New testing provides better information for parents of children with form of epilepsy

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Advances in genetic testing offer new insights to parents who have a child with a rare but serious form of epilepsy, epileptic encephalopathy (EE), found in one of about every 2,000 births and characterized by

developmental disabilities as well as horrible seizures.

New ways of sequencing the human genome mean geneticists and genetic counselors have much more to say to parents who wonder if future children might carry the disease, says Dr. Heather Mefford, associate professor of pediatrics (genetic medicine) at University of Washington School of Medicine and Deputy Scientific Director of the Brotman Baty Institute for Precision Medicine, co-senior author of findings published this week in the *New England Journal of Medicine*.

These advances offer insights for all of us because they are part of the growing study of mosaicism - the fact that many of us do not in fact have just one genome in us. We are what scientists call mosaics - bunches of cells that may have different genotypes buried deep within us.

"A mosaic mutation happens some time after fertilization when cells are dividing, which requires copying all of the DNA. If one of those cells makes a copying error, that introduces a mutation. All the cells that come from that cell will carry the same mutation. So you end up with a mosaic pattern where some cells have the mutation and some cells don't. That's the mosaic," Mefford said.

The fact that, say, 10 percent of your cells scattered throughout your body might be different than other cells may be completely unimportant. But if 10 percent of your sperm or oocytes have the mutation, that could be a big problem if that mutation affects the brain development of the child.

A big question from any parent of a child with EE is, What are the odds that our other children might have this condition? For decades, parents whose child had epilepsy were told there's a 1 to 5 percent chance that other children might inherit the mutation. This was based on clinical

evidence - the numbers of reoccurrences physicians saw in the clinic.

But armed with more precise testing, the geneticists found parental mosaicism that wasn't easily detected before in about 10 percent of families, putting these families at higher risk of passing the mutation to another child. What this means in practical terms is that this small group probably accounts for most of the reoccurrences. For some parents, there's good news: if this parental mosaicism was not detected, your odds of having another such child with epilepsy could be much less than 1 percent.

"We have the technology to pick out mosaic cells in a sea of otherwise normal cells. The percentage of families where we can identify mosaicism in the parent is higher than most of us thought it would be. While the overall recurrence risk (across all families) is about 1 percent, for those families where we can find the mosaic mutation in the parents, it's not a 1 percent risk. It's much higher than that. And we now have the tools to help give them that information, and help them with better family planning and decision-making down the road," Mefford said.

"Our study focused on patients with severe epilepsy. But the finding that 10 percent of the parents have mosaicism may actually apply to a broad range of other disorders, including autism and intellectual disability," Mefford added.

More information: Candace T. Myers et al. Parental Mosaicism in "De Novo" Epileptic Encephalopathies, *New England Journal of Medicine* (2018). DOI: 10.1056/NEJMc1714579 , www.nejm.org/doi/full/10.1056/NEJMc1714579

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