Gene-based association testing integrating xQTLs identifies candidate drug targets for Alzheimer's disease

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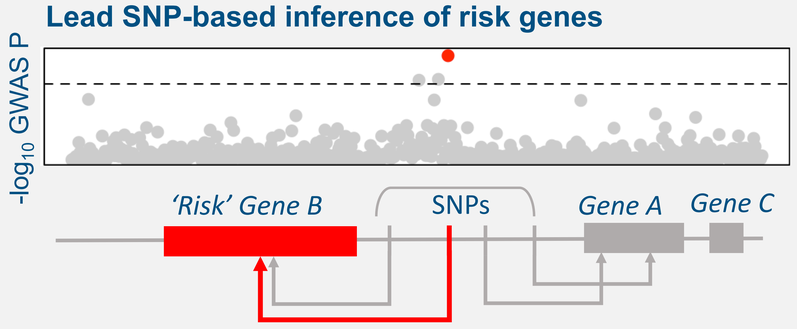
BACKGROUND

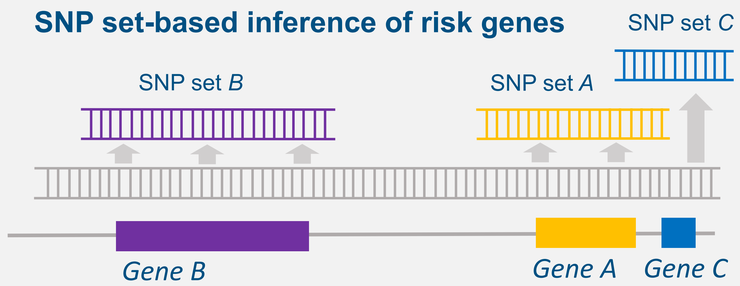
- Inferring risk genes using lead SNPs – i.e., those with the smallest AD association P-values – in neither powerful nor precise.
- Gene-based association testing overcomes these limitations, but current implementations of it have inflated Type I or II errors because they have not correctly specified the null distribution of the test statistic used to test the association null hypothesis.
- We provide the first closed-form expression of this null distribution, guaranteeing controlled Type I and II error of gene-based association tests.
- Integrating xQTL information in gene-based association testing can further improve power while providing causal inference under the assumption of no direct genetic effects on AD conditional on the xQTL phenotype, which is equivalent to the no horizontal pleiotropy assumption in Mendelian Randomization.

METHODS

Lead SNP-based inference of risk genes

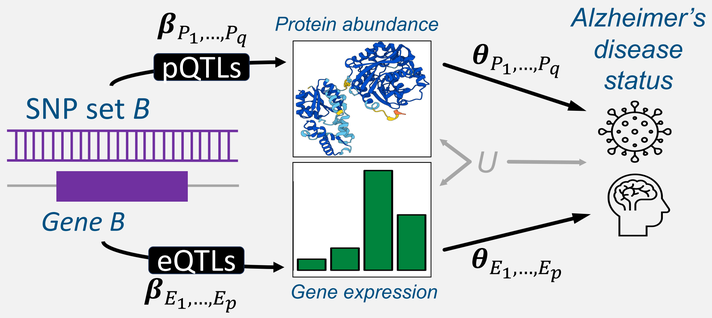


SNP set-based inference of risk genes



$$H_0^B: \cap_{j=1}^{M_B} \beta_j = 0 \text{ vs } H_1^B: \cup_{j=1}^{M_B} \beta_j \neq 0 \text{ using } T_B = \sum_{j=1}^{M_B} \frac{\widehat{\beta}_j^2}{\text{Var}(\widehat{\beta}_j)} \mid H_0^B \sim \Gamma(\alpha_B, \xi_B)$$

