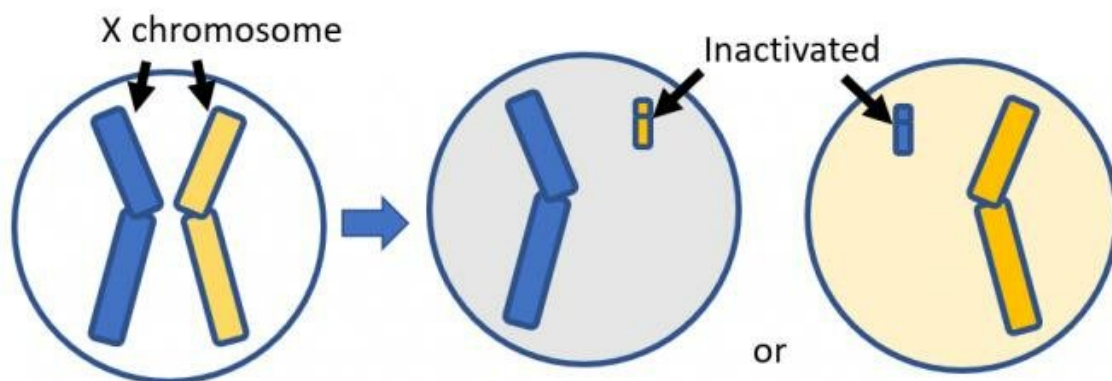


# Looking behind a rare brain disease for clues to treat more common mental disorders

February 18 2019

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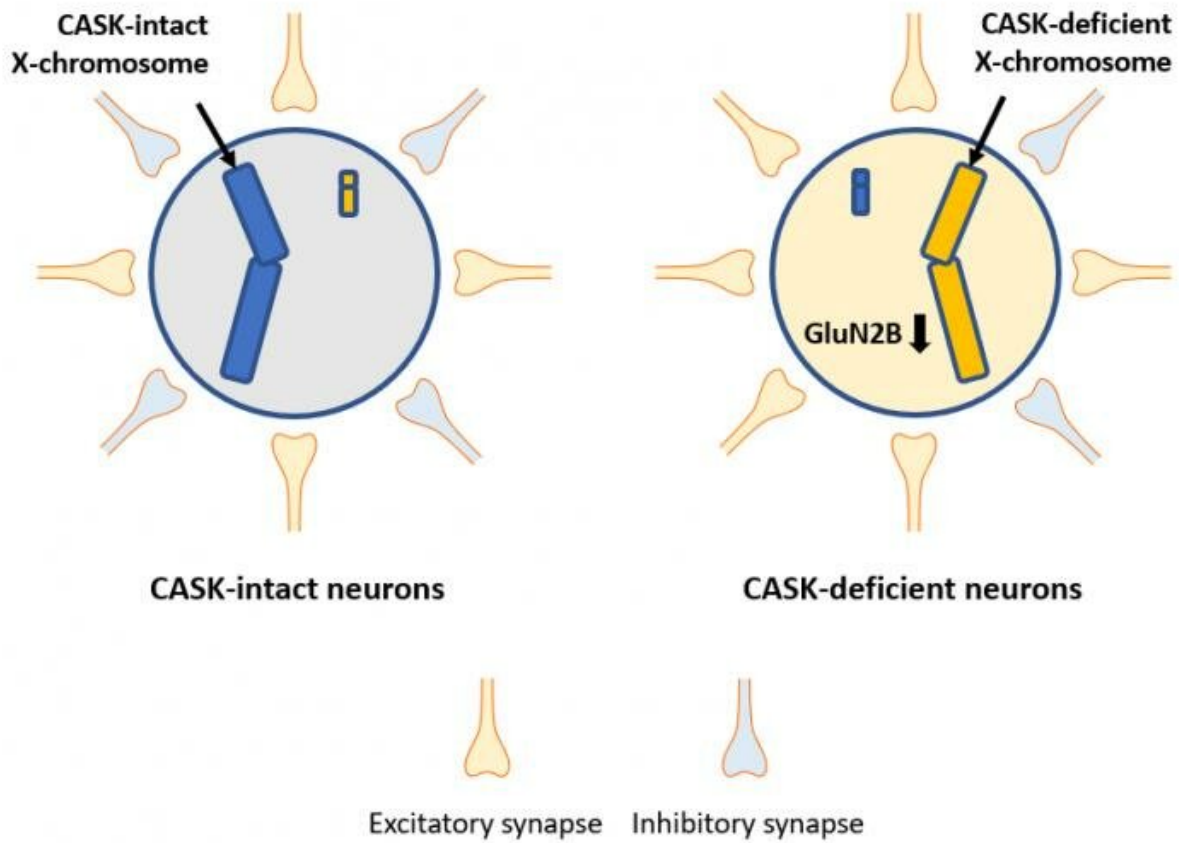
One of the two X-chromosomes is randomly selected and inactivated in the early embryonic stage in females (X-chromosome inactivation). Credit: Katsuhiko Tabuchi, Shinshu University, Japan

Researchers have reported for the first time the mechanism behind a very rare brain syndrome called disproportionate pontine and cerebellar hypoplasia (MICPCH), which causes microcephaly. Information gleaned from this animal study could also inform research into other, more common neurological diseases such as mental retardation, epilepsy and autism.

