Genetic cause found for premature ovarian failure

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A team led by researchers from the Spanish National Research Council and the University of Salamanca has found a genetic cause for premature ovarian failure, a disorder affecting 1 percent of women that provokes the loss of ovarian function years before menopause.

The results, published in *The New England Journal of Medicine* and *Human and Molecular Genetics* journals, demonstrate for the first time that mutation in STAG3 gene is the major cause of human fertility disorders as it provokes a loss of function of the protein it encodes.

STAG3 encodes a meiosis-specific subunit of the cohesin ring, the biological process through which, from a diploid somatic cell, a haploid cell or gamete is produced. Cohesins are protein complexes that bind two straps of DNA and are implicated in its repair, replication and recombination, as well as in its chromosomal stability, transcription regulation, stem-cell pluripotency, and cell differentiation.

Alberto M. Pendás, CSIC researcher at the Cancer Research Center (USAL/CSIC), states: "Our work enables us to causally relate mutations in a gene of the cohesin complex with human infertility. It also demonstrates for the first time in humans that POF and azoospermia, a disorder that impedes normal sperm production, are probably the two faces of the same genetic disease".

Genetic study in a family

Researchers have identified, through the analysis of samples obtained from a consanguineous Middle Eastern family, a region on chromosome 7q21 that has significant linkage with POF. In collaboration with US and French researchers, they have performed the whole-exome sequencing, the fraction of the genome that encodes proteins, of the DNA provided by two sisters within this family, being one of them healthy and the other one sterile. Through the combination of linkage data and exome sequencing, they have identified a deletion or loss of a single base in the gene encoding STAG3, which results in a prematurely truncated protein without function.

CSIC researcher adds: "We have confirmed that mutation is found in both copies of the gene, one inherited from the father and the other one inherited from the mother, in the four women affected by the disease, causing an absolute absence of STAG3 protein and meiotic cohesin complex in these women. Likewise, all the unaffected members have at least one of the two copies of the non-mutated STAG3 gene, which further supports that this is responsible for the POF".

The proof that STAG3 mutation is the cause of the disease has been achieved by generating mutant mice of this gene. The analysis of female mice has revealed that, same as the affected women, the absence of STAG3 provokes the disease.

In previous studies, researchers proved in mice that genes of the meiotic cohesin complex produce various degrees of infertility in mice. Pendás explains: "Now, the analysis of this STAG3-deficient mouse has enabled us to corroborate that is a cause of female sterility and a very strong candidate for male infertility".

More information: Elena Llano, Laura Gómez-H3, Ignacio GarcÍa-Tuñón, Manuel Sánchez-Martín, Sandrine Caburet, José Luis Barbero, John C. Schimenti, Reiner A. Veitia, y Alberto M. Pendas. STAG3 is a

strong candidate gene for male infertility. *Human Molecular Genetics*. DOI: 10.1093/hmg/ddu051