Combining genetics with real-world patient data enables ancestry-specific target identification and drug discovery in Alzheimer's disease

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BACKGROUND

Background: High-throughput DNA/RNA sequencing technologies have generated massive genetic and genomic data in human disease, and selecting genetically supported targets can double the success rate in clinical drug development. However, translation of these findings into new patient treatment has not materialized, in particular for race-conscious target identification and drug discovery from diverse population genetics data.

RESULTS

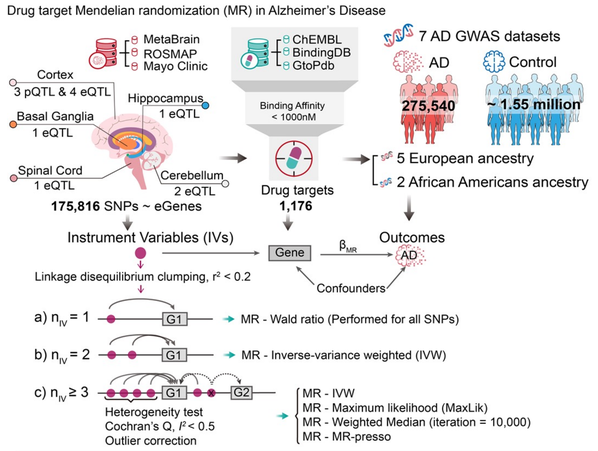

Fig. 1 A diagram illustrates the experimental pipeline of Mendelian Randomization (MR) and drugome-wide association studies (DWAS). a. This framework outlines the MR analysis process for Alzheimer's disease drug target identification and validation, with instrumental variables selected from various datasets and five MR methods used for reproducibility. **b.** The framework for drugome-wide association studies (DWAS) includes the evaluation of four drug cohort designs and 210 highly prescribed drugs, with adjustment for various confounding factors using a propensity score-matching method.

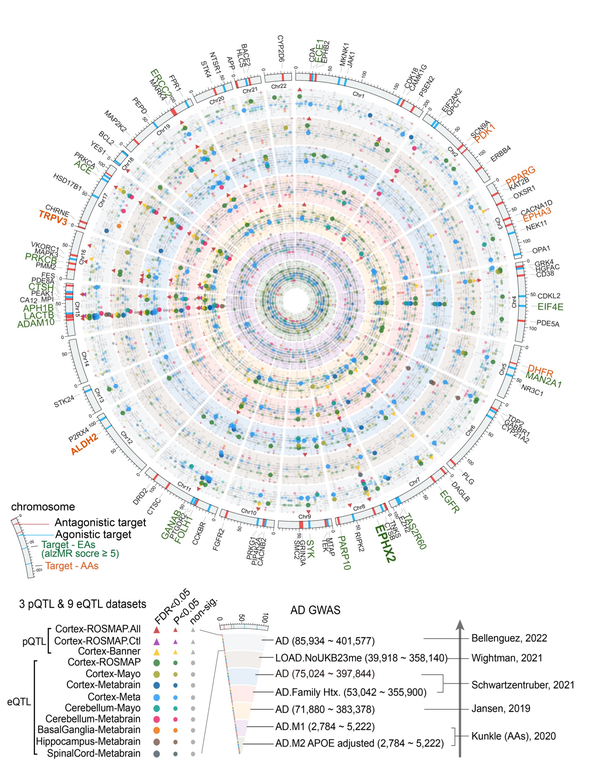

Fig. 2 A drug target compendium for Alzheimer's disease (AD) supported by human genetic evidence in both European Americans (EAs) and African Americans (AAs) ancestries. A circos plot illustrates Mendelian Randomization (MR) (IVW [inverse-variance weighted] method) results for 1,176 druggable targets across 3 pQTL datasets (coded by triangles), 9 eQTL datasets (coded by circles), and 7 AD GWAS datasets (coded by different colors). We use colored shapes to represent significant MR results: bigger size of colorful shapes denotes more significant False Discovery Rate (FDR) adjusted p-values < 0.05; and smaller size of colorful shapes denotes P < 0.05; the gray colored shapes denote non-significant MR results. The triangles represent the significant IVs for drug targets from pQTL datasets, and the shapes of circle represent the significant IVs for drug targets from eQTL datasets. 7 colored backgrounds highlight different AD GWAS datasets. The blue lines in the chromosomes link to the agonistic targets; the red lines link to antagonistic targets.

