NEWS

Old mice may pass on 'epimutations' to offspring

BY **VIRGINIA HUGHES**

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Sperm from 12-month-old male mice carry lower levels of DNA methylation, a type of epigenetic change to the genome, than the sperm of 3-month-old mice, the researchers found. What's more, the offspring of the older mice have many of the same abnormal methylation patterns in their brains and display some unusual behaviors.

The sperm of old mice has an unusual epigenome, the profile of chemical modifications to the underlying DNA code, according to a poster presented Saturday at the **2012 Society for Neuroscience annual meeting** in New Orleans.

The findings suggest an explanation for the so-called paternal age effect in autism. **Older men are more likely** to have a child with autism or schizophrenia than are younger men.

A study published in August reported that part of the effect is the result of **spontaneous mutations** that crop up in sperm. The new mouse study suggests that epigenetic changes also play a role.

"There's absolutely something that's happening in the sperm of older fathers," says Maria Milekic, a postdoctoral researcher in **Jay Gingrich**'s lab at Columbia University in New York, who presented the work. "I think that with aging, there is an accumulation of both of mutations and epimutations."

The researchers analyzed methylation patterns across the whole genomes of the sperm from the older mice. The sperm showed particularly striking decreases in methylation near promoters, regions of the genome that initiate the transcription of DNA into RNA. Brain tissue from the offspring of these mice also showed low levels of methylation near promoter regions.

The offspring also showed several unusual behaviors, including lesser exploratory activity and pre-pulse inhibition, a measure of how an animal unconsciously prepares for being startled, than

controls. Pre-pulse inhibition is low in people with schizophrenia and autism, Milekic notes. The researchers also tested the offspring for problems in social behavior but found nothing out of the ordinary.

The researchers are investigating the functional consequences of the methylation changes. Depending on the gene, methylation can turn a gene on or off. At promoters, methylation usually turns genes off.

To analyze how methylation affects gene expression, the researchers sequenced RNA from the same sperm and brain samples. Their preliminary results — in just last week — found that many of the methylation abnormalities occur in genes related to the cerebellum, a region that integrates sensory information and has been **linked to autism**.

It's not clear whether the sperm also carries spontaneous DNA mutations on some of the same genes. A study published earlier this year found that genomic regions lacking methylation are **more vulnerable to mutation**.

It's also possible that the changes seen in the offspring of older mice result from the mothers' interactions with the offspring or the fathers. Milekic is planning to test whether the females have breeding preferences. "Would they prefer to have their mate be an old father or a young father?" she asks.

*For more reports from the 2012 Society for Neuroscience annual meeting, please **click here**.*