



Original article

PCOSBase: a manually curated database of polycystic ovarian syndrome

Nor Afiqah-Aleng¹, Sarahani Harun¹, Mohd Rusman Arief A-Rahman¹,
Nor Azlan Nor Muhammad¹ and Zeti-Azura Mohamed-Hussein^{1,2,*}

¹Institute of Systems Biology (INBIOSIS) and ²Pusat Pengajian Biosains dan Bioteknologi, Fakulti Sains dan Teknologi, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor, Malaysia

*Corresponding author: Tel: 603 8921 4547; Fax: 603 8921 3398; Email: zeti.hussein@ukm.edu.my

Citation details: Afiqah-Aleng, N., Harun, S., A-Rahman, M.R.A. *et al.* PCOSBase: a manually curated database of polycystic ovarian syndrome. *Database* (2017) Vol. 2017: article ID bax098; doi:10.1093/database/bax098

Received 31 October 2017; Revised 27 November 2017; Accepted 30 November 2017

Abstract

Polycystic ovarian syndrome (PCOS) is one of the main causes of infertility and affects 5–20% women of reproductive age. Despite the increased prevalence of PCOS, the mechanisms involved in its pathogenesis and pathophysiology remains unclear. The expansion of omics on studying the mechanisms of PCOS has lead into vast amounts of proteins related to PCOS resulting to a challenge in collating and depositing this deluge of data into one place. A knowledge-based repository named as PCOSBase was developed to systematically store all proteins related to PCOS. These proteins were compiled from various online databases and published expression studies. Rigorous criteria were developed to identify those that were highly related to PCOS. They were manually curated and analysed to provide additional information on gene ontologies, pathways, domains, tissue localizations and diseases that associate with PCOS. Other proteins that might interact with PCOS-related proteins identified from this study were also included. Currently, 8185 PCOS-related proteins were identified and assigned to 13 237 gene ontology vocabulary, 1004 pathways, 7936 domains, 29 disease classes, 1928 diseases, 91 tissues and 320 472 interactions. All publications related to PCOS are also indexed in PCOSBase. Data entries are searchable in the main page, search, browse and datasets tabs. Protein advanced search is provided to search for specific proteins. To date, PCOSBase has the largest collection of PCOS-related proteins. PCOSBase aims to become a self-contained database that can be used to further understand the PCOS pathogenesis and towards the identification of potential PCOS biomarkers.

Database URL: <http://pcosbase.org>

Introduction

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that is characterized by a combination of two out of three features, i.e. ovulatory dysfunction, hyperandrogenism and/or the presence of polycystic ovaries (1). PCOS is difficult to diagnose as these features might lead to various phenotypic manifestations (2). Clinical findings showed that women with PCOS have higher risk to develop other complications such as endometrial cancer (3), diabetes (4), hypertension (5) and depression (6). These phenotypic manifestations and disease associations would significantly interrupt the progress in deciphering the cause of PCOS (7).

Transcriptomics (8) and proteomics (9) were used to identify genes and proteins differences between non-PCOS and PCOS women and the resulting data analysis could be used to elucidate the cause of PCOS. At present, numbers of published expression studies has increased significantly since 2003, and this contributes to the vast amount of PCOS-related molecular data. Unfortunately, these molecular data were randomly distributed in various general biological databases (GenBank and UniProt) and literatures thus contribute to the difficulties in finding all genes and proteins that are related to PCOS. This limitation has led us to develop PCOSBase to house 8185 PCOS-related proteins that were manually curated. These proteins were filtered from 17 492 identified proteins from 30 expression studies and 9 databases. Bioinformatic analyses were performed on these proteins to characterize and classify them into specific datasets based on their molecular characteristics. PCOSBase also provides indexed publications related to PCOS. These features signify the differences of PCOSBase to previously published, PCOSKB (10) (PCOSKB statistics as of July 2017 contains 241 sequences). Detailed information on proteins and diseases related to PCOS can be found in PCOSBase but none on the proteins-drugs association as described in Open Targets (www.targetvalidation.org). Open Targets has listed 1119 proteins identified as drug targets for PCOS and 73% of those can be found in PCOSBase (11). PCOS is a focus in this study due to inadequate information and understanding on its complex molecular mechanism and at the same time it associates with many well-described diseases identified from clinical findings. For this reason, PCOSBase serves as a comprehensive medically oriented repository that will be an excellent aid in providing and integrating accurate molecular information for in depth understanding on PCOS.

