Genetic risk factors for autism, MS and other diseases differ between sexes

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A pair of studies by researchers at UC San Francisco suggest that genetic variants that have distinct effects on physical traits such as height, weight, body mass, and body shape in men versus women are also linked to men’s and women’s risk for a range of diseases— including autism, multiple sclerosis, type 1 diabetes, and others. The results suggest that at least some of the fundamental biological drivers of disease may be significantly different in men and women, an idea that could have significant impacts on disease research and treatment, the authors say.

Lauren A. Weiss, PhD

The idea of sex differences in disease is an old one. Some disorders (such as multiple sclerosis) are more common in women, while others (such as autism) are more common in men. Other diseases, such as cardiovascular disease, can simply look very different in men and women, and the two sexes are also known to respond differently to certain drugs, making sex differences a crucial factor for doctors to take into account in diagnosis and treatment.

Despite the prevalence of sex differences in many diseases, however, scientists still do not have a comprehensive understanding of the biology that drives these differences. Many
studies in humans and model organisms have sought to address this question, but their results have been contradictory, according to Lauren A. Weiss, PhD [1], associate professor of psychiatry at UCSF, and senior author on the two new studies.

"While some studies have looked at small regions of the genome or tried to support one specific hypothesis with respect to sex differences, few studies have looked at the question from a comprehensive genome-wide perspective," Weiss said.

In the two new studies, Weiss and her team analyzed genome-wide association study (GWAS) data* to search for patterns that might support or rule out competing hypotheses about the origins of sex differences in a number of diseases, and compared these patterns with those associated with physical traits that obviously differ between the sexes, such as height, body mass index (BMI), and waist-to-hip ratios.

* Genome-wide association studies (GWAS) examine a set of genetic variants that vary among individuals ? typically differences in just one ?letter? of the genetic code, called single-nucleotide polymorphisms (SNPs; pronounced ?snips?) ? in large genome databases, searching for correlations between the presence of particular variants and a range of traits, from physical traits such as height or BMI to measures of disease risk. Often, identifying a genetic variant that is highly correlated with a particular trait suggests that there is a gene nearby that has an important role in the biology of that trait.

Research suggests genetic sex difference in autism

In the first study, published online November 15, 2016 in PLoS Genetics [2], researchers in the Weiss lab, which is affiliated with the Institute for Human Genetics [3] at UCSF, investigated why autism occurs nearly five times more often in boys than in girls, a mystery that has puzzled researchers for many years. The team investigated several leading hypotheses that attempt to explain this phenomenon, including the idea that clinicians are not as good at recognizing autism in females, that autism represents an ?extreme male brain? that is naturally more common in males, or that autism is driven by differences in sex hormones, and found that these did not appear to be major factors in the genetics of the disease.

Instead, the team found that autism risk is associated with genetic variants that are known to contribute differently to physical traits such as height, weight, BMI, and waist and hip measurements in men and women, suggesting that their effects on autism risk might differ between the sexes as well.

?The results indicate that there are fundamental genetic sex differences in autism,? Weiss said. ?It suggests that genetic variants that may be important predictors of autism risk for girls may not be so important for boys, or vice versa. This means that interpretation of genetic testing in autism could potentially be improved and refined by considering sex. Further in the future, similar implications should be considered for autism treatments ? if there are sex differences in the underlying biology, response to specific treatments might also be different by sex.?
A team of researchers led by Lauren A. Weiss, PhD, found that autism risk is associated with genetic variants that are known to contribute differently to physical traits such as height, weight, BMI, and waist and hip measurements in males and females, suggesting that their effects on autism risk might differ between the sexes as well.

**Genetic sex differences may influence common diseases**

Weiss’s team followed up this research with a second paper—published online December 14, 2016 in Genetics—and scheduled for print in February, 2017—exploring the role of sex differences on the genetics of nine other diseases, some that strike men more frequently (ankylosing spondylitis and type 1 diabetes), some that are more common in women (multiple sclerosis and rheumatoid arthritis), and others that occur with similar frequency in men and women (bipolar disorder, coronary artery disease, Crohn’s disease, hypertension, and type 2 diabetes).

