

Study finds hereditary link to premenstrual depression

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A specific genetic variation may be tied to an increased risk for severe premenstrual depression, scientists at the University of North Carolina at Chapel Hill and the National Institute of Mental Health have found.

Known medically as premenstrual dysphoric disorder, or PMDD, this psychiatric condition affects roughly 8 percent of women in their childbearing years. It's characterized by bouts of major depression and/or anxiety and severe irritability during the second half of the menstrual cycle. Symptoms subside with the onset of each menstrual period.

While PMDD has been thought to be linked to hormonal changes over the course of the menstrual cycle, until now an explanation for the susceptibility to hormone-related mood changes has been elusive. "Our initial hope in the study was that by looking at steroid-related genes like those for receptors for steroid hormones such as estrogen, we would be able to find gene differences that might explain why some women have these mood disorders and others don't," said Dr. David R. Rubinow, the study's senior author and the Meymandi distinguished professor and chair of psychiatry at UNC School of Medicine. "This study may begin to provide important clues to the nature of that susceptibility."

The study is the first to identify a genetic variation linked to a mood disorder associated with endocrine changes during the menstrual cycle, Rubinow said. The results will appear in an upcoming print edition of the journal *Biological Psychiatry* and were published online June 30,

2007. The study was supported by funds from the Intramural Research Program at the National Institute of Mental Health (NIMH).

The research involved 91 women for whom the authors prospectively confirmed a diagnosis of PMDD over at least three months. Another 56 women who had no history of mood disorders related to the menstrual cycle served as a comparison group. All the women provided blood samples for genetic analysis.

The team discovered four specific genetic variants, called single nucleotide polymorphisms, in one of the two genes that encode the estrogen receptor. The variants, which are differences in strings of DNA nucleotides A, G, C, or T, were identified in the estrogen receptor alpha gene, ESR1.

Compared to the control group, women with PMDD were significantly more likely to have the ESR1 gene variants, the study found.

"While these are preliminary findings that require replication in larger studies, we would argue that this may explain part of the variance among women in the susceptibility to developing this mood disorder," Rubinow said. "Studies have shown that PMDD is characterized by abnormal sensitivity to reproductive steroids like estrogen. As a receptor for the hormone that can trigger the onset of PMDD symptoms, ESR1 has clear physiologic relevance for this disorder."

The authors acknowledge that as with other complex genetic disorders, the contribution to PMDD of polymorphisms in a single gene may not be large. In addition, they also noted that the findings may be telling us more about the control group.

These women, who have no history of psychiatric problems or menstrual cycle-related symptoms, may have gene variants that protect against

PMDD. According to Rubinow, "this is equally interesting because it may help us to understand resilience and protection, which are also very important."

Dr. Susan S. Girdler, professor of psychiatry and director of the UNC Psychiatry Stress and Health Research Program, pointed out that the severity of PMDD symptoms are as great or can be as great as those of women with full-blown major depression or major anxiety disorder. "But what makes them different is that the symptoms are very time-limited and linked strongly with the women's menstrual cycle."

Girdler emphasizes that to qualify for PMDD, symptoms must be severe enough to interfere with everyday functioning - to disrupt relationships, result in social withdrawal, even prompt thoughts of suicide. "We are talking about women who meet very stringent diagnostic criteria for PMDD. This is not the garden variety PMS."

Source: University of North Carolina School of Medicine

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