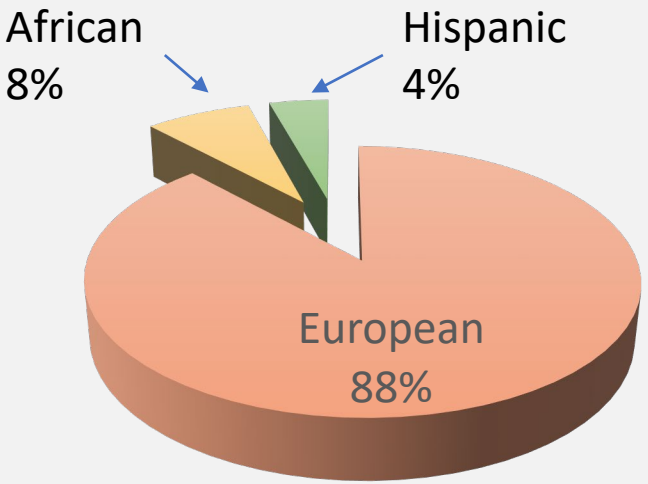
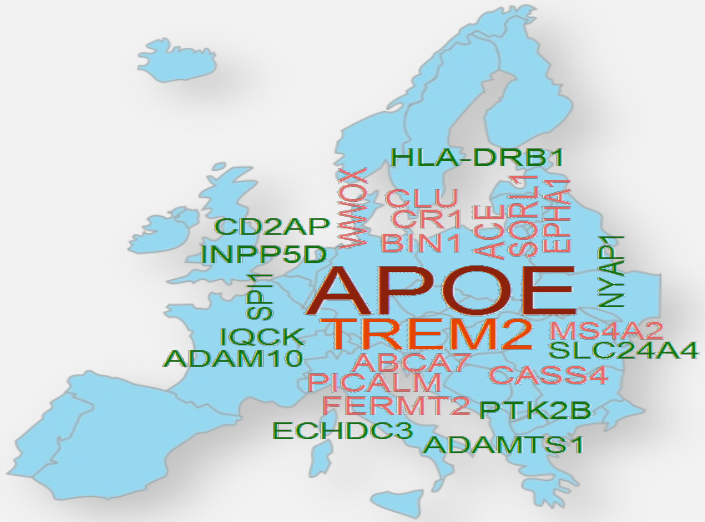
Background

Alzheimer's Disease Sequencing Project (ADSP)

The overarching goals of the ADSP are to:

- **Identify new genes and genetic variations that contribute to increased risk for or protection against AD/ADRD**
- Provide insight as to why these genes and variations impact AD/ADRD
- **Identify potential avenues or approaches to transform genetic results into meaningful therapeutic targets for further development.**

