ABSTRACT

Huntingtons´s disease (HD) is devastating neurodegenerative disorder manifesting by motor disturbances, cognitive decline and personal changes. The huge effort to find a cure for HD has brought several promising therapeutic treatments on the scene. Each of the prospective approaches needs to be investigated for safety, tolerability and efficacy. Mouse and rat models were a lot helpful in examination of pathological mechanisms of HD, but they are not sufficient for completion of pre-clinical testing.

Therefore, we aimed to generate transgenic HD minipig to overcome the gap between rodents and humans. Minipig transgenic for the first 548 aminoacids of human mutant huntingtin gene (TgHD) under the control of human HD promotor was manipulated by lentiviral transduction of porcine one-cell stage embryos. Currently, six generations of minipigs expressing single copy of N-truncated human mutant huntingtin protein (mtHtt) with a repetition of 124 glutamines are at disposal.

The more the model simulates the disease symptoms the better it is for translational research as the efficacy of the cure can be finer evaluated. Hence, the second aim was to demonstrate HD-like phenotype in our model. Testicular degeneration that preceded the clinical symptoms onset was observed as a consequence of expression of mtHtt. Continuous age-dependent accumulation of mtHtt fragments was detected in TgHD brains. Moreover, further age-related molecular alterations discriminative for HD brain were revealed in TgHD brain tissues, including neuronal loss, activated microglia and demyelination. Newly developed tests for examination of cognitive abilities and stress-induced behavior showed decline in their performance. Furthermore, impaired gait and increased physical activity were observed in TgHD minipigs. Manifestation of clinical symptoms at the age of 6-7.9 years is a result of mild but ongoing brain degeneration.

Slow progression of the disease makes TgHD minipig a suitable model for investigation of pre-clinical stage of the disease and long-term HD therapy research. The methods and results obtained in this study will be used for longitudinal evaluation of efficacy of the gene-lowering therapy for HD.