alexis Smith, MA
- Rebecca Winfree, PhD
- Shannon Turner, BA
- Skylar Walters, MA
- Alaina Durant, BA
- Jared Phillips, BA
- Ting-Chen Wang, BA

- **Logan Dumitrescu, PhD**
- Vaibhav Janve, PhD
- Michelle Clifton, MA
- Yiyang Wu, MD, PhD
- Jackie Eissman, ABD
- Tonnar Castellano, MA
- Alex Contreas, BS
- Julia Libby, BS
- Emily Mahoney, BA
- Abel Belachew, MA

Vanderbilt Memory & Alzheimer's Center

- Angela Jefferson, PhD
- Katie Gifford, PsyD
- Matthew Schrag, MD
- Bennett Landman, PhD

Vanderbilt Genetics Institute

- Nancy Cox, PhD
- Lea Davis, PhD
- Douglas Ruderfer, PhD

Rush University Medical Center

- David Bennett, MD
- Julie Schneider, MD

National Institute on Aging

- Susan Resnick, PhD
- Murat Bilgel, PhD

Jackson Laboratory

- Catherine Kaczorowski, PhD
- Amy Dunn, PhD
- Kristen O'Connell, PhD

University of Wisconsin

- Sterling Johnson, PhD
- Corinne Engelman, PhD
- Qiognshi Lu, PhD
- Yuetiva Deming, PhD

Columbia University

- Richard Mayeux, MD
- Vilas Menon, PhD
- Phil De Jager, MD, PhD
- Adam Brickman, PhD
- Jennifer Manly, PhD

University of Miami

- Michael Cuccaro, PhD
- Margaret Pericak-Vance, PhD
- Brian Kunkle, PhD
- Gary Beecham, PhD
- Eden Martin, PhD

Stanford University

- Elizabeth Mormino, PhD
- Thomas Montine, MD

University of Pennsylvania

- Gerard Schellenberg, PhD
- Li San Wang, PhD
- Amanda Kuzma, MS
- Christos Davatzikos, PhD

University of Southern California

- Paul Thompson, PhD
- Duygu Tosun, PhD

Harvard Medical School

- Rachel Buckley, PhD
- Mabel Seto, PhD
- Hyun-Sik Yang, MD
- Michael Properzi, BS

Case Western University

- Jonathan Haines, PhD
- William Bush, PhD

Johns Hopkins University

- Marilyn Albert, PhD
- Alden Gross, PhD

University of Washington

- Paul Crane, MD
- Joey Mukherjee, PhD
- Emily Trittschuh, PhD
- Walter Kukull, PhD

Washington University in St. Louis

- Carlos Cruchaga, PhD
- Oscar Harari, PhD
- Bruno Benitez, MD

Indiana University

- Andy Saykin, PsyD
- Shannon Risascher, PhD

Mt. Sinai Icahn School of Medicine

- Alison Goate, PhD
- Sarah Neuner, PhD

University of Kentucky

- David Fardo, PhD

Boston University

- Jesse Mez, MD

UTHSA

- Mohamad Habes, PhD
- Sudha Seshadri, PhD

Funding: U24-AG074855, *R01-AG061518 , R01-AG061518, P20-AG068082, U01-AG068057, R21-AG059941, K01-AG049164, K12-HD043483, HHSN311201600276P, RF1-AG059869*