Small RNA identified that offers clues for quieting the 'voices' of schizophrenia

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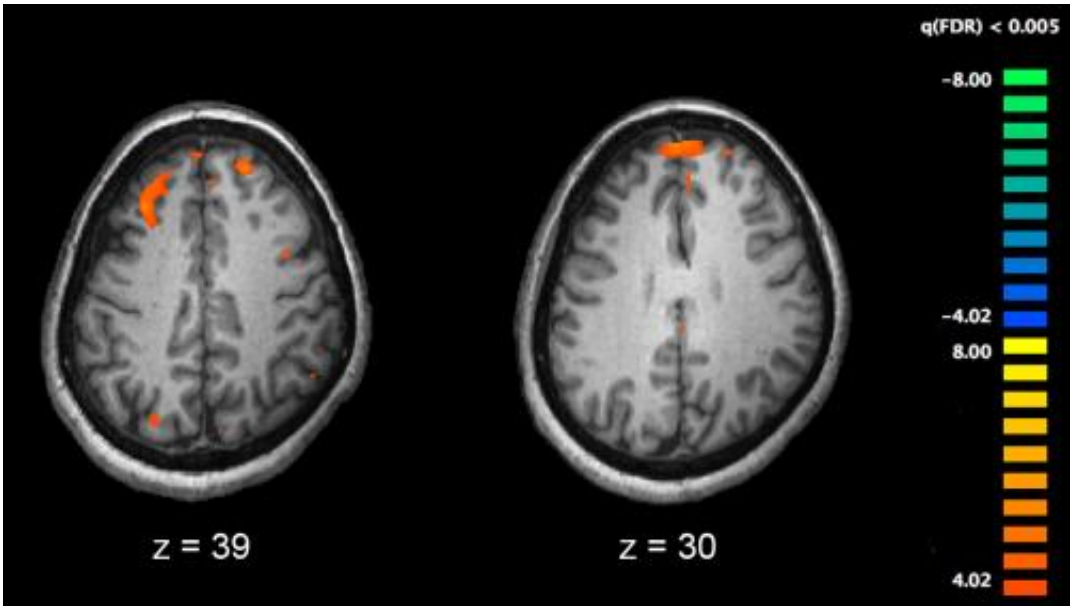

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

St. Jude Children's Research Hospital scientists have identified a small RNA (microRNA) that may be essential to restoring normal function in a brain circuit associated with the "voices" and other hallucinations of schizophrenia. The microRNA provides a possible focus for

antipsychotic drug development. The findings appear today in the journal *Nature Medicine*.

The work was done in a mouse model of a human disorder that is one of the genetic causes of schizophrenia. Building on previous St. Jude research, the results offer important new details about the molecular mechanism that disrupts the flow of information along a neural circuit connecting two brain regions involved in processing auditory information. The findings also provide clues about why psychotic symptoms of schizophrenia are often delayed until late adolescence or early adulthood.

"In 2014, we identified the specific circuit in the brain that is targeted by antipsychotic drugs. However, the existing antipsychotics also cause devastating side effects," said corresponding author Stanislav Zakharenko, M.D., Ph.D., a member of the St. Jude Department of Developmental Neurobiology. "In this study, we identified the microRNA that is a key player in disruption of that circuit and showed that depletion of the microRNA was necessary and sufficient to inhibit normal functioning of the circuit in the mouse models.

"We also found evidence suggesting that the microRNA, named miR-338-3p, could be targeted for development of a new class of antipsychotic drugs with fewer side effects."

There are more than 2,000 microRNAs whose function is to silence expression of particular genes and regulate the supply of the corresponding proteins. Working in a mouse model of 22q11 deletion syndrome, researchers identified miR-338-3p as the microRNA that regulates production of the protein D2 dopamine receptor (Drd2), which is the prime target of antipsychotics.

Individuals with the deletion syndrome are at risk for behavior problems

as children. Between 23 and 43 percent develop schizophrenia, a severe chronic disorder that affects thinking, memory and behavior. Researchers at St. Jude are studying schizophrenia and other brain disorders to improve understanding of how normal brains develop, which provides insights into the origins of diseases like cancer.

The scientists reported that Drd2 increased in the brain's auditory thalamus when levels of the microRNA declined. Previous research from Zakharenko's laboratory linked elevated levels of Drd2 in the auditory thalamus to brain-circuit disruptions in the mutant mice. Investigators also reported that the protein was elevated in the same brain region of individuals with schizophrenia, but not healthy adults.

Individuals with the deletion syndrome are missing part of chromosome 22, which leaves them with one rather than the normal two copies of more than 25 genes. The missing genes included Dgcr8, which facilitates production of microRNAs.

Working in mice, researchers have now linked the 22q11 deletion syndrome and deletion of a single Dgcr8 gene to age-related declines in miR-338-3p in the auditory thalamus. The decline was associated with an increase in Drd2 and reduced signaling in the circuit that links the thalamus and auditory cortex, a brain region implicated in auditory hallucination. Levels of miR-338-3p were lower in the thalamus of individuals with schizophrenia compared to individuals of the same age and sex without the diagnosis.

The miR-338-3p depletion did not disrupt other brain circuits in the mutant mice, and the findings offer a possible explanation. Researchers found that miR-338-3p levels were higher in the thalamus than in other brain regions. In addition, miR-338-3p was one of the most abundant microRNAs present in the thalamus.

Replenishing levels of the microRNA in the auditory thalamus of mutant mice reduced Drd2 protein and restored the circuit to normal functioning. That suggests that the microRNA could be the basis for a new class of antipsychotic drugs that act in a more targeted manner with fewer side effects. Antipsychotic drugs, which target Drd2, also restored circuit function.

The findings provide insight into the age-related delay in the onset of schizophrenia symptoms. Researchers noted that microRNA levels declined with age in all mice, but that mutant mice began with lower levels of miR-338-3p. "A minimum level of the microRNA may be necessary to prevent excessive production of the Drd2 that disrupts the circuit," Zakharenko said. "While miR-338-3p levels decline as normal mice age, levels may remain above the threshold necessary to prevent overexpression of the protein. In contrast, the deletion syndrome may leave mice at risk for dropping below that threshold."

More information: Thalamic miR-338-3p mediates auditory thalamocortical disruption and its late onset in 22q11.2 microdeletion models, *Nature Medicine*, nature.com/articles/doi:10.1038/nm.4240

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