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Modeling of fabry disease nephropathy using patient derived induced pluripotent stem cells and kidney organoids

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Objectives: The aim of this study is to explore the possibility of human induced pluripotent stem cells (hiPSC) -derived kidney organoids for fabry disease modeling using both patient derived iPSC and also genetically modified (GLA-KO) hiPSC.

Methods: First, we generated patient specific hiPSC lines (CMC-Fb01,02) using peripheral blood mononuclear cells from patients who were diagnosed as fabry disease by *GLA* gene sequencing. Second, we generated GLA-KO hiPSCs using wild-type hiPSC (WTC-11) by CRISPR/Cas9 technology. Lastly, using all of wild type, patient specific (CMC-Fb01, 02) and disease specific hiPSC lines (GLA-KO-WTC-11), we generated kidney organoids and compared alpha-galactosidase A (α-GLA) activity, globotriaosylceremide (GB-3)(LC_MS)and also GB-3 deposition using immunofluorescent (IF) staining and also zebra body formation under electromicroscopy (EM) among kidney organoids derived from 3 types of hiPSCs.

Results: Patient specific hiPSCs contained same frame shift mutation in *GLA* genes which was detected in PBMCs of their originating patients and both hiPSCs lines showed typical pluripotency markers and also normal karyotyping. Kidney organoids generated from 3 types of hiPSC lines showed typical nephron markers such as PODXL, LTL, and E-cad in IF staining. In both kidney organoids derived from patients specific hiPSC and disease specific hiPSCs, α-GLA activity was significantly decreased in comparison with wild type kidney organoids. In contrast, GB3 level measured by LC-MS and also GB-3 deposits by IF staining was significantly increased in the patient specific and also disease specific kidney organoids in comparison with wild-type kidney organoids. In EM finding, typical zebra body was detected in both patient specific and disease specific kidney organoids.

Conclusions: Kidney organoids generated using hiPSCs derived from fabry disease patients may recapitulate the phenotype of fabry disease nephropathy, and it may be used as a potential platform for an in vitro disease modeling.