

ARTICLE

CYP17A1 Network Analysis in Ovarian Serous Cystadenocarcinoma for Retrieval of Polycystic ovaries Targets

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Competing interests

The authors declare no competing interests.

Abstract

Background/Aims: CYP17A1 is great metabolic switch for androgen overproduction which is hallmark of polycystic ovary syndrome (PCOS) initiation and progression. There is an urgent need to determine CYP17A1 mediated set of metabolic therapeutic targets for PCOS to control androgen synthesis with wide range of molecular options.

Methodology: We apply rational in silico approach for determination of PCOS comprehensive set of drug targets. First, we retrieve CYP17A1 network dataset from STRING database (<https://string-db.org/>) by querying CYP17A1 name that gives us updated 30 nodes containing network with unique options of enrichment analysis and module extraction. The enrichment analysis determines CYP17A1 network involvement in steroidogenesis process with carcinogenesis and drug metabolism. We select ovarian serous cystadenocarcinoma dataset from cBioPortal server (<https://www.cbioportal.org/>) for CYP17A1 network differential analysis.

Results: In this study, several steroid synthesis pathway members showed overexpression including SRD5A1, AKR1C3, CYP11B1, CYP11B2, CYP7A1, AKR1C1, AKR1D1, CYP7B1, CYP21A2, POR and HSD17B8 and are ideal biomarkers that provide cell cycle energy requirements for ovarian carcinoma. Few anti-androgenic members such as HSD17B2, STS, SULT2B1 and CYB5A showed down regulation that predicts the impact of hyper androgenemia on carcinogenesis. Drug metabolism components also showed up regulation which can be potential biomarkers for drug resistance in chemotherapies.

Conclusion: Our work suggests androgen and its synthesis pathway paramount in tumorigenesis and is an excellent therapeutic target in ovarian carcinoma. In future, validation of CYP17A1 network as a signature in both ovarian serous cystadenocarcinoma and PCOS dataset may lead to novel shared therapeutic combinations and tremendous syndrome-syndrome molecular linkage for personalized medicine.

Key words: Hyperandrogenemia, Ovarian cystadenocarcinoma, PCOS and steroidogenesis

Introduction

Polycystic ovary syndrome (PCOS) is multifaceted endocrine syndrome that disturbs 5 to 20% of reproductive age women, and a major cause of anovulatory infertility and hirsutism (Azziz et al., 2016). PCOS is a collection of metabolic maladies such as diabetes, glucose intolerance, hypertension, dyslipidemia and hepatic steatosis (Gunning & Fauser, 2017). The chronic anovulation, hyperandrogenism, polycystic ovarian morphology and ovulatory dysfunction are key components for the primary diagnosis of PCOS (Bulsara et al., 2021).

PCOS is an intrinsic ovarian syndrome produced by overexpression of androgen synthesis cascade. Luteinizing hormone (LH) level elevation also directly affects androgen synthesis by regulating LH receptor and CYP17A1 expression regulation (Heidarzadehpilehrood et al., 2022). In response to LH, ovarian theca cells produce androgens by regulating P450c17 enzyme encoding CYP17A1. This further catalyzes 17 α -hydroxylase and 17, 20-lyase activity which are significant factors involved in steroidogenesis. The 17 α -hydroxylase and 17, 20-lyase activity is inhibiting in a paracrine/autocrine negative feedback fashion through androgen and estrogen pathways. CYP17A1 and LH receptor showed up regulation through collective effect of insulin

and IGFs stimulations that ultimately enhances androgen synthesis. PCOS affected ovaries generally overcome LH receptor down regulation problem to build LH hypersensitivity process. The hyperinsulinemia and insulin resistance are exogenous factors that interrupt normal intra-ovarian regulatory mechanisms (Gingras et al., 2001; Rasmussen et al., 2013; Al Alawi et al., 2019; Simard et al., 2005).

The theca cell hypertrophy has abnormal expression of ovarian steroidogenesis responsible pathway genes (Dadachanji et al., 2018). The ovarian follicles development, oocytes maturation and steroid hormones synthesis are done in ovary. The steroidogenesis process triggered through converting cholesterol precursor to biologically active steroid hormones via androgen, estrogen, glucocorticoid, mineralocorticoid and progestin steroidogenic enzymes. The whole steroidogenesis process consists of multiple specific steroid reductases, hydroxysteroid dehydrogenases (HSDs) and cytochrome P450 enzymes (CYPs) (McGee & Hsueh, 2000; Miller & Auchus, 2011).

