# Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles

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## Supplementary Material

## Supplementary Methods

**Oligonucleotide primers for qRT-PCR.** Primer sequences for qRT-PCR were deducted from the literature as follows: MTND4 [1]; B2M [2]; BACT [3]; LDHA [3]; PFKFB3 [4]; NMNAT2 [5]; NAMPT [6]; PARP1 [7]; SIRT1 [8]; SIRT3 [8]; MDH1 [9]; MDH2 [9]; OGDH [10]; IDH3A: FW 5'-TGCTGCCAAAGCACCTATTCA-3', RV 5'-CCCGGTCTGCCACAAAGT-3' (derived from PrimerBank: https://pga.mgh.harvard.edu/primerbank/).

## Supplementary Tables and Figures

| sample # | age | Sex | Diagnosis |
|---|---|---|---|
| 367 | 21 | M | Ctrl |
| 294 | 23 | M | Ctrl |
| 460 | 25 | M | Ctrl |
| 458 | 26 | M | Ctrl |
| 359 | 31 | M | Ctrl |
| 298 | 33 | M | Ctrl |
| 366 | 35 | M | Ctrl |
| 152 | 40 | M | Ctrl |
| 190 | 42 | M | Ctrl |
| 226 | 45 | M | Ctrl |
| 135 | 49 | M | Ctrl |
| 365 | 52 | M | Ctrl |
| 316 | 54 | M | Ctrl |
| **ave young** | **36.6** | | |
| 14 | 55 | M | Ctrl |
| 342 | 57 | M | Ctrl |
| 491 | 61 | M | Ctrl |
| 127 | 62 | M | Ctrl |
| 357 | 65 | M | Ctrl |
| 205 | 67 | M | Ctrl |
| 405 | 75 | F | Ctrl |
| **ave old** | **63.1** | | |
| 330 | 56 | M | AD |
| 374 | 59 | F | AD |
| 231 | 65 | M | AD |
| 311 | 70 | M | AD |
| 369 | 76 | M | AD |
| 281 | 79 | M | AD |
| 402 | 70 | F | AD |
| 399 | 71 | F | AD |
| 404 | 81 | M | AD |
| 332 | 82 | F | AD |
| **ave AD** | **70.9** | | |

