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An increase in the number of CAG repeats in the huntingtin gene enhances pathological ultrastructural aberrations in the cells and neurons

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Huntington's disease is a hereditary neurodegenerative illness caused by an increased CAG repeat number (> 35) in *HTT* resulting in elongation of the polyglutamine tract in the huntingtin protein and contributing to huntingtin aggregation. We compared previously documented ultrastructural aberrations in neurons and other cells featuring different numbers of CAG repeats: patient specific neurons (PSN) with 42–45 CAG repeats [1], neurons with transgenic insertion (TN) of 69 CAG repeats [2], and HEK293 cells with insertion of 150 CAG repeats [3]. Severe damage of mitochondria (Fig. 1, A), hypertrophy and vesiculation of the endoplasmic reticulum (see Fig. 1, B) and Golgi apparatus, disrupted autolysosomal membrane integrity (see Fig. 1, C) were noted in all studied mutant cells together with lower number of spines on dendrites in mutant neurons (see Fig. 1, D).

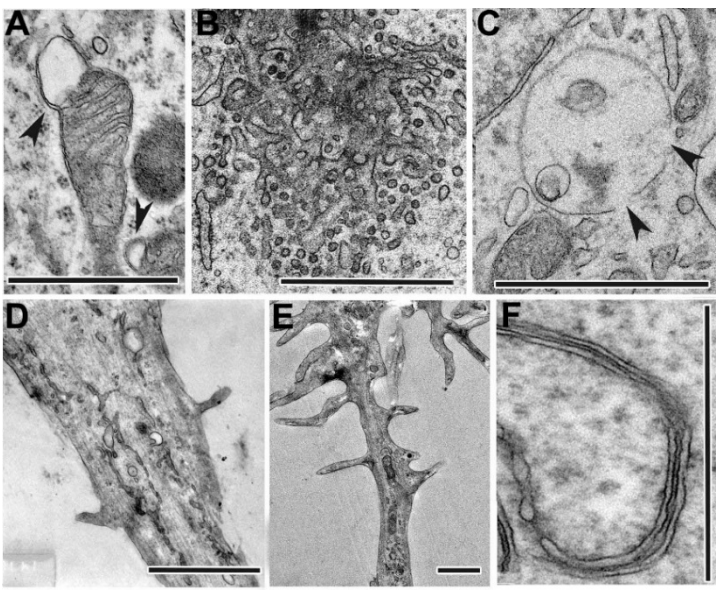

Fig. 1. Comparative analysis of morphological defects in mutant cells with an increased number of CAG repeats in the huntingtin gene. A – defective mitochondria with membrane disruption (arrowheads); B – ER membrane hypertrophy and vesiculation; C – breaks of autolysosome membrane integrity (arrowheads); D – dendrite with sparse spines; E – fragment of atypical neuron with a high frequency of spines distribution on hypertrophied dendrite; F – quadruple membranes of smooth ER in the cytoplasm HEK293 cell with insertion of 150 CAG repeats. Scale bar – 1 μm

Compared to the patient specific cells, in the cell of transgenic model were additionally observed greater neuronal heterogeneity at various stages of degradation, and appearance new atypical neurons with greater length and frequency of spines distribution on hypertrophied dendrites (see Fig. 1, E). In the HEK293 cells (largest number of repeats), numerous abnormal four-layer endoplasmic-reticulum membranes were identified for the first time in the cytoplasm (see Fig. 1, F). The study offers new information about the dynamics of progressive pathological changes in mutant cells and shows correlations with a greater CAG repeat number.

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References

1. Nekrasov E.D., Vigont V.A., Klyushnikov S.A., Lebedeva O.S., Vassina E.M., Bogomazova A.N., ..., Kiselev S.L. Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons. *Mol Neurodegener*. 2016;11:27.
2. Malankhanova T., Suldina L., Grigor'eva E., Medvedev S., Minina J., Morozova K., ..., Malakhova A. A human induced pluripotent stem cell-derived isogenic model of Huntington's disease based on neuronal cells has several relevant phenotypic abnormalities. *J Pers Med.* 2020;10(4):215.
3. Morozova K.N., Suldina L.A., Malankhanova T.B., Grigor'eva E.V., Zakian S.M., Kiseleva E., Malakhova A.A. Introducing an expanded CAG tract into the huntingtin gene causes a wide spectrum of ultrastructural defects in cultured human cells. *PLoS One.* 2018;13(10):e0204735.