Gene may be important in autism disorders, other neuropsychiatric syndromes

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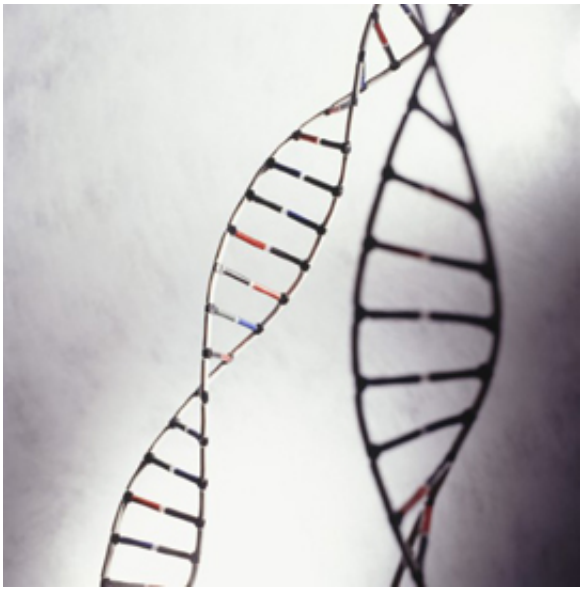

Credit: NIH

Scientists have identified a gene that appears to play a significant role in raising a person's risk of having more severe subtypes of autism that co-occur with other genetic diseases, such as the chromosomal disorder 22q11.2 deletion syndrome. Variations in this gene, RANBP1, may disrupt brain signaling in different neuropsychiatric conditions—a finding that could open new research opportunities for treatment for multiple neurological diseases.

"The gene we investigated may function as an important factor, not only

in forms of autism, but also in other neuropsychiatric conditions," said study leader, Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia (CHOP). "We have uncovered underlying molecular defects across disease categories, suggesting that these biological networks are good targets for future research."

The paper appears online today in *Scientific Reports*.

The study team compared DNA from 539 children with autism spectrum disorder (ASD) to DNA from 75 children with 22q11.2 deletion syndrome—25 of whom also had ASD. The researchers searched for copy number variations (CNVs) within a particular gene network, the metabotropic glutamate receptor (mGluR) pathway affecting the neurotransmitter glutamate.

In previous research, Hakonarson and colleagues showed that genes on the mGluR network were more likely to be perturbed in patients with ASD. His team also showed that members of this gene family also affected subsets of patients with attention-deficit hyperactivity disorder (ADHD) and schizophrenia.

Autism is the best known of the ASDs, a large group of heritable neuropsychiatric conditions in which patients have impaired social interaction and communication. The current study focused on the 20 percent of patients with syndromic ASD—that associated with identifiable genetic disorders. Among many such syndromes, the investigators focused particularly on 22q11.2 deletion syndrome, in which a portion of chromosome 22 is missing. CHOP has one of the world's largest research and clinical centers in this syndrome, and several leaders from that program co-authored the current study.

Although 22q11.2 deletion syndrome occurs in an estimated one in every

2000 to 4000 individuals, it remains under-recognized by the general public and even by many physicians. A multisystem disorder, it may affect the heart, immune system, face and palate, the gastrointestinal system and neurocognitive functioning. The deleted region of chromosome 22 contains multiple genes, none of which have been identified as causative.

The current study revealed that children with ASDs harboring CNVs in the mGluR network were more likely to have the syndromic subtype of ASD. Those patients had a 74 percent prevalence of syndromic ASD, compared to 16 percent in those without CNVs in mGluR.

The study team also analyzed a separate cohort of 75 children with 22q11.2 deletion syndrome. The deleted region contains the mGluR network gene RANBP1. Among these children, 20 percent of those who also had ASD had a "second hit"—a deletion of an mGluR network gene outside of the 22q11.2 region. In contrast, only 2 percent of children having the deletion syndrome without ASD had a second hit.

"Based on this study, we propose that the RANBP1 gene is a significant genetic factor in both ASD and 22q.11.2 deletion syndrome," said Hakonarson. "Furthermore, when the mGluR network is disrupted at multiple points, it predisposes individuals to a more severe disease." Numerous environmental studies also support a role for RANBP1 in autism.

Other scientists have shown that deactivating the animal version of the RNBP1 gene decreases neurons and disrupts brain circuitry. "Further research," added Hakonarson, "is aimed at uncovering additional gene variations in the mGluR network, and we anticipate that these studies will unveil important interactions among genetic and environmental factors that increase a child's risk of developing ASD."

"The mGluR variants we identified may be important in identifying those patients who are most likely to respond to new treatments," said Hakonarson. "As such, this could be the basis for one of the first examples of a precision medicine focus in drug development for complex disease."

More information: Tara L. Wenger et al. The Role of mGluR Copy Number Variation in Genetic and Environmental Forms of Syndromic Autism Spectrum Disorder, *Scientific Reports* (2016). DOI: 10.1038/srep19372

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