**Supplementary Table 1 |** Summary of fibroblasts samples used in this study.

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| Figure 1 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 1b Spare Resp. Cap. | 0.471589 | 1,24 | 0.53501 | **0.106101** | 1,27 | 2.79516 | 0.27863 | 1,17 | 1.25256 | **0.062741** | 1,20 | 3.88421 | 0.533765 | 1,15 | 0.40569 | 0.209233 | 3,44 | 1.57365 |
| Fig. 1b Glycol. Cap. | 0.306941 | 1,24 | 1.08969 | **0.096018** | 1,27 | 2.9745 | 0.128479 | 1,17 | 2.55337 | 0.349118 | 1,20 | 0.91926 | 0.019566 | 1,15 | 6.83033 | 0.119992 | 3,44 | 2.05491 |
| Fig. 1b PPR | 0.948499 | 1,24 | 0.00426 | **0.106976** | 1,27 | 2.81568 | 0.925229 | 1,17 | 0.00907 | 0.1335 | 1,20 | 2.44613 | 0.240079 | 1,15 | 1.49652 | 0.350623 | 3,44 | 1.12162 |
| Fig. 1d baseline OCR | 0.509416 | 1,24 | 0.44855 | 0.294311 | 1,27 | 1014384 | 0.357664 | 1,17 | 0.89392 | 0.56613 | 1,20 | 34038 | 0.197269 | 1,15 | 1.8205 | 0.523812 | 3,44 | 0.75783 |
| Fig. 1d stressed OCR | 0.850808 | 1,24 | 0.03615 | 0.184284 | 1,27 | 1.85653 | 0.788594 | 1,17 | 0.0742 | 0.293511 | 1,20 | 1.16384 | 0.281439 | 1,15 | 1.24838 | 0.480354 | 3,44 | 0.83797 |
| Fig. 1d baseline ECAR | 0.672606 | 1,24 | 0.18302 | 0.210291 | 1,27 | 1.64687 | 0.507377 | 1,17 | 0.45863 | 0.162704 | 1,20 | 2.10099 | 0.590647 | 1,15 | 0.30212 | 0.468226 | 3,44 | 0.86141 |
| Fig. 1d stressed ECAR | 0.758181 | 1,24 | 0.09697 | 0.166937 | 1,27 | 2.01754 | 0.640263 | 1,17 | 0.2264 | 0.264006 | 1,20 | 1.32081 | 0.22657 | 1,15 | 1.59012 | 0.449259 | 3,44 | 0.89914 |
| Fig. 1d met. pot. OCR | 0.470548 | 1,24 | 0.53756 | 0.871455 | 1,27 | 0.02669 | 0.266285 | 1,17 | 1.32124 | 0.468956 | 1,20 | 0.54497 | 0.564773 | 1,15 | 0.34666 | 0.695178 | 3,44 | 0.48391 |
| Fig. 1d Met. Pot. ECAR | 0.109992 | 1,24 | 2.75453 | 0.95892 | 1,27 | 0.0027 | **0.024352** | 1,17 | 6.10551 | 0.458452 | 1,20 | 0.57156 | **0.024352** | 1,15 | 6.10551 | 0.205508 | 3,44 | 1.58924 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 1c Basal Resp. | **0.000138** | 1,18 | 23.20985 | **0.000548** | 1,15 | 19.10171 | 1.31773 | 1,15 | 0.268978 | **0.000074** | 2,24 | 14.51661 |
| Fig. 1c ATP Prod. | **0.000194** | 1,18 | 21.72551 | **0.00078** | 1,15 | 17.6025 | 1.05738 | 1,15 | 0.320112 | **0.000121** | 2,24 | 13.43865 |
| Fig. 1c Proton Leak | **0.008583** | 1,18 | 8.69725 | **0.008583** | 1,15 | 8.69725 | 1.58119 | 1,15 | 0.227815 | **0.002196** | 2,24 | 7.98551 |
| Fig. 1c Max. Resp. | **0.103143** | 1,18 | 2.94797 | **6.01451** | 1,15 | 0.026912 | 0.308253 | 1,15 | 1011241 | **0.045822** | 2,24 | 3.51525 |
| Fig. 1c Spare Resp. Cap. | 0.39868 | 1,18 | 0.74739 | 0.927303 | 1,15 | 0.00861 | 0.533765 | 1,15 | 0.40569 | 0.658546 | 2,24 | 0.42508 |
| Fig. 1c Non-Mito Resp. | 0.603252 | 1,18 | 0.27987 | 0.183835 | 1,15 | 1.94127 | 0.339917 | 1,15 | 0.97159 | 0.411797 | 2,24 | 0.92085 |
| Fig. 1c Coupling Effect | **<0.00001** | 1,18 | 129.0867 | **<0.00001** | 1,15 | 53.60973 | 0.305148 | 1,15 | 1.1273 | **<0.00001** | 2,24 | 58.32071 |
| Fig. 1c Glycol. Cap. | **0.001303** | 1,18 | 14.46224 | **0.000114** | 1,15 | 26.71374 | **0.019566** | 1,15 | 6.83033 | 0.000023 | 2,24 | 17.21279 |
| Fig. 1c PPR | 0.144624 | 1,18 | 0.32579 | **0.026623** | 1,15 | 6.04141 | 0.240079 | 1,15 | 1.49652 | **0.051876** | 2,24 | 3.35562 |
| Fig. 1d Baseline OCR | 0.380595 | 1,18 | 0.80795 | **0.05041** | 1,15 | 4.2467 | 0.197269 | 1,15 | 1.8205 | 0.132248 | 2,24 | 2.20362 |
| Fig. 1d Stressed OCR | 0.811853 | 1,18 | 0.05835 | 0.20256 | 1,15 | 1.77577 | 0.281439 | 1,15 | 1.24838 | 0.422417 | 2,14 | 0.89346 |
| Fig. 1d Baseline ECAR | 0.578039 | 1,18 | 0.32094 | 0.969486 | 1,15 | 0.00151 | 0.590647 | 1,15 | 0.30212 | 0.80357 | 2,14 | 0.2207 |
| Fig. 1d Stressed ECAR | 0.609275 | 1,18 | 0.27059 | 0.113785 | 1,15 | 2.82024 | 0.22657 | 1,15 | 1.59012 | 0.238504 | 2,24 | 1.52249 |
| Fig. 1d Met. Pot. OCR | 0.139264 | 1,18 | 2.39322 | 0.139264 | 1,15 | 2.39322 | 0.564773 | 1,15 | 0.34666 | 0.18285 | 2,24 | 1.82526 |
| Fig. 1d Met. Pot. ECAR | **0.061997** | 1,18 | 3.96022 | **0.00418** | 1,15 | 11.38001 | 0.172928 | 1,15 | 2.04782 | **0.009414** | 2,24 | 5.7025 |

