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# First genetic link discovered to difficult-to-diagnose breast cancer sub-type

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Scientists have identified the first genetic variant specifically associated with the risk of a difficult-to-diagnose cancer sub-type accounting for around 10-15 per cent of all breast cancer cases.

The largest ever study of the breast cancer sub-type, called invasive lobular carcinoma, gives researchers important clues to the genetic causes of this particular kind of breast cancer, which can be missed through screening.

The research, published today (Thursday) in the journal *PloS Genetics*, was co-led by The Institute of Cancer Research, London, King's College London, and Queen Mary University of London. It used gene chip technology and complex statistical analysis to compare the DNA of more than 6,500 women with invasive lobular cancer with the DNA of more than 35,000 women without the disease.

The study involved more than 100 research institutions from around the world and was funded by several organisations in the UK including Breast Cancer Campaign, Cancer Research UK, Breakthrough Breast Cancer and The Institute of Cancer Research (ICR).

A woman with the genetic variant, called rs11977670, was found to have a 13 per cent higher chance of developing invasive lobular cancer than a woman without it. The variant is close to two genes on chromosome 7: BRAF, a known cancer-causing gene, and JHDM1D, which is involved in the activation and deactivation of other genes.

The discovery of the genetic variant, in conjunction with other markers, could help in the development of future genetic screening tools to assess women's risk of developing invasive lobular cancer, and also gives researchers important new clues about the genetic causes of the disease and a related precursor to cancer called lobular carcinoma in situ.

Invasive lobular carcinoma develops in the lobes of the breast that produce milk and can be particularly difficult to diagnose, because the cancer often does not form a definite lump and may not show up on mammograms. As a result, women with this type of cancer tend to be diagnosed when the cancer is more advanced and more difficult to treat.

As well as looking for new genetic risk factors, the researchers also evaluated 75 variants previously linked with breast cancer overall. They found that most of these were associated with risk of invasive lobular cancer specifically, as well as overall breast cancer risk.

The study also showed for the first time that genetic factors for invasive breast cancer can also predispose to lobular carcinoma in situ.

Study co-leader Professor Montserrat Garcia-Closas, Professor of Epidemiology at The Institute of Cancer Research, London, said:

"Our study is the first to link a genetic variant specifically with a higher risk of invasive lobular carcinoma, which accounts for around 10 to 15 per cent of all cases. It also finds that more than 50 previously discovered variants specifically increase the risk of lobular tumours, as well as making breast cancer overall more likely.

"Understanding the genetic factors at work in lobular cancers could be particularly important, because they are often missed by mammography because of their unusual growth patterns. In the future, we hope that improving our knowledge of the genes involved in lobular carcinoma

could improve our ability to prevent and treat it."

Study co-author Dr Elinor Sawyer, Clinical Reader in Oncology at King's College London and Guys and St Thomas' NHS Foundation Trust, said,

"A diagnosis of breast cancer can be devastating, particularly if it is not picked up early and the cancer is at a stage when it may be more difficult to treat. This can be the case for lobular breast cancers as they are difficult to see on mammograms. By identifying genetic factors that result in an increased risk of lobular cancer we hope in the future to be able to find better ways of assessing the risk of developing these cancers, so different screening tests can be offered to those at high risk, as well as finding new treatments for lobular cancer."

Dr Rebecca Roylance, Clinical Senior Lecturer at Queen Mary University of London, said:

"We know invasive lobular breast cancers can behave differently to other breast cancer types, as well as be more difficult to diagnose – both of which led us to believe there may be different genetic factors in their development. It is really exciting that our theories based on clinical observations have been confirmed by the identification of specific genetic changes in patients with invasive lobular breast cancer. The big challenge now is for these changes to be confirmed and for this information to be used for the benefit of patients."

Baroness Delyth Morgan, Chief Executive, Breast Cancer Campaign said:

"These results demonstrate just how vital it is to bring researchers together to collaborate in order to unlock the answers around genetics and risk for all sub-types of breast cancer. This could be the first step in

assessing who is at risk of developing this type of breast cancer that is so hard to diagnose.

"Breast Cancer Campaign is now funding the study's co-author Dr Elinor Sawyer for a further three years to understand what the new genetic variant found in this study could be doing within cells to increase breast cancer risk. Ultimately Dr Sawyer's work could improve the diagnosis and survival for women with this subtype of breast cancer."

Provided by Institute of Cancer Research