The theca cells mediated steroidogenesis dysfunction is triggered by various genetic/epigenetic mechanisms like cortisone reductases deficiency (Dadachanji et al., 2018). The digenic mutations in 11 β -hydroxysteroid dehydrogenase (11 β HSD) type I and hexose-6- phosphate dehydrogenase are reported in various PCOS affected women. When cortisone does not convert into cortisol, upregulates ACTH expression and leads to androgen synthesis under 11 β -HSD type I deficiency (Moggetti et al., 2013; Lizneva et al., 2016; Celik et al., 2016; Rosenfield & Ehrmann, 2016; Ashraf et al., 2019; Goodarzi et al., 2015; Louwers et al., 2013; Draper et al., 2003). There is an urgent need to delineate the association of *CYP17A1* network genes differential expression that encodes steroidogenesis enzymes as significant modulator of hyperandrogenism for PCOS development and progression.

Methodology

CYP17A1 network retrieval, pathway enrichment and clustering

STRING v11.0 (www.string-db.org) is a database that integrate all protein-protein interaction (PPI) information and provides user friendly interface for dataset analysis to serve system biology approach of bioinformatics. *CYP17A1* network was retrieved using STRING v11.0 based on confidence a scoring pattern 0.4-0.7 lower to higher binding affinity. Here, a query for *CYP17A* was set by selecting 0.7 highest confidence score, molecular interaction mode of network and highest number of interactors. After displaying network, STRING database allows us to manually arrange various proteins into specified positions and finally export the network in PNG format.

Pathway enrichment analysis of input protein-oriented network was further performed by well-known KEGG database pathway repository (<https://www.genome.jp/kegg/pathway.html>). Ideal relevant nodes from KEGG pathway table with diverse coloring fashion were selected. Finally enriched networks were exported in PNG format. To further extract functionally similar clusters of proteins, cluster option of database and K-MEANS algorithm with 5 modules were selected in STRING database. It displayed different coloring zones which are representation of separate functional modules. *CYP17A1* network modules based on same color identity were adjusted and finally exported in PNG format.

CYP17A1 network differential analysis in ovarian serous carcinoma

cBioPortal server (www.cbioportal.org) is a user-friendly interface that has a vast amount of TCGA and TARGET platforms generated molecular data of various tumors. *CYP17A1* network in ovarian serous cystadenocarcinoma through cBioPortal server was analyzed by exploring its differential expression. The cancer genomics server provided OncoPrint tab for differential expression representation and results were finally exported in PNG format.

CYP17A1 network analysis in PCOS

PCOSBase (www.pcosbase.org) has PCOS-related 8185 proteins, 1004 pathways, 7936 domains and 320472 interactions. The database has easy to access interface for differential expression analysis by querying individual genes to determine their association with PCOS by selecting Resources option. *CYP17A1* network in PCOS dataset was further analyzed using PCOSBase.

Results

CYP17A1 network retrieval

CYP17A1 network from STRING database that consist of 30 nodes and 220 edges was obtained. The query node located in center of network with interactions on periphery based on confidence score. The network blue line indicates binding interaction among various members and yellow lines represents transcriptional regulation with unspecified nature. In this network *CYP17A1* has majority of interactions with their own cytochrome 450 family members which are involved in diverse metabolic processes including sexual development and steroidogenesis (Figure 1A).

CYP17A1 network pathway enrichment analysis

Majority of network members are involved in steroidogenesis by red color representation. Steroid hormones have two types such as sex steroids and corticosteroids in which progesterone, estrogen, androgen (sex steroids), mineralocorticoid and glucocorticoid (corticosteroid). The steroid hormones are involved in water/salt balance, sexual development, immune system mediated metabolism and inflammation. *CYP17A1* network 4 members with green color representation are involved in drug metabolism in liver for easier elimination without side effects. These members are involved in drug metabolism significant reactions including condensation, hydration, hydrolysis, Oxidation and Reduction. The 6 members are involved in chemically induced carcinogenesis by initiation, promotion and progression stages. These stages have own morphological and physiological genetic/epigenetic deregulations which are inducer of rapid cell proliferation (Figure 1B).