Herein, the development and current status of PCOSBase were described. The provided web interfaces were further systematically discussed. PCOSBase can be

accessed online at <http://pcosbase.org> (PCOSBase v1.0, last updated on 21 November 2017).

Materials and methods

Data collection

Keywords including ‘Polycystic Ovary Syndrome,’ ‘Polycystic Ovary Syndrome 1,’ ‘PCOS,’ ‘polycystic ovaries,’ ‘PCOS,’ ‘PCO,’ ‘PCO1,’ ‘Stein-Leventhal,’ ‘Stein Leventhal,’ ‘Stein-Leventhal Syndrome,’ ‘Polycystic Ovary Disease,’ ‘Polycystic Ovarian Disease,’ ‘PCOD,’ ‘Sclerocystic Ovarian Degeneration,’ ‘Sclerocystic Ovary Syndrome,’ ‘Sclerocystic Ovarian Disease’ and ‘Bilateral PCOS’ were searched in nine disease-associated databases including OMIM (12), HGMD (13), DisGeNET (14), MalaCards (15), PhenoicDb (16), DISEASES (17), DGA (18), GWASdb (19) and GWAS catalog (20).

Previous keywords of PCOS and another keywords such as ‘gene expression,’ ‘protein expression,’ ‘expression,’ ‘transcriptomics,’ ‘proteomics’ or ‘microarray’ were also used to search for relevant publications from PubMed (21), ArrayExpress (22), ScienceDirect and Scopus. Genes and proteins that were significantly expressed in those publications were included as PCOS-related proteins. These publications were indexed and listed in PCOSBase.

All genes and proteins from disease-associated databases and published expression publications were compared against NCBI Gene (23) and UniProt (24) databases to obtain their unique Gene ID and UniProt ID. The overlapping data that were obtained in more than one database or studies were combined.

Functional annotations

To better understand the function of PCOS-related proteins, extensive information on the proteins such as chromosomal location, gene ontology (GO), pathway, proteins structural information, tissue localization, disease-related information and protein-protein interaction (PPI) were retrieved from online databases such as NCBI Gene (23), UniProt (24), Gene Ontology Consortium (25), KEGG (26), BioCarta (27), WikiPathways (28), Interpro (29), Human Protein Atlas (30), DisGeNET (14) and HIPPIE (31), or were obtained from our bioinformatics analysis (where necessary).

Database organization and architecture

All collected data including relevant information on PCOS-related proteins, functional annotation information and PCOS publications were organized in 29 tables.

