Therapeutic efficacy of base editing (BE) in a novel Wolfram syndrome (WS) mouse model.

Wolfram syndrome is a rare genetic disease that causes early-onset diabetes and progressive loss of vision due to damage of the optic nerve. At present, there is no treatment that can slow or prevent this vision loss. The goal of this project was to test whether a new gene-repair approach, called base editing, could help correct the underlying genetic defect and preserve vision.

We first studied a newly developed mouse model of Wolfram syndrome that carries the same type of genetic change seen in patients. In addition to diabetes, these mice developed a gradual and measurable loss of vision, especially in females. Detailed eye tests showed that the nerve cells responsible for sending visual signals from the eye to the brain were not functioning properly. These findings confirmed that this mouse model closely mimics the vision problems experienced by people with Wolfram syndrome and allowed us to identify the best time window to test treatment.

Next, we evaluated whether base editing could repair the faulty gene in these mice. Using a viral delivery system, we were able to efficiently deliver the gene-editing tools to the affected eye cells. In laboratory experiments, this approach successfully corrected a large proportion of the genetic errors.

When treated mice received base editing in the eye, their vision was significantly better than that of untreated mice and approached normal levels. Although vision still declined over time, treated animals retained better visual function, and eye nerve cells showed improved activity. Early tissue studies also suggested partial restoration of the missing protein.

Together, these results provide encouraging proof that gene-repair therapies may one day slow or prevent vision loss in Wolfram syndrome. Further studies will focus on confirming safety and optimizing this approach for future clinical use.