

Biological sex affects genes for body fat, cancer, birth weight

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Biological sex has a small but ubiquitous influence on gene expression in almost every type of human tissue, reports a new study from Northwestern Medicine, the University of Chicago and the Centre for Genomic Regulation in Barcelona. Gene expression is the amount of product created by a gene for cell function.

These sex differences are observed for [genes](#) involved in many functions, including how people respond to medication, how women control blood sugar levels in pregnancy, how the immune system functions, and how cancer develops.

The study will be published September 10 in *Science*.

Sex also has a weaker but important effect on how [genetic variation](#) between individuals impacts their gene expression levels. The scientists discovered 369 instances where a given genetic variant present in males and [females](#) impacted gene expression to a different degree in each sex. This enabled the scientists to discover 58 previously unreported links between genes and complex traits such as blood pressure, cholesterol levels, breast cancer and body fat percentage.

"These discoveries suggest the importance of considering sex as a biological variable in [human genetics](#) and genomics studies," said project leader Barbara Stranger, an associate professor of pharmacology at Northwestern University Feinberg School of Medicine.

By taking an approach that specifically looks for differences between males and females, the scientists discovered previously unknown links between [specific genes](#) and specific human traits that were missed by

approaches that considered males and females as a single group. Furthermore, the study reported a portion of previously reported gene-trait links were true only for a single sex.

"The significance of this is if specific genes or genetic variants contribute differentially to a given trait in males and females, it could suggest sex-specific biomarkers, therapeutics and drug dosing," Stranger said. "In the future, such knowledge may form a critical component of personalized medicine or may reveal disease biology that remains obscured when considering males and females as a single group."

Sex differences exist for many human traits and disease characteristics (e.g., age of onset, severity, response to treatment) and have been previously attributed to hormones, sex chromosomes and differences in behavior and environmental exposures. But the [molecular mechanisms](#) and underlying biology remain largely unknown.

In this study, scientists investigated sex differences in the human transcriptome, which is the sum of all RNA transcripts in a cell, from 44 types of healthy human tissue from 838 individuals. For each gene, the scientists tested whether the average amount of gene expression in females differed from the amount in males.

They discovered more than a third of all human genes (37%) were expressed at different levels in males and females in at least one type of tissue. Although these effects were abundant, the amount that gene expression differed was mostly small.

The genes with differential expression between males and females represented diverse molecular and biological functions, including genes relevant to disease and clinical traits, many of which had not been previously associated with sex differences.

All of these gene-trait associations suggest a causal link between specific genetic variants and a trait.

"Finding these links helps us to understand the biology underlying the trait," Stranger said. "If we understand the biology of a trait, we can try to use that information for diagnostics, drug development and predicting outcome."

In women, the genetic regulation of CCDC88 expression is strongly associated with the progression of breast cancer. The finding could motivate researchers to assess whether [gene expression](#) of CCDC88 is a useful biomarker for cancer progression in women, Stranger noted.

HKCD1 was associated with [birth weight](#) in women. Researchers hypothesize that HKDC1 may impact birth weight through altering glucose metabolism in the liver of a pregnant woman.

In men, DPYSL4 was associated with body fat percentage and CLDN7 with birth weight.

The genetic regulation of C9orf66 in males was associated with balding patterns in males. Prior to this study, little was known about the gene. With this discovery, investigators can design experiments to better characterize the role of this gene in balding patterns in males.

The study has some limitations. The researchers note despite extensive sex differences at the transcriptome level, the majority of human biology at all levels is shared between [males](#) and females. The findings are based on a snapshot of mostly older individuals. The analysis also does not account for [sex differences](#) that occur during different developmental stages or in specific environments.

More information: M. Oliva et al., "The impact of sex on gene

expression across human tissues," *Science* (2020).
[science.sciencemag.org/cgi/doi ... 1126/science.aba3066](https://science.sciencemag.org/cgi/doi/10.1126/science.aba3066)

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