



Genedex: a tool for unifying Alzheimer's disease

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INTRODUCTION

A multifactorial disease

Alzheimer's disease (AD) is driven by multiple interacting processes, including amyloid and tau pathology, neuroinflammation, and cell-specific responses that vary across disease stages and individuals.

The challenge



Fragmented signatures:
AD gene signatures are fragmented across studies.



Difficult interpretation:
Biological interpretation is challenging.

Aims



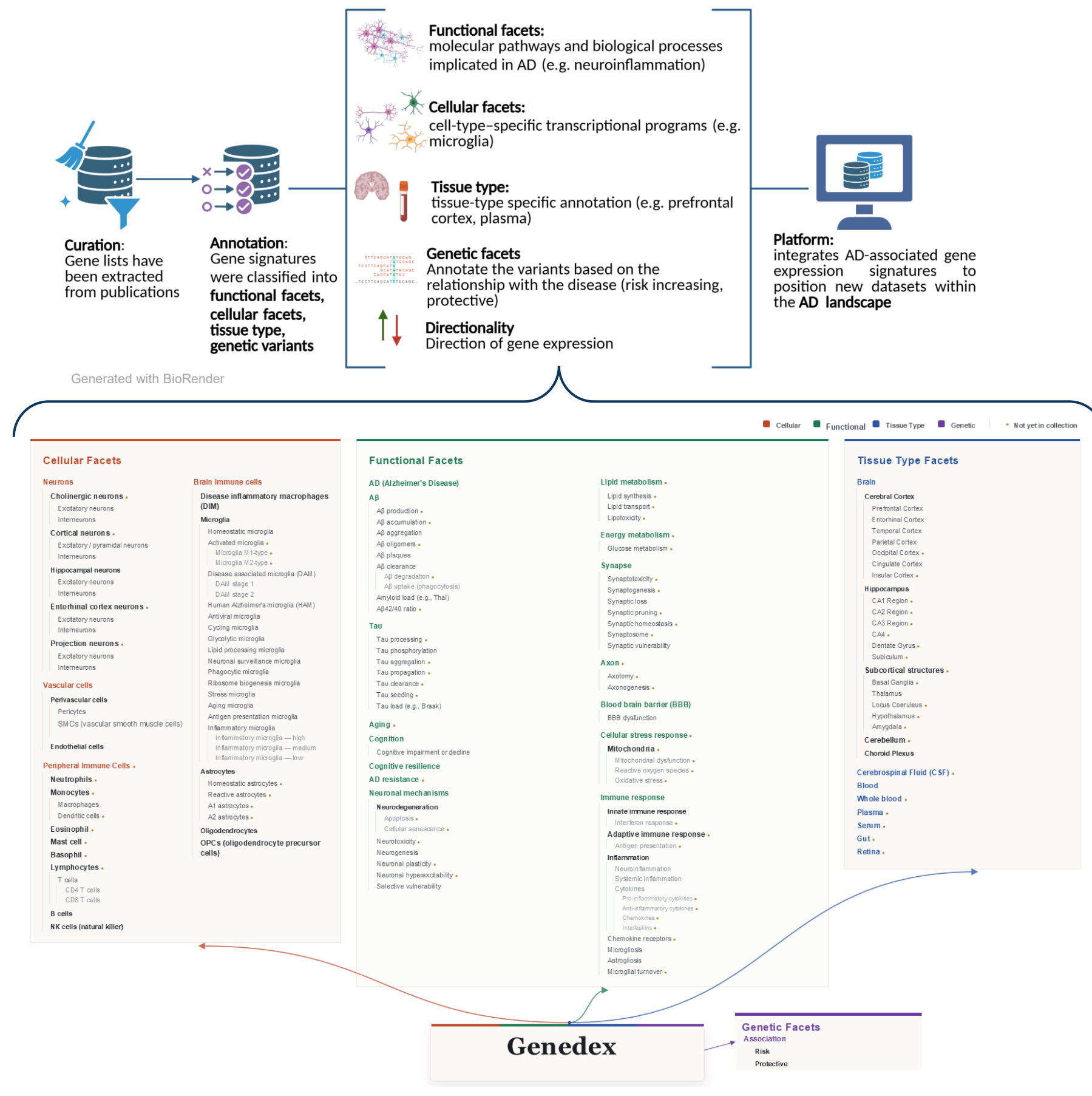
Integrate representative AD facets, defined as functional and cellular features of AD, across studies into a **unified reference framework**.



