**Supplemental Tables**

**Supplemental Table 1**: Exclusion criteria in the National Alzheimer’s Coordination Center Neuropathology (NACC NP) dataset.

|  |  |
| --- | --- |
| **Exclusion criteria** | **Variable name** |
| Down syndrome | NACCDOWN |
| Pigment-spheroid degeneration/NBIA | NPPDXA |
| Multiple system atrophy | NPPDXB |
| Trinucleotide disease (Huntington disease, SCA, other) | NPPDXD |
| Malformation of cortical development | NPPDXE |
| Metabolic/storage disorder of any type | NPPDXF |
| White matter disease, leukodystrophy | NPPDXG |
| White matter disease, multiple sclerosis or other demyelinating disease | NPPDXH |
| Contusion/traumatic brain injury of any type, acute | NPPDXI |
| Contusion/traumatic brain injury of any type, chronic | NPPDXJ |
| Neoplasm, primary | NPPDXK |
| Neoplasm, metastatic | NPPDXL |
| Infectious process of any type (encephalitis, abscess, etc.) | NPPDXM |
| Herniation, any site | NPPDXN |
| Prion disease | NACCPRIO |
| FTLD-tau | NPFTDTAU |
| ALS/motor neuron disease (MND) | NPALSMND |
| CADASIL | NPPATH10 |
| Other FTLD\* | NPOFTD |

\*Other FTLD includes atypical FTLD-U, neuronal intermediate filament inclusions disease (NIFID), basophilic inclusion body disease (BIBD), ubiquitin-proteasome system (FTLD-UPS), dementia lacking distinctive histology and FTLD with no inclusions detected by tau, TDP-43, or ubiquitin.p62 IHC (FTLD-NOS).

**Supplemental Table 2**: GRCh37/hg19 gene boundaries and the corresponding number of variants included in each analysis.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Chr.** | **Canonical Transcript** | | **Canonical Transcript ± 10kb** | | | | |
| **Start Pos.** | **End Pos.** | **No. of Variants Included in Analyses** | | |
| **Start Pos.** | **End Pos.** | **NACC** | **ROSMAP** | **Meta-Analysis** |
| *KCNMB2* | 3 | 178254085 | 178562217 | 178244085 | 178572217 | 955 | 953 | 929 |
| *TMEM106B* | 7 | 12250847 | 12276890 | 12240847 | 12286890 | 255 | 254 | 250 |
| *ABCC9* | 12 | 21950323 | 22089628 | 21940323 | 22099628 | 292 | 268 | 265 |
| *GRN* | 17 | 42422490 | 42430470 | 42412490 | 42440470 | 40 | 35 | 33 |
| *APOE* | 19 | 45409038 | 45412650 | 45399038 | 45422650 | 38 | 22 | 15 |

Chr. = chromosome; NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; MOI = mode of inheritance.

