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TITLE

FUNCTIONAL ANALYSIS OF PCOS GENES

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ABSTRACT

Genome wide association studies (GWAS) have identified some 22 loci associated with PCOS. The DENND1A locus has been associated with PCOS in a number of association/replication studies. PCOS theca cells were found to have increased level of a truncated variant of DENND1A protein (variant 2). This protein is associated with clathrin coated pits and appears to play a key role in recycling and downstream signaling triggered by ligands binding to plasma membrane-associated receptors. Functional studies in which normal human theca cells have been forced to overexpress a DENND1A variant produce increased amounts of androgens and have elevated CYP17A1 expression. Conversely, knockdown of the DENND1A variant in PCOS theca cells reduces androgen production and CYP17A1 expression. A transgenic mouse expressing human DENND1A variant 2 abnormally expressed Cyp17a1 in the adrenal glands and adrenal cells secreted cortisol rather than corticosterone, linking DENND1A variant 2 to increased expression of steroidogenic enzymes involved in androgen biosynthesis. The elevated DEND1A variant expression in PCOS theca cells appears to be related to genetic and epigenetic mechanisms including genetic variation, reduced DNA methylation state and reduced levels of microRNA 125a-3p, which targets DENND1A variant 2 transcripts.

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