**Table S1.** Primer sequences used in this study.

| Loci | Forward | Reverse | Purpose |
|---|---|---|---|
| *HBB* | CTCCTGGGCAACGTGATAGT | GGTTCAGAGGAAAAAGGGCTCCTCCT | Copy number |
| *HTT* | ATGAAGGCCTTCGAGTCCCTCAAGTCCTTC | CGGCGGCGGTGGCGGTTGCTGTTGCTGCTG | CAG sizing |
| *MT-RNR1* | TCGCAACTGCCTAAAACTCA | GAATTGGCAAGGGTTGGTAA | mtDNA damage/copy number/mutation frequency |
| *NDUFA9* | GTTGTGAATGGTGCTAACTGCT | ACCAGAGACAATAAAGCAGAGGAG | nDNA damage |

The table shows sequences of primers used for various experimental methods as indicated in right column.

**Table S2.** Information about antibodies used in supplementary western blotting (Fig.S3)

| Target | Name | Manufacturer | Catalogue no. | Species raised in | Dilution |
|---|---|---|---|---|---|
| PDH E1α, PDH E1β, PDH E2, PDH E2/E3bp, OSCP | PDH antibody cocktail | Mitosciences | MSP02 | Mouse | 1:2000 |
| | Complex III subunit Core 2 monoclonal antibody | Mitosciences | MS304 | Mouse | 1:10000 |
| NDUFA9 | Anti-NDUFA9 antibody [20C11B11B11] | Abcam | ab14713 | Mouse | 1:3000 |
| SDH70 | Anti-SDHA antibody [2E3GC12FB2AE2] | Abcam | ab14715 | Mouse | 1:5000 |
| SDH30 | Complex II subunit 30 kDa | Mitosciences | MS203 | | 1:2000 |
| CORE1 | Anti-Ubiquinol-Cytochrome C Reductase Core Protein I antibody [16D10AD9AH5] | Abcam | ab110252 | Mouse | 1:5000 |
| COX1 | Anti-MTCO1 antibody [1D6E1A8] | Abcam | ab14705 | Mouse | 1:2000 |
| COX5A | Anti-COX5A antibody [6E9B12D5] | Abcam | ab110262 | Mouse | 1:2000 |
| ATPA | Anti-ATP5A antibody [7H10BD4F9] | Abcam | ab110273 | Mouse | 1:1000 |
| Mitofilin | Anti-Mitofilin antibody [2E4AD5] - Mitochondrial Marker | Abcam | ab110329 | Mouse | 1:1000 |
| Aconitase | Anti-Aconitase 2 antibody [6F12BD9] | Abcam | ab110321 | Mouse | 1:2000 |
| OPA1 | Purified Mouse Anti-OPA1 Clone 18/OPA1 | BD Biosciences | 612606 | Mouse | 1:2000 |
| Porin | Anti-VDAC1 / Porin antibody [20B12AF2] | | ab14734 | Mouse | 1:2000 |
| ATPβ | Anti-ATPB antibody [3D5] - Mitochondrial Marker | Abcam | ab14730 | Mouse | 1:1000 |
| COX2 | Anti-MTCO2 antibody [12C4F12] | Abcam | ab110258 | Mouse | 1:10000 |
| CS | Anti-Citrate synthetase antibody [2H8BB6] | Abcam | ab128564 | Mouse | 1:2500 |
| GAPDH | Anti-GAPDH antibody [6C5] | Abcam | ab8245 | Mouse | 1:3333 |
| MRPS31 | Anti-MRPS31 antibody [EPR10707] | Abcam | ab167406 | Rabbit | 1:3333 |
| Anti-rabbit IgG | Anti-Rabbit IgG (whole molecule)–Peroxidase antibody produced in goat | Sigma-Aldrich | *A0545* | Goat | 1:2500 |
| Anti-mouse IgG | Anti-Mouse IgG (whole molecule)–Peroxidase antibody produced in goat | Sigma-Aldrich | *A8924* | Goat | 1:2500 |

