**Online Supplementary Materials**

This file contains 9 supplementary tables and 3 supplementary figures.

**Supplementary Table S1**

Sequence coverage of each gene in the targeted sequencing

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Mean depth** | **10**× **coverage (%)** | **20**× **coverage (%)** | **30**× **coverage (%)** | **50**× **coverage (%)** |
| *TGFB2* | 147.54 | 100.00 | 100.00 | 95.86 | 90.31 |
| *TGFBR1* | 160.30 | 88.32 | 88.32 | 88.32 | 88.32 |
| *TGFBR2* | 120.41 | 100.00 | 96.34 | 90.93 | 85.07 |
| *LTBP1* | 145.93 | 98.26 | 93.01 | 92.16 | 89.73 |
| *EGF* | 165.36 | 100.00 | 100.00 | 100.00 | 99.98 |
| *EGFR* | 119.27 | 99.21 | 95.93 | 92.19 | 89.27 |
| *HBEGF* | 120.38 | 100.00 | 93.17 | 86.03 | 70.48 |
| *INHBC* | 125.12 | 100.00 | 100.00 | 100.00 | 100.00 |
| *IGF1* | 159.22 | 100.00 | 100.00 | 100.00 | 95.50 |
| *IGF1R* | 152.05 | 100.00 | 99.93 | 99.33 | 96.52 |
| *IGF2* | 105.67 | 100.00 | 92.70 | 85.89 | 73.05 |
| *IGF2R* | 141.68 | 96.63 | 96.13 | 96.13 | 93.97 |
| *PDGFRA* | 168.49 | 100.00 | 100.00 | 100.00 | 99.81 |
| *PDGFRB* | 107.74 | 100.00 | 100.00 | 99.74 | 88.89 |
| *PDGFC* | 187.67 | 100.00 | 100.00 | 100.00 | 100.00 |
| *FGFR2* | 158.01 | 97.41 | 96.02 | 95.17 | 92.72 |
| *VEGFA* | 101.54 | 100.00 | 100.00 | 96.23 | 84.38 |
| *VEGFC* | 151.42 | 99.82 | 99.82 | 87.54 | 81.72 |
| *KDR* | 159.64 | 100.00 | 100.00 | 100.00 | 94.75 |
| *ANGPTL1* | 245.95 | 100.00 | 100.00 | 100.00 | 100.00 |
| *HGF* | 162.23 | 100.00 | 100.00 | 100.00 | 100.00 |
| *BDNF* | 234.00 | 100.00 | 100.00 | 100.00 | 99.17 |
| *GDNF* | 173.11 | 100.00 | 98.74 | 95.41 | 77.50 |

Mean depth of a gene was calculated by an equation = (total sequence data / gene length).

N× coverage was calculated by an equation = ((the total number of nucleobases in a gene that were sequenced over N times / total gene length) × 100%).

**Supplementary Table S2**

Rare variants of 23 growth factor genes in Han Chinese

This table is too big and is presented as an Excel file.

Rare variants were defined by an MAF < 0.01 in the control sample. All variants listed in this table had a sequencing coverage ≥ 20×.

**Supplementary Table S3**

Association of rare variants of *EGF* with AD in Han Chinese

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**Supplementary Table S4**

Allele frequencies of *EGF* rare variants in East Asian populations from the gnomAD dataset (<https://gnomad.broadinstitute.org/>) (Karczewski et al., 2020)

This table is too big and is presented as an Excel file.

**Supplementary Table S5**

Association of common variants in 23 growth factor genes with AD in Han Chinese

This table is too big and is presented as an Excel file.