| Figure 2 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 2a ATP | 0.547382 | 1,25 | 0.37207 | **0.006196** | 1,28 | 8.76305 | 0.427554 | 1,18 | 0.6589 | **0.037335** | 1,21 | 4.9413 | **0.013621** | 1,15 | 7.80689 | **0.013546** | 3,46 | 3.96313 |
| Fig. 2b Lactate | 0.49256 | 1,25 | 0.48507 | **0.00054** | 1,28 | 15.26135 | 0.378525 | 1,18 | 0.81515 | **0.007985** | 1,21 | 8.59008 | **0.000894** | 1,15 | 17.04062 | **0.000933** | 3,46 | 6.4934 |
| Fig. 2c glu | 0.159688 | 1,16 | 2.17486 | 0.211074 | 1,25 | 1.64747 | 0.159688 | 1,16 | 2.17486 | **0.078816** | 1,20 | 3.43064 | 0.893954 | 1,12 | 0.01854 | 0.255139 | 3,41 | 1.40466 |
| Fig. 2c IGF-1 | **0.047218** | 1,16 | 4.6213 | **0.056848** | 1,25 | 3.98708 | **0.047218** | 1,16 | 4.6213 | **0.011787** | 1,20 | 7.6787 | 0.775181 | 1,12 | 0.08534 | **0.033693** | 3,41 | 3.18506 |

| Values | all/all | | | young/young | | | old/old | | | AD/AD | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 2c glu/IGF-1 | **0.014082** | 1,34 | 6.70032 | **0.009156** | 1,24 | 8.03632 | 0.599975 | 1,8 | 0.29809 | 0.203184 | 1,16 | 1.76054 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 2a ATP | 0.406568 | 1,18 | 0.72225 | **0.005367** | 1,15 | 10.57201 | **0.022178** | 1,15 | 6.50481 | **0.014828** | 2,24 | 5.04478 |
| Fig. 2b Lactate | 0.137797 | 1,18 | 2.4122 | **0.000157** | 1,15 | 25.03465 | **0.000894** | 1,15 | 17.04062 | **0.000177** | 2,24 | 12.65165 |
| Fig. 2c glu | **0.013285** | 1,16 | 7.7501 | **0.054368** | 1,12 | 4.54512 | 0.893954 | 1,15 | 0.01854 | **0.02905** | 2,20 | 4.24575 |
| Fig. 2c IGF-1 | **0.000312** | 1,16 | 20.91642 | **0.00465** | 1,12 | 12.02547 | 0.775181 | 1,15 | 0.08534 | **0.000243** | 2,10 | 12.98618 |