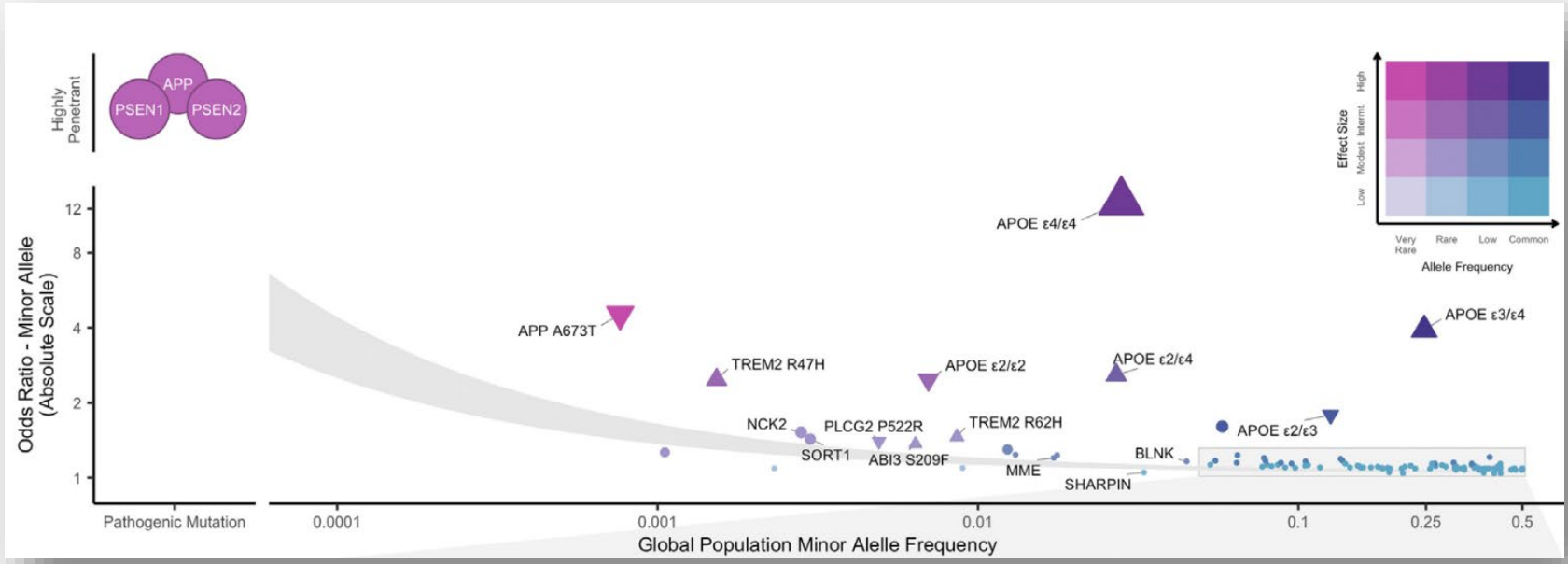




Research Progress

Alzheimer Disease Genetics: Recent Accomplishments

- Alzheimer Disease (AD) is a genetic disease that is between 70 and 80% heritable.
- **More than 80 regions of the genome contain risk factor genes for late-onset AD.**
- AD is not one entity; it is a genetic spectrum with a number of sub-phenotypes.
  - Early Onset and Late Onset AD are parts of a genetic continuum.
- **There are a few strong and common protective variant signals in the AD genome.**
- Many signals are rare or very rare variants are located in “non-coding” regions of the genome.
- **Pathways such as inflammation, lipid metabolism, endocytosis, and amyloid deposition are an important part of the etiology of the disease.**
- **Ancestral background plays an important role in AD risk and protection.**
- Important factor in determining risk and protection for AD.



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Clinical Progress

Genetically Driven NIA Supported Clinical Trials

INVOKE-2: Phase 2 clinical trial

Reduction in *TREM2* functionality may lead to AD and other forms of dementia.

- TREM2 is a transmembrane receptor expressed on a subset of innate immune cells and selectively on microglia.
- Evaluating the efficacy and safety of AL002, the first product candidate targeting *TREM2*.
- AL002 aims to counteract decreased functionality by optimizing TREM2 signaling to improve cell survival and proliferation, and activity of microglia.

APOE2 Phase 1/2 Clinical Trial

Gene Therapy for APOE4 Homozygotes of Alzheimer's Disease
– Using AAV 10 vector to transfer ApoE2 cDNA into CSF/CNS of 15 patients. Phase 1/2, Cornell Medical Center
– No substantial side-effects reported
-Decrease of initial CSF biomarkers