**Supplemental Table 3**: Sensitivity analyses for adjusted hippocampal sclerosis (HS) odds ratios.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Dataset** | **Subset** | **SNP** | **Effect Allele** | **MOI** | **No. of Obs.** | **OR** | **Lower 95% CL** | **Upper 95% CL** | **P-value** |
| NACC | All Available Observations | rs1914361 | G | Additive | 410 | 1.76 | 1.19 | 2.64 | 0.005051 |
| NACC | No HS+/LATE- Cases | rs1914361 | G | Additive | 393 | 1.81 | 1.16 | 2.87 | 0.010197 |
| NACC | All Available Observations | rs1914361 | G | Recessive | 410 | 2.85 | 1.52 | 5.28 | 0.000941 |
| NACC | No HS+/LATE- Cases | rs1914361 | G | Recessive | 393 | 2.61 | 1.26 | 5.25 | 0.007787 |
| NACC | All Available Observations | rs704178 | C | Additive | 410 | 0.74 | 0.49 | 1.11 | 0.151609 |
| NACC | No HS+/LATE- Cases | rs704178 | C | Additive | 393 | 0.8 | 0.5 | 1.28 | 0.363251 |
| NACC | All Available Observations | rs704178 | C | Recessive | 410 | 0.65 | 0.32 | 1.25 | 0.215645 |
| NACC | No HS+/LATE- Cases | rs704178 | C | Recessive | 393 | 0.75 | 0.33 | 1.53 | 0.445006 |
| ROSMAP | All Available Observations | rs1914361 | G | Additive | 732 | 1.38 | 0.97 | 1.97 | 0.078816 |
| ROSMAP | No HS+/LATE- Cases | rs1914361 | G | Additive | 727 | 1.5 | 1.04 | 2.19 | 0.031805 |
| ROSMAP | All Available Observations | rs1914361 | G | Recessive | 732 | 1.75 | 1 | 3 | 0.045225 |
| ROSMAP | No HS+/LATE- Cases | rs1914361 | G | Recessive | 727 | 1.99 | 1.12 | 3.46 | 0.016041 |
| ROSMAP | All Available Observations | rs704178 | C | Additive | 732 | 0.67 | 0.46 | 0.96 | 0.03165 |
| ROSMAP | No HS+/LATE- Cases | rs704178 | C | Additive | 727 | 0.66 | 0.45 | 0.97 | 0.035417 |
| ROSMAP | All Available Observations | rs704178 | C | Recessive | 732 | 0.5 | 0.22 | 0.98 | 0.059765 |
| ROSMAP | No HS+/LATE- Cases | rs704178 | C | Recessive | 727 | 0.47 | 0.2 | 0.96 | 0.055162 |

Sensitivity analyses showing the adjusted effects of single nucleotide variants (SNV) on hippocampal sclerosis (HS), excluding all LATE-NC-HS+ cases. All analyses were adjusted for sex, age at death, cohort/study, and the first three genetic principal components.

**Supplemental Table 4:** Additional participant characteristics for National Alzheimer’s Coordinating Center (NACC) participants stratified by combined limbic predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) and hippocampal sclerosis (HS) case status.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Overall** | **Stratified by Combined LATE-NC and HS Case Status** | | | | |
| **LATE- HS-** | **LATE+ HS-** | **LATE- HS+** | **LATE+ HS+** | **Unable to Ascertain** |
| **Number of Participants** | 633 | 273 | 72 | 17 | 48 | 223 |
| **Duration of symptoms, Mean (SD)** | 10.8 (4.9) | 10.5 (4.8) | 12.1 (4.8) | 12.0 (4.5) | 13.1 (3.7) | 9.9 (5.0) |
| **HS details, N (%)** |  |  |  |  |  |  |
| None | 543 (85.8) | 273 (100.0) | 72 (100.0) | 0 (0.0) | 0 (0.0) | 198 (88.8) |
| Unilateral | 8 (1.3) | 0 (0.0) | 0 (0.0) | 1 (5.9) | 6 (12.5) | 1 (0.4) |
| Bilateral | 16 (2.5) | 0 (0.0) | 0 (0.0) | 2 (11.8) | 13 (27.1) | 1 (0.4) |
| Present but laterality not assessed | 65 (10.3) | 0 (0.0) | 0 (0.0) | 14 (82.4) | 29 (60.4) | 22 (9.9) |
| Not assessed | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) |

Participant characteristics stratified by combined limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC) and hippocampal sclerosis (HS) case status. Participants missing data for either LATE-NC or HS are labeled as “unable to ascertain.” NACC = National Alzheimer's Coordinating Center; SD = standard deviation; HS = hippocampal sclerosis; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological changes.

