Genetic Evidence Supporting a Causal Role of Depression on Alzheimer's Disease

Supplement 1

Supplementary methods

GWAS summary statistics

Genetic associations with AD were obtained from the meta-analysis GWAS of 455,258 individuals of European ancestry (Table S1A). In brief, the meta-analysis included four independent cohorts, namely the Alzheimer's disease working group of the Psychiatric Genomics Consortium (N=17,477), the International Genomics of Alzheimer's Project (N=54,162), and the Alzheimer's Disease Sequencing Project (N=7,506), and the UK Biobank (N = 376,113). Genetic associations with depression were obtained from a larger meta-analysis GWAS of 807,553 individuals of European ancestry (Table S1A). In brief, the meta-analysis included of three independent cohorts, namely 23andMe, Inc (N=307,354), UK Biobank (N=361,315), Psychiatric Genomics Consortium (N=138,884). More details of the participants were described in the primary papers of AD (1) and depression (2).

Pathological phenotypes: For the ROS/MAP cohorts, we examined beta-amyloid and neurofibrillary tangle identified by immunohistochemistry from eight brain regions (Table S1B). For the Banner cohort, we examined amyloid plaques and tangles in the frontal lobe measured with the Campbell-Switzer silver stain and scored according to the Consortium to Establish a Registry for Alzheimer's Disease template (Table S1B). We took the square roots of these pathology measures to enhance their normal distribution.

Neuropsychiatric phenotypes: In ROS/MAP participants, depressive symptoms were assessed annually using the 10-item Center for Epidemiological Studies Depression scale (3), which ranges 0-10 with higher score indicating more depressive symptoms. We averaged the depression scores over the follow-up years to obtain an average depression score for each participant, which was then converted to a Z score to be used in the joint analysis including both ROS/MAP and Banner participants. Additionally,

each participant underwent a full clinical evaluation, including a comprehensive cognitive assessment each year and a final clinical diagnosis of AD which follows the National Institute on Aging Reagan criteria (4). Cognitive trajectory is person-specific rate of cognitive decline over time based on annual objective cognitive testing. Clinical diagnosis of AD diagnosis was made by a neurologist or clinician specialized in dementia. For Banner participants, depressive symptoms was assessed annually using the 15-item Hamilton Depression Rating Scale (5), which ranged 0-27, with higher score indicating more depressive symptoms. Additionally, participants underwent assessment by neurologists for a final clinicopathological diagnosis of cognitive status after death (6). Rate of cognitive decline over time was based on annual MMSE. We standardized the score of cognitive trajectories to improve statistical comparisons. Information on the characteristics of the subjects is in Table S1B.

Supplemental references

1. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, et al. (2019): Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature Genetics*. 51:404-413.
2. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. (2019): Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature neuroscience*. 22:343-352.
3. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J (1993): Two Shorter Forms of the CES-D Depression Symptoms Index. *Journal of Aging and Health*. 5:179-193.
4. Hyman BT, Trojanowski JQ (1997): Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol*. 56:1095-1097.
5. Hamilton M (1986): The Hamilton Rating Scale for Depression. In: Sartorius N, Ban TA, editors. *Assessment of Depression*. Berlin, Heidelberg: Springer Berlin Heidelberg, pp 143-152.
6. Beach TG, Adler CH, Sue LI, Serrano G, Shill HA, Walker DG, et al. (2015): Arizona Study of Aging and Neurodegenerative Disorders and Brain and Body Donation Program. *Neuropathology*. 35:354-389.