

PCOSDB: PolyCystic Ovary Syndrome Database for manually curated disease associated genes

Maniraja Jesintha Mary*¹, Umashankar Vetrivel², Deecaraman Munuswamy¹, Vijayalakshmi Melanathuru¹

¹Dr. MGR Educational and Research Institute University, Chennai, Tamil Nadu, India; ²Vision Research Foundation, Kamalnayan Bajaj Institute for Research in Vision and Ophthalmology, Sankara Nethralaya, Chennai, Tamil Nadu, India; Jesintha Mary M - Email: jesintha_21@yahoo.com; *Corresponding author

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Abstract:

Polycystic ovary syndrome (PCOS) is a complex disorder affecting approximately 5–10% of all women of reproductive age. It is a multi-factorial endocrine disorder, which demonstrates menstrual disturbance, infertility, anovulation, hirsutism, hyper androgenism and others. It has been indicated that differential expression of genes, genetic level variations, and other molecular alterations interplay in PCOS and are the target sites for clinical applications. Therefore, integrating the PCOS-associated genes along with its alteration and underpinning the underlying mechanism might definitely provide valuable information to understand the disease mechanism. We manually curated the information from 234 published literatures, including gene, molecular alteration, details of association, significance of association, ethnicity, age, drug, and other annotated summaries. PCOSDB is an online resource that brings comprehensive information about the disease, and the implication of various genes and its mechanism. We present the curated information from peer reviewed literatures, and organized the information at various levels including differentially expressed genes in PCOS, genetic variations such as polymorphisms, mutations causing PCOS across various ethnicities. We have covered both significant and non-significant associations along with conflicting studies. PCOSDB v1.0 contains 208 gene reports, 427 molecular alterations, and 46 phenotypes associated with PCOS.

Availability: The database is freely available at <http://www.pcosdb.net/>

Keywords PCOS; Polycystic Ovary Syndrome; SNP; Polymorphism

Background:

Polycystic ovary syndrome (PCOS) is considered to be the leading causes of female subfertility and the most frequent endocrine problems in women of reproductive age [1]. PCOS is a complex disorder affecting approximately 5–10% of all women of reproductive age [2]. It is a multifactorial endocrine disorder, which demonstrates menstrual disturbance, infertility, anovulation, hirsutism, and hyperandrogenism [3]. PCOS is characterized by arrested follicular development prior to selection of a dominant follicle. The increase in the secretion of androgens by the ovaries and the adrenal glands is one of the pathological effects observed in PCOS [4]. PCOS is also associated with an increased risk of developing Type 2 diabetes, dyslipidemia, and cardiovascular diseases [5]. Women with PCOS are also at an increased risk of developing gestational diabetes, preterm birth (PTB) and likely to give birth to premature babies [7]. The etiology of the disease has been difficult to determine because of its hetero genousity. The cause

of PCOS is still unclear; however, it has been observed that various environmental and genetic factors, such as genetic variations, differential regulation of genes, and affected pathways, may contribute to the pathogenesis of PCOS [5]. We have reviewed the association of differential regulation of genes at various levels, including genes that are upregulated and downregulated in PCOS and the associated effects of dysregulation of genes [6]. The detailed literature study revealed that the differential expression of genes involved in the androgen biosynthesis, angiogenesis, follicular development, and at different stages of the embryonic development, contributes to the various changes at the molecular level [7, 8], including the differential expression of genes and miRNAs in the PCOS and its serious effects, including endometrial receptivity, implantation failure, early pregnancy loss, PTB, insulin resistance, hyper androgenism in women with PCOS [9, 10]. The genetic variations play an important role in the pathogenesis of PCOS across different

ethnicities [11]. The detailed literature study revealed several genes and the genetic variations in PCOS and its critical effects, such as ovary failure, obesity [12], spontaneous abortion [13] and recurrent pregnancy loss [14].

