**Online Supplementary Materials**

**Supplementary Table S1.** SNP information of the COX-related genes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **SNP ID** | **Allele** | **MAF a** | **Chr.** | **Position** | **Annotation** | **HWE b (control)** | **Tag SNPs c** |
| *LRPPRC* | rs12465555 | A/G | 0.43 | 2 | 44118189 | intron | 0.268 | 2 |
| *LRPPRC* | rs13387221 | A/G | 0.43 | 2 | 44135314 | intron | 0.448 | 5 |
| *LRPPRC* | rs4953041 | A/G | 0.48 | 2 | 44194500 | intron | 0.538 | 3 |
| *LRPPRC* | rs4953042 | T/C | 0.47 | 2 | 44201376 | synonymous | 0.495 | 1 |
| *COX5B* | rs1800649 | T/C | 0.35 | 2 | 98264857 | 3' near | 0.763 | 20 |
| *COX5B* | rs1470625 | A/C | 0.43 | 2 | 98265491 | near gene | 0.889 | 24 |
| *COX7C* | rs13177204 | G/A | 0.25 | 5 | 85916034 | intron | 1.000 | 3 |
| *COX7A2* | rs240418 | C/T | 0.25 | 6 | 75950262 | intron | 1.000 | 34 |
| *COX7A2* | rs9360898 | G/T | 0.22 | 6 | 75953705 | 5' near | 0.040 | 1 |
| *NDUFA4* | rs12671052 | C/T | 0.15 | 7 | 10972673 | 3' UTR | 0.137 | 22 |
| *NDUFA4* | rs7789764 | C/T | 0.29 | 7 | 10973362 | intron | 1.000 | 11 |
| *NDUFA4* | rs218979 | G/A | 0.29 | 7 | 10975011 | intron | 0.188 | 3 |
| *NDUFA4* | rs12667441 | A/G | 0.18 | 7 | 10976057 | intron | 0.225 | 22 |
| *COX6C* | rs4626565 | C/T | 0.15 | 8 | 100890542 | intron | 0.586 | 37 |
| *COX6C* | rs1130569 | T/C | 0.22 | 8 | 100899793 | synonymous | 0.786 | 21 |
| *SURF1* | rs72619327 | G/C | 0.19 | 9 | 136219448 | p.D202H | 0.162 | 2 |
| *SURF1* | rs571549 | C/T | 0.29 | 9 | 136221213 | intron | 0.748 | 29 |
| *COX15* | rs2231687 | T/C | 0.21 | 10 | 101473218 | 3' UTR | 0.614 | 141 |
| *COX15* | rs2300984 | A/G | 0.38 | 10 | 101476857 | intron | 0.347 | 27 |
| *COX15* | rs2269196 | C/T | 0.45 | 10 | 101485091 | intron | 0.048 | 1 |
| *COX8A* | rs480211 | T/C | 0.17 | 11 | 63739439 | near gene | 0.503 | 3 |
| *COX6A1* | rs2076022 | C/T | 0.30 | 12 | 120875790 | 5'near | 0.727 | 13 |
| *COX5A* | rs1133322 | C/T | 0.22 | 15 | 75212357 | 3'near | 0.093 | 16 |
| *COX5A* | rs12909335 | G/T | 0.14 | 15 | 75214789 | intron | 0.307 | 14 |
| *COX4I1* | rs1800647 | T/C | 0.49 | 16 | 85834160 | intron | 0.784 | 8 |
| *COX4I1* | rs2733954 | T/C | 0.25 | 16 | 85836256 | intron | 0.547 | 20 |
| *SCO1* | rs2662959 | A/G | 0.44 | 17 | 10583589 | intron | 0.945 | 76 |
| *SCO1* | rs2662944 | T/C | 0.42 | 17 | 10594879 | intron | 0.232 | 57 |
| *COX10* | rs10775377 | A/C | 0.50 | 17 | 13964744 | intron | 0.026 | 29 |
| *COX10* | rs11078223 | A/G | 0.33 | 17 | 13984762 | intron | 0.470 | 22 |
| *COX10* | rs3785688 | A/G | 0.21 | 17 | 14004892 | intron | 0.466 | 4 |
| *COX10* | rs9891988 | A/T | 0.45 | 17 | 14024479 | intron | 0.580 | 10 |
| *COX10* | rs11078224 | T/C | 0.25 | 17 | 14033964 | intron | 0.845 | 9 |
| *COX10* | rs2530377 | T/C | 0.34 | 17 | 14067760 | intron | 0.419 | 46 |
| *COX10* | rs11078233 | C/T | 0.39 | 17 | 14110852 | 3' UTR | 0.031 | 18 |
| *COX6B1* | rs10420252 | A/G | 0.11 | 19 | 36139172 | 5' UTR | 0.775 | 4 |
| *COX6B1* | rs3761090 | A/G | 0.11 | 19 | 36149450 | intron | 0.714 | 46 |
| *COX6B1* | rs2267584 | G/A | 0.48 | 19 | 36156588 | 5'near gene | 0.838 | 7 |
| *COX6B2* | rs1466304 | A/G | 0.11 | 19 | 55864403 | intron | 0.327 | 8 |
| *COX6B2* | rs11084396 | C/T | 0.27 | 19 | 55865527 | intron | 0.778 | 2 |
| *SCO2* | rs140523 | G/C | 0.26 | 22 | 50962782 | p.R20P | 0.413 | 16 |

a MAF: minor allele frequency.

b HWE: *P*-value for Hardy-Weinberg equilibrium test was estimated based on the pooled 859 controls from the East China and Southwest China, a *P*-value < 0.01 indicates the deviation from Hardy-Weinberg equilibrium.

c Number of SNPs that could be tagged (*r2*>0.8) by the querying SNP. The “Tag SNPs” value of 2 for rs12465555 means that a total of 2 SNPs could be tagged by rs12465555.