Demonstrate Genedex functionality using a list of resilience-associated genes as a case study [1].

METHODS

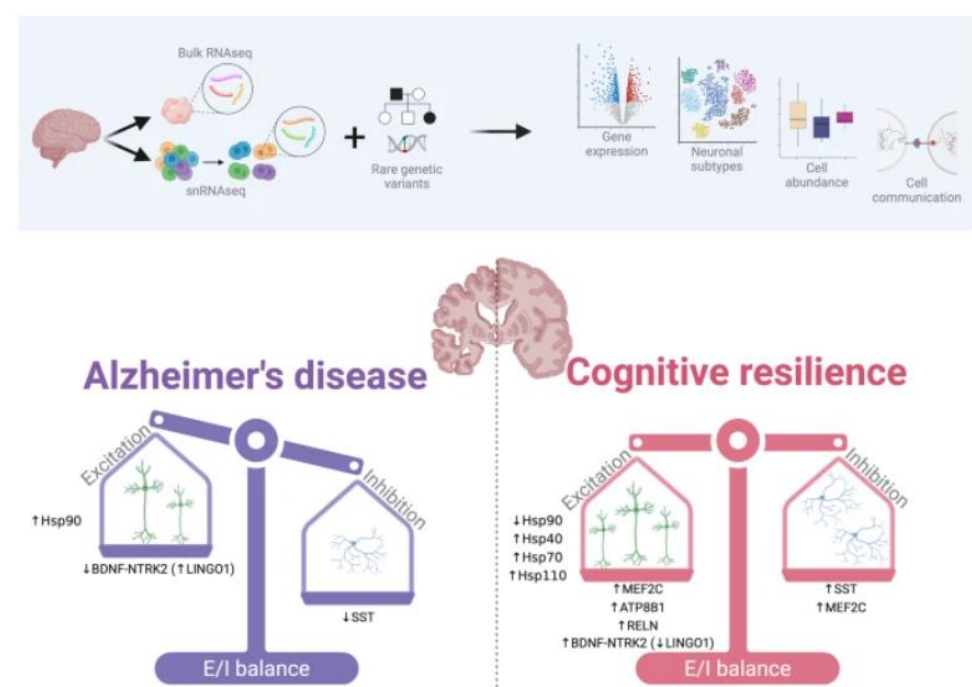
Study design



Case study

How do resilience-associated genes relate to AD pathology?

