UW-Madison Researchers Find New Subtype of Breast Cancer

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(PhysOrg.com) -- An alteration in a gene not normally associated with breast cancer has been found in up to 20 percent of breast cancer tumors and may help predict which breast cancers are more likely to turn aggressive and recur, University of Wisconsin-Madison researchers have found.

This marks the discovery of a previously unrecognized molecular subtype of breast cancer. Because it appears in about 20 percent of all breast cancer, it could prove as important as the better-known altered version of the BRCA-1 and BRCA-2 genes, which each appear in about five percent of breast cancers.

Writing in the June 10 edition of *Public Library of Science Genetics (*PLoS Genetics*)*, a team from the UW Carbone Cancer Center identifies a splice (or a change) in a gene that normally suppresses tumor growth by producing a specific protein (known as RE1 silencing transcription factor or REST).

Lead author Avtar Roopra says that breast cancer tumors with the alteration in the REST gene are much more likely to recur quickly after the initial treatment, and to turn lethal. Breast cancer tumors with the normal form of the REST gene tend to recur, on average, in about 15 percent of cases and over a much longer time frame. But tumors with the altered form of the gene (giving rise to what they call RESTless tumors) are much more aggressive.

"About 50 percent of the women who had breast cancer in which the REST gene was spliced had their cancer return within three years," says Roopra, assistant professor of neurology in the School of Medicine and Public Health. "This gene could prove to be an important diagnostic tool."

Since breast cancer is a common name for many different diseases, the discovery also is an important step in personalized medicine - identifying some of the most aggressive forms of the cancer and suggesting a target to attack with new drugs. Testing breast cancer tumors for whether they are RESTless could help clinicians plan more effective treatment and reduce uncertainty for women desperate for more information.

Matthew Wagoner, a graduate student in the Roopra lab, says the finding will be important to clinicians because it will let them know which patients are more likely to have their cancer recur within a few years.

"What makes breast cancer so difficult to predict is that these tumors appear to the eye to be identical, yet we know that some cancers will come back and some won't," Wagoner says. "This gene could help predict which patients need to be watched more closely for a recurrence of cancer."

The REST gene seems to play a role in both estrogen-sensitive breast cancer and cancers that don't need estrogen to grow.

The gene also plays a role in epilepsy, which is another focus of the Roopra lab. In the nervous system, a normal REST gene produces REST protein which plays a role in how nerve cells develop, differentiate and function. Following an epileptic seizure, the REST gene in the brain undergoes splicing but then returns to normal after one to two days.

"This gives us a potential target for drug therapy because it suggests that

the splicing is potentially reversible," Roopra says. "We just have to find a way to tweak it back again."

Roopra says that after his sister was diagnosed with breast cancer, he became curious whether the REST gene played a role. The REST gene controls the action of about 2,000 other genes, by turning them on or off, and some of those affected genes pointed to the possibility that REST was important in cancer.

Wagoner created a screening tool to see if the altered gene was also present in breast cancer and discovered it in about 20 percent of breast tumors, which included some of the most aggressive tumors.

Provided by University of Wisconsin-Madison