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

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Infertility is an increasingly common global health issue affecting around 18% of reproductive couples in developed countries. **Failure of embryo development** can happen at several stages, namely maturation of the oocytes, fertilization, and before/after implantation. Isolated mutations affecting genes involved in fundamental processes of oocyte fertilization and embryo development are potential candidates for unexplained infertility investigations.

AIM OF THE STUDY

To **identify genetic variants** affecting genes involved in fundamental processes of oocyte fertilization and embryo development

APPROACH

To build a predictive model that integrate genomic variation and functional annotations, based on the analysis of **whole-genome and whole-exome sequences of infertile women or miscarried embryos**

PIPELINE

STUDY POPULATIONS

1) 22 infertile women showing distinct phenotypes
2) 46 embryos from pregnancy loss

CONTROL POPULATIONS

Human Genome Diversity Project
- 929 healthy individuals
- whole genome sequence

Oocyte donors from Igenomix Dataset
- 1343 individuals
- whole exome sequence

100 REPLICATES
(Sampling with replacement)

VARIANT PRIORITIZATION

- **HIGH or MODERATE impact** (as estimated by Ensembl)
- **Allele Frequency <0.05** (1000 Genomes and gnomeAD)
- **Loss of function intolerant genes** (pLI >0.9) and **deleterious variants** (CADD >0.9 percentile) OR in genes relevant to the **early embryonic development**

