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Functional analysis using iPS cells for diseases derived from lipodystrophic / mitochondrial diabetes

(社会人大学院博士課程 4 年糖尿病・代謝・内分泌内科)

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Congenital lipodystrophic diabetes is an intractable rare disease that causes insulin-resistant diabetes mellitus and fatty liver due to lack of systemic adipose tissue. We established iPS cells from the peripheral blood of patients with lipodystrophic diabetes who carry the BSCL2 gene mutation. As a result of differentiating iPS cells into adipocytes, a decrease in the number of lipid droplets, the presence of giant lipid droplets, and a decrease in PPAR γ expression were observed in patient-derived adipocytes as compared with healthy human-derived cells.

Mitochondrial diabetes is caused by mutations in mitochondrial DNA, and is the most common type of diabetes caused by single gene mutations.

We established iPS cells from the peripheral blood of two mitochondrial diabetic patients with A3243G mutation in mitochondrial DNA and complicated cardiomyopathy and sensorineural deafness. As a result of analyzing the mutation rate of mitochondrial DNA of iPS cells by the ddPCR method, the mutation rate of heteroplasmy varies from clone to clone, and is widely distributed from cell lines with almost no mutation to cell lines with a mutation rate of about 95%. In addition, the cell proliferation ability was decreased in clones with a high mutation rate, and in clones with a mutation rate exceeding 90%, a significant decrease in ATP content and an increase in ROS were observed. In the future, it is expected that these cells will be used as tools to elucidate

the impaired mechanism of this disease.

6-10.

Functional Analysis of Human Variant (c.-137C > T) in Specificity Protein 1 Binding Site of Low Density Lipoprotein Receptor Promoter With familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is a hereditary metabolic disease known to be caused by the mutation of low density lipoprotein receptor (LDLR) protein, convertase subtilisin/kexin type 9, apolipoprotein B, and low density lipoprotein receptor adaptor protein1. Among them, FH deriving from the mutation of LDLR is the most frequent. Although many mutations have been reported on the database concerning causative mutation of FH, their functional analyses are few. The aim of this study was functional characterization of the promoter mutation in the LDLR.

We identified the c.-137C>T mutation of LDLR promoter gene in the patient with familial hypercholesterolemia. The functional analysis has not been carried out on c.-137C>T which is located at the binding site of the specificity protein 1 (SP1) transcription factor. We conducted luciferase assay and electrophoresis mobility shift assays to analyze its functional activity. In the mutation what was seen was a significant decrease in promoter activity and binding activity to the SP1 transcription factor. In conclusion,