CYP17A1 network module extraction

5 modules from network based on functional similarity including *CYP17A1* cluster contains 14 members, *CYB5A* cluster contains 2 members, *CYP1A1* cluster contains 4 members, *CYP3A5* cluster contains 3 members and *SRD5A1* cluster has 7 members were extracted. *CYP17A1* modules members are involved in CytochromeP450 proteins in mitochondria to metabolize either endo/exogenous chemical. This family of proteins is active in cholesterol synthesis, vitamin D metabolism and hormone synthesis. *CYB5A* cluster is

involved in reduction of ferric hemoglobin to ferrous hemoglobin. CYP1A1 cluster is involved in PUFAs metabolism that regulates arachidonic acid metabolism. CYP3A5 cluster is involved in NADPH-dependent electron transport pathway. SRD5A1 cluster involve in conversion of testosterone into the more potent androgen (Figure 1C).

CYP17A1 network differential analysis in ovarian serous carcinoma

Whole CYP17A1 network in ovarian serous cystadenocarcinoma TCGA were analyzed. Provisional dataset comprises of 311 samples in which 199 samples showed alterations of 64% network involvement in carcinoma. Majority of members showed amplification in terms of overexpression. Whereas a few numbers of samples showed mixed deletion/missense mutation leading to down regulation of key genes. The SRD5A1, AKR1C3, CYP11B1, CYP11B2, CYP7A1, AKR1C1, AKR1D1, CYP7B1, CYP21A2, POR and HSD17B8 showed significant up regulation. The HSD17B2, STS, SULT2B1 and CYB5A have important deletions in various samples that indicate lower expression. The CYP17A1 showed equal rate of amplification and deletion in samples that makes it diverse functional frame for metabolic engineering (Figure 2).

Discussion

CYP17A1 has great influence in androgen synthesis which is major contributor of PCOS. There are very limited studies to determine the association of CYP17A1 network level involvement in PCOS purely based on differential expression pattern. In this study *in silico* protocol explore various novel PCOS drug targets which are heavily participate in ovarian cystadenocarcinoma development and progression.

In this study we used network biology approach to extract linked co-targets for PCOS advanced therapeutics. We obtain 5 functionally similar modules in which CYP17A1 module is largest cluster has 14 members i.e. CYP11B1 (33%) and CYP11B2 (33%) has highest overexpression. The CYP11B/CYP11B2 involved in cortisol generation and mineralocorticoid biosynthesis. The CYP7A1 (9%) overexpression involve in bile acid synthesis. The CYP7B1 (7%) overexpression involve in steroid metabolism and its substrates are androgens precursor (Pallan et al., 2015; Vaidya & Carey, 2020; Alvarez-Madrado et al., 2013; Laing et al., 2019; Saha et al., 2021; Kuban & Daniel, 2020; Dulos et al., 2004; Rainey et al., 2004; Kim et al., 2003; Katyare et al., 2006; Hu et al., 2021; Nelson et al., 2013; Wu et al., 2013).

The CYP21A2 (6%) over expression has role in drug metabolism, cholesterol production. The HSD17B8 (5%) overexpression participate in estradiol synthesis The CYP11A1 (2%) overexpression involve cholesterol transformation into pregnenolone. The HSD3B1 (2%) overexpression involve in progesterone production. The HSD17B2 (3%) down regulation involve in androgens inactivation as anti-androgenic. The STS (3%) down regulation involve in steroidogenesis from sulfated steroid precursors and play role in endometriosis, breast cancer and prostate cancer (Lao & Merke, 2021; Keen-Kim et al., 2005; Villar et al., 2007; Miller, 2017; Taneja, 2017; Wang et al., 2016; Mueller et al., 2015; Rižner, 2016).

In SRD5A1 cluster AKR1C1, AKR1D1 and AKR1C3 has 10% amplification that leads to upregulation. AKR1C1 involve in