**Supplementary Table S6**

Association of *EGF* variants with AD in European populations

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variant IDa | *P*-value | Chr:positionb | Allelec | Frequencyd | ORe | 95% CIf | Beta | SEg |
| rs4444903 | 0.869 | 4:109912954 | A/G | 0.5961 | 0.999 | 0.983-1.015 | -0.0014 | 0.0082 |
| rs11568849 | 0.421 | 4:109913381 | A/C | 0.998 | 0.88 | 0.645-1.201 | -0.1277 | 0.1588 |
| rs11568886 | 0.236 | 4:109941207 | T/C | 0.0042 | 1.145 | 0.915-1.434 | 0.1358 | 0.1146 |
| rs10470911 | 0.766 | 4:109944115 | T/G | 0.662 | 1.003 | 0.986-1.02 | 0.0025 | 0.0086 |
| rs4698755 | 0.810 | 4:109945022 | A/C | 0.6586 | 1.002 | 0.986-1.019 | 0.0021 | 0.0085 |
| rs4698756 | 0.799 | 4:109945286 | A/G | 0.3414 | 0.998 | 0.981-1.015 | -0.0022 | 0.0085 |
| rs4698800 | 0.764 | 4:109945352 | T/C | 0.3391 | 0.997 | 0.981-1.014 | -0.0026 | 0.0085 |
| rs11568927 | 0.088 | 4:109959477 | T/C | 0.0036 | 1.297 | 0.962-1.748 | 0.2598 | 0.1523 |
| rs11568941 | 0.104 | 4:109961824 | T/G | 0.0036 | 1.282 | 0.95-1.73 | 0.2487 | 0.1529 |
| rs11568942 | 0.122 | 4:109961840 | T/C | 0.9955 | 1.129 | 0.968-1.316 | 0.1212 | 0.0784 |
| rs11568943 | 0.440 | 4:109961965 | A/G | 0.0632 | 1.013 | 0.98-1.047 | 0.0129 | 0.0167 |
| rs3733628 | 0.081 | 4:109963140 | T/C | 0.0036 | 1.305 | 0.967-1.76 | 0.266 | 0.1526 |
| rs11568990 | 0.279 | 4:109974691 | A/C | 0.0041 | 1.163 | 0.885-1.528 | 0.1509 | 0.1393 |
| rs2302135 | 0.111 | 4:109979991 | A/G | 0.9955 | 0.849 | 0.695-1.038 | -0.1634 | 0.1026 |
| rs2237051 | 0.338 | 4:109980042 | A/G | 0.3825 | 0.992 | 0.976-1.008 | -0.008 | 0.0083 |
| rs11569017 | 0.656 | 4:109980955 | A/T | 0.9457 | 1.008 | 0.973-1.044 | 0.008 | 0.0179 |
| rs11569018h | 0.249 | 4:109981010 | A/G | 0.0018 | 1.212 | 0.874-1.681 | 0.1924 | 0.1669 |
| rs6836684h | 0.850 | 4:109987933 | T/C | 0.0024 | 0.979 | 0.788-1.217 | -0.021 | 0.1108 |
| rs4698803h | 0.610 | 4:109993271 | A/T | 0.2072 | 1.005 | 0.986-1.025 | 0.0052 | 0.0101 |
| rs75935899h | 0.572 | 4:109999791 | A/G | 0.002 | 0.925 | 0.705-1.213 | -0.0781 | 0.1383 |
| rs11568937h | 0.564 | 4:109960895 | T/C | 0.966 | 0.987 | 0.944-1.032 | -0.0131 | 0.0227 |
| rs11568953h | 0.803 | 4:109963240 | A/G | 0.9839 | 1.008 | 0.944-1.077 | 0.0083 | 0.0334 |
| rs11568993h | 0.004 | 4:109976159 | T/C | 0.0837 | 0.959 | 0.932-0.987 | -0.042 | 0.0147 |

aSummary statistics from the meta-analysis (Bellenguez et al., 2022) are available through the National Human Genome Research Institute-European Bioinformatics Institute GWAS catalog under accession number GCST90027158 (https://www.ebi.ac.uk/gwas/).

bChr:position, position were shown in GRCh38

cEffect allele / other allele

dFrequency of effect allele

eOR, odds ratio of the effect allele

f95% confidence interval of OR

gStandard error

hRare variants (MAF < 0.01) in Han Chinese under study

**Supplementary Table S7**

eQTL effect of rs4698800 and rs10470911 on *EGF* expression

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SNP | eQTL dataset | A1/A2a | Freqb | Beta | SEc | *P*-value |
| rs4698800 | Brain\_eMeta (Qi et al., 2018) | T/C | 0.346 | 0.220 | 0.072 | 0.0022 |
| rs4698800 | cage\_whole\_blood (Lloyd-Jones et al., 2017) | T/C | 0.360 | 0.070 | 0.028 | 0.0118 |
| rs10470911 | Brain\_eMeta (Qi et al., 2018) | G/T | 0.336 | 0.235 | 0.072 | 0.0012 |
| rs10470911 | cage\_whole\_blood (Lloyd-Jones et al., 2017) | G/T | 0.357 | 0.063 | 0.028 | 0.0238 |

eQTL datasets include peripheral blood eQTL data from the Consortium for the Architecture of Gene Expression (CAGE) (Lloyd-Jones et al., 2017) and brain eQTL data from a meta-analysis (Qi et al., 2018) of GTEx brain (GTEx Consortium et al., 2017), CommonMind Consortium (CMC) (Fromer et al., 2016) and ROSMAP (Ng et al., 2017)

aEffect allele/other allele

bFrequency of the effect allele in the respective eQTL study

cSE, standard error

**Supplementary Table S8**

mRNA expression of 23 growth factors in six types of cells based on scRNA-seq data of human brain tissues (no-pathology vs. pathology)