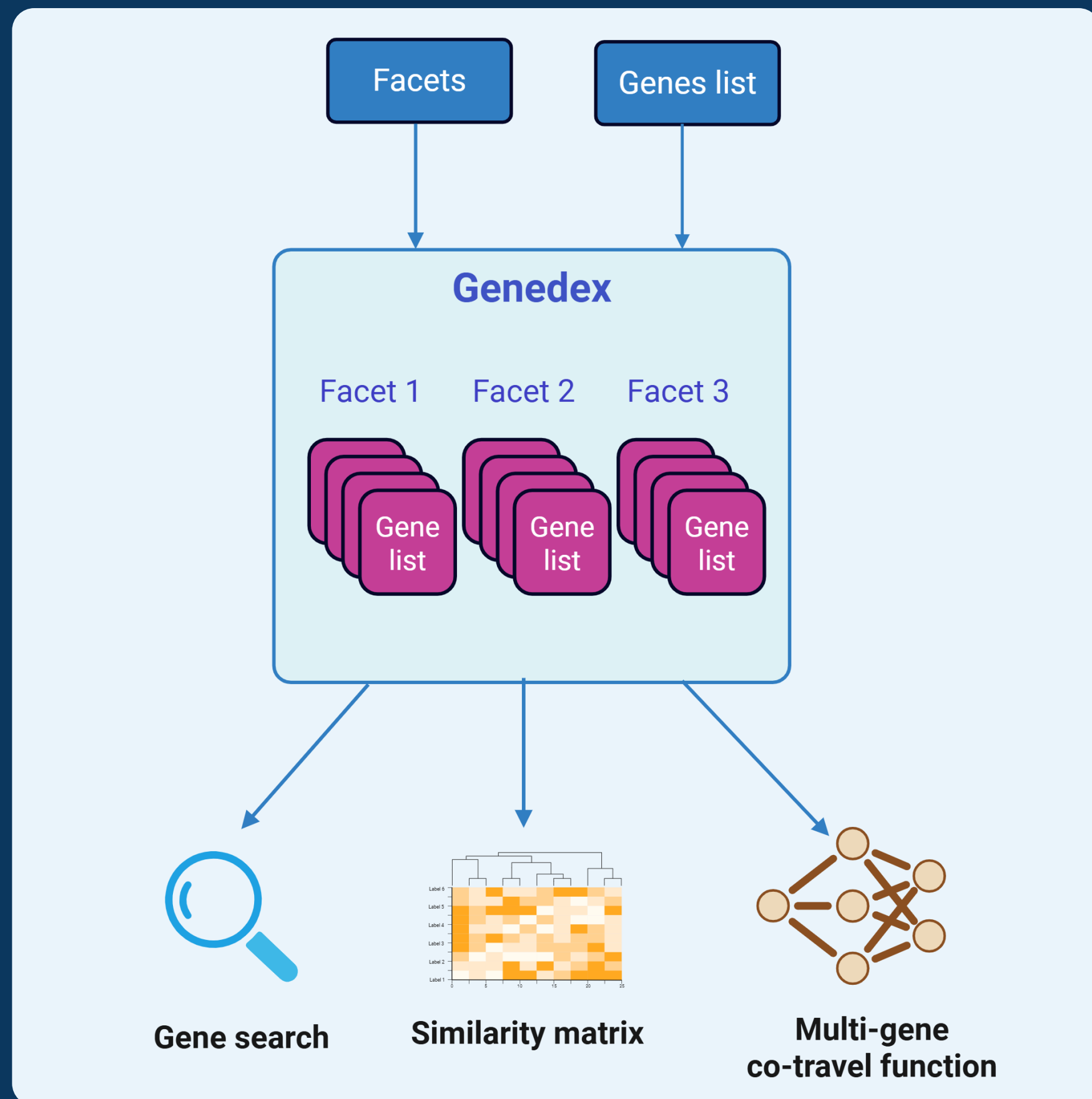
We queried Genedex with resilience-associated genes from Castanho and Naderi et al. (2025) and compared them with published signatures of neuritic plaque burden, tau burden, A β aggregation, and A β clearance, including cell-specific datasets.



Graphical abstract from Castanho & Naderi et al. [1]

Where does my gene list fit in Alzheimer's disease biology, and what relationships can it reveal?

Genedex is a reference framework for exploring functional and cellular features (“facets”) of AD.

