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Distinct social profile and high ASD risk, 3q29 deletion survey finds

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A survey of 93 people with 3q29 deletion syndrome reveals a distinct pattern of social disability and anxiety, even without a diagnosis of autism spectrum disorder. The results were published online in

Molecular Autism on July 16.

Geneticists at Emory University School of Medicine teamed up with clinicians at Children's Healthcare of Atlanta's Marcus Autism Center to evaluate the largest cohort of people with 3q29 deletion ever assembled. Because 3q29 deletion syndrome is relatively rare (1/30,000 people), most physicians who have seen a case have only seen one. Study participants were recruited through a registry website, and they or their parents completed questionnaires about social, communication and behavioral issues. The average age was 10, but adults up to age 41 were included.

In 3q29 deletion syndrome, a stretch of DNA containing several genes is missing from one of a child's chromosomes. 3q29 deletion—usually spontaneous, not inherited—is one of the strongest genetic risk factors for schizophrenia, increasing the risk at least 20 fold. It also increases the likelihood of autism spectrum disorder at a similar level, the survey indicates: 24 fold for males and more than 40 fold for females.

Most people with 3q29 deletion did not have autism spectrum disorder (ASD) diagnoses (29 percent did), but overall they did have higher scores for social disability and anxiety. While not all participants were the same, their average profile was distinct from the general picture of autism spectrum disorder, in that people with 3q29 deletion tended to have high scores for restricted interests and repetitive behaviors, but only mild impairment in social motivation.

"The kids are motivated to have peer relationships, and desperately want them, yet aside from social motivation, they often lack other skills with which to form those relationships," says senior author Jennifer Mulle, Ph.D., assistant professor of human genetics at Emory University School of Medicine.

"One of our recommendations is that all individuals with 3q29 deletion should receive a thorough ASD evaluation as standard of care, so that they can have access to social services and therapeutic programs." Mulle says. "Because their intellectual disability is generally mild, cognitive behavioral therapy to teach social skills may be an effective intervention."

Another distinctive aspect of 3q29 deletion syndrome is its relatively greater effects on ASD risk in females compared with males. In the general ASD population, males outnumber females 4 to 1; this ratio is reduced to 2 to 1 for ASD diagnoses in the 3q29 group.

The first author of the paper is Genetics and Molecular Biology graduate student Rebecca Pollak. She worked with associate scientist Melissa Murphy, Ph.D. at Emory and Celine Saulnier, Ph.D. and Cheryl Klaiman, Ph.D. at Marcus Autism Center. Emory geneticists Michael Epstein, Ph.D. and Michael Zwick, Ph.D. also contributed to the paper.

Mulle sees investigating 3q29 deletion syndrome—and other genetic variations connected with schizophrenia and autism—as a way of unraveling the biological complexity of both conditions.

The Emory team is beginning to investigate individual genes found within the 3q29 deletion, aiming to understand molecular mechanisms. Working with cell biology chair Gary Bassell, scientists plan to create a human neuronal model of 3q29 deletion, using induced pluripotent stem cell lines. They are also investigating the patterns of gene activity in blood samples from 3q29 donors.

In April, Mulle and her colleagues from the Department of Human Genetics, including Tamara Caspary, Ph.D., David Weinshenker, Ph.D. and Steve Warren, Ph.D. published a mouse model of 3q29 deletion in *Molecular Psychiatry*. The mice display social and cognitive impairments

that correspond to some symptoms of related neuropsychiatric disorders.

More information: Neuropsychiatric phenotypes and a distinct constellation of ASD features in 3q29 deletion syndrome: results from the 3q29 registry, *Molecular Autism* (2019). DOI: 10.1186/s13229-019-0281-5

Timothy P. Rutkowski et al, Behavioral changes and growth deficits in a CRISPR engineered mouse model of the schizophrenia-associated 3q29 deletion, *Molecular Psychiatry* (2019). DOI: 10.1038/s41380-019-0413-5

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