

Lay Summary

Our research aims to develop gene-based therapies that can correct the underlying genetic problem in PCDH19-clustering epilepsy. Our goal is to reduce or eliminate the harmful copy of the PCDH19 gene in affected individuals, helping to prevent or lessen the impact of the disease.

In this study, we focused on testing CRISPR/Cas9 gene editing, a breakthrough technology that can precisely cut and disable disease-causing genes. We designed and tested small molecules called guide RNAs (gRNAs) to make sure the gene-editing tools could accurately target *PCDH19* genes in human and mouse cells. Two gRNAs were found to be highly effective in switching off the “toxic” gene. We delivered these gene-editing tools into mice using harmless viral carriers injected into the bloodstream at early postnatal stages. This method allowed the therapy to reach many areas of the brain safely and effectively.

Key Findings

- **Precise Gene Targeting:** gRNAs successfully disrupted PCDH19 in both human and mouse cells.
- **Safe and Efficient Delivery:** Viral delivery in mouse pups spread throughout the brain without harming the animals. Their growth, behaviour, and survival were normal.
- **Functional Gene Disruption in the Brain:** Using CRISPR/Cas9 in mice, we achieved substantial reductions in the “toxic” PCDH19 protein, showing that our approach works in living brains.
- **Potential for Therapy:** Early intervention was feasible, safe, and led to significant reduction of the harmful protein, paving the way for further development.

Why This Matters

These findings represent a significant step forward in the search for a treatment for PCDH19-clustering epilepsy. Our results show that it is possible to safely and effectively target and reduce the harmful gene in the brain. This work lays the foundation for future studies to explore whether early gene therapy could improve seizures, learning, and development in affected children. However, continued research is crucial to advance these promising results to the next stage including evaluating long-term safety, confirming therapeutic benefits, and translating this approach toward a potential clinical treatment.

Acknowledgements

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