MICPCH only affects a total of 53 females and seven males worldwide. It is characterized by several developmental symptoms including small

head size, slowed growth, cognitive delays, epilepsy, seizures, vision and hearing problems, decreased muscle tone, and autism. MICPCH is linked to irregularities, or mutations, on the X chromosome that eventually lead to the chromosome's inactivation. The study was published in the January 4th, 2019 edition of the journal *Molecular Psychiatry*.

Neurons constantly send messages to one another. There are two types of neurons in the brain: those that increase activity in other cells (excitatory neurons) and those that decrease it (inhibitory neurons). The mechanism keeping the balance between excitation and inhibition in the brain is very similar to that of a thermostat. This mechanism is important because imbalances between excitation and inhibition can cause several serious disorders such as epilepsy and autism. One of the most important molecules that maintains the balance between excitation and inhibition is a protein found within the outer membrane of neurons, called the calcium/calmodulin-dependent serine protein kinase (CASK). Mutations in the gene that produce CASK therefore lead to several neurodevelopmental disorders such as mental retardation. A lack of the protein in the brain has been found to cause MICPCH syndrome.

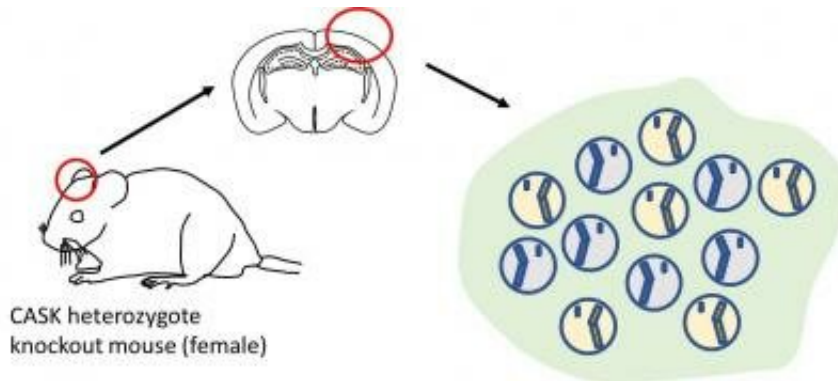


The number of excitatory synapse projecting to CASK-deficient neurons is increased but that of inhibitory synapse is decreased in the CASK heterozygote knockout mouse brains. Credit: Katsuhiko Tabuchi, Shinshu University, Japan

"The aim of the study was to understand the pathophysiology of CASK-deficiency disorders in females, such as MICPCH syndrome, which are supposed to be influenced by X-chromosome inactivation," said corresponding author Katsuhiko Tabuchi, a professor in the Department of Molecular and Cellular Physiology at the Institute of Medicine, Academic Assembly at Shinshu University in Nagano, Japan.

However, the details of CASK-deficiency consequences have thus far

been difficult to study, as mice that completely lack the protein die before they are developed enough to study. In order to understand the mechanism behind the CASK-deficiency, researchers at Shinshu University in Japan and Kafr Elsheikh University in Egypt used gene manipulation techniques that shut off the CASK gene through X chromosome inactivation in female mice without lethal consequences.



CASK-intact and CASK-deficient cells exist in a random mixture pattern in the CASK heterozygote knockout brains. Credit: Katsuhiko Tabuchi, Shinshu University, Japan

They found that neurons that lack CASK have a disrupted excitation and inhibition balance. They also found that this is because of a decrease in concentration of a specific receptor on the membrane that receives signals from other neurons. When the receptor concentration was increased, the excitatory and inhibitory balance was restored again, leading the researchers to believe that the receptor plays a central role in the mechanism in CASK-deficient neurons.

In the future, the researchers hope to address the effects of a CASK-deficiency in even greater detail by looking at its effects on the neural circuitry. "We hope to highlight the effect of two different types of [neurons](#) in one brain as well as the pathophysiology of CASK-deficiency

disorders at neural circuit levels," professor Tabuchi adds.

**More information:** Takuma Mori et al, Deficiency of calcium/calmodulin-dependent serine protein kinase disrupts the excitatory-inhibitory balance of synapses by down-regulating GluN2B, *Molecular Psychiatry* (2019). [DOI: 10.1038/s41380-018-0338-4](https://doi.org/10.1038/s41380-018-0338-4)

Provided by Shinshu University

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