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New autism genes are revealed in largest-ever study

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In the largest, most comprehensive genomic analysis of autism spectrum disorder (ASD) conducted to date, an international research team led by UCSF Department of Psychiatry scientists has identified 65 genes that play a role in the disorder, 28 of which are reported with ?very high confidence,? meaning that there is 99 percent certainty that these genes contribute to the risk of developing ASD.

In addition, the study confirms six ?risk regions??segments of chromosomes that contain several genes, which, when lost or gained, contribute to ASD risk. In combination with the 65 risk genes, this results in 71 ASD risk loci, or locations.

Stephan Sanders, BMBS, PhD [1]

Stephan Sanders, BMBS, PhD [1], assistant professor of psychiatry at UCSF and first author of the new study, said, ?This is the largest study of autism genetics to date, providing an unprecedented opportunity to discover the genes underlying this complex disorder.?

The 65 high-confidence genes, 27 of which are newly identified in this study, fall into two main functional categories, one related to the development and function of synapses?the crucial sites where communication among brain cells takes place?and the other involving chromatin, the term for the DNA-protein complex that packs the genome into chromosomes in cell nuclei and governs how and when genes are expressed.

?The relationship between these two broad categories is a key question in autism research,? said Sanders. ?They may be two separate biological paths to the disorder, or two sides of the same coin, with the chromatin-related genes identified in this study regulating the expression of those that drive synapse formation and function, or vice versa.?

The findings, published in the September 23, 2015 issue of Neuron [2], were made possible by a remarkable global collaboration that allowed Sanders and senior author Matthew W. State, MD, PhD [3], chair and Oberndorf Family Distinguished Professor of Psychiatry at UCSF, to combine new and published data into a single dataset containing genomic information from over 5,500 individuals with ASD, as well as from unaffected individuals.

?Autism researchers have been at the forefront of genomic data sharing,? said State. ?The current study shows again just how powerful this is. The coming together of widespread patient and family involvement in autism research, powerful new genomic technologies, and international collaboration has transformed our understanding of the genetics of ASD.?

The research also sheds light on how copy number variants (CNVs)?deletions or duplications of chunks of the genome, containing a number of genes, that have been tied to ASD in previous research by Sanders, State, and others?relate to individual high-risk ASD genes uncovered in sequencing studies that analyzed the genome letter-by-letter.

To achieve this, the work draws data from three sources. One, the Simons Simplex Collection (SSC), is a permanent repository of DNA samples from nearly 3,000 families created by the Simons Foundation Autism Research Initiative (SFARI) [4]. Each SSC family has one child affected with autism, parents unaffected by the disorder and, in a large proportion of the collection, unaffected siblings. The current work provides the first comprehensive analysis of CNVs and sequencing data from the SSC and is the culmination of seven years of work by a genetics consortium funded by SFARI.

The researchers also made use of published CNV data from the Autism Genome Project, a cohort of ASD samples from approximately 50 academic and research institutions funded by Autism Speaks [5] and the National Institutes of Health [6]. Finally, the study made use of data from Autism Sequencing Consortium (ASC), an initiative supported by the National Institute of Mental Health [7] that allows scientists from around the world to work together on large genomic studies that couldn?t be done by individual labs.

Matthew W. State, MD, PhD [8]

In previous published research on the SSC, Sanders and State showed that *de novo* (Latin for ?anew?) CNVs, which are not present in unaffected parents? genomes but arise spontaneously in a single sperm or egg cell just prior to conception of a child, contribute significant risk to ASD. CNVs were also implicated in ASD in previous studies of the AGP datasets. In addition, Sanders and State were part of one of the first groups to establish that small *de novo* changes in the DNA code that disrupt only a single gene also contribute to ASD. This analysis was performed using whole-exome sequencing, a high-resolution approach that allows scientists to analyze individual genes and the smallest mutations within them.