**Supplementary Table S2.** PCR and extension primers of SNPs in the COX-related genes

|  |  |  |  |
| --- | --- | --- | --- |
| **SNP ID** | **PCR primer upper/lower (5’-3’)** | **Extension primer** | **Tail a** |
| rs2300984 | TTCATTTCCTTTTCAGTGCTG / GCTGGGCTGAGGCATGTTA | TTACTTATGCTAAAATACTGTGCGC | - |
| rs10775377 | ATGATTCTAGTTGTCTGTCCATGTC / GTGTATTATGATGCTTAAGCTACTGTTTA | CTCACTGAATGCATCAACCAGGATG | t(agct)1 |
| rs218979 | ATTATTTGTTGCCATGCTATAATCTAG / CACAACATATTCTGATCTTAGCTTTG | AGGCCCAGCAATACTTCTCAACTGA | ct(agct)2 |
| rs1800647 | TCCCTGTGAGCTGTCACC / AAATGCTAACAAGGTGACTCTGA | CCCCACCGCTCCCTGAAGAATGGAG | gct(agct)3 |
| rs13387221 | AAGAGGAACGACAGAAAATC / AAACCATATTCTTAGGGAATTTAGG | AGTGCTACTCTCAAAAGATAAAGTA | (agct)5 |
| rs480211 | CCTCCAGAAGTCAGCTTTG / ATTAGCCTCTACTGTGTGTTAGGAA | GACAAGAAACTCTATCCACCTCGTT | t(agct)6 |
| rs72619327 | ATTCTGGCCATAGCTTCCA / ATGCAATCTCACACACCTTC | GTCAGCCTCACCATCCCAATGAGGT | t(agct)8 |
| rs12667441 | ATTATCGGAATCATCTGTTACACTTT / AAGTAAACAAACAAACAAAAAAACTAGC | CCCATAGATTCCAATACGCTCTTTG | t(agct)9 |
| rs2076022 | CATGCTCTCTCTTGCCCG / CCCTCCCACTGGCATTAA | ATGCCGAGGATTTTGACAAGGACTC | t(agct)10 |
| rs10420252 | ATGAACAAGCATTTAGCCCA / AAGCTGAGAGAGGTGGGG | AGTGGCCTCCTCCTGGGAGGGAGCT | t(agct)11 |
| rs12671052 | ACCCTGCACCAAGACTCA / GAAGTTGAAATCTGAGTTTATCAGTG | GCCAAAATTCTCAAGATCTCTTGAC | t(agct)12 |
| rs11078223 | TTAGCTAGATGAAGTGGATTGCTA / AAAATACCTGCTTCACCTCAAG | GAGACATAAAATAAGAGCTGAGAGC | t(agct)13 |
| rs2733954 | TTGGGATATTTGTGTGGTGAT / ATTGTAAGGAATGTTTGTCACCG | CACCTGAGTAAGGGGTGCCCAGATA | - |
| rs11078224 | TACCCTTATAGGATTTTTTTTCTAAGAGT / TGGCAAAGAAAACAGCCA | AATTTTTAAATTTTCTTTTTTGTTA | gct(agct)3 |
| rs9891988 | TAGTGATTTCAGTTCTGAAAATGTATTT / TGATATCAAGGGTGAGATGAAATA | TTCATAACTTCCAGTTCTCTTTTTA | t(agct)6 |
| rs2530377 | TCTGTACATTTTTAAAAGGGAATTTG / CTTGCACAAATGTATATCTTATTATTGTC | AAACATACAAAAACATGATAGAACA | t(agct)7 |
| rs240418 | CTCCTTAAATCCCTAGAATTAAAGTATTT / TGCTGACTTTTAGGAATTCTTATTTT | AAAAGACCTACAATTTTCTTTATTC | t(agct)9 |
| rs2269196 | TGGATATTCTAATTACCTTGATTTCAT / AGATAAGGTATGGGAGAAGAAAGTG | TGCAAGAGACATTGAAAGATGAAGA | t(agct)11 |
| rs12465555 | AACCCCTAAGACAGAGGTGA / AAGTTGACTTCATGGAAACAGC | ACGTTCAGCAATCAAAGAGTCTCCC | t(agct)12 |
| rs2231687 | AATTAATGTGATTTTGGTCTCTATTGA / ATGTTTCTGATGCCTTCATCC | TTCATAGGGCCCTGTCTTATTCAAC | t(agct)13 |
| rs1133322 | AATTTTCTTGTTGACACCCTAGG / TCAGTGACCACTTTTAAACATCAT | GGTTGTCTGTGGGGATAGATCAAAT | - |
| rs9360898 | TCAGTCCCGTGATCTCGT / TCATAAATCGTTTGCTTTTTCC | CTGACCTTTTCGATGTTCAGTAGGC | t(agct)1 |
| rs2662959 | ATGGGTGATGAGTGGGTAC / CAAGCGTCCCACCCACCT | TAGATGGCTGCACACAGTTCTCAGG | ct(agct)2 |
| rs1466304 | TACGCCTGGCTGTGGGTG / ATTTCCCCTCCCAGAACA | CGTGGACACCAGGGGATTCTGTTGG | t(agct)6 |
| rs4953042 | AGACACTTGGGCCATCTTC / TTTTACTTTTAGTCACTGAAAAATTGG | TTGATACGGGGCATGCTAGTAAAAT | t(agct)7 |
| 1541G>A | GCTGATGTACTTTGGCTTCA / TCTGCTTCCAGCTGCCGC | TCACTGCCCTGACATCTGCCCAGAC | t(agct)8 |
| rs4626565 | AACACAAGTCAGTGACAAACTTCTAG / TCTACTAGTAGGAATAGACCTCAGTTGAT | AAGTTAGAGATAAACACTCTCTCAA | t(agct)9 |
| rs2267584 | CATCCTTTCCCTCAGCCC / ACCGAGGCAGAGCAGTGG | CGCCCATGTAGTCAGCCTCCTAAGC | t(agct)10 |
| rs1800649 | AACCCGTAATGCAATGAATG / AAATGATGGAGCCAATATTTTAAG | GACCACCTGGTATGAGAGAAAGGGG | t(agct)11 |
| rs3761090 | TTGCTCATCCCAGTCTGTG / TGGATATTGGTTGAACAAACAG | TCCCTCCGCAGTGGGGAAACTGAAC | t(agct)12 |
| rs571549 | AAATCATTCAGGGCACTTTTT / AAAGTCTTATTTTGAGTCCTGGG | CTCACGGTGAGACCTACATTATCTG | t(agct)13 |
| rs1470625 | AAAAAAGCCCACTTTAGCTG / AATTTTGTGAAGATAGTAACTGAAGC | CTTGGGACAAGTTAAAATCTCAAAA | - |
| rs12909335 | TAGGTGACAGAGTGAGACTCCG / TAGAAAGAAAAATATTCAGAATTCAAGG | TTTTCAGCATTTTCTGTTCAGTTTC | t(agct)1 |
| rs2662944 | ATCGAGCCTTGAATTGAGAG / ATATGTTTGTTCTGATTTTACAATGC | AAGGACACATTGCTTCTAACTCCAG | ct(agct)2 |
| rs4953041 | AAGCCTGGGAGGTCAAGG / TATATCTGTCTTTCTATCAATCGATCAT | CAGAGTGAGACACTGTCTCCAAAAC | t(agct)6 |
| rs11084396 | AGTTCTTCGCTGCTTCGTC / TGATCTGGAAGGTGCGGG | ACTGCTCCTCCTACCCAGACCCTGC | t(agct)7 |
| rs7789764 | CTTGCTGTAATCCACATTCACT / ATTCATATCTGTAATTGTTACTGTAGAAAAC | GATATTTTAAGTAATCTCAAATACA | t(agct)9 |
| rs3785688 | TATAAGAGATGATGGTCCCAGC / AAAAGGAGCAGCCTTGGT | GAGATGATAATCCTACAAGCCACCA | t(agct)10 |
| rs1130569 | TTTTTAGTTTCGTGTGGCTGA / AAAGATACCAGCCTTCCTCATC | CATACGCAGATTTCTACAGAAACTA | t(agct)11 |
| rs13177204 | ATAATTATGCAATTGTAAATCTGTGC / AAGTTGGAACGATCAAAAATGT | TAAATGAGGATGATTTTACAACACA | t(agct)12 |
| rs11078233 | TATTCTGTTTCTTCCTCCTCACA / AAGTGCCACTCTGCTGGG | GGGTACACATACACAGCTTCCTCTT | t(agct)13 |