**Supplemental Table 5:** Participant characteristics and concomitant neuropathologies for National Alzheimer's Coordinating Center (NACC) and Religious Orders Study and Rush Memory and Aging Project (ROSMAP) participants.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **NACC** | | | | | | **ROSMAP** | | | | | |
| **Overall** | **LATE- HS-** | **LATE+ HS-** | **LATE- HS+** | **LATE+ HS+** | **Inconclusive** | **Overall** | **LATE- HS-** | **LATE+ HS-** | **LATE- HS+** | **LATE+ HS+** | **Inconclusive** |
| **Number of Participants** | 633 | 273 | 72 | 17 | 48 | 223 | 795 | 485 | 176 | 5 | 66 | 63 |
| **Age at death, Mean (SD)** | 85.9 (8.3) | 85.0 (8.0) | 85.4 (7.4) | 84.8 (9.1) | 85.4 (7.4) | 87.4 (8.8) | 88.7 (7.2) | 87.9 (7.2) | 91.0 (6.2) | 83.3 (9.6) | 92.6 (5.8) | 85.2 (7.3) |
| **Female, N (%)** | 320 (50.6) | 129 (47.3) | 40 (55.6) | 8 (47.1) | 29 (60.4) | 114 (51.1) | 534 (67.2) | 307 (63.3) | 134 (76.1) | 4 (80.0) | 52 (78.8) | 37 (58.7) |
| **Braak stage V/VI, N (%)** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 243 (38.4) | 123 (45.1) | 11 (15.3) | 5 (29.4) | 11 (22.9) | 93 (41.7) | 576 (72.5) | 382 (78.8) | 105 (59.7) | 2 (40.0) | 36 (54.5) | 51 (81.0) |
| Yes | 387 (61.1) | 150 (54.9) | 60 (83.3) | 12 (70.6) | 36 (75.0) | 129 (57.8) | 219 (27.5) | 103 (21.2) | 71 (40.3) | 3 (60.0) | 30 (45.5) | 12 (19.0) |
| Unknown | 3 (0.5) | 0 (0.0) | 1 (1.4) | 0 (0.0) | 1 (2.1) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **CERAD C3, N (%)** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 324 (51.2) | 144 (52.7) | 22 (30.6) | 9 (52.9) | 14 (29.2) | 135 (60.5) | 537 (67.5) | 359 (74.0) | 102 (58.0) | 2 (40.0) | 30 (45.5) | 44 (69.8) |
| Yes | 307 (48.5) | 128 (46.9) | 50 (69.4) | 8 (47.1) | 34 (70.8) | 87 (39.0) | 258 (32.5) | 126 (26.0) | 74 (42.0) | 3 (60.0) | 36 (54.5) | 19 (30.2) |
| Unknown | 2 (0.3) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Moderate/severe B-ASC, N (%)** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 297 (46.9) | 143 (52.4) | 19 (26.4) | 8 (47.1) | 15 (31.2) | 112 (50.2) | 568 (71.4) | 359 (74.0) | 124 (70.5) | 4 (80.0) | 41 (62.1) | 40 (63.5) |
| Yes | 310 (49.0) | 129 (47.3) | 53 (73.6) | 9 (52.9) | 33 (68.8) | 86 (38.6) | 227 (28.6) | 126 (26.0) | 52 (29.5) | 1 (20.0) | 25 (37.9) | 23 (36.5) |
| Unknown | 26 (4.1) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 25 (11.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Lewy Bodies, N (%)** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 421 (66.5) | 188 (68.9) | 41 (56.9) | 10 (58.8) | 23 (47.9) | 159 (71.3) | 609 (76.6) | 382 (78.8) | 125 (71.0) | 2 (40.0) | 66 (59.1) | 51 (81.0) |
| Yes | 208 (32.9) | 85 (31.1) | 31 (43.1) | 6 (35.3) | 25 (52.1) | 61 (27.4) | 186 (24.2) | 103 (21.9) | 46 (26.2) | 2 (40.0) | 23 (34.8) | 12 (19.0) |
| Unknown | 4 (0.6) | 0 (0.0) | 0 (0.0) | 1 (5.9) | 0 (0.0) | 3 (1.3) | 0 (0.0) | 0 (0.0) | 5 (2.8) | 1 (20.0) | 4 (6.1) | 0 (0.0) |

Participant characteristics stratified by combined limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC) and hippocampal sclerosis (HS) case status. Participants missing data for either LATE-NC or HS are labeled as “inconclusive.” NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; SD = standard deviation; HS = hippocampal sclerosis; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological changes; B-ASC = brain arteriolosclerosis.

