CAUSAL MODELING USING GEMINI DIGITAL TWINS IDENTIFIES SPI1 AS A POTENTIAL MODIFIER OF NEURODEGENERATIVE DISEASE PROGRESSION

CTAD 2026 Clinical Trials on Alzheimer's Disease

#120

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Introduction and Objective

- SPI1 (PU.1) is a master transcription factor implicated in AD risk, with both protective roles in microglial amyloid clearance[1] and detrimental effects through enhanced proinflammatory signaling[2].
- These contrasting effects suggest that SPI1 may influence neurodegeneration through distinct downstream regulatory pathways.
- Characterizing shared and disease-specific SPI1 regulatory circuits and their potential mediating roles in disease outcomes across AD, PD, HD, and ALS warrants further investigation.

Objective: Use Gemini digital twins (GDTs) to characterize the predicted causal effects of SPI1 expression on AD progression and investigate shared downstream networks and disease-associated genes across PD, HD, and ALS.

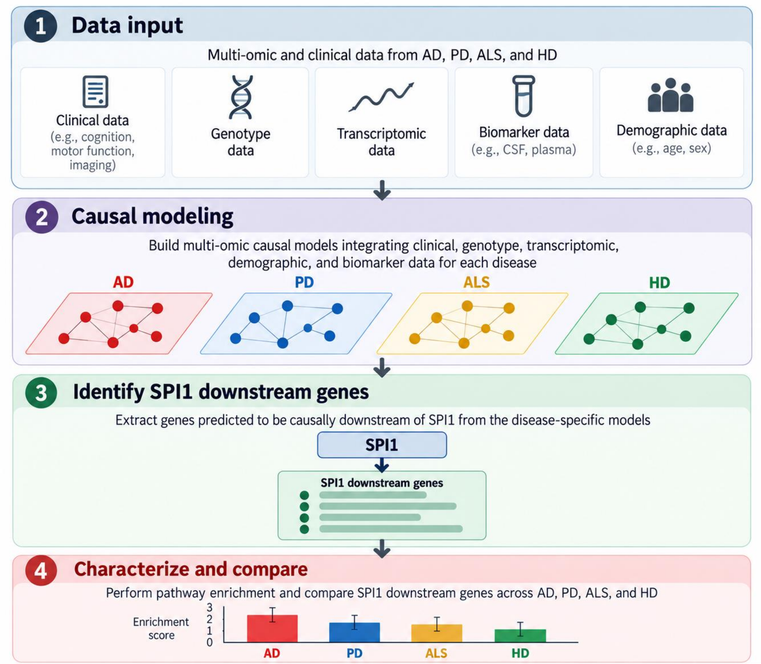
Data and Methods

GDT Datasets

Disease	Cohort	Study groups (N)	Tissue	Gene size	Key outcomes
AD	**ADNI**	AD 29, MCI 191, CN 97	Blood	~18k	Cognition, MRI, PET, amyloid/tau
PD	**PPMI**	PD 447, CN 424	Blood	~12.5K	MoCA, NfL, UPDRS-II
HD	**TRACK-HD**	HD 101, CN 19	Blood	~17K	Motor score (TMS)
ALS	**Target ALS**	ALS 156, CN 26	Cervical spinal cord	~22.3k	Survival

*AD: Alzheimer's disease; MCI: mild cognitive impairment; CN: cognitively normal; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease

Analytical workflow



Results: SPI1 Causal Effects and Shared Immune Pathways Across Neurodegenerative Diseases