aIn the “(agct)n”, n means repeats of “agct”.

**Supplementary Table S3.** The COX-related SNPs showed no association with AD in 333 AD cases and 435 normal controls from Southwest China

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP ID** | **Gene** | **Allele** | | ***P*-value a** | **Genotype** | | ***P*-value a** |
| **Case** | **Control** | **Case** | **Control** |
| rs12465555 | *LRPPRC* | 292/374 | 380/490 | 0.948 | 58/176/99 | 76/228/131 | 0.992 |
| rs13387221 | *LRPPRC* | 310/356 | 404/466 | 0.966 | 69/172/92 | 86/232/117 | 0.895 |
| rs4953041 | *LRPPRC* | 304/362 | 402/468 | 0.827 | 67/170/96 | 83/236/116 | 0.674 |
| rs4953042 | *LRPPRC* | 335/331 | 424/446 | 0.543 | 83/169/81 | 97/230/108 | 0.691 |
| rs1470625 | *COX5B* | 265/401 | 386/484 | 0.072 | 45/175/113 | 83/220/132 | 0.110 |
| rs240418 | *COX7A2* | 169/493 | 241/627 | 0.328 | 21/127/183 | 32/177/225 | 0.613 |
| rs7789764 | *NDUFA4* | 199/467 | 264/604 | 0.821 | 34/131/168 | 36/192/206 | 0.337 |
| rs218979 | *NDUFA4* | 144/516 | 221/649 | 0.103 | 19/106/205 | 24/173/238 | 0.090 |
| rs4626565 | *COX6C* | 97/569 | 118/752 | 0.575 | 2/93/238 | 6/106/323 | 0.330 |
| rs1130569 | *COX6C* | 98/568 | 118/752 | 0.520 | 2/94/237 | 6/106/323 | 0.298 |
| rs2231687 | *COX15* | 139/527 | 174/696 | 0.675 | 9/121/203 | 21/132/282 | 0.096 |
| rs2300984 | *COX15* | 260/406 | 335/535 | 0.832 | 51/158/124 | 69/197/169 | 0.837 |
| rs2269196 | *COX15* | 328/338 | 431/439 | 0.910 | 78/172/83 | 118/195/122 | 0.170 |
| rs480211 | *COX8A* | 131/535 | 163/707 | 0.645 | 12/107/214 | 17/129/289 | 0.756 |
| rs2076022 | *COX6A1* | 199/467 | 231/639 | 0.150 | 29/141/163 | 32/167/236 | 0.335 |
| rs1133322 | *COX5A* | 110/556 | 155/715 | 0.504 | 7/96/230 | 12/131/292 | 0.764 |
| rs12909335 | *COX5A* | 67/599 | 82/786 | 0.688 | 2/63/268 | 9/64/361 | 0.082 |
| rs1800647 | *COX4I1* | 308/358 | 408/462 | 0.800 | 64/180/89 | 98/212/125 | 0.317 |
| rs2733954 | *COX4I1* | 179/487 | 258/612 | 0.232 | 24/131/178 | 33/192/210 | 0.355 |
| rs2662959 | *SCO1* | 295/371 | 395/475 | 0.665 | 67/161/105 | 88/219/128 | 0.807 |
| rs2662944 | *SCO1* | 254/412 | 298/572 | 0.116 | 47/160/126 | 46/206/183 | 0.245 |
| rs10775377 | *COX10* | 285/381 | 370/500 | 0.917 | 61/163/109 | 85/200/150 | 0.715 |
| rs11078223 | *COX10* | 271/395 | 332/538 | 0.314 | 60/151/122 | 66/200/169 | 0.551 |
| rs3785688 | *COX10* | 138/526 | 186/684 | 0.777 | 13/112/207 | 24/138/273 | 0.538 |
| rs9891988 | *COX10* | 275/391 | 383/485 | 0.267 | 60/155/118 | 81/221/132 | 0.327 |
| rs11078224 | *COX10* | 138/528 | 207/661 | 0.146 | 11/116/206 | 25/157/252 | 0.226 |
| rs2530377 | *COX10* | 220/446 | 311/559 | 0.268 | 28/164/141 | 59/193/183 | 0.067 |
| rs3761090 | *COX6B1* | 62/600 | 93/777 | 0.395 | 2/58/271 | 3/87/345 | 0.676 |
| rs2267584 | *COX6B1* | 341/325 | 422/448 | 0.295 | 91/159/83 | 98/226/111 | 0.293 |
| rs1466304 | *COX6B2* | 48/618 | 77/793 | 0.243 | 2/44/287 | 2/73/360 | 0.385 |
| rs11084396 | *COX6B2* | 154/506 | 200/670 | 0.874 | 18/118/194 | 24/152/259 | 0.973 |
| rs140523 | *SCO2* | 208/458 | 266/604 | 0.783 | 33/142/158 | 41/184/210 | 0.962 |

a *P*-value, Fisher’s exact test.

