Three mutations at BRCA1 gene responsible for breast and ovarian hereditary cancer

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Researchers of the hereditary cancer research group at the Bellvitge Biomedical Research Institute (IDIBELL) and the Catalan Institute of Oncology (ICO) conducted a functional and structural study of seven missense variants of the BRCA1 gene concluding that three of these variants are pathogenic, linked to the risk of suffering breast or ovarian cancer. The study has been published in the journal *PLoS One*

The classification of these three variants will improve genetic counseling of patients and families who have these mutations and will serve to personalize the treatment.

Mutations in BRCA1 gene

Mutations in BRCA1 confer a high risk of developing breast or ovarian cancer. A woman carrying a mutation in this gene has a risk of developing breast cancer between 40% and 90% and of developing ovarian cancer between 20% and 70%.

According to the researcher Conxi Lázaro, "now we know a lot of genetic alterations in BRCA1 that are clearly pathogenic alterations, neutral alterations and sequence polymorphisms, but genetic diagnostic studies also identify changes in the DNA sequence which we don't know its biological significance."

For the researcher, finding out the biological consequences of these

missense variants is "a technological challenge, not only in breast cancer but in the field of genetic diagnostics in general."

Study of seven missense variants

The study analyzes seven BRCA1 gene variants from a structural and functional standpoint. Structural analysis is a theoric-computational analysis and compares the three-dimensional structure of normal protein with the analyzed changes. The researchers conclude that three of the seven variants analyzed modify the structure of the protein.

"In the functional study," said the researcher, "we analyzed in vitro one of the key functions of BRCA1: regulation of transcription. The analysis involves the generation of mutants of all variants in specific vectors to assess the transcriptional activity of the mutant compared to the control activity of the wild-type sequence of the BRCA1 gene.

From this analysis, the researchers concluded that three of the seven variants of unknown biological significance are actually pathogenic and will serve clinicians to a better genetic counseling to patients and families that present these variants, allowing personalized risk assessment cancer.

Genetic counselling

The knowledge of the clinical effects of these mutations will allow to offer genetic counselling to families. "To the individuals who carry the mutation we can offer a comprehensive clinical monitoring and the possibility of reproductive options, such as prenatal or preimplantation diagnosis", said Lazaro, "while members of the family who doesn't have the mutation can be considered as general population".

More information: Quiles F., Fernández-Rodríguez J., Mosca R, Feliubadaló L., Tornero E, Brunet J., Blanco I., Capella G., Pujana M.A., Aloy P., Monteiro A., and Lázaro C.. (2013) Functional and structural analysis of C-terminal BRCA1 missense variants. *PLoS ONE* 8(4): e61302. doi: 10.1371/journal.pone.0061302