The study looked for data that could distinguish a number of explanations for sex differences in these diseases: whether disease risk was correlated with distinct genetic variants in women and men, or whether the two sexes might instead have different sensitivities to the same genetic risk factors; whether sex differences in disease risk could be explained by different levels of the sex hormones testosterone or estrogen or as side effects of the development of other secondary sex characteristics (as is the case with breast and prostate cancers); or whether sex differences were linked to differences in the sex chromosomes—the fact that women have two X chromosomes while men have one X and one Y.

The authors found that sex had a significant influence on some of these diseases, including those thought to have similar prevalence in males and females. Many diseases appeared to be impacted by genes regulated by androgens or estrogens—the “male” and “female” sex hormones, respectively—and as with the new autism findings, the same common genetic differences that differently influence physical traits in men and women also appeared to contribute to risk for five of these nine diseases.

“We don’t know yet why this occurs, but it does imply that the same biological pathways that influence physical sex differences also impact a number of common diseases and disorders,” Weiss said. “Many people are excited about the idea of precision medicine, or how medical care can be optimized for an individual. Well, sex is something that we already know about every individual. A better understanding of how sex impacts genetic risk for disease could be a great start to improving our understanding, diagnosis, and treatment or prevention of common diseases.”

Particularly striking initial findings of the Genetics paper—which the researchers caution require further study and replication by other labs—include the identification of an interaction with sex for the genetic risk factors associated with multiple sclerosis, as well as a significantly higher heritability of hypertension in women compared to men. Since hypertension occurs with similar frequency in men and women, the authors speculate this finding might imply that environmental factors play a correspondingly bigger role in male hypertension.

Lead authors on the PLoS Genetics paper were Ileena Mitra and Kathryn Tsang of the UCSF Department of Psychiatry. Additional authors from UCSF included Robert L. Hendren, DO; Michaela Traglia, PhD; and Alinoë Lavillaureix. The study was supported with funds...
from the National Institutes of Health [8], Simons Foundation Autism Research Initiative [9], One Mind Institute [10] (formerly IMHRO), and the UCSF Research Evaluation and Allocation Committee [11].

Lead authors on the Genetics paper were Michela Traglia, PhD; and Dina Bseiso of the UCSF Department of Psychiatry; and Alexander Gusev, PhD, of the Broad Institute of Harvard and MIT and the Harvard School of Public Health. The work was supported by One Mind Institute (formerly IMHRO) and grants from the National Institutes of Health.

Read the studies

- Genetics: Genetic Mechanisms Leading to Sex Differences Across Common Diseases and Anthropometric Traits [4]

Further coverage

- Spectrum: Some autism risk may arise from sex-specific traits [12]
- NOVA Next: Mutations in sex-linked genes appear to drive more males cases of autism [13]

About UCSF Psychiatry

The UCSF Department of Psychiatry [14] 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 and the UCSF Weill Institute for Neurosciences, with a mission focused on research (basic, translational, clinical), teaching, patient care, and public service.

UCSF Psychiatry conducts its clinical, educational, and research efforts at a variety of locations in Northern California, including UCSF campuses at Parnassus Heights, Mission Bay, and Laurel Heights, the UCSF Medical Center at Mt. Zion, Zuckerberg San Francisco General Hospital and Trauma Center, the San Francisco VA Health Care System, and UCSF Fresno.

About the UCSF Weill Institute for Neurosciences

The UCSF Weill Institute for Neurosciences [15], established by the extraordinary generosity of Joan and Sanford I. "Sandy" Weill, brings together world-class researchers with top-ranked physicians to solve some of the most complex challenges in the human brain.

The UCSF Weill Institute leverages UCSF’s unrivaled bench-to-bedside excellence in the neurosciences. It unites three UCSF departments—Neurology, Psychiatry, and Neurological Surgery—that are highly esteemed for both patient care and research, as well as the Neuroscience Graduate Program, a cross-disciplinary alliance of nearly 100 UCSF faculty members from 15 basic-science departments, as well as the UCSF Institute for Neurodegenerative Diseases, a multidisciplinary research center focused on finding effective treatments for Alzheimer’s disease, frontotemporal dementia, Parkinson’s disease, and other
neurodegenerative disorders.

About UCSF

UC San Francisco (UCSF) 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; and a preeminent biomedical research enterprise. It also includes UCSF Health, which comprises two top-ranked hospitals, UCSF Medical Center and UCSF Benioff Children’s Hospital San Francisco, and other partner and affiliated hospitals and healthcare providers throughout the Bay Area.

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