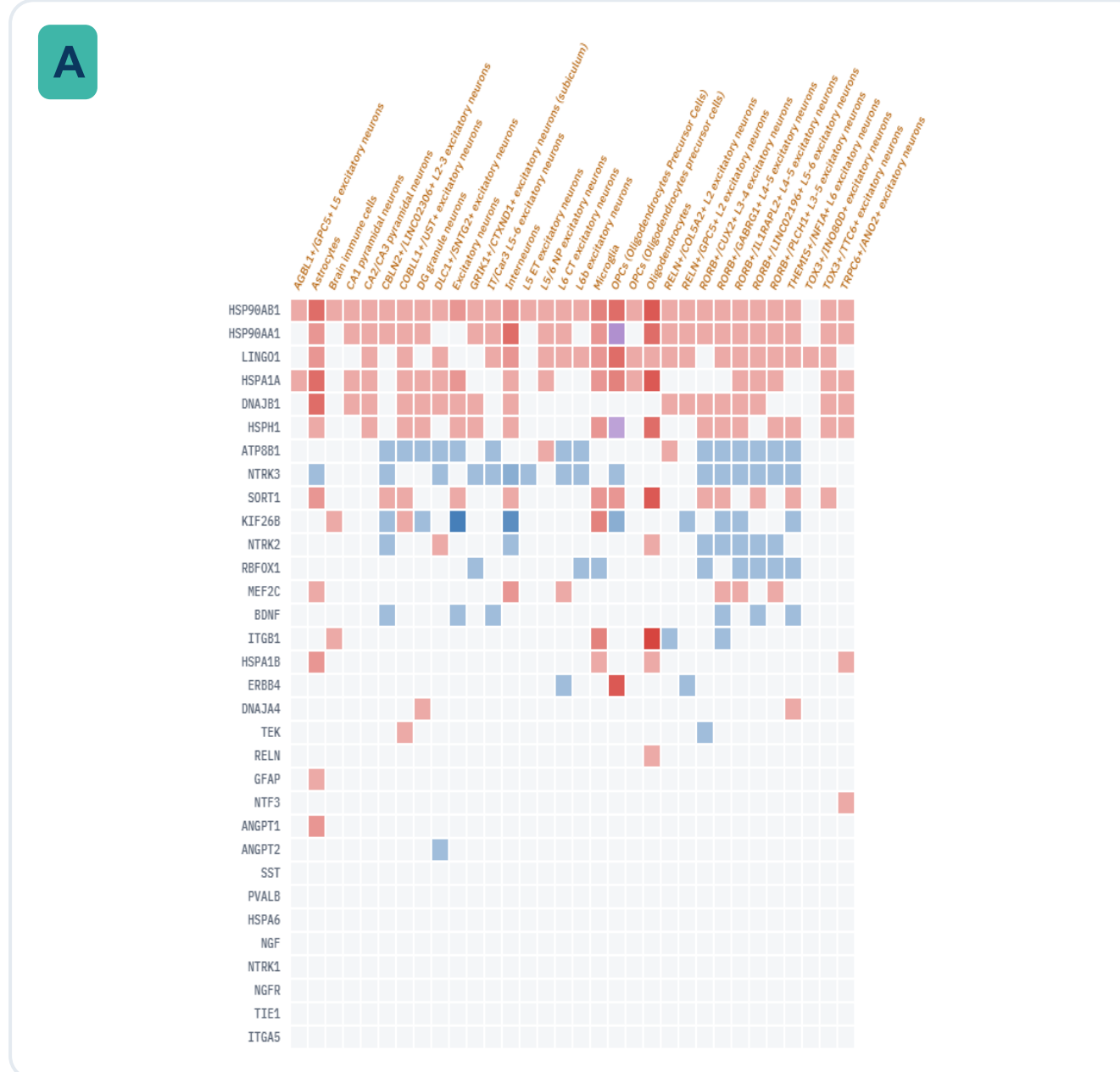


Genedex was queried with resilience-associated genes to investigate their relationship to AD pathology.

