Master gene affects neurons that govern breathing at birth and in adulthood

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When mice are born lacking the master gene Atoh1, none breathe well and all die in the newborn period. Why and how this occurs could provide new answers about sudden infant death syndrome (SIDS), but the solution has remained elusive until now.

Research led by Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital demonstrates that when the gene is lacking in a special population of neurons called RTN (retrotrapezoid nucleus), roughly half the young mice die at birth. Those who survive are less likely to respond to excess levels of carbon dioxide as adults. A report of their work appears online in the journal *Neuron*.

"The death of mice at birth clued us in that Atoh1 must be needed for the function of some neurons critical for neonatal breathing, so we set out to define these neurons," said Dr. Huda Zoghbi, senior author of the report and director of the Neurological Research Institute and a professor of molecular and human genetics, neuroscience, neurology and pediatrics at BCM. Zoghbi is also a Howard Hughes Medical Institute investigator.

"We took a genetic approach to find the critical neurons," said Wei-Hsiang Huang, a graduate student in the Program in Developmental Biology at BCM who works in Zoghbi's laboratory. With careful studies to "knockout" the activity of the gene in a narrower and narrower area in the brain, they slowly eliminated possible neurons to determine that loss

of Atoh1 in the RTN neurons was the source of the problem.

"Discovering that Atoh1 is indeed critical for the RTN neurons to take their right place in the brainstem and connect with the breathing center helped us uncover why they are important for neonatal breathing," said Zoghbi.

"This population of neurons resides in the ventral brainstem," said Huang. "When there is a change in the makeup of the blood (lack of oxygen or buildup of carbon dioxide), the RTN neurons sense that and tell the body to change the way it breathes." A defect in these neurons can disrupt this response.

"Without Atoh1 the mice have significant breathing problems because they do not automatically adjust their breathing to decrease carbon dioxide and oxygenate the blood," he said.

It turns out the findings from this mouse study are relevant to human studies.

"A paper just published* reports that developmental abnormalities in the RTN neurons of children with sudden infant death syndrome or sudden unexplained intrauterine death may be linked to altered ventilatory response to carbon dioxide", said Huang.

More information: *Lavezzi, A.M., et al., Developmental alterations of the respiratory human retrotrapezoid nucleus in sudden unexplained fetal and infant death, Auton. Neurosci. (2012), doi:10.1016/j.autneu.2012.06.005

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