One goal of the new paper was to take the ?chunkier? results of CNV analyses and line them up with fine-grained exome sequencing to determine if there are meaningful overlaps in the genes affected. The new study showed that small *de novo* deletions?those containing less than seven genes?often contain a single high-risk gene that is independently identified by the exome sequencing data. In contrast, *de novo* deletions or duplications of more than seven genes often contain multiple low-risk genes. This has a balancing effect, explaining how mutations of a single gene can have a similar effect to mutations that delete multiple genes.

A case in point is DiGeorge syndrome, a medical condition caused by a CNV deletion on chromosome 22, often resulting in a diagnosis of ASD. ?We have solved a decades-old question about which of the many genes deleted in DiGeorge Syndrome is the ?smoking gun? that leads to the neurological effects,? said Sanders. ?The exome data reveal that there is no such gene, but rather that there are multiple genes, each of which makes a small contribution to neurodevelopmental manifestations of the disorder when deleted.?

This work also provides clues regarding the well-documented sex disparity in ASD diagnoses, with males being four times as likely as females to be diagnosed with the disorder. The analysis revealed that, despite the sex bias in ASD diagnoses, the same genetic risk factors lead to ASD in both males and females. Furthermore, females diagnosed with ASD had a much greater number of *de novo* mutations. Together these two strands of evidence suggest that females are somehow protected from ASD, unless their mutation burden is great enough to reach a tipping point.

?Females appear to be protected from autism risk, but little is known about the nature of this protection; this represents a major research interest in my lab,? Sanders said. ?Obvious candidates include the effect of estrogen and testosterone on the developing brain, but so far there are no clear answers, even to these basic questions.?

Some researchers have raised the possibility that *de novo* mutations may be associated with only the cognitive impairments seen in some cases of ASD, and that the broader aspects of social behavior affected by the disorder have their roots in other more common genetic variants. But Sanders said that ?the observation of *de novo* mutations in individuals with ASD and high IQs supports that notion that some of these mutations can contribute to core ASD symptoms, independent of cognitive impairment.?

In a 2013 study, Jeremy Willsey, PhD [9], an assistant professor of psychiatry at UCSF, along with State and Sanders, showed that the effects of mutations in nine important ASD genes all converged on a single cell type in the prefrontal cortex during fetal development. ?Now that we have real traction discovering ASD genes, the next big challenge for the field is to understand when, where, and why autism develops,? State said. ?The expanded list of high-confidence autism genes from this study is going to help tremendously.?

The work was performed in collaboration with scientists and clinicians at more than 20 institutions, with particularly important contributions from Bernie Devlin, PhD, professor of psychiatry at the University of Pittsburgh School of Medicine, and Kathryn Roeder, PhD, professor of statistics and computational biology at Carnegie Mellon University. Additional co-authors from UCSF Psychiatry include Jeremy Willsey, PhD [9]; Vanessa Hus Bal, PhD [10]; Somer Bishop, PhD [11]; Jeffrey Mandell [12]; Louw Smith [13]; Michael Walker [14]; and Donna Werling, PhD [15].

The work was primarily funded by SFARI with additional funding from the National Institute of Mental Health.

Read the paper

- **Neuron:** Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci [16]

About UCSF Psychiatry

The UCSF Department of Psychiatry [17] and the Langley Porter Psychiatric Institute are among the nation's foremost resources in the fields of child, adolescent, adult and geriatric mental health. Together they constitute one of the largest departments in the UCSF School of Medicine, with a mission focused on research (basic, translational, clinical), teaching, patient care and public service. UCSF Psychiatry has an organizational structure that crosses all major UCSF sites - Parnassus, Mission Bay, Laurel Heights, Mt. Zion, San Francisco General Hospital and Trauma Center, the San Francisco VA Medical Center and UCSF Fresno.

About UCSF

UC San Francisco (UCSF) [18] is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy, a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences, as well as a preeminent biomedical research enterprise and two top-ranked hospitals, UCSF Medical Center and UCSF Benioff Children?s Hospital San Francisco.

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[1] http://profiles.ucsf.edu/stephan.sanders
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