

Description of Additional Supplementary Files

Supplementary Data 1. Genes expressed by the four populations identified by single-cell RNA sequencing analysis of midbrain organoids from WT/WT and 70Q/70Q (related to Fig. 2 and Supplementary Fig. 3).

Supplementary Data 2. Differentially expressed genes (DEG) in iPSCs, NPCs, cerebral organoids (COs) at d28 and CO at d49 derived from WT/WT and 70Q/70Q (related to Fig. 3 and Supplementary Fig. 4).

Supplementary Data 3. Common genes expressed in iPSCs, NPCs, cerebral organoids (COs) at d28 and CO at d49 derived from WT/WT and 70Q/70Q (related to Fig. 3 and Supp Fig. 4).

Supplementary Data 4. Proteomics: differentially expressed proteins in iPSCs 70Q/70Q compared to iPSCs WT/WT (two-tailed t-test with Benjamini-Hochberg correction for multiple comparisons; FDR<0.05) (related to Figure 3).

Supplementary Data 5. Proteomics: differentially expressed proteins in NPCs 70Q/70Q compared to NPCs WT/WT (two-tailed t-test with Benjamini-Hochberg correction for multiple comparisons; FDR<0.05) (related to Figure 3).

Supplementary Data 6. Functional metabolic analysis from proteomics of iPSCs 70Q/70Q compared to iPSCs WT/WT and NPCs 70Q/70Q compared to NPCs WT/WT (related to Fig. 5).

Supplementary Data 7. Total RNA-sequencing: differentially expressed genes and pathways in NGN2 neurons from healthy controls (C1, C2, C3) and individuals with HD (HD1, HD2, HD3) (two-

tailed Wald test with Benjamini-Hochberg correction for multiple comparisons; $FDR < 0.05$) (related to Fig. 6 and Supplementary Fig. 7).

Supplementary Data 8. Proteomics: differentially expressed proteins in NGN2 neurons from healthy controls (C1, C2, C3) and individuals with HD (HD1, HD2, HD3) (two-tailed Wald test with Benjamini-Hochberg correction for multiple comparisons; $FDR < 0.05$) (related to Fig. 6 and Supplementary Fig. 7).

Supplementary Data 9. Proteomics: gene set enrichment analysis (GSEA) in NGN2 neurons from healthy controls (C1, C2, C3) and individuals with HD (HD1, HD2, HD3) (two-tailed Wald test with Benjamini-Hochberg correction for multiple comparisons; $FDR < 0.05$) (related to Fig. 6 and Supplementary Fig. 7).

Supplementary Data 10. Metabolomics: differentially expressed metabolites in NGN2 neurons from healthy controls (C1, C2, C3) and individuals with HD (HD1, HD2, HD3) (two-tailed Wald test with Benjamini-Hochberg correction for multiple comparisons; $FDR < 0.05$) (related to Fig. 6 and Supplementary Fig. 7).

Supplementary Data 11. List of sequences and primers for PCR, QRT-PCR, siRNA knockdown, and CRISRP/eCas9 genome editing, and list of all antibodies.