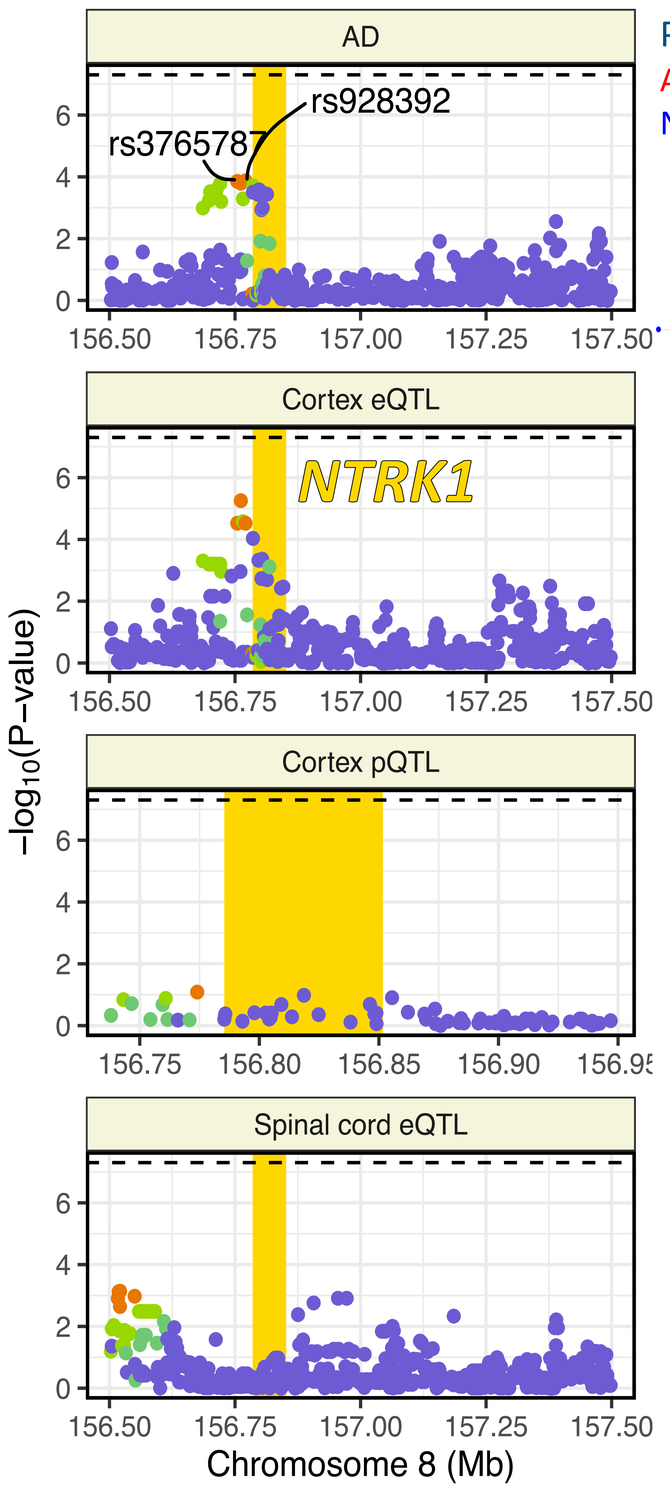
Integrating xQTLs in gene-based testing

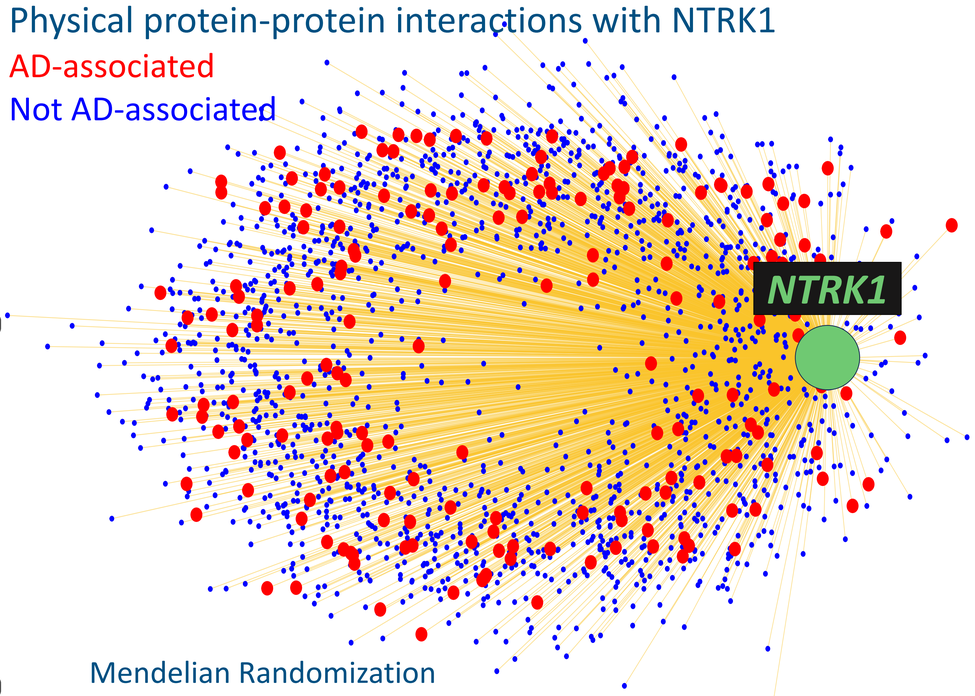


$$H_0^B: (\boldsymbol{\beta}_P, \boldsymbol{\beta}_E)(\boldsymbol{\theta}_\mathcal{P}^\top, \boldsymbol{\theta}_\mathcal{E}^\top)^\top = \mathbf{0} \text{ vs } H_1^B: (\boldsymbol{\beta}_P, \boldsymbol{\beta}_E)(\boldsymbol{\theta}_\mathcal{P}^\top, \boldsymbol{\theta}_\mathcal{E}^\top)^\top \neq \mathbf{0} \text{ using } S_B$$

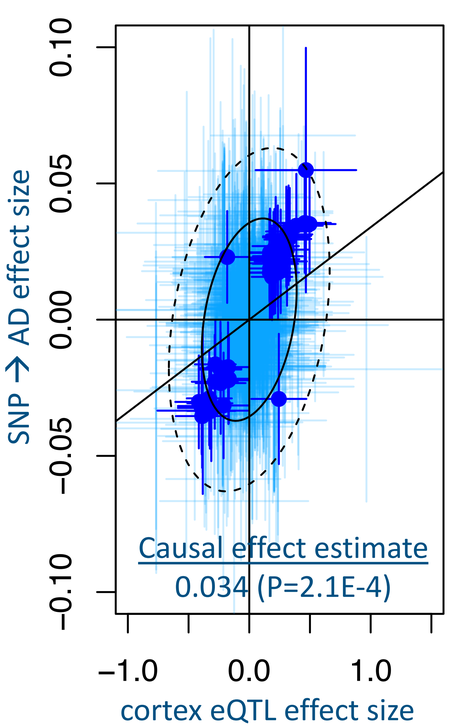
$$S_B = \mathbf{z}_{\text{AD}}^\top \left(\sum_{k=1}^{p+q} \mathbf{z}_{\text{xQTL(k)}} \mathbf{z}_{\text{xQTL(k)}}^\top \right) \mathbf{z}_{\text{AD}}, \quad \text{and} \quad S_B \mid \mathbf{Z}_{\text{xQTL}} \sim \Gamma(\alpha_B^{\text{x}}, \xi_B^{\text{x}})$$