APOLLOE4: Phase 3 clinical trial

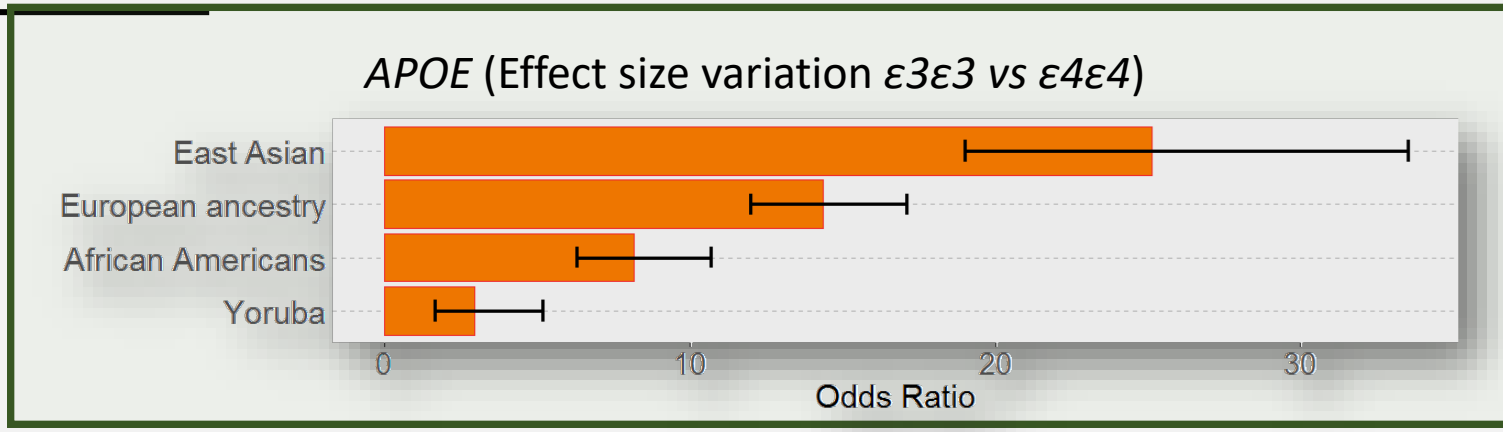
People with two copies of *APOE4* are at significantly elevated risk for developing AD.

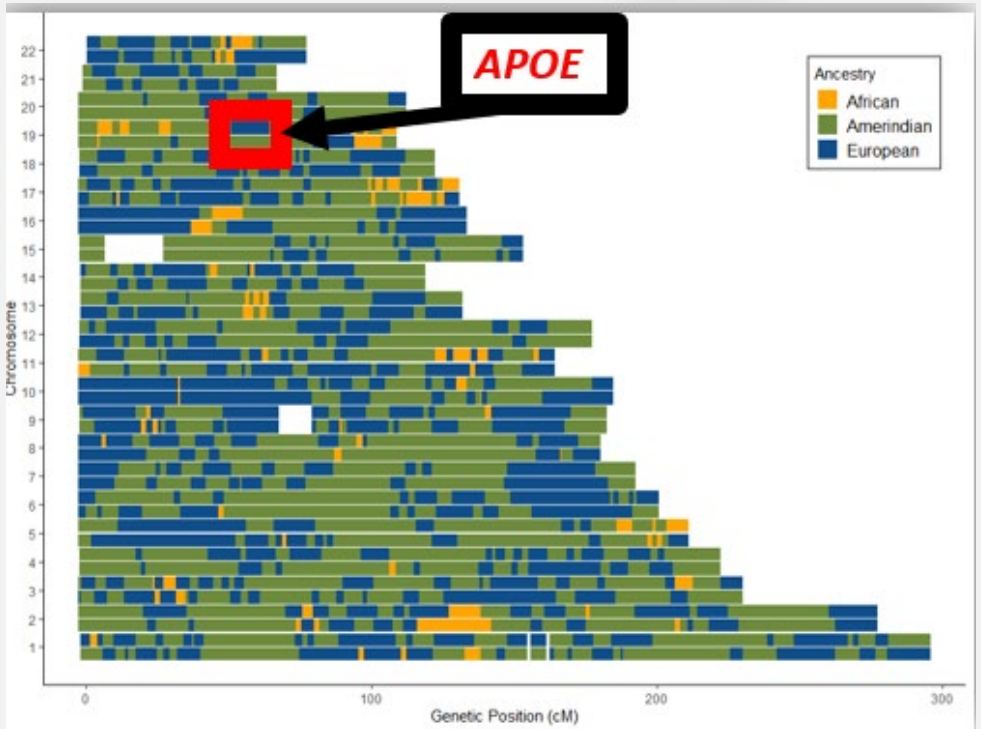
- Evaluating effects of the experimental drug ALZ-801 in older adults with early AD and two copies of the *APOE4* allele.
- ALZ-801 is designed to slow the progression of AD by reducing amyloid deposits, a hallmark of AD.

