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

- Genomics
- Molecular Biomarkers
- Structural Brain Imaging
- Cognition
Failed Clinical Trials Targeting Amyloid

<table>
<thead>
<tr>
<th>TARGET TYPE</th>
<th>THERAPY TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

The New York Times

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

Demographic data
Imaging data
Clinical data
Genetic data
Fluid biomarker data

Big data analysis and integration

Disease models

Prevention
Diagnosis
Prognosis
Personalized treatment
Prevention
Diagnosis
Prognosis
Personalized treatment

Ferretti et al., Nature Reviews Neurology, 2018
2021–2022: Excitement and Controversy

2021 Alzheimer’s Drug Development Pipeline

Subject Characteristics
- Healthy Volunteers
- Preclinical
- Prodromal/Prodromal - Mild
- Mild - Moderate Dementia
- Severe Dementia

Mechanism of Action
- Amyloid
- Tau
- Synaptic Plasticity/Neuroprotection
- Metabolism/Oxidoreductases
- Inflammation/Infection/Immunity
- Vascular
- Growth Factor/Hormone
- Epigenetic
- Proteostasis/Proteinopathies
- Other
- Symptomatic - Cognition
- Symptomatic - Neuropsychiatric

Disease-Modifying Biologic

PHASE 1
- Amyloid
- Tau
- Synaptic Plasticity/Neuroprotection
- Metabolism/Oxidoreductases
- Inflammation/Infection/Immunity
- Vascular
- Growth Factor/Hormone
- Epigenetic
- Proteostasis/Proteinopathies
- Other
- Symptomatic - Cognition
- Symptomatic - Neuropsychiatric

PHASE 2
- Amyloid
- Tau
- Synaptic Plasticity/Neuroprotection
- Metabolism/Oxidoreductases
- Inflammation/Infection/Immunity
- Vascular
- Growth Factor/Hormone
- Epigenetic
- Proteostasis/Proteinopathies
- Other
- Symptomatic - Cognition
- Symptomatic - Neuropsychiatric

PHASE 3
- Amyloid
- Tau
- Synaptic Plasticity/Neuroprotection
- Metabolism/Oxidoreductases
- Inflammation/Infection/Immunity
- Vascular
- Growth Factor/Hormone
- Epigenetic
- Proteostasis/Proteinopathies
- Other
- Symptomatic - Cognition
- Symptomatic - Neuropsychiatric

Disease-Modifying Small Molecule

1. Subject Characteristics
2. PHASE 1
3. PHASE 2
4. PHASE 3
5. Disease-Modifying Biologic
6. Disease-Modifying Small Molecule

2021–2022: Excitement and Controversy
Landmark Alzheimer’s drug approval confounds community

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

Medicare Officially Aduhelm to Patients

Officials cited data showing the new drug’s safety risks and may not help patients.

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

Woman’s brain hemorrhage while receiving Eisai’s widely heralded lecanemab heightens concerns over its safety.
Sex Difference in Lecanemab results?

<table>
<thead>
<tr>
<th></th>
<th>No. of Participants (placebo, lecanemab)</th>
<th>Favors lecanemab</th>
<th>Adjusted Mean Difference</th>
<th>Percent Slowing of Decline (%)</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>875,859</td>
<td>-0.45</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>ApoE4 Genotype Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Noncarrier</td>
<td>275,267</td>
<td>-0.75</td>
<td>41</td>
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<tr>
<td>Heterozygote</td>
<td>468,456</td>
<td>-0.50</td>
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<td>Homozygote</td>
<td>132,136</td>
<td>0.28</td>
<td>22</td>
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<td>Sex</td>
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<td>Female</td>
<td>464,443</td>
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<td>12</td>
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<td>Male</td>
<td>411,416</td>
<td>-0.73</td>
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<td>Age</td>
<td></td>
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</tr>
<tr>
<td>&lt;65</td>
<td>178,166</td>
<td>-0.08</td>
<td>6</td>
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<td>65-74</td>
<td>381,368</td>
<td>-0.37</td>
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<td>≥75</td>
<td>316,325</td>
<td>-0.72</td>
<td>40</td>
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<td>Ethnicity - Global</td>
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<td>Hispanic</td>
<td>108,107</td>
<td>-0.50</td>
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<td>Non-Hispanic</td>
<td>743,715</td>
<td>-0.46</td>
<td>25</td>
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<tr>
<td>Race - Global</td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>677,655</td>
<td>-0.49</td>
<td>27</td>
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<td>Asian</td>
<td>148,147</td>
<td>-0.35</td>
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<td>Black</td>
<td>24,20</td>
<td>-0.72</td>
<td>63</td>
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<td>Ethnicity – United States</td>
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<td>-0.53</td>
<td>113</td>
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<td>Non-Hispanic</td>
<td>356,354</td>
<td>-0.58</td>
<td>31</td>
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<tr>
<td>Race-United States</td>
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<tr>
<td>White</td>
<td>431,431</td>
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<td>36</td>
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<tr>
<td>Black</td>
<td>21,19</td>
<td>-0.55</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

