A NOVEL TKS4-KO HUMAN STEM CELL-BASED FTHS MODEL SYSTEM

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Frank-Ter Haar syndrome (FTHS) is a rare inherited developmental disease caused by the mutation of the tyrosine kinase substrate with four SH3 domains (Tks4) scaffold protein gene (SH3PXD2b). FTHS leads to cardiovascular disorders, facial and skeletal abnormalities, decreased adiposity and developmental delay in patients. Pluripotent stem cells (PSCs) can be used as in vitro human disease models. This cell type can be maintained in culture under laboratory conditions for an unlimited period of time, the resulting cell lines are able to differentiate into any cell type and show a more accurate match to human tissue than animal models. In this study, human PSCs were used for the modeling of this genetic disease to study the effect of the absence of the Tks4 protein in different cell types created by using CRISPR/Cas9 system to knock out the SH3PXD2b gene, resulting in homo- and heterozygous Tks4-KO HUES9 human embryonic stem cell lines. Gene knockout caused no change in pluripotency, therefore other cell types relevant to FTHS were examined. The differentiation of HUES9 cell lines into mesenchymal stem cells (MSCs), furthermore MSC-derived adipocytes and osteocytes, as well as future cardiomyocyte differentiation gives an opportunity to examine the influence of the absence of the Tks4 protein on cell lineage differentiation and maturation.

Keywords: Frank-Ter Haar syndrome; Tks4; human pluripotent stem cells; mesenchymal stem cells, cardiomyocytes.

Funding: This research was funded by grants from the National Research, Development, and Innovation Fund of Hungary K124045 (L.B.), K128369 (A.A.), FIEK_16-1-2016–0005, HunProtExc 2018-1.2.1-NKP-2018–00005 (L.B.) and Cooperation between ELKH TTK and PTE SzKK in Areas of Internationally Significant Biomedical Research (KÖ-39/2021) project (L.B. and V.V.). This project was supported by National Research, Development and Innovation Office (PharmaLab, RRF-2.3.1-21-2022-00015). The authors acknowledge the financial support received as a Centre of Excellence of the Hungarian Academy of Sciences.