RESULTS

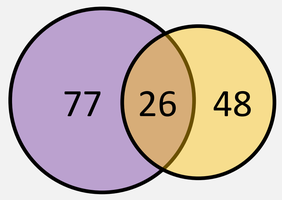




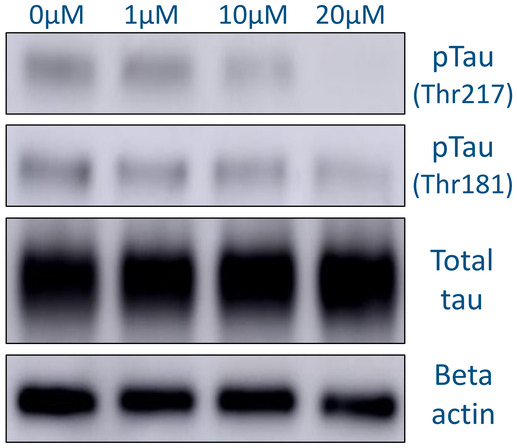
Mendelian Randomization replicates causality of *NTRK1* expression in cortex with AD



Counts of novel druggable genes associated with AD



NTRK1 inhibitor (GW441756)
Patient-derived iPSCs (P24 neurons)



CONCLUSION

- Gene-based association testing integrating xQTLs can identify AD-associated genes with additional evidence of causality.
- *NTRK1* is a candidate druggable target for AD onset.
- Future experimental studies are required to identify candidate drug targets for AD onset from our preliminary genome-wide screening.

ACKNOWLEDGEMENT & REFERENCES

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