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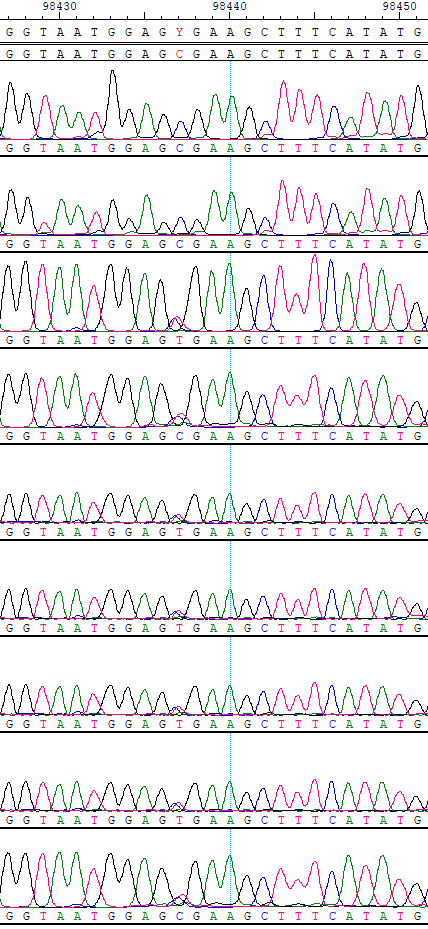
Data in this table were retrieved from Mathys et al. (2019). We quoted notes in the Excel file from the original paper for the convenience of the reader.

**Supplementary Table S9**

mRNA expression of 23 growth factors in six types of cells based on scRNA-seq data of human brain tissues (early-pathology vs. late-pathology)

This table is too big and is presented as an Excel file.

Data in this table were retrieved from Mathys et al. (2019). We quoted notes in the Excel file from the original paper for the convenience of the reader.



rs556105355

H101

H104

YAAD25

G61

AD487

SCAD60

ZJAD57

HNAD128

SHAD38

Reference genome

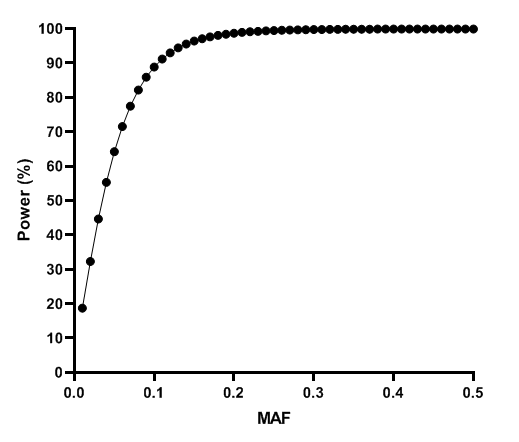
(NG\_011441.2)

rs556105355-CC

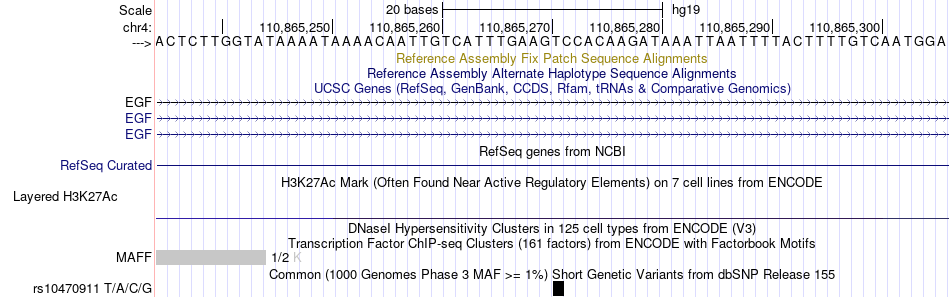
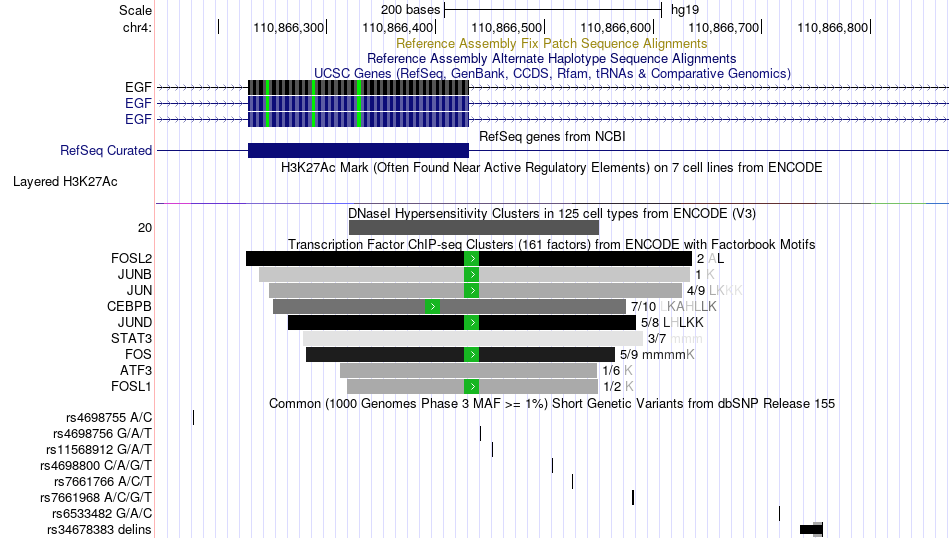
rs556105355-CT