1 Consistent SPI1 risk effects across neurodegenerative diseases

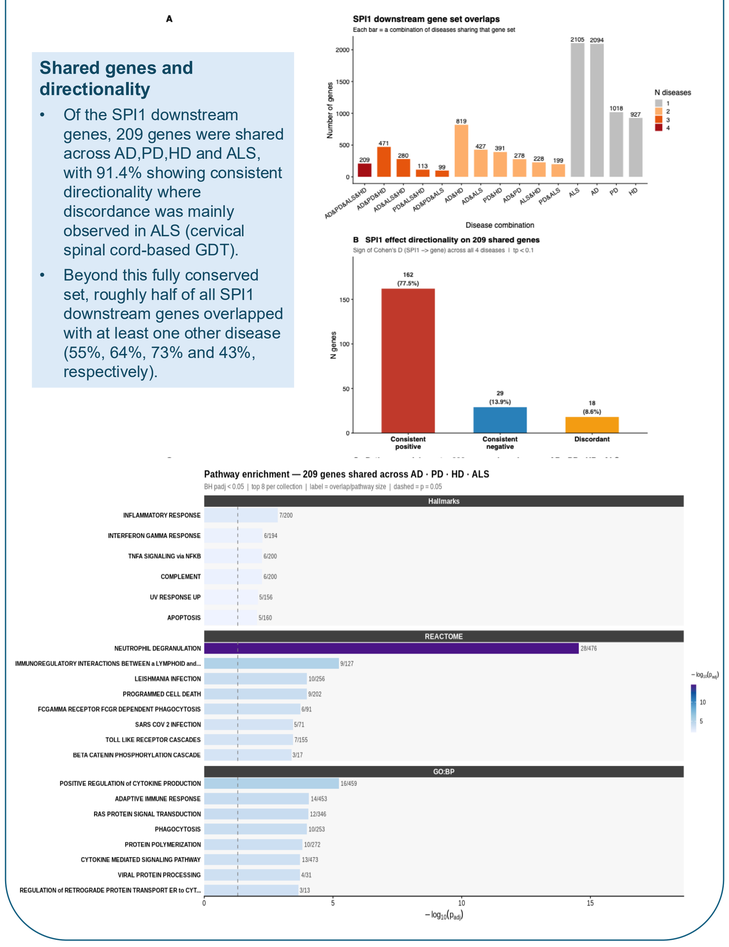
Disease	Outcome Domain	Outcome	Posterior Tail Probability*	Direction
AD	Amyloid	Amyloid PET (AV45)	0.32	Risky
	Neuro degeneration	Middle temporal volume decline	0.273	Risky
	Cognition	CDR-SB decline	0.305	Risky
	Cognition	MMSE decline	0.297	Risky
	Cognition	mPACC-Digit decline	0.234	Risky
	Cognition	mPACC-Trails B decline	0.242	Risky
PD	Cognition	MoCA decline	0.164	Risky
	Neuro degeneration	Serum NfL (longitudinal)	0.07	Risky
	Motor	UPDRS-II decline	0.281	Risky
HD	Motor	Total motor score decline	0.141	Risky
ALS	Survival	Survival	0.03	Risky

***Posterior tail probability:** Measures the confidence of causal effect, ranging from 0 to 0.5 where lower values indicate stronger evidence for the stated effect direction and 0.5 indicates no directional evidence (null).
Cutoffs applied to gene→outcome effect in this study: <0.4 for moderate evidence; <0.3 for stronger evidence according to the overall metric distribution and negative-controls

2 Shared SPI1 downstream genes converge on immune pathways

Shared genes and directionality

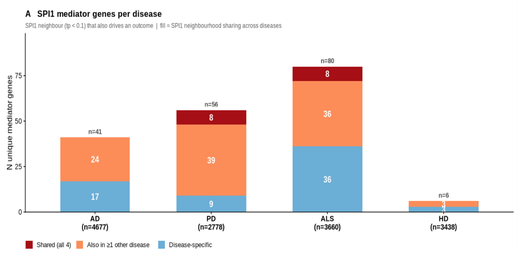
- Of the SPI1 downstream genes, 209 genes were shared across AD,PD,HD and ALS, with 91.4% showing consistent directionality where discordance was mainly observed in ALS (cervical spinal cord-based GDT).
- Beyond this fully conserved set, roughly half of all SPI1 downstream genes overlapped with at least one other disease (55%, 64%, 73% and 43%, respectively).