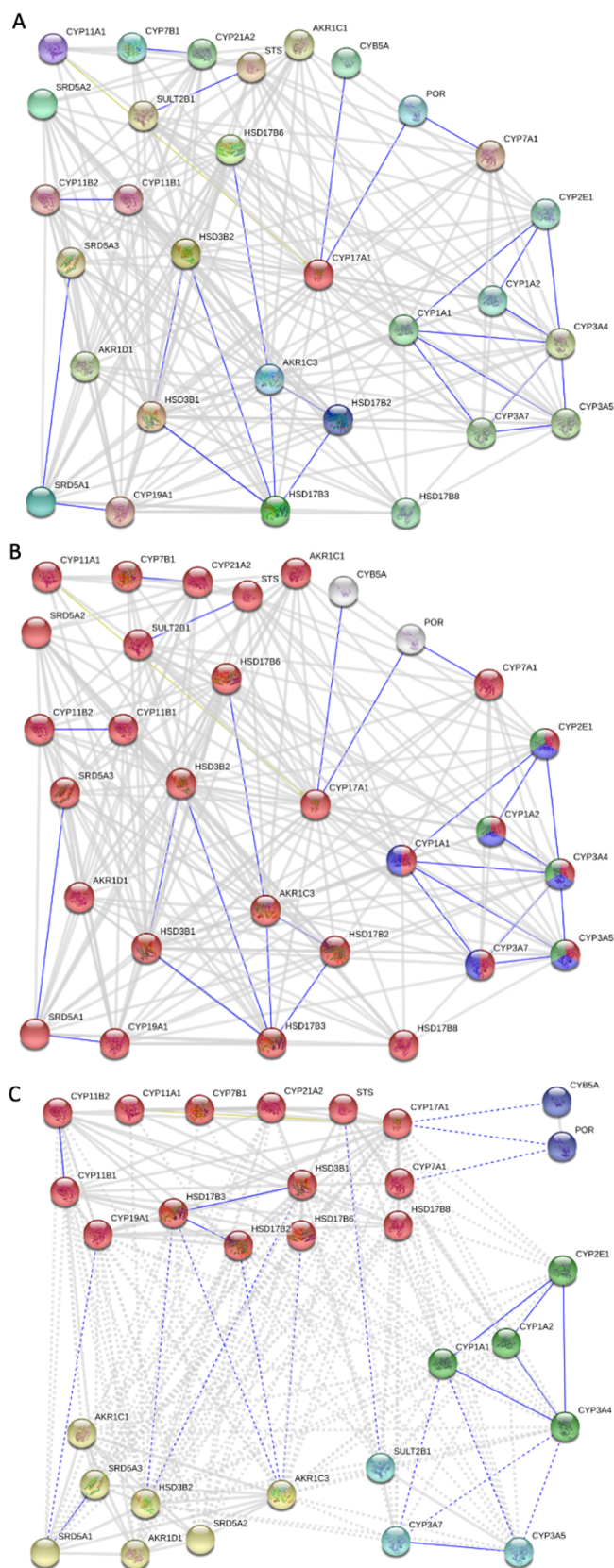


Figure 1: CYP17A1 network retrieval, pathway enrichment and clustering. (A): CYP17A1 network showing the interaction of specific genes of interest. (B): CYP17A1 network pathway enrichment analysis highlighting the interaction of selected genes. (C): CYP17A1 network modules highlighting the key genes related to PCOS.