**Supplemental Table 6:** Adjusted limbic predominant age-related TDP-43 encephalopathy (LATE) Stage 1 (vs. LATE Stage 0) odds ratios for risk variants.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **MOI** | **SNV** | **Effect Allele** | **NACC** | | **ROSMAP** | | **Meta-Analysis** | | |
| **OR** | **P-value** | **OR** | **P-value** | **OR** | **95% CI** | **P-value** |
| *TMEM106B* | Additive | rs7781670 | G | 1.65 | 0.192 | 1.26 | 0.121 | 1.30 | 0.99 - 1.70 | 0.055 |
| *TMEM106B* | Additive | rs1990622 | G | 1.94 | 0.088 | 1.29 | 0.082 | **1.36** | **1.04 - 1.78** | **0.026** |
| *GRN* | Additive | rs5848 | T | 1.30 | 0.474 | 1.11 | 0.537 | 1.14 | 0.85 - 1.54 | 0.391 |
| *ABCC9* | Additive | rs1914361 | G | 1.32 | 0.414 | 1.19 | 0.261 | 1.21 | 0.92 - 1.59 | 0.174 |
| *ABCC9* | Recessive | rs1914361 | G | 0.90 | 0.859 | 1.33 | 0.258 | 1.26 | 0.80 - 1.98 | 0.326 |
| *ABCC9* | Additive | rs704178 | C | 0.98 | 0.947 | 0.96 | 0.793 | 0.96 | 0.73 - 1.27 | 0.789 |
| *ABCC9* | Recessive | rs704178 | C | 0.87 | 0.818 | 0.97 | 0.892 | 0.95 | 0.60 - 1.51 | 0.830 |
| *APOE* | Additive | rs769449 | A | 0.78 | 0.564 | 1.67 | 0.032 | 1.39 | 0.92 - 2.09 | 0.114 |
| *APOE* | N/A | ε4 Carrier | N/A | 0.90 | 0.778 | 1.53 | 0.065 | 1.33 | 0.90 - 1.97 | 0.149 |

Adjusted effects of single nucleotide variants (SNV) on limbic predominant age-related TDP-43 encephalopathy (LATE) Stage 1 (vs. LATE Stage 0). A separate regression model was fit for each variant and mode of inheritance (MOI). All models also adjust for sex, age at death, first three principal components, and cohort/study. NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; MOI = mode of inheritance; SNV = single-nucleotide variant; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological change; OR = odds ratio; CI = confidence interval.

**Supplemental Table 7:** Adjusted neurofibrillary tangles (Braak NFT Stages V/VI) odds ratios for risk variants.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **MOI** | **SNV** | **Effect Allele** | **NACC** | | **ROSMAP** | | **Meta-Analysis** | | |
| **OR** | **P-value** | **OR** | **P-value** | **OR** | **95% CI** | **P-value** |
| *TMEM106B* | Additive | rs7781670 | G | 0.98 | 0.910 | 1.17 | 0.177 | 1.09 | 0.92 - 1.30 | 0.331 |
| *TMEM106B* | Additive | rs1990622 | G | 0.97 | 0.830 | 1.16 | 0.194 | 1.08 | 0.91 - 1.29 | 0.390 |
| *GRN* | Additive | rs5848 | T | 0.88 | 0.389 | 0.81 | 0.105 | 0.84 | 0.69 - 1.02 | 0.076 |
| *ABCC9* | Additive | rs1914361 | G | 1.07 | 0.600 | 1.07 | 0.564 | 1.07 | 0.90 - 1.28 | 0.436 |
| *ABCC9* | Recessive | rs1914361 | G | 1.19 | 0.486 | 1.07 | 0.740 | 1.11 | 0.82 - 1.51 | 0.488 |
| *ABCC9* | Additive | rs704178 | C | 1.03 | 0.820 | 1.02 | 0.867 | 1.03 | 0.86 - 1.22 | 0.783 |
| *ABCC9* | Recessive | rs704178 | C | 1.11 | 0.626 | 1.04 | 0.854 | 1.07 | 0.80 - 1.43 | 0.642 |
| *APOE* | Additive | rs769449 | A | 2.76 | 2.221 x 10-7 | 2.31 | 1.691 x 10-6 | **2.50** | **1.93 - 3.23** | **2.212 x 10-12** |
| *APOE* | N/A | ε4 Carrier | N/A | 3.82 | 1.561 x 10-10 | 2.84 | 2.367 x 10-8 | **3.24** | **2.46 - 4.26** | **3.580 x 10-17** |

