

SHARED GENETIC NETWORKS DRIVING NEURODEGENERATION ACROSS THE LIFESPAN

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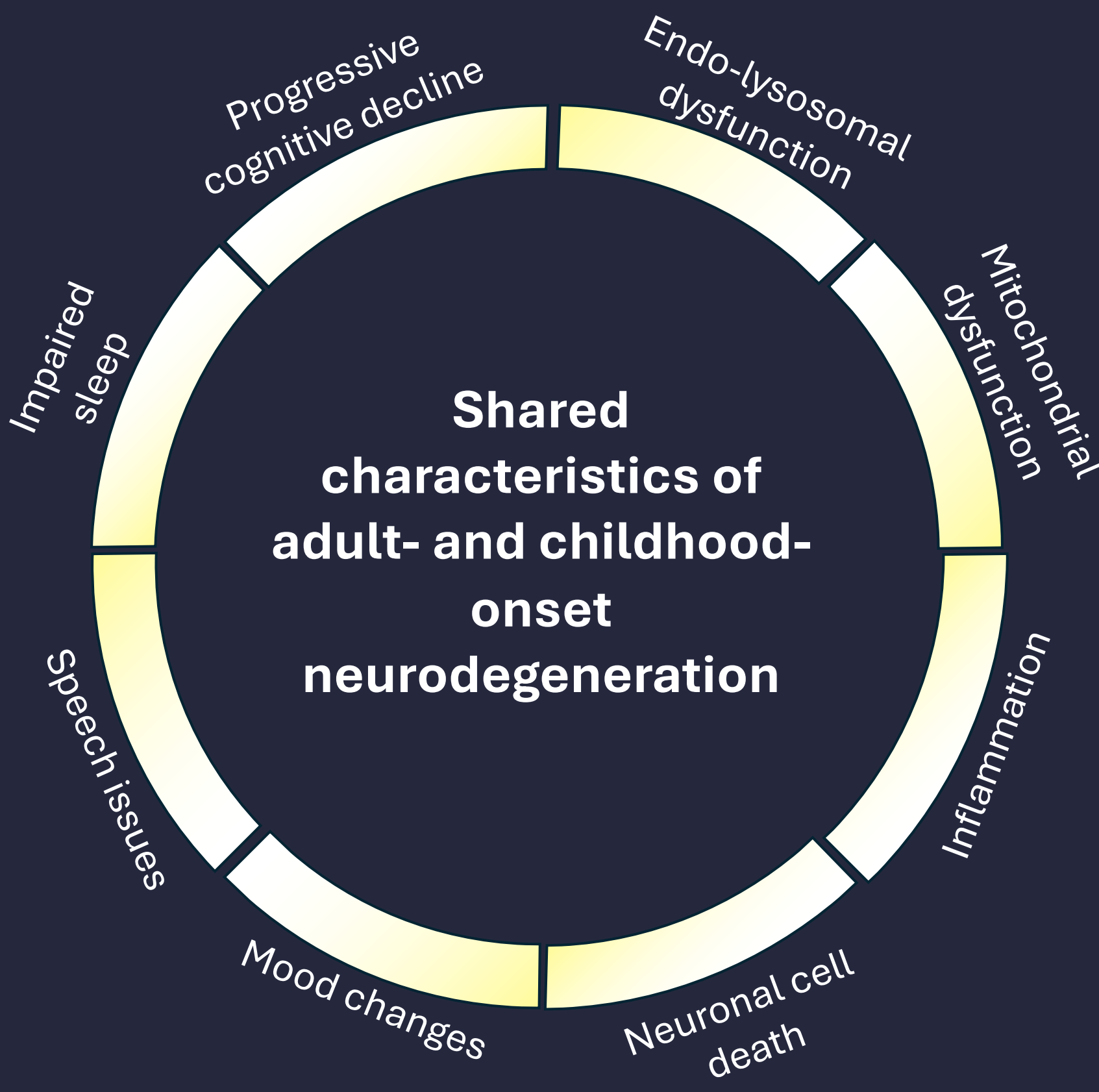
Adult- and childhood-onset neurodegenerative diseases are related

Adult- and childhood-onset neurodegenerative diseases (NDDs) represent a significant global health challenge, sharing common clinical features, molecular, and cellular pathologies.