**Supplementary Table S4.** The COX-related SNPs showed no association with AD in 380 AD cases and 424 normal controls from East China

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP ID** | **Gene** | **Allele** | | ***P*-value a** | **Genotype** | | ***P*-value a** |
| **Case** | **Control** | **Case** | **Control** |
| rs12465555 | *LRPPRC* | 327/429 | 374/474 | 0.732 | 60/207/111 | 81/212/131 | 0.331 |
| rs13387221 | *LRPPRC* | 322/438 | 367/481 | 0.713 | 62/198/120 | 81/205/138 | 0.473 |
| rs4953041 | *LRPPRC* | 373/387 | 407/439 | 0.698 | 88/197/95 | 103/201/119 | 0.447 |
| rs4953042 | *LRPPRC* | 357/403 | 402/446 | 0.863 | 77/203/100 | 96/210/118 | 0.525 |
| rs1470625 | *COX5B* | 329/431 | 335/513 | 0.124 | 66/197/117 | 67/201/156 | 0.200 |
| rs240418 | *COX7A2* | 180/580 | 225/623 | 0.189 | 21/138/221 | 31/163/230 | 0.411 |
| rs7789764 | *NDUFA4* | 234/522 | 264/584 | 0.938 | 33/168/177 | 45/174/205 | 0.504 |
| rs218979 | *NDUFA4* | 213/541 | 233/611 | 0.775 | 28/157/192 | 28/177/217 | 0.909 |
| rs2231687 | *COX15* | 165/595 | 195/653 | 0.537 | 15/135/230 | 21/153/250 | 0.759 |
| rs2300984 | *COX15* | 284/476 | 317/531 | 0.996 | 51/182/147 | 48/221/155 | 0.433 |
| rs2269196 | *COX15* | 344/412 | 389/459 | 0.882 | 77/190/111 | 92/205/127 | 0.844 |
| rs480211 | *COX8A* | 158/602 | 159/689 | 0.305 | 15/128/237 | 16/127/281 | 0.504 |
| rs2076022 | *COX6A1* | 227/533 | 224/624 | 0.124 | 24/179/177 | 26/172/226 | 0.151 |
| rs1133322 | *COX5A* | 128/628 | 139/709 | 0.772 | 8/112/258 | 6/127/291 | 0.750 |
| rs12909335 | *COX5A* | 74/682 | 77/765 | 0.661 | 4/66/308 | 1/75/345 | 0.339 |
| rs1800647 | *COX4I1* | 376/384 | 393/453 | 0.227 | 93/190/97 | 91/211/121 | 0.481 |
| rs2733954 | *COX4I1* | 195/561 | 210/630 | 0.716 | 25/145/208 | 27/156/237 | 0.924 |
| rs2662959 | *SCO1* | 340/416 | 375/471 | 0.795 | 73/194/111 | 84/207/132 | 0.787 |
| rs2662944 | *SCO1* | 267/493 | 306/540 | 0.664 | 42/183/155 | 52/202/169 | 0.859 |
| rs10775377 | *COX10* | 325/431 | 375/459 | 0.428 | 81/163/134 | 94/187/136 | 0.700 |
| rs11078223 | *COX10* | 299/459 | 321/527 | 0.513 | 66/167/146 | 63/195/166 | 0.607 |
| rs3785688 | *COX10* | 147/613 | 168/676 | 0.777 | 14/119/247 | 16/136/270 | 0.956 |
| rs11078224 | *COX10* | 161/595 | 178/670 | 0.881 | 16/129/233 | 19/140/265 | 0.939 |
| rs3761090 | *COX6B1* | 66/692 | 85/763 | 0.367 | 1/64/314 | 7/71/346 | 0.142 |
| rs2267584 | *COX6B1* | 349/409 | 398/450 | 0.721 | 82/185/112 | 96/206/122 | 0.935 |
| rs1466304 | *COX6B2* | 81/679 | 89/759 | 0.916 | 4/73/303 | 3/83/338 | 0.866 |
| rs11084396 | *COX6B2* | 188/572 | 209/623 | 0.860 | 17/154/209 | 23/163/230 | 0.766 |
| rs140523 | *SCO2* | 186/574 | 243/603 | 0.055 | 21/144/215 | 29/185/209 | 0.124 |

a *P*-value, Fisher’s exact test.

