A team of researchers at the National Cancer Institute has found a possible link between genes responsible for regulating the circadian rhythm and the spread of a certain type of breast cancer. The team has posted a paper describing their study and results on the open access site [PLOS Genetics](https://doi.org/10.1371/journal.pgen.1006267).

The team found the gene by interbreeding mice more prone to metastatic breast cancer with low-risk mice and then looking at their genetic differences. Once the gene was isolated, the team edited it in some test mice and then monitored the development of cancers. Those injected with high amounts of Arntl2 showed much more metastatic growth than those given low doses. Convinced that they had found a link, the researchers tested human patients that had estrogen receptor negative breast cancer and found that those who had inherited highly active variants of Arntl2 were more likely to die due to their cancer spreading.

These findings suggest that disruptions to the circadian sleep pattern may put people with aggressive forms of cancer at higher risk of dying from metastasized cancer than those with normal sleep patterns, particularly those with the active variant of Arntl2.


**Abstract**

Breast cancer mortality is primarily due to metastasis rather than primary tumors, yet...
relatively little is understood regarding the etiology of metastatic breast cancer. Previously, using a mouse genetics approach, we demonstrated that inherited germline polymorphisms contribute to metastatic disease, and that these single nucleotide polymorphisms (SNPs) could be used to predict outcome in breast cancer patients. In this study, a backcross between a highly metastatic (FVB/NJ) and low metastatic (MOLF/EiJ) mouse strain identified Arntl2, a gene encoding a circadian rhythm transcription factor, as a metastasis susceptibility gene associated with progression, specifically in estrogen receptor-negative breast cancer patients. Integrated whole genome sequence analysis with DNase hypersensitivity sites reveals SNPs in the predicted promoter of Arntl2. Using CRISPR/Cas9-mediated substitution of the MOLF promoter, we demonstrate that the SNPs regulate Arntl2 transcription and affect metastatic burden. Finally, analysis of SNPs associated with ARNTL2 expression in human breast cancer patients revealed reproducible associations of ARNTL2 expression quantitative trait loci (eQTL) SNPs with disease-free survival, consistent with the mouse studies.


© 2016 Medical Xpress

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.