

A genome-wide association study links small-vessel ischemic stroke to autophagy

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Supplementary Table 1. Summary of discovery studies of top 33 SNPs in trend tests.

| Chr. | Position | SNP | Gene | Allele 1 | Allele 2 | Risk allele | RAF controls | RAF cases | Discovery | Trend P | Risk allele OR | 95%CI |
|------|-----------|-------------|-----------------------------|----------|----------|-------------|--------------|-----------|-----------|---------|----------------|-------------|
| 2 | 742685 | rs60477084 | <i>TMEM18, LINC01115</i> | A | G | A | 0.3326 | 0.4065 | 1.70E-04 | | 1.374 | 1.16 1.628 |
| 2 | 57922033 | rs6732639 | <i>VRK2, CCDC85A</i> | C | T | C | 0.2182 | 0.2794 | 4.35E-04 | | 1.39 | 1.154 1.674 |
| 2 | 120187344 | rs11123523 | <i>TMEM37, DBI</i> | A | G | A | 0.4236 | 0.4868 | 2.18E-03 | | 1.291 | 1.095 1.522 |
| 2 | 120191460 | rs2579631 | <i>TMEM37</i> | C | T | C | 0.4222 | 0.4839 | 2.91E-03 | | 1.283 | 1.089 1.513 |
| 2 | 129505509 | rs3907871 | <i>HS6ST1, LOC101927881</i> | T | C | C | 0.6952 | 0.7559 | 1.33E-03 | | 1.358 | 1.123 1.642 |
| 2 | 146779043 | rs12479100 | <i>PABPC1P2, TEX41</i> | C | T | C | 0.104 | 0.153 | 2.27E-04 | | 1.557 | 1.227 1.977 |
| 3 | 11325276 | rs2594966 | <i>ATG7</i> | G | A | A | 0.6155 | 0.6959 | 7.00E-05 | | 1.43 | 1.198 1.706 |
| 3 | 11395821 | rs2594973 | <i>ATG7</i> | C | G | G | 0.5948 | 0.6795 | 3.24E-05 | | 1.445 | 1.212 1.722 |
| 3 | 11443223 | rs4684776 | <i>ATG7</i> | C | T | T | 0.6096 | 0.6877 | 1.08E-04 | | 1.41 | 1.183 1.681 |
| 3 | 11450873 | rs34843621 | <i>ATG7</i> | G | A | A | 0.6914 | 0.7625 | 1.79E-04 | | 1.433 | 1.184 1.734 |
| 3 | 11474823 | rs12637318 | <i>ATG7</i> | T | C | C | 0.693 | 0.7625 | 2.50E-04 | | 1.422 | 1.176 1.721 |
| 3 | 140492139 | rs3923751 | <i>SLC25A36, TRIM42</i> | G | A | A | 0.9094 | 0.9515 | 2.65E-04 | | 1.952 | 1.351 2.823 |
| 3 | 140527761 | rs74282906 | <i>SLC25A36, TRIM42</i> | G | T | T | 0.9097 | 0.9518 | 2.62E-04 | | 1.958 | 1.354 2.83 |
| 3 | 186451236 | rs4686799 | <i>KNG1</i> | T | C | C | 0.6598 | 0.7108 | 9.95E-03 | | 1.268 | 1.057 1.521 |