| Figure 3 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 3a NADt | 0.658008 | 1,25 | 0.20071 | **0.069448** | 1,27 | 3.57456 | 0.524097 | 1,18 | 0.4221 | 0.123928 | 1,20 | 2.57953 | **0.036667** | 1,14 | 5.33489 | 0.223454 | 3,43 | 1.5179 |
| Fig. 3b NADH | 0.59242 | 1,25 | 0.29408 | **0.05232** | 1,27 | 4.15076 | 0.64844 | 1,18 | 0.431179 | **0.092316** | 1,20 | 3.12579 | **0.028723** | 1,14 | 5.9417 | 0.178992 | 3,43 | 1.71074 |
| Fig. 3c NAD+ | 0.792168 | 1,25 | 0.07093 | 0.135894 | 1,27 | 2.36283 | 0.716928 | 1,18 | 0.13566 | 0.222359 | 1,20 | 1.58628 | **0.07485** | 1,14 | 3.70397 | 0.386044 | 3,43 | 1.03644 |
| Fig. 3d ratios NAD+/NADH | | | | | | | 0.923745 | 1,18 | 0.00942 | 0.328384 | 1,20 | 1.00131 | 0.412244 | 1,14 | 0.71135 | 0.429081 | 3,43 | 0.94127 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 3a NADt | 0.26741 | 1,18 | 1.30987 | **0.021197** | 1,15 | 6.62168 | **0.040956** | 1,15 | 5.00075 | **0.009933** | 2,24 | 5.62339 |
| Fig. 3b NADH | 0.165247 | 1,18 | 2.09215 | **0.016968** | 1,15 | 7.20818 | **0.032312** | 1,15 | 5.56456 | **0.006346** | 2,24 | 6.29383 |
| Fig. 3c NAD+ | 0.62969 | 1,18 | 0.24061 | **0.046076** | 1,15 | 4.7287 | **0.081443** | 1,15 | 3.4889 | **0.045177** | 2,24 | 3.53359 |

| Figure 4 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 4a mtMinArc | 0.273096 | 1,22 | 1.26355 | 0.795938 | 1,25 | 0.06832 | 0.167003 | 1,16 | 2.09593 | 0.444566 | 1,19 | 0.60958 | 0.127131 | 1,13 | 2.65612 | 0.496459 | 3,41 | 0.80853 |
| Fig. 4b citrate synthase | **0.080535** | 1,24 | 3.32917 | 0.71023 | 1,26 | 0.14111 | **0.009759** | 1,17 | 8.4666 | 0.145599 | 1,19 | 2.30286 | **0.078564** | 1,14 | 3.60093 | **0.063194** | 3,42 | 2.61603 |
| Fig. 4c MitoTracker | 0.296862 | 1,20 | 1.4735 | 0.909028 | 1,22 | 0.01336 | 0.125382 | 1,14 | 2.65697 | 0.396134 | 1,16 | 0.76029 | 0.270792 | 1,12 | 1.33274 | 0.421599 | 3,36 | 0.96113 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 4a mtMinArc | **0.022781** | 1,16 | 6.34586 | **0.021267** | 1,13 | 6.85391 | 0.127131 | 1,13 | 2.65612 | **0.006757** | 2,21 | 6.39966 |
| Fig. 4b citrate synthase | **0.001903** | 1,16 | 13.76197 | **0.078564** | 1,14 | 3.60093 | **0.000104** | 1,14 | 28.51785 | **0.000054** | 2,22 | 15.85914 |
| Fig. 4c MitoTracker | **0.016057** | 1,14 | 7.48982 | **0.008195** | 1,12 | 9.99647 | 0.270792 | 1,12 | 1.33274 | **0.007367** | 2,19 | 6.43008 |

| Figure 5 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 5a mtMajArc | 0.261658 | 1,22 | 1.32726 | 0.605477 | 1,25 | 0.27369 | 0.152764 | 1,16 | 2.25378 | 0.32371 | 1,19 | 1.03674 | 0.982132 | 1,13 | 0.00052 | 0.439456 | 3,41 | 0.92049 |
| Fig. 5c MTND4 | 0.97254 | 1,25 | 0.00121 | **0.052942** | 1,28 | 4.08416 | 0.959986 | 1,18 | 0.00259 | **0.049733** | 1,21 | 4.33587 | 0.12632 | 1,15 | 2.62051 | 0.249527 | 3,46 | 1.41828 |
| Fig. 5d ROS | 0.454524 | 1,25 | 0.57718 | 0.901284 | 1,28 | 0.01567 | 0.296998 | 1,18 | 1.15354 | 0.75182 | 1,21 | 0.10267 | 0.39652 | 1,15 | 0.76181 | 0.745131 | 3,46 | 0.41203 |
| Fig. 5e MitoSox | 0.193546 | 1,20 | 1.81016 | 0.701845 | 1,22 | 0.15044 | **0.059758** | 1,14 | 4.10581 | 0.331683 | 1,16 | 1.00219 | 0.496764 | 1,12 | 0.49119 | 0.343737 | 3,36 | 1.14595 |