The causal genetic variants were assembled at various levels, including mutation, single nucleotide polymorphism, etc., in PCOS and the associated phenotypic effects. Although several studies have been performed on PCOS, the information is dispersed in the literature, which is the most specific challenge for researchers. Hence, the need to have a comprehensive coverage of evidence-based information on PCOS-associated genes and its molecular mechanism becomes evident. At present, we do not have a database available in the public domain; other alternatives are more on the clinical trials [15], patient information on PCOS [16], pathways and networks [17]. Furthermore, literature-based information on PCOS genes with associated evidence to understand the underlying mechanism becomes crucial for better prognosis and treatment. Therefore, it is clear that integration of the PCOS genes along with literature support is of prime concern. Thus, we developed a database, called PCOSDB (Polycystic Ovary Syndrome Database), with the literature-based structured information of genes and its molecular alterations in PCOS condition. We populated the database with literature-driven information on several susceptible genes in PCOS condition, including significant and non-significant association of variations in PCOS, along with conflicting data has been covered in the database. We have underpinned the critical genetic variations in PCOS across different ethnicities and its associated effects, comprehensively in PCOSDB. The database would help in identifying the candidate genes or biomarkers in the disease

condition. More than two hundreds of genes have been covered in PCOSDB. The gene identifiers are hyperlinked to external database, Entrez Gene; the references are linked to PubMed. The database is freely available at <http://www.pcosdb.net>

Methodology:

Article Screening and Strategy:

'PCOS' or 'Polycystic Ovary Syndrome' AND 'Gene' AND 'Mutation OR Polymorphism OR Variation OR SNP' were used as keywords in PubMed Medline Database to search for the research papers. Around 1200 references were screened at the abstract level to segregate the false positive papers from the hit list. All potential published studies on candidate genes and PCOS were evaluated. The true positive papers were collected to perform the manual data curation process.

Data extraction:

Manual curation process was adopted to extract the information. All papers were read, and specific information on PCOS, associated genes, mechanism of association, details of the association, significance of association mentioned in the papers were carefully captured according to the authors' interpretation of the results. Database organization and web interface: PCOSDB is built with Hypertext preprocessor program PHP (<http://www.php.net/>). The database tables are stored in MySQL Server relational database, a lightweight database management system. MySQL, PHP, and JavaScript technology were preferred as they are open source software. A simple and efficient search tool was developed using Ajax technology. A user-friendly web interface has been designed and implemented for 'PCOSDB', which provides interfaces to search, browse, retrieve, and visualize the information freely.

Polycystic Ovarian Syndrome Database PCOSDB
Library of manually curated molecular biomarkers

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Welcome to the website of Polycystic Ovarian Syndrome Database (PCOSDB)

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age with a prevalence of approximately 7-10% worldwide. Polycystic ovary syndrome is a common reproductive disorder characterized by arrested follicular development prior to selection of a dominant follicle. PCOS is one of the most complex diseases, as more and more evidences indicate that this cannot be attributed to a single gene, but due to multiple genes, differential expressions, genetic variations, environmental factors, and associated diseases. The most challenging problems in biomedical research are to understand the underlying mechanisms of the disease.

PCOSDB is an online resource that brings comprehensive information about the polycystic ovarian syndrome disease, and the implication of various genes and its mechanism. In this database we present the manually curated information from peer reviewed literatures, and organized the association at various levels includes genes that are differentially expressed in PCOS, Genes with genetic variations like, Polymorphisms, Mutations and other genetic variations causing PCOS across various ethnicities. PCOSDB can be queried through both Search and Browse functionalities.

Search by Gene name:

Browse by Disease:

PCOSDB Statistics	
No. of Genes	208
No. of Molecular Alterations	427
No. of Associated Phenotypes	46
No. of References	234

Department of Biotechnology, Dr. MGR Educational and Research Institute UNIVERSITY, Chennai, India
PCOS database has been developed as a part of the doctoral research project, and the database is available for free for the scientific community
PCOSDB Version 1.0 - Copyright 2015. All rights Reserved - Designed by [TechieTat](#)
Last updated: July 2015

Figure 1: Web interface of the PCOSDB Basic home page displaying the search and browser tool with PCOSDB data statistics.

Table 1: PCOSDB data fields - a short description of the data fields along with examples.