Currently, there are limited, if any, effective therapeutic options available for either adult- or childhood-onset NDDs.

Our understanding of causative mechanisms for adult-onset NDDs is often concentrated on popular, well-characterised targets, frequently neglecting lesser-studied pathways.

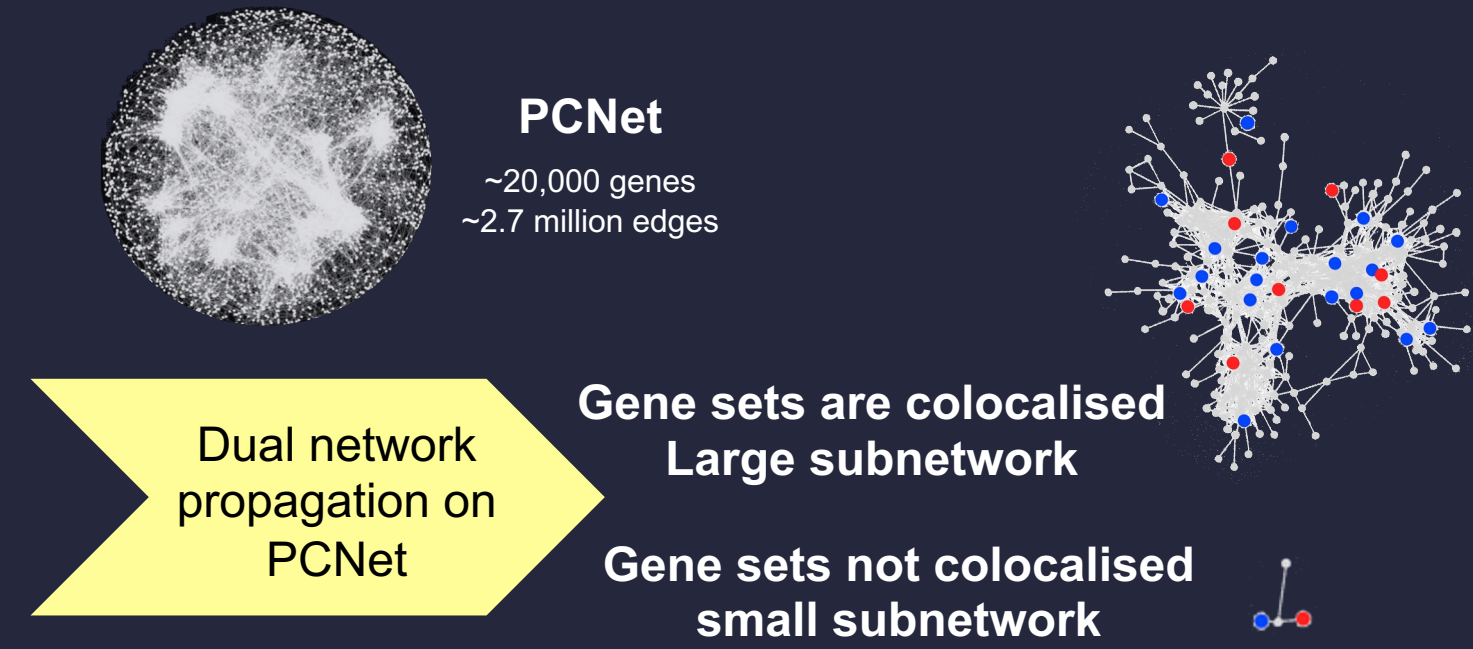
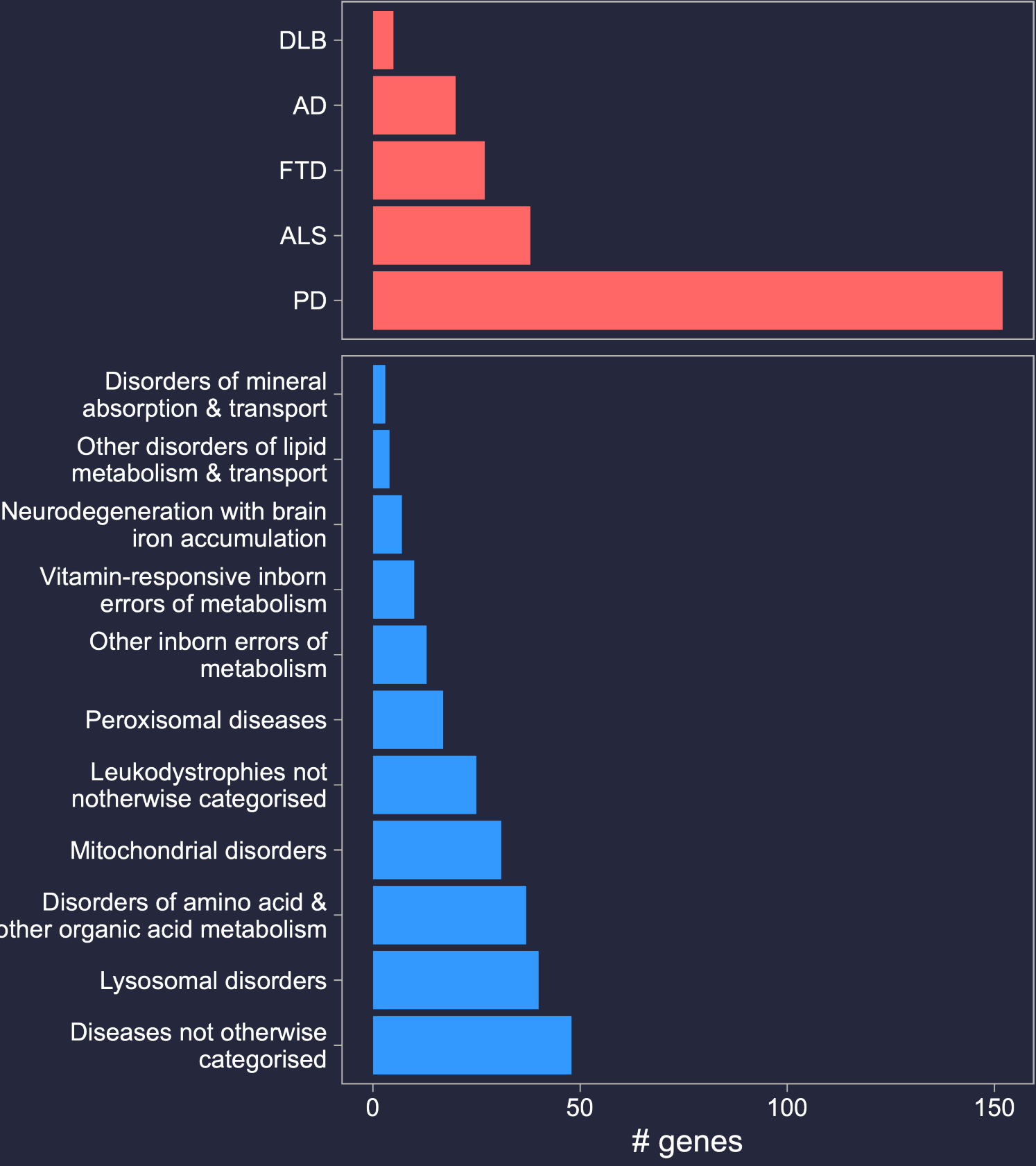
Critically, there has been no systematic attempt to identify and leverage the biological commonalities between these two distinct disease groups.



Our objective is to bridge this gap by identifying shared genetic architecture between adult- and childhood-onset neurodegenerative diseases to uncover novel, convergent pathways for therapeutic development.