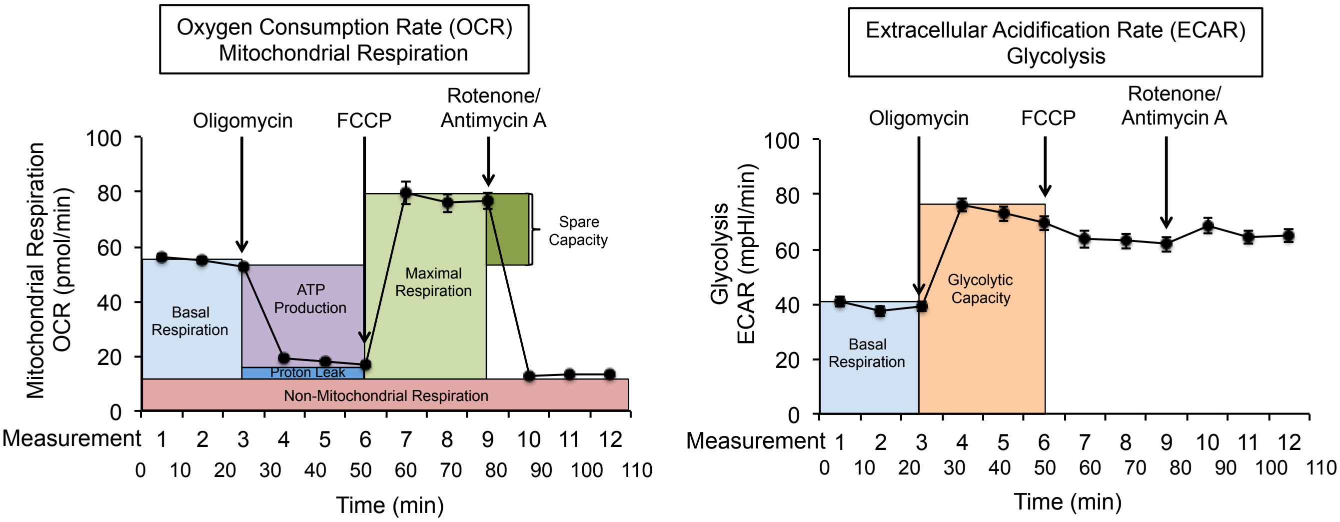
| Values | young | | | old | | | AD | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 5b ratios Min/MajArc | 0.732633 | 1,16 | 0.12086 | 0.703651 | 1,19 | 0.14914 | 0.982132 | 1,13 | 0.00052 | 0.883234 | 2,24 | 0.12481 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* | *p*-value | | *F* |
| Fig. 5a mtMajArc | **0.056615** | 1,16 | 4.22183 | **0.044662** | 1,13 | 4.93685 | 0.313243 | 1,13 | 1.10062 | **0.027781** | 2,21 | 4.27079 |
| Fig. 5c MTND4 | 0.961343 | 1,18 | 0.00242 | 0.133851 | 1,15 | 2.51177 | 0.12632 | 1,15 | 2.62051 | 0.141882 | 2,24 | 2.12063 |
| Fig. 5d ROS | 0.206554 | 1,18 | 1.71701 | **0.056325** | 1,15 | 4.2772 | 0.39652 | 1,15 | 0.76181 | 0.133176 | 2,24 | 2.19534 |
| Fig. 5e MitoSox | 0.161721 | 1,14 | 2.18258 | **0.02801** | 1,12 | 6.2408 | 0.496764 | 1,12 | 0.49119 | **0.095828** | 1,19 | 2.66003 |