Discoveries

Ancestry-Related Variations in AD Genetic Studies*

- The *APOE*4 allele has a heterogeneous AD risk effect across diverse ancestral populations.
- The difference in risk between European and African ancestries for *APOE4* is due to differences between the local ancestry region surrounding *APOE*.
- AD patients with African Local Ancestry express significantly lower levels of *APOE* compared *APOE4* carriers with European Local Ancestry.
- These differences in *APOE4* expression could contribute to the reduced risk for AD seen in African *APOE4* carriers.

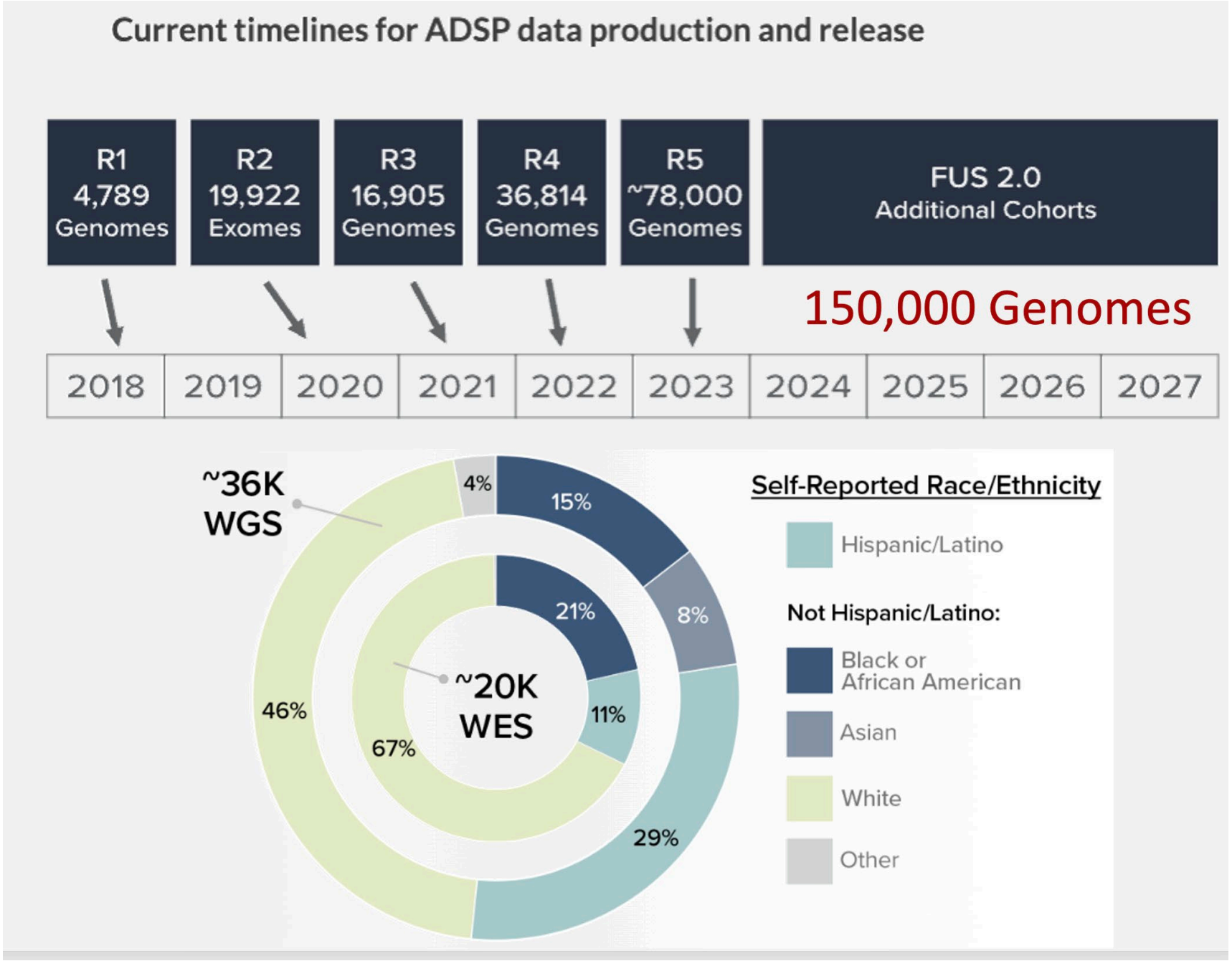




*Rajabli et al., Hendrie et al., Blue et al., Griswold et al.