Van Dyck et al., New England Journal of Medicine, 2023
Sex Difference in Aducanumab results?

**Haeberlein et al., 2022**

### Table: Aducanumab Results vs Placebo

<table>
<thead>
<tr>
<th>Laboratory ApoE status</th>
<th>No. of patients</th>
<th>Placebo decline</th>
<th>Aducanumab decline</th>
<th>Placebo vs Aducanumab</th>
<th>% Difference vs placebo</th>
<th>% Difference vs Aducanumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier (370, 365)</td>
<td></td>
<td>1.93</td>
<td>-0.53</td>
<td>-27%</td>
<td>-0.93</td>
<td>-27%</td>
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<tr>
<td>Noncarrier (178, 182)</td>
<td></td>
<td>1.30</td>
<td>0.08</td>
<td>6%</td>
<td>1.38</td>
<td>6%</td>
</tr>
<tr>
<td>Baseline clinical stage</td>
<td>MCI due to AD (448, 438)</td>
<td>1.53</td>
<td>-0.30</td>
<td>-20%</td>
<td>-1.83</td>
<td>-20%</td>
</tr>
<tr>
<td></td>
<td>Noncarrier (178, 182)</td>
<td>1.30</td>
<td>0.08</td>
<td>6%</td>
<td>1.38</td>
<td>6%</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>MMSE ≤ 27 (282, 250)</td>
<td>1.43</td>
<td>-0.27</td>
<td>-19%</td>
<td>-1.70</td>
<td>-19%</td>
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<tr>
<td></td>
<td>MMSE &gt; 26 (296, 297)</td>
<td>2.01</td>
<td>-0.51</td>
<td>-25%</td>
<td>-2.52</td>
<td>-25%</td>
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<tr>
<td>Baseline AD Medication Use</td>
<td>Yes (382, 385)</td>
<td>2.06</td>
<td>-0.36</td>
<td>-17%</td>
<td>-2.42</td>
<td>-17%</td>
</tr>
<tr>
<td></td>
<td>No (288, 282)</td>
<td>1.40</td>
<td>0.04</td>
<td>3%</td>
<td>1.44</td>
<td>3%</td>
</tr>
<tr>
<td>Region</td>
<td>United States (218, 216)</td>
<td>1.73</td>
<td>-0.55</td>
<td>-32%</td>
<td>-2.28</td>
<td>-32%</td>
</tr>
<tr>
<td></td>
<td>Europe/Canada (287, 291)</td>
<td>1.86</td>
<td>-0.16</td>
<td>-9%</td>
<td>1.70</td>
<td>-9%</td>
</tr>
<tr>
<td></td>
<td>Asia (43, 40)</td>
<td>1.46</td>
<td>-1.19</td>
<td>-82%</td>
<td>0.27</td>
<td>-82%</td>
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<tr>
<td>Age</td>
<td>≤ 64 (104, 113)</td>
<td>1.76</td>
<td>-0.26</td>
<td>-15%</td>
<td>1.50</td>
<td>-15%</td>
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<tr>
<td></td>
<td>65-74 (255, 257)</td>
<td>1.50</td>
<td>-0.19</td>
<td>-13%</td>
<td>1.39</td>
<td>-13%</td>
</tr>
<tr>
<td></td>
<td>≥ 75 (188, 177)</td>
<td>1.97</td>
<td>-0.81</td>
<td>-41%</td>
<td>1.16</td>
<td>-41%</td>
</tr>
</tbody>
</table>