Data fields	Content Description	Example
GeneID	Entrez Gene identifier	Gene id: 367
Gene Description	Full description of the Gene name	Androgen Receptor
Gene Symbol	Official Gene Symbol	AR
Gene Aliases	Synonyms and alternative names of the gene	RP11-383C12.1, AIS, DHTR, HUMARA, HYSP1, KD, NR3C4, SBMA, SMAX1, TFM
Chromosome Loci	Chromosome locus position	Xq12
Species	Species information	Human
Disease	Primary disease name	PCOS, Polycystic Ovary Syndrome Disease, PCOD
Associated Diseases	Secondary and associated diseases	Androgen excess; infertility
Type of Association	Type of molecular alteration	Polymorphism; Gene expression
Details of Association	Details of the molecular alteration	Androgen receptor gene CAG trinucleotide repeats
Significance of Association	Significance of molecular alteration	Risk of PCOS development
Population	Studied population or ethnicity	Indian and Chinese, Australian, Caucasian
Drug Name	It contains drug name	
Additional Information	Annotated comments briefly describing the experimental details or the author's conclusion or results described in the article	Androgens function through the X-linked androgen receptor (AR), studies based on the investigation of the AR encoded by an increasingly polymorphic CAG trinucleotide repeat tract in polycystic ovary syndrome revealed that there is an association between short CAG repeat length and the pathological process of polycystic ovaries in PCOS patients (PMID: 10999852)
Contradictory results	Negative correlation, contradictory information related to molecular alterations	A study was conducted to determine the relationship between CAG length variations in AR gene and polycystic ovary syndrome. The results revealed that the CAG length variations in AR gene was not associated with polycystic ovary syndrome (PMID: 23628801)
Reference	List of curated references specific to the gene report	Association of the CAG repeats polymorphisms in androgen receptor gene with polycystic ovary syndrome: a systemic review and meta-analysis. Gene. 2013 (PMID: 23628801)

