

Male biological clock possibly linked to autism, other disorders

Over the last few years, epidemiological evidence has suggested that as men age their odds of having a child with autism, schizophrenia or bipolar disorder might increase. The findings—along with more recent genetic data—have led researchers to ask whether the mutations that accumulate in sperm DNA with age might underlie this observed association.

“If this paternal age effect has something to do with mutations, then that opens up all sorts of interesting and sort of scary possibilities,” says Jonathan Sebat, a human geneticist at Cold Spring Harbor Laboratory in New York State. He says it is conceivable that the trend of delaying fatherhood might contribute to an increased incidence of mutations in the population that can give rise to neuropsychiatric disorders.

In a study of more than 100,000 people, along with records about their parents' ages, Avi Reichenberg at King's College London and his colleagues found that 33 out of every

10,000 offspring of men 40 years or older had autism spectrum disorder—a 475% increase compared to offspring of men younger than 30, who fathered afflicted children at a rate of 6 per 10,000 (*Arch. Gen. Psychiatry* **63**, 1026–1032; 2006). This association is now being tested in a larger study, says Reichenberg. A study this September showed a similar but less pronounced association of parental age with bipolar disorder (*Arch. Gen. Psychiatry* **65**, 1034–1040; 2008).

Spontaneous mutations can arise in both sperm and eggs. As women age, for example, they have an increased risk of delivering a child with Down's syndrome and other disorders caused by large-scale chromosome problems in eggs, such as trisomy. But unlike eggs, sperm arise from stem cells that continuously divide—about 840 times by the time a man is 50 years old (*Cytogenet. Genome Res.* **111**, 213–228; 2005). The theory is that the chances of mutations increase with each round of DNA replication—a process that could underlie estimates that the mutation rate in males is about five times that in females (*Nature* **416**, 624–626; 2002).

“Any mutation you can think of occurs more frequently in the sperm of older men,” says Sebat.

Meanwhile, recent genetic surveys of people with autism and other neuropsychiatric disorders have bolstered this controversial—and still tenuous—hypothesis. The DNA studies have suggested that ‘spontaneous’ mutations contribute to schizophrenia and autism. This type of mutation can arise in the sperm or egg of the parents.

Sebat and his colleagues, for instance, looked at spontaneous deletions and duplications

measuring about 100,000 DNA base pairs and longer—a length that often contain dozens of genes—in the genome of people with autism spectrum disorders (*Science* **316**, 445–449; 2007). Such spontaneous mutations occurred in only 1% of unaffected people, but they occurred in about 10% of subjects with sporadic forms of the disorder, meaning they had no family history. The researchers' methods only pick up a fraction of mutations, so the effect of sporadic mutations is probably substantially larger, says Sebat.

Similar studies this year have shown that people with nonfamilial forms of schizophrenia also have a higher rate of spontaneous duplications and deletions, and Sebat says his unpublished data show a similar association in bipolar disorder.

But whether the mutations that arise spontaneously in neuropsychiatric disorders come mainly from mom or dad is still unclear, as is their association with parental age. Sebat says larger studies underway should help clarify these questions.

And researchers caution that they have very little idea how the disrupted genes in eggs and sperm might potentially give rise to neuropsychiatric disease. “It is not established, and it can put a class of individuals in a negative light,” says Rita Cantor, a human geneticist at the University of California, Los Angeles.

Moreover, other, even more tenuous explanations could underlie the parental age effect—such as the idea that fathers who delay parenthood somehow have genes that affect their social behavior and make their offspring more prone to neuropsychiatric disorders. Says Cantor, “I think it's a delicate subject.”

Charlotte Schubert, Washington, DC



Time for fatherhood: Aging affects sperm

New techniques preserve fertility hope for women

For a man battling cancer, preserving the option to have children later in life is simple: store samples of semen. Even a single ejaculate contains millions of sperm that can later be used to fertilize an egg.

A woman facing cancer, on the other hand, has far fewer choices, which depend on her age, how much time she has before treatment must begin and the availability of a partner who can provide sperm. Oocytes, or eggs, are particularly vulnerable to chemotherapy and radiation, leaving many women infertile after being treated for cancer.

The most successful option for a woman of child-bearing age is to create embryos

through *in vitro* fertilization and freeze them. (Even if the woman's ovaries are removed, her uterus can still carry a transplanted embryo to term.) Doctors have turned to this method for over two decades, with a success rate of up to 40%. “That's a procedure that doesn't need improvement,” says Kutluk Oktay, director of reproductive medicine and infertility at New York Medical College.

Women who don't have a partner can try to freeze unfertilized eggs. But, unlike hardy embryos, eggs are sensitive to chilling. Hundreds of babies have been born with this technique, but the success rate overall hovers around 3%. “It's a big drop from embryo freezing,” says Tommaso Falcone, chair of

obstetrics and gynecology at the Cleveland Clinic. “[But] within the next five years, we'll solve a lot of the cryogenic challenges for freezing eggs.”

Those who do have a partner who can supply sperm to create an embryo, however, might face another challenge: it takes about two weeks to stimulate the ovary to produce enough eggs for this procedure—time a woman with cancer may not have. In such cases, doctors can remove egg follicles from an ovary and bathe them in nutrients to turn them into mature eggs. This method, dubbed *in vitro* maturation, also has a low rate of success and carries a higher risk of miscarriage.