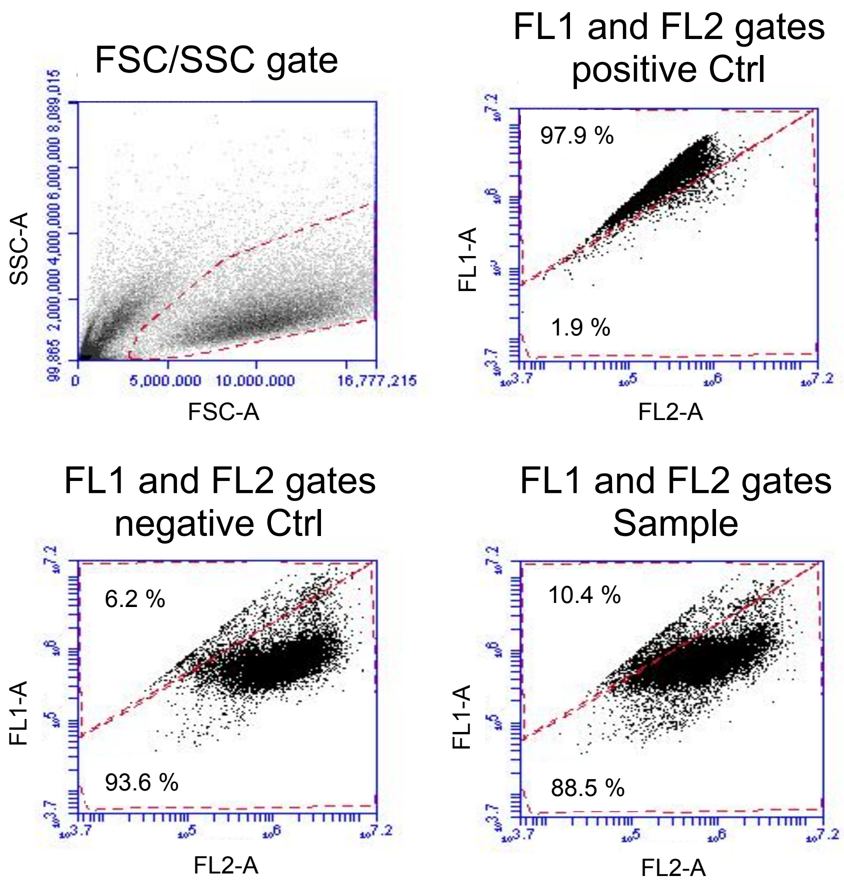
| Figure 6 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Values | all/old | | | all/AD | | | young/old | | | young/AD | | | old/AD | | | all groups | | |
| | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | |
| Fig. 6a PFKFB3 | 0.376775 | 1,23 | 0.81232 | 0.559347 | 1,26 | 0.34978 | 0.26475 | 1,17 | 1.33008 | 0.35001 | 1,20 | 0.91579 | 0.517872 | 1,13 | 0.4418 | 0.596567 | 3,43 | 0.63494 |
| Fig. 6a LDH | 0.301566 | 1,23 | 1.11688 | 0.676208 | 1,26 | 0.17842 | 0.19165 | 1,17 | 1.84911 | 0.37822 | 1,20 | 0.81141 | 0.162777 | 1,13 | 2.18949 | 0.511262 | 3,43 | 0.78066 |
| Fig. 6b NMNAT2 | 0.480827 | 1,23 | 0.51354 | 0.632242 | 1,26 | 0.23453 | 0.350661 | 1,17 | 0.92101 | 0.958193 | 1,20 | 0.00282 | 0.157315 | 1,13 | 2.25222 | 0.722533 | 3,43 | 0.44434 |
| Fig. 6b NAMPT | 0.846593 | 1,23 | 0.03828 | 0.221133 | 1,26 | 1.56872 | 0.802091 | 1,17 | 0.06482 | 0.228427 | 1,20 | 1.53915 | 0.300545 | 1,13 | 1.15567 | 0.734866 | 3,43 | 0.4267 |
| Fig. 6b PARP1 | 0.989364 | 1,22 | 0.00018 | 0.16267 | 1,25 | 2.06953 | 0.984552 | 1,16 | 0.00039 | 0.147933 | 1,19 | 2.2749 | 0.29834 | 1,13 | 1.17364 | 0.540827 | 3,41 | 0.72863 |
| Fig. 6b SIRT1 | 0.471141 | 1,25 | 0.53542 | 0.386216 | 1,28 | 0.77484 | 0.348102 | 1,18 | 0.92818 | 0.259095 | 1,21 | 1.34544 | 0.99503 | 1,15 | 0.00004 | 0.593704 | 3,46 | 0.63913 |
| Fig. 6b SIRT3 | 0.774264 | 1,25 | 0.08406 | 0.561469 | 1,27 | 0.34565 | 0.712509 | 1,18 | 0.14015 | 0.522698 | 1,20 | 0.4233 | 0.712245 | 1,14 | 0.1417 | 0.913815 | 3,45 | 0.17343 |
| Fig. 6c IDH3A | 0.163564 | 1,23 | 2.07131 | 0.5429 | 1,27 | 0.37969 | **0.074048** | 1,17 | 3.62327 | 0.949606 | 1,21 | 0.00409 | **0.083126** | 1,14 | 3.48207 | 0.309398 | 3,44 | 1.23214 |
| Fig. 6c OGHD | 0.112796 | 1,23 | 2.71832 | 0.643661 | 1,26 | 0.21905 | **0.020241** | 1,17 | 6.55939 | 0.553531 | 1,20 | 0.36316 | **0.016819** | 1,13 | 7.51396 | **0.089023** | 3,43 | 2.31692 |
| Fig. 6c MDH1 | 0.672473 | 1,23 | 0.18337 | 0.615738 | 1,26 | 0.25806 | 0.569063 | 1,17 | 0.33721 | 0.802017 | 1,20 | 0.06456 | 0.442727 | 1,13 | 0.62683 | 0.946253 | 3,42 | 0.12262 |
| Fig. 6c MDH2 | 0.670145 | 1,21 | 0.18662 | 0.663165 | 1,26 | 0.1941 | 0.618493 | 1,16 | 0.2579 | 0.57057 | 1,21 | 0.33207 | 0.648287 | 1,13 | 0.21801 | 0.898213 | 3,41 | 0.19645 |

