

Researchers build a better mouse model to study depression

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Researchers at the University of Pittsburgh School of Medicine have developed a mouse model of major depressive disorder (MDD) that is based on a rare genetic mutation that appears to cause MDD in the majority of people who inherit it. The findings, which were published online today in the *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics EarlyView*, could help to clarify the brain events that lead to MDD, and contribute to the development of new and better means of treatment and prevention. This report also illustrates an advance in the design of recombinant mouse models that should be applicable to many human diseases.

"[Major depressive disorder](#) is a leading cause of suffering, disability and premature death from all causes including suicide. While the cause currently is unknown, twin and adoption studies indicate that genetic factors account for 40 to 70 percent of the risk for developing this common disorder," explained lead author George Zubenko, M.D., Ph.D., professor of psychiatry, Pitt School of Medicine.

"In this report, we describe how we constructed a laboratory mouse strain that mimics the [brain mechanism](#) that leads to major depression in humans, rather than symptoms," he said. "Nonetheless, in our initial characterization, the [mutant mice](#) exhibited several features that were reminiscent of the human disorder, including alterations of brain anatomy, gene expression, behavior, as well as increased infant mortality."

"These findings support the role of the genetic variant in the development of MDD, and affirm the mutant mouse strain as a model of MDD worthy of further study," Dr. Zubenko said. Hugh B. Hughes, III, M.S., served as the co-author of this report.

Previous studies of families with a severe and strongly familial form of MDD revealed a mutation in the control region of CREB1, a gene that orchestrates the expression of many other genes that play important roles in normal brain functioning. Mice have a CREB1 gene that is very similar to the human version and, with the aid of genetic engineering techniques, the researchers were able to establish a mutant mouse strain that bore the same genetic error. Since the control regions of corresponding human and mouse genes often have regions of high similarity, the methods described in this report may be useful in creating mouse models of other human diseases.

"Treatments that are the most effective and produce the fewest side effects typically address the root causes of the disease," Dr. Zubenko noted. "Animal models that recapitulate those root causes should better inform us about the brain mechanisms that lead to MDD, and have the best chance of leading to advances in treatment and prevention."

Provided by University of Pittsburgh Schools of the Health Sciences

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