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Researchers identify causes and mechanisms of polycystic ovary syndrome using family-based genetic analysis

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A first-of-its-kind study using family-based genetic analysis has confirmed a gene involved in male hormone production, DENND1A, plays a major role in the development of polycystic ovary syndrome (PCOS). The discovery will enable personalized medicine approaches to PCOS, including better disease prediction. The findings are available online in *The Journal of Clinical Endocrinology & Metabolism*.

PCOS is among the most common endocrine conditions in reproductive-age women and is the leading cause of infertility and type 2 diabetes. The cause of PCOS is unknown, but there is a strong inherited susceptibility to the disorder. A number of common PCOS genetic variants that slightly increase disease risk have been mapped in previous genome-wide association studies, however the genes found to date account for only a small amount of PCOS disease risk.

"PCOS is a major cause of female infertility and is associated with other serious health problems," said one of the lead authors of the study, Andrea Dunaif, MD, Chief of the Hilda and J. Lester Gabrilove Division of Endocrinology, Diabetes and Bone Disease at the Icahn School of Medicine at Mount Sinai. "Our findings provide important new insights into the mechanisms by which genetic variation causes PCOS. The rare genetic variants we found may be much better for predicting the condition than the common variants. Further, targeting pathways regulated by this gene could lead to new therapies for the condition."

In the study, the researchers explored the genetic basis of PCOS by conducting whole-genome sequencing on DNA from the members of 62 families of women with PCOS. These families included both parents and one or more reproductive-age daughters with PCOS as well as unaffected daughters. Bioinformatic analyses were performed to determine which genes contained variants that were likely to be damaging. Only genes that were inherited from a parent were included for further analysis.

Dr. Dunaif and her colleagues found that reproductive and metabolic hormone levels were associated with rare genetic variants in DENND1A in approximately half of the families. This gene is important in testosterone production in the ovary; increased ovarian testosterone production is a major hormonal abnormality in PCOS. The findings indicate that this type of genetic variation contributes to the distinctive hormonal profile of the disorder.

The research was begun by Dr. Dunaif at Northwestern University Feinberg School of Medicine and completed at the Icahn School of Medicine Mount Sinai.

"After sequencing the entire genomes of many families affected by the disease, this has enabled us to study how certain rare genetic variants are associated with PCOS," said Geoffrey Hayes, Ph.D., Associate Professor in the Department of Medicine—Endocrinology, Metabolism and Molecular Medicine at Northwestern University Feinberg School of Medicine, and co-lead lead author of this study. "We hope our results will help uncover some of the involved hereditary mechanisms and ultimately teach us more about the molecular drivers of the disorder."

Provided by The Mount Sinai Hospital