Genetic network analysis can identify the relationship between diseases

Adult-onset neurodegenerative disease genes were sourced from Genome-Wide Association Studies (GWAS) focused on clinically ascertained cases for AD, PD, DLB, FTD, and ALS, intentionally excluding parental proxy GWAS to maintain data quality. The childhood dementia genes and their classifications were also obtained. We then employed a network colocalisation approach (*NetColoc*) to identify significant genetic overlap between the input gene lists within the context of the *PCNet* molecular interaction network.

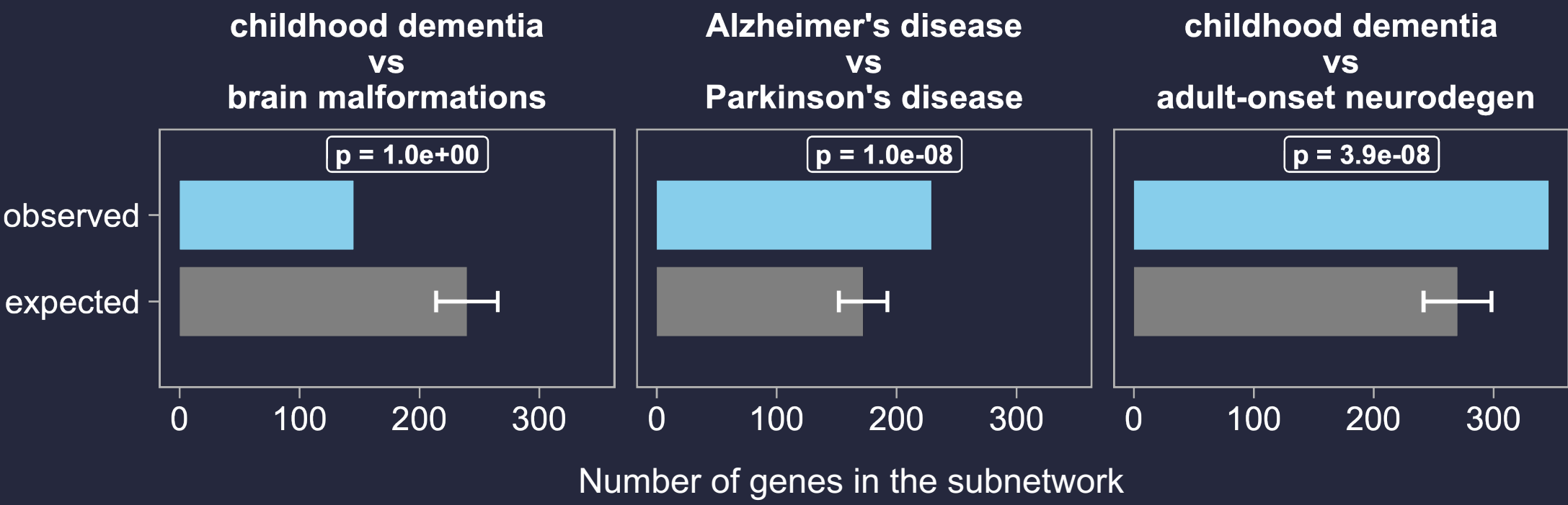


Gene list sources:

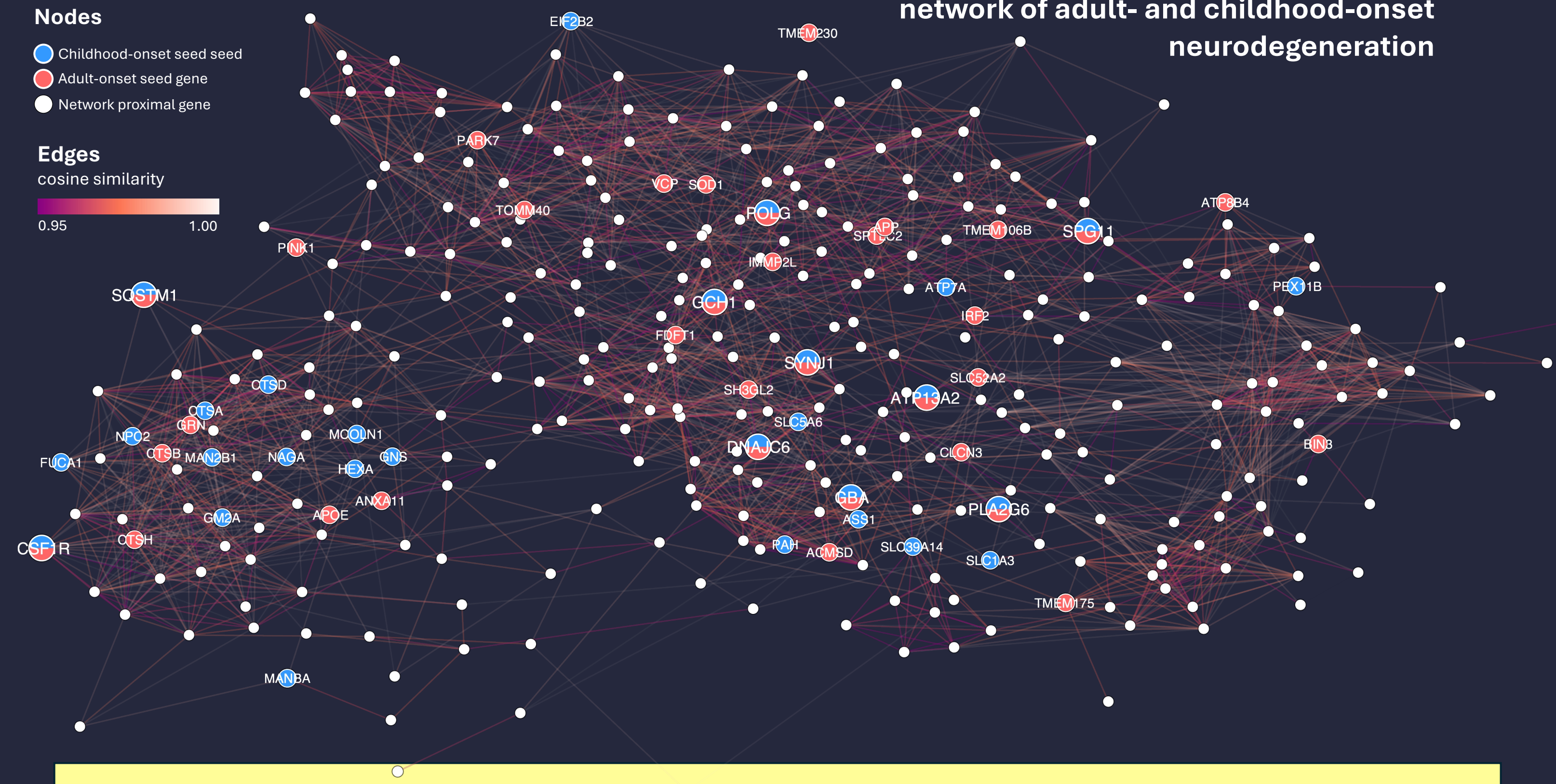
AD	Kunkle et al. 2019 <i>Nature Genetics</i>
PD	Leanord et al. 2025 <i>medRxiv</i>
DLB	Chia et al. 2021 <i>Nature Genetics</i>
FTD	Manzoni et al. 2024 <i>AJHG</i>
ALS	van Rheenen et al. 2021 <i>Nature Genetics</i>
Childhood dementia	Elvidge et al. 2023 <i>Brain</i>

Adult- and childhood-onset neurodegeneration genetics colocalise in the network space

To validate our colocalisation approach, we performed two control experiments. As a negative control, we confirmed that all childhood dementia genes do not colocalise with genes associated with brain malformations (without neurodegeneration). Our positive control showed colocalisation between genes associated with AD and PD. Significant genetic colocalisation between childhood and adult-onset neurodegenerative disease genes suggests shared underlying biology.