**Supplementary Table S5.** The COX-related SNPs showed no association with AD in combined Han Chinese population

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP ID** | **Gene** | **Case** | **Control-1 a** | ***P*-value b** | **Control-2 c** | ***P*-value b** | **IGAP**  ***P*-value d** | **PHRED e** | **eQTL *P*-value f** | **eQTL ID f** |
| rs12465555 | *LRPPRC* | 619/803 | 754/964 | 0.841 | 936/1198 | 0.863 | 0.41 | 3.214 | 0.59 | t2550790 |
| rs13387221 | *LRPPRC* | 632/794 | 771/947 | 0.754 | 960/1174 | 0.705 | 0.05 | 2.391 | 0.10 | t2550790 |
| rs4953041 | *LRPPRC* | 677/749 | 809/907 | 0.853 | 1007/1125 | 0.891 | 0.27 | 0.872 | 0.19 | t2550790 |
| rs4953042 | *LRPPRC* | 688/738 | 848/870 | 0.534 | 1061/1073 | 0.393 | 0.02 | 0.053 | 0.15 | t2550790 |
| rs1800649 | *COX5B* | 467/959 | 596/1122 | 0.252 | 724/1410 | 0.469 | 0.92 | 2.613 | 0.42 | t2495121 |
| rs1470625 | *COX5B* | 594/832 | 721/997 | 0.860 | 879/1255 | 0.808 | - | 7.203 | 0.21 | t2495121 |
| rs13177204 | *COX7C* | 315/1105 | 414/1300 | 0.194 | 523/1607 | 0.107 | 0.11 | 2.926 | - | - |
| rs240418 | *COX7A2* | 349/1073 | 466/1250 | 0.097 | 573/1559 | 0.128 | 0.66 | 2.099 | - | - |
| rs9360898 | *COX7A2* | 354/1072 | 388/1330 | 0.141 | 476/1658 | 0.082 | 0.34 | 8.002 | 0.51 | t2961300 |
| rs7789764 | *NDUFA4* | 433/989 | 528/1188 | 0.847 | 658/1474 | 0.824 | 0.32 | 1.515 | 0.91 | t3038617 |
| rs218979 | *NDUFA4* | 357/1057 | 454/1260 | 0.431 | 570/1560 | 0.329 | 0.22 | 1.242 | 0.79 | t3038617 |
| rs4626565 | *COX6C* | 188/1238 | 252/1466 | 0.232 | 322/1812 | 0.118 | 0.79 | 2.949 | 0.09 | t3146433 |
| rs1130569 | *COX6C* | 190/1236 | 254/1464 | 0.242 | 323/1811 | 0.144 | 0.74 | 1.088 | 0.09 | t3146433 |
| rs72619327 | *SURF1* | 221/1205 | 273/1445 | 0.763 | 342/1792 | 0.708 | - | 32 | - | - |
| rs2231687 | *COX15* | 304/1122 | 369/1349 | 0.913 | 468/1666 | 0.678 | 0.60 | 10.16 | 0.09 | t3303109 |
| rs2300984 | *COX15* | 544/882 | 652/1066 | 0.910 | 825/1309 | 0.779 | - | 6.155 | 0.36 | t3303109 |
| rs2269196 | *COX15* | 682/740 | 828/890 | 0.896 | 1033/1101 | 0.811 | 0.97 | 1.916 | 0.03 | t3303109 |
| rs480211 | *COX8A* | 289/1137 | 322/1396 | 0.282 | 394/1740 | 0.193 | 0.005 | 3.196 | 0.65 | t3334125 |
| rs1133322 | *COX5A* | 238/1184 | 294/1424 | 0.780 | 375/1759 | 0.526 | 0.11 | 11.15 | 0.28 | t3633221 |
| rs12909335 | *COX5A* | 141/1281 | 159/1551 | 0.559 | 206/1920 | 0.818 | 0.19 | 5.651 | 0.15 | t3633221 |
| rs1800647 | *COX4I1* | 684/742 | 801/915 | 0.472 | 1002/1130 | 0.584 | 0.87 | 5.917 | 0.61 | t3672455 |
| rs2733954 | *COX4I1* | 374/1048 | 468/1242 | 0.502 | 572/1554 | 0.699 | 0.83 | 1.487 | 0.99 | t3672455 |
| rs2662959 | *SCO1* | 635/787 | 770/946 | 0.903 | 939/1193 | 0.730 | 0.29 | 1.043 | 0.47 | t3745504 |
| rs2662944 | *SCO1* | 521/905 | 604/1112 | 0.436 | 765/1367 | 0.695 | 0.45 | 1.742 | 0.43 | t3745504 |
| rs10775377 | *COX10* | 610/812 | 745/959 | 0.644 | 945/1175 | 0.334 | 0.55 | 1.396 | 0.003 | t3711165 |
| rs11078223 | *COX10* | 570/854 | 653/1065 | 0.248 | 800/1334 | 0.131 | 0.54 | 0.399 | 0.01 | t3711165 |
| rs3785688 | *COX10* | 285/1139 | 354/1360 | 0.658 | 436/1694 | 0.766 | 0.27 | 4.022 | 0.66 | t3711165 |
| rs11078224 | *COX10* | 299/1123 | 385/1331 | 0.341 | 483/1649 | 0.265 | 0.72 | 0.505 | 0.05 | t3711165 |
| rs3761090 | *COX6B1* | 128/1292 | 178/1540 | 0.206 | 213/1921 | 0.353 | - | 5.072 | - | - |
| rs2267584 | *COX6B1* | 690/734 | 820/898 | 0.686 | 1015/1119 | 0.608 | 0.13 | 1.367 | 0.95 | t3830649 |
| rs1466304 | *COX6B2* | 129/1297 | 166/1552 | 0.555 | 205/1929 | 0.598 | - | 2.809 | - | - |
| rs11084396 | *COX6B2* | 342/1078 | 409/1293 | 0.972 | 525/1593 | 0.661 | 0.92 | 10.29 | 0.79 | t3871355 |
| rs140523 | *SCO2* | 394/1032 | 509/1207 | 0.210 | 632/1500 | 0.199 | 0.13 | 4.154 | 0.07 | t3965984 |

a Control-1 include 859 normal Han Chinese in this study.

b *P*-value, Fisher’s exact test

c Control-2 include 1067 normal controls (859 normal Han Chinese in this study, 103 Han Chinese from Beijing and 105 Han Chinese from South China in the 1000 Genomes Project phase 3 (<http://www.1000genomes.org>) ([Abecasis](#_ENREF_1" \o "Abecasis, 2012 #65) *[et al,](#_ENREF_1" \o "Abecasis, 2012 #65)* [2012](#_ENREF_1" \o "Abecasis, 2012 #65); [Auton](#_ENREF_3" \o "Auton, 2015 #64) *[et al,](#_ENREF_3" \o "Auton, 2015 #64)* [2015](#_ENREF_3" \o "Auton, 2015 #64)).

d The IGAP *P*-values for these SNPs were retrieved from IGAP datasets ([Lambert](#_ENREF_7" \o "Lambert, 2013 #6) *[et al,](#_ENREF_7" \o "Lambert, 2013 #6)* [2013](#_ENREF_7" \o "Lambert, 2013 #6)).

e The PHRED-like scaled CADD-score: a score greater than 10 indicates that the variant belongs to the top 10% most deleterious substitutions in human genome ([Kircher](#_ENREF_5" \o "Kircher, 2014 #67) *[et al,](#_ENREF_5" \o "Kircher, 2014 #67)* [2014](#_ENREF_5" \o "Kircher, 2014 #67)).

f The expression quantitative trait loci (eQTLs) data were retrieved from the BRAINEAC database ([Ramasamy](#_ENREF_13" \o "Ramasamy, 2014 #68) *[et al,](#_ENREF_13" \o "Ramasamy, 2014 #68)* [2014](#_ENREF_13" \o "Ramasamy, 2014 #68)) (<http://www.braineac.org/>).

