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Basic Science

Abstract Title
Investigating atypical neuronal communication mechanisms between ELFN1 and mGluR4 in rare neurodevelopmental disorders

Background
Glutamatergic neurotransmission plays a central role in neurodevelopmental disorders (NDDs) such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), intellectual disability, and obsessive–compulsive disorder (OCD). Metabotropic glutamate receptors (mGluRs), a family of G-protein–coupled receptors (GPCRs), regulate excitatory signaling and have emerged as promising therapeutic targets in NDDs. Among them, group III mGluRs (mGluR4, 6, 7, and 8) are uniquely modulated by synaptic adhesion molecules (SAMs). Extracellular leucine-rich fibronectin type III domain–containing protein 1 (ELFN1), a postsynaptic SAM, engages group III mGluRs and modifies their pharmacological properties. Recent genetic studies have identified disease-associated ELFN1 variants in diverse NDDs; however, their molecular and functional consequences remain largely undefined.

Objective
Given the clinical development of mGluR4-targeting drugs, we investigated how ELFN1 variants affect mGluR4 function. Therefore here, we hypothesized that pathogenic ELFN1 variants disrupt normal mGluR4 regulation.

Methods
To test the hypothesis, we performed Western blotting, co-immunoprecipitation (co-IP), and transcellular signaling assays. Protein expression and receptor interactions were quantified, and functional modulation of mGluR4 activity was assessed. Statistical analysis was performed using ANOVA.

Results
Western blotting demonstrated comparable expression levels between wild-type and variant ELFN1, excluding differential stability or expression as confounding factors. Co-IP revealed that wild-type ELFN1 interacts transcellularly with mGluR4, while an extracellular ELFN1 variant showed markedly reduced receptor binding. Transcellular signaling assay further indicated that wild-type ELFN1 downregulated mGluR4 signaling, consistent with its established modulatory role, whereas the variant failed to alter receptor activity, resulting in dysregulated mGluR4 function.

Conclusion
These results provide mechanistic evidence that pathogenic ELFN1 variants impair mGluR4 regulation, offering insight into how such mutations may contribute to NDD pathogenesis. By linking ELFN1 dysfunction to disrupted glutamatergic signaling, this study underscores the importance of SAM–mGluR4 interactions and supports continued therapeutic exploration of mGluR4 in neurodevelopmental disorders.

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