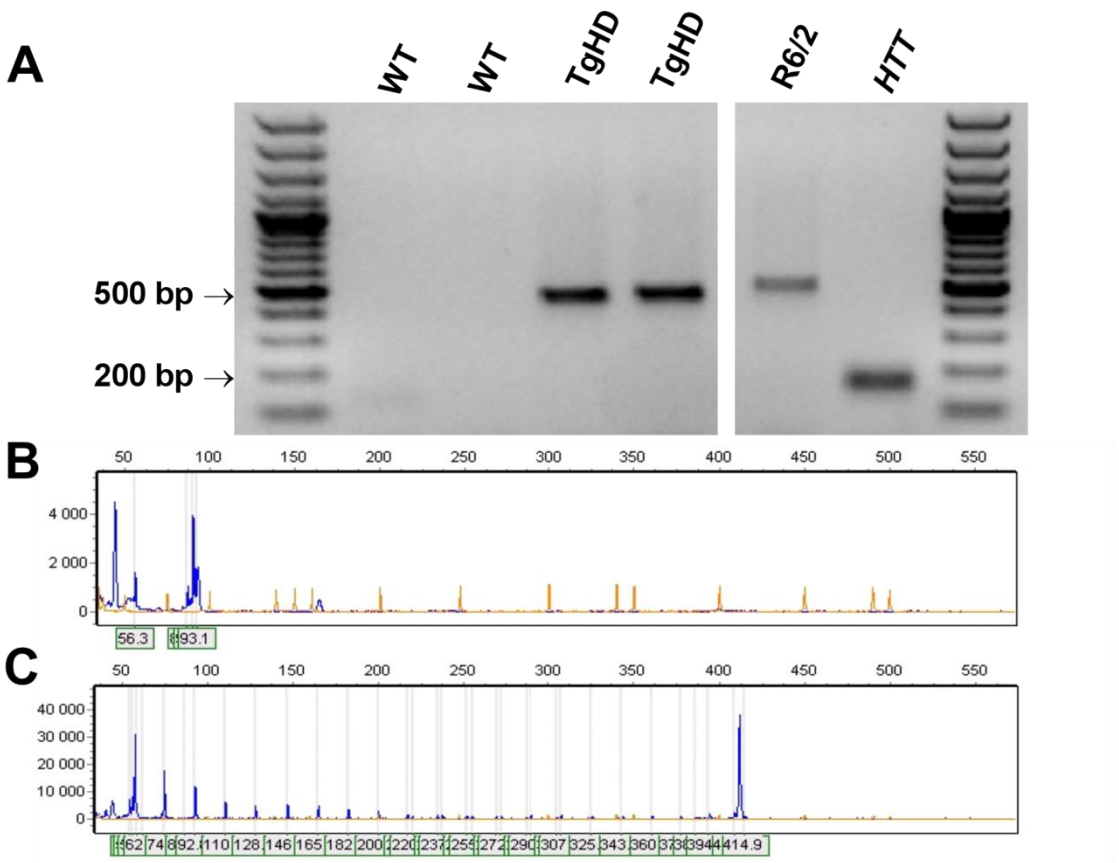


**Fig. S1. Validation of TgHD minipig model.** (A) PCR-mediated genotyping of the TgHD model transgene. Electrophoretic separation of PCR products made using *HTT* specific primers confirmed the presence of the expanded CAG repeat in TgHD minipigs. (B) Size determination of CAG repeat tracts. Capilliary electrophoresis and fragment analysis using size standards (yellow) and GeneMapper® software confirmed the absence of polyQ *mHTT* in WT minipigs (C) and showed presence of *mHTT* with ~121 CAG repeats in TgHD minipigs. Representative samples shown.

