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Patient-Derived Cortical Organoids from Ischemic Stroke Surrogates Reveal Neuronal Excitotoxicity Mechanisms Mediated by *GRIN2B* Glutamate Receptor Variants

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Abstract

The molecular determinants of selective neuronal vulnerability in acute ischemic stroke remain poorly characterized. We established patient-derived cortical organoids from fibroblasts of stroke survivors with extreme phenotypes (large infarct volume versus small lesion size) and subjected them to oxygen-glucose deprivation (OGD). Organoids derived from high-vulnerability patients exhibited exaggerated calcium influx and delayed neuronal death following OGD. Whole-exome sequencing identified rare deleterious variants in *GRIN2B* encoding the GluN2B NMDA receptor subunit. CRISPR-Cas9 correction of the *GRIN2B* variant in patient iPSCs normalized calcium responses and conferred resistance to excitotoxicity. Pharmacological blockade with ifenprodil, a GluN2B-selective antagonist, rescued viability in susceptible organoids. This precision medicine model identifies *GRIN2B* as a pharmacogenomic determinant of stroke outcome and validates organoid platforms for cerebrovascular disease modeling.

Keywords: cortical organoids, ischemic stroke, GRIN2B, excitotoxicity, NMDA receptor, precision medicine