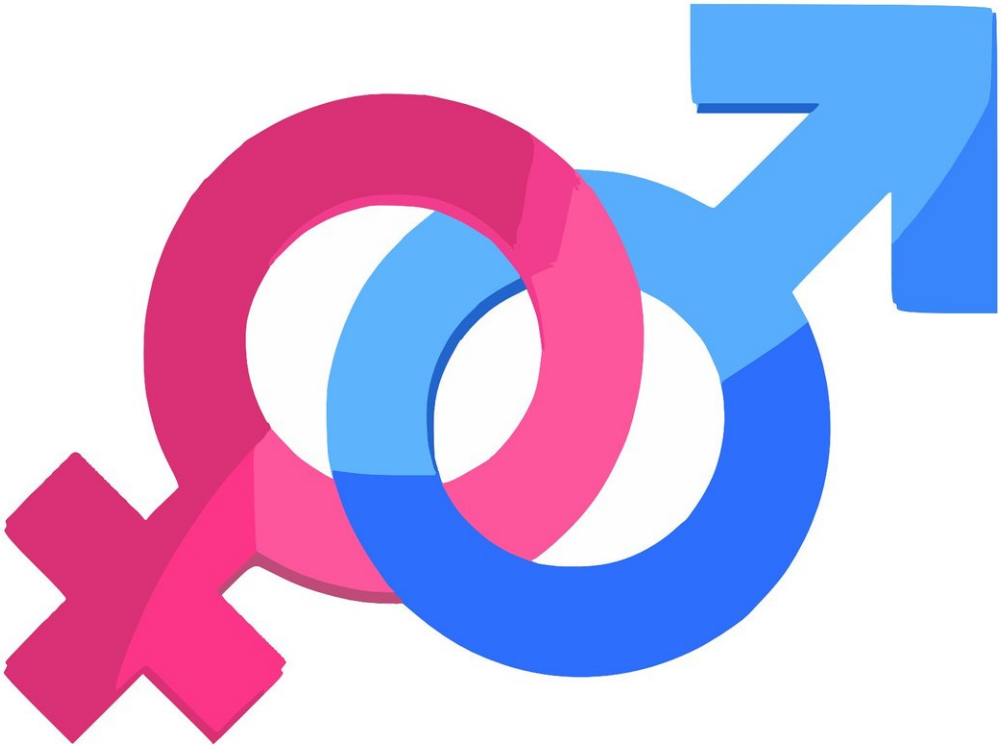
Male-female differences in heart disease could start before birth

October 19 2021



Credit: CC0 Public Domain

Males and females differ in prevalence, treatment responses, and survival rates for a variety of diseases. For cardiac disease, women almost uniformly fare far worse than men. There are likely many reasons for this, and scientists at the University of North Carolina at Chapel Hill and Princeton University seemed to have found one deep inside cells before we're even born.

Published in the journal *Developmental Cell*, this research suggests that male-female differences in protein expression occur immediately after embryonic cells become heart cells called cardiomyocytes. This is the earliest stage of heart development, well before the embryo is exposed to sex hormones.

This comprehensive report is the first to detail the mechanisms of cardiac sex disparities at such an early stage, providing new opportunities for research of cardiac disease and treatment, as well as advancing the biological study of sex differences in this burgeoning field.

"Our studies show that sex biases in heart development occur prior to primary sex determination and can be, and are, associated with sex bias congenital heart disease," said co-senior author Frank Conlon, Ph.D., professor of genetics and biology at the University of North Carolina at Chapel Hill. "Since sex disparities have been reported in many other disease states, including cancer, dementia, chronic kidney disease, obesity, autoimmune disease, and COVID-19, our studies provide a framework for uncovering the mechanisms and pathways of these disease states, as well."

This research was a collaboration between Conlon lab at the UNC School of Medicine, and the lab of co-senior author Ileana Cristea, Ph.D., the Henry L. Hillman Professor of Molecular Biology at Princeton.

Such health disparities between males and females have been known for a long time and led to "Report of the National Heart, Lung, and Blood Institute Working Group on Sex Differences Research in Cardiovascular Disease" in 2016. Although sex plays a critical role in cardiac disease, the mechanisms underlying sex differences in cardiac health and disease have been unknown.

Co-first authors Wei Shi, Ph.D., a postdoctoral researcher in the Conlon lab, and Xinlei Sheng, Ph.D., a postdoctoral researcher in the Cristae lab, led a systems-based approach to identifying the molecular differences, at both the RNA and protein levels of cells, between male and female embryonic and adult hearts in mice. They leveraged the power of the Collaborative Cross (CC) as a surrogate for human diversity, identifying the proteins, protein complexes, and protein pathways that are common between mammals and those that diverge between males and females. The CC is composed of eight founding strains of genetically diverse mice to address the many research shortcomings in most other available mouse-strain resources, including small numbers of strains, limited genetic diversity, and a less than ideal population structure.

Conlon's team then defined the cell types that express a subset of these proteins to show differences in expression in the cardiomyocyte lineage between male and female hearts.

"Contrary to the current paradigm, we discovered that male-female cardiac sex differences are not solely controlled by hormones but also through a sex chromosome mechanism independent of sex hormones," said Conlon, who is also a member of the UNC McAllister Heart Institute. "Our analysis showed that protein expression differs between male and female hearts at the embryonic period prior to primary sex determination and prior to the embryo being exposed to sex hormones."

Understanding the basic biology of heart development at this very early

stage provides crucial information for stem cell biologists interested in using cardiac progenitor cells for regeneration of heart tissue and other cardiac replacement therapies.

More information: Wei Shi et al, Cardiac proteomics reveals sex chromosome-dependent differences between males and females that arise prior to gonad formation, *Developmental Cell* (2021). DOI: 10.1016/j.devcel.2021.09.022

Christine Maric-Bilkan et al, Report of the National Heart, Lung, and Blood Institute Working Group on Sex Differences Research in Cardiovascular Disease, *Hypertension* (2016). DOI: 10.1161/hypertensionaha.115.06967

Provided by University of North Carolina at Chapel Hill School of Medicine