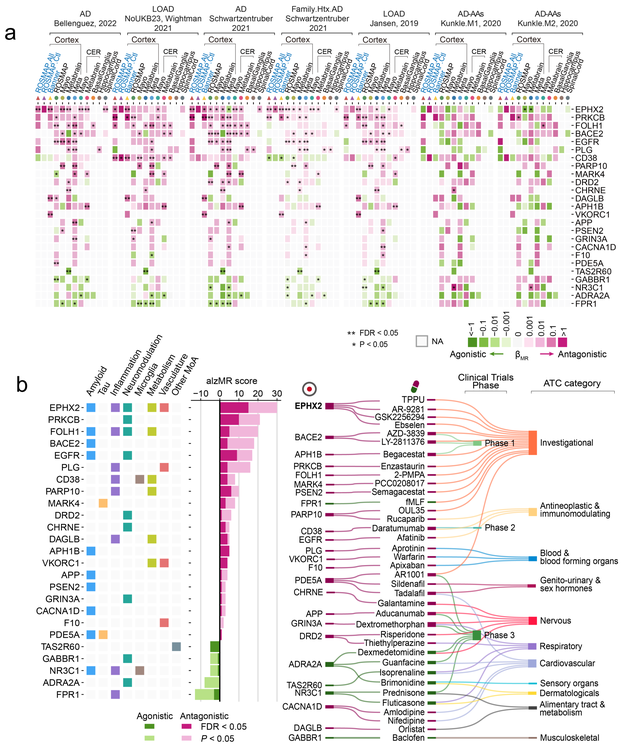

Fig. 3 The support of human genetic evidence for Alzheimer's disease drug target in European American (EAs) Ancestry. a. A heatmap shows the β coefficient score of 25 drug targets for EAs. β coefficient > 0 indicates antagonistic targets; β coefficient < 0 indicates agonistic targets. ** denotes the significant cutoff at False Discovery Rate (FDR) < 0.05 using multiple testing correction. * denotes significant P < 0.05. **b** Distribution of AD drug targets across different mechanism-of-actions. The left panel shows 8 mechanism-of-actions (MoAs) categories of AD: amyloid, tau, inflammation, neuromodulation, microglia, metabolism, vasculature, and others. The right bar graph presents the alzMR score of 25 drug targets: Pink denotes antagonistic targets and green denotes agonistic targets. The dark color highlights the significant threshold at FDR < 0.05, and the light color shows significant threshold at P < 0.05. **c** Sankey plot shows the relationship between repurposed drugs and alzMR score-predicted targets for AD. The dark green color denotes that the drug is an agonist of the target; Ruby color denotes that the drug is an inhibitor/antagonist of the target

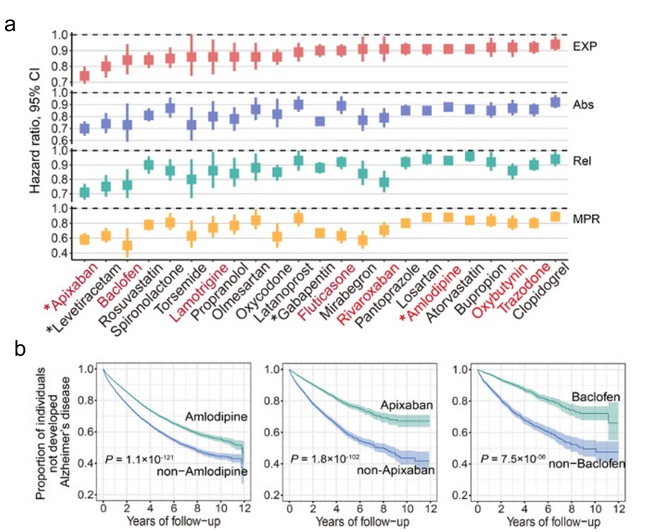

Fig. 2 A repurposable drug compendium of Alzheimer's disease using drugome-wide association studies (DWAS) and Mendelian randomization (MR) analyses. a Hazard ratios (HR) indicate 23 potential repurposable drugs for AD. (i) Exposed vs non exposed model (Exp.), (ii) Absolute higher exposed vs. low exposed (Abs.), (iii) Relative high exposed vs. low exposed (Rel.), and (iv) Medication possession ratio (MPR). Two statistical cutoff P < 0.05 and FDR < 0.05 were shown in pie plot. Drugs highlighted by red color have the targets supported by MR evidence at P < 0.05. **b.** Propensity score-matched survival analyses for three highlighted drugs. Non-exposure drug cohorts were matched to the exposures by adjusting age, gender, race, disease comorbidities, and other confounding factors.

CONCLUSION

In summary, combining genetics and real-world patient data identified ancestry-specific therapeutic targets and medicines for AD and other neurodegenerative diseases if broadly applied.

ACKNOWLEDGEMENT

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