Adjusted effects of single nucleotide variants (SNV) on neurofibrillary tangles. Neurofibrillary tangles were defined as a Braak stage of V or VI. A separate regression model was fit for each variant and mode of inheritance (MOI). All models also adjust for sex, age at death, first three principal components, and cohort/study. NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; MOI = mode of inheritance; SNV = single-nucleotide variant; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological change; OR = odds ratio; CI = confidence interval.

**Supplemental Table 8:** Adjusted frequent neuritic plaque odds ratios for risk variants.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **MOI** | **SNV** | **Effect Allele** | **NACC** | | **ROSMAP** | | **Meta-Analysis** | | |
| **OR** | **P-value** | **OR** | **P-value** | **OR** | **95% CI** | **P-value** |
| *TMEM106B* | Additive | rs7781670 | G | 0.89 | 0.389 | 0.90 | 0.319 | 0.89 | 0.75 - 1.06 | 0.188 |
| *TMEM106B* | Additive | rs1990622 | G | 0.84 | 0.212 | 0.92 | 0.436 | 0.89 | 0.75 - 1.05 | 0.165 |
| *GRN* | Additive | rs5848 | T | 0.78 | 0.086 | 0.99 | 0.902 | 0.89 | 0.75 - 1.07 | 0.228 |
| *ABCC9* | Additive | rs1914361 | G | 1.16 | 0.278 | 1.07 | 0.548 | 1.10 | 0.93 - 1.31 | 0.248 |
| *ABCC9* | Recessive | rs1914361 | G | 1.44 | 0.137 | 1.03 | 0.860 | 1.17 | 0.87 - 1.57 | 0.297 |
| *ABCC9* | Additive | rs704178 | C | 1.08 | 0.549 | 0.95 | 0.636 | 1.00 | 0.85 - 1.19 | 0.984 |
| *ABCC9* | Recessive | rs704178 | C | 1.10 | 0.650 | 0.94 | 0.728 | 1.01 | 0.76 - 1.33 | 0.962 |
| *APOE* | Additive | rs769449 | A | 1.98 | 3.805 x 10-5 | 2.84 | 8.477 x 10-10 | **2.36** | **1.87 - 2.98** | **4.664 x 10-13** |
| *APOE* | N/A | ε4 Carrier | N/A | 2.36 | 1.150 x 10-5 | 3.09 | 1.819 x 10-10 | **2.74** | **2.12 - 3.54** | **1.712 x 10-14** |

Adjusted effects of single nucleotide variants (SNV) on frequent neuritic plaques. A separate regression model was fit for each variant and mode of inheritance (MOI). All models also adjust for sex, age at death, first three principal components, and cohort/study. NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; MOI = mode of inheritance; SNV = single-nucleotide variant; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological change; OR = odds ratio; CI = confidence interval.

**Supplemental Figure**

**Supplemental Figure 1:** Variant-level results for *KCNMB2*.

Chart, scatter chart

Description automatically generated

Adjusted, meta-analytic, single nucleotide variant (SNV)-level p-values for hippocampal sclerosis (HS) and limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) across KCNMB2 ± 10kb. All analyses were adjusted for sex, age at death, cohort/study, and the first three genetic principal components. The horizontal dashed line represents the Bonferroni-corrected threshold for significance that accounts for the number of independent tests in the KCNMB2 ± 10kb region. A diamond represents the SNV with the smallest p-value. The previously identified KCNMB2 SNV (Beecham et al., 2014) is labeled and identified with an arrow. MOI = mode of inheritance; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological change; HS = hippocampal sclerosis.