CRISPR/Cas9 gene editing: A breakthrough approach for treating hereditary tyrosinemia type I in newborn animal models

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Abstract. This news and views article critically examines the use of CRISPR/Cas9 technology for gene correction in hereditary tyrosinemia type I (HT1), a rare metabolic disorder caused by fumarylacetoacetate hydrolase (FAH) gene mutations. The study highlights the successful application of CRISPR/Cas9 in a rabbit model, where precise gene editing via adeno-associated virus (AAV8) delivery corrected the FAH mutation, restoring normal liver and kidney function. Treated rabbits demonstrated long-term health benefits, including the ability to reproduce, without requiring NTBC therapy. These findings provide preclinical evidence for the efficacy and safety of CRISPR/Cas9 in addressing metabolic liver diseases, bridging the gap between rodent models and human clinical applications.
Key Words: FAH gene, gene therapy, metabolic liver disease, adeno-associated virus, gene editing, preclinical research, newborn rabbits, precision medicine.

This news and views article aims to critically evaluate the use of CRISPR/Cas9 technology for gene correction in hereditary tyrosinemia type I (HT1), highlighting its potential to address metabolic liver disorders through precise genetic interventions in newborn animal models.

A study, conducted by Nan Li, Shixue Gou, Jiaowei Wang, Quanjun Zhang, and their colleagues from renowned institutions such as the Chinese Academy of Sciences and Guangzhou Medical University, explored the use of CRISPR/Cas9 technology to address hereditary tyrosinemia type I (HT1) in newborn rabbits (Li et al 2017). HT1 is a rare autosomal-recessive metabolic disorder caused by a deficiency in the fumarylacetoacetate hydrolase (FAH) enzyme, leading to toxic metabolite accumulation in the liver and kidneys (Tang & Kong 2021). Current treatments, including dietary restrictions and NTBC therapy, have significant limitations, such as incomplete metabolic control and the potential for severe side effects (González-Lamuño et al 2021). Liver transplantation remains a definitive treatment but is constrained by donor shortages and risks of immune rejection (Li et al 2021). The researchers sought to develop an alternative therapy through CRISPR/Cas9-mediated gene correction, focusing on newborns to prevent irreversible organ damage and optimize therapeutic outcomes (Li et al 2021).