| 4 | 126077143 | rs78868369 | <i>ANKRD50, FAT4</i> | T | C | T | 0.08449 | 0.1268 | 4.81E-04 | | 1.574 | 1.219 2.033 |
| 4 | 175913798 | rs10026079 | <i>ADAM29, GPM6A</i> | T | C | C | 0.9286 | 0.9575 | 6.28E-03 | | 1.731 | 1.168 2.566 |
| 4 | 175919987 | rs10005382 | <i>ADAM29, GPM6A</i> | G | C | C | 0.9283 | 0.9576 | 5.51E-03 | | 1.745 | 1.177 2.587 |
| 5 | 81778496 | rs224844 | <i>MIR3977, ATP6AP1L</i> | T | C | T | 0.455 | 0.5297 | 4.63E-04 | | 1.349 | 1.143 1.592 |
| 5 | 139539514 | rs2291878 | | G | A | G | 0.1969 | 0.2574 | 2.91E-04 | | 1.413 | 1.167 1.711 |
| 6 | 168098215 | rs536348 | <i>LOC441178, C6orf123</i> | T | C | C | 0.6407 | 0.7132 | 2.52E-04 | | 1.395 | 1.165 1.67 |
| 8 | 6067096 | rs73188691 | <i>CSMD1, LOC100287015</i> | C | A | C | 0.07093 | 0.1033 | 2.72E-03 | | 1.51 | 1.138 2.003 |
| 8 | 104096256 | rs17201317 | <i>ATP6V1C1, BAALCOS</i> | C | T | C | 0.1096 | 0.1485 | 3.45E-03 | | 1.417 | 1.118 1.796 |
| 10 | 70380498 | rs12764361 | <i>TET1</i> | A | C | A | 0.1288 | 0.1672 | 7.05E-03 | | 1.358 | 1.085 1.7 |
| 10 | 72944439 | rs117743525 | <i>PCBD1, UNC5B</i> | T | G | G | 0.9324 | 0.9603 | 6.60E-03 | | 1.753 | 1.167 2.634 |
| 11 | 100057536 | rs11223142 | <i>CNTN5</i> | G | A | G | 0.4477 | 0.5294 | 9.72E-05 | | 1.388 | 1.177 1.637 |
| 12 | 12810328 | rs2900298 | <i>CREBL2, GPR19</i> | C | G | G | 0.4991 | 0.5718 | 6.37E-04 | | 1.34 | 1.136 1.582 |
| 12 | 15176510 | rs2263590 | <i>LOC101928340, RERG</i> | A | G | A | 0.2693 | 0.3413 | 1.93E-04 | | 1.406 | 1.178 1.678 |
| 12 | 58097750 | rs75013973 | <i>OS9</i> | G | A | G | 0.141 | 0.1969 | 2.60E-04 | | 1.494 | 1.204 1.853 |
| 13 | 59812089 | rs9570072 | <i>LOC101926897, DIAPH3</i> | C | T | T | 0.8327 | 0.8864 | 4.56E-04 | | 1.569 | 1.217 2.021 |
| 14 | 22587753 | rs2141974 | <i>OR4E2, DAD1</i> | C | T | C | 0.07259 | 0.1147 | 2.65E-04 | | 1.655 | 1.26 2.174 |
| 14 | 80872021 | rs11846182 | <i>DIO2-AS1</i> | C | T | T | 0.602 | 0.6754 | 2.58E-04 | | 1.376 | 1.156 1.638 |
| 15 | 82234966 | rs7163891 | <i>LOC101929655, MEX3B</i> | C | T | C | 0.07423 | 0.1147 | 4.28E-04 | | 1.616 | 1.236 2.112 |
| 19 | 575964 | rs2238542 | <i>BSG</i> | T | C | T | 0.2188 | 0.2657 | 8.07E-03 | | 1.291 | 1.069 1.561 |