CONTROL FOR FALSE POSITIVES

1. *GENE LENGTH AND PSEUDOGENES*
2. *EXCLUDE FREQUENTLY OCCURRING GENES*

RESULTS

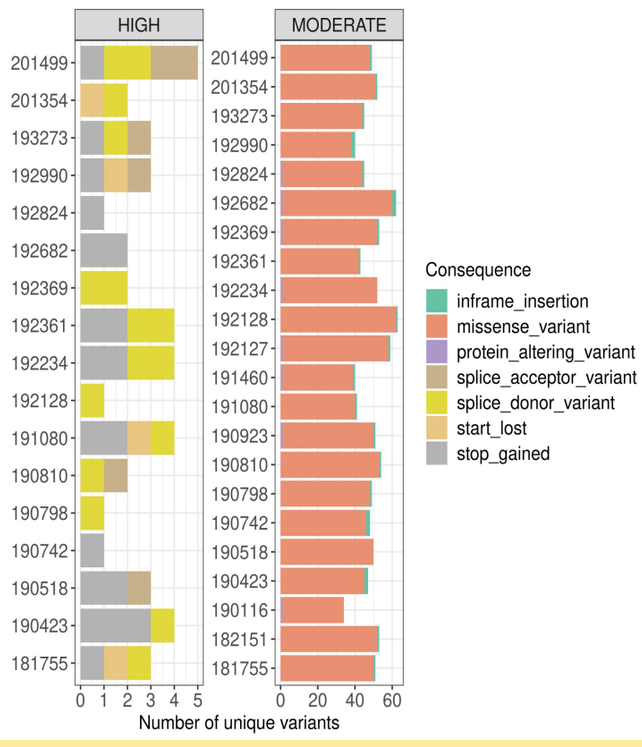
1. OOCYTE MATURATION DEFECTS AND PREIMPLANTATION DEVELOPMENT ARREST

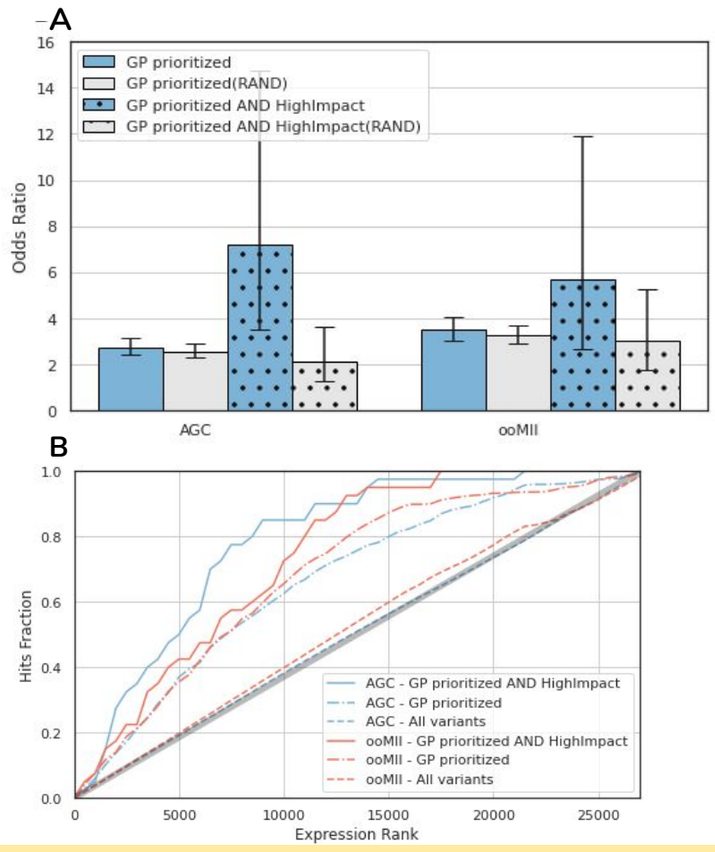
11221 infertile women

22 patients with oocyte maturation defects (OOMD) and preimplantation embryonic lethality (PREMBL)

Whole exome sequencing

60.5 ± 3.55 variants per individual are retained after prioritization

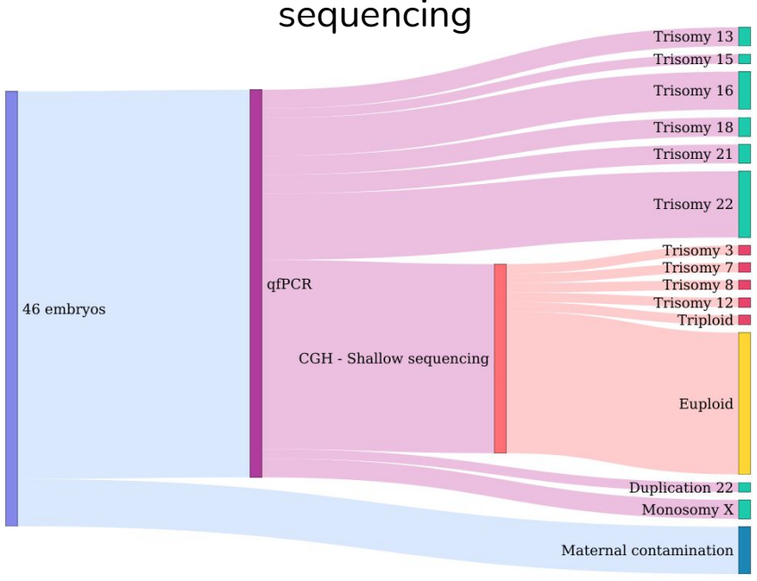




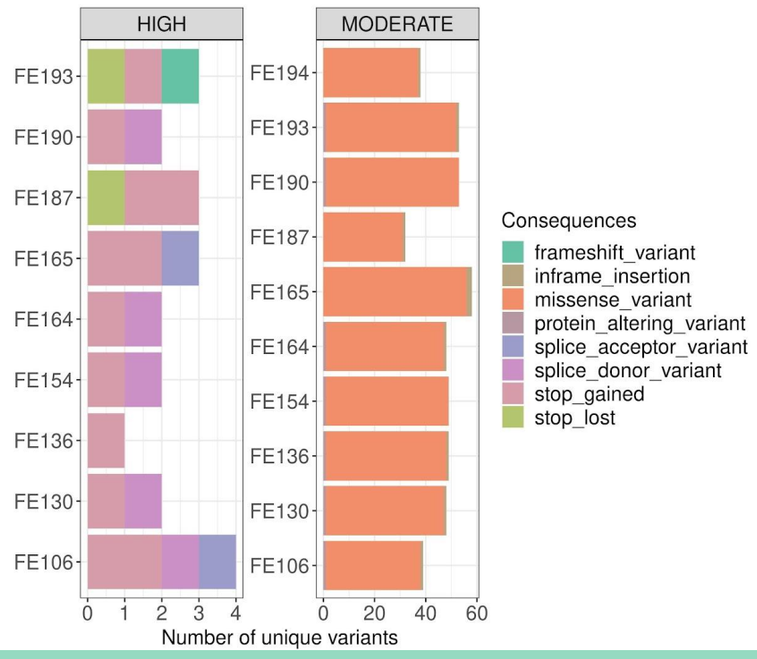
(A) Odds ratios between genes expressed in Antral Granulosa Cells and MII Oocytes, and gene prioritized according to different criteria (B)Quantitative gene expression analysis.

2. EMBRYO DEVELOPMENT ARREST

46 embryos are screened to determine aneuploidies. 30% of embryos is euploid and is analysed by whole-genome sequencing



48.9 ± 8.02 variants per individual are retained after prioritization



Variants in 60 genes are shared among samples

CONCLUSION AND FUTURE PERSPECTIVES

Whole genome and whole exome sequencing can help to clarify the causes of different infertility phenotypes. The pilot study described here discovered plausible candidate infertility-associated variants and provides essential indications for the realization of a larger study.

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