

NEWS

Father's advanced age feeds autism risk

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Are older fathers more likely to have children with autism? A series of epidemiological studies is giving credence to the idea, suggesting that, with age, sperm may accumulate damage that increases risk in the next generation.

Advancing age of the father is known to be a significant risk factor for schizophrenia¹. These studies ? along with anecdotal suggestions that fathers of children with autism tend to be older than average ? prompted Avi Reichenberg of Mount Sinai School of Medicine, in New York, to launch one of the first thorough epidemiological investigations into a link between the two.

Reichenberg and his colleagues had access to a vast database of health information collected from more than 132,000 Israeli adolescents who underwent draft board assessment, including psychiatric screening, before entering the army. The researchers were able to identify those who were diagnosed with autism spectrum disorders (ASD), along with the age of their parents.

Children of fathers in their 30s are about 1.6 times more likely to have ASD than children of fathers below age 30, the study found². Compared with the youngest group, children of fathers aged 40 or older were nearly six times more likely to have ASD. "It was much stronger than we had thought," Reichenberg says.

Since then, a handful of other epidemiology studies have backed the autism-paternal age connection. In one of these³, a team led by **Lisa Croen** of Kaiser Permanente Northern California Division of Research in Oakland, California, mined a health database of more than 130,000 births and found that each decade of paternal or maternal age increased risk of autism spectrum disorder by around 30 percent.

Paternal age "is still a relatively small contributor," Croen says, "but when you see something that keeps coming up in different populations and study designs you start thinking there must be something to this."

The link may be real, but researchers have yet to explain what causes it. Perhaps, says Croen, older parents are simply more attuned to the development of their children and therefore more likely to get a diagnosis. "It could be an artifact," she says. "We don't have enough data yet to really rule that out."

Genetic origins:

Another simple explanation is that fathers who themselves have autism or mild social deficits are likely to marry and have children at a later age than other men, and these children inherit factors putting them at high risk of developing the condition themselves.

But Reichenberg says that in his studies he has found no link between traits such as shyness, sensitivity and aloofness in parents and the age at which they have children. "It's not definitive, but the evidence is definitely against such an explanation," he says.

Many researchers instead favor a genetic origin for the phenomenon. Male germ cells go through multiple rounds of division to manufacture sperm throughout a man's life and, according to one idea, they may accumulate DNA damage as the molecule is copied again and again.

Sperm produced by older men are more likely to carry genetic defects, and these defects could boost their children's risk of autism. Female germ cells divide far fewer times.

It is also possible that older sperm are more likely to acquire epigenetic defects: ones that do not change the DNA sequence itself, but that alter the activity of genes due to structural or chemical changes to DNA such as methylation.

These genetic changes arise in the egg or sperm rather than being inherited from the parents. Both concepts fit with the knowledge that the majority of ASD cases have a genetic cause, even though they are also the first in a family.

For precedent, geneticists point to a condition called achondroplasia, a common cause of dwarfism and the textbook example of a genetic condition associated with paternal age. The risk of sperm carrying a single point mutation in the gene for a growth factor receptor is thought to increase with the age of the father.

"It would be overwhelmingly logical," for something similar to be going on in some cases of autism, says human geneticist **Arthur Beaudet** at Baylor College of Medicine in Houston, Texas. Perhaps just one or two of the many genes associated with the disorder are susceptible to detrimental point mutations as the germ cells age.

Beaudet says he would like to see genetic and epigenetic analyses of single sperm to see if mutation rates differ in the fathers of autistic children, and between younger and older men. "That

would be the approach I'd be enthusiastic about," he says. Reichenberg says that he is pursuing such studies.

Because there are few clearly defined genes for autism risk, it's not yet clear where to look for these increased mutation rates. And genome-wide studies looking for differences in the rates of point mutations in many sperm are still too expensive and laborious.

Copy numbers

Last year, molecular studies showed that mutations called copy number variations (CNVs) ? genomic chunks that can be deleted or duplicated from one person to the next ? appear to be major contributors to sporadic autism.

A group led by **Michael Wigler** and **Jonathan Sebat** at Cold Spring Harbor Laboratory in New York looked for CNVs that were present in individuals with autism, but not in their parents. They found CNVs in 10 percent of children with sporadic autism, 2 percent of those with familial autism and 1 percent of controls⁴.

This suggests that many more cases of sporadic autism may be attributable to spontaneous mutations ? either CNVs or more subtle mutations ? than had been realized.

Sebat has not examined whether the frequency of these CNV mutations increases in aging germ cells ? but he suspects it might. "We don't have data one way or the other," he says, "but it's a very tantalizing hypothesis."

Many of the cellular systems that protect DNA from mutation might begin to fail in aging germ cells, so that their mutation rate increases, Sebat suggests. He is planning to test in a larger group of individuals with autism whether the CNV mutations are more common in children of older parents.

Reichenberg and his colleagues are also testing these hypotheses. In one study, they are trying to compare old and young fathers of children with autism, looking for differences in the rate of new mutations and their association to genetic hot spots previously linked to autism.

They are also doing mouse studies to explore whether offspring of older males tend to suffer more behavioral problems that mimic autism.

There remains some debate about whether the mother's age is as important a risk factor as that of the father, and studies have differed in their findings. A maternal age effect is harder to tease out, partly because women have children within a more limited age range than men: very few over-40 women have children.

In her study, Croen found that maternal age is just as important and says that other studies have

lacked the statistical power to tease this out. "Our data show that maternal age is also in the mix," she says.

The fact that schizophrenia risk also increases with parental age leads some researchers to wonder whether some of the same genes may contribute to both disorders -- and perhaps to other psychiatric conditions as well.

It's a "feasible hypothesis," Reichenberg says, "and I believe a worthwhile one to pursue."

References:

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