Alternative splicing of the androgen receptor in ovulatory dysfunction

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Abstract
Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders and a leading cause of female subfertility. The mechanism underlying the pathophysiology of PCOS remains to be illustrated. Here, we identify two alternative splice variants (ASVs) of the androgen receptor (AR), insertion and deletion isoforms, in granulosa cells (GCs) in ~62% of patients with PCOS. AR ASVs are strongly associated with remarkable hyperandrogenism and abnormalities in folliculogenesis, and are absent from all control subjects without PCOS. Alternative splicing dramatically alters genome-wide AR recruitment and androgen-induced expression of genes related to androgen metabolism and folliculogenesis in human GCs. These findings establish alternative splicing of AR in GCs as the major pathogenic mechanism for hyperandrogenism and abnormal folliculogenesis in PCOS.