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Schizophrenia ‘risk genes’ are not so risky if the mother’s pregnancy was healthy

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Far be it from us to tell 23andMe[1] how to run its business, but if it or any other DNA company wants to give customers a better read of disease risk, they might start asking how mom’s pregnancy went.

That’s the key message of a schizophrenia study[2], published Monday, which showed that 108 regions of the genome previously identified[3] as raising the risk of schizophrenia do so only slightly if the mother experiences no complications during pregnancy — but by some twelvefold if she does.

Taking into account prenatal conditions gives a starkly different read of how risky schizophrenia risk genes are: Taken together, they raise the chance of developing the disease to 12 in 1,000 if there are no complications — or to 80 in 1,000 if there are.

“This should be an eye-opening study, especially for anyone who thinks disease risk is all genetic,” said

Janine LaSalle, of the University of California, Davis, who studies the genetics of autism and was not involved in the schizophrenia research. “Genes don’t exist in a lock-box away from everything else that happens to you.”

The idea that both genes and environment affect risk of disease is conventional scientific wisdom. But that usually means that while both genes and environment are involved, they act via separate biological pathways. BRCA mutations can raise the risk of breast cancer, for instance, and so can not bearing children, but the two don’t work by the same molecular mechanism.

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The schizophrenia study, in Nature Medicine, finds something more intriguing. Whether or not risk genes live up to their billing depends on what environment they find themselves in. For schizophrenia, that means the placenta: It can act like either a bump stock on a rifle, increasing the power of schizophrenia genes, or a broken firing pin, rendering the genes non-functional.

To figure this out, Dr. Daniel Weinberger of Johns Hopkins University and his colleagues started with the 108 genes linked to schizophrenia. They constructed what’s called a polygenic risk score, which calculates the extra risk of a disease from numerous genetic variants. In thousands of healthy people and people with schizophrenia, the scientists found that what is thought to be a high risk score raised the risk of schizophrenia substantially only if in utero complications such as a mother’s diabetes, obesity, pre-eclampsia, or smoking were also present.

For instance, a high score raised the risk more than 800 percent if any of these conditions was present, but just 50 percent if the pregnancy had been healthy. A 50 percent higher risk translates to 12 rather than 8 per 1,000 people developing schizophrenia.

The 108 genes that make up the risk score are expressed at particularly high levels in the placenta, the study also found, and at higher levels in the placentas of male fetuses than female ones. That fits with the fact that more men than women develop schizophrenia, usually in young adulthood.

The activity of the schizophrenia genes is dialed up especially if the mother has pre-eclampsia or another pregnancy complication. Presumably, “this reflects the placenta’s response to stress,” Weinberger said, such that when it’s flooded with inflammatory molecules (the standard response to stress), “it turns on genes related to immune response.” Recent discoveries[7] connect schizophrenia to the immune system.

Though specifics of how placental health and immune status affect fetal brain health are poorly understood, there is strong circumstantial evidence that it does. The chance of developing the disease is three to seven times greater in people whose mother had a respiratory infection during pregnancy, which can cause inflammation in the placenta, and up to twice as great if the mother had pre-eclampsia, a

difficult delivery, or diabetes, obesity, alcohol use, vaginal bleeding, maternal smoking, or preterm birth, all of which can also affect the placenta.

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"We need to create a new risk score for schizophrenia, incorporating not only genes but also placental health," Weinberger said. "The odds of becoming schizophrenic based on your polygenic risk score is more than 10 times greater with these early-life complications than without them." But the genes-only risk score, "in the absence of a serious complicated pregnancy, explains very little risk for schizophrenia — less that 2 percent" of the chance the individual will develop the disease.

UC Davis' LaSalle, who studies the expression of autism-related genes in the placenta, also thinks it important to include the environment in genetic risk scores, since "if you don't have the environmental risk you don't have the genetic risk." But more work needs to be done to identify which specific environmental influences on the placenta matter, she said.

23andMe doesn't disagree. The company's disease-risk analyses emphasize that, with the exception of single-gene disorders such as Huntington's, you can have disease genes yet not develop the disease, or develop a disease despite not having the disease genes.

None of the analyses currently incorporate genotype-environment interactions like those found in the schizophrenia study. But at some point, said a 23andMe spokesman, if the technology and research identify more "GxE"'s for more disorders, and if the Food and Drug Administration signs off, that could well change.

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