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Aging and gene expression—possible links to autism and schizophrenia in offspring

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Advanced paternal age has been associated with greater risk for psychiatric disorders, such as schizophrenia and autism. With an increase in paternal age, there is a greater frequency of certain types of mutations that contribute to these disorders in offspring. Mutations are changes in the genetic code. Recent research, however, looks beyond the genetic code to "epigenetic effects", which do not involve changes in the genes themselves, but rather in how they are expressed to determine one's characteristics. Such epigenetic changes in sperm, related to ageing, have been linked with psychiatric disorders in offspring.

Maria Milekic, PhD, reported today, at the American College of Neuropsychopharmacology annual meeting in Hollywood Florida, that old mice have an epigenetic change – a loss of DNA methylation at the locations where the genetic code starts being transcribed. DNA methylation is a biochemical process that plays an important regulatory role in development and disease. The work was done by a research team in the Department of Psychiatry at Columbia University.

Offspring of old fathers showed the same deficit in DNA methylation, and they differed in their behavior from the offspring of the young fathers. They showed less exploratory activity and differed in the startle response and in habituation.

Two groups, with 10 breeder mice per group, were tested. The breeders were either old (12 month) or young (3 month) males, each bred with two young (3 month) female mice. Then the behavior of the offspring

was tested when they were 3 months old. DNA methylation also was tested in the young and old fathers' sperm, and brains of the offspring were tested for DNA methylation as well as gene expression.

"We were interested in understanding the mechanism of the paternal age effect", said Dr. Milekic."The risk for schizophrenia increases 2-fold when a father is over 45 years of age, and the risk for autism increases 2-5-fold. It seemed unlikely that mutation alone could account for this. We therefore speculated that DNA methylation could provide an alternative mechanism."

Not only did the offspring of the old fathers differ from their counterparts with young fathers in DNA methylation, they also showed significant differences in the expression of genes that have been implicated in autism spectrum disorders and that are known to regulate the development and function of the brain. These findings point to possible factors that can lead to autism spectrum disorders and schizophrenia, and ultimately may lead to more effective therapeutic interventions.

With respect to studies in the immediate future, Dr. Milekic said,"We are trying to evaluate changes in different brain regions. Our studies before did not compare brain regions. Most of the genes that have altered expression are in the cerebellum. We are interested in how DNA methylation in the cerebellum is affected by paternal age."

Provided by American College of Neuropsychopharmacology