Therapeutic Methods, Treatment of Genetic Diseases

AB043. Correction of the *GLA* IVS4+919 G>A mutation with CRISPR/Cas9 deletion strategy in fibroblasts of Fabry disease

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Background: Fabry disease (FD) is an X-linked inheritable lysosomal storage disease caused by genetic defects on *GLA* gene encoding the α-galactosidase (α-GLA) protein. Lack of α-GLA resulted in accumulation of globotriaosylceramide (Gb3) in the lysosomes, and induced clinicopathological manifestations in heart, kidney and vessels. Previously, we found a *GLA* IVS4+919 G>A mutation with a surprising high incidence in cardiac FD of Taiwanese population (about 1 in 1,500 of males). This mutation interfered the normal RNA splicing and produced a truncated GLA protein without enzyme activity. Recently, the CRISPR/Cas9-mediated genome editing technology has provided a new insight in the field of gene therapy and shown therapeutic feasibility in the animal models of inherited diseases, such as Type I tyrosinemia, metabolic liver disease and muscular dystrophy. Therefore, the application of CRISPR/Cas9-mediated gene therapy is a promising approach for treatment of inherited diseases.

Methods: The CRISPR/Cas9 with two sgRNAs approach was designed to delete the *GLA* IVS4+919 G>A mutation and applied in fibroblasts of FD patients. The GLA RNA splicing pattern, enzyme activity and the clearance of Gb3 accumulation were assayed to investigate the therapeutic efficiency of CRISPR/Cas9 technology in treatment of FD.

Results: We successfully used CRISPR/Cas9 with dual sgRNAs to delete the *GLA* IVS4+919 G>A mutation in FD patient fibroblast (C054). After removing the *GLA* IVS4+919 G>A mutation, the aberrant splicing manner of *GLA* can be restored to normal in FD fibroblasts. The enzyme activity of GLA protein was significantly increased and comparable with normal fibroblasts. Moreover, the accumulation of intracellular Gb3 in FD fibroblasts was found to be cleared efficiently using immunofluorescent staining.

Conclusions: This study indicated that CRISPR/Cas9-mediated deletion of *GLA* IVS4+919 G>A mutation could be a feasible approach for cardiac type FD patients.

Keywords: IVS4+919 G>A; Fabry disease (FD); CRISPR/Cas9; gene therapy

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