NEWS

Parental age ups rate of new mutations passed to children

BY **ALLA KATSNELSON**

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Men and women both transmit an increasing number of new mutations to their children as they age, according to a study published today in *Nature*[1].

The finding is based on an analysis of whole genomes from nearly 5,000 people. The increase in these ‘de novo’ mutations may explain why older parents are more likely to have a child with a condition such as autism.

Men accumulate de novo mutations four times faster than women, the researchers found. However, in about 10 percent of the genome, mutations accumulate twice as quickly as elsewhere, and appear at an equal rate in both women and men.

“The majority of the contribution still comes from the father, particularly when the father is in an older age range,” says lead investigator **Kári Stefánsson**, chief executive of deCODE Genetics. “But the mutation rate is not equal across the genome, so we have to make sure we do not generalize too much.”

The new study builds on earlier work by deCODE Genetics, a company based in Reykjavik, Iceland. In 2012, the researchers reported that the rate at which people acquire mutations and pass them down to their children **increases sharply with age in men** but stays level in women. Those findings were based on whole-genome sequences from just 78 individuals and their parents.

The findings provide one possible explanation for the increased risk of autism among children born to older parents. But it is still unclear how much of the risk the increased mutation rate explains, says **Daniel Weinberger**, professor of psychiatry, neurology and neuroscience at Johns Hopkins University in Baltimore, who was not involved in the study. “We just don’t know the answer to that,” Weinberger says. “Some of it probably is, but it’s very possible that most of it isn’t.”

Mounting mutations:

Stefánsson and his team analyzed the whole-genome sequences of 1,548 Icelanders, their parents and, in 225 cases, at least one child — providing three generations of genomes in those cases. The researchers identified 108,778 de novo mutations in these intergenerational genomes and were able to determine the parent of origin for 42,961 of them.

They found that mothers gain an average of 0.37 de novo mutations each year; fathers, by contrast, gain an average of 1.51 de novo mutations.

Maternal de novo mutations are especially concentrated in hotspots that comprise about 10 percent of the genome. In those regions, the mutation rate is equal between mothers and fathers. Based on their previous work, the researchers say, the maternal mutations seem to occur as errors in the repair of DNA breaks.

Similar mutational hotspots also exist in the chimpanzee genome and to a lesser extent in the gorilla genome, but not in the orangutan genome. These three primates are increasingly more distant from humans on the evolutionary tree, pointing to an evolutionarily conserved system for

introducing variation into the human genome.

“The de novo mutation rate in this part of the genome is almost twice what it is in the rest of the genome because of this big contribution from mothers,” Stefánsson says.

The results suggest that the accumulation of mutations from the mother and from the father occur through different underlying mechanisms, says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco, who was not involved in the study.

Previous studies have identified hotspots in the genome in which mutations accrue especially quickly, Sanders says. But no one has shown whether or how they have a clinical effect. Stefánsson says his team has not yet been able to identify the function of the hotspots.

Risk assessment:

Based on the new data, a 45-year-old mother and father are 5 to 10 percent more likely to have a child with autism than are a 20-year-old mother and father. But the absolute risk of autism among children born to older parents is still small: roughly 1.5 percent for children born to parents in their 20s, and 1.58 percent for those with parents in their 40s.

“In the big picture, that is a very small effect,” Sanders says.

That’s because most of the mutations don’t hit a gene that affects autism risk, if they even hit a gene at all, Sanders says. “It’s like James Bond standing in front of a machine gun. While there are a lot of bullets flying, very few are actually hitting the target.”

The more likely explanation for how parental age contributes to autism risk — particularly from fathers — is that, for unknown reasons, men who have children later in life tend to carry common variants that predispose their children to autism, experts say. It is also possible that the increased incidence of autism among children born to older parents is related to changes in chemical tags on the parents’ DNA, rather than in the DNA sequence, Weinberger says. “My guess is, most of the age association is not explained by de novo mutations.”

Stefánsson and his team are analyzing de novo mutations shared by siblings. The results may help researchers determine the likelihood that the sibling of a child with a condition caused by de novo mutations will also carry the mutation.

REFERENCES:

1. Jónsson H. *et al. Nature* Epub ahead of print (2017) **Abstract**