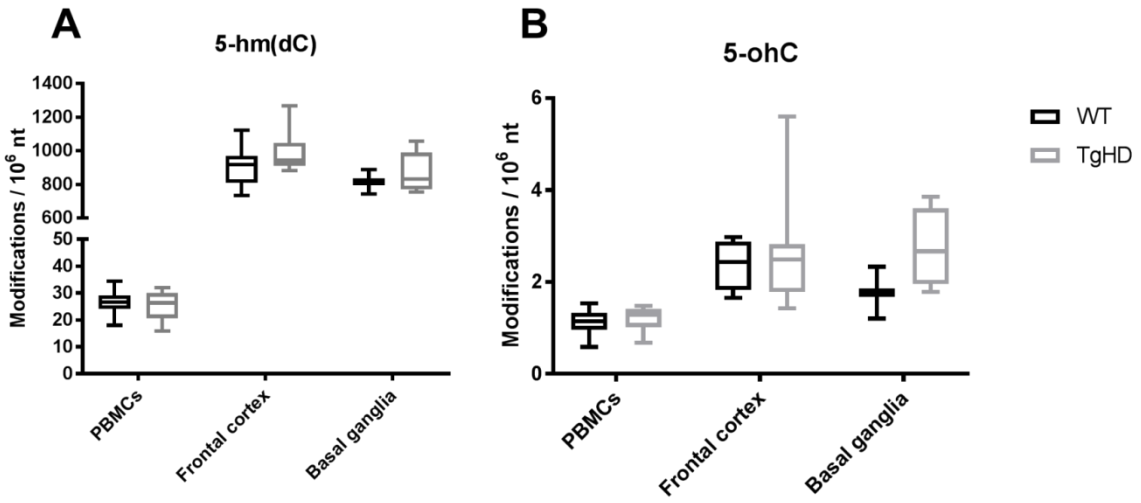


**Fig. S2. Base modifications in the TgHD minipig model.** LC-/MS/MS analysis of DNA showed normal levels of 5-hm(dC) and 5-ohC in all tissues (A, B). Student's t-test. Box plot whiskers indicate minimum to maximum values, with hinges representing the 25$^{th}$ and 75$^{th}$ percentile and median indicated by the center line. Sample sizes: PBMCs: WT n=10, TgHD n=6; frontal cortex: WT n=10, TgHD n=7; basal ganglia: WT n=2, TgHD n=5.