**Supplementary Table S6.** Variants identified in the exons and flanking regions of the COX-related genes in 107 unrelated AD patients with high probability of hereditarily transmitted AD

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **rsID** | **Position** | **Variant** | **Function** | **Damaging a** | **AD b** | **Control c** | ***P*-value d** | **ExAC e** | **ExAC *P*-value d** |
| *COX15* | . | chr10: 101474424 | T/C | p.A385T | 3 | 1/195 | 0/160 | 1.00 | 22/7840 | 0.43 |
| *COX15* | rs201663231 | chr10: 101474377 | G/C | p.W400C | 4 | 1/193 | 3/733 | 1.00 | 7/7857 | 0.18 |
| *COX15* | rs202223821 | chr10: 101487348 | A/G | intron | - | 1/211 | 0/160 | 1.00 | 8/7858 | 0.21 |
| *COX15* | rs2231687 | chr10: 101473218 | G/A | p.F374L | 0 | 139/47 | 576/160 | 0.33 | 6048/1764 | 0.38 |
| *COX15* | rs2231682 | chr10: 101483799 | A/G | p.R222C | 4 | 2/210 | 2/574 | 0.29 | 42/7824 | 0.32 |
| *COX15* | rs142685489 | chr10: 101478296 | C/G | intron | - | 1/211 | 3/523 | 1.00 | 13/7773 | 0.31 |
| *COX8A* | rs7130187 | chr11: 63742174 | T/C | p.L8L | - | 10/202 | 33/703 | 0.85 | 372/4726 | 0.18 |
| *COX4I1* | rs11557187 | chr16: 85834818 | A/G | p.A3T | 1 | 66/146 | 223/513 | 0.87 | 2449/5407 | 1.00 |
| *COX4I1* | rs184745241 | chr16: 85840474 | A/G | p.K168K | - | 4/208 | 8/728 | 0.32 | 88/7752 | 0.31 |
| *COX4I1* | rs201890635 | chr16: 85840340 | T/G | spliceSite | - | 1/211 | 0/160 | 1.00 | 5/7859 | 0.15 |
| *COX4I1* | rs2733965 | chr16: 85838532 | G/A | intron | - | 212/0 | 736/0 | 1.00 | 7864/0 | 1.00 |
| *SCO1* | rs2271228 | chr17: 10595250 | C/T | p.P198P | - | 6/206 | 15/721 | 0.44 | 196/7670 | 0.66 |
| *COX10* | rs8076787 | chr17: 13972955 | T/C | p.R11R | - | 6/206 | 27/709 | 0.67 | 255/7553 | 1.00 |
| *COX10* | rs143814384 | chr17: 13977813 | CTTTA/C | intron | - | 195/5 | 725/11 | 0.36 | 7741/123 | 0.25 |
| *COX10* | rs2230351 | chr17: 13980058 | T/A | p.T62S | 1 | 27/185 | 85/651 | 0.63 | 926/6884 | 0.67 |
| *COX10* | rs2072279 | chr17: 13980350 | A/G | p.R159Q | 0 | 83/129 | 260/476 | 0.33 | 2988/4846 | 0.77 |
| *COX10* | rs144352489 | chr17: 14005395 | T/C | intron | - | 6/194 | 19/717 | 0.80 | 193/7657 | 0.64 |
| *COX10* | rs2159132 | chr17: 14005439 | A/G | p.L168L | - | 75/137 | 258/478 | 0.94 | 2683/5155 | 0.71 |
| *COX10* | . | chr17: 14063194 | C/T | p.F209L | 2 | 1/207 | 0/160 | 1.00 | 11/6583 | 0.31 |
| *COX10* | rs144296730 | chr17: 14110115 | ACCC/A | intron | - | 4/208 | 3/573 | 0.09 | 189/7651 | 0.82 |
| *COX6B1* | rs61220012 | chr19: 36142296 | A/G | intron | - | 27/185 | 90/646 | 0.81 | 911/5589 | 0.69 |
| *COX6B2* | rs144967211 | chr19: 55865062 | C/T | 3-UTR | - | 9/203 | 25/711 | 0.53 | 161/5173 | 0.31 |
| *LRPPRC* | rs2955280 | chr2: 44116836 | T/C | intron | - | 203/11 | 712/24 | 0.22 | 7436/406 | 1.00 |
| *LRPPRC* | rs2955281 | chr2: 44117046 | C/A | intron | - | 20/194 | 65/671 | 0.79 | 597/7115 | 0.37 |
| *LRPPRC* | rs74919473 | chr2: 44117563 | C/A | intron | - | 1/181 | 8/728 | 1.00 | - | - |
| *LRPPRC* | rs59645716 | chr2: 44117578 | T/C | intron | - | 64/118 | 289/447 | 0.35 | - | - |
| *LRPPRC* | rs76850904 | chr2: 44123758 | A/G | intron | - | 1/213 | 8/728 | 0.69 | 60/7764 | 1.00 |
| *LRPPRC* | rs3795859 | chr2: 44123759 | A/G | intron | - | 93/121 | 325/411 | 0.88 | 3479/4347 | 0.78 |
| *LRPPRC* | rs202033109 | chr2: 44139587 | C/T | p.M1087V | 0 | 1/213 | 2/574 | 1.00 | 10/7826 | 0.26 |
| *LRPPRC* | rs574336721 | chr2: 44145129 | T/C | intron | - | 1/213 | 0/366 | 0.37 | 5/6129 | 0.19 |
| *LRPPRC* | rs7568481 | chr2: 44145374 | T/G | intron | - | 202/12 | 713/23 | 0.10 | 7496/340 | 0.39 |
| *LRPPRC* | rs199706677 | chr2: 44145469 | A/G | p.R989C | 4 | 1/213 | 1/365 | 1.00 | 39/7789 | 1.00 |
| *LRPPRC* | rs4952694 | chr2: 44152180 | A/G | intron | - | 206/8 | 719/17 | 0.23 | 7558/296 | 1.00 |
| *LRPPRC* | rs117077213 | chr2: 44152190 | C/T | intron | - | 2/212 | 16/720 | 0.39 | 112/7748 | 0.77 |
| *LRPPRC* | rs72877173 | chr2: 44161457 | G/A | intron | - | 3/211 | 5/731 | 0.39 | 43/5527 | 0.24 |
| *LRPPRC* | rs143170527 | chr2: 44161854 | GA/G | intron | - | 6/204 | 4/316 | 0.20 | - | - |
| *LRPPRC* | rs28394191 | chr2: 44172444 | C/A | intron | - | 205/9 | 718/18 | 0.17 | 7543/285 | 0.58 |
| *LRPPRC* | rs118188415 | chr2: 44173344 | C/T | p.E706E | - | 5/209 | 13/723 | 0.57 | 141/7687 | 0.60 |
| *LRPPRC* | rs7594526 | chr2: 44173422 | G/T | intron | - | 201/11 | 713/23 | 0.21 | 7392/330 | 0.49 |
| *LRPPRC* | rs35768060 | chr2: 44174968 | A/T | intron | - | 6/208 | 8/728 | 0.10 | - | - |
| *LRPPRC* | rs372982157 | chr2: 44176725 | A/G | intron | - | 1/213 | 1/365 | 1.00 | 14/7678 | 0.34 |
| *LRPPRC* | rs569569757 | chr2: 44186257 | G/GGAT | intron | - | 2/178 | - | - | - | - |
| *LRPPRC* | rs35035668 | chr2: 44190783 | C/T | p.T478A | 0 | 3/211 | 5/731 | 0.39 | 46/7820 | 0.14 |
| *LRPPRC* | rs543745486 | chr2: 44200928 | C/T | intron | - | 1/213 | 0/366 | 0.37 | 5/7861 | 0.15 |
| *LRPPRC* | rs4953042 | chr2: 44201376 | C/T | p.Q356Q | - | 107/107 | 365/371 | 0.94 | 3929/3923 | 1.00 |
| *LRPPRC* | rs554786615 | chr2: 44203223 | T/C | intron | - | 1/211 | 1/365 | 1.00 | - | - |
| *LRPPRC* | rs201058655 | chr2: 44204207 | A/G | intron | - | 1/213 | 1/575 | 0.47 | 10/7836 | 0.26 |
| *LRPPRC* | rs138378033 | chr2: 44206992 | G/T | p.R148R | - | 1/213 | 1/365 | 1.00 | 6/7858 | 0.17 |
| *LRPPRC* | rs6741066 | chr2: 44209477 | T/C | p.Q82Q | - | 9/205 | 21/715 | 0.37 | 282/7582 | 0.58 |
| *LRPPRC* | rs188424940 | chr2: 44223097 | C/T | 5-UTR | - | 5/183 | 32/658 | 0.31 | 3/127 | 1.00 |
| *COX5B* | rs117644956 | chr2: 98263645 | A/G | intron | - | 13/201 | 61/675 | 0.31 | 638/7074 | 0.31 |
| *SCO2* | rs12148 | chr22: 50962208 | G/T | p.A211A | - | 148/64 | 478/258 | 0.22 | 5516/2324 | 0.88 |
| *SCO2* | . | chr22: 50962627 | T/C | p.G72S | 0 | 1/211 | 0/160 | 1.00 | 1/7823 | 0.05 |
| *SCO2* | rs140523 | chr22: 50962782 | G/C | p.R20P | 0 | 147/65 | 479/257 | 0.28 | 5443/2299 | 0.76 |
| *SCO2* | rs131805 | chr22: 50964153 | C/T | intron | - | 191/9 | 701/31 | 0.84 | 5002/240 | 1.00 |
| *COX7C* | rs116683123 | chr5: 85916305 | C/T | intron | - | 3/193 | 25/711 | 0.24 | 0/14 | 1.00 |
| *COX7A2* | rs557868927 | chr6: 75947573 | T/G | 3-UTR | - | 2/206 | 0/366 | 0.13 | 8/2926 | 0.14 |
| *COX7A2* | rs183161280 | chr6: 75953565 | T/C | 5-UTR | - | 7/205 | 15/721 | 0.30 | 156/6622 | 0.35 |
| *NDUFA4* | rs148181305 | chr7: 10979619 | A/T | intron | - | 3/209 | 7/729 | 0.70 | 144/7708 | 1.00 |
| *NDUFA4* | rs17163797 | chr7: 10979697 | A/G | 5-UTR | - | 23/189 | 98/638 | 0.41 | 1002/6830 | 0.46 |
| *NDUFA4* | rs371767998 | chr7: 10979716 | C/G | 5-UTR | - | 1/211 | 0/160 | 1.00 | 1/7831 | 0.05 |
| *COX6C* | rs1130569 | chr8: 100899793 | A/G | p.Y56Y | - | 31/181 | 117/619 | 0.75 | 1009/6835 | 0.47 |
| *SURF1* | rs72619327 | chr9: 136219448 | G/C | p.D202H | 3 | 33/179 | 127/609 | 0.60 | 1150/6618 | 0.77 |

