A pipeline for prioritization of putatively damaging genetic variants in cases of oocytes/embryo developmental arrest.

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Failure of embryo development can happen at several stages, namely maturation of the oocytes, fertilization, and before/after implantation. Causes might be both environmental and genetic. Among the last, mutations affecting genes involved in fundamental processes of oocyte fertilization and embryo development are candidates for unexplained infertility investigations.

We developed the GP pipeline to prioritize putatively damaging genetic variants in coding regions, based on the prediction of the functional effect of the variants. Our pipeline can incorporate prior information on genes involved in the trait under study, but is also robust to the discovery of novel genes.

We applied the GP pipeline in pre- and post-implantation phenotypes in women and embryos respectively. From the analysis of 22 maternal exomes we identify 987 unique variants in 880 genes. Genome-wide functional validation revealed that 87.8% of the prioritized genes harboring high-impact variants are expressed by individual human mature oocytes and/or in the antral granulosa cells. From the analysis of the whole-genome of 10 euploid miscarried embryos we prioritized 439 putatively causative single nucleotide polymorphisms in 399 genes. Among the prioritized genes in the embryos we found *STAG2* coding for the cohesin complex subunit, for which inactivation in mice is lethal, and *TLE4* a target of Notch and Wnt, physically interacting with a region on chromosome 9 associated with miscarriages.