### Graphs: Adjusted Mean Change

**CDR-SB adjusted mean change vs placebo**

**MMSE adjusted mean change vs placebo**
Sex Difference in Efficacy of Immunotherapies?

Gender-associated factors

Health-seeking behavior
  Reporting
  Access

Greater efficacy of biologics that **stimulate** immune function (e.g., vaccines)

Females/Women

Genes
  Sex steroids

Sex-related factors

Greater efficacy of biologics that **repress** immune function (e.g., checkpoint inhibitors, TNF inhibitors)

Males/Men

Klein & Morgan, Biology of Sex Differences, 2020
Table 1. Anticancer agents with relevant differences in clearance between men and women

<table>
<thead>
<tr>
<th>Class/drug, name</th>
<th>Indication</th>
<th>n (men)/ (women)</th>
<th>Variability on CL (CV%)</th>
<th>Relative change in women versus men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiogenesis inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab [48, 49]</td>
<td>Gastric cancer; solid tumours</td>
<td>1101/949</td>
<td>26%</td>
<td>CL</td>
</tr>
<tr>
<td><strong>Antineoplastic agents: antimetabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil [50, 51] and metabolite</td>
<td>GI malignancies; metastatic colorectal cancer</td>
<td>74/42</td>
<td>22%–40%</td>
<td>CL, CLmet</td>
</tr>
<tr>
<td><strong>Myeloblastic agents</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan [52]</td>
<td>Marrow transplantation</td>
<td>904/689</td>
<td>22%</td>
<td>V</td>
</tr>
<tr>
<td><strong>Antineoplastic agent: alkylating agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide [53, 54]</td>
<td>Glioma, glioblastoma, melanoma</td>
<td>303/177</td>
<td>5%–10%</td>
<td>CL</td>
</tr>
<tr>
<td>Mephalan [55]</td>
<td>Advanced malignancies</td>
<td>22/42</td>
<td>45%</td>
<td>CL</td>
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<tr>
<td>Tacibedrin [56]</td>
<td>PD study</td>
<td>232/467</td>
<td>51%</td>
<td>V, Keo</td>
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<tr>
<td><strong>Antineoplastic agents: alkaloids</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Paclitaxel [57, 58]</td>
<td>Solid tumours</td>
<td>159/160</td>
<td></td>
<td>CL, Vmax</td>
</tr>
<tr>
<td>Irinotecan (SN38) [59–61]</td>
<td>Solid tumours, glioblastoma</td>
<td>67/58</td>
<td>47%</td>
<td>CL</td>
</tr>
<tr>
<td><strong>Antineoplastic agent: antibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab [62]</td>
<td>Lymphoma</td>
<td>16/13</td>
<td>19%</td>
<td>CL</td>
</tr>
</tbody>
</table>

CL, total clearance; CLfu, clearance of the unbound fraction; V, volume of distribution; Vfu, volume of distribution of the unbound fraction; Vmax, maximal metabolism 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

- **Male-Specific Drivers** (underline)
- **Female-Specific Drivers**
- **Shared Genetic Drivers**

- Amyloid
- Tau
- Brain Atrophy
- Cognitive Impairment
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
rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex.
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
  - Likely through regulation of neutrophils
- 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**

### RNA and Protein Expression Summary

<table>
<thead>
<tr>
<th>Tissue</th>
<th>RNA expression (TPM)</th>
<th>Protein expression (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td></td>
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<tr>
<td>Endocrine tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow &amp; immune system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver &amp; gallbladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; urinary bladder</td>
<td></td>
<td></td>
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<tr>
<td>Male tissues</td>
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<td>Female tissues</td>
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<tr>
<td>Adipose &amp; soft tissue</td>
<td></td>
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<tr>
<td>Skin</td>
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</table>