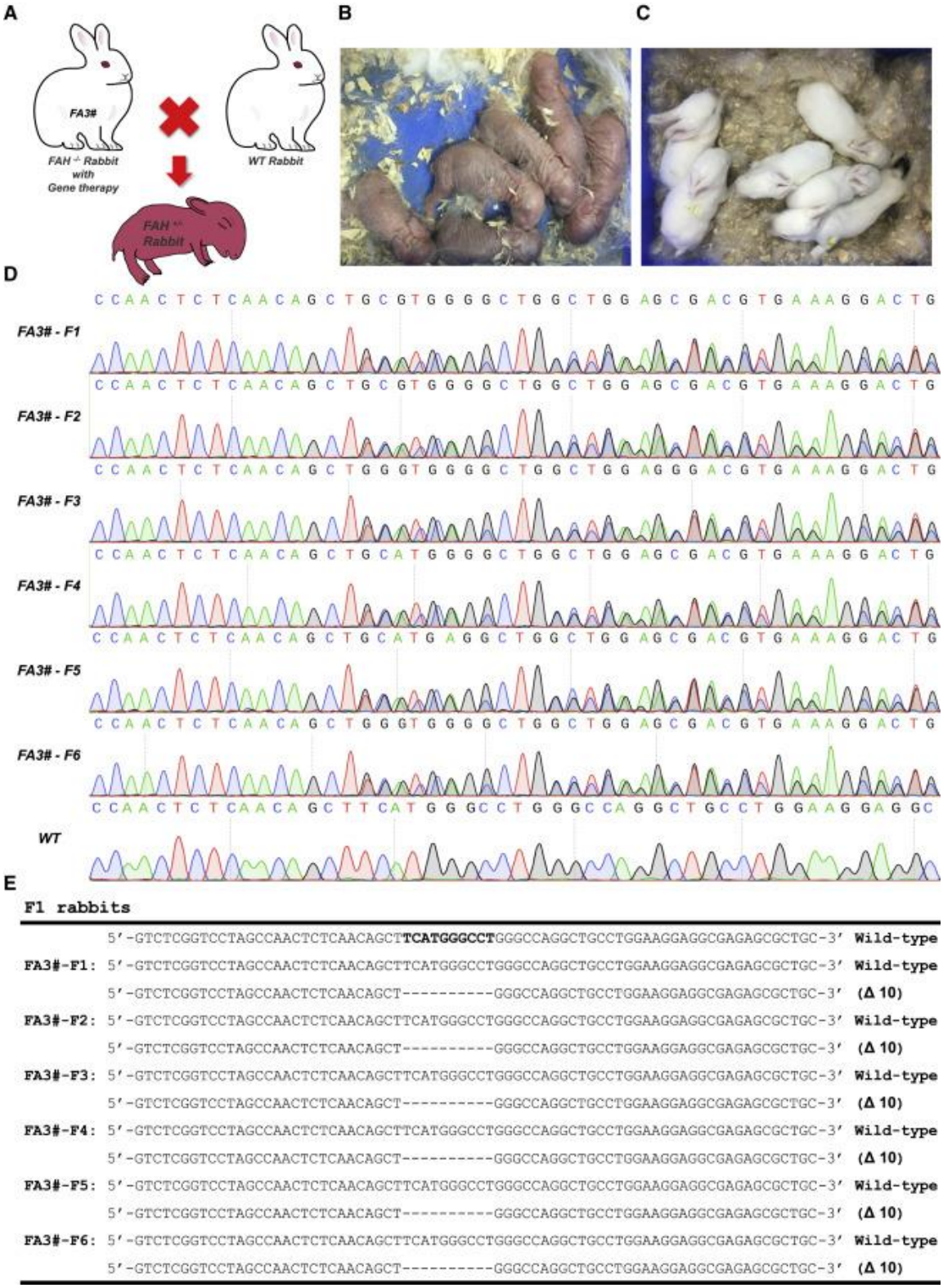

Figure 1. Gene-corrected HT1 rabbits can give birth to normal offspring (source: Li et al 2021). (A) Overview of mating of a wild-type male rabbit with a gene-corrected female HT1 rabbit (FA3). (B and C) Photographs of the 1-day-old (B) and 20-day-old (C) F1 rabbits. (D) Sanger sequencing results of the PCR products of the FAH gene amplified from six F1 bunnies. (E) Summary of the genotypes of all six F1 bunnies.

Using a rabbit model with a 10-base pair deletion in the FAH gene, Li et al (2021) delivered CRISPR/Cas9 components and a donor template via adeno-associated virus (AAV8) into 15-day-old HT1 rabbits. This approach allowed for precise gene editing through homology-directed repair (HDR) and non-homologous end joining (NHEJ), correcting the mutation and restoring FAH protein expression in hepatocytes. The treated rabbits exhibited normal liver and kidney function, as evidenced by normalized biochemical markers and histological analysis, without requiring NTBC therapy. They grew to adulthood, reproduced successfully (Figure 1), and passed on heterozygous FAH genotypes to their offspring, demonstrating the long-term efficacy and safety of the intervention (Li et al 2021).

The study revealed that CRISPR/Cas9-mediated corrections achieved editing efficiencies of 0.90–3.71% for HDR and 2.39–6.35% for NHEJ, sufficient to rescue the lethal phenotype (Li et al 2021). Notably, gene-corrected hepatocytes expanded in the liver over time, compensating for the relatively low initial editing efficiency. Histological analysis confirmed the absence of liver fibrosis, hemorrhage, or other structural abnormalities. At the same time, kidney function was fully restored, addressing a critical limitation of rodent models that fail to recapitulate human-like renal symptoms (Li et al 2021). RNA sequencing further demonstrated that metabolic pathways and gene expression profiles in treated rabbits were comparable to those of wild-type animals, underscoring the comprehensive restoration of normal physiology (Li et al 2021).

This research provides critical preclinical data supporting the feasibility of CRISPR/Cas9-based gene therapy for monogenic metabolic liver diseases in large mammals. The results highlight the potential of early intervention to mitigate disease progression, reduce toxic metabolite accumulation, and prevent irreversible organ damage. Moreover, the successful application of this technology in a rabbit model bridges the translational gap between rodent studies and clinical trials in humans, paving the way for more effective treatments for HT1 and other genetic disorders.

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