Genes Provide Clues to Gender Disparity in Human Hearts

Healthy men and women show little difference in their hearts, except for small electrocardiographic disparities. But new genetic differences found by Washington University in St. Louis researchers in hearts with disease could ultimately lead to personalized treatment of various heart ailments.

Generally, men are more susceptible to developing atrial fibrillation, an irregular, rapid heartbeat that may lead to stroke, while women are more likely to develop long-QT syndrome, a rhythm disorder that can cause rapid heartbeats and sudden cardiac death.

While prior studies have clearly established differences in the development of heart disease between men and women, very few studies had looked at the molecular mechanisms behind those differences in human hearts.

Igor Efimov, PhD, the Lucy and Stanley Lopata Distinguished Professor of Biomedical Engineering in the School of Engineering & Applied Science at Washington University in St. Louis, and a former doctoral student, Christina Ambrosi, PhD, analyzed 34 human hearts looking for genetic differences that might explain gender differences in heart disease.

The team took advantage of the unique opportunity at the university to obtain failing human hearts at the time of transplantation from Barnes-Jewish Hospital and non-failing hearts unsuitable for transplantation from Mid-America Transplant Services, a St. Louis-based organ procurement service.

The team screened for 89 major genes in electrophysiology, ion channel subunits, calcium handling proteins and transcription factors important in cardiac conduction and in the development of arrhythmia and the left atria and ventricles in human hearts.

“What was striking in this study is that we expected very large gender differences in expression of genes in the ventricles, but we did not find such differences,” says Efimov, also a professor of medicine, of radiology and of cell biology and physiology at Washington University School of Medicine. “Unexpectedly, we found huge gender differences in the atria.”

The results showed that women with failing hearts have a weaker system of gene expression than men — males showed overall higher expression levels of nearly all of the 89 genes than women.

Women showed particularly lower atrial expression levels of several important genes encoding for potassium channels, including Kv4.3, KChIP2, Kv1.5 and Kir3.1.

In fact, the atria of women with heart disease had less than half of the KChIP2 mRNA than atria in men.

Results of the research were published in *PLOS ONE*.

Efimov says while there are still many questions that need to be answered to explain these molecular differences, one factor that could be contributing to the difference is estrogen.

“When women have the highest levels of estrogen, they are least vulnerable to arrhythmia — women are protected by estrogen,” he says. “But after menopause, women develop atrial fibrillation at the same rate as men. We don’t understand this and need to study this in humans.”

Another potential factor is circadian rhythm, Efimov says.

“Humans are much more likely to die suddenly from heart disease early in the morning, between 5-7 a.m.,” he says. “In the cardiac system in mice, it has been shown that there is an oscillation of gene expression, so certain genes expressed at 5 a.m. could be different by threefold at 5 p.m.”

Efimov says the study on human hearts is unique to Washington University, as much cardiac research elsewhere is done mostly in animal models. In the future, the team would like to expand the research into pediatric hearts, taking advantage of Washington University’s leading pediatric heart transplant program to learn more about pediatric physiology.

Source: Washington University in St. Louis [1]

Links:
[1] http://news.wustl.edu/news/Pages/24827.aspx