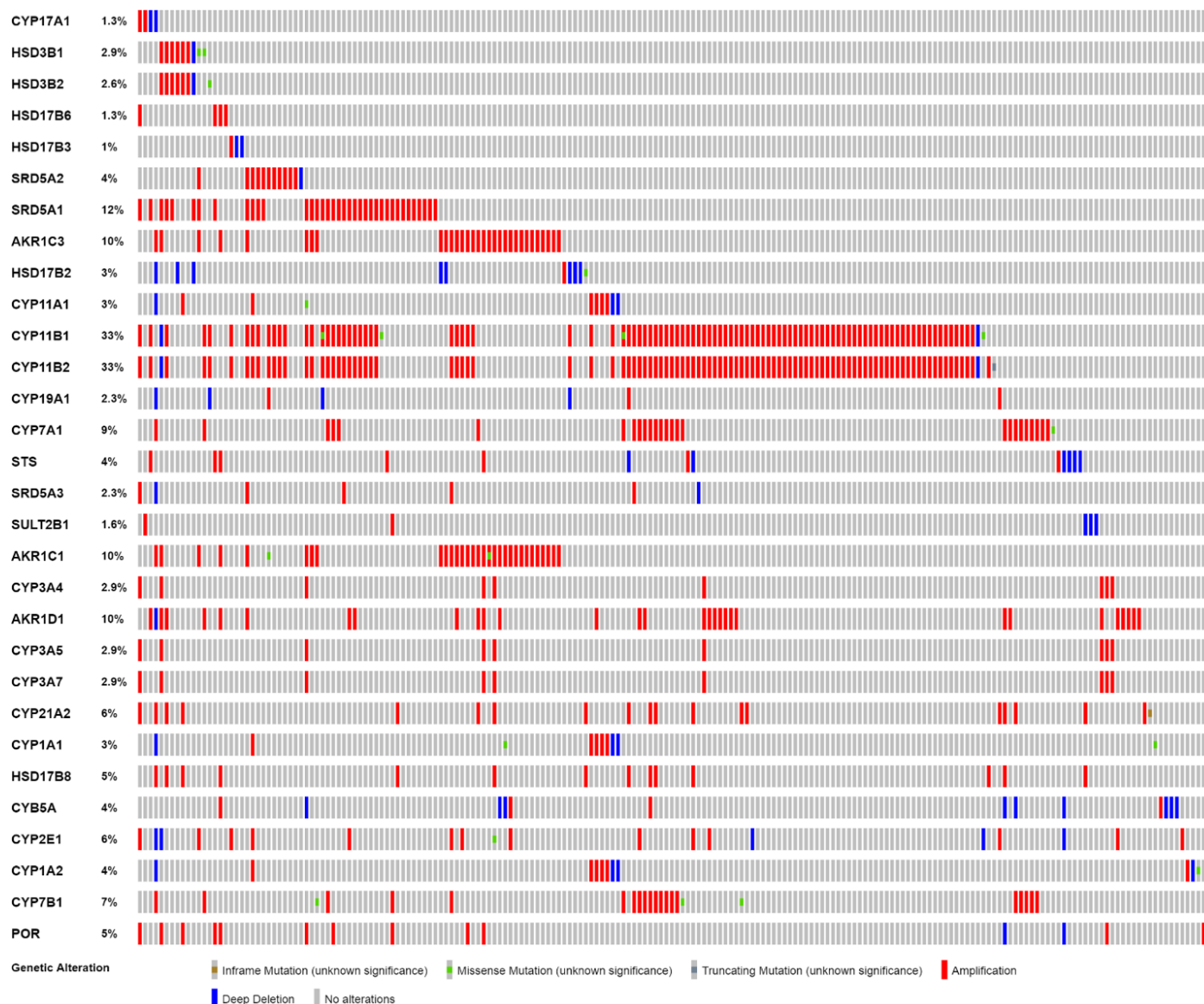


Figure 2: CYP17A1 network analysis in ovarian serous cystadenocarcinoma showing clustering of key genes related to PCOS.

aldehydes conversion to alcohols by consuming NADPH/NADH cofactors. AKR1D1 involve in 5β -metabolites synthesis from testosterone and progesterone. AKR1C3 involve in phenanthrenequinone and prostaglandin reduction with significant contribution in allergic diseases. AKR1C3 overexpression is biomarker in prostate cancer (Penning, 2014; Xiao et al., 2020; Tian et al., 2014). SRD5A1 has highest over expression (12%) which involve in androgen synthesis from testosterone. SRD5A2 has (4%) overexpression which involve in androgen sensitivity in prostate tissue. SRD5A3 has (2.2%) overexpression which involve in regulation of androgen receptor pathway (Tosi et al., 2011; Batista & Mendonca, 2020; Kousal et al., 2019).

In CYB5A cluster POR has highest 4.5% overexpression which involve in electron transport chain. CYB5A has 3% down regulation which involve in type IV methemoglobinemia. In CYP3A5 cluster CYP3A5 and CYP3A7 has 2.9% highest over expressions which are involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. SULT2B1 has 1.3%down regulation which involve in xenobiotic drugs, hormones and neurotransmitters catalysis. In CYP1A1 cluster

CYP1A1, CYP1A2 and CYP3A4 has 2% over expression with CYP2E1 has highest 4% over expressions which are involved in aniline, halogenated hydrocarbons and other laboratory chemicals metabolism (Pandey & Flück, 2013; Sacco et al., 2012; Valente et al., 2015; Chen et al., 2016; Kitam et al., 2012; Doty et al., 2007; Koide et al., 2011).

In CYP17A1 network analysis, 23 members showed significant overexpression in which 12 members related to Cytochrome P450 protein family, 3 members of AKR1C family, 3 members of SRD5A family and 4 members of HSD family. The CYP17A1, CYP1A1 and SRD5A1 are enriched clusters of up regulated genes that are involved in androgen over production, energy synthesis and metabolic basis of cellular proliferation. The CYB5A and SULT2B1 clusters have low expression members which are involved in anti-androgenic activities.

Conclusion

Our *in silico* data suggests androgenic overproduction proteome participate in tumorigenesis to carcinogenesis and showed strong association between altered steroidogenesis and ovarian

serous cystadenocarcinoma. In future, CYP17A1 network ovarian serous cystadenocarcinoma signatures validation in PCOS dataset provides novel shared therapeutic combinations and tremendous syndrome-syndrome molecular linkage for personalized medicine.

Author contributions

AT; perceived the idea, designed the study, analyzed the data, corrected and approved the manuscript, ZAS executed the study, compiled the data, and prepared the manuscript draft.

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