CHALLENGES

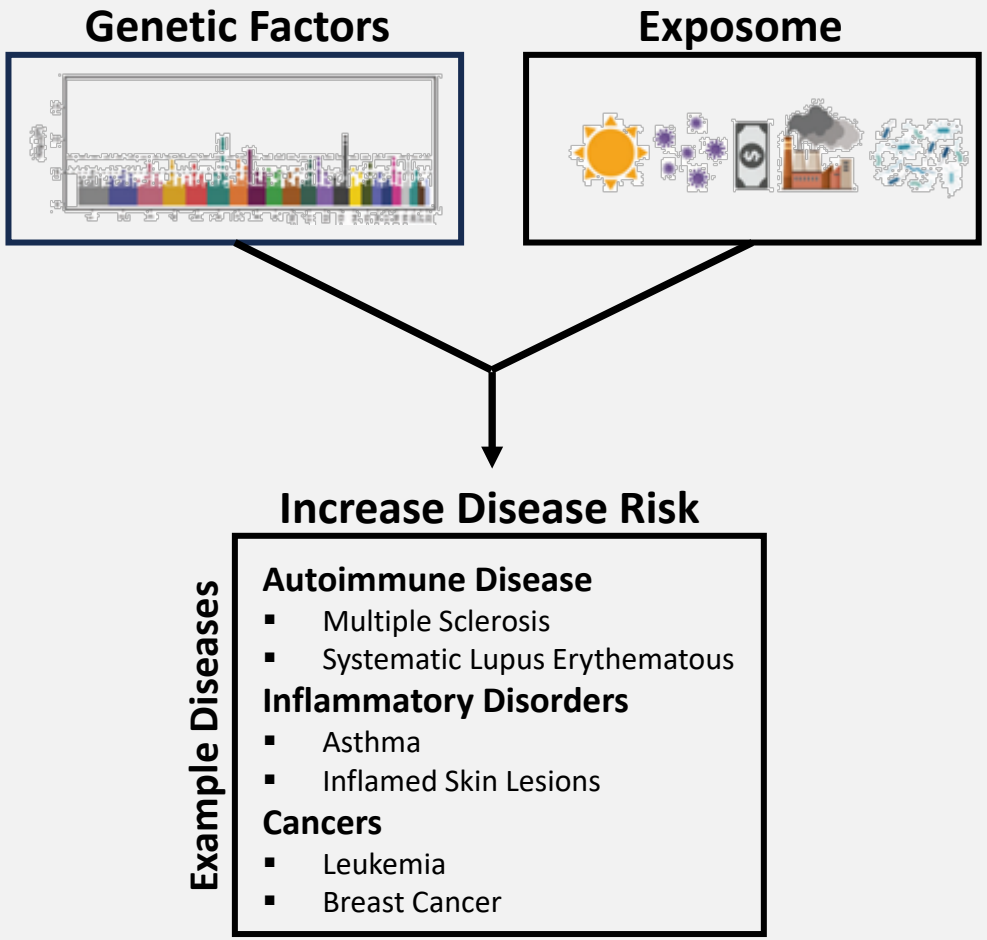
Pathway Towards Inclusion: Increasing Diversity



CHALLENGES

Integrating Genetics and Exposome to Advance AD Research

- **The Exposome in Alzheimer Disease,**
  - Encompasses all non-genetic factors: social, behavioral, environmental, etc.
- **Interplay of Genetics and Exposome is important for**
  - Developing comprehensive AD risk models
  - Assessing factors contributing to cognitive resilience
  - Identifying interactions between exposome and genetics that affect AD risk and progression
- **Implications for Treatment and Prevention**,
  - Emphasizing prevention strategies including exposome modifications
  - Aiming for early detection and personalized intervention approaches



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Future Efforts

Key Components for Addressing Alzheimer Disease

adsp
Alzheimer's Disease Sequencing Project

- Genetics
  - -Biomarkers
- Functional Genomics
- Diversity
- Artificial Intelligence

Social

Behavioral

Environmental