Supplementary Table 2. Summary of replication studies of top 33 SNPs in trend tests.

| Chr. | Position | SNP | Gene | Allele 1 | Allele 2 | Risk allele | RAF controls | RAF cases | Discovery | Trend <i>P</i> | Risk allele OR | 95%CI | |
|------|-----------|-------------|-----------------------------|----------|----------|-------------|--------------|-----------|-----------|----------------|----------------|--------|-------|
| 2 | 742685 | rs60477084 | <i>TMEM18, LINC01115</i> | A | G | A | 0.347 | 0.4016 | 4.08E-02 | | 1.263 | 1.011 | 1.577 |
| 2 | 57922033 | rs6732639 | <i>VRK2, CCDC85A</i> | C | T | C | 0.2146 | 0.266 | 2.51E-02 | | 1.326 | 1.035 | 1.699 |
| 2 | 120187344 | rs11123523 | <i>TMEM37, DBI</i> | A | G | A | 0.4243 | 0.4973 | 7.79E-03 | | 1.342 | 1.08 | 1.668 |
| 2 | 120191460 | rs2579631 | <i>TMEM37</i> | C | T | C | 0.4202 | 0.4973 | 5.03E-03 | | 1.365 | 1.098 | 1.697 |
| 2 | 129505509 | rs3907871 | <i>HS6ST1, LOC101927881</i> | T | C | C | 0.6979 | 0.7633 | 9.60E-03 | | 1.396 | 1.084 | 1.797 |
| 2 | 146779043 | rs12479100 | <i>PABPC1P2, TEX41</i> | C | T | C | 0.0949 | 0.129 | 4.06E-02 | | 1.413 | 1.015 | 1.968 |
| 3 | 11325276 | rs2594966 | <i>ATG7</i> | G | A | A | 0.6105 | 0.6765 | 1.31E-02 | | 1.334 | 1.059 | 1.681 |
| 3 | 11395821 | rs2594973 | <i>ATG7</i> | C | G | G | 0.5918 | 0.6489 | 3.38E-02 | | 1.275 | 1.017 | 1.598 |
| 3 | 11443223 | rs4684776 | <i>ATG7</i> | C | T | T | 0.6067 | 0.6729 | 1.19E-02 | | 1.334 | 1.06 | 1.678 |
| 3 | 11450873 | rs34843621 | <i>ATG7</i> | G | A | A | 0.6839 | 0.738 | 3.35E-02 | | 1.302 | 1.019 | 1.664 |
| 3 | 11474823 | rs12637318 | <i>ATG7</i> | T | C | C | 0.6865 | 0.742 | 2.87E-02 | | 1.314 | 1.027 | 1.68 |
| 3 | 140492139 | rs3923751 | <i>SLC25A36, TRIM42</i> | G | A | A | 0.9233 | 0.9521 | 4.75E-02 | | 1.652 | 1.006 | 2.711 |
| 3 | 140527761 | rs74282906 | <i>SLC25A36, TRIM42</i> | G | T | T | 0.9233 | 0.9521 | 4.72E-02 | | 1.653 | 1.007 | 2.714 |
| 3 | 186451236 | rs4686799 | <i>KNG1</i> | T | C | C | 0.6454 | 0.7486 | 1.06E-04 | | 1.637 | 1.276 | 2.099 |
| 4 | 126077143 | rs78868369 | <i>ANKRD50, FAT4</i> | T | C | T | 0.08796 | 0.133 | 4.55E-03 | | 1.59 | 1.146 | 2.208 |
| 4 | 175913798 | rs10026079 | <i>ADAM29, GPM6A</i> | T | C | C | 0.9229 | 0.9681 | 1.71E-03 | | 2.535 | 1.401 | 4.589 |
| 4 | 175919987 | rs10005382 | <i>ADAM29, GPM6A</i> | G | C | C | 0.9225 | 0.9654 | 3.01E-03 | | 2.345 | 1.323 | 4.155 |
| 5 | 81778496 | rs224844 | <i>MIR3977, ATP6AP1L</i> | T | C | T | 0.4419 | 0.5133 | 1.05E-02 | | 1.332 | 1.072 | 1.655 |
| 5 | 139539514 | rs2291878 | | G | A | G | 0.1883 | 0.242 | 1.45E-02 | | 1.376 | 1.065 | 1.778 |