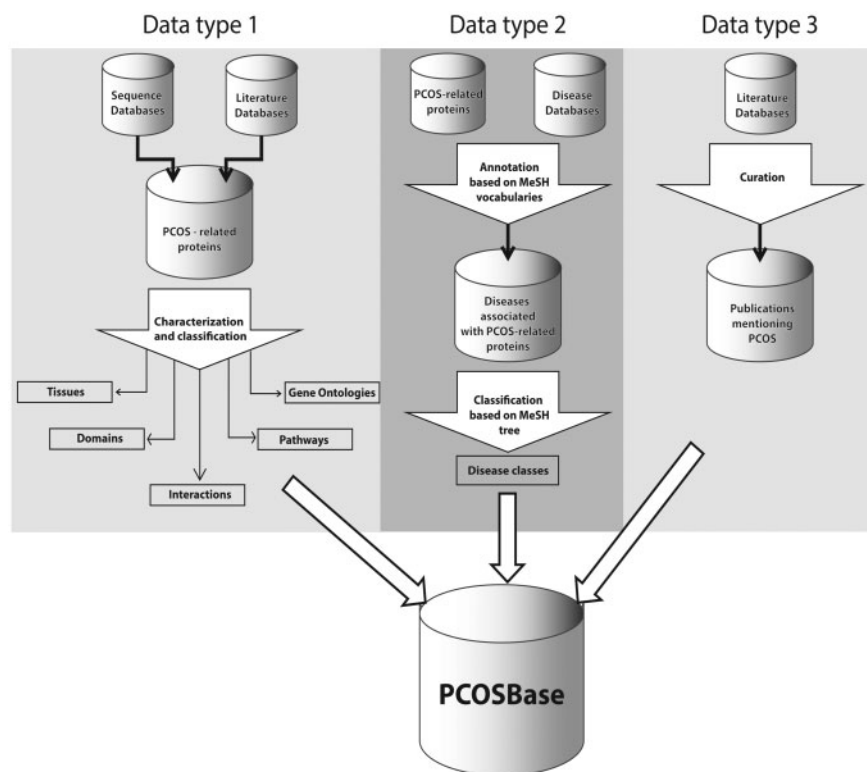


Figure 2. PCOSBase data types structure organization. These data types are tables that can be found in Browse and Datasets menu.

Table 1. Number of entries in the datasets of PCOSBase

Dataset	Entries
PCOS-related proteins	8185
Gene ontologies	13 237
Biological processes	8971
Cellular components	1305
Molecular functions	2961
Domains	7936
Pathways	1004
Interactions	320 472
PCOS-related diseases	1928
Disease classes	29
Tissues	91
Databases	9
Resources	30
Transcriptomics	19
Proteomics	11
Publications	14 368

- c. Pathways dataset: contains all identified pathways where PCOS-related proteins are involved in.
- d. Interactions dataset: contains information on PPIs of PCOS-related proteins.
- e. Domains dataset: contains information on the domains present in all PCOS-related proteins.

- f. Tissues dataset: provides information on which tissues and cell types where PCOS-related proteins were expressed.
- g. Databases dataset: contains list of publicly available databases, where PCOS-related proteins were obtained.
- h. Resources dataset: contains the expression studies of all PCOS-related proteins retrieved from transcriptomic and proteomic data.
- i. PCOS-related diseases dataset: contains identified diseases that are related to PCOS-related proteins.
- j. Disease classes dataset: contains information on PCOS-related diseases based on Medical Subject Headings tree.
- k. Publications dataset: provides all publications from PubMed that relates to PCOS.
- v. Datasets dropdown menu links all datasets in PCOSBase. Datasets tab are placed at the header and appear on every page of PCOSBase, which allow the users to quickly select and redirect to their desired datasets page.
- vi. Network menu contains all networks constructed using PCOS-related proteins, Interactions and PCOS-related diseases datasets. Currently, PCOSBase only provides several static PCOS networks. Figure 3 is one of the networks that can be found in this menu, where

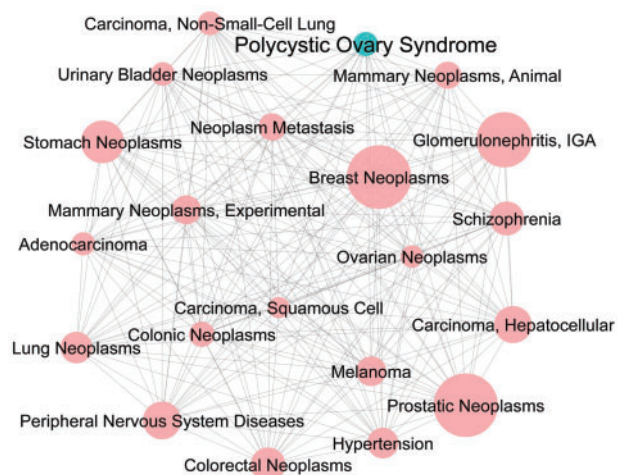


Figure 3. PCOS-disease interaction network. This network is predicted based on PPI and 20 diseases have been predicted to be highly associated with PCOS. The network demonstrates the complexity of PCOS-diseases association and the size of the nodes indicates the degree of association between PCOS and diseases. Green node represents PCOS and size of each node denotes number of shared proteins between PCOS and its respective associated disease.

this network clearly depicted the association of PCOS with other diseases.

