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Stressed-out mice reveal role of epigenetics in behavior

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Research conducted by a team in Switzerland suggests that a family of genes involved in regulating the expression of other genes in the brain is responsible for helping us deal with external inputs such as stress. Their results, appearing in the December 11 advance online version of the journal *Neuron*, may also give a clue to why some people are more susceptible to anxiety or depression than others.

The researchers from EPFL and the National Competence Center "Frontiers in Genetics" studied the role of a family of genes known as KRAB-ZFP, which acts like a group of genetic censors, selectively silencing the expression of other genes. These repressors make up about 2% of our genetic material, but little is known about how this "epigenetic" silencing process works, what the long-term consequences are, and even which genes are targeted. (Epigenetics refers to a change in gene expression that is caused by something other than a change in the underlying DNA sequence.)

The researchers bred a strain of mice that lacked in the hippocampus, a part of the forebrain involved in short-term memory and inhibition, a key cofactor used by the KRAB family. The genetically altered mice appeared completely normal until they were placed in a stressful situation. Then they became extremely anxious. Although the normal mice quickly adapted, the altered mice never managed to overcome their stress, and remained anxious and unable to complete simple cognitive tasks. The disruption of the KRAB-mediated regulatory process thus altered the mice's normal behavioral response to stress.

"The KRAB regulators appeared fairly recently on an evolutionary scale," notes EPFL professor Didier Trono, lead author on the study, " and it's very likely that there is a fair degree of polymorphism between individuals. We postulate that variability in these genes is one factor that may participate in predisposing people to anxiety syndromes or depression. "

Because epigenetic alterations are often long-lasting and sometimes permanent, one could also interpret them as a way in which an individual's personal history can have a lasting impact on his or her genetic expression. "It's a way for a cell to have a sort of memory," explains Trono.

This work opens promising leads for further exploration, because evidence of epigenetic modification has been observed in animal models of depression, addiction, schizophrenia and neuro-developmental disorders. Some psychoactive drugs like cocaine or anti-psychotics also cause changes in some of the co-factors involved in this genetic regulatory system. With an understanding of the molecular mechanisms involved in epigenetic modulation, it might be possible to develop targeted therapies for those individuals in whom it malfunctions.

Source: Ecole Polytechnique Fédérale de Lausanne