a The potential pathogenicity of missense variants were predicted by five algorithms: PolyPhen2 HunDiv and HunVar ([Adzhubei](#_ENREF_2" \o "Adzhubei, 2010 #95) *[et al,](#_ENREF_2" \o "Adzhubei, 2010 #95)* [2010](#_ENREF_2" \o "Adzhubei, 2010 #95)), LRT ([Chun and Fay 2009](#_ENREF_4" \o "Chun, 2009 #93)), MutationTaster ([Schwarz](#_ENREF_14" \o "Schwarz, 2014 #96) *[et al,](#_ENREF_14" \o "Schwarz, 2014 #96)* [2014](#_ENREF_14" \o "Schwarz, 2014 #96)), and SIFT ([Kumar](#_ENREF_6" \o "Kumar, 2009 #94) *[et al,](#_ENREF_6" \o "Kumar, 2009 #94)* [2009](#_ENREF_6" \o "Kumar, 2009 #94); [Ng and Henikoff 2003](#_ENREF_11" \o "Ng, 2003 #92)). A score of 4 means the missense variant was predicted to be damaging by four out of five algorithms.

b AD: including 107 Chinese AD patients with familial history and/or with an early onset age <= 55 years old.

c Control: including 160 in-house controls ([Wang](#_ENREF_15" \o "Wang, 2018 #106) *[et al,](#_ENREF_15" \o "Wang, 2018 #106)* [2018](#_ENREF_15" \o "Wang, 2018 #106)), the data of Han Chinese in Beijing (CHB, N=103) and Southern Han Chinese (CHS, N=105) from the 1000 genomes Project phase 3 ([Abecasis](#_ENREF_1" \o "Abecasis, 2012 #65) *[et al,](#_ENREF_1" \o "Abecasis, 2012 #65)* [2012](#_ENREF_1" \o "Abecasis, 2012 #65); [Auton](#_ENREF_3" \o "Auton, 2015 #64) *[et al,](#_ENREF_3" \o "Auton, 2015 #64)* [2015](#_ENREF_3" \o "Auton, 2015 #64)).

d *P*-value, Fisher’s exact test.

e The allele frequency in East Asian population in ExAC dataset (<http://exac.broadinstitute.org>) ([Lek](#_ENREF_8" \o "Lek, 2016 #66) *[et al,](#_ENREF_8" \o "Lek, 2016 #66)* [2016](#_ENREF_8" \o "Lek, 2016 #66)).