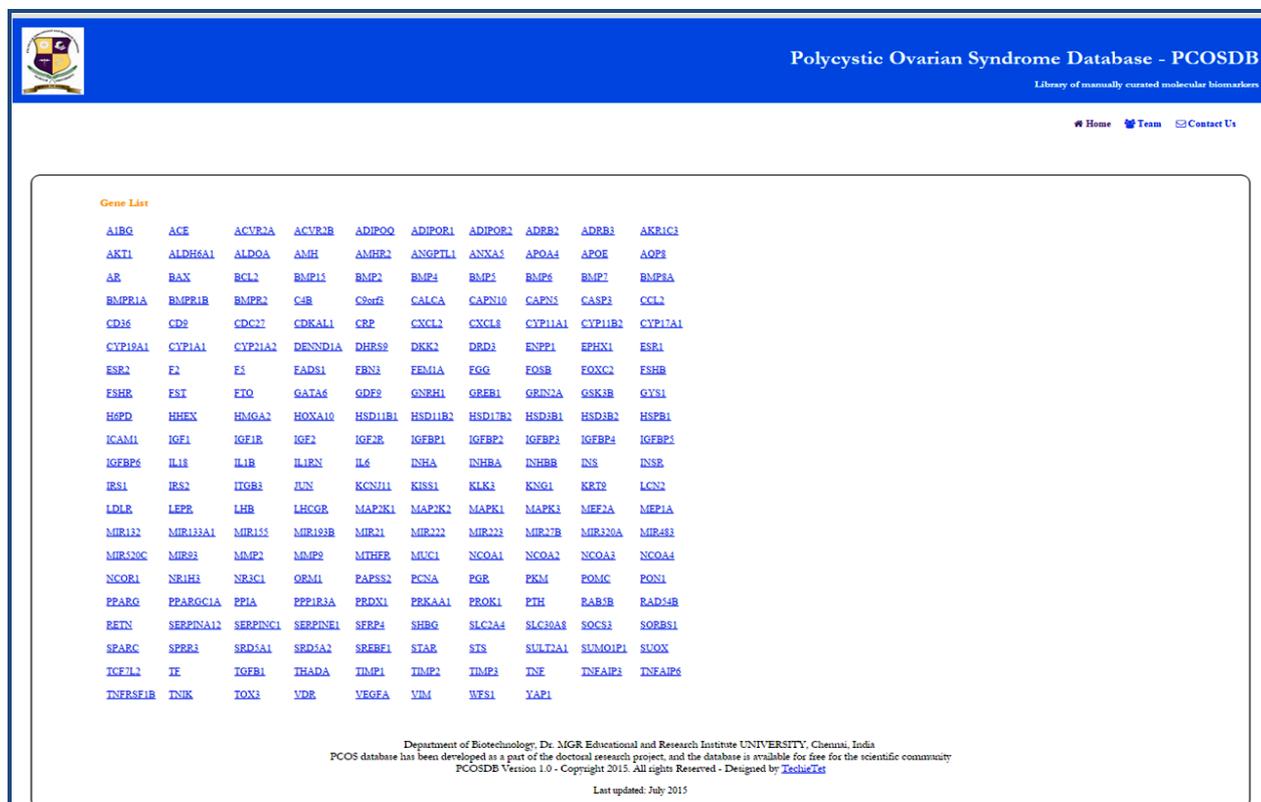


Figure 2: Web interface of the PCOSDB browser view. List of genes available in the PCOSDB displayed.

Utility:

The aim of PCOSDB is to provide reliable information on disease gene association. It is a unique catalogue of reliable manually curated database on experimentally associated information on molecular alterations in PCOS. It includes up-to-date information on the genes, and all associated genetic variations, dysregulation of genes and miRNAs in PCOS condition.

PCOSDB Web Interface:

The PCOSDB portal is composed of a database and a web interface. The web interface supports searching and browsing of PCOS data (Figure 1). The web interface offers two entry points: 1. Search view: It allows the user to search a specific

gene in the database using gene name or gene symbol. A dropdown menu appears with the potential list of genes, and the user can select the gene of interest. As a result, the user retrieves a gene report (or gene page), which will contain all information, as described in Table 1 along with the literature reference. 2. Browse view: It allows the user to explore the complete list of genes associated with PCOS (Figure 2). From the list of the genes, user can select the gene of interest and the respective gene report (Figure 3) can be accessed, i.e. the results are shown in the same way as when using the Search view. The gene report also provides links to external resources such as Entrez Gene (NCBI) and PubMed for references. Gene reports are accessed via both Search and Browse tool. Gene reports are represented as one page report, covers information about Gene and Disease.

Gene report:SERPINE1

Gene ID: [5854](#)
 Gene Description: serpin peptidase inhibitor, clade E (serpin, plasminogen activator inhibitor type 1), member 1
 Gene Symbol: SERPINE1
 Gene Aliases: PAI, PAI-1, PAI1, PLAINH1
 Chromosome Loc: 7q21
 Species: Human

Disease
 PCOS, Polycystic Ovarian Syndrome Disease, PCOD

Associated Diseases
 Hypofibrinolysis, miscarriage
 Thrombophilia, hypofibrinolysis ; recurrent pregnancy loss (RPL)
 Thrombophilia, hypofibrinolysis, spontaneous abortion (SAB)
 Obesity; hyperinsulinemia; hypertriglyceridemia
 Insulin resistance, proinflammatory factors, overweight

Type of Association
 Mutation and Polymorphism
 Mutation
 Polymorphism

Details of Association
 Plasminogen activator inhibitor activity is an independent risk factor for the high miscarriage rate during pregnancy in women with PCOS (1039993)
 plasminogen activator inhibitor 4G/5G (1469168)
 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene (13191349)
 4G/4G mutation of the plasminogen activator inhibitor-1 (PAI-1) gene. (1197013)
 5G/4G polymorphism of the plasminogen activator inhibitor-1 gene (PAI1). (16102884)
 PAI-1 gene polymorphism 4G type (4G/4G genotype) and 5G type (5G/5G, 4G/5G genotype). (16202290)
 The PAI-1 gene 4G polymorphism (16433878)

Significance of Association
 Risk factor for miscarriage in women with PCOS.
 Increased PAI-1 levels
 Recurrent pregnancy loss (RPL)
 Pathogenesis of PCOS
 First-trimester miscarriage

Population
 Caucasian, White women, Chinese.