**SERPINB1 Staining in AD Cortex**

![Image of SERPINB1 staining in AD Cortex](image_url)
Sex-Specific Drivers of Resilience

Sex differences in the association between AD biomarkers

Original Research

Published: 03 February 2016

Mary Ellen L. Koran, N Initiative

Brain Imaging and Beh

Accesses: 11

Sex-Specific Drivers of Resilience

Sex differences in the genetic predictors of Alzheimer’s pathology


David A Bennett, Julie

Source: JAMA Neurol. 2

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. Engelma... Show more

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

Published: 13 May 2022 Article history

Brain, Volume 142, Iss 20 July 2019

Published: 20 July 2019 Article history

Share
Incorporating Sex Differences into Transcriptomic Discovery
Sex-Specific Changes in Transcription during Aging

Sanfilippo et al., Neuroscience, 2019
Sex-Specific Drivers of Tangle Pathology

Gene Expression Association with Neurofibrillary Tangles in Prefrontal Cortex

Michelle Clifton, MA

Clifton et al., In Preparation
Sex-Specific Drivers of Tangle Pathology

HDAC6 is implicated in Tau Pathogenesis and Regulated by Estrogen

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

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

Clifton et al., In Preparation
Precision Medicine through Collaboration

**Sex-Specific Discovery in Mouse**

**Sex-Specific Discovery in Human Brain**

Protocol Alignment

Identify Consensus Candidates Human and Mouse Brain

Genomic Association with AD Endophenotypes

Bioinformatic Filtering for Druggability & Known Therapeutics

RNA Scope Validation

Sex-Specific Mechanistic Exploration in Mouse

- APOE
- SERPINB6
- KDM6A
- ??
- ??
# Cell + Sex-Specific Drivers of Tangles

## Pathway Enrichment Results

<table>
<thead>
<tr>
<th>Pathway</th>
<th>m (S)</th>
<th>m (C)</th>
<th>p</th>
<th>pL (S)</th>
<th>pL (C)</th>
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<tr>
<td>cellular macromolecule metabolic process</td>
<td>2518</td>
<td>342</td>
<td>231.76</td>
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<td>intracellular transport</td>
<td>1360</td>
<td>211</td>
<td>125.17</td>
<td>1.69</td>
<td>4.47E-12</td>
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<td>adaptive immune response</td>
<td>659</td>
<td>16</td>
<td>60.65</td>
<td>.26</td>
<td>5.07E-11</td>
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<td>establishment of localization in cell</td>
<td>1752</td>
<td>250</td>
<td>161.25</td>
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<td>9.17E-11</td>
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<td>ribonucleoprotein complex biogenesis</td>
<td>449</td>
<td>91</td>
<td>41.33</td>
<td>2.20</td>
<td>1.67E-10</td>
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<td>establishment of protein localization</td>
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<td>192</td>
<td>116.61</td>
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<td>2.61E-10</td>
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<td>protein transport</td>
<td>1179</td>
<td>181</td>
<td>108.51</td>
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<td>CLEC4F</td>
<td>6606</td>
<td>742</td>
<td>608.01</td>
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<td>cellular localization</td>
<td>2655</td>
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<td>SDF4</td>
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<td>NOC2L</td>
<td>6710</td>
<td>742</td>
<td>617.58</td>
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<td>MYSM1</td>
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<td>176.62</td>
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<td>27.89</td>
<td>2.29</td>
<td>2.14E-08</td>
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<td>256</td>
<td>177.18</td>
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Wu et al., In Preparation
### Subject and cohort counts for each domain:

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[Neuroimaging Coming 2023](https://dss.niagads.org/)

[Vascular Risk Factors Coming 2023](https://dss.niagads.org/)
Sex-Stratified Memory GWAS

rs2590395 is eQTL for SERPINB2 and SERPINB10 in Blood

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