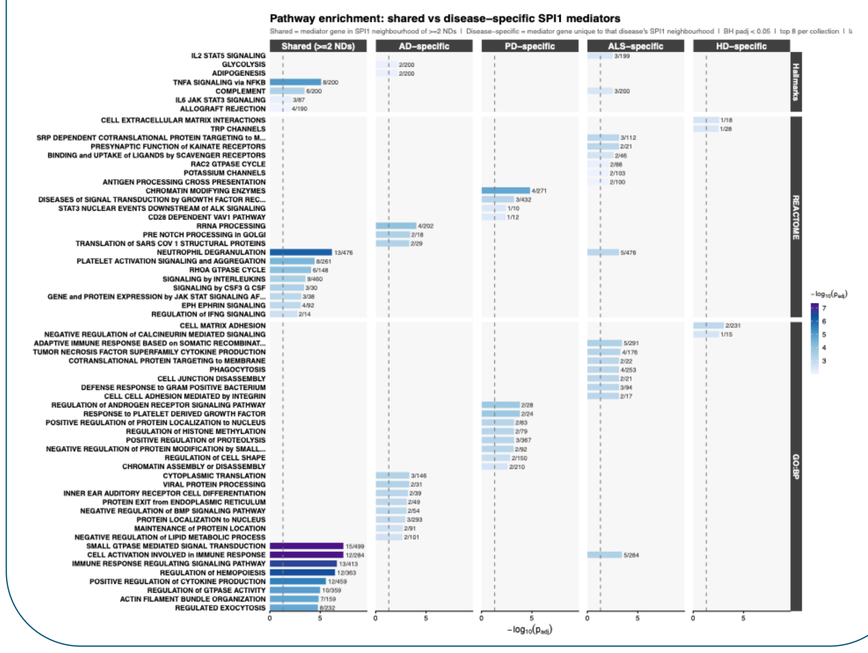


3 Shared mediators converge on immune pathways, while disease-specific mediators reflect distinct mechanisms

Mediator genes

- Candidate mediators (SPI1-driven genes that also drive disease outcomes) were largely distinct from the 209 cross-disease conserved genes (~8% overlap), yet 45-70% overlapped with the broader SPI1 downstream gene pool in at least one other disease.
- This cross-disease sharing in mediators was significantly higher than the overall SPI1 downstream sharing in PD and ALS, and nominally higher in AD, and these mediators reflected both shared neuroinflammatory and disease-specific elements.





Conclusion and References

- SPI1 emerged as a promising gene, with consistent risk-associated, model-inferred causal effects on progression outcomes across AD, PD, ALS, and HD.
- Despite predominantly disease-specific downstream networks, roughly half of SPI1 downstream genes were shared with at least one other disease, and 209 were conserved across all four, highlighting common immune-related functions including phagocytosis and inflammatory signaling.
- Candidate SPI1 mediators (those that also drove disease outcomes) were more cross-disease than the broader SPI1 downstream genes, significantly so in PD and ALS, and nominally in AD, converging on shared immune-related pathways.
- Yet disease-specific mediators remained, and these were biologically meaningful: AD-specific mediators pointed to ER stress and protein translation, while PD-specific mediators implicated epigenetic regulation.
- For future studies, a key open question is what drives this divergence and how the same immune regulator leads to distinct neurodegenerative outcomes.
- Overall, these findings implicate SPI1 as a shared modifier of neurodegenerative disease progression, with both conserved immune mechanisms and disease-specific downstream programs that warrant further investigation.

References
1. Kim B, et al. Nat Commun. 2024;15(1):3996. doi:10.1038/s41467-024-48484-x.
2. Pimenova AA, et al. Neurobiol Dis. 2021;148:105217. doi:10.1016/j.nbd.2020.105217.