Drug Name
 Enoxaparin-urefoumin

Additional Information
 1) Plasminogen activator inhibitor activity (PAI-Fa) is known to be the self-determining risk factor for miscarriage in polycystic ovary syndrome and studies based on this have proved that PAI-Fa is a key reversible risk factor for miscarriage in women with polycystic ovary syndrome. (1039993)
 2) Variant 4G/5G of PAI gene is found to be associated with PCOS (1469168)
 3) Study based on the relationship between the variation of the 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene and polycystic ovary syndrome have concluded that this polymorphism is associated with polycystic ovary syndrome and in addition it increases the PAI-1 levels in PCOS patients. (13191349)
 4) Factor V Leiden mutation is one of the causes for recurrent pregnancy loss (RPL) and spontaneous abortion (SAB) in PCOS patients. Administration of Enoxaparin-urefoumin leads to a reduction of pregnancy loss in these patients with one or more prior spontaneous abortions along with thrombophilia and/or hypofibrinolysis. (1497013)
 5) Investigation based on the relationship between the variation of the 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene and polycystic ovary syndrome have concluded that this polymorphism is associated with polycystic ovary syndrome in Chinese women and particularly in non-obese PCOS patients and those with spontaneous miscarriage. (16202290)
 6) Research based on the relationship between the variation of the 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene and polycystic ovary syndrome have concluded that high PAI-1 levels seems to be linked with first-trimester miscarriage in PCOS women. (16433878)
 7) Study based on the relationship between the variation of the 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene and polycystic ovary syndrome have concluded that this polymorphism is associated with polycystic ovary syndrome and in addition it increases the PAI-1 levels which are positively linked with the proinflammatory factors in PCOS patients. (2398913)

Contradictory results
 Research based on the relationship between the variation of the 5G/4G polymorphism of the plasminogen activator inhibitor-1 gene (PAI1) and polycystic ovary syndrome have concluded that this polymorphism has no association with polycystic ovary syndrome in Caucasian women. (16102884)

Reference
 1) 1039993 Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism. 1999 PMID:1039993
 2) 1469168 Polycystic ovary syndrome, the G1691A factor V Leiden mutation, and plasminogen activator inhibitor activity: associations with recurrent pregnancy loss. Metabolism. 2003 PMID:1469168
 3) 13191349 The pertinence of 4G/5G polymorphism of plasminogen activator inhibitor-1 (PAI-1) gene in polycystic ovarian syndrome and its association with plasma PAI-1 levels. Eur J Endocrinol. 2004 PMID:13191349
 4) 1497013 Pregnancy loss, polycystic ovary syndrome, thrombophilia, hypofibrinolysis, enoxaparin, urefoumin. Clin Appl Thromb Hemost. 2004 PMID:1497013
 5) 14102884 A polymorphism of the plasminogen activator inhibitor-1 gene promotes and the polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2005 PMID:14102884
 6) 16202290 Correlation between 4G and 5G genotypes distribution of plasminogen activator inhibitor-1 gene polymorphism in its patients region with polycystic ovarian syndrome. Zhonghua Fu Chan Ke Za Zhi. 2005 PMID:16202290
 7) 16433878 Plasminogen activator inhibitor activity: 4G/5G polymorphism of the plasminogen activator inhibitor 1 gene, and first-trimester miscarriage in women with polycystic ovary syndrome. Metabolism. 2006 PMID:16433878
 8) 2398913 Correlation between plasminogen activator inhibitor-1 (PAI-1) polymorphism 4G/5G polymorphism and metabolic/proinflammatory factors in polycystic ovary syndrome. Gynecol Endocrinol. 2013 PMID:2398913

Figure 3: A detailed gene report.

Summary of the information currently available in PCOSDB

PCOSDB.v1 contains 208 PCOS-associated genes, 427 molecular alterations along with detailed annotations, 46 associated phenotypes, curated from 234 references.

Conclusion & future scope

PCOSDB has been developed as a new resource to help the scientific and medical community. Currently, PCOSDB provide useful targets or biomarkers relevant for clinical diagnosis. It helps in accelerating the research as it presents the underlying molecular mechanism of the disease, underpinning the targets. The database content is carefully maintained and updated. Repeated literature searches and curation are planned to allow for identification and periodic update of new data into the database. A module on the integration of UCSC genome browser for genome analysis is planned for future. We plan to streamline the search functionality by accommodating the search based on gene identifiers, disease name. We will also consider the inclusion of data for other related diseases, to broaden the scope of the database to a larger audience.

Competing Interest:

It should be noted that a concurrent database with similar interest is also available elsewhere [18]. Comparison of data between databases is of interest for further development and advancement.

Author's contributions:

JM performed the research. DM conceived the study, VM assisted on data fields. JM constructed the database and website with the help of UV.

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