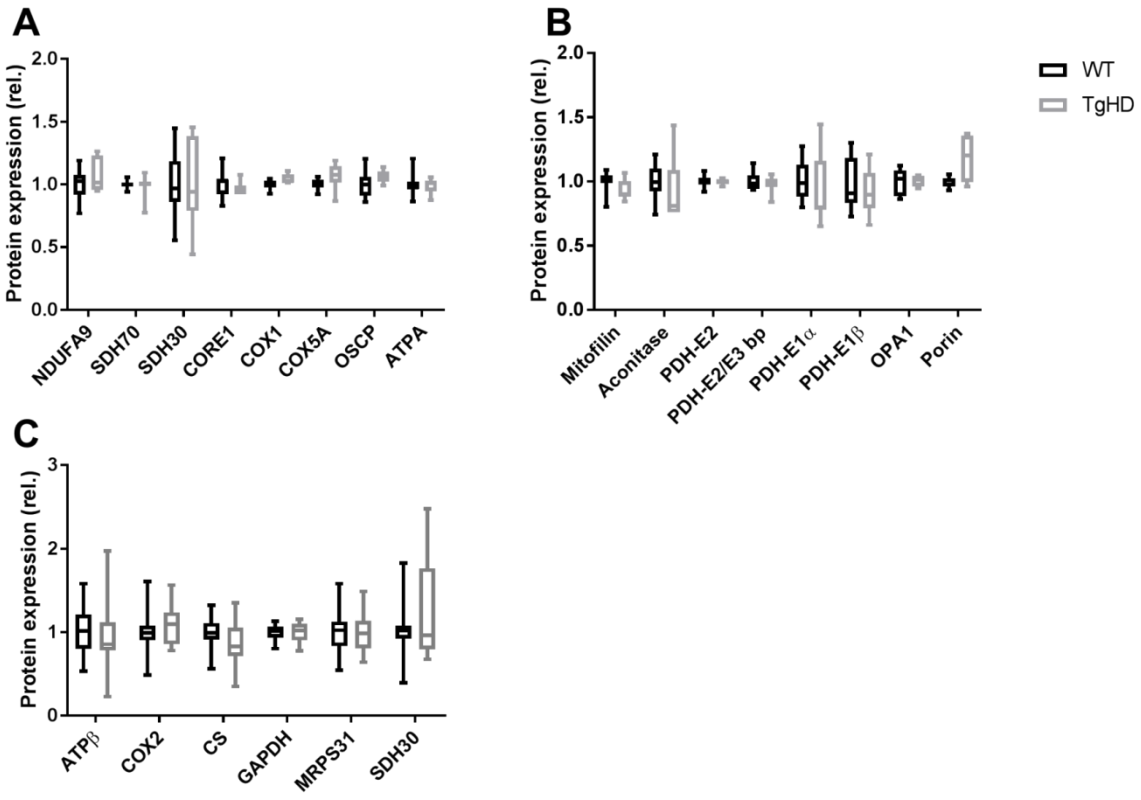


**Fig. S3. Mitochondria-related protein expression in the TgHD minipig model.** Western analysis showed normal levels of mitochondria associated proteins in frontal cortex (A,B) and PBMCs (C). Box plot whiskers indicate minimum to maximum values, with hinges representing the 25$^{th}$ and 75$^{th}$ percentile and median indicated by the center line. Student's t-test, adjusted for multiple comparisons using the Holm-Sidak method. Sample sizes: Frontal cortex: WT n=9, TgHD n=7, except OPA1 and Porin WT n=6, TgHD n=4; PBMCs: WT n=13, TgHD n=13, except CS WT n=13, TgHD n=12, MRPS31 WT n=11, TgHD n=12, SDH30 WT n=13, TgHD n=12.

