Predicting neurodevelopmental disease in children from parents' traits

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Neurodevelopmental and psychiatric disorders, and the genes that can lead to them, vary in a population (left, brighter red colors represent more severe symptoms, asterisks represent individuals with genetic variants that convey high risk for developing such disorders). A new study that looked at 97,000 families observed assortative mating for these traits with good correlation between the traits in the parents (middle). The researchers showed that evaluating both parents for these traits, in addition to the high-risk genetic variants, improved their ability to predict the prevalence and, potentially, severity of the disorders in children (right). Credit: Girirajan Laboratory, Penn State

Predicting the trajectory of neurodevelopmental and psychiatric disorders like autism or schizophrenia is difficult because they can be

influenced by many different genetic and environmental factors.

A new study, led by Penn State researchers, demonstrates that evaluating parents for their manifestation of traits of these disorders—and related diseases like depression and anxiety—may provide a more accurate method of predicting the prevalence and potential severity of the disorders in affected children than screening for genetic variants alone. This is likely due, at least in part, to genetic variants the parents transmit to the child that would not be routinely picked up in a genetic screen and lead to more severe disease, the researchers explained.

A paper describing the research appears in the *American Journal of Human Genetics*. According to the researchers, understanding how both parents contribute to their child's diagnosis could inform genetic counseling and the development of therapeutic intervention plans for children impacted by these disorders.

"We looked at the presence of neurodevelopmental and psychiatric traits in children and parents from a large set of families," said Santhosh Girirajan, interim department head and T. Ming Chu Professor of Biochemistry and Molecular Biology in the Penn State Eberly College of Science, and lead author of the paper. "We saw an increase in the presence of neurodevelopmental disorders in children whose parents both report having the trait, including psychiatric traits like anxiety or depression."

The team looked at 97,000 families, many including children with neurodevelopmental disorders such as autism or intellectual disability, and evaluated how risk factors—genetic features and the presence of the traits—in both parents impact the trajectory of the disease in the children. The datasets included genetic information and questionnaire data from families in a large public biobank, as well as from families from specific studies of neurodevelopmental disorders.

The researchers evaluated parents and their children for symptoms of the various disorders and assessed known genetic mutations that can give rise to such disorders. Their analysis revealed that parents tend to select partners with the same or related disorders, leading to increased prevalence and potential severity of the disorder in their children.

"Most neurodevelopmental disorders are genetically complex, meaning that they aren't caused by a single gene," Girirajan said. "This makes it hard to trace the exact genetic underpinnings of a disorder in an individual and even harder to predict how the disorder will play out in affected children."

The researchers explained that complex genetic diseases can be caused by mutations in many genes, each of which could be inherited from one or both parents, or occur spontaneously in the newly formed genome of the child. The child's disease prognosis results from the combination of mutations that they inherit and how they interact with one another during development. This is called the "multi-hit model" because the disease results from multiple different mutations in many different genes.

"We have been studying one such mutation—a deletion of a small segment of chromosome 16—that has been implicated as a risk factor for several neurodevelopmental disorders," Girirajan said. Symptoms of these disorders can manifest as seizures, schizophrenic features, depression and anxiety, along with characteristics related to addiction.

"This mutation is often passed from a parent to a child, but the child regularly has more severe symptoms of the disorder than the parent. We wanted to know if other 'hits' for the disorder could be coming from the other parent. So, we looked at the traits of both parents in a large cohort of families with children with neurodevelopmental disorders," Girirajan added.

The research team found that the parent that had passed on the deletion had less severe symptoms than their child, or even different but related psychiatric disorders like depression or anxiety. They also found that the other parent often had similar psychiatric traits.

"What we realized, and it's been studied for a long time, is that in people there is a phenomenon called 'assortative mating,'" said Corrine Smolen, a graduate student at Penn State working with Girirajan and the first author of the paper. "Whether it's consciously or unconsciously, people with similar features preferentially find each other as partners. Although there could be other explanations, we see this in our data and that is probably what is leading to what we are seeing in the families that we studied."

The parent that doesn't have the deletion must have these traits because of some other genetic mutations, the researchers explained, and when these mutations are combined with the deletion in the genome of the child, the result is more severe disease.

By assessing the traits in both parents, the researchers could more accurately predict the trajectory of the disease in their children than would be possible via genetic screening alone. They also could eventually use this information to try to identify new mutations—those inherited from the parent without the deletion—that are involved in causing these traits.

"We found that there is a good correlation between the traits in the parents," Girirajan said. "Someone with schizophrenia is more likely to find a partner with schizophrenia, someone with anxiety and depression is more likely to find a partner with anxiety and depression. This is well-known for other things, like tall people marrying other tall people. Because all of these traits have at least some genetic component that could be similar between the partners, this leads to a situation that is

akin—but less pronounced—to consanguineous marriage, when people who are related through ancestry marry."

In this case, Girirajan explained, the assortative mating based on traits—rather than relatedness—appears to be driving genetic similarity between the partners, which could be leading to more cases and potentially more severe traits in their offspring.

As an example, the researchers saw that when neither partner had anxiety, 12.6% of their male children had anxiety. That number jumped to 25.7% when one parent reported having anxiety and to 33.8% when both parents had anxiety. This increase in prevalence is indicative of an increase in severity, because more severe traits are more likely to be identified, according to the research team.

More information: Corrine Smolen et al, Assortative mating and parental genetic relatedness contribute to the pathogenicity of variably expressive variants, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.10.015

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