

# The mysterious GRIN3A and the cause of schizophrenia

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Since the 1960s, psychiatrists have been hunting for substances made by the body that might accumulate in abnormally high levels to produce the symptoms associated with schizophrenia. In particular, there was a search for chemicals that might be related to the hallucinogens phencyclidine (PCP) or lysergic acid diethylamide (LSD), which could explain the emergence of psychotic symptoms in schizophrenia. This "auto-intoxication" hypothesis led investigators on a wild goose chase where substances, including the "Pink Spot" and the "Frohman Factor", were isolated from people with schizophrenia and implicated in their illness, but these findings were later discredited.

The mysterious GRIN3A is a new version of the hunt for an intrinsic mechanism that produces schizophrenia-like symptoms. GRIN3A is a gene that codes for the GluN3A subunit of the N-methyl-D-aspartate-type (NMDA) receptor, a target for the [neurotransmitter glutamate](#) in the brain. Functional [NMDA receptors](#) usually have two GluN1 subunits and two GluN2 subunits. The ability of glutamate to activate these receptors is blocked by PCP and the anesthetic/hallucinogen, ketamine. When the GluN3A subunit is incorporated, it prevents the NMDA receptor from being activated by glutamate, almost as if the receptor had been blocked by PCP.

It is unclear why the brain needs this mechanism for normal brain development and function, hence the mystery surrounding GRIN3A. One piece of evidence supporting a link between GluN3A and schizophrenia is the finding that GluN3A levels are elevated in the post-

mortem [brain tissue](#) from people who had been diagnosed with schizophrenia.

In this issue of *Biological Psychiatry*, [Japanese researchers](#) led by Dr. Takeo Yoshikawa provide new support for this hypothesis by implicating variation in GRIN3A in the heritable risk for schizophrenia.

Schizophrenia is thought to have a substantial [genetic background](#) which is, to some extent, population-specific. Genome-wide searches have revealed many common genomic variants with weak effects, but the remaining "missing heritability" is largely unknown. Scientists theorize that it may be partly explained by rare variants with large effect.

To identify genetic variants with larger effect sizes, Yoshikawa and his colleagues examined genetic data from several Asian populations. They identified a rare variant in GRIN3A with study-wide significance.

"This discovery is important, because the 'NMDA receptor hypothesis' for schizophrenia is a common disease model," said Yoshikawa. "We propose a novel point of therapeutic intervention in the NMDA receptor signaling system for schizophrenia."

Dr. John Krystal, Editor of [Biological Psychiatry](#), commented, "The notion that a genetic trait that acts like PCP in the brain produces schizophrenia is a very attractive but over-simplistic hypothesis. It is that the biology of schizophrenia is much more complicated than this single factor. Nonetheless, perhaps this study of GRIN3A brings us another step closer to understanding glutamate abnormalities in schizophrenia."

**More information:** "A Population-Specific Uncommon Variant in GRIN3A Associated with Schizophrenia" by Atsushi Takata, Yoshimi Iwayama, Yasuhisa Fukuo, Masashi Ikeda, Tomo Okochi, Motoko Maekawa, Tomoko Toyota, Kazuo Yamada, Eiji Hattori, Tetsuo

Ohnishi, Manabu Toyoshima, Hiroshi Ujike, Toshiya Inada, Hiroshi Kunugi, Norio Ozaki, Shinichiro Nanko, Kazuhiko Nakamura, Norio Mori, Shigenobu Kanba, Nakao Iwata, Tadafumi Kato, and Takeo Yoshikawa (doi: 10.1016/j.biopsych.2012.10.024). The article appears in *Biological Psychiatry*, Volume 73, Issue 6 (March 15, 2013)

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