Figure 1A
Figure 1B+1C
WS5A
Figure 1B+1C
CP2A
Figure 3G

MFN1
Figure 3G

OPA1
Figure 3G

MFF
Figure 3G

P-DRP1 616
Figure 3G

DRP1
Figure 3G

GAPDH
Figure 3G

ALL GEL-1
Figure 3G
Figure 3K

TOMM20
Figure 3K

PGC-1β
Figure 3K

GAPDH
Figure 4A
CP2A
Figure 4C

LAMP2A
Figure 4C

LC3B
Figure 4C

GAPDH
Figure 4D

PINK1
Figure 4D

PARKIN
Figure 4D

GAPDH
Figure 5A

p-mTOR
Figure 5A

mTOR
Figure 5A

GAPDH
Figure 5B

p-ULK1
Figure 5B

ULK1
Figure 5B

GAPDH
Figure 5C

p-AKT
Figure 5C

AKT
Figure 5C

GAPDH
Figure 5D

p-AMPK (T183+T172)
Figure 5D

AMPK
Figure 5D

GAPDH
Figure 6D

p-AMPK (T183+T172)

AMPK
Figure 6D

p-mTOR

mTOR
Figure 6D

GAPDH
Figure 6E

LC3B
Figure 6E

p62
Figure 6E

GAPDH
Figure 6F

p-SIRT1

SIRT1
Figure 6F

p-AMPK (T183+T172)

AMPK
Figure 6F

p-mTOR

mTOR
Figure 6F

GAPDH
Figure 6G

LC3B
Figure 6G

p62
Figure 6G

GAPDH
Figure 7A

p-SIRT1

SIRT1
Figure 7A

p-AMPK (T183+T172)

AMPK
Figure 7A

p-mTOR

mTOR
Figure 7A

GAPDH
Figure 7B

LC3B
Figure 7B

p62
Figure 7B

GAPDH
Figure 7C
WS5A Non-treated
Figure 7C
WS5A NR 0.5mM+M2.5mM
Figure 7C
CP2A Non-treated
Figure 7C
CP2A NR 0.5mM+M2.5mM
Figure 7C
CP2A NR 0.5mM+M2.5mM
Figure 7C
CP2A NR 0.5mM+M2.5mM
Figure 7C
CP2A NR 0.5mM+M2.5mM
Figure 8A

NDUF10

NR
Figure 8A

NR

GAPDH
Figure 8A

Metformin

PGC-1α
Figure 8A

NDUFB10

Metformin
Figure 8A

Metformin

GAPDH
Figure 8A

NR+Metformin

PGC-1α
Figure 8A

NR+Metformin

NDUFB10
Figure 8A

NR+Metformin

GAPDH
Figure 8B

Protein expressions with NR treatment

- PGC-1α
- NDUFB10

Relative protein content

- Non-treated
- NR 0.25 mM
- NR 0.5 mM
- NR 1 mM
- NR 2 mM
Figure 8C

Protein expressions with metformin treatment

Relative protein content

PGC-1α  NDUFB10

Non-treated
M 1.25 mM
M 2.5 mM
M 5 mM
M 10 mM
Figure 8D

Protein expressions with NR and metformin co-treatment

|                | PGC-1α | NDUFB10 |
|----------------|--------|---------|
| Non-treated    |        |         |
| NR 0.25 + M 1.25 mM | ¥      | ¥       |
| NR 0.5 + M 2.5 mM  | ¥      |         |
| NR 1 + M 5 mM    | ¥      |         |
| NR 2 + M 10 mM   | ¥      |         |

Relative protein content

* ns
Figure 8E

CTRL Non-treated

CTRL NR 0.5 mM + Metformin 2.5 mM
Figure 8E

WS5A Non-treated

WS5A NR 0.5 mM + Metformin 2.5 mM
Figure 8E

CP2A Non-treated

CP2A NR 0.5 mM + Metformin 2.5 mM
Figure 8F

Cell no. before and after treatment

CTRL-Non-treated
CTRL-NR 0.25 mM
WS5A-Non-treated
WS5A-NR 0.25 mM
CP2A-Non-treated
CP2A-NR 0.25 mM +M 2.5 mM

* * *
Figure 8G

MTG before and after treatment

Fold change over control

CTRL-Non-treated
CTRL-NR 0.25 mM +M 2.5 mM
WS5A-Non-treated
WS5A-NR 0.25 mM +M 2.5 mM
CP2A-NR 0.25 mM +M 2.5 mM
CP2A-Non-treated

* *
Figure 8H

Total MMP before and after treatment

Fold change over control

CTRL-Non-treated
CTRL-NR 0.25 mM +M 2.5 mM
WS5A-Non-treated
WS5A-NR 0.25 mM +M 2.5 mM
CP2A-Non-treated
CP2A-NR 0.25 mM +M 2.5 mM
Figure 8I

Specific MMP before and after treatment

Fold change over control

CTRL-Non-treated
CTRL-NR 0.25 mM +M 2.5 mM
WS5A-Non-treated
WS5A-NR 0.25 mM +M 2.5 mM
CP2A-Non-treated
CP2A-NR 0.25 mM +M 2.5 mM

* *
Figure 8J

Diagram showing the relationship between mtDNA deletions, loss of complex I and IV, and various cellular processes such as mitochondrial dysfunction, energy failure, and loss of ATP, resulting in defective mitophagy, astrocyte reactivity and neurotoxicity, neuronal death, and improved mitophagy and neuronal survival.