(p.Arg1163\* [p.R1163\*])

**Supplementary Fig. S1.** Validation of rare variant rs556105355 C>T in T allele carriers (n = 7) and non-carriers (n = 2) by Sanger sequencing. The ID of each sample was shown in the left of the corresponding sequences. We used a primer pair rs556105355-F (5’-GGCTGAGGTGGAAGGATCAC-3’) / rs556105355-R (5’-CTCCATTTGGTGTGGTGGGT-3’) to amplify and sequence a 506 bp fragment harboring rs556105355. \*, stop codon.



**Supplementary Fig. S2.** Power estimate for the case-control association analysis. Statistical power was computed under the gene only hypothesis and log additive model, with the following parameters: risk allele ranges from 0.01 to 0.5 in increments of 0.01; overall disease risk in the general population = 0.03; sample size = 1280 cases vs. 5044 controls; OR = 1.25.



a

b

**Supplementary Fig. S3.** Regulatory functional annotation of rs4698800 (a) and rs10470911 (b). Functional genomic annotations for enhancers (H3K27ac), chromatin accessibility (DNaseI hypersensitivity sites), and transcription factor binding sites (TFBSs) of each target variant were based on the ENCODE data retrieved from the UCSC Genome Browser (https://genome.ucsc.edu/). The target variants were marked with a red box.

**References**

Bellenguez C., Küçükali F., Jansen I.E., Kleineidam L., Moreno-Grau S., Amin N., Naj A.C., Campos-Martin R., Grenier-Boley B., Andrade V., Holmans P.A., et al., 2022. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat. Genet. 54, 412-436.

Fromer M., Roussos P., Sieberts S.K., Johnson J.S., Kavanagh D.H., Perumal T.M., Ruderfer D.M., Oh E.C., Topol A., Shah H.R., Klei L.L., et al., 2016. Gene expression elucidates functional impact of polygenic risk for schizophrenia. Nat. Neurosci. 19, 1442-1453.

GTEx Consortium, Laboratory Data Analysis &Coordinating Center (LDACC)-Analysis Working Group, Statistical Methods groups-Analysis Working Group, Enhancing GTEx (eGTEx) groups, NIH Common Fund, NIH/NCI, NIH/NHGRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site-NDRI, Biospecimen Collection Source Site-RPCI, et al., 2017. Genetic effects on gene expression across human tissues. Nature 550, 204-213.

Karczewski K.J., Francioli L.C., Tiao G., Cummings B.B., Alföldi J., Wang Q., Collins R.L., Laricchia K.M., Ganna A., Birnbaum D.P., Gauthier L.D., et al., 2020. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 581, 434-443.

Lloyd-Jones L.R., Holloway A., McRae A., Yang J., Small K., Zhao J., Zeng B., Bakshi A., Metspalu A., Dermitzakis M., Gibson G., Spector T., Montgomery G., Esko T., Visscher P.M.Powell J.E., 2017. The genetic architecture of gene expression in peripheral blood. Am. J. Hum. Genet. 100, 228-237.

Mathys H., Davila-Velderrain J., Peng Z., Gao F., Mohammadi S., Young J.Z., Menon M., He L., Abdurrob F., Jiang X., Martorell A.J., Ransohoff R.M., Hafler B.P., Bennett D.A., Kellis M.Tsai L.H., 2019. Single-cell transcriptomic analysis of Alzheimer's disease. Nature 570, 332-337.

Ng B., White C.C., Klein H.U., Sieberts S.K., McCabe C., Patrick E., Xu J., Yu L., Gaiteri C., Bennett D.A., Mostafavi S.De Jager P.L., 2017. An xQTL map integrates the genetic architecture of the human brain's transcriptome and epigenome. Nat. Neurosci. 20, 1418-1426.

Qi T., Wu Y., Zeng J., Zhang F., Xue A., Jiang L., Zhu Z., Kemper K., Yengo L., Zheng Z., et al., 2018. Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. Nat. Commun. 9, 2282.