A NOVEL VARIANT IN RNF212B AND ITS CONTRIBUTION TO FEMALE INFERTILITY AND RECURRENT PREGNANCY LOSS

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Background

Women with genetic causes of infertility are more likely to experience recurrent pregnancy loss (RPL) [1]. Only a small subset of genes have been implicated in human infertility, and an even smaller proportion have shown a strong association with female infertility [2]. Modern advancements in whole genome sequencing have allowed for the detection of various genes involved in the pathogenesis of infertility [3] [4]. One reproductively young patient with a history of RPL underwent three in vitro fertilization (IVF) cycles with nearly complete arrest of blastocyst development and ubiquitous aneuploidy of maternal origin in her arrested embryos. The cause of her RPL and uniquely abnormal embryos was unknown.

Objective

Present the discovery of a novel gene variant, RNF212B, previously only implicated in two cases of male-factor infertility, as a possible genetic cause of infertility and RPL

Materials and Methods

To investigate a potential genetic determinant of this patient's phenotype, DNA was extracted from white blood cells and submitted for WGS at 30x coverage using the Illumina short read platform. Data preprocessing, alignment, and variant calling were performed using the GATK best practice pipeline for germline short variant discovery with the reference genome hg38 [1]. Variant annotation was conducted using ANNOVAR [5]. The initial analysis targeted known genes associated with male and female infertility, however none of these genes harbored variants that were either clinically relevant or predicted to be damaging to the protein [5]. The investigation was expanded to encompass the entire genome with refined focus on variants likely to be pathogenic or those that are putative loss-of-function, in accordance with ACMG's interpretation guidelines [6]. After filtering out variants with gnomAD allele frequencies exceeding 0.25%, we identified a total of 87 unique variants. Notably, none of these variants had ClinVar annotations linked to infertility, childlessness, or miscarriage. A literature search was conducted on each of the remaining 87 genes to identify potential associations with infertility.

Results

Trophectoderm biopsy, multiple displacement amplification and targeted next generation sequencing (tNGS) of the arrested embryos revealed extensive aneuploidies affecting many chromosomes [Figure 1]. The contribution was noted to be maternal in origin. The female patient was identified as being homozygous for a stop-gain mutation in the RNF212B gene (chr14-23262678-C-T (hg38). RNF212 has been shown to interact with proteins involved in meiotic recombination, such as recombinase DMC1 and DNA repair protein RAD51 [6]. Most recently, RNF212B has been implicated in male infertility, with men found to be homozygous carriers of the same stop-gain variant found in our patient [7]. Our female patient's multiple IVF failures, with recurrent and widespread aneuploidy of maternal origin detected in her embryos, provide supporting evidence that the pathologic RNF212B variant may be the causative variant in both male- and female-factor infertility in patients who are homozygous for the mutation.

Conclusions

The homozygous nonsense mutation resulting in the RNF212B variant may be responsible for the presence of aberrant oogonium and disrupting the meiotic recombination process, thereby causing female infertility and RPL.

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FIGURE 1: Patient's embryo sample showing widespread genomic triploidy [from JUNO Genetics]