

Large-scale genome analysis identifies differences by sex in major psychiatric disorders

March 23 2021, by Noah Brown



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An analysis of sex differences in the genetics of schizophrenia, bipolar disorder and major depressive disorders indicates that while there is substantial genetic overlap between males and females, there are

noticeable sex-dependent differences in how genes related to the central nervous system, immune system, and blood vessels affect people with these disorders.

The findings, from a multinational consortium of psychiatric researchers including investigators and a senior author at Massachusetts General Hospital (MGH), could spur better treatments for major psychiatric disorders. They are published in the journal *Biological Psychiatry*.

The findings were made possible only through the cooperation of more than 100 investigators and research groups, who combed through the genomes of 33,403 people with schizophrenia, 19,924 with [bipolar disorder](#), and 32,408 with [major depressive disorder](#), as well as 109,946 controls (people without any of these diagnoses).

Their goal was to understand why these major psychiatric [disorders](#) differed between the sexes. For example, women have a significantly higher risk for major depressive disorder, whereas the risk for schizophrenia is significantly higher among men. The risk of bipolar disorder is about the same for both women and men, but [disease](#) onset, course, and prognosis differ markedly between the two.

"We're in the era of Big Data, and we're looking for genes that are associated with illnesses to identify druggable targets associated with the genotype, in order to develop more effective treatments for that illness that may differ by sex," says senior author Jill M. Goldstein, Ph.D., founder and executive director of the Innovation Center on Sex Differences in Medicine (ICON) at MGH.

Goldstein and colleagues searched for clues in the form of single nucleotide polymorphisms, or SNPs ("snips"), in which a single DNA "letter" (nucleotide) differs from one person to the next and between sexes.

"There are sex differences in the frequency of chronic diseases and cancers as well. It's pervasive," says Goldstein, who is also a professor of Psychiatry and Medicine at Harvard Medical School. "But medicine, essentially, has been built on models of men's health and male animals. We need to develop our precision medicine models incorporating the effect of sex."

By taking advantage of large psychiatric databases, the investigators were able to demonstrate that the risks for schizophrenia, bipolar disorder and major depressive disorder are affected by interactions of specific genes with sex, apart from the effects of sex hormones such as estradiol or testosterone.

For example, the investigators found interactions with schizophrenia and depression and sex in genes controlling for the production of vascular endothelial growth factor, a protein that promotes the growth of new blood vessels.

"My lab is studying the substantial co-occurrence of depression and cardiovascular disease. It turns out that both depression and schizophrenia have a very high co-occurrence with cardiovascular disease. We believe there are shared causes between psychiatric and cardiovascular diseases that are not due to the effects of medication," she says. "In addition, the co-occurrence of depression and [cardiovascular disease](#) is twice as high in women as in men, and this may, in part, be associated with our finding in depression of sex differences in a gene controlling vascular endothelial growth factor."

The investigators emphasize that although the specific causes of the diseases they studied are still unknown, "our study underscores the importance of designing large-scale genetic studies that have the statistical power to test for interactions with sex. Dissecting the impact of sex, genes, and pathophysiology will identify potential targets for sex-

dependent or sex-specific therapeutic interventions creating more effective therapies for both men and women," she says.

More information: Gabriëlla A.M. Blokland et al, Sex-Dependent Shared and Non-Shared Genetic Architecture, Across Mood and Psychotic Disorders, *Biological Psychiatry* (2021). [DOI: 10.1016/j.biopsych.2021.02.972](https://doi.org/10.1016/j.biopsych.2021.02.972)

Provided by Massachusetts General Hospital

Citation: Large-scale genome analysis identifies differences by sex in major psychiatric disorders (2021, March 23) retrieved 8 May 2024 from <https://medicalxpress.com/news/2021-03-large-scale-genome-analysis-differences-sex.html>

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