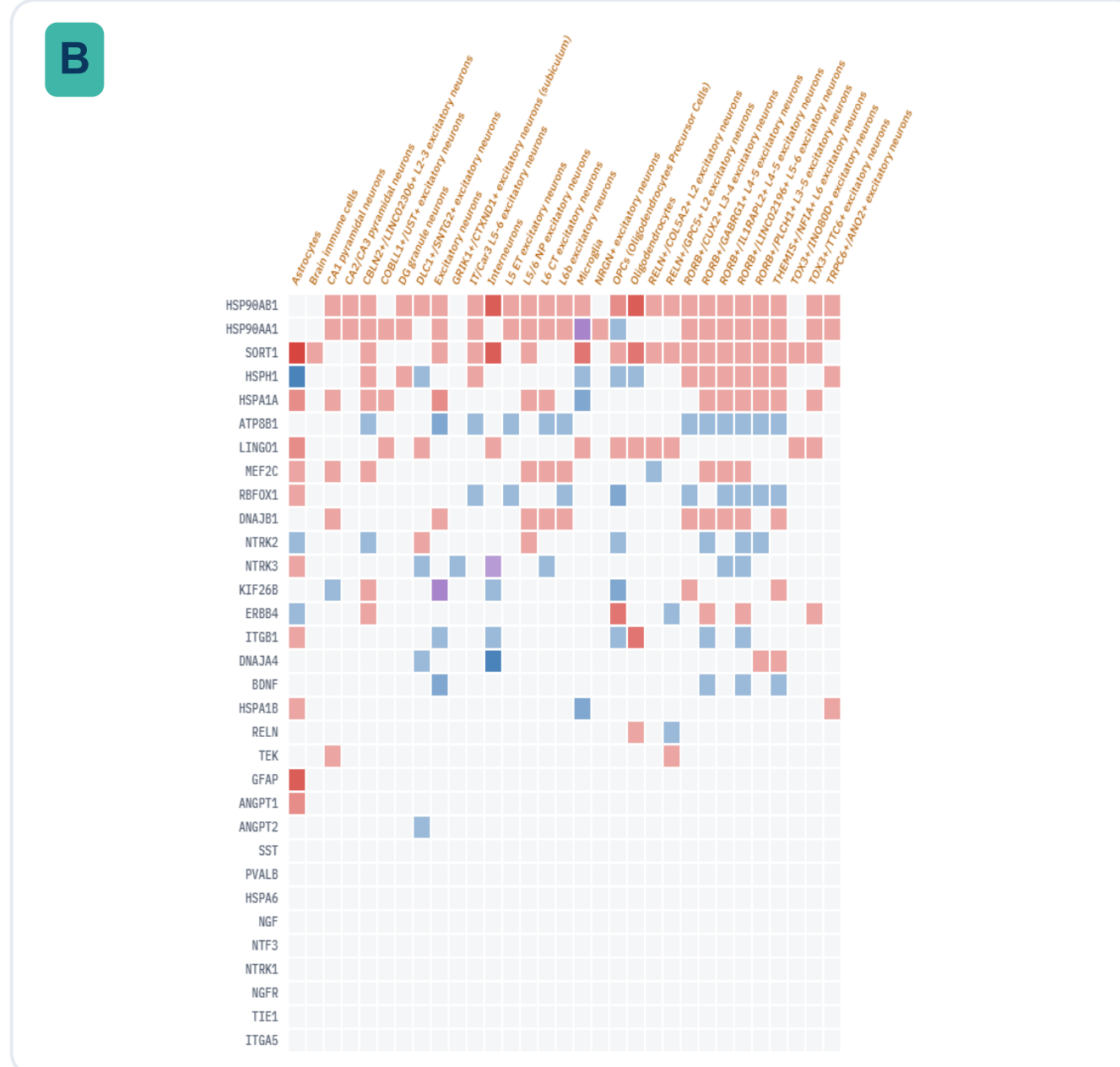
Heat shock chaperones *HSP90AA1/AB1* showed consistent positive associations with tau burden and amyloid pathology across multiple cell types, but opposite associations with A β clearance.