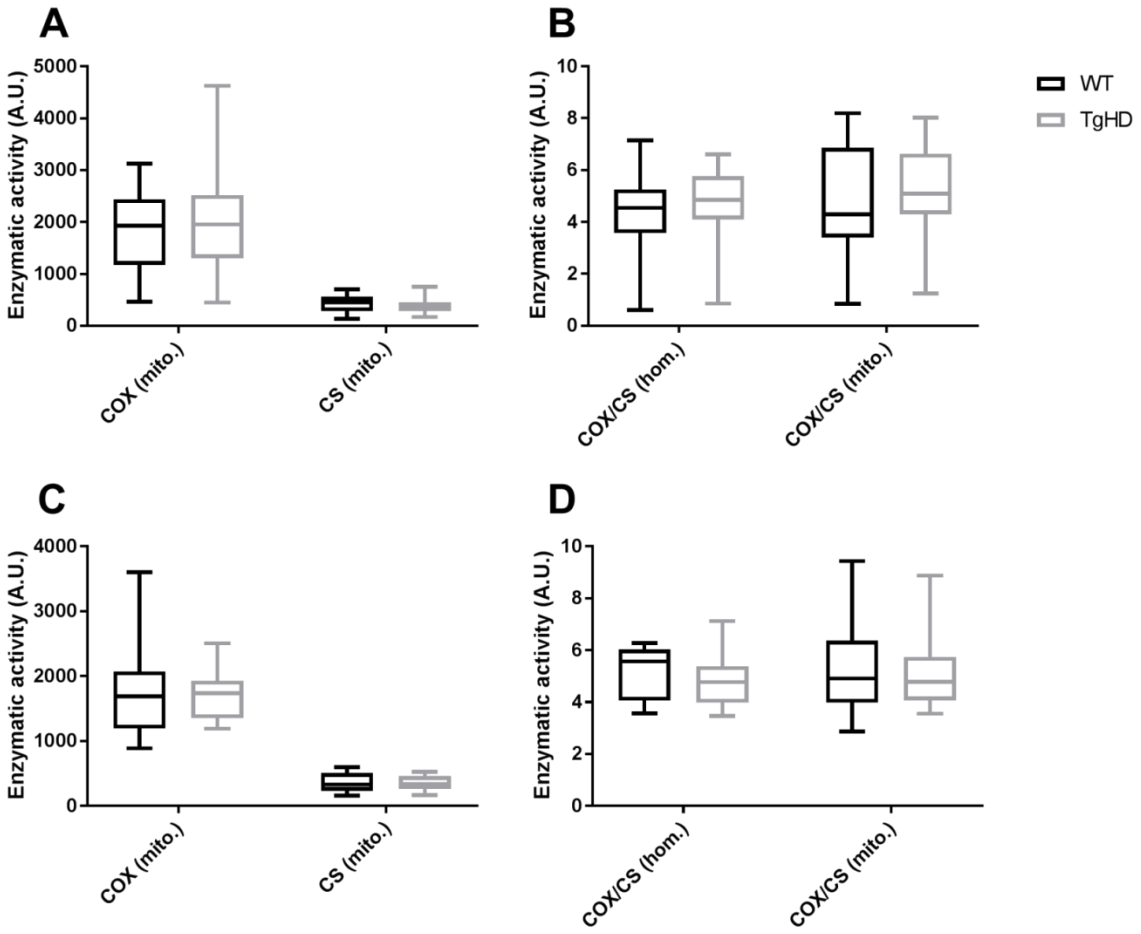


**Fig. S4. Cytochrome c oxidase (COX) and citrate synthase (CS) activity in homogenates and isolated mitochondria from TgHD minipig brain**. COX and CS activity unchanged in mitochondrial isolates in frontal cortex (A) and after normalizing to CS (B). COX and CS activity unchanged in mitochondrial isolates in basal ganglia (C) and after normalizing to CS (D). Arbitrary units (A.U.) represent enzymatic activity as nmol/min/mg. Student's t-test. Box plot whiskers indicate minimum to maximum values, with hinges representing the 25$^{th}$ and 75$^{th}$ percentile and median indicated by the center line. Sample sizes: Frontal cortex: COX (mito.) WT n=19, TgHD n=21, CS (mito.) WT n=19, TgHD n=21, COX/CS (hom.) WT n=19, TgHD n=21, COX/CS (mito.) WT n=19, TgHD n=21; basal ganglia: COX (mito.) WT n=10, TgHD n=9, CS (mito.) WT n=10, TgHD n=9, COX/CS (hom.) WT n=10, TgHD n=9, COX/CS (mito.) WT n=10, TgHD n=9. «mito": isolated mitochondria; "hom": homogenate.

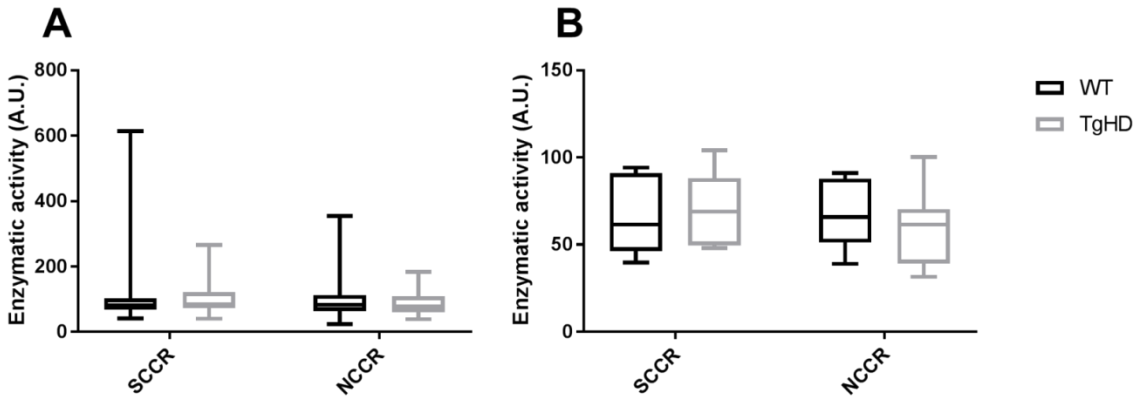


**Fig. S5. Coupled activity of mitochondrial complex II+III and I+III in TgHD minipig model brain.** SCCR activity (II+III) and NCCR activity (I+III) in frontal cortex (A) and basal ganglia (B) showed normal levels compared to WT animals. Arbitrary units (A.U.) represent enzymatic activity as nmol/min/mg. Student's t-test. Box plot whiskers indicate minimum to maximum values, with hinges representing the 25$^{th}$ and 75$^{th}$ percentile and median indicated by the center line. Sample sizes: Frontal cortex: SCCR WT n=19, TgHD n=21, NCCR WT n=19, TgHD n=21; basal ganglia: SCCR WT n=10, TgHD n=9, NCCR WT n=10, TgHD n=9. SCCR- succinate cytochrome c oxidase, NCCR- rotenone sensitive NADH cytochrome c oxidase.