Genomic sequencing confirms breast cancer link between sisters

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Two Leicester sisters who had their entire genomes sequenced in the hope of finding answers to their family history of breast cancer have learned they both carry a genetic variant that significantly increases their

risk of developing the disease.

Mary and Sandra, together with their sister Kerry, all developed breast cancer within 13 months of each other. Their mother and two other close relatives had also been affected by breast cancer. Standard genetic testing of the most common genes associated with breast cancer, BRCA1 and BRCA2, proved inconclusive and so in 2015 they kindly agreed to be among the first cancer patients in the UK to join the 100,000 Genomes Project. Today it has been revealed that Mary and Sandra have a pathogenic DNA change in the PALB2 gene which was predicted to severely impair its function and increase the risk of breast cancer.

Kerry's tumor was not caused by the same PALB2 mutation. A fourth sister, Bethan, who did not have her entire genome sequenced with the other sisters, has recently learned that she also carries this PALB2 mutation. Sandra commented: "I rather know than not know. I mean, if you know [you are a carrier of the mutation] you can consider all the options available, such as to wait and see, have more monitoring like regular mammograms, or take preventative action with a mastectomy."

Dr. Julian Barwell, who is a consultant in clinical genetics at Leicester's Hospitals and an honorary professor in the Department of Genetics at the University of Leicester, said, "The findings help explain a great deal about why this family had such a high propensity for breast cancer.

It also gives insights into how to prevent new tumors in the future and provides a simple blood test to determine which relatives might also be at an increased risk so they can be monitored and, if necessary, given early preventative treatment. "The findings also suggest that families with a history of breast cancer who have had negative results with BRCA could consider testing for PALB2." To take part in the 100,000 Genomes Projects, each sister had their DNA extracted from a small blood sample and examined using a technique called Whole Genome

Sequencing (WGS). This procedure generated approximatively one billion individual small fragments of DNA, which were then lined up with the human genome sequence of reference, revealing more than four million DNA variants per individual. More specifically, all variants underwent an initial assessment in order to exclude subtle DNA changes that are normally present in the majority of people. This step reduced the number of variants from four million to 100,000, and then to approximately 400, which were then analyzed in detail.

Links between genes affected by these 400 variants and breast cancer were then investigated, allowing the positive identification of only one culprit gene. The final step was to confirm this genetic variation with Leicester's Hospitals' laboratory staff. To make this discovery possible, a team in the Department of Genetics and Genome Biology at the University of Leicester developed specific mathematical computer algorithms to hunt for the variant. Working with members of the Genomics England Clinical Interpretation Partnership (GECIP), they then applied this tailored algorithm to painstakingly analyze the variants to detect any potential links between single mutations and breast cancer.

Professor Carlo Rivolta, who is a professor at the Department of Genetics and Genome Biology at the University of Leicester, and who, with his Ph.D. student Mathieu Quinodoz, undertook the complex genetic analysis of the data, said: "The development of the algorithms allowing this discovery has been a difficult task for our lab, lasting a few years. However, results such as this repay us instantly from all the frustrating moments we experienced and the long hours spent in front of the computer." "Working with Leicester's Hospitals and Genomics England has enabled us to understand inherited disease even further. It is hoped that finding the culprit gene in this family could also lead to more targeted treatments, for them and other families in similar situations, in the future."

Professor Jacqui Shaw, director of the Leicester Precision Medicine Institute—a joint venture between the University of Leicester and Leicester's Hospitals, commented: "This study highlights how families have generously supported the 100,000 Genomes Project. For families that have undergone genetic testing in the past, but for whom no genetic links have been found to date, research like this provides hope that many families will be able to benefit from the new information that is coming out, which could be used to help personalize each patient's treatment to enable more people to live longer, healthier lives."

Professor Barwell added: "These types of partnerships through the 100,000 Genome Project have helped develop the newly established national Genomic Medicine Service that will oversee molecular testing. This aims to predict, detect and monitor diseases more effectively in the future and plan treatments and screening with more precision."

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