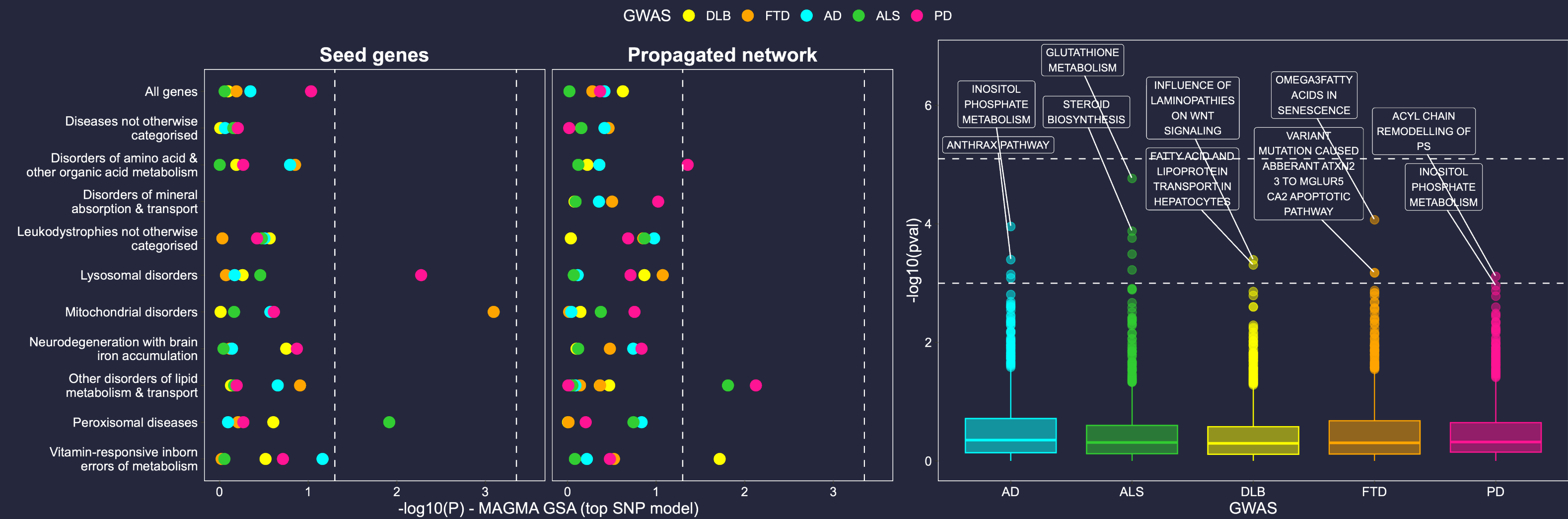


The shared molecular interaction network of adult- and childhood-onset neurodegeneration



Common variant genetic support for network-prioritised genes and pathways identified with MAGMA

As an alternative approach, we tested using *MAGMA* whether the childhood dementia genes and their propagated networks were enriched with adult-onset common variants. We also tested whether the top pathways enriched in each pairwise-subnetwork were enriched with adult-onset risk loci. Nominal statistical evidence was observed (first dotted line) for each analysis.



Specific pairs of adult- and childhood-onset neurodegeneration show significant colocalisation

Adult- and childhood-onset neurodegenerative diseases have different underlying biology. Therefore, we performed colocalisation analyses of each adult-onset neurodegenerative disease with each list of genes associated with the different pathological classifications of childhood dementia. Pairs of diseases were identified which are likely to share disease mechanisms.



Conclusion: Identifying shared biology to drive therapeutic discovery

Using a combination of genetic and network biology approaches, we have successfully predicted shared biological architecture between diseases causing adult- and childhood-onset neurodegeneration. This represents a completely novel, innovative and systematic approach to bridge the study of these distinct disease groups.

Ongoing work is testing whether these network-prioritised candidate genes and pathways are altered in single-cell RNA sequencing data of adult- and childhood-onset neurodegenerative diseases (post-mortem tissues and/or animal models). We also wish to confirm these genes and pathways are altered in the diseases experimentally.

These crucial predictions will eventually be leveraged to identify and prioritise novel therapeutic targets that hold the potential to benefit affected individuals across both sets of neurodegenerative diseases, driving the development of urgently needed therapies.