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Inherited parental methylation shifts over time, may have functional effects in the brain and other tissues

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Parental imprinting—a form of gene control passed down from parents to offspring—is far more dynamic than previously thought and may contribute to changes in the brain and other tissues over time. This finding by Whitehead Institute scientists challenges current

understandings of gene regulation via DNA methylation, from development through adulthood.

"All of this dynamic variation between individuals and within individuals is really very surprising," says Whitehead Founding Member Rudolf Jaenisch, who is also a professor of biology at MIT. "We don't yet understand the significance of this. Is it functionally important and does it reflect, particularly in the brain, the history of neurons—activity states, for example? These are all interesting possibilities."

Methylation—the attachment of molecules, known as methyl groups, to DNA—is an epigenetic phenomenon that affects gene expression. Generally, methylated genes are turned off while unmethylated genes are active and ready for transcription. Although advances in sequencing technology have yielded informative methylation maps in a variety of tissues, such approaches only capture static "snapshots" of methylation and are unable to reveal the dynamics of methylation in real time in tissues and individual cells.

Because of this limitation, researchers have theorized that inherited methylation, also referred to as parental imprinting, largely remains stable throughout development, except during two important developmental milestones: after fertilization and during the creation of sperm and egg cells. Altered gene imprinting at other times has been associated with developmental disorders and cancer.

To investigate active methylation in individual cells, Jaenisch lab postdoctoral researcher Yonatan Stelzer developed a reporter system that tracks genomic methylation in real-time. When a target gene is unmethylated, the reporter is also unmethylated, triggering expression of a glowing protein that illuminates the cell. When the target is methylated, so too is the reporter. The glowing protein is then unexpressed, leaving the cell dark. As the target gene's methylation changes, so does the

reporter's.

In the latest research, described online this week in the journal *Cell Reports*, Stelzer used the reporter system in mice to discover that imprinted methylation in developing and adult tissues is actively regulated rather than merely maintained in stable fashion.

"What we see with the reporter in adult tissues is very surprising and much more complex than we had thought," says Stelzer, who is a co-author of the *Cell Reports* paper. "The regulation of imprinted methylation results in these very consistent patterns in different tissues and even in a cell-type dependent manner. In the case of neural cells, it means that imprinted methylation is dynamically shaping the adult brain over time and could play a role in aging. Because this imprinting affects hundreds of genes that are non-coding, including microRNAs and non-coding RNAs, it's a very interesting fine-tuning mechanism for the dosage of gene expression in the brain and elsewhere in the body."

Although Stelzer notes that the results of his latest research are indeed exciting, they are just a beginning.

"Our work is the first observation of these changes," he says. "Now we need to understand their functional consequences and the mechanism that regulates these changes in methylation."

More information: "Parent-of-origin DNA methylation dynamics during mouse development" *Cell Reports*, online September 20, 2016. dx.doi.org/10.1016/j.celrep.2016.08.066

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