| 6 | 168098215 | rs536348 | <i>LOC441178, C6orf123</i> | T | C | C | 0.6395 | 0.7234 | 1.26E-03 | | 1.474 | 1.16 | 1.874 |
| 8 | 6067096 | rs73188691 | <i>CSMD1, LOC100287015</i> | C | A | C | 0.06926 | 0.1117 | 3.05E-03 | | 1.69 | 1.184 | 2.413 |
| 8 | 104096256 | rs17201317 | <i>ATP6V1C1, BAALCOS</i> | C | T | C | 0.1093 | 0.1738 | 2.99E-04 | | 1.715 | 1.276 | 2.304 |
| 10 | 70380498 | rs12764361 | <i>TET1</i> | A | C | A | 0.1296 | 0.1962 | 5.56E-04 | | 1.639 | 1.238 | 2.171 |
| 10 | 72944439 | rs117743525 | <i>PCBD1, UNC5B</i> | T | G | G | 0.9324 | 0.9814 | 1.75E-04 | | 3.824 | 1.782 | 8.208 |
| 11 | 100057536 | rs11223142 | <i>CNTN5</i> | G | A | G | 0.453 | 0.5134 | 2.80E-02 | | 1.274 | 1.025 | 1.583 |
| 12 | 12810328 | rs2900298 | <i>CREBL2, GPR19</i> | C | G | G | 0.5028 | 0.5695 | 1.71E-02 | | 1.308 | 1.051 | 1.629 |
| 12 | 15176510 | rs2263590 | <i>LOC101928340, RERG</i> | A | G | A | 0.2882 | 0.3431 | 2.91E-02 | | 1.29 | 1.025 | 1.623 |
| 12 | 58097750 | rs75013973 | <i>OS9</i> | G | A | G | 0.1308 | 0.1685 | 4.68E-02 | | 1.346 | 0.9998 | 1.812 |
| 13 | 59812089 | rs9570072 | <i>LOC101926897, DIAPH3</i> | C | T | T | 0.827 | 0.8803 | 9.36E-03 | | 1.539 | 1.108 | 2.136 |
| 14 | 22587753 | rs2141974 | <i>OR4E2, DAD1</i> | C | T | C | 0.06365 | 0.09358 | 2.73E-02 | | 1.519 | 1.035 | 2.228 |
| 14 | 80872021 | rs11846182 | <i>DIO2-AS1</i> | C | T | T | 0.6135 | 0.6818 | 9.98E-03 | | 1.35 | 1.07 | 1.702 |
| 15 | 82234966 | rs7163891 | <i>LOC101929655, MEX3B</i> | C | T | C | 0.06759 | 0.09893 | 2.71E-02 | | 1.515 | 1.043 | 2.2 |
| 19 | 575964 | rs2238542 | <i>BSG</i> | T | C | T | 0.2233 | 0.3059 | 4.53E-04 | | 1.533 | 1.207 | 1.946 |

Supplementary Figure 1:

B.

| ATG7 SNP1 | ATG7 SNP2 | D' | r ² |
|------------|------------|-------|----------------|
| rs2594966 | rs2594973 | 0.987 | 0.893 |
| rs2594966 | rs4684776 | 0.820 | 0.655 |
| rs2594966 | rs34843621 | 0.818 | 0.48 |
| rs2594966 | rs12637318 | 0.827 | 0.486 |
| rs2594973 | rs4684776 | 0.881 | 0.729 |
| rs2594973 | rs34843621 | 0.924 | 0.564 |
| rs2594973 | rs12637318 | 0.937 | 0.573 |
| rs4684776 | rs34843621 | 0.983 | 0.678 |
| rs4684776 | rs12637318 | 0.993 | 0.683 |
| rs34843621 | rs12637318 | 0.998 | 0.984 |

Supplementary Figure 1: LD structure and logistic regression analyses within the *ATG7* region. (A) $-\log_{10}$ (P values) of SNPs for the best test from the primary scan as a function of genomic positions for the *ATG7* region. (B) LD patterns, D' value and r^2 among the disease-associated SNPs within the *ATG7* region (Chr3: 11,313,995-11,599,139 based on ensemble version v.GRCh37).