| Ratios | AD/old - AD/young | | | AD/old - old/young | | | AD/young - old/young | | | all groups | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | | *p*-value | *F* | |
| Fig. 6a PFKFB3 | **0.051921** | 1,16 | 4.41085 | **0.041281** | 1,13 | 5.12826 | 0.517872 | 1,13 | 0.4418 | **0.035768** | 2,21 | 3.91953 |
| Fig. 6a LDH | **0.002451** | 1,16 | 12.88749 | **0.001832** | 1,13 | 15.1959 | 0.162777 | 1,13 | 2.18949 | **0.00034** | 2,21 | 11.96584 |
| Fig. 6b NMNAT2 | 0.119243 | 1,16 | 2.70962 | **0.021282** | 1,13 | 6.85193 | 0.157581 | 1,13 | 2.2491 | **0.032876** | 2,21 | 4.03582 |
| Fig. 6b NAMPT | 0.603268 | 1,18 | 0.27984 | 0.481704 | 1,14 | 52244 | 0.300545 | 1,14 | 1.15567 | 0.507036 | 2,23 | 0.69963 |
| Fig. 6b PARP1 | 0.976 | 1,16 | 0.00093 | 0.306346 | 1,13 | 1.13381 | 0.29834 | 1,13 | 1.17364 | 0.410849 | 2,21 | 0.92829 |
| Fig. 6b SIRT1 | **0.092617** | 1,18 | 3.15466 | 0.158986 | 1,15 | 2.19696 | 0.99503 | 1,15 | 0.00004 | 0.160051 | 2,24 | 1.97955 |
| Fig. 6b SIRT3 | 0.313629 | 1,18 | 1.0824 | 0.732078 | 1,14 | 0.122 | 0.712245 | 1,14 | 0.1417 | 0.702811 | 2,22 | 0.35838 |
| Fig. 6c IDH3A | **0.037418** | 1,18 | 5.04914 | **0.012477** | 1,14 | 8.20792 | **0.083126** | 1,14 | 3.48208 | **0.017106** | 2,22 | 4.92265 |
| Fig. 6c OGHD | **0.000505** | 1,16 | 18.8484 | **0.000214** | 1,13 | 25.7212 | **0.016819** | 1,13 | 7.51396 | **0.000055** | 2,21 | 16.23784 |
| Fig. 6c MDH1 | 0.452315 | 1,16 | 0.59345 | 0.199147 | 1,13 | 1.83036 | 0.442727 | 1,13 | 0.62683 | 0.373622 | 2,21 | 1.03214 |
| Fig. 6c MDH2 | **0.024422** | 1,18 | 6.03357 | **0.037884** | 1,13 | 5.34026 | 0.648287 | 1,13 | 0.21801 | **0.022292** | 2,22 | 4.54392 |

