Alevian

# Human Genetic Evidence Supporting GDF11as a Therapeutic Target

## Mendelian Randomization Validates GDF11's Role in Brain Health and Neurological Recovery

### Executive Summary

Recent human genetic studies using Mendelian randomization (MR) have identified GDF11 as a causal therapeutic target for cognitive performance and brain health. This genetic evidence complements Alevian's preclinical stroke research, providing critical human validation for GDF11's regenerative potential in neurological conditions.

### What is Mendelian Randomization?

Mendelian randomization is a powerful epidemiological method that uses genetic variants as natural experiments to determine whether an exposure (such as GDF11 levels) causes an outcome (such as improved brain function). Because genetic variants are randomly assigned at conception, MR studies can establish causal relationships without the confounding that limits traditional observational studies—making them analogous to randomized controlled trials using nature's own randomization.

For drug development, MR provides a cost-effective way to validate therapeutic targets before clinical trials. Drugs targeting genetically validated pathways have been shown to have significantly higher success rates in clinical development.

### Key GDF11 Findings from Mendelian Randomization

A comprehensive 2025 study published in Translational Psychiatry analyzed over 4,300 druggable genes and identified GDF11 as one of only 13 candidate drug targets with robust causal evidence for improving cognitive performance.

#### GDF11 Genetic Evidence Summary

| Finding | Details |
|---|---|
| Cognitive Performance | GDF11 identified as causal therapeutic target among 4,300+ druggable genes (colocalization PPH4 > 0.8) |
| Reaction Time | Causal association: OR = 1.073, 95% CI 1.036–1.112, p = $9.02\times10^{-5}$ |
| White Matter Integrity | Higher GDF11 associated with lower mean diffusivity (healthier tissue) in multiple brain tracts ($p < 0.001$) |
| Brain Connectivity | Protected inferior fronto-occipital and inferior longitudinal fasciculi bilaterally |

### White Matter Protection

The MR analysis revealed that genetically determined higher GDF11 expression is associated with preserved white matter microstructure across multiple brain regions:

| Brain Region | Odds Ratio | P-value |
|---|---|---|
| Left Inferior Fronto-Occipital Fasciculus | 0.691 | $2.71\times10^{-5}$ |
| Right Inferior Fronto-Occipital Fasciculus | 0.691 | $2.75\times10^{-5}$ |
| Left Inferior Longitudinal Fasciculus | 0.745 | $8.37\times10^{-4}$ |
| Right Inferior Longitudinal Fasciculus | 0.730 | $3.41\times10^{-4}$ |

Note: Lower mean diffusivity values indicate healthier white matter tissue with better structural integrity.

## Significance for Stroke Recovery

These human genetic findings directly support Alevian's therapeutic hypothesis and complement our preclinical stroke research:

Human Genetic Validation: MR provides causal evidence in humans that higher GDF11 levels improve cognitive function and protect brain tissue—evidence that animal studies alone cannot provide.

Mechanistic Alignment: The white matter protection observed in MR studies aligns with our preclinical findings showing rGDF11 enhances neovascularization, reduces inflammation, and promotes neurogenesis after stroke.

Cognitive Endpoints: The genetic association with cognitive performance supports including cognitive assessments as meaningful endpoints in stroke recovery clinical trials.

Higher Clinical Success Probability: Drug targets with human genetic support have demonstrated significantly higher success rates in clinical development, reducing the risk of late-stage failures.

## Preclinical Validation

Our February 2025 publication in Stroke demonstrated that recombinant GDF11 (rGDF11) promotes recovery in a rat permanent ischemia model of stroke. Six independent preclinical studies with blinding and randomization consistently showed:

- Improved sensorimotor function
- Enhanced neovascularization in the cortex
- Increased neurogenesis in the ventricular zone
- Reduced inflammation (dose-dependent CRP reduction)
- Identification of pharmacodynamic biomarkers for clinical translation

## Conclusion

The convergence of human genetic evidence from Mendelian randomization with our rigorous preclinical studies establishes a compelling scientific foundation for GDF11 as a therapeutic target for stroke recovery and neurological regeneration. This dual validation—from human genetics and animal models—positions ALE-001 as a scientifically differentiated approach to addressing the massive unmet need in post-stroke recovery.

## References

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