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### Treatment targeted at a genetic mutation relieves psychosis symptoms

*Proof-of-principle findings pave the way for precision medicine in psychiatry*

**Philadelphia, July 3, 2019** – Treatment of psychosis can be targeted to a specific genetic mutation in patients with psychotic disorders, according to a [study](#) in *Biological Psychiatry*, published by Elsevier. The study provides a proof-of-principle demonstration that treatments can be tailored to a specific genotype, rather than diagnosis, to relieve symptoms. The findings also link an individual structural mutation to the underlying biology of psychosis and treatment response.

Genetic mutations that have large effects on psychiatric disease risk are rare, with some known to occur in only one or a few families, like the mutation described in the study led by Deborah L. Levy, PhD, McLean Hospital, a psychiatric affiliate of Harvard Medical School, Cambridge, MA, USA. The mutation was a copy number variant (CNV) in which the two patients in the study had four, instead of the usual two, copies of the *GLDC* gene. The authors hypothesized that this mutation might reduce brain glycine, a key factor for proper glutamatergic functioning, which is disrupted in schizophrenia.

“The compelling aspect is that this CNV can be linked to pathophysiology, and, as the new study shows, to treatment,” said Dr. Levy.

The researchers assessed whether this CNV could help guide treatment decisions by targeting the mutation to normalize its effects, a “genotype first” approach. “This approach contrasts with the standard clinical practice of treating individuals on the basis of clinical symptoms or diagnosis independent of specific genetic variants,” said Dr. Levy.

Addition of agents to restore glutamate function, glycine or D-cycloserine, to the patients’ standard medications improved psychotic symptoms in both patients beyond their usual treatment regimens. Each of the patients also saw some reductions in other symptoms, including mood symptoms and negative symptoms of schizophrenia, including enhanced emotional engagement and less social withdrawal.

“It is important to note that the two subjects studied here bore little clinical resemblance, with distinctly different symptom burdens, and highly dissimilar courses of illness,” noted first author J. Alexander Bodkin, MD, McLean Hospital. This suggests that response to the treatment arose from targeting a specific biological process, rather than clinical diagnosis *per se*.

“Most studies of rare structural variants will have very small sample sizes, complicating the usual approach to statistical analysis. Nevertheless, because the effects of a targeted treatment can be large, it is important to prioritize opportunities to study even small groups of patients who may benefit,” observed author Charity J. Morgan, University of Alabama, Birmingham, AL, USA.

“Psychiatry is in the very early days of precision medicine, i.e., the effort to match particular patients to the specific treatments that they need. In their article, Dr. Levy and her colleagues provide a wonderful example of this approach,” said John Krystal, MD, Editor of *Biological Psychiatry*. “The substances that they administered, glycine and D-cycloserine, do not produce noticeable behavioral effects in healthy people or in patients with psychotic disorders. However, because these substances replaced a deficient co-factor involved in neural communication in these particular individuals, their administration alleviated mood and psychosis symptoms. As in these cases, we expect psychiatry to develop more instances where specific treatments can be developed to meet the needs of particular groups of patients.”

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### Notes for editors

The article is "Targeted Treatment of Individuals with Psychosis Carrying a Copy Number Variant Containing a Genomic Triplication of the Glycine Decarboxylase Gene," by J. Alexander Bodkin, Michael J. Coleman, Laura J. Godfrey, Claudia M. B. Carvalho, Charity Johanna Morgan, Raymond F. Suckow, Thea Anderson, Dost Ongur, Marc J. Kaufman, Kathryn E. Lewandowski, Arthur J. Siegel, Elliot Waldstreicher, Christopher M. Grochowski, Daniel C. Javitt, Dan Rujescu, Scott Hebring, Richard Weinshilboum, Stephanie Burgos Rodriguez, Colette Kirchhoff, Timothy Visscher, Alexander Vuckovic, Allison Fialkowski, Shane McCarthy, Dheeraj Malhotra, Jonathan Sebat, Donald C. Goff, James I. Hudson, James R. Lupski, Joseph T. Coyle, Uwe Rudolph, and Deborah L. Levy (<https://doi.org/10.1016/j.biopsych.2019.04.031>).

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Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at [Biol.Psych@sobp.org](mailto:Biol.Psych@sobp.org) or +1 214 648 0880. Journalists wishing to interview the authors may contact Laura Neves, McLean Hospital Media Relations, at [LNEVES1@partners.org](mailto:LNEVES1@partners.org) or +1 617 855 2177.

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