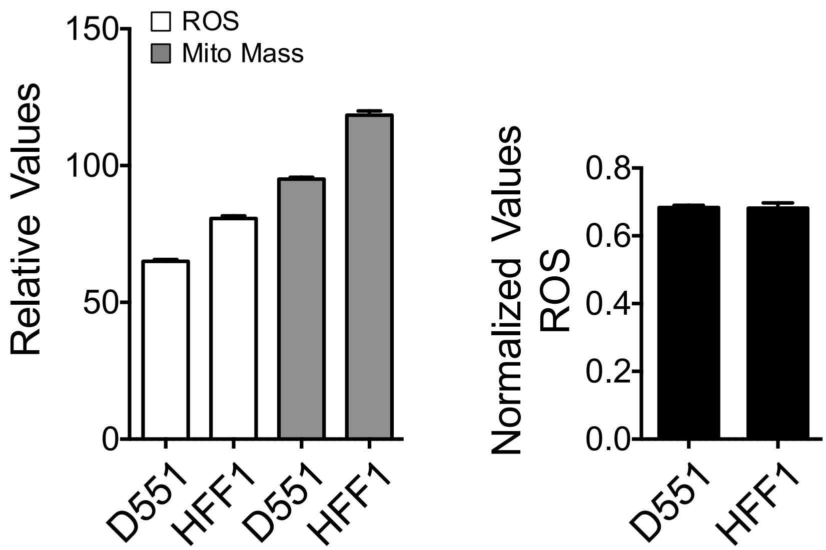
**Supplementary Table 2 |** Statistical data using one-way analysis of variance (ANOVA) tests for independent measures.




**Supplementary Figure 1 | Schematic representation of Seahorse experiments-derived data.** Profiles for oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) with arrows indicating injections of specific pharmacologic stressors targeting the electron transport chain (ETC) and ATP production: Oligomycin, which inhibits complex IV (ATP synthase), decreasing OCR and ATP production; Carbonyl cyanite-4 (trifluoromethoxy) phenylhydrazone (FCCP), which disrupts the mitochondrial membrane potential and collapses the proton gradient at the ETC leading to maximal respiration ($O_2$ consumption by complex IV); and Rotenone/Antimycin A, which inhibit complex I and III resulting in the shut down of mitochondrial respiration. From the data generated, several additional measures can be calculated, including the spare respiratory capacity (maximal respiration minus basal respiration), the proton leak, non-mitochondrial respiration, and the coupling effect, which determines ATP production relative to basal respiration. The assay deducts the ECAR is an indicator of the cells' glycolytic capacity, and the proton production rate (PPR). Images are adapted from Seahorse Agilent Technologies.




**Supplementary Figure 2 | Gating strategy in the MitoPT JC-1 FCM assays.** For positive and negative controls cells were treated with 50 µM of the depolarizing agent Carbonyl cyanide m-chlorophenyl hydrazone (CCCP) in DMSO or DMSO alone, respectively.




**Supplementary Figure 3 | MitoSox and MitoTracker assay controls.** Human foreskin cell line HFF1 and human fetal skin fibroblast cell line D551 were used as positive controls in combined MitoSox/MitoTracker assays measuring red (MitoSox) and green (MitoTracker) fluorescence in a BioTek plate reader. (**a**) Relative values of ROS (MitoSox) and mitochondrial mass (MitoTracker) after protein normalization with a BioRad Protein assay. (**b**) Both cell lines show similar levels of ROS after normalizing the MitoSox data with MitoTracker values.

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