Breast cancer predisposition genes exposed

Scientists know that a subset of genes are linked to familial breast cancer. However, this link has yet to be clearly determined or ruled out for many newly emerging genes. The FBC predisposition project aims to clear up remaining doubts.

HEALTH

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Of all women affected by breast cancer every year, 5 % to 10 % of cases result directly from gene variants passed on from a parent. This is called familial breast cancer (FBC), and there is still much we don't know about it. In over 60 % of FBC cases, the genes responsible – although unequivocally present – remain undetermined.

The FBC predisposition (Unraveling novel Familial Breast Cancer (FBC) predisposition genes) project, supported by the Marie Skłodowska-Curie Actions programme, was set up with these cases in mind. Its goal is to identify novel genes and disease-causing variants in FBC and use them to improve patient monitoring and counselling. Claus Storgaard Sørensen, coordinator of the project on behalf of the University of Copenhagen, has been screening an FBC patient cohort of 135 early-onset patients since 2020, which has led to the identification of 270 new genes that may be involved in breast cancer onset.

Why are experts still unsure about the genetic predispositions of most FBC cases? What makes these genes particularly difficult to identify?

Claus Storgaard Sørensen: There are two major issues at play. Firstly, dozens of genes work together to limit genome instability and prevent cancer development such as FBC. Each gene encodes a protein that is comprised of hundreds of amino acids.

In principle, every single amino acid can be mutated in several ways (into other amino acids, deleted or duplicated). This all results in a very high number of possible mutations, some of which are neutral and show no negative effect. For all of the detected mutations, we need to conduct precision experiments to understand whether they are detrimental to patients. This is an enormous task spanning tens of thousands of mutations.

Secondly, BRCA1 and BRCA2 are the two best-characterised FBC genes, where many mutations are known to predispose FBC. However, BRCA1 and BRCA2 mutations only occur in a minority of FBC cases (frequently estimated to account for about 15 % of cases). Thus, we now need to identify the remaining genes that have so far managed to escape our research efforts. These new genes are less frequently mutated, which means that they are more challenging to identify.

How does your project overcome these difficulties and what makes your approach particularly innovative?

We have gathered a unique cohort of women with early-onset breast cancer, under 33 years old with no mutations in BRCA1/BRCA2. In all these patients, the genetic predisposition is very marked, but we clinicians have so far been unable to identify the cause. Next generation sequencing of blood samples has identified mutations in a number of genes that could be predisposing. Concretely, this means that these women may have inherited variants in new FBC-predisposing genes.

We investigated whether the flagged genes are involved in genome maintenance. This is done with parallel screens in human cell lines, where we downregulate all potential FBC genes. This has yielded a list of potential new FBC genes that serve to promote genome stability.

Speaking of results, what would you say is the most important outcome of the project so far?

The key finding is that we have now confirmed how new putative predisposition genes serve to maintain genome integrity or, in other words, hinder a key step in cancer development.

Have you identified specific predisposition genes yet? Can you tell us more about these?

This is still ongoing, but I can already tell you that the results are very promising. We do expect several of the genes to be bona fide FBC genes.

What do you still need to achieve before the project's end?

We need to characterise the mechanism of function of the new FBC genes, since we are not sure of how they function in cells to promote genome stability. We also need to establish whether mutations identified in our cohort display reduced function, that is, whether cells expressing mutated genes are prone to genomic instability.

What would be the ultimate benefits of your research for patients?

Our project will identify new tumour suppressors that will provide tools for early diagnosis and counselling. Our findings also hold promise for targeted cancer treatment, as several of the FBC genes protect cells against cancer therapies. Thus, when these particular genes are disabled by mutations, we can employ targeted treatments exploiting this cancer-specific vulnerability.

Keywords

FBC predisposition, breast cancer, familial breast cancer, BRCA1, BRCA2, genes, predisposition, mutations, genome

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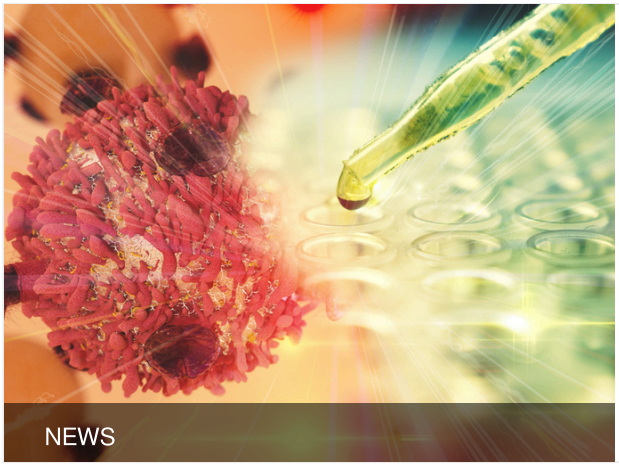

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