- vii. Help menu provides the user manual of PCOSBase, database schema and all the references that were used to retrieve the data. All terms, definition and references that were used in PCOSBase were also provided in the Help page.

Each entry in PCOSBase provides brief description. For example, if the user searches or selects one of the proteins in PCOSBase, for instance ‘androgen receptor,’ it will navigate the user to the Description page of ‘androgen receptor.’ Seven tabs containing different information of ‘androgen receptor’ will appear. If the user clicks on one of the entries in GO tab, it will redirect to the description’s page of that GO. The list of PCOS-related proteins that are associated with this ontology will also appear below the GO description. The description of pathways, domains, diseases, tissues, databases, resources and partners will appear if the user clicks on those entries.

Conclusion and future perspective

In the next few years, the size of PCOS molecular data is expected to increase, especially with the application of new sequencing technologies such as next-generation sequencing in analysing in PCOS samples. To ensure PCOSBase is always up-to-date, all information in this database will be periodically updated. It is very important to consider a comprehensive cataloging on all types of data in any PCOS publications so as to ensure they are accessible to PCOS

researchers and clinicians for their quick and easy reference. Ultimately, genomic and molecular information in this database will serve as a reliable repository that can be used to search for potential PCOS biomarker towards the development of improved diagnostics and treatment for PCOS.

Acknowledgements

Pusat Penyelidikan Bioinformatik, Institut Biologi Sistem (INBIOSIS), Universiti Kebangsaan Malaysia provides the computing facilities used in this project. The authors thank the reviewers in providing constructive suggestions to improve this manuscript and PCOSBase.

Funding

This work was supported by Malaysia Ministry of Higher Education (FRGS/1/2014/SG05/UKM/02/6 and ERGS/1/2013/STG07/UKM/02/3) and Ministry of Science, Technology and Innovation (UKM-MGI-NBD0005-2007) awarded to ZAMH. The Ph.D. scholarship to NAA is funded by MyBrain15, Ministry of Higher Education.

Conflict of interest. None declared.

References

1. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop. (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil. Steril.*, **81**, 19–25.
2. De Leo, V., Musacchio, M.C., Cappelli, V. *et al.* (2016) Genetic, hormonal and metabolic aspects of PCOS: an update. *Reprod. Biol. Endocrinol.*, **14**, 38.
3. Li, X. and Shao, R. (2014) PCOS and obesity: insulin resistance might be a common etiology for the development of type I endometrial carcinoma. *Am. J. Cancer Res.*, **4**, 73–79.
4. Gambineri, A., Patton, L., Altieri, P. *et al.* (2012) Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. *Diabetes*, **61**, 2369–2374.
5. Bentley-Lewis, R., Seely, E. and Dunaif, A. (2011) Ovarian hypertension: polycystic ovary syndrome. *Endocrinol. Metab. Clin. North Am.*, **40**, 433–449.
6. Blay, S.L., Aguiar, J.V.A. and Passos, I.C. (2016) Polycystic ovary syndrome and mental disorders: a systematic review and exploratory meta-analysis. *Neuropsychiatr. Dis. Treat.*, **12**, 2895–2903.
7. Azziz, R., Carmina, E., Chen, Z. *et al.* (2016) Polycystic ovary syndrome. *Nat. Rev. Dis. Prim.*, **2**, 16057.
8. Lan, C.-W., Chen, M.-J., Tai, K.-Y. *et al.* (2015) Functional microarray analysis of differentially expressed genes in granulosa cells from women with polycystic ovary syndrome related to MAPK/ERK signaling. *Sci. Rep.*, **5**, 14994.
9. Ambekar, A.S., Kelkar, D.S., Pinto, S.M. *et al.* (2015) Proteomics of follicular fluid from women with polycystic ovary syndrome suggests molecular defects in follicular development. *J. Clin. Endocrinol. Metab.*, **100**, 744–753.

