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Title:
WHOLE GENOME SEQUENCING REVEALS COMMON GENETIC PATHWAYS UNDERLYING OVARIAN FUNCTION DISORDERS

Authors:
Berro R[1], Hu Seliger T[1], Parfitt DE[1], Globus ST[1], Miller BT[2], Gutmann JN[3], Arredondo F[4], Nulsen JC[5], Copperman AB[6], Yurttas Beim P[1]

Affiliations:
1: Celmatix Inc., New York, NY 2: Reproductive Medicine Associates of Michigan, Troy, MI 3: Reproductive Medicine Associates of Philadelphia, Philadelphia, PA 4: Reproductive Medicine Associates of Texas, San Antonio, TX 5: Center for Advanced Reproductive Services at University of Connecticut, Farmington, CT 6: Reproductive Medicine Associates of New York, New York, NY

Background:
Ovarian function disorders are currently classified into distinct diagnoses, based on the clinical manifestation of each condition. Premature decline in ovarian reserve and function often results in a diagnosis of diminished ovarian reserve (DOR) or primary ovarian insufficiency (POI), while ovulatory dysfunction in the context of metabolic disorders and excess androgen is often characterized as polycystic ovary syndrome (PCOS). Given that molecular events leading up to these conditions occur in similar compartments within the ovary, it is possible that the same molecular players may be involved in their etiology.

Objective:
We aimed to identify genetic pathways altered in women across a spectrum of infertility diagnoses.

Materials and Methods:
Our retrospective cohort consisted of more than 200 women seeking fertility treatment at five academic and private fertility clinics in the US. Women in our cohort were diagnosed with PCOS, DOR, POI, or received an idiopathic diagnosis. As a control, we also included women with tubal factor and women whose partners were diagnosed with male factor. Genomic DNA was extracted from blood and whole genome sequences (with an average read depth of 30X) were generated using the Illumina HiSeq platform. Sequences were analyzed using GATK best practices. Single nucleotide variants (SNVs) predicted to disrupt gene function were identified using SNPeff and filtered using an in house fertility-centric bioinformatics pipeline that incorporated pathway analysis tools. The Database for Annotation, Visualization and Integrated Discovery (DAVID) pathway analysis tool was used for gene annotation into functional pathways.

Results:
We observed that 141 genes, in total, were disrupted by deleterious sequence alterations in woman diagnosed with ovarian function disorders (POI, DOR, and PCOS). Most genes clustered into 10 biological pathways. We found that female gonad development and ovulation pathways were altered in all

3 ovarian function disorder cohorts, but not in the tubal patients or those whose partners were diagnosed with male factor. Beyond these shared pathways, women diagnosed with DOR also had alternations in DNA repair pathways, and women diagnosed with PCOS had alterations in glucose and hormone metabolism pathways. Interestingly, the subclinical, idiopathic infertility patients had disruptions in several of the pathways that were disrupted in patients with clinical infertility diagnoses.

Conclusions:

Using a whole genome approach, we identified pathway-level genetic defects in women with infertility. While some of these deleterious alterations were shared, others were diagnosis-specific.

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