**Supplementary Table S7.** Comparison of mRNA levels of the COX-related genes between 415 AD brain and 291 control brain tissues.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Temporal Cortex a** | | | **Frontal Cortex a** | | |
| **log2 Fold** | ***P*-value** | **FDR** | **log2 Fold** | ***P*-value** | **FDR** |
| **Change** | **Change** |
| ***LRPPRC*** | -0.33 | 1.73E-06 | 6.35E-06 | -0.31 | 1.52E-12 | 9.79E-12 |
| ***COX5B*** | -0.04 | 0.270 | 0.324 | -0.22 | 2.15E-13 | 1.57E-12 |
| ***COX7C*** | -0.01 | 0.925 | 0.938 | -0.17 | 1.44E-08 | 5.56E-08 |
| ***COX7A2*** | -0.29 | 3.82E-07 | 1.66E-06 | -0.41 | 1.16E-25 | 9.77E-24 |
| ***NDUFA4*** | -0.16 | 0.009 | 0.015 | -0.60 | 3.84E-22 | 1.43E-20 |
| ***COX6C*** | -0.29 | 7.99E-10 | 7.58E-09 | -0.37 | 1.11E-16 | 1.37E-15 |
| ***SURF1*** | 0.22 | 1.43E-05 | 4.15E-05 | -0.05 | 0.221 | 0.283 |
| *COX15* | 0.03 | 0.668 | 0.712 | NA | NA | NA |
| ***COX6A1*** | -0.11 | 0.027 | 0.039 | -0.20 | 6.79E-13 | 4.56E-12 |
| *COX8A* | -0.15 | 0.007 | 0.012 | NA | NA | NA |
| ***COX5A*** | -0.20 | 3.18E-04 | 7.02E-04 | -0.41 | 8.06E-14 | 6.24E-13 |
| ***COX4I1*** | -0.03 | 0.242 | 0.294 | -0.37 | 1.03E-21 | 3.47E-20 |
| ***SCO1*** | -0.19 | 6.79E-05 | 1.72E-04 | -0.23 | 5.69E-09 | 2.31E-08 |
| ***COX10*** | NA | NA | NA | -0.33 | 6.22E-14 | 4.90E-13 |
| ***COX6B1*** | -0.25 | 1.10E-05 | 3.30E-05 | -0.29 | 3.95E-13 | 2.76E-12 |
| ***COX6B2*** | NA | NA | NA | 0.12 | 6.79E-04 | 0.001 |
| ***SCO2*** | -0.19 | 0.003 | 0.006 | -0.09 | 4.17E-04 | 0.001 |

The expression data were retrieved from the NCBI Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo>) and were normalized and analyzed in the AlzData database ([www.alzdata.org](http://www.alzdata.org)) ([Xu](#_ENREF_17" \o "Xu, 2018 #72) *[et al,](#_ENREF_17" \o "Xu, 2018 #72)* [2018](#_ENREF_17" \o "Xu, 2018 #72)). Genes showed significantly different expression level between AD cases and controls were marked in bold.

a Two expression datasets of temporal cortex and frontal cortex from 415 AD patients and 291 controls were retrieved from the GEO: GSE15222 ([Webster](#_ENREF_16" \o "Webster, 2009 #83) *[et al,](#_ENREF_16" \o "Webster, 2009 #83)* [2009](#_ENREF_16" \o "Webster, 2009 #83)) and GSE33000 ([Narayanan](#_ENREF_10" \o "Narayanan, 2014 #103) *[et al,](#_ENREF_10" \o "Narayanan, 2014 #103)* [2014](#_ENREF_10" \o "Narayanan, 2014 #103)).

**Supplementary Figure S1**



**Supplementary Figure S1. Linkage disequilibrium (LD) pattern of the AD-associated SNPs identified in the *COX10* and *COX6B1* genes.** (A)The pairwise LD pattern of SNPs in the *COX10* gene with the most strongly associated SNP rs2530377; (B) The pairwise LD pattern of SNPs in the *COX6B1* gene with the most strongly associated SNP rs10420252. The analysis of LD pattern was performed on LocusZoom (<http://locuszoom.org/>) ([Pruim](#_ENREF_12" \o "Pruim, 2010 #102) *[et al,](#_ENREF_12" \o "Pruim, 2010 #102)* [2010](#_ENREF_12" \o "Pruim, 2010 #102))

**Supplementary Figure S2**



**Supplementary Figure S2. The mRNA expression levels of the COX-related genes were correlated with the level of Aβ plaque in cortex tissues of AD mouse models.** The gene expression data and pathology data were retrieved from Mouseac (www.mouseac.org) ([Matarin](#_ENREF_9" \o "Matarin, 2015 #73) *[et al,](#_ENREF_9" \o "Matarin, 2015 #73)* [2015](#_ENREF_9" \o "Matarin, 2015 #73)). Data shown were the age-related mRNA expression (*left*) and the correlation between mRNA level and Aβ plaque (*right*) of each of 15 genes (A-O). *Sco1* and *Sco2* had no data available in Mouseac ([Matarin](#_ENREF_9" \o "Matarin, 2015 #73) *[et al,](#_ENREF_9" \o "Matarin, 2015 #73)* [2015](#_ENREF_9" \o "Matarin, 2015 #73)). The age-related mRNA expression level was measured in cortex tissues of wild type (n=7) and HO \_TASTPM mice (with homogenous APP K670N/M671L and PSEN1M146V mutations, n=3) at different life stages (2, 4, 8 and 18 months). Error bars represent the standard error of the mean. \*, *P*-value < 0.05; \*\*, *P*-value < 0.01; \*\*\*, *P*-value < 0.001; ns, not significant; two-tailed Student’s *t* test. The correlation between mRNA level and Aβ plaques in mice with *APP*K670N/M671L mutation (n=44) was measured using the Pearson correlation test. A *P*-value < 0.05 was considered as statistically significant, ns: not significant.

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