RESULTS

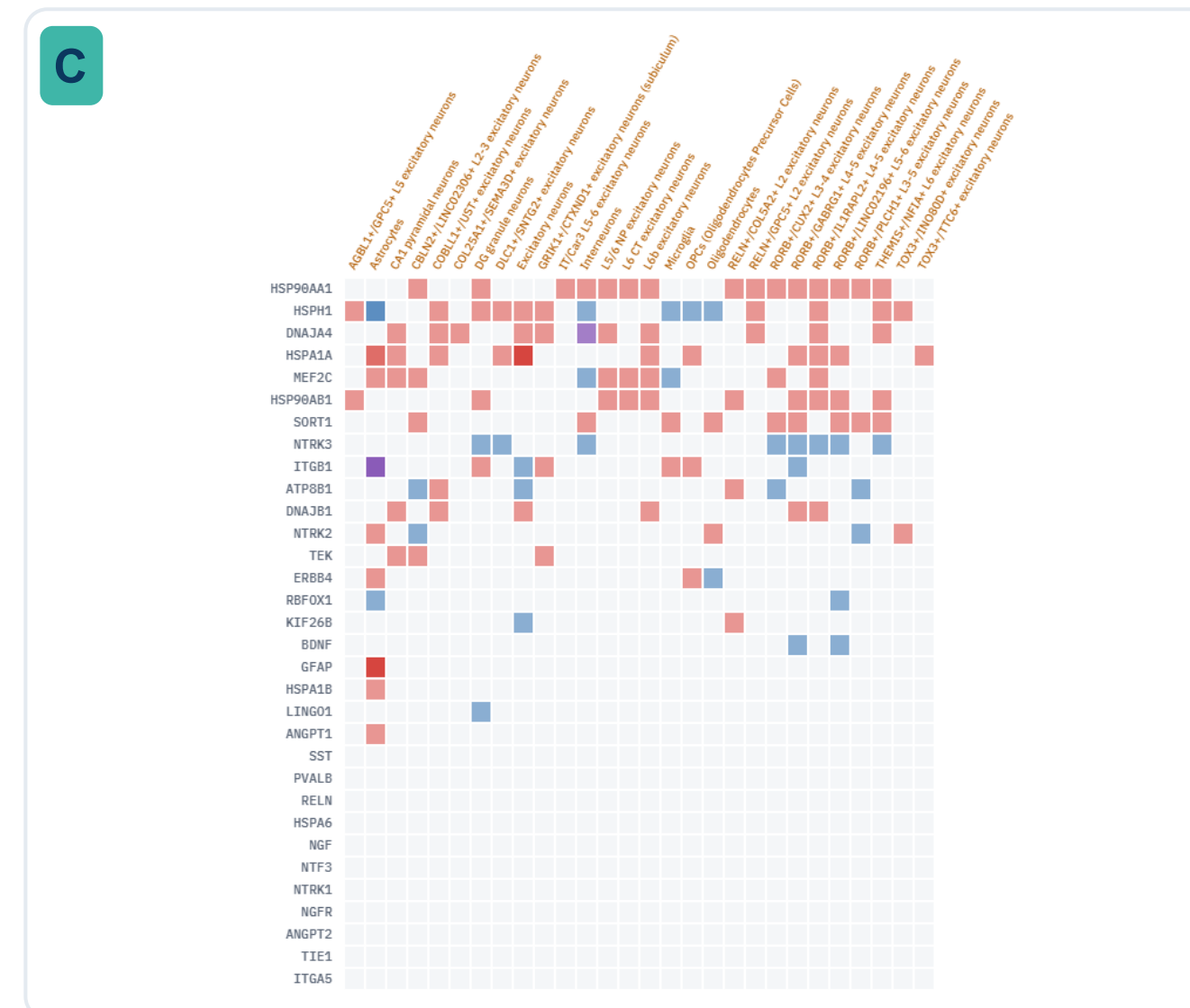
Up-regulated Down-regulated Mixed Not present