10. Joseph,S., Barai,R.S., Bhujbalrao,R. *et al.* (2016) PCOSKB: a knowledgebase on genes, diseases, ontology terms and biochemical pathways associated with polycystic ovary syndrome. *Nucleic Acids Res.*, **44**, D1032–D1035.
11. Koscielny,G., An,P., Carvalho-Silva,D. *et al.* (2017) Open targets: a platform for therapeutic target identification and validation. *Nucleic Acids Res.*, **45**, D985–D994.
12. Amberger,J.S., Bocchini,C.A., Schiettecatte,F. *et al.* (2015) OMIM.org: Online Mendelian Inheritance in Man (OMIM[®]), an Online catalog of human genes and genetic disorders. *Nucleic Acids Res.*, **43**, D789–D798.
13. Stenson,P.D., Mort,M., Ball,E.V. *et al.* (2014) The Human Gene Mutation Database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. *Hum. Genet.*, **133**, 1–9.
14. Piñero,J., Bravo,A., Queralt-Rosinach,N. *et al.* (2017) DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. *Nucleic Acids Res.*, **45**, D833–D839.
15. Rappaport,N., Twik,M., Plaschkes,I. *et al.* (2017) MalaCards: an amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. *Nucleic Acids Res.*, **45**, D877–D887.
16. Kahraman,A., Avramov,A., Nashev,L.G. *et al.* (2005) PhenomicDB: a multi-species genotype/phenotype database for comparative phenomics. *Bioinformatics*, **21**, 418–420.
17. Pletscher-Frankild,S., Pallejà,A., Tsafou,K. *et al.* (2015) DISEASES: text mining and data integration of disease-gene associations. *Methods*, **74**, 83–89.
18. Peng,K., Xu,W., Zheng,J. *et al.* (2013) The disease and gene annotations (DGA): an annotation resource for human disease. *Nucleic Acids Res.*, **41**, D553–D560.
19. Li,M.J., Liu,Z., Wang,P. *et al.* (2016) GWASdb v2: an update database for human genetic variants identified by genome-wide association studies. *Nucleic Acids Res.*, **44**, D869–D876.
20. Welter,D., MacArthur,J., Morales,J. *et al.* (2014) The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res.*, **42**, D1001–D1006.
21. NCBI Resource Coordinators. (2017) Database resources of the National center for biotechnology information. *Nucleic Acids Res.*, **45**, D12–D17.
22. Kolesnikov,N., Hastings,E., Keays,M. *et al.* (2015) ArrayExpress update-simplifying data submissions. *Nucleic Acids Res.*, **43**, D1113–D1116.
23. Brown,G.R., Hem,V., Katz,K.S. *et al.* (2015) Gene: a gene-centered information resource at NCBI. *Nucleic Acids Res.*, **43**, D36–D42.
24. Bateman,A., Martin,M.J., O'donovan,C. *et al.* (2015) UniProt: a hub for protein information. *Nucleic Acids Res.*, **43**, D204–D212.
25. Gene Ontology Consortium. (2015) Gene ontology consortium: going forward. *Nucleic Acids Res.*, **43**, D1049–D1056.
26. Kanehisa,M., Sato,Y., Kawashima,M. *et al.* (2016) KEGG as a reference resource for gene and protein annotation. *Nucleic Acids Res.*, **44**, D457–D462.
27. Nishimura,D. (2001) A view from the Web, BioCarta. *Biotech. Software Internet Rep.*, **2**, 117–120.
28. Pico,A.R., Kelder,T., Van Iersel,M.P. *et al.* (2008) WikiPathways: pathway editing for the people. *PLoS Biol.*, **6**, e184.
29. Finn,R.D., Attwood,T.K., Babbitt,P.C. *et al.* (2017) InterPro in 2017-beyond protein family and domain annotations. *Nucleic Acids Res.*, **45**, D190–D199.
30. Uhlén,M., Fagerberg,L., Hallström,B.M. *et al.* (2015) Tissue-based map of the human proteome. *Science*, **347**, 1260419.
31. Alanis-Lobato,G., Andrade-Navarro,M.A. and Schaefer,M.H. (2017) HIPPIE v2.0: Enhancing meaningfulness and reliability of protein-protein interaction networks. *Nucleic Acids Res.*, **45**, D408–D414.