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Patterns of new DNA letter in brain suggest distinct function

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In 2009, the DNA alphabet expanded. Scientists discovered that an extra letter or "sixth nucleotide" was surprisingly abundant in DNA from stem cells and brain cells.

Now, researchers at Emory University School of Medicine have mapped the patterns formed by that letter in the brains of mice, observing how its pattern of distribution in the genome changes during development and aging.

Those patterns, stable or dynamic depending on the gene, suggest that 5-hydroxymethylcytosine (5-hmC) has its own distinct functions, which still need to be fully brought to light.

"Our data tells us that 5-hmC is not just an intermediate state," says senior author Peng Jin, PhD, associate professor of human genetics at Emory University School of Medicine. "It looks like it has specific functions in stem cells and brain. 5-hmC may poise a gene to be turned on after being repressed."

The results were published online Sunday by the journal Nature Neuroscience. The paper is the first report on how the patterns of 5-hmC's distribution change in mouse brain during development, and also contains data on 5-hmC in DNA samples from human brain.

Postdoctoral fellow Keith Szulwach and instructor Xuekun Li are co-first authors, and collaborators from the University of Chicago and the

University of Wisconsin-Madison contributed to the paper.

5-hydroxymethylcytosine (5-hmC) is an epigenetic modification of cytosine, one of the four bases or "letters" making up DNA. Epigenetic modifications are changes in the way genes are turned on or off, but are not part of the underlying DNA sequence. 5-hmC resembles 5-methylcytosine (5-mC), another modified DNA base that scientists have been studying for decades. Until recently, chemical techniques did not allow scientists to tell the difference between them.

In contrast to 5-mC, 5-hmC appears to be enriched on active genes, especially in brain cells. 5-mC is generally found on genes that are turned off or on repetitive "junk" regions of the genome. When stem cells change into the cells that make up blood, muscle or brain, 5-mC helps shut off genes that aren't supposed to be turned on. Changes in 5-mC's distribution also underpin a healthy cell's transformation into a cancer cell.

It looks like 5-hmC can only appear on DNA where 5-mC already was present. This could be a clue that 5-hmC could be a transitory sign that the cell is going to remove a 5-mC mark. Jin says the patterns his team sees tell a different story, at least for some genes. On those genes, the level of 5-hmC is stably maintained and increases with age.

The Emory team used a method for chemically labeling 5-hmC they developed in cooperation with scientists at the University of Chicago. They find that 5-hmC is ten times more abundant in brain than in stem cells, and it is found more in the body of some genes, compared to stem cells.

In addition, the researchers found a relative lack of 5-hmC on X chromosomes in both males and females. That result is a surprise, Jin says, because it was already known that the X chromosome is subject to

a special form of regulation in females only. Males have one X chromosome and females have two, and in female cells one of the X chromosomes is inactivated.

Jin's team is beginning to map how 5-hmC changes in neurological disorders, including Rett syndrome and autism, and refining techniques for detecting 5-hmC in DNA at high resolution.

More information: K.E. Szulwach et al 5-hydroxymethylcytosine–mediated epigenetic dynamics during postnatal neurodevelopment and aging. *Nature Neuroscience*. (2011).

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