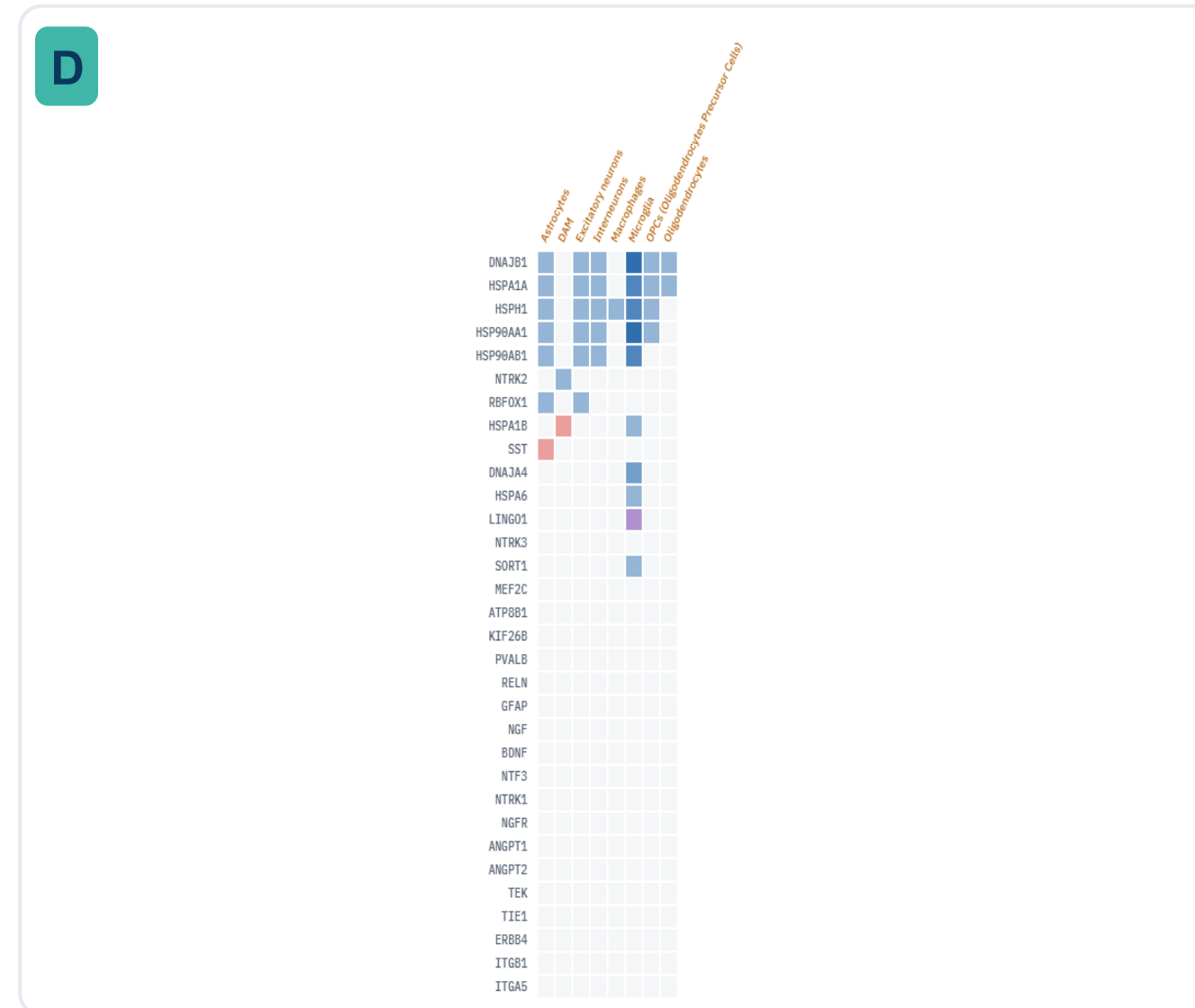
List-membership of the resilience-associated genes across cell-type facets restricted to gene lists associated with tau pathology burden. Colour intensity scales with the total number of lists in which the gene appears under each facet. The heat-shock chaperone cluster (*HSP90AA1/AB1*, *HSPA1A*, *DNAJB1*) shows a broad, consistent positive association across nearly every cell type tested, while protective markers *RBFOX1* and *KIF26B* trend negative across several excitatory neuronal subtypes.



List-membership of the resilience-associated genes across cell-type facets restricted to gene lists associated with amyloid load. Colour intensity scales with the total number of lists in which the gene appears under each facet. The heat-shock chaperones *HSP90AA1/AB1* show broader and consistent positive association as shown with tau, including in glial cell types where *HSPH1* appears in the opposite direction in glial cells, a divergence from its tau-associated pattern, suggesting some chaperone signals might be tau-driven rather than generically pathology-driven.



List-membership of the resilience-associated genes across cell-type facets restricted to gene lists associated with A β aggregation. Colour intensity scales with the total number of lists in which the gene appears under each facet. The heat-shock chaperone cluster (*HSP90AA1/AB1*, *HSPA1A*, *DNAJB1*) shows a broad positive association, except for *HSPH1*, which, as with amyloid load, shows a downregulation in glial cells. *LINGO1*, robustly positive in association with amyloid and tau load, nearly disappears, indicating its association may be specific to more advanced pathology rather than early diffuse A β deposition.



List-membership of the resilience-associated genes across cell-type facets restricted to gene lists associated with A β clearance. Colour intensity scales with the total number of lists in which the gene appears under each facet. The chaperone cluster that was consistently up-regulated with pathology burden (*HSP90AA1/AB1*, *HSPA1A*, *DNAJB1*) flips to consistently down-regulated here, suggesting these chaperones may track proteostatic stress from unresolved pathology rather than actively drive its clearance. SST, hypothesised in the paper to promote A β degradation and clearance, shows a positive signal with clearance in astrocytes.

CONCLUSIONS

Take-home message

Heat-shock chaperones show broad positive associations with amyloid and tau burden, but negative associations with A β clearance, suggesting these genes may reflect unresolved proteostatic stress caused by pathology rather than driving its clearance.

Impact

Genedex provides a **unified, facet-structured framework** for comparing AD-associated gene lists and programs across datasets, cell types, and disease mechanisms.

Future directions

Genedex is being expanded with **AI-supported curation and interpretation** to enable scalable updates, automated annotation, and hypothesis-driven exploration.

REFERENCES

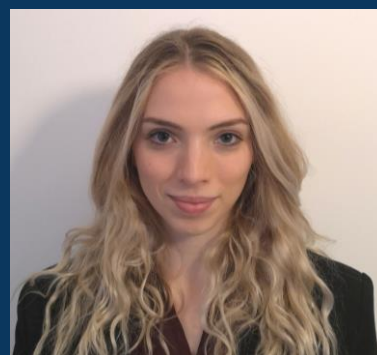
[1] Castanho I, Naderi Yeganeh P, Boix CA, Morgan SL, Mathys H, Prokopenko D, White B, Soto LM, Pegoraro G, Shah S, Ploumakis A, Kalavros N, Bennett DA, Lange C, Kim DY, Bertram L, Tsai LH, Kellis M, Tanzi RE, Hide W. Molecular hallmarks of excitatory and inhibitory neuronal resilience to Alzheimer's disease. Mol Neurodegener. 2025 Oct 1;20(1):103. doi: 10.1186/s13024-025-00892-3. PMID: 41035073; PMCID: PMC12487324.

FUNDERS



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Title: Cellular And Spatial Signatures Of Resilience And Resistance To Alzheimer'S Disease In Centenarian Brains
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